Tin- and Indium-Mediated Allylation in Aqueous Media: Application to Unprotected Carbohydrates

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The convenient and efficient indium- and tin-mediated allylation method for extending the carbon chain of unprotected carbohydrates is illustrated by preparation of 4-6 and 9-10. Various 2-deoxyaldoses can be synthesized by the allylation of aldoses. Indium-mediated reactions between ethyl 2-(bromomethyl)acrylate and aldoses provide access to 2-keto-3-deoxyulosonic acids. These reactions are diastereoselective; the major product contains a threo relationship between the newly generated hydroxyl group and the C-2 hydroxyl group of the starting carbohydrate. Results obtained from reactions involving authentic organotin and organoindium reagents and from the corresponding heterogeneous reactions are similar.

Carbohydrate synthesis lacks a repertoire of efficient and versatile C-C bond forming reactions that can be carried out on unprotected carbohydrates in protic media. This paper reports the addition of allyl anion equivalents to the carbonyl group of unprotected carbohydrates mediated by metals such as indium, tin, and zinc (eq 1). The double bond of the product homoallylic alcohols can be transformed to carbonyl or other functional groups. In preliminary experiments, the allylation showed high diastereoselectivity.\(^{1}\) This methodology might be exploited in the preparation of a range of sugars, including heptoses, octoses, and other higher sugars.

The carbohydrate allylation methodology is an extension of procedures originally developed and applied to non-sugar aldehydes and ketones by Luche,\(^{5}\) Kokami,\(^{6}\) Benezra,\(^{7}\) and others.\(^{8}\) The method was extended to unprotected carbohydrates by Schmid and Whitesides.\(^{1}\) The work of Li and Chan\(^{9,10}\) established the utility of indium in aqueous media. Recently, Mosset and co-workers reported an indium-mediated allylation of aldilmines.\(^{11}\)

The characteristics of organometallic reactions that are useful in the chemistry of unprotected carbohydrates are that (a) they can be carried out in protic media, (b) the experimental protocol is straightforward, (c) they are both regio- and stereoselective, and (d) they are applicable to large-scale (multigram) preparations. In this paper, we describe the exploration and use of In and Sn in the elaboration of carbohydrates, compare the efficiencies and reactivities of these metals, and examine the hypothesis that organometallic reagents are intermediates in these transformations. The results reported here are the product of exploratory work, and the reactions were not optimized; therefore, inferences regarding the limitations of these protocols might be inappropriate.

Results and Discussion

**Stereochemistry and Regioselectivity.** The configuration at the new stereocenter of the product homoallylic alcohols was unambiguously assigned by transforming adducts 1-3, derived from D-arabinose, D-ribose, and D-glucose, respectively, to the corresponding peracetylated heptose and octose derivatives 4-6 (Scheme I). Analysis of the \(^1\)H NMR spectra of pyranoses 4-6 allowed assignment of the relative stereochemistry at the newly generated stereocenter. In each case, we observed a threo relationship between the newly generated hydroxyl group and the C-2 hydroxyl group of the starting carbohydrate.

The same strategy was used to assign the stereochemistry of the newly generated stereocenter in reactions involving a more complex allylic halide. Indium-mediated reactions of ethyl 2-(bromomethyl)acrylate with D-arabinose and D-ribose, followed by ozonolysis, yielded 9 and 10 (Scheme II). Li and Chan reported an indium-mediated reaction of methyl 2-(bromomethyl)acrylate and a nonsugar aldehyde in an aqueous medium and that this reaction could be used to synthesize 2-ketoalolutonate derivatives.\(^{12}\) Once again, the \(^1\)H NMR spectra of these pyranoses indicated a threo relationship between the newly generated stereocenter and the C-2 hydroxyl group of the starting carbohydrate. This sequence can be used to synthesize 2-keto-3-deoxycolutonate derivatives.\(^{13}\)

Limited experience suggests that only the most reactive carbonyl group reacts with allyl halides when multiple carbonyl groups are present; products from reduction or multiple addition are not observed. For example, D-glucurono-6,3-lactone (11) reacted with allyl bromide, under the standard conditions, to give 12,\(^{13}\) derived from selective

\[ \text{OH} \quad \text{CH}_2\text{CH}_2\text{CHO} \quad \xrightarrow{X} \quad \text{OH} \quad \text{CH}_2\text{CH}_2\text{CH} \text{R}_1 \quad \text{CH}_2\text{CH}_2\text{CHO} \quad \text{CH}_2\text{CH}_2\text{CH} \text{R}_2 \] \[ \text{(1)} \]

\[ \text{OH} \quad \text{CH}_2\text{CH}_2\text{CHO} \quad \xrightarrow{\text{Sn, or Zn}} \quad \text{OH} \quad \text{CH}_2\text{CH}_2\text{CH} \text{R}_1 \quad \text{OH} \quad \text{CH}_2\text{CH}_2\text{CH} \text{R}_2 \] \[ \text{(2)} \]
allylation of the aldehyde group (Scheme III). No products resulting from allylation of the lactone were recovered.

**Tin-Mediated Reactions.** We previously described the use of tin metal in the addition of allyl anion equivalents to aldoses. We have since explored a number of procedures for the reaction: the most convenient procedure involves heating a suspension of allylic bromide, tin powder, and aldose in a polar organic solvent containing enough water to dissolve the sugar. The yield and diastereoselectivity of the reaction are largely independent of solvent, with the exception of the dioxane/water system where the diastereoselectivity was diminished (Table I). Rates of reaction are influenced by the solvent system: the rate of reaction in THF/H₂O is only about one-fifth that in EtOH/H₂O. For a given solvent system, the rate of the reaction is qualitatively proportional to the mole
fraction of organic solvent in the mixture; however, there must be sufficient water in the reaction mixture to dissolve the sugar.

When stirred at room temperature, tin-mediated reactions proceed too slowly to be useful, but ultrasonication significantly increases the rate. Although both heating and ultrasonication accelerate the allylation reaction, heating is more convenient and gives greater acceleration. The allylation of D-arabinose requires 2 h under reflux and ultrasonication significantly increases the rate. Although both heating and tin-mediated reactions are similar.

The rates of reaction increase with increasing surface area of tin, other conditions being equal. Agitation of the tin with powdered glass or glass beads (≤100 mesh) also increases the rate of reaction. The reaction under reflux with powdered glass is completed in less than 1 h, and no loss of diastereoselectivity is observed, although the yield is slightly diminished. No special pretreatment of the metal is required, although finely powdered metal reacts more rapidly than coarsely granulated metal.

**Indium-Mediated Reactions.** Indium metal has been used in the allylation of carbonyl compounds and in the Reformatsky reaction. The use of indium in carbohydrate chemistry has been sparse. Indium is more reactive toward allylic halides than tin, while still being incapable of reducing the aldehyde function. Reactions using indium, unlike those involving tin, proceed smoothly at room temperature with vigorous stirring. The rate of a reaction mediated by indium at room temperature is faster than that mediated by tin using ultrasonication and is comparable to that of a tin-mediated reaction carried out at reflux. The stereoselectivity and yield of indium- and tin-mediated reactions are similar.

**Zinc-Mediated Reactions.** A mixture of zinc powder and allyl bromide in ethanol/water (10/1) does not yield an allylation product after ultrasonication. Following reaction conditions described by Luche and Reissig, we used a solution of THF (or EtOH) and saturated aqueous NH₄Cl, but very little sugar dissolves in these solutions, and no reaction was observed.

**Reactions with Organometallic Reagents.** The direct addition of organometallic reagents, generated separately, to a solution of a sugar in a protic solvent gives homoallylic halide product.
The reactions we report proceeded with allyl chloride, bromide, and iodide; the bromide gave the best combination of reactivity and stability toward solvolysis.

Crotyl bromide participated in a tin-mediated reaction with D-arabinose and generated 14 as the major product, an adduct that is formally formed by an Sn2' process.25 Two new stereocenters are generated in this process, and four stereoisomers are possible. When the crude product is purified by chromatography, two isomers are isolated in 5:1 ratio; the major product contained a 1:1 mixture of two epimers at C-6 of the product. Prenyl bromide reacted with an aldose in the presence of indium in an Sn2' process as observed in 15, albeit in low yield, perhaps due to steric hindrance.

\[ \text{1-Bromo-2-butylene reacted smoothly with aldoses and yielded allene-containing products 16 and 18; alkene-containing products were not observed. Propargyl bromide has been reported to react with non-sugar aldehydes, in the presence of tin metal,32 to yield both allene- and alkene-containing products but failed to react with aldoses under our reaction conditions using either tin or indium.} \]

**Sugar.** In general, pentoses react more readily than hexoses, and aldoses react more readily than ketoses. D-Fructose reacted with allyl bromide in a tin-mediated reaction to generate 17. D-Glucosamine did not react under the usual reaction conditions or at higher temperatures. Various N-protected derivatives of d-glucosamine and d-mannosamine did not participate in either tin- or indium-mediated reactions. Aldose oximes and gluconic acids were also unreactive. The allyl addition products can be converted into higher aldoses via ozonolysis of their double bonds (Scheme II). They can also be converted to ketoses using a palladium-catalyzed oxidation34 (Scheme VI). The terminal double bond can conceivably be used in other transformations.

**Conclusions**

The unoptimized tin- and indium-mediated addition of allyl anion equivalents to unprotected carbohydrates is
versatile, convenient, and efficient. This methodology provides access to various 2-deoxyaldoses. The use of authentic organotin and organoindium reagents gave outcomes essentially identical to those obtained under heterogeneous conditions, implying common reactive species. Indium metal is superior to tin in most applications due to its increased reactivity. Indium-mediated reactions produce fewer byproducts and are more diastereoselective than the corresponding tin-mediated reactions.

**Experimental Section**

**General Procedure A: Addition of Allyl Groups to Carbohydrates Using Tin Metal.** To a solution of 1 mmol of the carbohydrate in 25 mL of ethanol/water (9/1) were added 2
mmol of tin powder (Alfa, 99.999%, 100 mesh), and 3 mmol of allyl bromide. The suspension was sonicated in a ultrasonic cleaning bath or heated to reflux until the reaction was complete, as judged by consumption of the carbohydrate in 10 mL of dry methanol. The product was prepared from 170 mg (51%, mixture of the two anomers, a/β = 2:3, not separated); \textsuperscript{1}H NMR (400 MHz) \delta 4.40 (ddd, 1H, J = 4.29 and 9.70 Hz, H\textsubscript{7}), 4.35 (dd, 1H, J = 3.60 and 9.70 Hz, H\textsubscript{7}), 4.17 (dd, 1H, J = 3.60 and 9.70 Hz, H\textsubscript{7}), 4.02 (ddd, 1H, J = 1.96 and 2.14 Hz, H\textsubscript{2}), 0.93 (s, 3H, H\textsubscript{3}), 0.81 (s, 3H, H\textsubscript{3}), 0.74 (s, 3H, H\textsubscript{3}).

**Scheme VI**

\[
\begin{align*}
\text{PdCl}_2 & \text{CH}_2 \text{O} \\
\text{THF/H}_2\text{O} & \text{82\%}
\end{align*}
\]

**Methyl 3,4,6,7-Tetra-O-acetyl-2-deoxy-\textbeta-D-glycero-\textbeta-D-gulo-heptopyranoside (4).** To a solution of 230 mg (0.57 mmol) of 1, in 10 mL of dry methanol, 25 mmol of sodium were added. The reaction mixture was stirred at room temperature for 2 h and then quenched by addition of the solid CO\textsubscript{2} until the solution was neutral. The precipitate formed was washed in centrifuge (5 mL) and the filtrate concentrated in Dctcuo. The residue was dissolved in dichloromethane (15 mL) and methanol (3 mL). The solution was cooled to -70°C, and ozone was bubbled through it for 10 min at -70°C. Sodium sulfite (50 mg) was added to the reaction mixture at -70°C, and the mixture was allowed to warm to rt over 1 h and then stirred at rt for 18 h. The mixture was filtered, and the filtrate concentrated in vacuo. The residue was dissolved in 5 mL of dry pyridine and 3 mL of acetic anhydride, and 10 mg of DMAP were added. After stirring for 18 h at rt, the solvents were removed in vacuo. The residue was purified by SiO\textsubscript{2} chromatography (eluent: hexanes/aceton = 3/1).

**Methyl 3,4,6,7-Tetra-O-acetyl-2-deoxy-\textbeta-D-glycero-\textbeta-D-gulo-heptopyranoside (5).** The product was prepared from 80 mg (0.2 mmol) of 2 using the procedure described for 4: yield 12 mg (15%) and 48 mg (a + \textbeta) mixture not further purified; \textsuperscript{13}C NMR (CD\textsubscript{3}OD, 400 MHz) \delta 4.35 (dd, 1H, J = 3.75 and 12.41 Hz, H\textsubscript{7}), 3.95 (dd, 1H, J = 1.90 and 2.49 Hz, 4.00, 14.30 Hz, H\textsubscript{3}), 1.92 (dd, 1H, J = 3.75 and 12.41 Hz, H\textsubscript{7}), 1.89 (s, 3H, H\textsubscript{3}), 1.81 (s, 3H, H\textsubscript{3}), 1.72 (s, 3H, H\textsubscript{3}), 1.69 (s, 3H, H\textsubscript{3}), 1.63 (s, 3H, H\textsubscript{3}), 1.53 (s, 3H, H\textsubscript{3}), 1.49 (s, 3H, H\textsubscript{3}), 1.38 (s, 3H, H\textsubscript{3}), 1.22 (s, 3H, H\textsubscript{3}), 1.12 (s, 3H, H\textsubscript{3}), 1.00 (s, 3H, H\textsubscript{3}), 0.97 (s, 3H, H\textsubscript{3}), 0.89 (s, 3H, H\textsubscript{3}), 0.82 (s, 3H, H\textsubscript{3}), 0.78 (s, 3H, H\textsubscript{3}), 0.73 (s, 3H, H\textsubscript{3}), 0.69 (s, 3H, H\textsubscript{3}), 0.63 (s, 3H, H\textsubscript{3}), 0.58 (s, 3H, H\textsubscript{3}), 0.54 (s, 3H, H\textsubscript{3}), 0.50 (s, 3H, H\textsubscript{3}), 0.47 (s, 3H, H\textsubscript{3}), 0.43 (s, 3H, H\textsubscript{3}), 0.40 (s, 3H, H\textsubscript{3}), 0.36 (s, 3H, H\textsubscript{3}), 0.32 (s, 3H, H\textsubscript{3}), 0.28 (s, 3H, H\textsubscript{3}), 0.24 (s, 3H, H\textsubscript{3}), 0.20 (s, 3H, H\textsubscript{3}), 0.17 (s, 3H, H\textsubscript{3}), 0.13 (s, 3H, H\textsubscript{3}), 0.09 (s, 3H, H\textsubscript{3}), 0.05 (s, 3H, H\textsubscript{3}).

**Methyl 3,4,6,7-Tetra-O-acetyl-2-deoxy-\textbeta-D-glycero-\textbeta-D-gulo-heptopyranoside (6).** The product was prepared from 170
The product was purified by SiO₂ chromatography (eluent: MeOH/CH₂Cl₂ 1/3) to give 193 mg (60% yield) of a white powder. The product was prepared using general procedure A with 120 mg of D-erythrose and 2 mmol of ethyl (2-bromomethyl)acrylate. The product was prepared using the procedures for 9, starting from 200 mg of D-ribose and 2 mmol of ethyl (2-bromomethyl)acrylate.

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6-Methyl-1,2,3,4,5-penta-acyl-6,7,8-trideoxy-1-gulo-
6,7-octadienitol (18). The product was prepared using general procedure A with 150 mg of d-arabinose and 2 mmol of
1,2-bromonicotinic: yield 190 mg (46%), colorless solid; [α] D +3.44° (c 3.5, acetone); 1H NMR (CDCl3, 400 MHz) δ 5.47 (dd, 1H, J = 2.82 and 8.25 Hz, H5), 5.35 (dd, 1H, J = 2.78 and 7.70 Hz, H6), 5.31 (d, 1H, J = 5.28 Hz, H7), 5.07 (m, 1H, H8), 4.81 (m, 2H, -CH2), 4.25 (dd, 1H, J = 3.33 and 12.36 Hz, H9), 4.07 (dd, 1H, J = 5.84 and 12.98 Hz, H10), 3.11, 2.09, 2.08, 2.07 (5s, 15H, 5 × Ac); 13C NMR (CDCl3, 100 MHz) δ 203.95, 170.52, 170.18, 169.87, 68.72, 67.96, 66.84, 65.78, 64.59, 61.90, 61.59, 43.89, 29.92, 20.70, 20.50; HRMS (FAB) calcd for C21H20O12Na 475.1800, found 475.1816.

1-Deoxy-3,5,6,7,8-penta-acyl-1-gulo-2-heptulitol (19). Ozone was bubbled through a solution of 70 mg of 18 in 15 mL of
dichloromethane and 5 mL of MeOH at −78 °C for 10 min.

After addition of dimethyl sulfide (0.5 mL), the reaction mixture
was warmed to room temperature and stirred for 18 h. The
residue was purified by SiO2 chromatography (eluent: hexanes/acetone 1/1). Yield: 2.65 g (90%).

4,5,6,7,8-Hexa-acytelyl-1,3-dideoxy-D-glycero-D-idulo-2-
nonulose (21). To a solution of 10 mg (0.21 mmol) of 3 in 11 mL of THF/water (10/1) was added 45 mg (0.25 mmol) of PDCl2 in
one portion. The suspension was stirred at room temperature
until TLC (hexanes/ethyl acetate = 2:1) showed completion of
the reaction (3 h; RI = 0.2). The reaction mixture was filtered
through a bed of Celite, and the filtrate was concentrated in
vacuo.

The residue was purified by SiO2 chromatography (eluent: hexanes/ethyl acetate 1/1): yield 85 mg (82%); 1H NMR (CDCl3, 400 MHz) δ 5.50 (m, 1H, H5), 5.45 (dd, 1H, J = 2.10 and 8.91 Hz, H6), 5.17 (dd, 1H, J = 1.67 and 8.81 Hz, H7), 5.00 (m, 1H, H8), 4.20 (dd, 1H, J = 2.77 and 12.50 Hz, H9), 4.08 (dd, 1H, J = 5.10 and 12.37 Hz, H10), 2.61 (m, 2H, H11), 2.21, 2.08, 2.07, 2.05, 2.04, 2.02 × 2 (3s, 2H, 7 × Ac); 13C NMR (CDCl3, 100 MHz) δ 203.95, 170.67, 170.13, 170.09, 169.83, 169.79, 71.08, 2 × 68.44, 67.75, 67.09, 61.58, 43.93, 39.22, 20.70, 20.50; HRMS (FAB) calcd for C21H20O12Na 513.1584, found 513.1598.

1-Deoxy-3,5,6,7,8-penta-acyl-1-gulo-2-heptulitol (19). Ozone was bubbled through a solution of 70 mg of 18 in 15 mL of
dichloromethane and 5 mL of MeOH at −78 °C for 10 min.

After addition of dimethyl sulfide (0.5 mL), the reaction mixture
was warmed to room temperature and stirred for 18 h. The
mixture was concentrated in vacuo, the residue was dissolved in
5 mL of dry pyridine and 3 mL of acetic anhydride, and 10 mg
of DMAP was added. After being stirred at ambient temperature
for 18 h, the reaction mixture was concentrated in vacuo, and the
residue was purified by SiO2 chromatography (eluent: hexanes/ethyl acetate 1/1): yield 55 mg (81%); colorless glass; 1H NMR (CDCl3, 400 MHz) δ 5.62 (dd, 1H, J = 3.77 and 4.98 Hz, H5), 5.50 (m, 1H, H6), 5.45 (dd, 1H, J = 2.10 and 8.91 Hz, H7), 5.17 (dd, 1H, J = 1.67 and 8.81 Hz, H8), 5.00 (m, 1H, H9), 4.20 (dd, 1H, J = 2.77 and 12.50 Hz, H10), 4.08 (dd, 1H, J = 5.10 and 12.37 Hz, H11), 2.61 (m, 2H, H12), 2.21, 2.08, 2.07, 2.05, 2.04, 2.02 × 2 (3s, 2H, 7 × Ac); 13C NMR (CDCl3, 100 MHz) δ 201.04, 170.48, 170.13, 169.79, 169.75, 169.54, 169.45, 94.06, 76.64, 72.85, 69.00, 68.64, 65.52, 64.48, 61.73, 21.04, 20.75, 20.68, 20.57, 20.46, 14.37; HRMS (FAB) calcd for C21H20O12Na 513.1584, found 513.1598.

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Supplementary Material Available: Copies of 13C NMR
spectra of 7-10, 12, 14-19, 21, and 22 (14 pages). This material
is contained in libraries on microfiche, immediately follows this
article in the microfilm version of the journal, and can be ordered
from the ACS; see current masthead page for ordering information.