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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 **8**–**15** has been achieved by oxidation with UHP in MeOH catalyzed by MTO. The products have been conveniently isolated as 2-acetoxy derivatives **16**–**23a, b** by direct acetylation of the crude mixtures. Homogeneous MTO-amine complexes **5**–**7**, heterogeneous poly(4-vinylpyridine)/MTO compounds **I**–**III**, and microencapsulated polystyrene/MTO systems **IV**–**VII** were also tested and demonstrated their effectiveness as catalysts for the oxidation step. The facial diastereoselectivity of the oxidation ranged from satisfactory to excellent depending on the substrate and could be optimized by ample screening of catalysts. Complete conversions of substrates and nearly quantitative yields of products were obtained under environmentally friendly experimental conditions and with the use of simple work-up procedures.

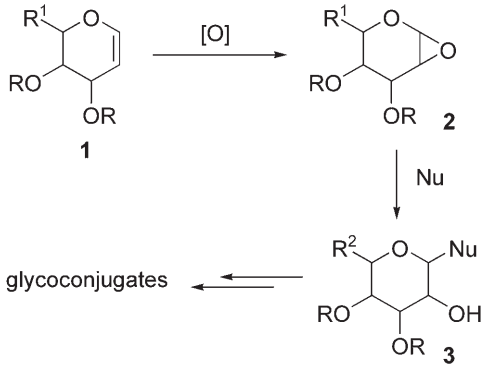
Keywords: glycals; green chemistry; hydrogen peroxide; methylrhenium trioxide; oxidation; supported catalysts

Introduction

The recent advances in glycobiology have established oligosaccharides and glycoconjugates as essential components for the transfer of information in biological systems. Therefore, the synthesis of carbohydrate-based structures has become an important field of research and one of the biggest challenges of organic synthesis. In this context, glycals have recently found a wide application as synthetic building blocks in the construction of various glycoconjugates.[1]

The most common strategy to synthesize glycoconjugates from glycals **1** involves an initial epoxidation of the double bond to give the corresponding 1,2-anhydro sugar derivatives **2**, that behave as good glycosyl donors and, in the presence of suitable nucleophiles, generate directly the desired C-2 hydroxy glycosides **3** (Scheme 1).

The epoxidation of glycals is not a trivial task, due also to the sensitive nature of **2**, particularly in acidic media. This transformation is usually performed using dimethyldioxirane (DMDO).[2] DMDO is unstable, has to be freshly prepared and poses serious safety problems connected with its potential explosiveness. Therefore, its replacement with safer and more stable oxidants, particularly for large-scale preparations, is a valuable task.



Scheme 1. Synthetic sequence for use of glycals as building blocks in the construction of glycoconjugates.

Other reagents have been proposed to perform the epoxidation, namely methyl(trifluoromethyl)dioxirane,[3] MCPBA/KF,[4] or perfluoro-*cis*-2,3-dialkyloxaziridines,[5] always as stoichiometric oxidants, but have never entered into practical use. No general catalytic oxidation procedure had been reported for this type of transformation until our recent disclosure of a domino oxidation-nucleophilic addition catalyzed by methyltrioxorhenium.[6,7]

Methyltrioxorhenium (CH_3ReO_3, MTO, **4**),[8] in combination with hydrogen peroxide (or urea hydrogen peroxide, UHP[9]), has become in recent years an important catalyst for a variety of synthetic transformations, such as oxidation of olefins,[10] alkynes,[11] aromatic derivatives,[12] sulfur compounds,[13] amines and other nitrogenated compounds,[14] phosphines,[15] Bayer–Villiger rearrangement,[16] and oxygen insertion into C–H bonds.[17]

Recently, with the aim of developing clean oxidation processes, we described the preparation of novel heterogeneous rhenium compounds of general formula $(polymer)_f/(MTO)_g$ (the f/g quotient expresses the ratio by weight of the two components) by heterogenization of MTO on poly(4-vinylpyridine) and poly(4-vinylpyridine *N*-oxide) 2% and 25% cross-linked with divinylbenzene (**I**–**III**) and polystyrene 2% cross-linked with divinylbenzene (**IV**; Figure 1),[18] applying an extension of the "mediator" concept[19] and the microencapsulation technique,[20] respectively. All the new MTO compounds were characterized by FT-IR, scanning electron microscopy (SEM), and wide-angle X-ray diffraction (WAXS).[18] To the best of our knowledge, apart from MTO supported on silica,[21] derivatized silica,[22] or niobia,[23] and a NaY zeolite/MTO supercage system,[24] no further data are available in the literature about heterogenized MTO catalysts for oxidation reactions. Polymer/MTO catalysts have already been proved as efficient and selective systems for the epoxidation of simple olefins,[18] terpenes,[25] for Baeyer–Villiger oxidation of flavonoids,[26] as well as for the oxidation of substituted phenol and anisole derivatives,[27] C–H bonds,[28] and hydroxylamines.[29]

In this paper we report full details of the domino MTO-catalyzed epoxidation-methanolysis of a series of structurally diversified glycals, which we have previously reported in preliminary form only for glucal derivatives.[6] Although MTO/H_2O_2 had been used for the epoxidation of a large variety of differently substituted alkenes,[10] its use with enol ethers was barely documented,[30] while a properly modified procedure had been reported for the oxidation of silyl enol ethers.[31] Shortly after our preliminary communication, Quayle and coworkers reported full details of a similar procedure, employing aqueous H_2O_2 instead of UHP.[32]

Lewis base adducts of MTO with nitrogen-containing ligands, such as pyridine,[33] pyridine derivatives,[34] pyrazole[35] and others are known to influence significantly

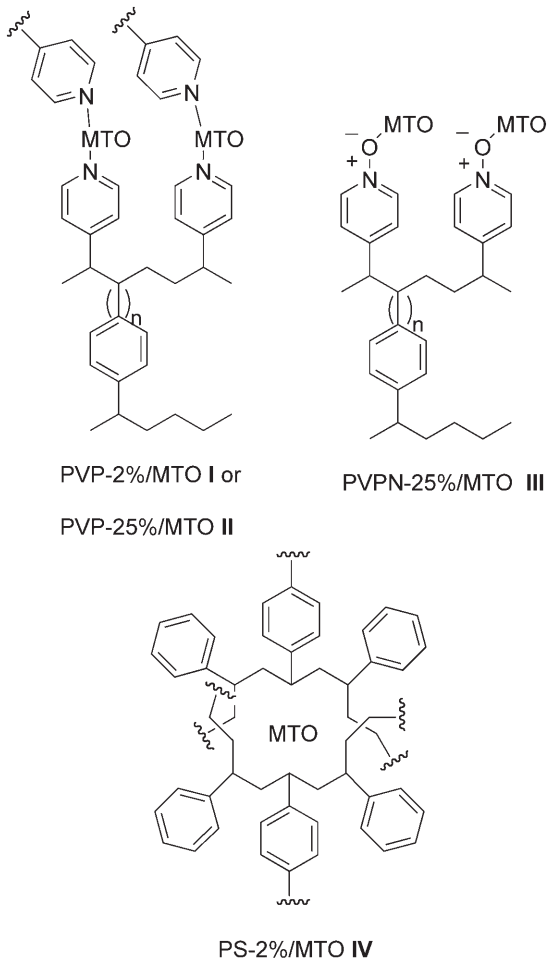


Figure 1. Structures of poly(4-vinylpyridine)/MTO and polystyrene/MTO catalysts **I**–**IV**.

the oxidation processes, for example, decreasing the formation of diols in epoxidation reactions, especially in the case of sensitive substrates, and increasing the catalytic efficiency. MTO reacts with monodentate and bidentate nitrogen ligands to give trigonal bipyramidal and distorted octahedral adducts, respectively.[36] Since a strong influence of added nitrogen ligands has been observed in a related MTO-catalyzed epoxidation-phosphorylation of glycals either in the reaction rate or the stereoselectivity,[37] a series of pre-formed amine-MTO compounds **5**–**7** has been also prepared and tested in this reaction [Figure 2, Eq. (A)]. Moreover, compounds **5**–**7** were used to prepare microencapsulated Lewis base adducts of MTO, compounds **V**–**VII** [Figure 2, Eq. (B)]. Heterogeneous poly(4-vinylpyridine)/MTO, polystyrene/MTO catalysts **I**–**IV** and polystyrene/MTO.L (L = **5**–**7**) catalysts **V**–**VII** have been employed in this oxidative addition to some of the glycal substrates, in order to compare the results with those from the reactions under homogeneous conditions.

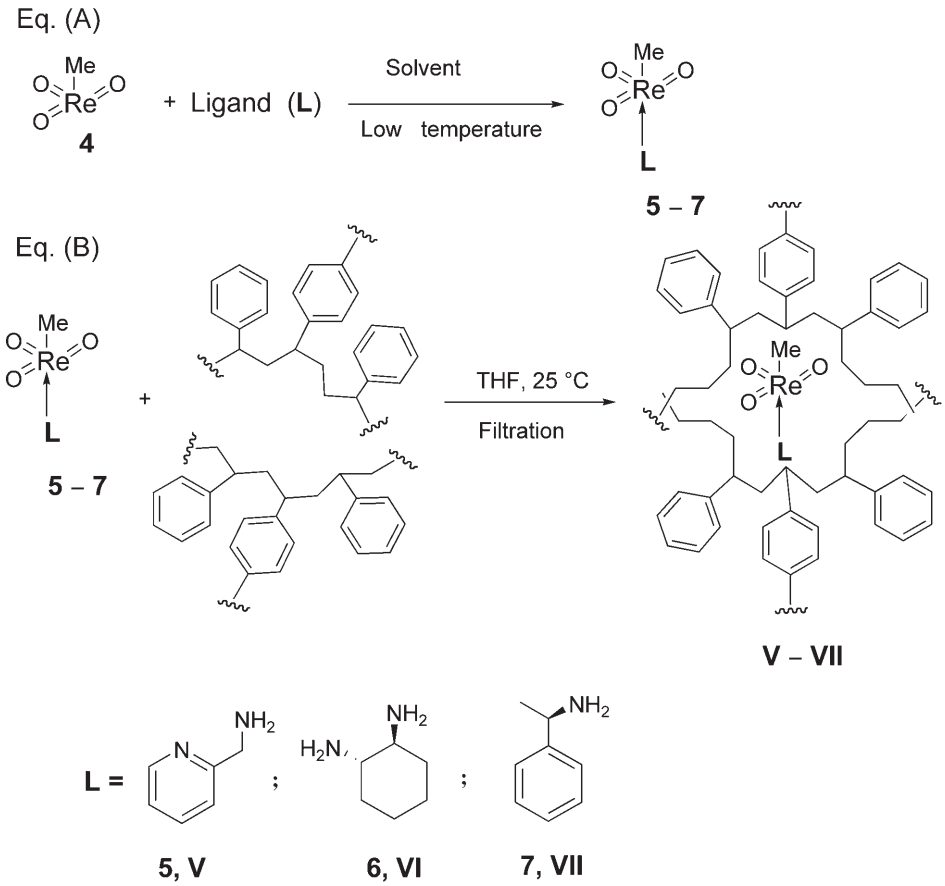


Figure 2. Lewis bases-MTO adducts **5**–**7** and microencapsulated PS 2%/MTO-Lewis base adducts **V**–**VII** used as catalysts.

Results and Discussion

Complexes **5** (L = 2-aminomethylpyridine),[38] **6** (L = *trans*-1,2-diaminocyclohexane),[38] and **7** (L = 1-phenylethylamine) of MTO, poly(4-vinylpyridine) 2% and 25% cross-linked (with divinylbenzene)/MTO (PVP-2%/MTO **I** and PVP-25%/MTO **II**, respectively), poly(4-vinylpyridine-*N*-oxide) 25% cross-linked/MTO (PVPN-25%/MTO **III**), microencapsulated polystyrene 2% cross-linked/MTO (PS-2%/MTO **IV**) and microencapsulated polystyrene complexes/**5**–**7** (PS-2%/**5**, **V**;[38] PS-2%/**6**, **VI**;[38] PS-2%/**7**, **VII**), schematically represented in Figures 1 and 2, have been synthesized according to our recently published procedures.[18,38]

Acetyl- and benzyl-protected D-glucal **8** and **9**, D-galactal **10** and **11**, L-rhamnal **12** and **13** and D-arabinal **14** and **15** (Figure 3) have been synthesized using literature procedures[39] and have been used as substrates in the epoxidation-methanolysis domino process.

Preliminary experiments were focused to test the effectiveness of the system MTO/UHP in the epoxidation of glucals.

Standard conditions, employing catalytic amount of MTO (2%) and UHP (3 equivs.) in MeOH as solvent, were applied in the oxidation of triacetyl-D-glucal (**8**) and tribenzyl-D-glucal (**9**). The MTO/UHP system was able to transform the starting glucals **8** and **9** into the corresponding β/α mixtures of methyl glycosides **16a/b**[40] and **17a/b**,[41] respectively, with complete conversion and very high yield (entries 1 and 2, Table 1). These products are derived from methanolytic ring opening of the intermediate epoxides. The epoxides were not isolable under the reaction conditions because of their high reactivity: they were selectively opened by the solvent *via* S_N2 nucleophilic displacement at the anomeric carbon. For practical reasons, it was more convenient to analyze the crude reaction mixtures after acetylation of the free hydroxy group of the resulting products. Thus,

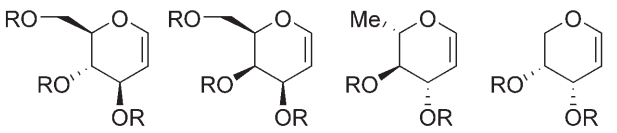
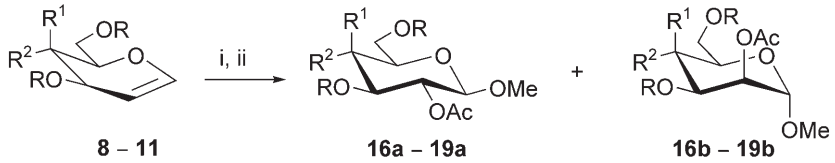


Figure 3. Glycals used as substrates for the catalyzed domino epoxidation-methanolysis.

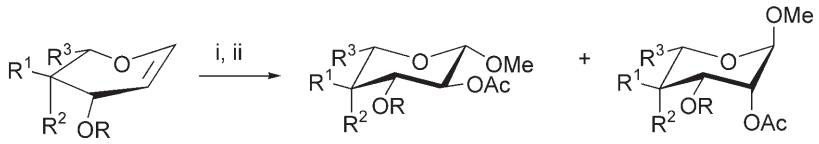
Table 1. Oxidation of triacetyl- and tribenzyl-protected D-glucal and D-galactal under homogeneous conditions.[a]



Entry	Glycal	Time [h]	Product ratio **a**:**b**[b]	Yield [%][c]
1	**8**: R = Ac, R^1 = H, R^2 = OAc	20	**16**: 1.9:1	92
2	**9**: R = Bn, R^1 = H, R^2 = OBn	15	**17**: 5.3:1	87
3	**10**: R = Ac, R^1 = OAc, R^2 = H	19	**18**: 7.5:1	97
4	**11**: R = Bn, R^1 = OBn, R^2 = H	3.5	**19**: 1.7:1	90

[a] *Reagents and conditions*: i) MTO (2%), UHP (3 equivs.), MeOH, room temperature; ii) Pyridine, Ac_2O, room temperature, 15 h.
[b] Calculated by integration of the ^{1}H NMR spectra of the crude mixtures.
[c] Isolated yields after purification by flash column chromatography (all conversions > 98%).

Table 2. Oxidation of diacetyl- and dibenzyl-protected L-rhamnal and D-arabinal under homogeneous conditions.[a]



Entry	Glycal	Time [h]	Product ratio **a**:**b**[b]	Yield [%][c]
1	**12**: R = Ac, R^1 = OAc, R^2 = H, R^3 = Me	3	**20**: 1.5:1	95
2	**13**: R = Bn, R^1 = OBn, R^2 = H, R^3 = Me	1.5	**21**: 5.1:1	90
3	**14**: R = Ac, R^1 = H, R^2 = OAc, R^3 = H	1.5	**22**: > 50:1	95
4	**15**: R = Bn, R^1 = H, R^2 = OBn, R^3 = H	1.5	**23**: > 50:1	96

[a] *Reagents and conditions*: i) MTO (2%), UHP (3 equivs.), MeOH, room temperature; ii) Pyridine, Ac_2O, room temperature, 15 h.
[b] Calculated by integration of the ^{1}H NMR spectra of the crude mixtures.
[c] Isolated yields after purification by flash column chromatography (all conversions > 98%).

the diastereoselectivity of the epoxidation was calculated by integration of the ^{1}H NMR signals of the crude product mixture after acetylation of the free C-2 OH. Indeed, configuration at C-2 is determined in the epoxidation step. Attack from the bottom gives the α-epoxide (Figure 4), which ultimately affords the *gluco* derivatives **16a** and **17a**. Conversely, attack from the top gives a β-epoxide, which leads to the *manno* derivatives **16b** and **17b**.

The diastereoselectivity is governed mainly by steric factors, with the epoxidation occurring preferentially at the face of the double bond opposite to the OR group at C-3. As expected on this basis, the epoxidation-methanolysis of tri-*O*-benzylglucal (**9**) afforded the glucose derivative **17a** with a much higher preference compared to triacetylglucal **8** (entry 2 *vs.* 1, Table 1).

Encouraged by these results, we investigated the scope of this epoxidation-ring opening sequence by subjecting glycals **10**–**15** to the same reaction conditions. The results are shown in Tables 1 and 2. In all cases complete conversions and high yields (90–97%) of the corresponding methyl glycosides were obtained.

Concerning the diastereoselectivity, epoxidation of triacetyl D-galactal (**10**) proceeded with a considerably greater selectivity with respect to the corresponding glucal derivative **8** (entry 3 *vs.* 1, Table 1). This shows that the configuration at C-4 plays a major role in determining the degree of stereoselection, with the OR group at C-4 directing the attack of oxygen preferentially to the opposite face when it is placed in an axial position. Surprisingly however, the β-D-galactopyranoside **18a**[42] was formed with a higher degree of selectivity than compound **19a**[43] (entry 3 *vs.* 4, Table 1). Tribenzyl-D-galactal (**11**) behaved anomalously, affording compound **19** with a lower selectivity, even when compared to glucal **9**. Moreover, the epoxidation reaction was much quicker than that for the acetyl derivative **10**, indicating that other factors must play a role in the oxidation of galactal **11**.

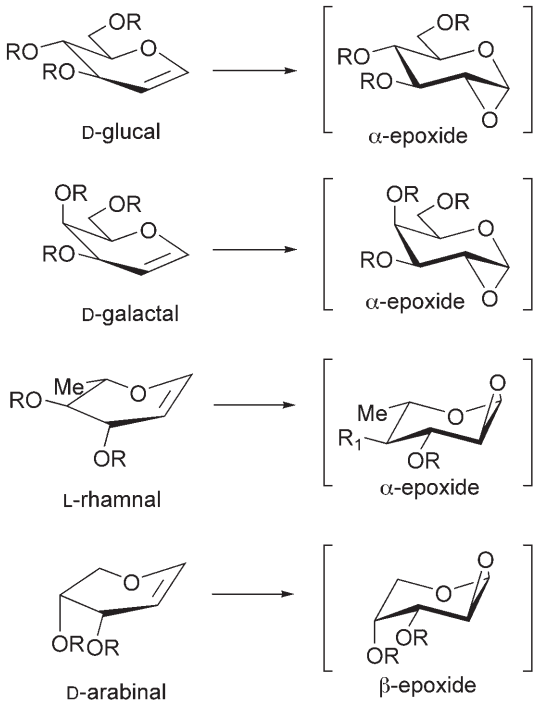


Figure 4. Favoured intermediate epoxides.

Diacetyl-L-rhamnal (**12**) and dibenzyl-L-rhamnal (**13**) led to similar diastereoselectivity results as their glucal counterparts **8** (entry 1, Table 2 *vs.* entry 1, Table 1) and **9** (entry 2, Table 2 *vs.* entry 2, Table 1), respectively. The epoxidation occurred preferentially, in both cases, *anti* to the OR group at C-3 and the intermediate α-epoxides were formed preferentially (Figure 4). These epoxides afforded the derivatives **20a**[44] and **21a**[45] *via* S_N2 ring opening with MeOH at the anomeric carbon. The minor derivatives **20b**[46] and **21b**[47] are derived from the diastereomeric β-epoxides. Finally, the MTO-catalyzed epoxidation of D-arabinal derivatives occurred with high stereoselectivity. Indeed, the methyl glycosides **22a**[48] and **23a**,[49] derived from the corresponding β-epoxide intermediates (Figure 4), were obtained as the only products from arabinals **14** and **15**, respectively (entries 3 and 4, Table 2). These latter results, presumably, were due to the hindrance offered by the pseudoaxial OR groups at C-4 of D-arabinal, thus securing a complete stereoselectivity in the epoxidation.

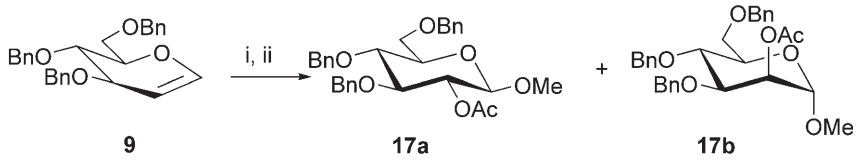
A comparison of these results with those reported by Quayle and co-workers with the use of aqueous H_2O_2,[32] where only glucal and galactal derivatives have been used as substrates, allows us to establish that our procedure with UHP in MeOH affords generally higher product yields. From the point of view of stereoselectivity of epoxidation, while the glucals **8** and **9** gave similar ratios, a considerably higher selectivity was observed by us in the reaction of galactal **10** (7.5:1) with respect to that reported in aqueous H_2O_2 (3:1). Moreover, that procedure caused in some cases (e.g., in the oxidation of **9**) an erosion of the stereospecificity in the ring opening of the intermediate epoxide, suggesting that in the aqueous medium alternative ring opening pathways, or epimerization of the final methyl glycosides at the anomeric center, might occur. On comparison with the alternative epoxidation methods of glycals based on DMDO[2] or MCPBA/KF,[4] the MTO/UHP procedure showed a lower level of stereoselectivity, except in the oxidation of D-arabinal derivatives. However, we have shown that the stereoselectivity in the MTO-catalyzed epoxidation of glycals is strongly affected by the solvent used and the presence of donor additives.[37]

Having ascertained the efficiency and generality of the domino oxidation-methanolysis of glycals under homogeneous conditions with UHP as the oxidant and MTO as the catalyst, we turned our interest to test the performance of catalysts **I**–**VII** for carrying out the same reactions under heterogeneous conditions. These catalysts have already shown their ability in oxidizing a number of different substrates, offering the advantages of heterogeneous catalysts, such as the easy and practical work-up of the reaction, with recovery by simple filtration, and recyclability without any substantial loss of activity over several successive runs.[18,29,38]

Glycals **9** and **11**–**13** were selected as representative substrates for the oxidations with heterogeneous catalysts **I**–**VII**, in order to evaluate the generality of this transformation with a considerable variety of substrates. The selection of substrates which showed lower selectivities with the homogeneous catalyst was chosen in order to study the effects of the heterogeneous catalysts on the selectivity of the reaction. As a general procedure, the glycal (0.2 mmol) to be oxidized and UHP (2.0–4.0 equivs., see Tables 3–6) were added to a suspension of freshly prepared catalysts **I**–**VII** (loading factor 1, that is 1 mmol MTO per gram of resin) in MeOH (1.0 mL), and the mixture was stirred at 25 °C. The oxidation results are summarized in Tables 3–6, entries 1–4 of each Table for catalysts **I**–**IV** and entries 6, 8, and 10 for catalysts **V**, **VI**, and **VII**, respectively. In this latter case, the corresponding reactions with homogeneous complexes **5**–**7** were also carried out as references (Table 3–6, entries 5, 7 and 9, respectively). In absence of the catalyst, less than 5% substrate conversion took place under otherwise identical conditions.

The results of the reactions summarized in Tables 3–6 show that most of the catalysts were effective in accomplishing the oxidation of benzylglycals **9**, **11**, and **13** and led to complete conversions under the appropriate experimental conditions. Conversely, the supported or microencapsulated heterogeneous catalysts **I**–**VII**, as well as the amine-MTO complexes **5**–**7**, failed to convert completely the less reactive diacetylrhamnal **12**. However, excellent conversions in the 90% range were achieved with many catalysts in 1–2 days. As expected, both the reactions with heterogenized catalysts **I**–**VII** and complexed MTO **5**–**7** were considerably slower

Table 3. Oxidation of tribenzyl-D-glucal (**9**) under heterogeneous conditions.[a]

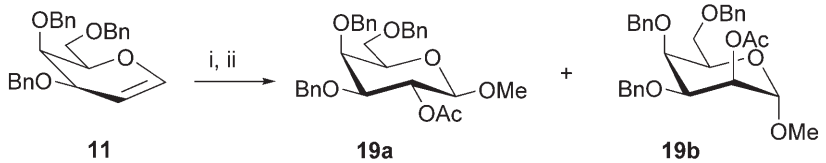


9 **17a** **17b**

Entry	Catalyst	UHP (equivs.)	Conversion [%]	Time [h]	**a:b** Ratio[b]
1	PVP-2%/MTO **I**	4.0	71	72	5.0:1
2	PVP-25%/MTO **II**	3.0	>98	42	6.0:1
3	PVPN-25%/MTO **III**	1.0	>98	18	7.3:1
4	PS-2%/MTO **IV**	2.0	>98	22	6.0:1
5	**5**	2.0	>98	22	7.7:1
6	PS/**5 V**	4.0	85	64	8.0:1
7	**6**	2.0	>98	27	5.6:1
8	PS/**6 VI**	4.0	50	27	7.5:1
9	**7**	2.0	>98	20	6.8:1
10	PS/**7 VII**	4.0	98	47	6.6:1

[a] *Reagents and conditions*: i) catalyst (corresponding to 1% MTO), UHP, MeOH, room temperature; ii) pyridine, Ac_2O, room temperature, 15 h.
[b] Calculated by integration of the ^1H NMR spectra of the crude mixtures.

Table 4. Oxidation of tribenzyl-D-galactal (**11**) under heterogeneous conditions.[a]



11 **19a** **19b**

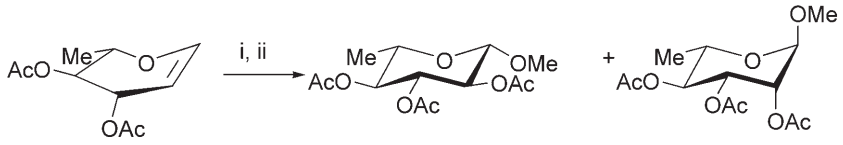
Entry	Catalyst	UHP [equivs.]	Conversion [%]	Time [h]	**a:b** Ratio[b]
1	PVP-2%/MTO **I**	4.5	>98	47	3.2:1
2	PVP-25%/MTO **II**	2.5	>98	24	3.8:1
3	PVPN-25%/MTO **III**	1.5	>98	21	1.3:1
4	PS-2%/MTO **IV**	2.5	>98	24	2.6:1
5	**5**	3.5	>98	47	2.1:1
6	PS/**5 V**	5.5	84	73	1.6:1
7	**6**	1.5	>98	18	4.9:1
8	PS/**6 VI**	3.5	86	52	5.0:1
9	**7**	5.0	94	72	2.2:1
10	PS/**7 VII**	4.5	84	73	1.5:1

[a] *Reagents and conditions*: i) catalyst (corresponding to 1% MTO), UHP, MeOH, room temperature; ii) pyridine, Ac_2O, room temperature, 15 h.
[b] Calculated by integration of the ^1H NMR spectra of the crude mixtures.

than those catalyzed by MTO itself, required much longer reaction times and, often, a higher excess of oxidant. Among the poly(4-vinylpyridine)/MTO systems **I**–**III**, a rough order of reactivity **III** > **II** > **I** was generally followed, suggesting an increase of the reaction rate with a higher value of reticulation grade of the matrix, and on passing from pyridine to pyridine *N*-oxide units. While a faster reaction with the increase of reticulation grade is in agreement with our previously reported results on the selective epoxidation of olefins (and oxidation of other substrates) with polymer-supported methylrhenium trioxide systems, the increase of reactivity with the pyridine *N*-oxide catalyst **III** is rather unusual.[18,29] Among the microencapsulated polystyrene/MTO systems **IV**–**VII**, the catalysts **V**–**VII**, containing the MTO complexes **5**–**7**, reacted more sluggishly than catalyst **IV**.

Concerning the selectivity of the reaction, all the catalysts employed displayed high levels of facial diastereoselectivity in the epoxidation step, affording ultimately

Table 5. Oxidation of diacetyl-L-rhamnal (**12**) under heterogeneous conditions.[a]

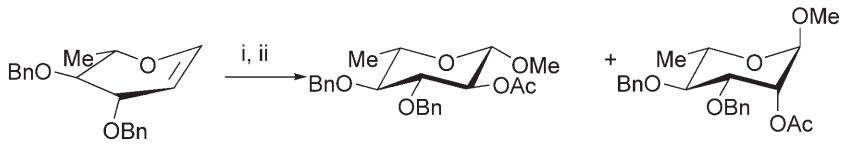


12 **20a** **20b**

Entry	Catalyst	UHP [equivs.]	Conversion [%]	Time [h]	**a:b** Ratio[b]
1	PVP-2%/MTO **I**	5.5	67	53	1.8:1
2	PVP-25%/MTO **II**	2.5	92	25	2.0:1
3	PVPN-25%/MTO **III**	2.0	94	23	1.9:1
4	PS-2%/MTO **IV**	4.0	91	54	1.8:1
5	**5**	3.0	94	30	1.8:1
6	PS/**5 V**	4.0	87	53	1.8:1
7	**6**	2.0	90	24	2.5:1
8	PS/**6 VI**	5.5	77	70	2.7:1
9	**7**	2.5	92	21	2.5:1
10	PS/**7 VII**	3.0	88	44	3.5:1

[a] *Reagents and conditions*: i) catalyst (corresponding to 1% MTO), UHP, MeOH, room temperature; ii) pyridine, Ac_2O, room temperature, 15 h.
[b] Calculated by integration of the ^1H NMR spectra of the crude mixtures.

Table 6. Oxidation of dibenzyl-L-rhamnal (**13**) under heterogeneous conditions.[a]



13 **21a** **21b**

Entry	Catalyst	UHP [equivs.]	Conversion [%]	Time [h]	**a:b** Ratio[b]
1	PVP-2%/MTO **I**	4.0	>98	46	5.2:1
2	PVP-25%/MTO **II**	2.0	>98	22	6.0:1
3	PVPN-25%/MTO **III**	1.5	>98	18	5.3:1
4	PS-2%/MTO **IV**	4.0	>98	20	5.0:1
5	**5**	2.5	>98	24	5.5:1
6	PS/**5 V**	3.5	>98	46	7.5:1
7	**6**	1.5	>98	6	6.2:1
8	PS/**6 VI**	3.0	>98	45	5.9:1
9	**7**	3.0	>98	26	6.2:1
10	PS/**7 VII**	3.0	>98	24	6.3:1

[a] *Reagents and conditions*: i) catalyst (corresponding to 1% MTO), UHP, MeOH, room temperature; ii) pyridine, Ac_2O, room temperature, 15 h.
[b] Calculated by integration of the ^1H NMR spectra of the crude mixtures.

products **a** which exceeded consistently their isomers **b**. Usually, slight variations of selectivity were observed within a family of catalysts, and also on comparing the heterogeneous reactions with those carried out under homogeneous conditions with the related catalysts. No generalized trend can be drawn, in the sense that none of the catalysts performs uniformly best with all the substrates. However, optimized conditions can be identified for each substrate, which allow us to enhance considerably the selectivity previously observed by using MTO. For example, the selectivity for the oxidation-methanolysis of glucal **9** increased from 5.3:1 with MTO to 8.0:1 with catalyst **V** (Table 3, entry 6). Analogously, the facial diastereoselectivity increased from 1.7:1 to 5.0:1 with catalyst **VI** for galactal **11** (Table 4, entry 8), from 1.5:1 to 3.5:1 with catalyst **VII** for rhamnal **12** (Table 5, entry 10), and from 5.1:1 to 7.5:1 with catalyst **V** for rhamnal **13** (Table 6, entry 6). The complexation of

MTO with amines, while decreasing the reactivity, resulted generally in higher selectivities for the oxidation reaction, either under homogeneous or heterogeneous conditions. Among the poly(4-vinylpyridine)/MTO systems **I**–**III**, slight variations of selectivity were observed, with the catalyst **II** affording generally the most selective oxidation. To resume, broad screening of the homogeneous (MTO and MTO complexes **5**–**7**) and heterogeneous (supported or microencapsulated **I**–**VII**) catalysts allowed us to define for each glycal substrate the optimal reaction conditions, either in terms of conversion or stereoselectivity.

Conclusion

Structurally diversified and differently protected glycals **8**–**15** underwent a mild and facile oxidation by means of UHP in MeOH catalyzed by MTO. The nucleophilic solvent caused the immediate ring opening of the epoxide formed *in situ* by S_N2 attack at the anomeric carbon. The methyl glycosides formed were directly acetylated to **16**–**23a, b** for a more convenient analysis of the reaction mixtures and characterization of the products. Homogeneous MTO-amine complexes **5**–**7** and heterogeneous poly(4-vinylpyridine)/MTO compounds **I**–**III**, and microencapsulated polystyrene/MTO systems **IV**–**VII** were also tested and demonstrated their effectiveness as catalysts for the oxidation step. The facial diastereoselectivity of the oxidation ranged from satisfactory to excellent depending on the substrate and could be optimized by ample screening of the catalysts. The heterogeneous catalysts **V**–**VII** based on MTO-amine complexes **5**–**7** microencapsulated in polystyrene generally afforded the best stereoselectivities. Under optimized conditions, all the substrates displayed synthetically meaningful selectivities, up to 100% for arabinal derivatives. Polymer-supported MTO compounds, which can be easily recovered by filtration from the reaction mixture and used for successive transformations, confirmed their high versatility and broaden their use as catalysts for the oxidation of organic compounds.

The process described here constitutes a novel domino reaction, which allows us to convert glycals into methyl glycosides with complete conversion and excellent yields, under environmentally friendly experimental conditions and with the use of simple work-up procedures, employing a number of different homogeneous and heterogeneous MTO-based catalysts.

Experimental Section

General Remarks

All commercial products were of the highest grade available and were used without any further purification. Glycals **8**–**15** were prepared according to literature procedures.[39] 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 flash technique; R_f values refer to the eluent mixture used for the purification.

Characterization data for products **16**–**23** can be found in the Supporting Information.

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.[18] 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 envelope 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.

Synthesis of Lewis Base Adducts of MTO, Compounds 5–7

Lewis base adducts of MTO **5**–**7** containing the nitrogen ligands 2-aminomethylpyridine, *trans*-1,2-diaminocyclohexane and 1-phenylethylamine, respectively, were prepared following a synthetic procedure previously reported in the literature.[38] As a general procedure, 1.0 mmol of the appropriate monodentate ligand **7**, or 0.5 mmol of bidentate ligand **5** or **6**, were added to 1.0 mmol of MTO in toluene (10 mL) at room temperature. A yellow precipitate was immediately formed. The reaction mixture was concentrated, cooled to $-35\,^{\circ}C$ and the precipitate isolated by filtration.

Synthesis of Microencapsulated Lewis Base Adducts of MTO, Compounds V–VII

Microencapsulated Lewis base adducts of MTO, compounds **V**–**VII**, were prepared following a modified procedure previously reported for the synthesis of polystyrene/MTO catalyst.[38] In summary, to a suspension of 600 mg of polystyrene in 4 mL of tetrahydrofuran (THF) was added 0.3 mmol of the appropriate adduct **5**–**7**, and the mixture was stirred for 1 h using a magnetic stirrer. Coacervates were found to envelope the solid core dispersed in the medium and 5.0 mL of hexane were 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 each case, MTO complexes had completely become bound to 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.

Oxidation of Glycals. General Procedures

(a) Homogeneous oxidation with MTO; General procedure: A 10-mL reaction flask was charged sequentially with MTO (0.01 mmol), MeOH (1 mL), and UHP (1.5 mmol). The stirred solution became yellow due to the formation of peroxy species and after 5 minutes the glycal (0.5 mmol) was added. The reaction mixture was stirred at room temperature until no more starting material was detected by TLC. After removed the solvent under reduced pressure the crude reaction mixture was added with CH_2Cl_2 and the undissolved urea filtered off 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 15 hours 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, then the products were purified by flash column chromatography. The product ratios and NMR characterization of the products obtained from the reactions with MTO are reported below and in the Supporting Information. All the products have been identified by comparison with literature data.

*(b) Homogeneous oxidation with MTO complexes **5**–**7**; General procedure:* To the suspension of the appropriate catalysts **5**–**7** (0.01 mmol) and UHP (2.5 mmol) in MeOH (1.0 mL) was added the substrate (1.0 mmol) to be oxidized. The reaction mixture was stirred at room temperature until no more starting material was detected by TLC, or the reaction did not progress further. After removal of the solvent under reduced pressure, the crude reaction mixture was added with CH_2Cl_2 and the undissolved urea filtered off to afford the crude reaction mixture as a pale yellow oil.

To an ice-cooled solution of the crude product in dry pyridine (1 mL), acetic anhydride (0.5 mL) was added dropwise. After stirring 15 hours at room temperature the mixture was concentrated under vacuum to afford the crude product mixture as a pale yellow oil. The crude material was analyzed by ^{1}H NMR spectroscopy in order to determine the selectivity of the oxidation, then the products were purified by flash column chromatography.

*(c) Heterogeneous oxidation with catalysts **I**–**VII**; General procedure:* To the suspension of the appropriate catalysts **I**–**VII** (corresponding to 1.0% in weight of MTO, loading factor 1.0) and UHP (4.0 mmol) in MeOH (1.0 mL) was added the substrate (1.0 mmol) to be oxidized. 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 the catalyst was recovered by filtration and washed with MeOH. After removal of the solvent under reduced pressure, the crude reaction mixture was added with CH_2Cl_2 and the undissolved urea filtered off to afford the crude as a pale yellow oil.

To an ice-cooled solution of the crude product in dry pyridine (1 mL), acetic anhydride (0.5 mL) was added dropwise. After stirring 15 hours at room temperature the mixture was concentrated under vacuum to afford the crude product as a pale yellow oil. The crude material was analyzed by ^{1}H NMR spectroscopy in order to determine the selectivity of the oxidation, then the products were purified by flash column chromatography.

Epoxidation-Methanolysis of 3,4,6-Triacetyl-D-glucal (8): Reaction time: 20 h. Product ratio: **16a/16b** = 1.9:1. Purification by flash column chromatography on silica gel (petroleum ether-AcOEt, 7:5) afforded a mixture of compounds **16a** and **16b** (R_f = 0.50) as a colorless oil, 92% overall yield.

Epoxidation-Methanolysis of 3,4,6-Tribenzyl-D-glucal (9): Reaction time: 15 h. Product ratio: **17a/17b** = 5.3:1. Purification by flash column chromatography on silica gel (petroleum ether-AcOEt, 4:1) afforded pure **17a** (R_f = 0.32) and the product **17b** (R_f = 0.36), contaminated with **17a**, as colorless oils, 87% overall yield.

Epoxidation-Methanolysis of 3,4,6-Triacetyl-D-galactal (10): Reaction time: 19 h. Product ratio: **18a/18b** = 7.5:1. Purification by flash column chromatography on silica gel (ethyl ether-petroleum ether, 2:1) afforded pure **18a** (R_f = 0.35) and the product **18b** (R_f = 0.40), contaminated with **18a**, as colorless oils, 97% overall yield.

Epoxidation-Methanolysis of 3,4,6-Tribenzyl-D-galactal (11): Reaction time: 3.5 h. Product ratio: **19a/19b** = 1.7:1. Purification by flash column chromatography on silica gel (petroleum ether-ethyl ether, 2:1) afforded pure **19a** (R_f = 0.16) and the product **19b** (R_f = 0.23), contaminated with **19a**, as colorless oils, 90% overall yield.

Epoxidation-Methanolysis of 3,4-Diacetyl-L-rhamnal (12): Reaction time: 3 h. Product ratio: **20a/20b** = 1.5:1. Purification by flash column chromatography on silica gel (petroleum ether-AcOEt, 7:2) afforded pure products **20a** (R_f = 0.21) and **20b** (R_f = 0.26) as colorless oils, 95% overall yield.

Epoxidation-Methanolysis of 3,4-Dibenzyl-L-rhamnal (13): Reaction time: 1.5 h. Product ratio: **21a/21b** = 5.1:1. Purification by flash column chromatography on silica gel (petroleum ether-AcOEt, 5:1) afforded mixtures of products **21a** (R_f = 0.36) and **21b** (R_f = 0.41), each one contaminated with the isomer, as colorless oils, 90% overall yield.

Epoxidation-Methanolysis of 3,4-Diacetyl-D-arabinal (14): Reaction time: 1.5 h. Compound **22a** was obtained with a selectivity > 50:1. Purification by flash column chromatography on silica gel (petroleum ether-AcOEt, 2:1) afforded pure **22a** (R_f = 0.42) as a colorless oil, 95% yield.

Epoxidation-Methanolysis of 3,4-Dibenzyl-D-arabinal (15): Reaction time: 1.5 h. Compound **23a** was obtained with a selectivity > 50:1. Purification by flash column chromatography on silica gel (petroleum ether-AcOEt, 3:1) afforded pure **23a** (R_f = 0.34) as a colorless oil, 96% yield.

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