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Highly Selective Indium Mediated Allylation of Unprotected Pentosylamines

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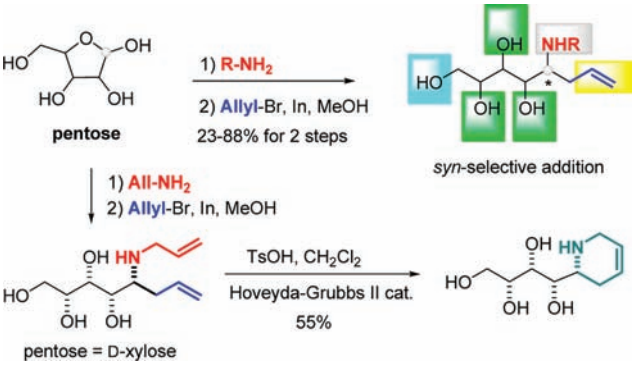
ABSTRACT



A straightforward functionalization of D-pentoses is reported, which affords homoallylaminopolyols in two steps and uses ion exchange chromatography as the only purification operation. The key indium-mediated allylation is effected on unprotected glycosylamines and occurs with good to excellent *syn* stereoselection. Validation of the synthetic utility of the method was exemplified by a 3-step synthesis of an optically active 1,2,3,6-tetrahydropyridine from D-xylose.

Allylation of carbonyl compounds using Indium as a promoter is an efficient and versatile C−C bond forming reaction that has elicited considerable interest since its discovery in 1988.[1] The organoindium nucleophiles are stable in both water and air, which allows very simple experimental protocols for the allylation of unprotected substrates in water or protic media.[2] A remarkable application of this reaction is the allylation of aldoses, a method that permitted the protecting-group free synthesis of higher-carbon sugars and biologically active polyols.[3] At least in the case of sugar-aldehydes, Barbier allylations with indium metal afforded higher yields and selectivity than the more standard Zn or Sn. In contrast to carbonyl chemistry, the In-mediated allylation of C−N double bonds has been less explored mainly because of the lower stability of imines in protic solvents and their poor electrophilicity. Nevertheless, after a first communication on the use of In as a promoter for allylation of aldimines in 1992,[4] several reports described such a transformation, evaluating its scopes and limitations.[5] Glycosylamines are a class of carbohydrate derivatives that are formed by condensation

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of an aldose with an amine. As for sugars, they exhibit mutarotation and might rearrange to a tautomeric imine form. However, glycosylamines are usually considered as unstable substrates: in protic solvents, they might hydrolyze back to the parent aldose or might undergo Amadori rearrangement, impeding their use for synthetic purpose.[6] Nevertheless, it has been shown that protected glycosylamines like **1** (Figure 1) react efficiently with allylzinc or allylmagnesium species in a diastereoselective manner affording diastereomeric aminopolyols like **2** and **3**.[7]

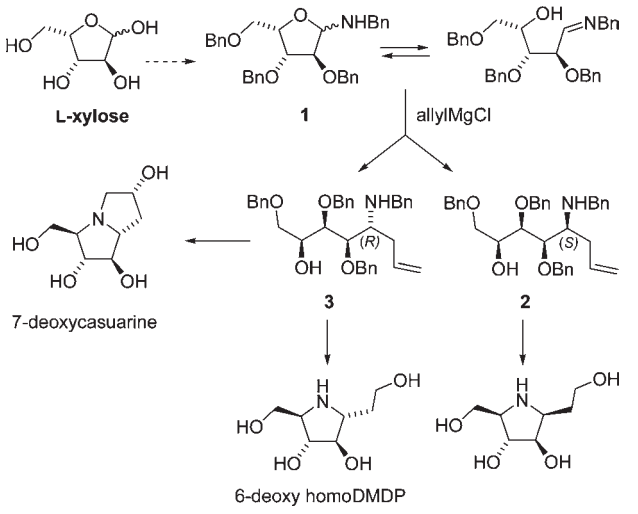
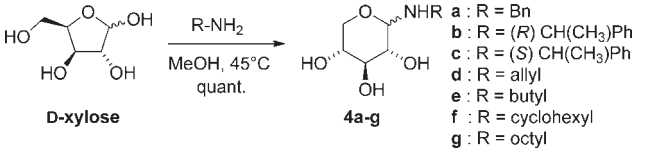


Figure 1. Protected glycosylamines in total synthesis.

These intermediates are key precursors of many biologically active compounds including iminosugars or sphingosine derivatives.[8] In view of this, allylation of *unprotected* glycosylamines under Barbier conditions in "environmentally preferable"[9] solvents would expand the repertoire of Green Chemist's toolbox, bringing significative improvements to the existing syntheses of aminopolyols in term of atom economy and length, by avoiding the use of protection/deprotection steps. We report here the protecting-group free transformation of glycosylamines into homoallylaminols, using indium as a promoter and methanol as the solvent. The scope of this transformation in the field of alkaloid synthesis is exemplified by the straightforward synthesis of a chiral dihydropyridine using subsequent RCM.

Among the few preparative procedures for obtaining unprotected glycosylamines, the condensation between an aldose and the appropriate amine using an alcohol as the solvent is the simplest.[10] The stability of such compounds is dependent on the nature of the starting sugar, the type of the amine used (degree of substitution, basicity, hybridization state) and the pH of the solution. To investigate a simple and general preparation of glycosylamines, we used D-xylose and benzylamine as models. When a suspension of D-xylose in MeOH was stirred at 45 °C in the presence of stoichiometric benzylamine, the insoluble carbohydrate disappeared within 40 min, after which the reaction mixture was evaporated to yield a colorless solid. NMR analysis revealed a set of signals different from that of the starting aldose with the presence of an aromatic system, a supplementary methylene and a significant shielding of anomeric proton and carbon compatible with the structure of *N*-benzylxylosylamine **4a** in a favored pyranose form.[10a] NMR monitoring of a D_2O solution of **4a** showed that it hydrolyzed back to xylose ($t_{1/2}$ = 24 h at natural pH) whereas a methanolic solution was more stable.[11] By applying the same methodology, we were able to prepare glycosylamines **4b**–**g** after reaction of D-xylose with one equivalent of (*R*)- and (*S*)-α-methylbenzylamine, allylamine, butylamine, cyclohexylamine and octylamine respectively (Scheme 1).[11] The reaction of the other D-pentoses with benzylamine worked equally well and afforded the corresponding D-*arabino*, D-*lyxo* and D-*ribo* *N*-benzylglycosylamines **5**, **6** and **7** (structures not shown).[11] All of these glycosylamines were used in the next step without further purification.

Scheme 1. Synthesis of Glycosylamines **4**



Next, we investigated the allylation reaction of xylosylamine **4a** under Barbier conditions (Table 1). Due to the instability of our glycosylamines in water we used methanol as the solvent for all our attempts. For the same reason, TLC or HPLC monitoring of the reaction appeared difficult. All the experiments were thus conducted overnight and analysis of the crude mixture was operated after suitable workup. In a first attempt (Table 1, entry 1), a solution of *N*-benzylxylosylamine **4a** was stirred in the

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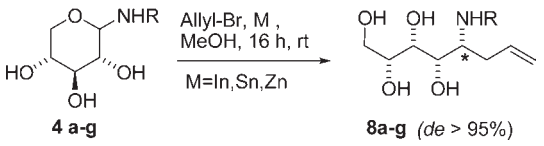
(11) See Supporting Information for NMR data.

Table 1. Conditions Screening



4 a-g **8a-g** (*de* > 95%)

entry	R	metal (equiv)	allyl-Br equiv	product[a]	yield[b] (%)
1	Bn	In (1)	2	**8a**	30
2	Bn	In (1)	3	**8a**	61
3	Bn	In (1.5)	3	**8a**	65
4	Bn	In (1.5)	4	**8a**	61
5	**Bn**	**In (2)**	**3**	**8a**	**72**
6	Bn	In (2)	4	**8a**	71
7	Bn	Sn (2)	3	**8a**	0
8	Bn	Zn (2)	3	**8a**	0
9	(*R*) $CH(CH_3)Ph$	In (2)	3	**8b**	37[c]
10	(*S*) $CH(CH_3)Ph$	In (2)	3	**8c**	55[d]
11	allyl	In (2)	3	**8d**	79
12	butyl	In (2)	3	**8e**	77
13	cyclohexyl	In (2)	3	**8f**	23[d]
14	$(CH_2)_7CH_3$	In (2)	3	**8g**	57

[a] All diastereoisomeric ratios were determined by ^{13}C NMR analysis of the crude reaction mixture. [b] Isolated yield. [c] *de* = 64%. [d] *de* = 68%.

presence of allylbromide (2 equiv) and powdered indium (1 equiv) at room temperature under air atmosphere. After 10 min a slightly exothermic reaction started, which ceased rapidly and the mixture was left to react for 16 h. Analysis of the crude reaction mixture and isolation of the compound proved somewhat difficult because of complexation of the aminopolyol with indium.[12] Only the addition of 1 *M* hydrochloric acid permitted to liberate the product, obtained as a colorless mixture after concentration. Gratifyingly, NMR analysis showed the presence of the expected homoallylamine **8a** in addition with almost equal amount of xylose (provided by hydrolysis of unreacted glycosylamine). Purification was simply reduced to ion-exchange chromatography: application of the crude on a Dowex50W-X8 column followed by elution with 0.8 *M* NH_4OH yielded aminopolyol **8a** in 30% yield.

To optimize the reaction conditions (Table 1, entries 2–6), we varied the relative quantities of either indium (1, 1.5, 2 equiv) or allyl bromide (2, 3, 4 equiv). Best conditions used 2 equiv of indium with 3 equivalents of allyl bromide, resulting in 72% isolated yield of **8a** (overall yield for the two steps). The optimal 2:3 ratio of indium and allyl bromide is consistent with the formation a sesquihalide allylindium intermediate ($Allyl_3In_2Br_3$), a structure generally proposed as the active species in indium-mediated allylation under Barbier conditions.[13]

The ability of other metals to induce allylation of unprotected glycosylamines was tried under the conditions stated above (Table 1, entries 7 and 8). However, when **4a** was stirred for 12 h with allyl bromide in the presence of either Sn or Zn, no reaction occurred and xylose was recovered quantitatively after acidic treatment.

The stereochemical outcome of the reaction was investigated next. Allylation of benzylxylosylamine **4a** afforded the sole diastereomer **8a**, the absolute configuration of which had to be determined. To this aim, we correlated the structure of **8a** to that of known L-*xylo* analogues **2** and **3** (Scheme 2).[8b,c] *O*-Debenzylation of formerly prepared **2** and **3** was performed in excellent yields with BCl_3,[14] leading to epimers ent-**8a** and **9**, respectively. The ^1H and ^{13}C NMR spectra of **8a** were strictly superimposable with that of ent-**8a**, which permitted assignment of the absolute configuration of **8a** and establishment of the relative *syn* selectivity for the indium mediated allylation of xylosylamines.

To see whether it was possible to control the orientation of the addition with a chiral *N*-auxiliary, we subjected (*R*)- and (*S*)-α-methylbenzylglycosylamines **4b** and **4c** to this In-mediated allylation (Table 1, entries 9 and 10). The reaction was expected to afford mixtures of diastereomers reflecting the directing effect of both stereogenic units.[15] We anticipated, at least in one case, a significant drop in selectivity due to the conflicting influence of mismatch relationships. However, the allylation of **4b** and **4c** gave comparable results affording mainly a single diastereoisomer **8b** or **8c** respectively. The isolated yields were significantly lower, certainly because of steric effects hindering the approach of the allylindium species. The same (*R*) configuration was determined for the new stereocenter in **8b** and **8c**, after their respective hydrogenolysis which led to the same compound **10**, which correlated with a sample of **10** obtained from **8a** by an analogous reaction (Scheme 2). Thus, the orientation of the addition could not be mediated by the chiral auxiliary, and the *syn* diastereoisomer was the major compound obtained in each case. This is in good agreement with the well-known 1,2-*syn* stereopreference in indium-promoted allylations of aldohexoses.[3f]

A set of reactions was performed to widen the scope of this transformation to other amines (Table 1, entry 11–14) or pentoses (Scheme 3). Thus homoallyl amines **8d–g** were prepared featuring allyl, butyl, cyclohexyl or octyl substituents on nitrogen. Yields were good (57–79% for two steps), except for the *N*-cyclohexylglycosylamine (23%), which reflects the sensitivity of the reaction to steric hindrance. In the same manner, *N*-benzylglycosylamines derived from D-arabinose, D-lyxose or D-ribose reacted as

(12) Direct evaporation of the volatiles afforded a white precipitate with unanalyzable broad NMR signals. Alternatively, when aqueous ammonia was added both to neutralize the acidic reaction mixture and to precipitate indium hydroxyde, evaporation of the liquor yielded only trace amount of material, most of the organic fraction being incorporated into the insoluble solid. In(III) forms stable complexes with *N*-containing ligands: Mahmoud, S. A.; Issa, I. M.; El-Gyar, S. A. *Monatsh. Chem.* **1980**, *111*, 431–438.

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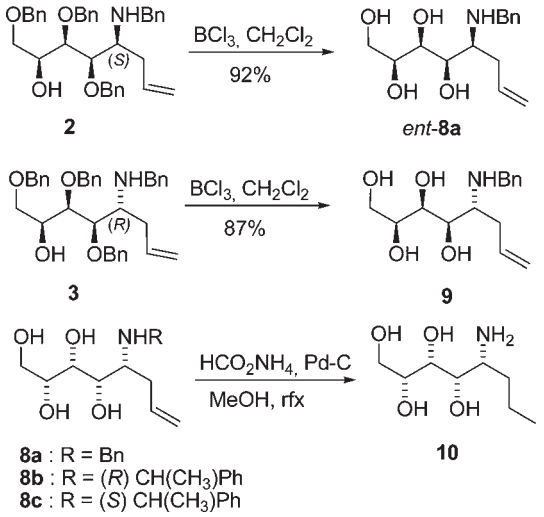
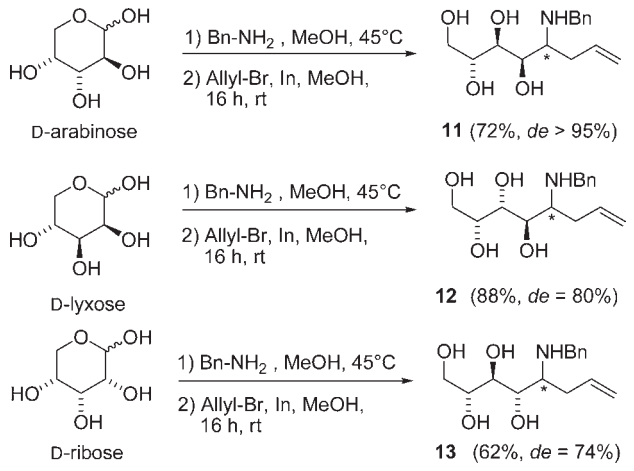
Scheme 2. Absolute Configurations of **8a**–**c** via Chemical Correlation



Scheme 3. Synthesis of Homoallylamines **11**–**13**



well affording the corresponding homoallylamines **11**–**13** in good yield and selectivity. By analogy with the results obtained with xylosylamines **4a**–**c** (this work) or more generally with arabinose, lyxose or ribose (*syn* addition in all cases),[3e,h] the formation of **11**–**13** is assumed to be *syn*-directed, but this has to be confirmed by further experiments.

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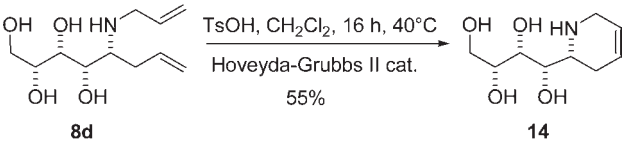
Interestingly, the two-step transformation to **11** could be performed in a single pot, by first stirring D-arabinose with $BnNH_2$ at 45 °C and adding AllylBr and In^0 at rt, which afforded **11** in excellent 82% yield. All the compounds were purified by ion exchange chromatography as the only purification operation, and could be used as such in subsequent chemical transformations. In several cases, small amounts of the corresponding stereoisomer were also present, the separation of which was not attempted here, but could be performed later in a synthetic route.

To exemplify the utility of the prepared homoallylamines as synthetic intermediates, we explored the possibility of accessing, in very few steps, the core structure of chiral tetrahydropyridines, a remarkable class of precursors of bioactive compounds.[16] To this aim, unprotected *N*-allylhomoallylamine **8d** was subjected to ring-closing metathesis (Scheme 4). Gratifyingly, the reaction worked in the presence of Hoveyda-Grubbs II catalyst (2.5%) and toluenesulfonic acid (1 equiv) as a transient protecting group for nitrogen.[17] Tetrahydropyridine **14** was obtained in 55% yield after purification by silica-gel chromatography.

Scheme 4. Synthesis of **14** by Direct RCM of **8d**



In conclusion, indium-mediated allylation was applied to a variety of glycosylamines deriving from "naked" pentoses, which afforded functionalized homoallylaminopolyols in good yield and high *syn* selectivity. The transformation might be performed in a single pot directly from pentoses. The compounds obtained after ion-exchange chromatography were almost pure and might be used as such in subsequent transformations, as exemplified by the synthesis of an optically active 1,2,3,6-tetrahydropyridine in very few steps.

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Supporting Information Available. Experimental procedures and analytical data of final compounds **8**–**14**, copies of NMR spectra for compounds **4**–**14**, hydrolysis experiments of glycosylamine **4a**. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.