Synthesis of C1-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 C1-alkylglycals and C1-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.

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

Glycals are versatile, readily available synthetic intermediates with a wide range of applications in the synthesis of carbohydrates, C-linked carbohydrate analogs, C-aryl glycosides, and a variety of other natural products. In the course of a diversity-oriented synthesis project, we required a flexible, efficient method to convert glycals to C1-alkylglycals and C1-acylglycals. 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 dihydropyranys can be lithiated at the C1-position (glycal numbering) with t-BuLi, then trapped with electrophiles to yield C1-substituted products. Glycals have also been deprotonated with the Schlosser base (n-BuLi, KOt-Bu), then trapped with Bu3SnCl to form isolable C1-tributylstannylglycals. Subsequent tin–lithium exchange using n-BuLi regenerates the C1-lithioglycal nucleophile for reaction with electrophiles. Despite the straightforward nature of these approaches, several limitations have emerged. C1-Lithioglycals are relatively weak nucleophiles whose reactivity is attenuated further by the presence of oxygen substituents on the glycal ring. Consequently, alkylation reactions are particularly challenging, generally requiring the use of alkyl iodides, often with HMPA cosolvent and an excess of the C1-lithioglycal. The competing reactivity of C1-lithioglycals as bases can also lead to undesired side reactions. These considerations significantly limit the flexibility of this approach, an issue of paramount importance in diversity-oriented synthesis.

These concerns were borne out in our initial efforts to alkylate glycals having an oxygen substituent at the C3-position (Scheme 1). TIPS-protected glycals 1a and

![Scheme 1. Attempted direct alkylation of C1-lithioglycals.](https://example.com/scheme1.png)


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from readily available glycals and olefins. We were also encouraged by previous reports of related cross couplings.\textsuperscript{17,26}

\textbf{Cl-Iodoglycal substrates} 5a and 5b were prepared according to Friesen’s two-step protocol (Scheme 2).\textsuperscript{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 Cl-alkylglycal 7. However, under a number of reaction conditions, including those of the original Suzuki–Miyaura procedure (shown in Scheme 2),\textsuperscript{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.\textsuperscript{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 Cl-alkylglycal and palladium catalyst. This protocol reduced the amount of reduction to \(< 5\%\) 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\textsubscript{3}, proving detrimental to both selectivity and yield (entries 3 and 5).\textsuperscript{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.\textsuperscript{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>
<thead>
<tr>
<th>Entry</th>
<th>Temperature (°C)</th>
<th>Base</th>
<th>Ligand</th>
<th>7:1a</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>70</td>
<td>K\textsubscript{2}CO\textsubscript{3}</td>
<td>None</td>
<td>96:4</td>
<td>63</td>
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<tr>
<td>2</td>
<td>70</td>
<td>Cs\textsubscript{2}CO\textsubscript{3}</td>
<td>None</td>
<td>96:4</td>
<td>71</td>
</tr>
<tr>
<td>3</td>
<td>70</td>
<td>Cs\textsubscript{2}CO\textsubscript{3}</td>
<td>AsPh\textsubscript{3}</td>
<td>90:10</td>
<td>59</td>
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<tr>
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<td>70</td>
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<td>None</td>
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<td>87</td>
</tr>
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<td>NaOH</td>
<td>AsPh\textsubscript{3}</td>
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<tr>
<td>6</td>
<td>rt</td>
<td>NaOH</td>
<td>None</td>
<td>98:2</td>
<td>91</td>
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</tbody>
</table>

\textsuperscript{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\textsubscript{2}, \pm 20 mol% AsPh\textsubscript{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 Cl-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 Cl-iodoglycal is exposed to residual free hydroxide in the presence of the palladium catalyst, a competing reaction manifold leads to Cl-iodoglycal reduction. This may occur via a mechanism analogous to the known hydroxide-induced disproportionation of (Ph\(_3\)P)\(_2\)PdCl\(_2\) to triphenylphosphine oxide and Pd(0).\(^ {32} \) Thus, oxidative insertion of Pd(0) into the Cl-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.

![Scheme 3. Proposed mechanism for hydroxide-mediated reduction.](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Iodide</th>
<th>Olefin</th>
<th>Product: ( R' = )</th>
<th>Yield (%)(^ b )</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>( 5a )</td>
<td>( 8 )</td>
<td>( 3a )</td>
<td>88</td>
</tr>
<tr>
<td>2</td>
<td>( 5b )</td>
<td>( 8 )</td>
<td>( 3b )</td>
<td>81</td>
</tr>
<tr>
<td>3</td>
<td>( 5a )</td>
<td>( 9 )</td>
<td>( 15 )</td>
<td>89</td>
</tr>
<tr>
<td>4</td>
<td>( 5a )</td>
<td>( 10 )</td>
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<td>( 11 )</td>
<td>( 17 )</td>
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<td>( 12 )</td>
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<td>7</td>
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<td>( 13 )</td>
<td>( 19 )</td>
<td>97</td>
</tr>
<tr>
<td>8</td>
<td>( 5a )</td>
<td>( 14 )</td>
<td>( 20 )</td>
<td>95</td>
</tr>
</tbody>
</table>

\(^ a \) (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\(_2\)O (6.25:1 final ratio), rt, 1 h.

\(^ b \) All purified products exhibited satisfactory NMR, IR, and mass spectral data.
proposals is consistent with the observed correlation between the amount of phosphine present and the extent of Cl-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. 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. A variety of primary alkylboranes can be coupled with Cl-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), highlighting the potential utility of this approach for the synthesis of C-linked oligosaccharides and glycopeptides via subsequent stereoselective double bond transformations. Finally, we note that direct acylation of C1-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 Cl-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.


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References and notes

18. Successful glycal deprotonation was confirmed by D2O quenching in separate experiments under identical conditions. The t-BuLi-derived Cl-lithioglycals were also trapped successfully with Bu3SnCl (Scheme 2).
19. In contrast, successful alkylation of a dihydropyran lacking a C3-oxygen substituent has been reported using alkyl iodide 2: Amouroux, R. Heterocycles 1984, 22, 1489–1492.
27. Attempts to access the Cl-iodoglycals directly from the Cl-lithioglycals were unsuccessful.
31. The dppe monophosphine oxide is presumably formed initially during reduction of Pd(II) to the active Pd(0) catalyst (Ref. 32).
32. Grushin, V. V.; Alper, H. Organometallics 1993, 12, 1890–1901.
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) was added and the reaction was stirred for an additional 30 min at rt. In a separate flame-dried 10 mL conical flask, 1-iodoglycal 5a (100 mg, 135 μmol, 1.0 equiv) was dissolved in THF (1 mL) and water (395 μL). Pd(dppe)Cl2 (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 Et2O (50 mL), washed with 1 N aq NaOH, H2O, and brine, then dried (MgSO4) and filtered. Evaporation of solvent and silica flash chromatography (5:1 hexanes/CH2Cl2) yielded Cl-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 Cl-substituents under our conditions (cf. Ref. 26a).