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COMMUNICATION

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

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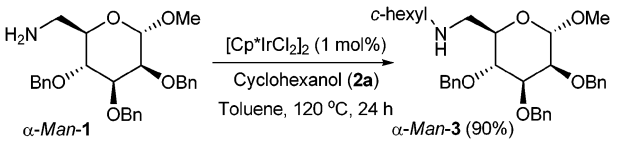
Primary carbohydrate amines at primary and secondary carbons are alkylated by alcohols in the presence of $[Cp^*IrCl_2]_2$. When primary carbohydrate alcohols are used as the coupling partners and in the presence of Cs_2CO_3, amine-linked pseudodisaccharides are obtained. Secondary carbohydrate alcohols are unaffected under these conditions, which allows regioselective reactions.

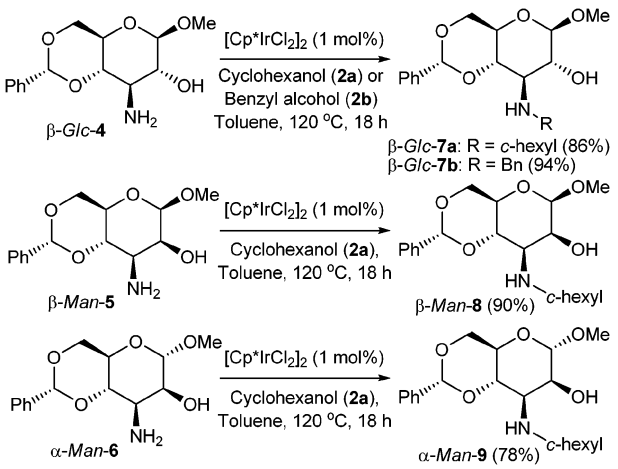
In this communication, we address the use of carbohydrates as cheap, renewable and densely functionalised potential building blocks[1] for transition metal-catalysed organic synthesis. In particular, we focus on C–N bond formation in the synthesis of structurally varied aminosugars, either by alkylation 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 Mitsunobu[4] 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 rather simple molecules. The reactivity of carbohydrate alcohols in the catalytic amination reaction does not appear to be known, while the catalytic alkylation of carbohydrate amines with simple alcohols (as solvents) over heterogeneous catalysts has been reported,[15] but not studied in detail. Focussing on the $[Cp^*IrCl_2]_2$ complex‡ as introduced by Fujita *et al.*,[8] we have examined the scope of the reaction with respect to functionalisation of carbohydrate amines with alcohols; and also the functionalisation of carbohydrate alcohols with amines, including regioselectivity aspects.

First, we considered the reactivity of carbohydrate amines towards non-carbohydrate alcohols. A primary C6 amine with the hydroxyl groups protected (α-*Man*-**1**) was used as a test system with cyclohexanol **2a** (5 equiv.) as the alkylating reagent (Scheme 1). We found that with a catalyst loading of 1 mol% of $[Cp^*IrCl_2]_2$, at 120 °C in toluene, the secondary amine α-*Man*-**3** was formed in excellent yield (see ESI† for optimisation of the reaction conditions). The addition of $NaHCO_3$ (25 mol%) did not affect the efficacy of this reaction, which contrasts with earlier results on different substrates (anilines rather than carbohydrate amines).[8b]



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

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 epimerisation[16,17] 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 2 Alkylation of C3 carbohydrate amines with alcohols.

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† Electronic supplementary information (ESI) available: Optimisation of reaction conditions, experimental details and spectra of new compounds. See DOI: 10.1039/c1cc12800k

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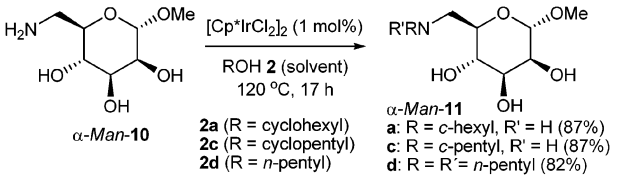


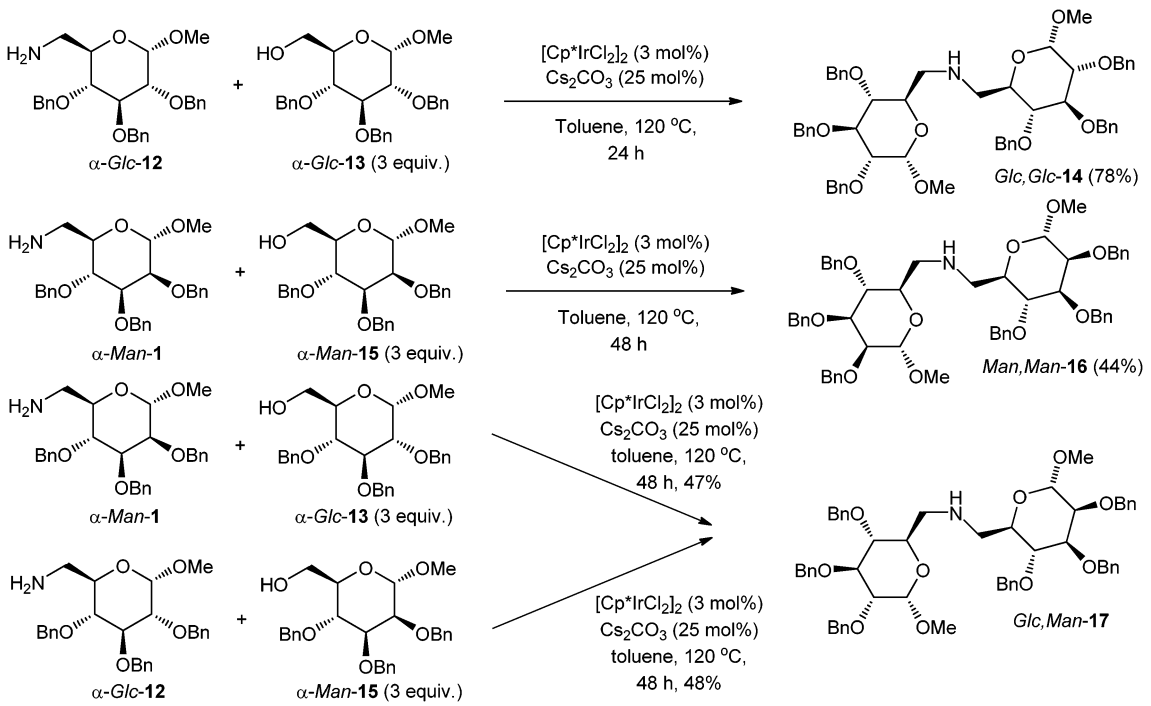
Scheme 3 Alkylation of amine α-*Man*-**10** with alcohols **2a**, **2c–d**.

We went on to investigate the alkylation of an essentially unprotected aminosugar α-*Man*-**10**. Earlier reactions had been carried out in toluene, but this solvent was unsuitable here as the substrate α-*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 by a transition-metal-catalysed hydrogen-transfer mechanism. To the best of our knowledge, there are no reports on the redox-activated amination reaction of carbohydrate alcohols with either homogeneous or heterogeneous catalysts.‡,§ Carbohydrate alcohol α-*Glc*-**13** was treated with carbohydrate amine α-*Glc*-**12** under the reaction conditions used in Scheme 2, but the coupling product was not formed. In this case, the addition of an inorganic base resulted in a significant improvement. With $NaHCO_3$ (25 mol%) at 160 °C, the reaction gave a secondary amine product (*Glc,Glc*-**14**), a pseudodisaccharide, in 66% yield. With Cs_2CO_3, we saw a further improvement, and the secondary amine was formed more quickly at a lower temperature (120 °C) and in higher yield (Scheme 4). This result contrasts again with the observations of Fujita *et al.* in the coupling of anilines with benzylic alcohols, where better results were obtained with $NaHCO_3$ than with Cs_2CO_3.[8b] In a control experiment without added alcohol, the carbohydrate amine α-*Glc*-**12** failed to give a pseudodisaccharide product, indicating that the C_2 symmetric diglucose *Glc,Glc*-**14** does arise from a redox condensation involving the carbohydrate alcohol α-*Glc*-**13**. A dimannose (*Man,Man*-**16**) was similarly formed by reaction of amine α-*Man*-**1** with C6 alcohol α-*Man*-**15**, and an unsymmetrical *Glc,Man*-**17** pseudodisaccharide was formed either by condensation of amine α-*Man*-**1** with alcohol α-*Glc*-**13**, or by reaction of amine α-*Glc*-**12** with alcohol α-*Man*-**15** (Scheme 4). In these three reactions, the yields were lower, the remainder being unreacted starting materials and unidentified non-polar by-products.

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 β-*Glc*-**18** with free OH4 and OH6 was treated with amine α-*Glc*-**12** under the coupling reaction conditions with Cs_2CO_3, and a single pseudodisaccharide product (*Glc,Glc*-**19**) due to amination of the primary hydroxyl was seen (Scheme 5).

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.[6] This latter observation contrasts with an earlier result on a protected glycerol.[9d] 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



Scheme 4 Synthesis of pseudodisaccharides by amination of primary carbohydrate alcohols.

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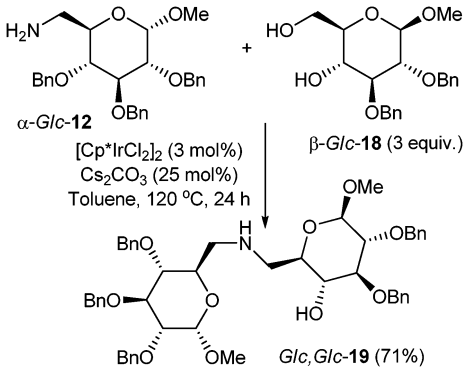

Scheme 5 Regioselective amination of a primary carbohydrate alcohol.

base, whereas for non-carbohydrate alcohols a base is not required. Cs_2CO_3 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 carbohydrate amines have been shown to inhibit glycosidases;[18] and it has been suggested that they could act as ligands for RNA.[19] Modification of the structure of natural aminoglycosides could lead to new antibiotics.[20]

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Notes and references

‡ We found that other organometallic complexes that have been reported for the amine–alcohol redox condensation failed to give good results with carbohydrate alcohols (amongst others, Ru(*p*-cymene)-dppf, K_2CO_3[9d] and $Ru_3(CO)_{12}$, P(*o*-tol)$_3$[10b]), giving either no reaction at all, or traces (< 5%) of the aminated product. For the reaction between carbohydrate amines and non-carbohydrate alcohols, some reactivity was seen using Ru(*p*-cymene)dppf, K_2CO_3, toluene, 4 Å sieves, 120 °C, 36 h: amine α-*Glc*-**12** and *n*-butanol gave the corresponding tertiary amine (65%), but this system was not investigated in detail.
§ Oxidation of the anomeric hydroxyl of hemiacetals or of primary alcohols by hydrogen-transfer to form lactones has been demonstrated using ruthenium[21] and rhodium[22] catalysts with partially protected or unprotected carbohydrates or alditols as substrates. Reaction of secondary hydroxyl groups is most unusual.[17,21d]

1 F. W. Lichtenthaler and S. Mondel, *Pure Appl. Chem.*, 1997, **69**, 1853.
2 For example, see: (*a*) T. M. Tagamose and M. Bols, *Chem.–Eur. J.*, 1997, **3**, 453; (*b*) M. J. McDonough, R. V. Stick, D. M. G. Tilbrook and A. G. Watts, *Aust. J. Chem.*, 2004, **57**, 233.
3 (*a*) J. Neumann, S. Weingarten and J. Thiem, *Eur. J. Org. Chem.*, 2007, 1130; (*b*) D. J. Walton and J. D. McPherson, *Carbohydr. Res.*, 1987, **167**, 123; (*c*) S. Horii, H. Fukase, T. Matsuo, Y. Kameda, N. Asano and K. Matsui, *J. Med. Chem.*, 1986, **29**, 1038.
4 (*a*) A. Zamojski, W. A. Szarek and J. K. N. Jones, *Carbohydr. Res.*, 1972, **23**, 460; (*b*) J. J. Turner, D. V. Filippov, M. Overhand, G. A. van der Marel and J. H. van Boom, *Tetrahedron Lett.*, 2001, **42**, 5763; (*c*) T. Akhtar and I. Cumpstey, *Tetrahedron Lett.*, 2007, **48**, 8673.
5 For reviews, see: (*a*) G. Guillena, D. J. Ramón and M. Yus, *Angew. Chem., Int. Ed.*, 2007, **46**, 2358; (*b*) T. D. Nixon, M. K. Whittlesey and J. M. J. Williams, *Dalton Trans.*, 2009, 753; (*c*) R. Yamaguchi, K.-i. Fujita and M. Zhu, *Heterocycles*, 2010, **81**, 1093; (*d*) G. E. Dobereiner and R. H. Crabtree, *Chem. Rev.*, 2010, **110**, 681; (*e*) G. Gillena, D. J. Ramón and M. Yus, *Chem. Rev.*, 2010, **110**, 1611.
6 D. Balcells, A. Nova, E. Clot, D. Gnanamgari, R. H. Crabtree and O. Eisenstein, *Organometallics*, 2008, **27**, 2529.
7 (*a*) Y. Watanabe, Y. Tsuji and Y. Ohsugi, *Tetrahedron Lett.*, 1981, **22**, 2667; (*b*) R. Grigg, T. R. B. Mitchell, S. Sutthivaiyakit and N. Tongpenyai, *J. Chem. Soc., Chem. Commun.*, 1981, 611; (*c*) S. I. Murahashi, K. Kondo and T. Hakata, *Tetrahedron Lett.*, 1982, **23**, 229; (*d*) A. Arcelli, B.-T. Khai and G. Porzi, *J. Organomet. Chem.*, 1982, **235**, 93.
8 (*a*) K.-i. Fujita, Z. Li, N. Ozeki and R. Yamaguchi, *Tetrahedron Lett.*, 2003, **44**, 2687; (*b*) K.-i. Fujita, Y. Enoki and R. Yamaguchi, *Tetrahedron*, 2008, **64**, 1943; (*c*) R. Kawahara, K.-i. Fujita and R. Yamaguchi, *J. Am. Chem. Soc.*, 2010, **132**, 15108.
9 (*a*) G. Cami-Kobeci, P. A. Slatford, M. K. Whittlesey and J. M. J. Williams, *Bioorg. Med. Chem. Lett.*, 2005, **15**, 535; (*b*) M. H. S. A. Hamid, P. A. Slatford and J. M. J. Williams, *Adv. Synth. Catal.*, 2007, **349**, 1555; (*c*) M. H. S. A. Hamid and J. M. J. Williams, *Chem. Commun.*, 2007, 725; (*d*) M. H. S. A. Hamid, C. L. Allen, G. W. Lamb, A. C. Maxwell, H. C. Maytum, A. J. A. Watson and J. M. J. Williams, *J. Am. Chem. Soc.*, 2009, **131**, 1766; (*e*) O. Saidi, A. J. Blacker, M. M. Farah, S. P. Marsden and J. M. J. Williams, *Chem. Commun.*, 2010, **46**, 1541.
10 (*a*) D. Hollmann, A. Tillack, D. Michalik, R. Jackstell and M. Beller, *Chem.–Asian J.*, 2007, **2**, 403; (*b*) S. Imm, S. Bähn, L. Neubert, H. Neumann and M. Beller, *Angew. Chem., Int. Ed.*, 2010, **49**, 8126.
11 (*a*) B. Blank, M. Madalska and R. Kempe, *Adv. Synth. Catal.*, 2008, **350**, 749; (*b*) B. Blank, S. Michlik and R. Kempe, *Adv. Synth. Catal.*, 2009, **351**, 2903; (*c*) B. Blank and R. Kempe, *J. Am. Chem. Soc.*, 2010, **132**, 924; (*d*) S. Michlik and R. Kempe, *Chem.–Eur. J.*, 2010, **16**, 13193.
12 S. Whitney, R. Grigg, A. Derrick and A. Keep, *Org. Lett.*, 2007, **9**, 3299.
13 (*a*) R. Martínez, D. J. Ramón and M. Yus, *Org. Biomol. Chem.*, 2009, **7**, 2176; (*b*) A. Martínez-Asencio, D. J. Ramón and M. Yus, *Tetrahedron Lett.*, 2010, **51**, 325.
14 (*a*) L. U. Nordstrøm and R. Madsen, *Chem. Commun.*, 2007, 5034; (*b*) R. N. Monrad and R. Madsen, *Org. Biomol. Chem.*, 2011, **9**, 610 and references therein.
15 N. Choubdar, R. G. Bhat, K. A. Stubbs, S. Yuzwa and B. M. Pinto, *Carbohydr. Res.*, 2008, **343**, 1766.
16 (*a*) J. S. M. Samec, J.-E. Bäckvall, P. G. Andersson and P. Brandt, *Chem. Soc. Rev.*, 2006, **35**, 237; (*b*) G. Csjernyik, K. Bogár and J.-E. Bäckvall, *Tetrahedron Lett.*, 2004, **45**, 6799.
17 C. Ramstadius, A. M. Träff, P. Krumlinde, J.-E. Bäckvall and I. Cumpstey, *Eur. J. Org. Chem*, DOI: 10.1002/ejoc.201100504.
18 V. L. Maxwell, E. L. Evinson, D. P. G. Emmerson and P. R. Jenkins, *Org. Biomol. Chem.*, 2006, **4**, 2724.
19 M. Madalinski, M. Stoll, U. Dietrich and H. Kunz, *Synthesis*, 2008, 1106.
20 (*a*) T. Hermann, *Cell. Mol. Life Sci.*, 2007, **64**, 1841; (*b*) M. Hainrichson, I. Nudelman and T. Baasov, *Org. Biomol. Chem.*, 2008, **6**, 227.
21 (*a*) M. Bierenstiel and M. Schlaf, *Eur. J. Org. Chem.*, 2004, 1474; (*b*) M. Saburi, Y. Ishii, N. Kaji, T. Aoi, I. Sasaki, S. Yoshikawa and Y. Uchida, *Chem. Lett.*, 1989, 563; (*c*) G. Descotes, J.-P. Praly and D. Sinou, *J. Mol. Catal.*, 1979, **6**, 421; (*d*) G. Descotes, D. Sinou and J.-P. Praly, *Carbohydr. Res.*, 1980, **78**, 25.
22 (*a*) I. Isaac, G. Aizel, I. Stasik, A. Wadouachi and D. Beaupère, *Synlett*, 1998, 475; (*b*) I. Isaac, I. Stasik, D. Beaupère and R. Uzan, *Tetrahedron Lett.*, 1995, **36**, 383.