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Catalytic Oxidation–Phosphorylation of Glycals: Rate Acceleration and Enhancement of Selectivity with Added Nitrogen Ligands in Common Organic Solvents

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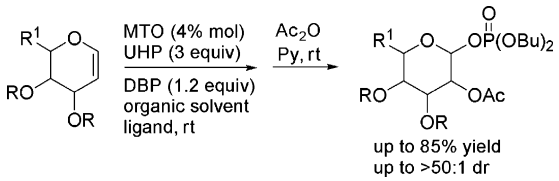
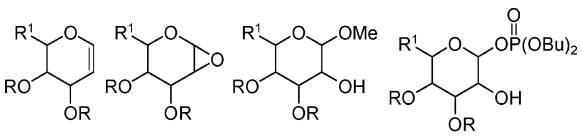
ABSTRACT



The first general catalytic oxidation of glycals has been developed to afford useful glycosyl phosphates in high yield and selectivity in a domino process with the use of catalytic methyltrioxorhenium, urea hydrogen peroxide, stoichiometric dibutyl phosphate as nucleophile, and a substoichiometric amount of nitrogen ligands, such as pyridine or imidazole, in organic solvents.

Glycals **1** are very useful and versatile substrates for the synthesis of glycoconjugates and oligosaccharides.[1] Their conversion involves an initial epoxidation to give the corresponding 1,2-dehydrosugar derivatives **2**, used as glycosyl donors with appropriate acceptors or as precursors of more stable glycosyl donors, which can be used successively.[2]



1 **2** **3** **4**

Dimethyldioxirane (DMDO) is practically the only reagent used for the epoxidation step.[3] DMDO is unstable, has to be freshly prepared, and poses serious safety problems connected with its potential explosiveness. Therefore, the development of a practical alternative for this transformation is highly desirable, especially for large-scale syntheses. In particular, no general catalytic method had been reported for the epoxidation of glycals before we recently disclosed that methyltrioxorhenium (MTO)[4] is able to catalyze this oxidation in methanol, with the complex urea hydrogen peroxide (UHP)[5] as the stoichiometric oxidant, giving the corresponding methyl glycosides **3**.[6,7] In the presence of dibutyl phosphate (DBP) in ionic liquids, the oxidation furnished,

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(2) Gordon, D. M.; Danishefsky, S. J. *Carbohydr. Res.* **1990**, *206*, 361−366.
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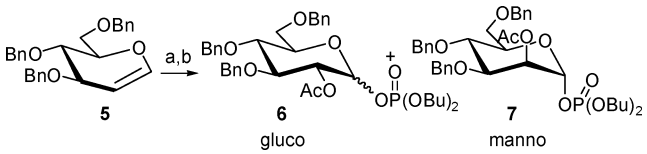
with moderate chemo- and stereoselectivities, the corresponding glycosyl phosphates **4**,[6] which are extremely useful and convenient glycosyl donors.[8] Novel methods for their preparation are very timely, due to their extensive use in the first automated oligosaccharide syntheses recently developed by Seeberger.[9]

In this paper, we report that the use of nitrogen ligands in this reaction gives tremendous beneficial effects in terms of conversion of substrate, rate acceleration, product selectivity, and diastereoselectivity of the epoxidation and allows standard organic solvents to be used. This results in a novel practical and convenient method for the synthesis of glycosyl phosphates.

Although MTO/H_2O_2 (or UHP) has been used for the epoxidation of a large variety of differently substituted alkenes,[10] its use with enol ethers is barely documented, while a properly modified procedure has been reported for oxidation of silyl enol ethers.[11] Glycals proved quite sluggish substrates toward MTO/UHP. When an up to 3-fold excess of DBP was used in the domino epoxidation−phosphorylation, the conversion of tribenzylglucal (**5**) chosen as a model substrate was incomplete in THF, CH_2Cl_2, CH_3CN, and other organic solvents. Dimethylimidazolium tetrafluoroborate ([BMIM]BF_4) is necessary in order to force the oxidation to completion. Ionic liquids are difficult to obtain with reproducible purity and especially completely anhydrous; therefore, the competing ring-opening by water was always a serious drawback and acceptable yields of glycosyl phosphates **6** and **7** were obtained only with a large excess of DBP (≥5 equiv). With such an excess of DBP, however, the reaction went to completion also in common organic solvents, affording better yields of glycosyl phosphates (Table 1, entries 3 vs 2 and 7 vs 5). Moreover, the selectivity of the reaction turned out to be quite solvent dependent, the higher gluco/manno selectivity occurring with the more coordinating solvent THF (Table 1, entry 7).

Table 1. "One-Pot" Synthesis of Glycosyl Phosphates[a]



5 6 gluco 7 manno

entry	solvent	DBP (equiv)	time (h)	conv (%) (yield, %)[b]	epox select.[c] gluco/manno
1[d]	[BMIM]BF_4	5	3.5	100 (58)	5.5:1
2	CH_2Cl_2	3	5	80	
3[d]	CH_2Cl_2	5	1.5	100 (75)	3.8:1
4	CH_2Cl_2	5	6.5	100 (74)	2.7:1
5	THF	3	4.5	60	
6[d]	THF	5	1.5	60	
7	THF	5	7	100 (65)	9.8:1
8	CH_3CN	5	7	100	3.8:1

[a] Conditions: (a) MTO (4 mol %), UHP (3 equiv), dry solvent, DBP, 0 °C; (b) Py, Ac_2O, rt, overnight. [b] Isolated yields. [c] Calculated by integration of the ^{31}P NMR spectra of the crude mixtures. [d] Reaction performed at room temperature.

It is worth noting that, while **7** was obtained as the α-anomer only, phosphate **6** was always produced as a mixture of α- and β-anomers. However, this is not a critical point, since both anomers participate in subsequent glycosyl transfer affording the same product.[12] Moreover, α-glycosyl phosphates can be formed from the corresponding β-isomers by temperature-dependent acid-catalyzed anomerization, promoted by the excess of DBP in the reaction mixture, as already shown by previous work.[13] Therefore, anomeric equilibration affords α/β ratios which are variable with temperature and time, with the more stable α-glucosyl phosphate prevailing at longer reaction time and higher temperature. In our case, for instance, when the reaction was performed at 0 °C (Table 1, entry 4), α-glucosyl phosphate α-**6** and β-glucosyl phosphate β-**6** were obtained in 1:1.5 ratio. The same reaction afforded a 4:1 ratio in favor of the α-anomer when carried out at 25 °C (Table 1, entry 3). The α/β ratios found for each reaction are reported in the Supporting Information.

The effect of DBP on the conversion suggested that DBP might work as a donor ligand toward Re in the catalyst precursor and/or catalytic species, thus influencing the turnover rate and/or catalyst lifetime. We then decided to test other better ligands for Re in this reaction, and particularly nitrogen ligands, such as pyridine (Py), pyrazole and 3-cyanopiridine, which have already shown beneficial effects in epoxidation of alkenes, enhancing the reaction rate and limiting the hydrolysis of epoxides to diols.[10] Moreover, the use of ligands should limit the DBP to be used to a stoichiometric amount. Then, 1.2 equiv of DBP as nucleophile and 0.5 equiv of the ligands reported in Table 2 have been used in the model reaction in CH_2Cl_2 or THF.

The results in Table 2 (see the Supporting Information for results with a larger number of ligands) demonstrate the effectiveness of nitrogen ligands in promoting the reaction with stoichiometric amounts of DBP. Oxygen ligands, such as *N*-oxides, gave poorer results (entries 13 and 14). In the absence of ligand, the reaction does not go to completion in CH_2Cl_2 or in THF (Table 2, entries 1 and 2). With added ligands, complete conversion is attained. Some of them are particularly remarkable in terms of conversion of substrate, rate acceleration, and facial diastereoselectivity of epoxidation, which determines the selectivity at C-2 (gluco/manno).[14]

(6) Soldaini, G.; Cardona, F.; Goti, A. *Tetrahedron Lett.* **2003**, *44*, 5589−5592.
(7) For a different example of one-pot oxidation−nucleophile addition, see: Di Bussolo, V.; Kim, Y.-J.; Gin, D. Y. *J. Am. Chem. Soc.* **1998**, *120*, 13515−13516.
(8) Palmacci, E. R.; Plante, O. J.; Seeberger, P. H. *Eur. J. Org. Chem.* **2002**, 595−606.
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(10) Adolfsson, H. In *Modern Oxidation Methods*; Bäckvall, J.-E., Ed.; Wiley-VCH: Weinheim, 2004; pp 32−43 and references therein.
(11) Stankovic, S.; Espenson, J. H. *J. Org. Chem.* **1998**, *63*, 4129−4130.
(12) Plante, O. J.; Andrade, R. B.; Seeberger, P. H. *Org. Lett.* **1999**, *1*, 211−214.
(13) Plante, O. J.; Palmacci, E. R.; Andrade, R. B.; Seeberger, P. H. *J. Am. Chem. Soc.* **2001**, *123*, 9545−9554.
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Table 2. "One-Pot" Synthesis of Glycosyl Phosphates **6** and **7** from Tribenzylglucal (**5**) in the Presence of Nitrogen Ligands[a]

5 $\xrightarrow{a,b}$ **6** + **7**

entry	ligand (0.5 equiv)	solvent	time (h)	conv (%) (yield,%)[b]	epox select.[c] gluco/manno
1		CH_2Cl_2	2.0	50	
2		THF	1.5	81	
3	pyridine	CH_2Cl_2	0.2	**100 (76)**	7.0:1
4	pyridine	THF	1.5	**100 (68)**	**10.5:1**
5	3-cyanopyridine	CH_2Cl_2	1.0	100	4.1:1
6	3-cyanopyridine	THF	1.5	55	7.8:1
7	pyrazole	CH_2Cl_2	0.7	100	2.9:1
8	pyrazole	THF	2.0	90	11.1:1
9	imidazole	CH_2Cl_2	1.0	**100 (75)**	9.0:1
10	imidazole	THF	1.5	**100 (69)**	**14.0:1**
11	1,10-phenanthroline	CH_2Cl_2	1.2	100	4.7:1
12	1,10-phenanthroline	THF	1.0	100	8.3:1
13	bipyridine *N*-oxide	CH_2Cl_2	2.0	100	4.7:1
14	bipyridine *N*-oxide	THF	2.0	81	9.4:1

[a] Conditions: (a) MTO (4 mol %), UHP (3 equiv), dry solvent, DBP (1.2 equiv), ligand (0.5 equiv); (b) Py, Ac_2O, rt, overnight. [b] Isolated yields. [c] Calculated by integration of the ^{31}P NMR spectra of the crude mixtures.

Contrary to most of the ligands used, imidazole (ImH) has no precedent in the literature in MTO-catalyzed epoxidations. More importantly, the strong ligand and solvent effect on the diastereoselectivity of the reaction is completely unprecedented.[15] As a rule, epoxidation selectivity is always better in THF than in CH_2Cl_2 with any ligand (Table 2).

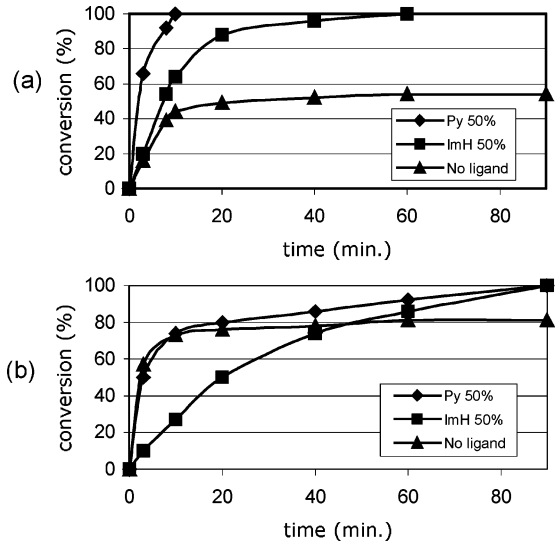

Figure 1. Conversion of tribenzylglucal (**5**) in the MTO-catalyzed oxidation−phosphorylation in (a) CH_2Cl_2 and (b) THF (conditions as in Table 2).

Py and ImH gave the best results, leading to complete conversions and good diastereoselectivities in both solvents used, and were selected for further experiments. The reaction is faster in CH_2Cl_2 (Figure 1a) than in THF (Figure 1b). The two ligands display a considerable accelerating effect in CH_2Cl_2, with Py being most effective and driving the reaction to completion in only 10 min (Figure 1a). Notably, under these conditions a reduced amount of MTO (1 mol %) was sufficient to give a complete conversion of substrate in 1.5 h. Conversely, in THF the ligands did not show a similar effect on rate, with ImH giving an opposite decelerating effect (Figure 1b). Nevertheless, their use was beneficial to catalyst lifetime, allowing the reaction to go to completion. The best result in terms of C-2 selectivity (gluco/manno) was obtained with ImH (up to 14:1 with 0.5 equiv of ImH in THF (Table 2, entry 10).

The effect of the amount of added imidazole on selectivity in CH_2Cl_2 and THF was also investigated (Figure 2). This

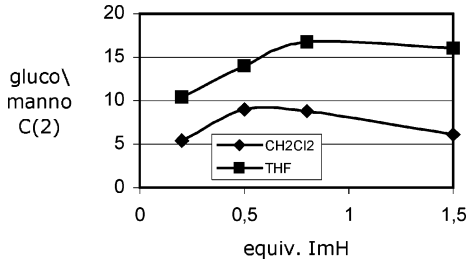

Figure 2. Influence of the amount of imidazole on the facial (gluco/manno) selectivity in the MTO-catalyzed oxidation−phosphorylation of tribenzylglucal (**5**) in CH_2Cl_2 and THF (other conditions as in Table 2).

allowed establishment of an optimal amount of 0.8 equiv of ImH to increase the facial selectivity in THF up to a synthetically meaningful 16.7:1 ratio. It is worthy to note that all the isomeric ratios have been evaluated by integration of the singlet signals from ^{31}P NMR spectra of the crude reaction mixtures. This method allows an extremely accurate and reliable determination, even of very minor isomers which might elude different techniques.

This methodology is of general scope, as proved by the synthesis of glycosyl phosphates **8**−**14**, in good to excellent yields and up to complete stereoselectivity, from the corresponding glycals derived from D-glucose, D-galactose, L-rhamnose, and D-arabinose, either protected with benzyl or acetyl groups (Figure 3). The nature of the protecting groups influences strongly the rate of reaction. Substrates with electron withdrawing acetyl groups were oxidized much more sluggishly and generally were not completely converted in THF. Use of dichloromethane and pyridine as additive proved the best conditions for such substrates. Pyridine ensured shorter reaction time compared to imidazole, without

(15) For an example of a solvent-dependent diastereoselective oxidation of an allylic alcohol with free OH, see: Adam, W.; Mitchell, C. M.; Saha-Möller, C. R. *Eur. J. Org. Chem.* **1999**, 785−790.

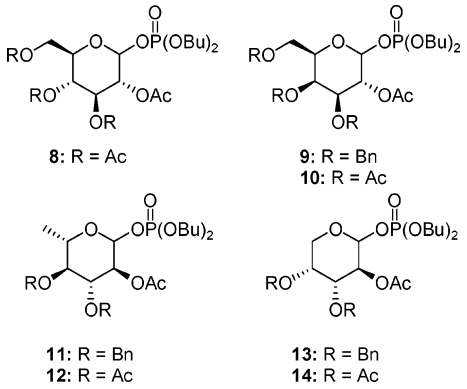

Figure 3. Reagents and conditions: glycal, MTO (4 mol %), UHP (3 equiv), DBP (1.2 equiv), pyridine (0.5 equiv), CH_2Cl_2, then pyridine, Ac_2O, rt, 15 h. Yields, C-2 selectivities, and reaction times: **8**, 85%, 3.3:1, 6.5 h; **9**, 69%, >50:1, 1.5 h; **10**, 83%, 39:1, 17.5 h; **11**, 70%, 6:1, 0.5 h (63%, 9.9:1, 1 h in THF with 0.8 equiv of imidazole); **12**, 85%, 3.3:1, 6 h; **13**, 70%, >50:1, 2 h; **14**, 85%, >50:1, 5 h.

affecting the selectivity to a substantial extent. For tribenzyl-L-rhamnal, precursor to **11**, effects of ligands have been observed that parallel those reported above for tribenzylglucal. Thus, the selectivity at C-2 could be increased to a 10:1 ratio when the domino process was carried out in THF in the presence of imidazole (see the Supporting Information).

In summary, the first general catalytic oxidation of glycals has been developed to afford useful glycosyl phosphates in high yield and selectivity in a domino process with stoichiometric DBP and substoichiometric Py or ImH in organic solvents.

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Supporting Information Available: Experimental procedures, complete data on selectivities, characterization data, and NMR spectra of compounds **6**−**14** and of minor diastereoisomers. This material is available free of charge via the Internet at http://pubs.acs.org.

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