Organocatalytic Glycosylation

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Organocatalytic Glycosylation by Using Electron-Deficient Pyridinium Salts**

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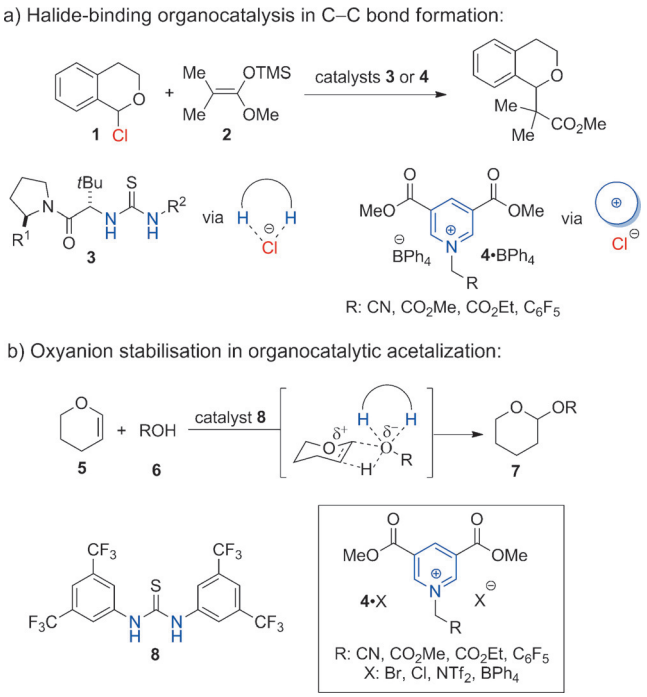
Dedicated to Professor David Milstein

Abstract: *A new organocatalytic glycosylation method based on electron-deficient pyridinium salts is reported. At ambient temperature and catalyst loadings as low as 1 mol%, 2-deoxyglycosides were formed from benzyl- and silyl-protected glycals and primary or secondary glycosyl acceptors, with excellent yields and anomeric selectivity. Mechanistic investigations point to alcohol–pyridinium conjugates (1,2-addition products) as key intermediates in the catalytic cycle.*

Glycosylation is arguably one of the most important yet difficult reactions in carbohydrate chemistry.[1] In particular, the stereoselective synthesis of 2-deoxyglycosides remains a challenge owing to the absence of any directing group at the 2-position and the inherent susceptibility of the product towards hydrolysis.[2] 2-Deoxyglycosides are important building blocks for many bioactive natural products.[3] They also occur frequently in antibiotics and anticancer agents, and play an important role in the bioactivity of various drugs.[4] One direct approach to synthesize these molecules involves the addition of alcohols to glycals, that is, the acetalization of a vinyl ether. Although there have been several recent reports on organocatalytic acetalizations,[5] only two publications by Galan and co-workers appear to deal with the glycosylation of glycals.[6] In their approach, thioureas serve as organocatalysts to promote alcohol addition to glycals, albeit with a rather limited substrate scope.[6,7]

We have recently shown that the electron-deficient pyridinium salts **4**·BPh_4 act as anion-binding catalysts for the addition of silyl ketene acetals (such as **2**) to 1-chloroisochroman (**1**), a transformation initially introduced by Jacobsen et al. through the use of the thiourea catalyst **3** (Scheme 1 a).[8,9] Organocatalytic transformations based on thioureas are by now manifold,[10] and the similarity in reactivity between pyridinium salts and thioureas in terms of anion binding made us wonder whether it might be possible



Scheme 1. Organocatalysis by thioureas and pyridinium salts: a) halide binding and C–C bond formation between α-chloroethers and silyl ketene acetals; b) oxyanion stabilization in the addition of alcohols to vinyl ethers.

to extend the scope of pyridinium catalysis beyond halide binding. Specifically, we focused our attention on the tetrahydropyranyl (THP) protection of alcohols, as developed by Schreiner et al. (Scheme 1 b).[11] The latter transformation proceeds efficiently at thiourea catalyst loadings as low as 0.001 mol%. Experimental and computational evidence points to two-fold hydrogen bonding of thiourea **8** to the alcohol component as the key mechanistic feature: the acidity of the alcohol is enhanced as the developing negative charge on oxygen is stabilized by the thiourea oxyanion hole.[11] We wondered whether an analogous oxyanion stabilization, and thus organocatalytic acetalization, might be effected by the pyridinium salts **4**·X instead of thioureas.[12]

As a first set of experiments, we studied the THP protection of benzyl alcohol. To our delight, the pyridinium bromide salts **4a–d**·Br efficiently catalyzed this reaction at RT in dichloromethane (DCM; Scheme 2). For the most electron-deficient pyridinium salt **4a**·Br, only 1 mol% loading was enough to give full conversion and high yield (88%) of the THP-protected product **7a**. Other pyridinium salts, such as the bis(trifluoromethanesulfonyl)imide **4d**·NTf_2, the tetra-

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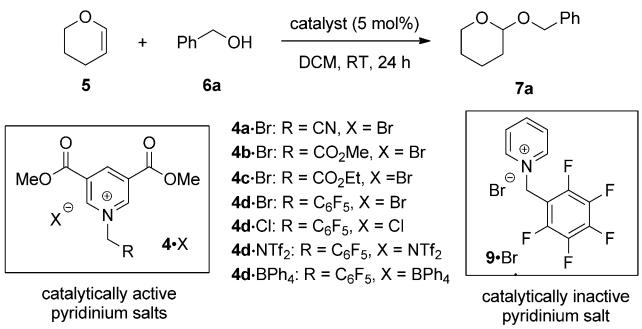


Scheme 2. Tetrahydropyranyl protection of benzyl alcohol (**6a**), as catalyzed by the pyridinium salts **4**·X.

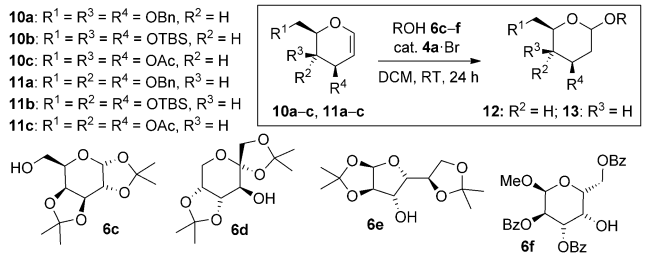
phenylborate **4d**·BPh_4, and the chloride **4d**·Cl were catalytically active as well.[13] Interestingly, the *N*-(pentafluorobenzyl)pyridinium bromide **9**·Br, which has no electron-withdrawing substituents at the pyridine ring, failed to promote product formation. Note that this importance of electron deficiency for catalytic activity is in line with our earlier observations on pyridinium catalytic activity/inactivity in silyl ketene acetal additions to α-chloroethers.[8]

After successful establishment of the THP protection of benzyl alcohol, we turned our attention towards the more challenging glycosylations (Table 1). As glycal components, we chose benzyl-, silyl-, and acetyl-protected galactals (**10a–c**) and glucals (**11a–c**). As glycosyl acceptors, we selected bis-acetonide-protected D-galactose **6c** (primary alcohol) and secondary acceptors derived from D-fructose (**6d**), D-glucose (**6e**), and D-galactose (**6f**). Entries 1–5 of Table 1 summarize the results achieved with benzyl-protected galactal **10a**.

We were delighted to see that not only primary acceptors [MeOH (**6b**) and **6c**; entries 1,2], but also the secondary ones (**6d–f**, entries 3–5) reacted smoothly at 1–2 mol% catalyst loading and efficiently provided the glycoside products **12ab–af**. For the electron-rich acceptors **6c–e**, quantitative conversion was reached within 24 h (entries 2–4), whereas the benzoyl-protected acceptor reacted somewhat more slowly (entry 5). Note that **12ac–af** were exclusively formed as the α-anomers. The results obtained with the silyl-protected galactal **10b** are summarized in entries 6–8. When combined with primary (**6c**) and secondary (**6d,e**) acceptors, the silyl-protected donor **10b** also afforded high glycosylation yields, with only the α-anomer detectable. Under our standard reaction conditions, the acetyl-protected galactal **10c** did not undergo alcohol addition, even with methanol (**6b**; entry 9). This deactivating effect of acetyl protection has been observed before.[6a] In the more challenging glucal series, the benzyl-protected donor **11a** reacted smoothly with the primary acceptor galactose acetonide **6c** with very high anomeric selectivity (entry 10).[14a,b] The same holds for the silyl-protected glucal **11b** (entry 11), although the yield of isolated glycoside was somewhat lower (63% vs. quantitative). As in the case of the galactal **10c**, the acetyl-protected glucal **11c** did not undergo alcohol addition (entry 12). Note that Ferrier rearrangement products were not detected for any of the examples reported in Table 1.

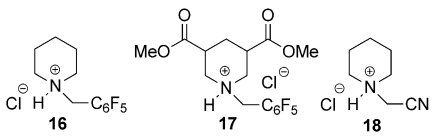
The remarkable activity of electron-deficient pyridinium salts in glycosylation prompted us to investigate the mechanism of catalysis. We selected the addition of methanol (**6b**) to the benzyl-protected D-glucal **11a** as the model transformation. We speculated that the combination of pyridinium salt and alcohol might generate some kind of alcohol–pyridinium complex/conjugate that is acidic enough to effect catalysis. With this in mind, we first synthesized the ammonium salts **16–18** and tested them in the acetalization of D-glucal **11a** (see the Supporting Information for the synthesis and crystal structures of **16–18**).

Table 1: Addition of alcohols to the glycals **10a–c** and **11a–c** in the presence of the pyridinium salt **4a**·Br.



Entry[a]	Glycal	Alcohol	Cat. loading [mol%]	Conv. [%][b]	Product, Yield [%][c,d]
1	**10a**	**6b**	1	quant.	**12ab**, 89 [5.9:1]
2	**10a**	**6c**	1	quant.	**12ac**, 94 [α only]
3	**10a**[e]	**6d**	2	quant.	**12ad**, 97 [α only]
4	**10a**[e]	**6e**	2	quant.	**12ae**, 97 [α only]
5	**10a**[e]	**6f**	2	66	**12af**, 60 [α only]
6	**10b**	**6c**	2	quant.	**12bc**, 96 [α only]
7	**10b**[e]	**6d**	2	quant.	**12bd**, 82 [α only]
8	**10b**[e]	**6e**	2	quant.	**12be**, 88 [α only]
9	**10c**[e]	**6b**	2	0	n.a.
10	**11a**[e]	**6c**	2	quant.	**13ac**, 89 [33:1]
11	**11b**[e]	**6c**	2	quant.	**13bc**, 63 [α only]
12	**11c**[e]	**6b**	2	0	n.a.

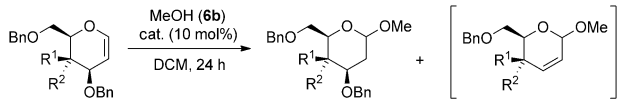
[a] 3 equiv of MeOH (**6b**) were used, all other alcohol nucleophiles were used at 1.2 equiv. [b] From ^{1}H NMR spectroscopy of the crude reaction mixture. [c] Isolated product after column chromatography. [d] α/β ratios in brackets from ^{1}H NMR spectroscopy. [e] Reaction was carried out at 40 °C.



It was found that the piperidinium salt **16** was much less reactive than its corresponding diester analogue **17** (Table 2, entries 1 and 2). This result parallels the reactivity of the related pyridinium salts **9**·Br vs. **4d**·Br. Also, *N*-(cyanomethyl)piperidinium chloride (**18**) was found to be more reactive than its *N*-pentafluorobenzyl analogue **16** (Table 2, entry 1 vs. entries 3,4). These results indicate that electron-deficient ammonium salts, but not simple trialkyl ones, are acidic enough to promote acetalization.[14c]

Our next concern was to exclude free HX as a potential catalyst. We did so by deliberately performing the acetalization of D-glucal **11a** in the presence of 10 mol% of HBr and

Table 2: Addition of methanol to the glycals **10a** and **11a** in the presence of the pyridinium salts **4d**·Br and **4d**·Cl and other catalyst candidates.



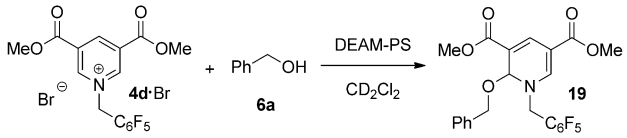
10a: R^1 = OBn, R^2 = H; **11a**: R^1 = H, R^2 = OBn
12ab: R^1 = OBn, R^2 = H; **13ab**: R^1 = H, R^2 = OBn
14ab: R^1 = OBn, R^2 = H; **15ab**: R^1 = H, R^2 = OBn

Entry[a]	Glycal	Catalyst	Temperature	Conversion [%][b]
1	**11a**	**16**	40 °C	0
2	**11a**	**17**	40 °C	quant.
3	**11a**	**18**	RT	30
4	**11a**	**18**	40 °C	quant.
5	**11a**	**4d**·Br	40 °C	71
6	**11a**	**4d**·Cl	40 °C	82
7	**11a**	HBr	40 °C	quant.
8	**11a**	HCl	40 °C	quant. (22)[c]
9	**10a**	–[d]	RT	0
10	**10a**	**8**	RT	0
11	**11a**	**8**	40 °C	0

[a] 3 equiv of methanol were used in all reactions. [b] From ^{1}H NMR spectroscopy of the crude reaction mixture (conversion to the products **12** and **13**); the product anomeric ratio was typically ca. 5.5–6 (α/β) for the methyl galactoside **12ab** and ca. 4.5 for the glucoside **13ab**. [c] The amount of Ferrier rearrangement product **15ab** is given in brackets. [d] Carried out in the presence of 10 mol% of pentafluorobenzyl bromide or pentafluorobenzoic acid.

HCl, and comparing the product distribution with that resulting from the use of **4d**·Cl and **4d**·Br (Table 2, entries 5,6 vs. entries 7,8). If a free acid generated from the pyridinium salts was the sole catalyst, the product distribution obtained for a Brønsted acid HX should be similar to that obtained from the pyridinium salt **4**·X. While **4d**·Cl and **4d**·Br show similar reactivities for this transformations, HBr and HCl behaved quite differently. HBr gave quantitative conversion of **11a** to the product **13ab** (Table 2, entry 7); in contrast, HCl gave substantial amounts of the Ferrier rearrangement product **15ab**, along with the glycosylation product **13ab** (Table 2, entry 8). This result speaks against free HX as the catalyst and points to a crucial role for the pyridinium salt itself. N-Dealkylation of the pyridinium catalysts by the alcohol nucleophile could also be a potential source of HX. However, even 10 mol% of pentafluorobenzyl bromide did not lead to any product formation (Table 2, entry 9). Likewise, no product formation occurred when 10 mol% of pentafluorobenzoic acid (p*K*a 1.60) was used (Table 2, entry 9). In summary, the above control experiments strongly argue against catalysis by adventitious HX and thus support a specific mechanism of catalysis involving pyridinium cations. Under our reaction conditions, thiourea **8** did not promote methanol addition to the glycals **10a** or **11a** (entries 10,11).

Addition of the solid-phase-bound base diethylaminomethyl polystyrene (DEAM-PS) to the reaction mixture prevents acetal formation, and the 1,2-addition product of the alcohol nucleophile to the pyridine nucleus of, for example, **4d**·Br, can be detected (^{1}H NMR). Analogously, when the pyridinium bromide **4d**·Br was exposed to an equimolar amount of benzyl alcohol in the presence of DEAM-PS in deuterated DCM, we observed quantitative formation of the addition product **19**, with exclusive 1,2-regioselectivity (Scheme 3, see the Supporting Information for full characterization of **19**).[15,16] We were also able to crystallize the 2-addition product **19** and determine its structure (Figure 1).[17] We observed addition in the 2-position for other alcohol nucleophiles, as well as for benzyl amine. Benzyl thiol, on the other hand, gave mixtures of the 2- and 4-addition products (see the Supporting Information).[18]



Scheme 3. 1,2-Addition of benzyl alcohol (**6a**) to the pyridinium salt **4d**·Br affords the hemiaminal **19** (DEAM-PS = diethylaminomethyl polystyrene).

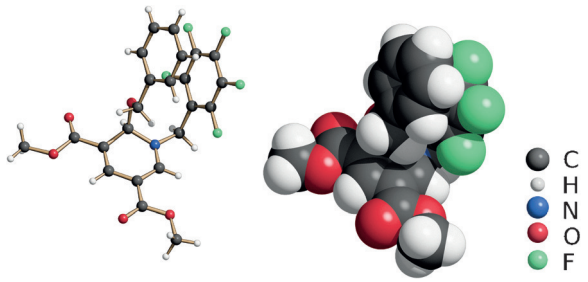
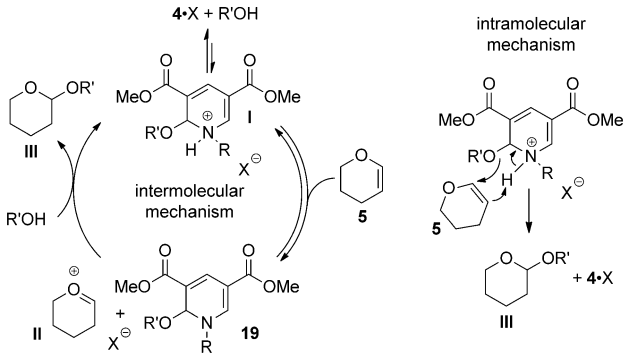


Figure 1. X-ray crystal structure of the hemiaminal **19**; note the tight stacking of the phenyl/pentafluorophenyl rings.

Combining all of these observations, we propose a stepwise catalytic mechanism as demonstrated for dihydropyran (**5**) in Scheme 4 (left). The first step involves addition of the alcohol to the 2-position of the pyridinium salt **4**·X to form the protonated hemiaminal **I**. The enol ether **5** is then protonated by the ammonium cation **I** to give the oxonium ion **II**. The latter is captured by a second alcohol molecule in an intermolecular fashion to give the product acetal **III**, with



Scheme 4. Proposed mechanism for the addition of alcohol to the cyclic vinyl ether **5**, as catalyzed by a pyridinium salt **4**·X.

concomitant regeneration of the ammonium ion **I**. An intramolecular variant of this mechanism (Scheme 4, right) may be envisaged in which proton transfer from the ammonium cation **I** to the enol ether **5** is followed by alcoholate transfer from the aminal. A clear distinction between the intermolecular and intramolecular mechanisms cannot be put forward at this point. However, the catalytic efficiency of the piperidinium cations **17** and **18** indicates that the external nucleophile pathway may well be operative for the pyridinium salts. For both mechanistic alternatives, enol ether activation rests on β-protonation. Consequently, it is not surprising that the deprotonated neutral aminal **19** does not promote acetal formation.

In conclusion, we report a new organocatalytic glycosylation method based on electron-deficient pyridinium salts. The addition of alcohol nucleophiles to glycals proceeds efficiently at low catalyst loading. The method provides excellent yields of isolated glycosylation products and high anomeric selectivity, and prevents the formation of byproducts, for example, from Ferrier rearrangement. Mechanistic studies point to 2-addition of the alcohol nucleophile to the pyridinium catalyst as the crucial step. Further work in this laboratory aims at the exploitation of this mechanism for the promotion of other addition reactions across polar double bonds.

Experimental Section

Glycosylation of the D-galactal **10a** with 1,2:3,4-di-O-isopropylidene-α-D-galactopyranose (**6c**) as the glycosyl acceptor: In a screw-capped vial and under Ar atmosphere, D-galactal **10a** (110 mg, 0.26 mmol, 1.0 equiv) was dissolved in 5.0 mL dry DCM. To this solution, catalyst **4a**·Br (0.8 mg, 2.6 μmol, 0.01 equiv) was added, followed by the glycosyl acceptor **6c** (82 mg, 0.31 mmol, 1.2 equiv), and the cap was closed tightly. The reaction mixture was stirred at RT for 24 h and then the solvent was evaporated under vacuum. The remaining crude product was purified by column chromatography on silica gel to give the galactoside **12ac** as a clear oil. Yield: 166 mg (94%); $R_f = 0.29$ (20% EtOAc in *c*-hex); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.39$–7.18 (m, 15), 5.52 (d, $J = 5.0$ Hz, 1H), 5.03 (d, $J = 2.9$ Hz, 1H), 4.92 (d, $J = 11.6$ Hz, 1H), 4.67–4.55 (m, 3H), 4.48 (d, $J = 11.8$ Hz, 1H), 4.42 (d, $J = 11.8$ Hz, 1H), 4.30 (dd, $J = 4.8$, 2.2 Hz, 1H), 4.20 (dd, $J = 7.9$, 1.7 Hz, 1H), 4.00–3.92 (m, 4H), 3.70–3.63 (m, 1H), 3.69–3.65 (m, 1H), 3.65–3.60 (m, 1H), 3.55–3.51 (m, 1H), 2.12 (m, 1H), 2.03 (m, 1H), 1.51 (s, 3H), 1.42 (s, 3H), 1.32 (s, 6H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): $\delta =$ 139.1, 138.7, 138.3, 128.5, 128.4, 128.3, 127.9, 127.8, 127.6, 127.4, 109.4, 108.6, 97.7, 96.5, 74.8, 74.4, 73.5, 73.0, 71.2, 70.8, 70.7, 70.5, 69.8, 69.3, 66.0, 65.7, 31.3, 26.3, 26.1, 25.1, 24.7 ppm; IR (ATR): $\tilde{\nu} = 2985$, 2933, 2910, 1454, 1209, 1166, 1093, 1064, 999, 732, 696 cm^{-1}; HRMS (ESI): calcd. for $C_{39}H_{48}O_{10}Na$ ($[M+Na]^+$) 699.3139, found 699.3141. Proton and carbon NMR spectra of the product **12ac** were fully consistent with the literature (Ref. [6a]).

Keywords: acetals · anion binding · glycosylation · organocatalysis · pyridinium cations

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[13] The tetraphenylborate salts **4**·BPh_4 were found to be of limited stability in DCM. Therefore, further transformations with pyridinium tetraphenylborate salts as catalysts were not attempted.

[14] a) Tribenzyl-protected D-glucal **11a** was reported to give substantial amounts of Ferrier rearrangement product and poor anomeric selectivity when thiourea **8** was used as the catalyst: see Ref. [6]; b) See the Supporting Information for the addition of benzyl alcohol, methanol, 2-propanol and *tert*-butanol to **10a** and **11a**; c) Trialkylammonium salts, such as triethylammonium

chloride, are reported in Ref. [6a] (see the Supporting Information) to be catalytically inactive in this transformation.
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[16] Synthesis of N,O-aminals: a) S. Wan, M. E. Green, J.-H. Park, P. E. Floreancig, *Org. Lett.* **2007**, *9*, 5385 – 5388; b) G. Li, F. R. Fronczek, J. C. Antilla, *J. Am. Chem. Soc.* **2008**, *130*, 12216 – 12217.
[17] CCDC 1057632 (**17**), 1057633 (**S6**), 1057634 (**16**), 1057635 (**19**), 1057636 (**4d**·NTf_2), and 1067637 (**18**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.
[18] Note that in Ref. [12a], Connon et al. proposed a mechanism based on the 4-addition of the alcohol to a pyridinium salt to generate HBr.
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