

# Palladium-Catalyzed Cross-Coupling Reactions between Dihydropyranylium Reagents and Aryl Halides. Synthesis of C-Aryl Glycols

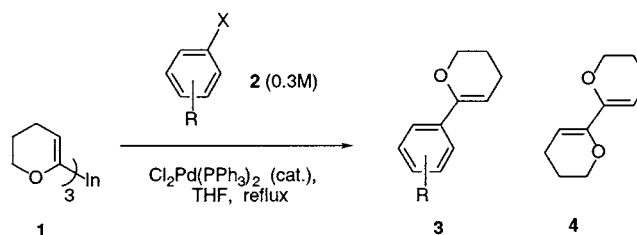
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## ABSTRACT



Palladium(0)-catalyzed cross-coupling reactions between tris(dihydropyranylium)indium **1** and aryl halides **2** have been investigated. Aryl iodides and electron-deficient aryl bromides couple efficiently with the in situ-generated indium reagents in the presence of 1–5 mol % Cl<sub>2</sub>Pd(PPh<sub>3</sub>)<sub>2</sub> to produce substituted dihydropyrans **3** with minimal (<10%) dimer (**4**) formation. Organoindium reagents derived from D-glucal also undergo cross couplings with aryl iodides to produce C-aryl glycols.

Transition metal-catalyzed cross-coupling reactions of organometallic reagents with organic electrophiles represent one of the most powerful methods for the construction of carbon–carbon bonds.<sup>1</sup> Linkages between unsaturated carbon centers can efficiently be formed by palladium- or nickel-catalyzed cross-coupling reactions between aryl and alkenyl (pseudo)halides and organostannanes (Stille reaction),<sup>2</sup> organoboranes (Suzuki coupling),<sup>3</sup> and organozinc reagents (Negishi coupling).<sup>4</sup>

The development of environmentally friendly and atom-economical reactions for forming carbon–carbon bonds is

currently of great interest.<sup>5</sup> Sarandeses<sup>6</sup> has recently shown that triorganoindium reagents can efficiently transfer all three ligands in palladium- and nickel-catalyzed cross-coupling reactions. There is also evidence<sup>7</sup> that organoindiums undergo similar cross couplings in aqueous media. This method has the potential to provide a practical alternative to the problems

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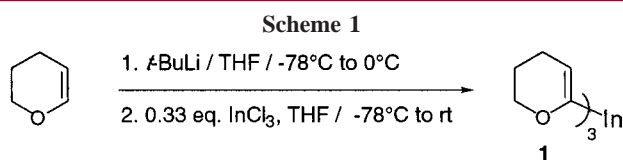
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of toxicity (tin) and handling (boron, zinc) associated with other organometallic reagents.<sup>8</sup> In this study, we report that easily prepared tris-(dihydropyranyl)indium reagents cross-couple with a variety of aryl halides in high yield under palladium catalysis.<sup>9</sup> The extension of this method to the preparation of C-aryl glycols is also detailed.

Metalation of dihydropyran was accomplished in THF by treatment with *t*-BuLi according to the procedure of Boeckman.<sup>10</sup> Addition of a 1.5 M lithiodihydropyran solution to indium trichloride (33 mol %) in THF produced a cloudy white suspension of tris(dihydropyranyl)indium **1** that could be stored under argon with protection from light for several days without appreciable loss of reactivity (Scheme 1).



We undertook our investigation of the palladium(0)-catalyzed cross-coupling reaction by adding one-third of an equivalent of **1** to a boiling solution of iodobenzene and Pd(PPh<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub> (2 mol %). Within 1 h, consumption of starting material was complete as evidenced by TLC and GC-MS analysis. Dihydropyran **3m** was obtained in 94% yield after purification. As has been noted previously, the instability of the product to air and silica gel necessitated the use of rapid flash chromatography with short elution times.<sup>11</sup>

Reactions of **1** with bromoarenes containing electron-withdrawing groups gave moderate to high yields of the desired substituted dihydropyrans (Table 1, entries 1–7) in the presence of catalytic amounts of palladium salt. Interestingly, both 1-bromo-2-nitrobenzene **2f** and 2-bromobenzaldehyde **2g** required more catalyst (5 and 3 mol %, respectively) and **1** (1 equiv) to reach completion, and in each case **4** (presumably arising from palladium(II)-mediated dimerization of the indium reagent) was obtained in competitive amounts.

Consistent with previous observations on the cross-coupling of glycol tin reagents with aryl halides,<sup>12</sup> bromoarenes containing electron-donating groups (Table 1, entries 9–12) gave poor yields of coupling product. These reactions also gave rise to significant amounts (5–14%) of **4**. Use of Pd(PPh<sub>3</sub>)<sub>4</sub> as a catalyst did not reduce the amount of dimer formed and gave lower yields of the desired product. Cross-coupling reactions of the corresponding aryl iodides with **1** were therefore tested. In all cases (Table 1, entries 13–17),

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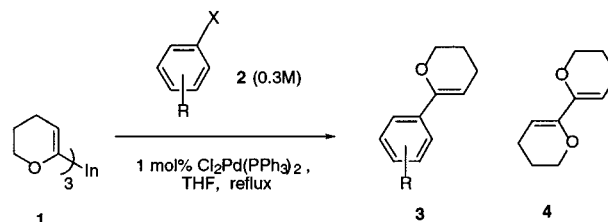
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**Table 1.** Coupling Reaction of Trisdihydropyranylindium **1** with Aryl Halides



entry	<b>2</b>	R	X	equiv <b>1</b>	% yield of <b>3</b> ( <b>4</b> ) <sup>a</sup>
1	<b>2a</b>	4-COCH <sub>3</sub>	Br	0.33	72
2	<b>2b</b>	4-CO <sub>2</sub> Et	Br	0.33	87
3	<b>2c</b>	3-CO <sub>2</sub> Et	Br	1	85 (15) <sup>b</sup>
4	<b>2d</b>	2-CO <sub>2</sub> Et	Br	1	76
5	<b>2e</b>	4-Cl	Br	0.33	95
6	<b>2f</b>	2-NO <sub>2</sub>	Br	1	69 (17) <sup>c</sup>
7	<b>2g</b>	2-CHO	Br	1	44 (46) <sup>b</sup>
8	<b>2h</b>	1-naphthyl	Br	1	87 (6) <sup>b</sup>
9	<b>2i</b>	4-CH <sub>3</sub>	Br	0.5	27 (5) <sup>c,d</sup>
10	<b>2j</b>	4-OCH <sub>3</sub>	Br	1	36 (6)
11	<b>2k</b>	2-OCH <sub>3</sub>	Br	1	23 (9)
12	<b>2l</b>	4-OAc	Br	0.66	34 (14)
13	<b>2m</b>	H	I	0.33	100 <sup>e</sup>
14	<b>2n</b>	4-CH <sub>3</sub>	I	1	89 (7) <sup>c</sup>
15	<b>2o</b>	2-CH <sub>3</sub>	I	1	96 (4) <sup>b</sup>
16	<b>2p</b>	4-OCH <sub>3</sub>	I	1	88 <sup>b</sup>
17	<b>2q</b>	2-OCH <sub>3</sub>	I	1	89 (5) <sup>b</sup>

<sup>a</sup> Because of product volatility/instability, reaction yields were determined by GC-MS analysis. <sup>b</sup> PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> (3 mol %) was used in the reaction. <sup>c</sup> PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> (5 mol %) was used. <sup>d</sup> Yield determined by integration of aromatic proton signals in <sup>1</sup>H NMR. <sup>e</sup> PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> (2 mol %) was used.

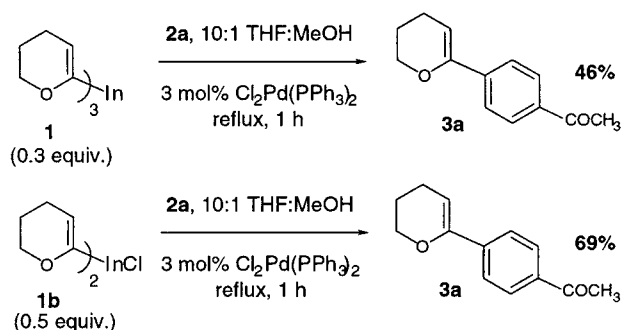
high yields of the desired substituted dihydropyrans were obtained. However, the use of excess indium reagent (1 equiv) and 3–5 mol % catalyst were required in order to obtain optimal yields in these cases. Extended reaction times with either less **1** or lower catalyst loading led to decreased overall yields.

To investigate the hydrolytic stability of **1**, we attempted a reaction with **2a** in a 10:1 THF/MeOH mixture at reflux for 1 h, employing 3 mol % Pd(PPh<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub> as a catalyst. Compound **3a** was again obtained but in lower yield (46%). Interestingly, subjecting bis(dihydropyranyl)indium chloride **1b**<sup>13</sup> to the same conditions (**2a**, 10:1 THF/MeOH, 3 mol % Pd(PPh<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub>) led to essentially no diminution in the yield of **3a** obtained (69%, Scheme 2). These results, in line with the observations of Oshima,<sup>7</sup> suggest that protic solvents hydrolyze one ligand from triorganoindium reagents, leaving the remaining groups to participate in the cross-coupling reaction. Attempted cross coupling in 10:1 THF/H<sub>2</sub>O gave none of the desired product, and indeed it was found in general that anhydrous conditions were required to obtain high yields of cross-coupled product and minimize dimer formation.

Chan et al. have demonstrated that the active intermediate in indium-mediated aqueous Barbier reactions is an indium-

(13) Formed by addition of lithiodihydropyran to a THF solution of 0.5 equiv of indium trichloride.

Scheme 2



(I) species;<sup>14</sup> furthermore, organoindium (I) reagents have been successfully employed in carbon–carbon bond-forming reactions in organic solvents.<sup>15</sup> However, attempted transmetalation of lithiodihydropyran with 1 equiv of InBr led to the production of indium metal as a grayish-silver precipitate, and minimal amounts (~10%) of cross coupling were observed in the presence of 1 mol % Pd(PPh<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub> and 4-bromoacetophenone after 1 h at reflux.

We next turned our attention to the possibility of using this method to form C-aryl glycols, which have been employed in the preparation of a variety of biologically important C-aryl glycosides.<sup>16</sup> 1-Lithio-3,4,6-tri-*O*-(triisopropylsilyl)-D-glucal, prepared by treatment of per-TIPS glucal **5**<sup>17</sup> with 1.5 equiv of *t*-BuLi at –78 °C followed by stirring at 0 °C for 1.5 h, was added to a solution of 0.5 equiv of InCl<sub>3</sub> at –78 °C. Subsequent cross coupling in the presence of 3 mol % Pd(PPh<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub> and 2-iodotoluene **2o** (1.5 equiv, 24 h, reflux) gave 60% yield of the C-aryl glycol **6o**, along with ~5% dimer **7** and 35% recovered starting material (Table 2). Reactions with both electron-deficient (entries 1–2) and electron-rich (entries 3–6) aryl iodides proceed in good yields, and negligible amounts of **7** were detected in the reaction mixtures (assayed by <sup>1</sup>HNMR of the crude material) except for entry 6. Starting material **5** was also cleanly recovered from these reactions and reused in subsequent couplings. The use of aryl bromides instead of aryl iodides uniformly resulted in low yields.<sup>18</sup>

Incomplete lithiation of **5** may account for the moderate yields of C-aryl glycols obtained. To address this issue, the same reactions were performed with longer deprotonation times (1.5–3 h) and using a greater excess of *t*-BuLi (from

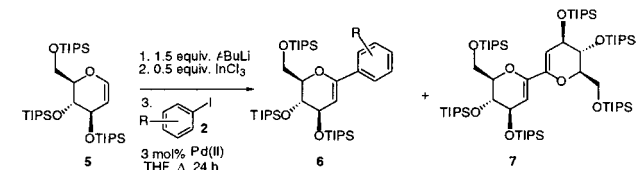
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(18) We have also employed bulky phosphines as ligands for palladium (Pd<sub>2</sub>dba<sub>3</sub>/P(*t*-Bu)<sub>3</sub> and Pd<sub>2</sub>dba<sub>3</sub>/P(*o*-tolyl)<sub>3</sub>) in an attempt to improve yields in this process; although these reactions in some cases proceed to completion in shorter times (4 vs 24 h), the overall yields did not change significantly from those reported in Table 2.

Table 2. Cross-Coupling Reactions of Per-TIPS-glucal **5** with Aryl Iodides

entry	<b>2</b> <sup>a</sup>	R	% yield <sup>b</sup> of <b>6</b> ( <b>7</b> )
1	<b>2a</b>	4-COCH <sub>3</sub>	55% (<5%)
2	<b>2d</b>	2-CO <sub>2</sub> CH <sub>3</sub>	54% (<5%)
3	<b>2h</b>	1-naphthyl	59% (9%)
4	<b>2o</b>	2-CH <sub>3</sub>	60% (5%)
5	<b>2q</b>	2-OCH <sub>3</sub>	60% (<5%)
6	<b>2p</b>	4-OCH <sub>3</sub>	40% (19%)

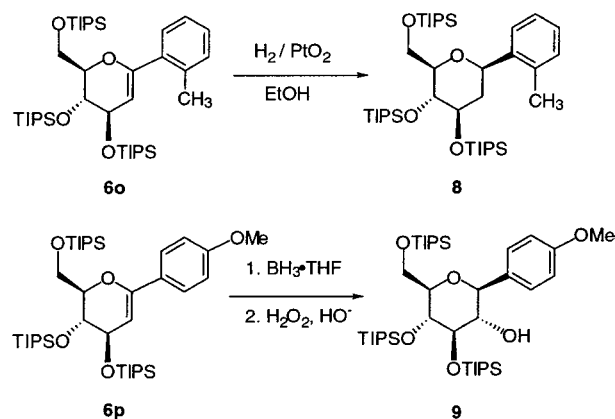
<sup>a</sup> Used 1.5 equiv of **2**. <sup>b</sup> Yields are of purified material.

2 to 6 equivalents), along with up to 1 equiv of InCl<sub>3</sub>. In all cases, little or no product formation was observed, likely indicating that the excess base consumes InCl<sub>3</sub> before transmetalation of lithioglucal can occur.

Since 0.5 equiv of InCl<sub>3</sub> and 1.5 equiv of *t*-BuLi are employed in the optimized procedure, it is possible that mono- and/or diglucal indium species are formed during the transmetalation (i.e., (glucal)In(*t*-Bu)<sub>2</sub> or (glucal)<sub>2</sub>In(*t*-Bu)) and that these intermediates preferentially transfer their carbohydrate ligands in the palladium-mediated cross-coupling reaction.

The reactions above were also tested in the presence of protic solvents. Addition of methanol (10 equiv) prior to addition of the aryl iodide **2o** and Pd(PPh<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub> lowered the yield of C-aryl glycol **6o** obtained (32%). One possible explanation is that preferential hydrolysis of one of the glucal ligands from an intermediate such as (glucal)<sub>2</sub>In(*t*-Bu) leads to an organometallic species that can transfer only one carbohydrate moiety, giving the observed yield of product. Addition of water (5–10 equiv) instead of methanol resulted in formation of an insoluble white precipitate that failed to

Scheme 3



redissolve even at reflux; no *C*-aryl glycols were formed, and only starting material was recovered from the reaction mixture.

The *C*-aryl glycols obtained in this study can be easily transformed into *C*-aryl glycosides by established procedures (Scheme 3). Catalytic hydrogenation of compound **6o** in the presence of PtO<sub>2</sub> furnishes the corresponding 2-deoxy- $\beta$ -*C*-aryl glycoside **8** in 90% yield; hydroboration/oxidation of **6p** employing the protocol of Friesen<sup>19</sup> produces glycoside **9** in 40% yield.

In summary, palladium-mediated cross-coupling reactions of glycalindium (III) compounds offer a practical and environmentally friendly alternative for obtaining *C*-aryl glycols. This one-pot method avoids the use of toxic tin

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reagents typically employed in *C*-aryl glycol synthesis and can be performed in the presence of protic solvents.

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**Supporting Information Available:** Complete experimental details for all compounds prepared in Tables 1 and 2, including spectroscopic data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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