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Synthesis of *C*1-alkyl- and acylglycals from glycals using a *B*-alkyl Suzuki–Miyaura cross coupling approach ☆

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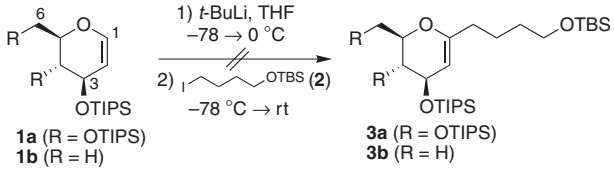
Abstract—A *B*-alkyl Suzuki–Miyaura cross coupling approach provides a flexible, efficient means to convert glycals to *C*1-alkylglycals and *C*1-acylglycals that are versatile synthetic intermediates. This approach uses readily available glycal starting materials and overcomes major limitations associated with direct alkylation or acylation of glycals. Further, a commonly observed side reaction involving reduction of the halide coupling partner is suppressed by preincubation of the borane coupling partner with aqueous base, providing new mechanistic insights into the side reaction.

Glycals are versatile, readily available synthetic intermediates with a wide range of applications in the synthesis of carbohydrates,[1] *C*-linked carbohydrate analogs,[2] *C*-aryl glycosides,[3] and a variety of other natural products.[4,5] In the course of a diversity-oriented synthesis project, we required a flexible, efficient method to convert glycals to *C*1-alkylglycals and *C*1-acylglycals.[6] Herein we report a *B*-alkyl Suzuki–Miyaura cross coupling approach to this overall transformation that overcomes major limitations associated with direct alkylation or acylation of glycals. Furthermore, we demonstrate that a commonly observed side reaction involving reduction of the halide coupling partner is effectively suppressed by preincubation of the borane coupling partner with aqueous base. Consequently, we propose a new alternative mechanism for this side reaction.

The seminal studies of Boeckman demonstrated that dihydropyrans can be lithiated at the *C*1-position (glycal numbering) with *t*-BuLi, then trapped with electrophiles to yield *C*1-substituted products.[7,8] Glycals have also been deprotonated with the Schlosser base[9] (*n*-BuLi, KO*t*-Bu), then trapped with Bu_3SnCl to form isolable *C*1-tributylstannylglycals.[10] Subsequent tin–lithium exchange using *n*-BuLi regenerates the *C*1-lithioglycal nucleophile for reaction with electrophiles.[11] Despite the straightforward nature of these approaches, several limitations have emerged. *C*1-Lithioglycals are relatively weak nucleophiles whose reactivity is attenuated further by the presence of oxygen substituents on the glycal ring.[12] Consequently, alkylation reactions are particularly challenging, generally requiring the use of alkyl iodides, often with HMPA cosolvent and an excess of the *C*1-lithioglycal.[13] The competing reactivity of *C*1-lithioglycals as bases can also lead to undesired side reactions.[7b] These considerations significantly limit the flexibility of this approach, an issue of paramount importance in diversity-oriented synthesis.[14]

These concerns were borne out in our initial efforts to alkylate glycals having an oxygen substituent at the *C*3-position (Scheme 1). TIPS-protected glycals **1a** and



1a (R = OTIPS)
1b (R = H)

3a (R = OTIPS)
3b (R = H)

Scheme 1. Attempted direct alkylation of *C*1-lithioglycals.

Keywords: Glycal; Cross coupling; *B*-Alkyl Suzuki–Miyaura; *C*-glycoside.

☆ Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2003.12.006

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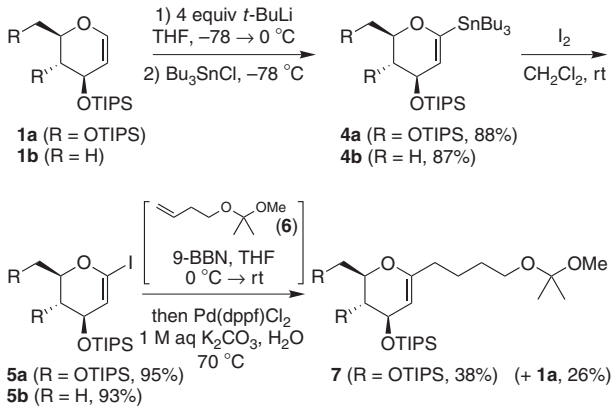


Scheme 2. Synthesis of *C*1-iodoglycals and first cross coupling reaction.

1b were prepared from D-glucal and 4,6-dideoxy-DL-glucal[15] under standard conditions (TIPSCl, imidazole, DMF, rt).[16] Lithiation of **1a** with *t*-BuLi was accomplished using Friesen's modified protocol.[17,18] However, the resulting *C*1-lithioglycal was completely unreactive with alkyl iodide **2**, even in the presence of HMPA.[19] The *C*1-lithioglycal derived from the corresponding stannane (**4a**, Scheme 2) by tin–lithium exchange was likewise unreactive. Deprotonation of **1a** with the Schlosser base,[18] followed by direct addition of excess alkyl iodide **2** did afford partial conversion to the desired *C*1-alkylglycal **3a**. However, a significant amount of iodide elimination was observed, suggesting competing basicity of the *C*1-lithioglycal–KO*t*-Bu complex. Alkylations involving the typical transmetalated species (*t*-BuLi *then* $MgBr_2$,[20] MgI_2, CuI,[12a] $MgBr_2$/CuI,[21] $MgBr_2$/Li_2CuCl_4,[22] or $MgBr_2$/Pd(dppf)Cl_2[23]) failed to afford any coupling product at all. Reactions in the 4,6-dideoxy-DL-glucal series (**1b** and **4b**) yielded similar results.

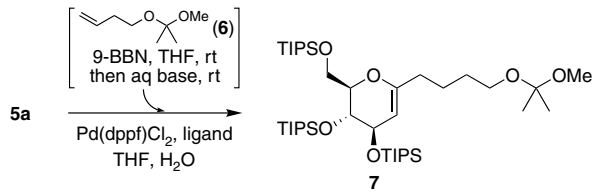
Thus, we elected to pursue an alternative strategy involving conversion of the parent glycals **1a** and **1b** to *C*1-iodoglycals followed by a *B*-alkyl Suzuki–Miyaura cross coupling reaction with alkylborane coupling partners.[24,25] We envisioned that this approach would provide flexible access to a variety of *C*1-alkylglycals from readily available glycals and olefins. We were also encouraged by previous reports of related cross couplings.[17,26]

*C*1-Iodoglycal substrates **5a** and **5b** were prepared according to Friesen's two-step protocol (Scheme 2).[17,27] In accordance with literature precedent, we found that these compounds, especially **5b**, exhibited capricious stability that varied from batch to batch. Nonetheless, degassing of all solvents with argon and protection from light allowed purification of the iodides by column chromatography for immediate use in cross coupling reactions. In early attempts, we had some success at effecting the desired coupling of iodide **5a** with the alkylborane derived from olefin **6** to yield *C*1-alkylglycal **7**. However, under a number of reaction conditions, including those of the original Suzuki–Miyaura procedure (shown in Scheme 2),[24] a substantial amount of reduction back to the parent glycal **1a** was also observed. This problematic reduction side reaction has also been observed with other halide substrates.[24,28,29]

We next set out to optimize the cross coupling reaction. After extensive experimentation, we observed a major improvement when we preincubated the hydroboration product with aqueous base for 30 min before addition to the *C*1-iodoglycal and palladium catalyst. This protocol reduced the amount of reduction to $\leqslant 5\%$ based upon NMR analysis of the crude product (Table 1, entry 1). Subsequent experiments identified NaOH as the optimal base (entries 1, 2, and 4) with the addition of $AsPh_3$ proving detrimental to both selectivity and yield (entries 3 and 5).[28] At this fairly high catalyst loading level (20 mol%), selected in consideration of anticipated future applications to solid phase synthesis, the reaction also proceeds rapidly and effectively at room temperature (entry 6).

Only a handful of groups have used base preincubation protocols in Suzuki–Miyaura cross couplings.[26,30] Moreover, to our knowledge, the striking impact of this protocol upon the reduction side reaction has not been recognized previously. This side reaction is generally attributed to reductive elimination of a palladium

Table 1. Optimization of the *B*-alkyl Suzuki–Miyaura cross coupling reaction[a]

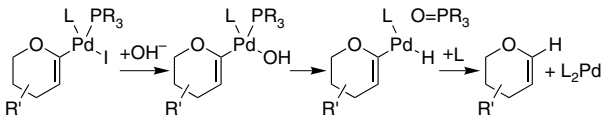


Entry	Temperature (°C)	Base	Ligand	**7**:**1a**	Yield (%)
1	70	K_2CO_3	None	96:4	63
2	70	Cs_2CO_3	None	96:4	71
3	70	Cs_2CO_3	$AsPh_3$	90:10	59
4	70	NaOH	None	99:1	87
5	70	NaOH	$AsPh_3$	98:2	78
6	rt	NaOH	None	98:2	91

[a] 1.5 equiv olefin, 3.0 equiv 9-BBN, 1 h; then 3.0 equiv base (1 M aq), 30 min; then add mixture to **5a** and 20 mol% Pd(dppf)Cl_2, ±20 mol% $AsPh_3$.

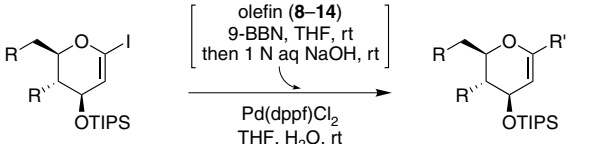
hydride species formed by (1) β-hydride elimination of the alkylpalladium intermediate[24,28] or (2) hydride transfer from the excess 9-BBN usually used to drive the hydroboration reaction to completion.[29] However, in a control experiment with *C*1-iodoglycal **5a**, $Pd(dppf)Cl_2$, and aq NaOH, we observed 23% reduction to glycal **1a** (remainder unreacted **5a**). Notably, the two sources of hydride above—alkylborane and 9-BBN—were absent from this reaction. Further investigations revealed a direct correlation between the extent of reduction and the amount of $Pd(dppf)Cl_2$ used in this control reaction. Concurrent oxidation of the dppf ligand to the corresponding bis(phosphine oxide)[31] was detected by NMR and MS analysis and was evidenced by Pd(0) plating out of the reaction. Inclusion of PPh_3 in the control reaction resulted in a commensurate increase in conversion of **5a** to **1a**, with triphenylphosphine oxide generated as a byproduct.

In view of these results, we propose that preincubation of aqueous base with the hydroboration reaction mixture is critical for fully engaging hydroxide as the boron 'ate' complex. If this preincubation protocol is not used and the *C*1-iodoglycal is exposed to residual free hydroxide in the presence of the palladium catalyst, a competing reaction manifold leads to *C*1-iodoglycal reduction. This may occur via a mechanism analogous to the known hydroxide-induced disproportionation of $(Ph_3P)_2PdCl_2$ to triphenylphosphine oxide and Pd(0).[32] Thus, oxidative insertion of Pd(0) into the *C*1-iodoglycal would be followed by displacement of iodide by hydroxide (Scheme 3). Oxygen transfer from Pd to phosphine would generate a phosphine oxide and a glycalpalladium hydride species that would undergo reductive elimination to yield the parent glycal. This



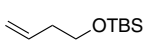
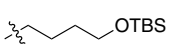
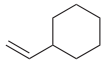
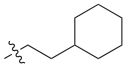
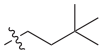
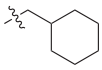
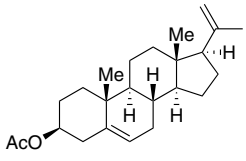
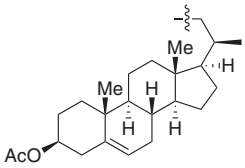
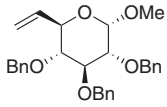
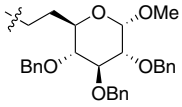
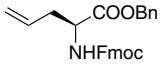
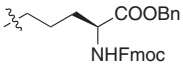
Scheme 3. Proposed mechanism for hydroxide-mediated reduction.

Table 2. Scope of the *B*-alkyl Suzuki–Miyaura cross coupling route to *C*1-alkylglycals[a]



5a (R = OTIPS)
5b (R = H)

3a, **15**–**20** (R = OTIPS)
3b (R = H)

Entry	Iodide		Olefin		Product: R′ =	Yield (%)[b]
1	**5a**	**8**		**3a**		88
2	**5b**	**8**		**3b**		81
3	**5a**	**9**		**15**		89
4	**5a**	**10**		**16**		95
5	**5a**	**11**		**17**		85
6	**5a**	**12**		**18**		86
7	**5a**	**13**		**19**		97
8	**5a**	**14**		**20**		95

[a] (i) 1.5 equiv olefin, 3.0 equiv 9-BBN, THF, rt, 3 h; (ii) 3.0 equiv 1 N aq NaOH, rt, 30 min; (iii) add to iodide and 20 mol % $Pd(dppf)Cl_2$, THF/H_2O (6.25:1 final ratio), rt, 1 h.

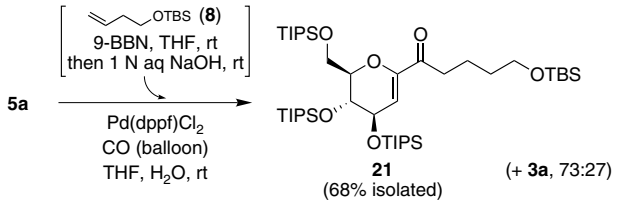
[b] All purified products exhibited satisfactory NMR, IR, and mass spectral data.

proposal is consistent with the observed correlation between the amount of phosphine present and the extent of *C*1-iodoglycal reduction. Notably, in their detailed mechanistic investigations of the *B*-alkyl Suzuki–Miyaura cross coupling reaction, Matos and Soderquist also observed an analogous reduction of bromobenzene to benzene with concomitant triphenylphosphine oxidation.[33] However, the significance of this additional alternative mechanism for the reduction side reaction in cross couplings has apparently not been fully appreciated until now.

With optimized reaction conditions in hand, we next set out to explore the scope of the *B*-alkyl Suzuki–Miyaura cross coupling reaction.[34] A variety of primary alkylboranes can be coupled with *C*1-iodoglycals rapidly and efficiently at room temperature (Table 2). Although, as anticipated, cyclohexene-derived secondary alkylboranes are ineffective coupling partners (not shown), steric hindrance is well tolerated at the α- and β-positions (entries 3–6). Sugar- and amino acid-derived substrates can also be coupled (entries 7 and 8),[35] highlighting the potential utility of this approach for the synthesis of *C*-linked oligosaccharides and glycopeptides via subsequent stereoselective double bond transformations.[6c,d,36]

Finally, we note that direct acylation of *C*1-lithiodihydropyrans is also a highly problematic reaction that is ineffective using acid chlorides, anhydrides, and esters.[7b] Limited success has been achieved with DMF, *N*,*N*-dimethaylacetamide,[7b] and γ-butyrolactone.[37] Thus, we were gratified to find that our *B*-alkyl Suzuki–Miyaura cross coupling approach can also be applied under carbonylative conditions to provide *C*1-acylglycal **21** (Scheme 4).[38] While this reaction merits further optimization, it extends the scope of our approach to provide access to a variety of *C*1-acylglycals using readily available olefin coupling partners.

In conclusion, we have developed a flexible, efficient method to convert glycals to *C*1-substituted glycals using a *B*-alkyl Suzuki–Miyaura cross coupling approach. This method provides access to *C*1-substituted glycals that are not available by direct alkylation or acylation of *C*1-lithioglycals. Furthermore, a wide range of both the glycal[1,39] and olefin coupling partners are readily available. We have also developed new insights into the problematic reduction side reaction that often occurs during *B*-alkyl Suzuki–Miyaura couplings.



Scheme 4. Synthesis of a *C*1-acylglycal using a carbonylative *B*-alkyl Suzuki–Miyaura cross coupling reaction.

We have demonstrated that aq NaOH alone can effect palladium-mediated reduction of *C*1-iodoglycals and that this side reaction is essentially eliminated in cross couplings by preincubation of the aq NaOH with the alkylborane prior to addition of the mixture to the *C*1-iodoglycal and palladium catalyst. Our current efforts are directed toward further improvement of this synthetic approach, translation to solid phase synthesis, and elaboration of both solution and solid phase coupling products in diversity-oriented synthesis.

Supplementary material. Experimental procedures and spectral data for compounds **1b**, **3**–**7**, **15**–**21** are available at doi:10.1016/j.tetlet.2003.12.006.

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References and notes

1. Danishefsky, S. J.; Bilodeau, M. T. *Angew. Chem. Int. Ed.* **1996**, *35*, 1380–1419.
2. (a) Dondoni, A.; Marra, A. *Chem. Rev.* **2000**, *100*, 4395–4421; (b) Du, Y.; Linhardt, R. J.; Vlahov, I. R. *Tetrahedron* **1998**, *54*, 9913–9959.
3. Jaramillo, C.; Knapp, S. *Synthesis* **1994**, 1–20.
4. Postema, M. H. D. *Tetrahedron* **1992**, *48*, 8545–8599.
5. For recent examples, see: (a) Majumder, U.; Cox, J. M.; Rainier, J. D. *Org. Lett.* **2003**, *5*, 913–916; (b) Gaul, C.; Njardarson, J. T.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2003**, *125*, 6042–6043; (c) Ohyabu, N.; Nishikawa, T.; Isobe, M. *J. Am. Chem. Soc.* **2003**, *125*, 8798–8805.
6. For alternative approaches from non-glycal starting materials, see: (a) Gómez, A. M.; Casillas, M.; Valverde, S.; López, J. C. *Chem. Commun.* **1996**, 2357–2358; (b) Calimente, D.; Postema, M. H. D. *J. Org. Chem.* **1999**, *64*, 1770–1771; (c) Khan, N.; Cheng, X.; Mootoo, D. R. *J. Am. Chem. Soc.* **1999**, *121*, 4918–4919; (d) Popsavin, V.; Berić, O.; Popsavin, M.; Radić, L.; Csanádi, J.; Ćirin-Novta, V. *Tetrahedron* **2000**, *56*, 5929–5940; (e) Gómez, A. M.; Barrio, A.; Pedregosa, A.; Valverde, S.; López, J. C. *Tetrahedron Lett.* **2003**, *44*, 8433–8435.
7. (a) Boeckman, R. K., Jr.; Bruza, K. J. *Tetrahedron Lett.* **1977**, 4187–4190; (b) Boeckman, R. K., Jr.; Bruza, K. J. *Tetrahedron* **1981**, *37*, 3997–4006.
8. Somsák, L. *Chem. Rev.* **2001**, *101*, 81–135.
9. Schlosser, M.; Strunk, S. *Tetrahedron Lett.* **1984**, *25*, 741–744.
10. Hanessian, S.; Martin, M.; Desai, R. C. *J. Chem. Soc., Chem. Commun.* **1986**, 926–927.
11. Lesimple, P.; Beau, J. M.; Jaurand, G.; Sinay, P. *Tetrahedron Lett.* **1986**, *27*, 6201–6204.

12. (a) Nicolaou, K. C.; Hwang, C. K.; Duggan, M. E. *J. Chem. Soc. Chem. Commun.* **1986**, 925–926; (b) Paquette, L. A.; Oplinger, J. A. *Tetrahedron* **1989**, *45*, 107–124.
13. (a) Boeckman, R. K., Jr.; Bruza, K. J.; Heinrich, G. R. *J. Am. Chem. Soc.* **1978**, *100*, 7101–7103; (b) Boeckman, R. K., Jr.; Charette, A. B.; Asberom, T.; Johnston, B. H. *J. Am. Chem. Soc.* **1987**, *109*, 7553–7555.
14. Weber, L. *Curr. Opin. Chem. Biol.* **2000**, *4*, 295–302.
15. Varelis, P.; Graham, A. J.; Johnson, B. L.; Skelton, B. W.; White, A. H. *Aust. J. Chem.* **1994**, *47*, 1735–1739.
16. Friesen, R. W.; Sturino, C. F.; Daljeet, A. K.; Kolaczewska, A. *J. Org. Chem.* **1991**, *56*, 1944–1947.
17. Friesen, R. W.; Loo, R. W. *J. Org. Chem.* **1991**, *56*, 4821–4823.
18. Successful glycal deprotonation was confirmed by D_2O quenching in separate experiments under identical conditions. The *t*-BuLi-derived *C*1-lithioglycals were also trapped successfully with Bu_3SnCl (Scheme 2).
19. In contrast, successful alkylation of a dihydropyran lacking a *C*3-oxygen substituent has been reported using alkyl iodide **2**: Amouroux, R. *Heterocycles* **1984**, *22*, 1489–1492.
20. (a) Jung, M. E.; Hagenah, J. A. *J. Org. Chem.* **1987**, *52*, 1889–1902; (b) Jung, M. E.; Gervay, J. *J. Am. Chem. Soc.* **1991**, *113*, 224–232.
21. Derguini-Boumechal, F.; Linstrumelle, G. *Tetrahedron Lett.* **1976**, 3225–3226.
22. Tamura, M.; Kochi, J. *Synthesis* **1971**, 303–305.
23. Castle, P. L.; Widdowson, D. A. *Tetrahedron Lett.* **1986**, *27*, 6013–6016.
24. Miyaura, N.; Ishiyama, T.; Sasaki, H.; Ishikawa, M.; Sato, M.; Suzuki, A. *J. Am. Chem. Soc.* **1989**, *111*, 314–321.
25. Reviewed in: (a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457–2483; (b) Chemler, S. R.; Trauner, D.; Danishefsky, S. J. *Angew. Chem. Int. Ed.* **2001**, *40*, 4544–4568.
26. (a) Sasaki, M.; Fuwa, H.; Inoue, M.; Tachibana, K. *Tetrahedron Lett.* **1998**, *39*, 9027–9030; (b) Sasaki, M.; Fuwa, H.; Ishikawa, M.; Tachibana, K. *Org. Lett.* **1999**, *1*, 1075–1077.
27. Attempts to access the *C*1-iodoglycals directly from the *C*1-lithioglycals were unsuccessful.
28. Johnson, C. R.; Braun, M. P. *J. Am. Chem. Soc.* **1993**, *115*, 11014–11015.
29. (a) Kondo, K.; Sodeoka, M.; Shibasaki, M. *J. Org. Chem.* **1995**, *60*, 4322–4323; (b) Kondo, K.; Sodeoka, M.; Shibasaki, M. *Tetrahedron: Asymmetry* **1995**, *6*, 2453–2464; (c) Ohba, M.; Kawase, N.; Fujii, T. *J. Am. Chem. Soc.* **1996**, *118*, 8250–8257.
30. (a) Soderquist, J. A.; Colberg, J. C. *Synlett* **1989**, 25–27; (b) Soderquist, J. A.; León, G.; Colberg, J. C.; Martinez, I. *Tetrahedron Lett.* **1995**, *36*, 3119–3122; (c) Fürstner, A.; Seidel, G.; Gabor, B.; Kopiske, C.; Krüger, C.; Mynott, R. *Tetrahedron* **1995**, *51*, 8875–8888; (d) Mandal, A. K. *Org. Lett.* **2002**, *4*, 2043–2045.
31. The dppf mono(phosphine oxide) is presumably formed initally during reduction of Pd(II) to the active Pd(0) catalyst (Ref. 32).
32. Grushin, V. V.; Alper, H. *Organometallics* **1993**, *12*, 1890–1901.
33. Matos, K.; Soderquist, J. A. *J. Org. Chem.* **1998**, *63*, 461–470.
34. Representative experimental procedure: In a flame dried 10 mL conical flask equipped with a magnetic stir bar, septum, and argon inlet needle, olefin **8** (37.8 mg, 203 μmol, 1.5 equiv) was dissolved in anhyd THF (2 mL). A freshly prepared solution of 9-BBN (0.5 M in THF, 810 μL, 405 μmol, 3.0 equiv) was added dropwise at rt. After 3 h, 1 N aq NaOH (405 μL, 405 μmol, 3.0 equiv) was added and the reaction was stirred for an additional 30 min at rt. In a separate flame-dried 10 mL conical flask, *C*1-iodoglycal **5a** (100 mg, 135 μmol, 1.0 equiv) was dissolved in THF (1 mL) and water (395 μL). $Pd(dppf)Cl_2$ (22 mg, 27 μmol, 0.2 equiv) was added. The hydroboration reaction mixture was then added to the solution of **5a** and catalyst via syringe. The hydroboration flask was rinsed twice more with 600 μL THF. The reaction was stirred for 1 h at rt, then diluted with Et_2O (50 mL), washed with 1 N aq NaOH, H_2O, and brine, then dried ($MgSO_4$) and filtered. Evaporation of solvent and silica flash chromatography (5:1 hexanes/CH_2Cl_2) yielded *C*1-alkylglycal **3a** as a colorless oil (95.5 mg, 88%).
35. Attempted couplings with *exo*-glycal-derived alkyl boranes yielded mixtures of cyclic and ring-opened *C*1-substituents under our conditions (cf. Ref. 26a).
36. Lehmann, U.; Awasthi, S.; Minehan, T. *Org. Lett.* **2003**, *5*, 2405–2408.
37. Chavdarian, C. G.; Chang, L. L.; Onisko, B. C. *Heterocycles* **1988**, *27*, 651–656.
38. Ishiyama, T.; Miyaura, N.; Suzuki, A. *Bull. Chem. Soc. Jpn.* **1991**, *64*, 1999–2001.
39. (a) Jørgensen, K. A. *Angew. Chem. Int. Ed.* **2000**, *39*, 3558–3588; (b) McDonald, F. E. *Chem. Eur. J.* **1999**, *5*, 3103–3106; (c) Zipp, G. G.; Hilfiker, M. A.; Nelson, S. G. *Org. Lett.* **2002**, *4*, 1823–1826.