Iridium-catalysed condensation of alcohols and amines as a method for aminosugar synthesis†

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Primary carbohydrate amines at primary and secondary carbons are alkylated by alcohols in the presence of [Cp*IrCl2]2. When primary carbohydrate alcohols are used as the coupling partners and in the presence of Cs2CO3, amine-linked pseudodisaccharides are obtained. Secondary carbohydrate alcohols are unaffected under these conditions, which allows regioselective reactions.

In this communication, we address the use of carbohydrates as cheap, renewable and densely functionalised potential building blocks1 for transition metal-catalysed organic synthesis. In particular, we focus on C–N bond formation in the synthesis of structurally varied aminosugars, either by alkylation of carbohydrate primary amines, or by amination of carbohydrate alcohols. Classical methods for amine bond formation, such as alkylation with halides or pseudohalides,2 oxidation and reductive amination,3 or Mitsunobu4 chemistry with sulfonamides, result in the production of stoichiometric by-products and involve multistep sequences. A catalytic redox-activated condensation reaction between alcohols and amines to give higher order amines and water is an attractive alternative.5,6 This process was described in the early 1980s,5,7 and has recently gained popularity with the development of efficient homogeneous catalysts based on ruthenium, rhodium and iridium.8–14 To date, the substrate scope has been limited to alkylations of C6 amine5b with halides or pseudohalides,5b oxidation and reductive amination,8 or Mitsunobu4 chemistry with sulfonamides,9 resulting in the production of stoichiometric by-products and involve multistep sequences. A catalytic redox-activated condensation reaction between alcohols and amines to give higher order amines and water is an attractive alternative.5,6

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In a somewhat more challenging system, hexopyranosides with a primary amine at C3 and with a secondary alcohol unprotected (viz β-Glc-4, β-Man-5 and α-Man-6) were tested as substrates (Scheme 2). Here again the alkylation reaction with cyclohexanol (2a) proceeded efficiently to give the secondary amine products for all of the different configurations tested. Products due to redox epimerisation16,17 or amination of the unprotected secondary alcohol groups were not detected. Benzyl alcohol (2b) could also be used as an alkylating reagent, affording β-Glc-7b in excellent yield.

![Scheme 1](image1)

**Scheme 1** Alkylation of C6 amine α-Man-1 with cyclohexanol (2a).

![Scheme 2](image2)

**Scheme 2** Alkylation of C3 carbohydrate amines with alcohols.
with either homogeneous or heterogeneous catalysts. The redox-activated amination reaction of carbohydrate alcohols has been carried out in toluene, but this solvent was unsuitable here as the substrate \( \alpha-Man-10 \) was insoluble. Using the alcohol itself as solvent was found to work well. With secondary alcohols \( 2a \) and \( 2c \), the products were the secondary amines, while a primary alcohol \( 2d \) gave the tertiary amine as the only product as a result of two consecutive alkylations (Scheme 3).

The use of carbohydrate alcohols as latent electrophiles is a challenging goal. The alcohol carbons of carbohydrates are electron-poor, which makes them resistant to oxidation due to amination of the primary hydroxyl.\(^6\) This centres vicinal to the presumed intermediate carbonyl.\(^6\) This transition-metal-catalysed reaction between alcohols and amines. Based on these results, it is possible to draw some provisional conclusions about the behaviour of carbohydrates in the transition-metal-catalysed reaction between alcohols and amines. All products were isolated as single diastereomers. Epimerisation of secondary carbohydrate alcohols was not observed under these conditions, and neither was epimerisation detected at the centres vicinal to the presumed intermediate carbonyl.\(^5\) This latter observation contrasts with an earlier result on a protected carbohydrate amines can be alkylated in the presence of unprotected carbohydrate hydroxyl groups, using non-carbohydrate alcohols as alkylating agents. The primary alcohol of a carbohydrate is more readily functionalised than the secondary alcohols, which allows regioselective functionalisation. The amination of carbohydrate alcohols requires addition of a NaHCO\(_3\) than with Cs\(_2\)CO\(_3\).\(^5\) In a control experiment without added alcohol, the carbohydrate amine \( \alpha\text{-Glc-12} \) failed to give a pseudodisaccharide product, indicating that the C\(_2\) symmetric diglucose \( \text{Glc-Glc-14} \) does arise from a redox condensation involving the carbohydrate alcohol \( \alpha\text{-Glc-13} \). A dimannose \( \text{Man,Man-16} \) was similarly formed by reaction of amine \( \alpha\text{-Man-1} \) with C\(_6\) alcohol \( \alpha\text{-Man-15} \), and an unsymmetrical \( \text{Glc,Man-17} \) pseudodisaccharide was formed either by condensation of amine \( \alpha\text{-Man-1} \) with alcohol \( \alpha\text{-Glc-13} \), or by reaction of amine \( \alpha\text{-Glc-12} \) with alcohol \( \alpha\text{-Man-15} \) (Scheme 4).

In these three reactions, the yields were lower, the remainder being unreacted starting materials and unidentified non-polar by-products.

Scheme 3

\[ \text{Alkylation of amine } \alpha\text{-Man-10} \text{ with alcohols } 2a, 2c-d. \]

We went on to investigate the alkylation of an essentially unprotected aminosugar \( \alpha\text{-Man-10} \). Earlier reactions had been carried out in toluene, but this solvent was unsuitable here as the substrate \( \alpha\text{-Man-10} \) was insoluble. Using the alcohol itself as solvent was found to work well. With secondary alcohols \( 2a \) and \( 2c \), the products were the secondary amines, while a primary alcohol \( 2d \) gave the tertiary amine as the only product as a result of two consecutive alkylations (Scheme 3).

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The reactivity of primary carbohydrate alcohols and the unreactive nature of secondary carbohydrate alcohols suggest the possibility of a regioselective amination reaction. Hence the diol \( \beta\text{-Glc-18} \) with free OH\(_4\) and OH\(_6\) was treated with amine \( \alpha\text{-Glc-12} \) under the coupling reaction conditions with Cs\(_2\)CO\(_3\), and a single pseudodisaccharide product (\( \text{Glc-Glc-19} \)) due to amination of the primary hydroxyl was seen (Scheme 5).

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Scheme 4

\[ \text{Synthesis of pseudodisaccharides by amination of primary carbohydrate alcohols.} \]
base, whereas for non-carbohydrate alcohols a base is not required. Cs₂CO₃ gave good results for the functionalisation of primary carbohydrate alcohols.

We envisage that the methods for the synthesis of structural variants of N-substituted aminosugars described in this communication could find numerous applications in the optimisation of structures for a given purpose, e.g. as ligands for biomolecules. Synthetic N-substituted carbohydrates or alditols as substrates. Reaction of unprotected carbohydrates or alditols as substrates. Oxidation of the anomeric hydroxyl of hemiacetals or of primary hydroxyl groups is most unusual. It has been suggested that they could act as ligands for RNA. "

Notes and references


