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Ionic liquids in methyltrioxorhenium catalyzed epoxidation–methanolysis of glycals under homogeneous and heterogeneous conditions

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Abstract

The efficient and high yielding domino epoxidation–methanolysis of glycals has been achieved under environment friendly conditions by oxidation with urea hydrogen peroxide adduct (UHP) and H_2O_2 in ionic liquids (ILs) catalyzed by methyltrioxorhenium and different heterogeneous methyltrioxorhenium derivatives. The facial diastereoselectivity of the oxidation ranged from satisfactory to excellent ones depending on the substrate and could be optimized by ample screening of catalysts. The oxidations performed with UHP proceeded with a higher degree of diastereoselectivity than those performed with H_2O_2. High yields of products and conversions of substrates were obtained under mild experimental conditions and by the use of simple work-up procedures.

Keywords: Homogeneous catalysis; Heterogeneous catalysis; Hydrogen peroxide; Ionic liquids; Glycals

1. Introduction

The use of ionic liquids (ILs) as solvents in organic synthesis has enormously increased over the last decade [1]. In particular, growing attention has been devoted to the use of ILs for catalytic reactions [2]. Indeed, several catalytic reactions display considerable rate acceleration effect when carried out in ILs. Moreover, ILs form biphasic systems with many organic solvents, opening the way to the opportunity of easy isolation and recovery of the homogeneous catalysts. ILs are often considered as green alternative solvents to conventional molecular solvents, due to their negligible volatility that allows easy storage without contamination of the surrounding environment. Nevertheless, their toxicity and biodegradability have not been fully determined yet. Oxidation reactions are among the most important trasformations in organic synthesis, but often use polluting metal oxides and over stoichiometric amounts of oxidants. In spite of notable advances [3], oxidation reactions are mainly carried out in molecular solvents. Only recently, some catalytic oxidations in ILs have been reported, mainly by adapting the traditional molecular solvent methods to ILs [4]. Advances in this regard have been obtained by the use of ILs such as 1-*n*-butyl-3-methylimidazolium hexafluoro phosphate [BMIM][PF_6] [5], 1-ethyl-3-methylimidazolium tetrafluoroborate [EMIM][BF_4] [6] and 1-ethyl-3-methylimidazolium bis-triflic amide [EMIM][Tf_2N] [7], which are oxygen and water stable compounds. In the last years, increasing attention has been focused on the use of methyltrioxorhenium (CH_3ReO_3, MTO) [8], in conjunction with environment friendly hydrogen peroxide (H_2O_2) or the urea hydrogen peroxide adduct (UHP) [9] as oxygen atom donors, due to the excellent catalytic properties showed by this system [10]. These reactions proceed through the formation of the monoperoxo [$MeRe(O)_2O_2$] (**A**)

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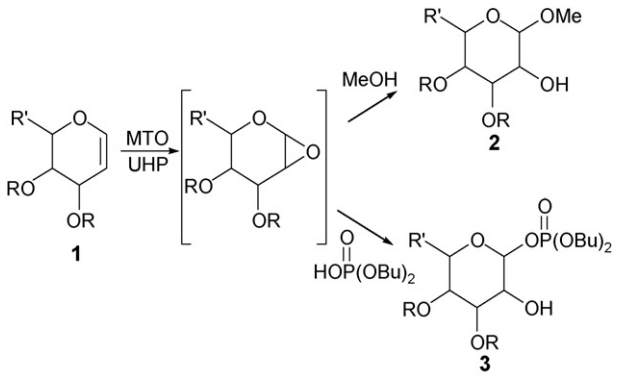
and the bis-peroxo [$MeReO(O_2)_2$] (**B**) η^2-rhenium complexes that have been isolated and fully characterized by single-crystal X-ray analysis [11]. Furthermore, MTO showed excellent conversions and selectivities for the epoxidation of olefins in ILs. Under these experimental conditions, the intermediate (**B**) was more reactive than (**A**) [12]. Heterogeneous compounds based on the anchorage of MTO on easily available, non-toxic and inexpensive poly(4-vinylpyridine) and polystyrene resins, are also efficient catalysts for the oxidation of hydrocarbons in ILs [13]. Noteworthily, in these transformations the activity of the heterogeneous catalysts was greater than that previously observed in molecular solvents. Moreover, heterogeneous MTO catalysts were easily recycled by filtration and used for successive transformations with similar selectivity and reactivity. We recently reported an efficient and high yielding domino epoxidation–methanolysis of glycals **1** with MTO and UHP in MeOH to afford methyl glycosides **2** under both homogeneous and heterogeneous conditions (Scheme 1) [14]. Similar results have been reported by Quayle and his co-workers for some glucals and galactals under biphasic conditions by the use of catalytic MTO and 30% aqueous H_2O_2 [15]. The oxidation of glycals is a challenging aim, due to the sensitive nature of the intermediate epoxide. It is therefore essential to perform this reaction in anhydrous and non-nucleophilic solvents. With the aim to develop a greener procedure for the epoxidation–methanolysis of glycals employing methanol not only as the nucleophile of the process but also as the solvent of reaction, we tried to test some ILs as solvent media for this transformation. In the preliminary communication [14a], we also reported our results of a test in [BMIM][BF_4] as solvent for a related interesting transformation of glycals into glycosyl phosphates **3** (Scheme 1). Indeed in that case, the use of the IL instead of acetone as solvent avoided undesired ring opening of the intermediate epoxide by water. Albeit we have found later that glycosyl phosphates **3** are obtained in higher yields and better selectivities in molecular solvents with the addition of substoichiometric amount of a nitrogen ligand, such as pyridine or imidazole [16], our preliminary results in ILs were very encouraging.

As a continuation of these studies, we report herein an efficient, stereoselective and environment friendly procedure for the domino epoxidation–methanolysis of a series of structurally



Scheme 1.

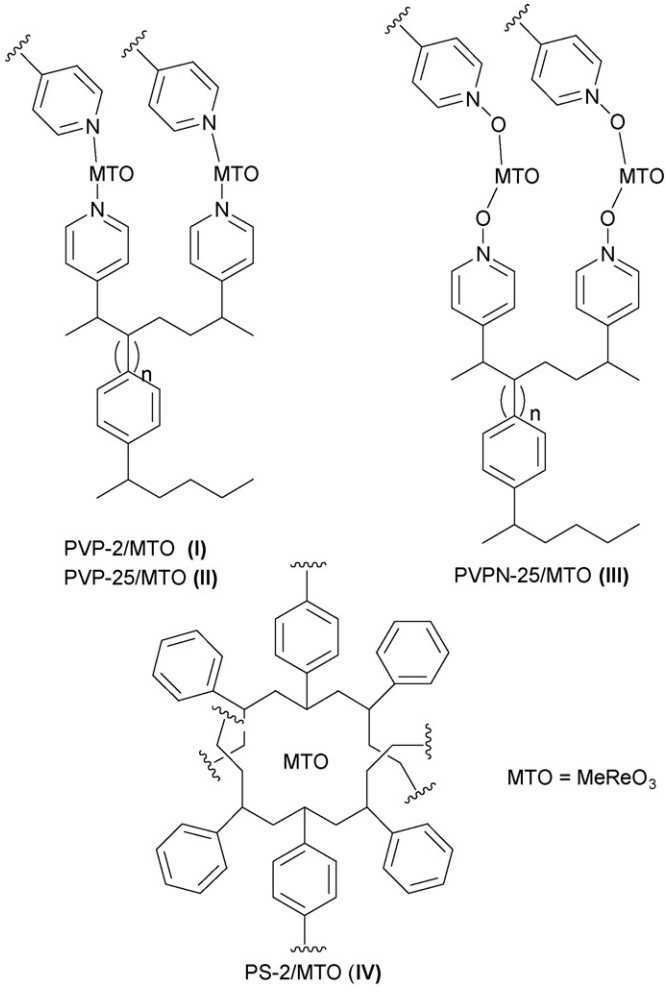


Fig. 1. Structure of MTO catalysts (I–IV).

diversified glycals to the corresponding methyl glycosides with MTO and heterogeneous MTO systems (**I–IV**, Fig. 1) in two stable ILs, [BMIM][BF_4] and [BMIM][PF_6], using H_2O_2 and UHP as primary oxidants. The facial diastereoselectivity of the oxidation ranged from satisfactory to excellent ones depending on the substrate and could be optimized for each glycal employed by ample screening of catalysts.

2. Experimental

All commercial products were of the highest grade available and were used as such. Glycals **4–8** were prepared according to literature procedures [17,18]. NMR spectra were recorded on a Varian Mercury 400 (^{1}H, 400 MHz) or a Bruker (^{1}H, 200 MHz) spectrometer. Chromatographic purifications were performed on columns packed with silica gel, 230–400 mesh, for a flash technique.

2.1. Preparation of heterogeneous MTO catalysts I–IV

Poly(4-vinylpyridine)/MTO (PVP-2/MTO **I**, PVP-25/MTO **II**, and PVPN-25/MTO **III**) and polystyrene/MTO (PS-2/MTO **IV**) catalysts were prepared as previously reported [19,20]. In

summary, MTO (77 mg, 0.3 mmol) was added to a suspension of the appropriate resin (600 mg) in ethanol (4 mL), or tetrahydrofuran in the case of polystyrene. The mixture was stirred for 1 h using a magnetic stirrer. Coacervates were found to envelop the solid core dispersed in the medium and hexane (5 mL) was added to harden the capsule walls. The solvent was removed by filtration, and the solid residue was washed with ethyl acetate and finally dried under high vacuum. In every case, MTO was completely included into the polymer. This result was confirmed by spectroscopic analysis of the residue obtained after evaporation of the organic layers. The catalysts were used without any further purification.

2.2. Oxidation of glycals in ILs: general procedures

2.2.1. Homogeneous oxidation with MTO: general procedure

A 10-mL reaction flask containing the glycal (1.0 mmol) dissolved in the appropriate IL ([BMIM][BF_4] or [BMIM][PF_6]; 2.0 mL) and MeOH (0.1 mL, 2.5 mmol) was charged sequentially with MTO (0.1 mmol) and 35% aq. H_2O_2 or UHP (3.0 equiv.) at 25 °C for 2 days. UHP and its side-product urea were found to be soluble in the IL/MeOH mixture in the range of concentration used for the oxidations. The reaction mixture was stirred at room temperature until no more starting material was detected by TLC, or the reaction did not progress further. IL was extracted with diethyl ether (3× 30 mL) and the organic volatiles were removed under vacuum to afford the crude reaction mixture as a pale yellow oil. To an ice-cooled solution of the crude mixture in dry pyridine (1 mL), acetic anhydride (0.5 mL) was added dropwise. After stirring for 24 h at room temperature, the mixture was concentrated under vacuum to afford the crude product mixture as a pale yellow oil. The crude was analyzed by ^{1}H NMR spectroscopy in order to determine the selectivity of the oxidation (see Tables 1–6), and then the products were purified by flash column chromatography.

2.2.2. Heterogeneous oxidation with catalysts **I–IV**: general procedure

A 10-mL reaction flask containing the glycal (1.0 mmol) dissolved in the appropriate IL ([BMIM][BF_4] or [BMIM][PF_6]; 2.0 mL) and MeOH (0.1 mL, 2.5 mmol) was charged sequentially with the appropriate catalysts **I–IV** (ca. 30 mg with loading factor 1; loading factor is mmol of MTO per gram of resin) and 35% aq. H_2O_2 or UHP (3.0–5.0 equiv.) at 25 °C for 2–4 days (see Tables 1–6). UHP and its side-product urea were found to be soluble in the IL/MeOH mixture in the range of concentration used for the oxidations. The reaction mixture was stirred at room temperature until no more starting material was detected by TLC, or the reaction did not progress further. At the end of the reaction, ethyl acetate (1.0–2.0 mL) was added to dilute the reaction mixture and the catalyst was recovered by filtration and washed with MeOH. IL was extracted with diethyl ether (3× 30 mL) and the organic volatiles were removed under vacuum to afford the crude reaction mixture as a pale yellow oil. To an ice-cooled solution of the crude mixture in dry pyridine (1 mL), acetic anhydride (0.5 mL) was added dropwise. After stirring for 24 h at room temperature, the mixture was concentrated under vacuum to afford the crude product mixture as a pale yellow oil. The crude was analysed by ^{1}H NMR spectroscopy in order to determine the selectivity of the oxidation (see Tables 1–6), then the products were purified by flash column chromatography. The characterization of the products obtained from the reactions with MTO are reported below. All the products have been identified by comparison with literature data (see next).

*2.2.2.1. Methyl-2,3,4,6-tetra-O-acetyl-β-*D*-galactopyranoside (**9**) [21].* ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.39 (dd, J = 3.4, 1.2 Hz, 1H, H-C(4)), 5.14 (dd, J = 10.4, 7.8 Hz, 1H, H-C(2)), 5.01 (dd, J = 10.1, 3.4 Hz, 1H, H-C(3)), 4.39 (d, J = 7.8 Hz, 1H, H-C(1)), 4.20 (dd, J = 11.2, 6.5 Hz, 1H, Ha-C(6)), 4.13 (dd, J = 11.2, 6.9 Hz, 1H, Hb-C(6)), 3.90 (td, J = 6.7, 1.2 Hz, 1H, H-C(5)), 3.51 (s, 3H, OMe), 2.15, 2.06, 2.05, 1.98 (s, 12H, Ac). Anal. Calcd for $C_{15}H_{22}O_{10}$: C, 49.72; H, 6.12. Found: C, 49.70; H, 6.12. MS EI m/z = 362 (M^+).

*2.2.2.2. Methyl-2,3,4,6-tetra-O-acetyl-α-*D*-talopyranoside (**10**) [22].* R_f = 0.40 (ethyl ether-petroleum ether 2:1). Detected signals: ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.40 (s, 3H, OMe). For complete characterization, see Ref. [22]. Anal. Calcd for $C_{15}H_{22}O_{10}$: C, 49.72; H, 6.12. Found: C, 49.71; H, 6.12. MS EI m/z = 362 (M^+).

*2.2.2.3. Methyl-2-O-acetyl-3,4-di-O-benzyl-6-deoxy-β-*L*-glucopyranoside (**11**) [23].* ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34–7.28 (m, 10H, Ph), 4.97 (dd, J = 9.4, 8.2 Hz, 1H, H-C(2)), 4.85 (d, J = 10.9 Hz, 1H, CH_2Ph), 4.80 (d, J = 11.3 Hz, 1H, CH_2Ph), 4.66 (d, J = 11.3 Hz, 1H, CH_2Ph), 4.65 (d, J = 10.9 Hz, 1H, CH_2Ph), 4.26 (d, J = 8.2 Hz, 1H, H-C(1)), 3.63 (dd, J = 9.4, 9.0 Hz, 1H, H-C(3)), 3.46 (s, 3H, OMe), 3.42 (m, 1H, H-C(5)), 3.28 (t, J = 9.0 Hz, 1H, H-C(4)), 1.97 (s, 3H, Ac), 1.34 (d, J = 6.2 Hz, 3H, Me). Anal. Calcd for $C_{23}H_{28}O_6$: C, 68.98; H, 7.05. Found: C, 68.93; H, 7.05. MS EI m/z = 400 (M^+).

*2.2.2.4. Methyl-2-O-acetyl-3,4-di-O-benzyl-α-*L*-rhamnopyranoside (**12**) [24].* ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36–7.28 (m, 10H, Ph), 5.37 (dd, J = 3.5, 1.6 Hz, 1H, H-C(2)), 4.92 (d, J = 10.9 Hz, 1H, CH_2Ph), 4.69 (d, J = 11.3 Hz, 1H, CH_2Ph), 4.62 (d, J = 1.6 Hz, 1H, H-C(1)), 4.61 (d, J = 10.9 Hz, 1H, CH_2Ph), 4.52 (d, J = 11.3 Hz, 1H, CH_2Ph), 3.92 (dd, J = 9.4, 3.5 Hz, 1H, H-C(3)), 3.73 (dq, J = 9.4, 6.2 Hz, 1H, H-C(5)), 3.43 (t, J = 9.4 Hz, 1H, H-C(4)), 3.34 (s, 3H, OMe), 2.16 (s, 3H, Ac), 1.34 (d, J = 6.2 Hz, 3H, Me). Anal. Calcd for $C_{23}H_{28}O_6$: C, 68.98; H, 7.05. Found: C, 68.95; H, 7.05. MS EI m/z = 400 (M^+).

*2.2.2.5. Methyl-2-O-acetyl-3,4-di-O-benzyl-α-*D*-arabinopyranoside (**13**) [25].* ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36–7.27 (m, 10H, Ph), 5.25 (dd, J = 7.3, 5.4 Hz, 1H, H-C(2)), 4.67–4.58 (m, 4H, CH_2Ph), 4.32 (d, J = 5.4 Hz, 1H, H-C(1)), 4.09 (dd, J = 12.2, 5.4 Hz, 1H, Ha-C(5)), 3.74 (m, 1H, H-C(4)), 3.60 (dd, J = 7.3, 3.4 Hz, 1H, H-C(3)), 3.44 (s, 3H, OMe), 3.39 (dd, J = 12.2, 2.4 Hz, 1H, Hb-C(5)), 2.05 (s, 3H, Ac). Anal.

Calcd for $C_{22}H_{26}O_6$: C, 68.38; H, 6.78. Found: C, 68.10; H, 6.35. MS EI $m/z = 386$ (M^+).

*2.2.2.6. Methyl 2,3,4-tri-O-acetyl-α-D-arabinopyranoside (**14**) [26].* ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.26 (m, 1H, H-C(4)), 5.18 (dd, $J = 9.8$, 7.0 Hz, 1H, H-C(2)), 5.04 (dd, $J = 9.4$, 3.5 Hz, 1H, H-C(3)), 4.33 (d, $J = 6.8$ Hz, 1H, H-C(1)), 4.04 (dd, $J = 13.1$, 3.1 Hz, 1H, Ha-C(5)), 3.63 (dd, $J = 13.1$, 1.6 Hz, 1H, Hb-C(5)), 3.49 (s, 3H, OMe), 2.13, 2.07, 2.02 (s, 9H, Ac). Anal. Calcd for $C_{12}H_{18}O_8$: C, 49.65; H, 6.25. Found: C, 49.62; H, 6.25. MS EI $m/z = 290$ (M^+).

*2.2.2.7. Methyl-2,3,4,6-tetra-O-acetyl-β-D-glucopyranoside (**15**) [21b,27].* ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.20 (t, $J = 9.6$ Hz, 1H, H-C(3)), 5.09 (dd, $J = 9.8$, 9.6 Hz, 1H, H-C(4)), 4.98 (dd, $J = 9.6$, 8.0 Hz, 1H, H-C(2)), 4.43 (d, $J = 8.0$ Hz, 1H, H-C(1)), 4.27 (dd, $J = 12.1$, 4.7 Hz, 1H, Ha-C(6)), 4.14 (dd, $J = 12.1$, 2.3 Hz, 1H, Hb-C(6)), 3.70 (ddd, $J = 9.8$, 4.7, 2.3 Hz, 1H, H-C(5)), 3.50 (s, 3H, OMe), 2.08, 2.04, 2.02, 2.00 (s, 12H, Ac). Anal. Calcd for $C_{15}H_{22}O_{10}$: C, 49.72; H, 6.12. Found: C, 49.70; H, 6.12. MS EI $m/z = 362$ (M^+).

*2.2.2.8. Methyl-2,3,4,6-tetra-O-acetyl-α-D-mannopyranoside (**16**) [27].* ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.33 (dd, $J = 9.8$, 3.3 Hz, 1H, H-C(3)), 5.27 (t, $J = 9.8$ Hz, 1H, H-C(4)), 5.23 (dd, $J = 3.3$, 1.7 Hz, 1H, H-C(2)), 4.71 (d, $J = 1.7$ Hz, 1H, H-C(1)), 4.28 (dd, $J = 12.1$, 5.5 Hz, 1H, Ha-C(6)), 4.10 (dd, $J = 12.1$, 2.5 Hz, 1H, Hb-C(6)), 3.96 (ddd, $J = 9.8$, 5.5, 2.5 Hz, 1H, H-C(5)), 3.40 (s, 3H, OMe), 2.15, 2.10, 2.03, 1.98 (s, 12H, Ac). Anal. Calcd for $C_{15}H_{22}O_{10}$: C, 49.72; H, 6.12. Found: C, 49.72; H, 6.12. MS EI $m/z = 362$ (M^+).

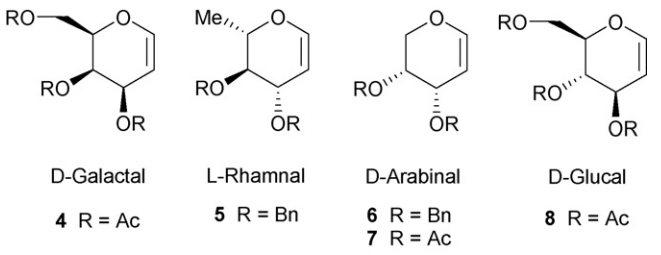


Fig. 2. Glycals used as substrates for the catalyzed MTO domino epoxidation–methanolysis in ionic liquids.

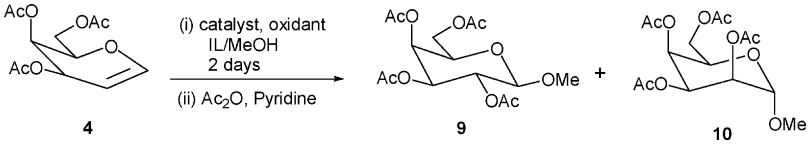
3. Results and discussion

Reactions were performed using catalytic MTO or related catalysts based on the heterogeneisation of MTO on easily available, non-toxic and inexpensive poly(4-vinylpyridine) and poly(4-vinylpyridine *N*-oxide) 2% [PVP-2/MTO (**I**)] and 25% [PVP-25/MTO (**II**) and PVPN-25/MTO (**III**), respectively] cross-linked with divinylbenzene [19,20]. Microencapsulated catalyst PS-2/MTO (**IV**) based on the physical entrapment of MTO on polystyrene 2% cross-linked with divinylbenzene was also used [28,29]. The structures of catalysts are reported in Fig. 1.

Representative glycals, properly protected as *O*-acetyl and *O*-benzyl derivatives, i.e. 3,4,6-triacetyl-D-galactal **4**, 3,4-dibenzyl-L-rhamnal **5**, 3,4-dibenzyl-D-arabinal **6**, 3,4-diacetyl-D-arabinal **7** and 3,4,6-triacetyl-D-glucal **8** (Fig. 2), have been synthesized by using literature procedures [17,18] and used as substrates in the epoxidation–methanolysis domino process.

Preliminary experiments were focused on testing the effectiveness of homogeneous MTO/H_2O_2 and MTO/UHP systems in the oxidation of D-galactal **4**. Reactions were performed in both [BMIM][BF_4] and [BMIM][PF_6] ionic liquids to investigate the effect of solvent on the efficiency of the oxidation.

Table 1
Oxidation of tri-*O*-acetyl-D-galactal **4** with MTO and heterogeneous MTO catalysts (**I**–**IV**) in ILs



Entry	Catalysts	IL	Oxidant (equiv.)	Conversion (%)	Ratio[a] **9:10**
1	MTO	[BMIM][BF_4]	35% aq. H_2O_2 (3)	91	1.2:1.0
2	MTO	[BMIM][PF_6]	35% aq. H_2O_2 (3)	99	1.1:1.0
3	MTO	[BMIM][BF_4]	UHP (3)	96	4.0:1.0
4	MTO	[BMIM][PF_6]	UHP (3)	84	2.5:1.0
5	**I**	[BMIM][BF_4]	35% aq. H_2O_2 (3)	85	1.1:1.0
6	**I**	[BMIM][BF_4]	UHP (3)	96	2.6:1.0
7	**I**	[BMIM][PF_6]	UHP (3)	>98	2.0:1.0
8	**II**	[BMIM][BF_4]	UHP (3)	>98	5.0:1.0
9	**II**	[BMIM][PF_6]	UHP (3)	97	3.0:1.0
10	**III**	[BMIM][BF_4]	UHP (3)	>98	3.5:1.0
11	**III**	[BMIM][PF_6]	UHP (3)	97	3.0:1.0
12	**IV**	[BMIM][BF_4]	UHP (5)	96	1.8:1.0
13	**IV**	[BMIM][PF_6]	UHP (5)	97	2.7:1.0

[a] Calculated by integration of the ^{1}H NMR spectra of the crude mixture.

As a general procedure, D-galactal **4** (1.0 mmol), was dissolved in the appropriate IL (2.0 mL) and MeOH (0.1 mL, 2.5 mmol) was added portionwise and reacted with a catalytic amount of MTO (0.1 mmol) and H_2O_2 or UHP (3.0 equiv.) at 25 °C for 2 days. Irrespective of the experimental conditions, the corresponding mixture of methyl glycosides **9** and **10** was obtained with high conversion and yield (entries 1–4, Table 1) after acetylation. Products **9** and **10** derived from methanolytic ring opening of the intermediate α/β epoxides, respectively. The epoxides were not isolable under the reaction conditions because of their high reactivity: they were selectively opened by MeOH via S_N2 nucleophilic displacement at the anomeric carbon. For practical reasons, the diastereoselectivity of the epoxidation was calculated by integration of the ^{1}H NMR signals of the crude product mixture after acetylation of the C-2 free OH. Indeed, configuration at C-2 is determined in the epoxidation step. Epoxidations of **4** with H_2O_2 proceeded with a low diastereoselectivity yielding β-D-galactopyranoside **9** and β-D-talopyranoside **10** in similar ratios (Table 1, entries 1 and 2). This selectivity is lower than that previously obtained with the MTO/H_2O_2 system in MeOH alone [14b], where methyl glycoside **9** was recovered in higher yield, presumably reflecting a major role of the steric hindrance of the substituent at C-4 in determining the degree of stereoselection in molecular solvents.

Quayle and his co-workers have observed essentially the same stereoselectivity ratios when replacing H_2O_2 with UHP [15]. Noteworthily, we have found instead that the oxidation of **4** with UHP in ILs afforded **9** with a much higher degree of selectivity than that obtained with H_2O_2 (Table 1, entries 3–4 vs. entries 1–2) [BMIM][BF_4] being the best solvent for the stereoselection. It has been reported that helical urea-channels, mainly produced by hydrogen-bonded networks, in which the urea matrix serves as host for the substrate, are responsible for the high conversion and selectivity in the oxidation of silanes with MTO and UHP. In this confined environment a high degree of stereoselection can be obtained [30]. Even if data on the formation of similar helical urea-channels in ionic liquids are not available, it is reasonable to suggest that the higher selectivity observed in the epoxidation of **4** in ILs with respect to MeOH alone might be due to a stabilizing effect exerted by ionic liquids on UHP aggregation.

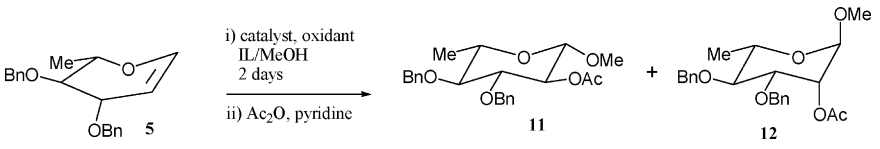
Next, our attention was turned to the performance of catalysts (**I**–**IV**) for carrying out the same reaction under heterogeneous conditions. These catalysts have already shown their efficacy in the oxidation of different substrates, offering the advantages of practical work-up of the reaction, with recovery by simple filtration and recyclability without any substantial loss of activity over successive runs [31]. As a general procedure, glycal **4** (0.2 mmol) and H_2O_2 or UHP (3.0 or 5.0 equiv.) were added to a suspension of freshly prepared catalyst (ca. 30 mg with loading factor 1; loading factor is mmol of MTO per gram of resin) in the appropriate IL (1.0 mL) and MeOH (0.1 mL), and the mixture was stirred at room temperature for 2–4 days.

The oxidation of **4** with PVP-2/MTO (**I**) and H_2O_2 in [BMIM][BF_4] afforded methyl glycosides **9** and **10** in high yields, but essentially without any diastereoselectivity (Table 1, entry 5), in agreement with the behaviour of MTO under biphasic conditions with aq. H_2O_2. On the other hand, when the reaction was conducted with UHP, β-D-galactopyranoside **9** was recovered as the main reaction product, confirming a major role of UHP in the stereoselectivity of the oxidation of glycals in ILs (Table 1, entry 6 vs. entry 5).

In agreement with data previously obtained under homogeneous conditions, a higher selectivity was obtained in [BMIM][BF_4] compared to [BMIM][PF_6] (Table 1, entry 6 vs. entry 7). On the basis of these results, successive oxidations with supported catalysts were performed with the most selective UHP as primary oxidant. Irrespective of the experimental conditions, compounds (**II**–**IV**) were also efficient catalysts for the oxidation of **4** to give **9** and **10** (Table 1, entries 8–13).

The microencapsulated catalyst (**IV**) showed a lower reactivity than (**I**–**III**), requiring a large excess of oxidant (Table 1, entries 12 and 13 vs. entries 5–11). Concerning the selectivity of the oxidation, the facial diastereoselectivity observed with the poly(4-vinyl pyridine) family in the epoxidation step affording methyl glycoside **9** as the major product increased together with the reticulation grade of the polymer (that is 25% vs. 2% with divinyl benzene, Table 1, entry 8 vs. entry 6). An acceptable level of selectivity in both ILs was also showed by pyridine *N*-oxide polymer (Table 1, entries 10 and 11), the catalytic system PVP-25/MTO being the best one. The effect of the reticulation grade of the polymer and of the oxidation state of the pyridine moi-

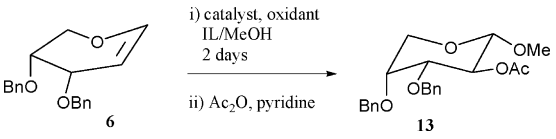
Table 2
Oxidation of dibenzyl-L-rhamnal **5** with MTO and heterogeneous MTO catalysts (**I**–**IV**)



Entry	Catalysts	IL	Oxidant (equiv.)	Conversion (%)	Ratio[a] **11:12**
1	MTO	[BMIM][BF_4]	UHP (3)	86	3.5:1.0
2	**I**	[BMIM][BF_4]	UHP (3)	81	3.3:1.0
3	**II**	[BMIM][BF_4]	UHP (3)	87	4.0:1.0
4	**III**	[BMIM][BF_4]	UHP (3)	83	3.5:1.0
5	**IV**	[BMIM][BF_4]	UHP (3)	80	1.7:1.0

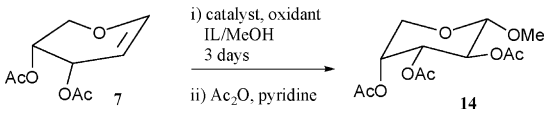
[a] Calculated by integration of the ^{1}H NMR spectra of the crude mixture.

Table 3
Oxidation of dibenzyl-D-arabinal **6** with MTO and heterogeneous MTO catalysts (**I–IV**) in ILs



Entry	Catalysts	IL	Oxidant (equiv.)	Conversion (%)
1	MTO	[BMIM][BF_4]	UHP (3)	92
2	**I**	[BMIM][BF_4]	UHP (3)	95
3	**II**	[BMIM][BF_4]	UHP (3)	90
4	**III**	[BMIM][BF_4]	UHP (3)	89
5	**IV**	[BMIM][BF_4]	UHP (5)	86

Table 4
Oxidation of 3,4-di-*O*-acetyl-D-arabinal **7** with MTO and heterogeneous MTO catalysts (**I–IV**) in ILs



Entry	Catalysts	IL	Oxidant (equiv.)	Conversion (%)
1	MTO	[BMIM][BF_4]	UHP (4)	94
2	**I**	[BMIM][BF_4]	UHP (4)	85
3	**II**	[BMIM][BF_4]	UHP (4)	89
4	**III**	[BMIM][BF_4]	UHP (4)	97
5	**IV**	[BMIM][BF_4]	UHP (5)	92

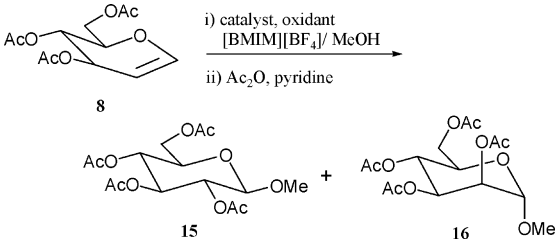
ety on the performance of catalysts (**I–III**) has been previously described (see for example Ref. [31b]. Again, a higher degree of diastereoselectivity was obtained in reactions performed in [BMIM][BF_4] than in [BMIM][PF_6] (Table 1, entries 8 and 10 vs. entries 9 and 11). The effect of the ionic liquid on the selectivity of the oxidation was reversed with the microencapsulated catalyst PS/MTO (**IV**), where [BMIM][PF_6] resulted in higher selectivity for the formation of **9** (Table 1, entry 13 vs. entry 12).

Encouraged by these results, we further investigated the oxidation of a selected group of glycals **5–8** in [BMIM][BF_4] under both homogeneous and heterogeneous conditions. The results are shown in Tables 2–5. As a general reaction pattern, glycals **5–8** were converted in high yield to the corresponding methyl glycosides, the reactivity and selectivity of the heterogeneous catalysts being comparable to those displayed by MTO. In the oxidations of glycals **6–8**, the microencapsulated catalyst (**IV**) was less active than either MTO or poly(4-vinylpyridine)-based systems (**I–III**), requiring a higher amount of oxidant (Tables 3–5, entry 5 vs. entries 1–4) and in one case, the oxidation of glycal **8**, also a higher reaction time (Table 5). Irrespective of the experimental conditions, the epoxidation of dibenzyl-L-rhamnal **5** occurred preferentially anti to the OBn group at C-3 and the intermediate β-epoxide was formed preferentially. This epoxide afforded the L-glucopyranoside derivative **11** via S_N2 ring opening by MeOH at the anomeric carbon. The minor product **12** derived from the diastereomeric β-epoxide (Table 2, entries 1–5).

Among the poly(4-vinylpyridine) catalysts, the order of selectivity **II** > **III** > **I** was followed, in accordance with an increase in diastereoselectivity in the epoxidation step with an increase in the reticulation grade (Table 2, entry 2 vs. entries 3 and 4). The microencapsulated catalyst **IV** showed a lower diastereoselectivity than poly(4-vinylpyridine)-based systems (Table 2, entry 5). The epoxidation of D-arabinal derivatives **6** and **7** occurred with complete diastereoselectivity, and methyl glycosides **13** and **14**, derived from the corresponding β-epoxides, were obtained as the only recovered product in high yields (Tables 3 and 4). The high diastereoselectivity observed in the oxidations of **6** and **7** is probably due to the hindrance offered by the pseudoaxial OR substituent at the C-4 position of the sugar scaffold.

The dibenzyl derivative **6** showed a higher reactivity than its diacetyl relative **7**, requiring shorter reaction times and lower amount of oxidant. Unlike the previously reported trend, a low selectivity in the oxidation of triacetyl D-glucal **8** was observed, and methyl glycosides **15** and **16** were generally recovered in similar yields under both homogeneous and heterogeneous con-

Table 5
Oxidation of tri-*O*-acetyl-D-Glucal **8** with MTO and heterogeneous MTO catalysts (**I–IV**) in ILs



Entry	Catalysts	Oxidant (equiv.)	Time (days)	Conversion (%)	Ratio[a] **15:16**
1	MTO	UHP (3)	3	>98	1.2:1.0
2	**I**	UHP (3)	3	>98	1.0:1.0
3	**II**	UHP (3)	3	>98	1.7:1.0
4	**III**	UHP (3)	3	>98	1.8:1.0
5	**IV**	UHP (5)	4	>98	1.1:1.0

[a] Calculated by integration of the ^{1}H NMR spectra of the crude mixture.

Table 6
Activity of MTO and catalysts **II** and **IV** in the oxidation of 3,4-dibenzyl-D-arabinal **6** with UHP in [BMIM][BF_4] to give **13**

Entry	Oxidant (equiv.)	Catalysts	Conversion (%)			
			Run 1[a]	Run 2	Run 3	Run 4
1	UHP (3)	MTO	92	0	/	/
2	UHP (3)	**II**	90	78	60	45
3	UHP (3)	**IV**	86	60	52	30

[a] After the first reaction, next runs were performed adding only fresh substrate and oxidant to the ionic liquid, and working under the same experimental conditions (2 days, rt).

ditions, with the exception of catalysts **II** and **III**, where a higher degree of selectivity was observed for methyl glycoside **15** (Table 5).

In these latter cases the diastereoselectivity was governed mainly by steric factors, with the epoxidation occurring preferentially at the face of the double bond opposite to the acetyl group at C-3. Concerning the diastereoselectivity of the oxidation, the ample screening of catalysts carried out allows us to establish that the heterogeneous catalyst PVP25/MTO (**II**) is to be considered the catalyst of choice for this transformation in ILs, having afforded good stereoselectivities in practically all cases. To evaluate the stability of heterogeneous MTO catalysts in ionic liquids, the oxidation of 3,4-dibenzyl-D-arabinal **6** with representative catalysts **II** and **IV** in [BMIM][BF_4] and UHP was repeated in successive transformations and compared with MTO alone. It is noteworthy that while the activity of MTO was not retained in [BMIM][BF_4] after the work-up of reaction mixture, recycled **II** and **IV** showed acceptable efficiency in the oxidation even after four runs, affording methyl-D-arabinopyranoside **13** as the main recovered product in high yields (see Table 6). However, a decrease in the reactivity was observed (more pronounced in the case of **IV**), probably due to a partial leaching of the catalyst in the organic solvent used for extraction of the product.

4. Conclusions

Common room temperature ionic liquids have been found to behave as appropriate media for the MTO catalyzed domino epoxidation–methanolysis of a series of glycals with UHP. Both [BMIM][BF_4] and [BMIM][PF_6] turned out to work well, with the former one being generally preferable in terms of diastereoselection. Both homogeneous MTO and heterogeneised MTO-based catalysts **I–IV** afforded the corresponding methyl glycosides efficiently, with excellent chemoselectivity and isolated yields. The facial diastereoselectivity of the reaction ranged from poor to complete ones depending on the glycal employed and was similar to that obtained previously in molecular solvents. However, in ILs the use of UHP as the terminal oxidant gave a much higher stereoselectivity than the use of aq. H_2O_2. Ample screening of catalysts allowed us to establish optimal conditions for enhancing the diastereoselectivity of this transformation, with the heterogeneous catalyst PVP25/MTO (**II**) behaving generally as the catalyst of choice.

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