Hydroformylation of Glucal Derivatives with Rhodium Catalysts. Crucial Influence of the Auxiliary Ligand Tris(*ortho-tert*-butylphenyl) Phosphite

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Rhodium catalyst mediated hydroformylation of glucal derivatives has been achieved for the first time in good yields and selectivities using $[Rh_2\{\mu\text{-}S(CH_2)_3NMe_2\}_2(cycloocta\text{-}1,5\text{-}diene)_2]$ and tris(*ortho-tert*-butylphenyl) phosphite as auxiliary ligand giving, principally, 2-formyl derivatives.

Glycals have been extensively used as chiral synthons in the synthesis of natural products[1] as well as in the synthesis of branched-chain sugars.[2] Thus, the hydroformylation of glycals appears to be a direct method of preparing branched chain carbohydrates. The hydroformylation of tri-*O*-acetyl-D-glucal **2a** using $[Co_2(CO)_8]$ as catalyst giving 1-hydroxymethyl-2-deoxy carbohydrates **3a** and **4a** as an α/β mixture has been studied.[3] In this case, when the gas consumption was strictly controlled, aldehydes **5a** and **6a** were preferentially obtained,[4] but always as an α/β mixture (Scheme 1). Surprisingly, the use of a rhodium catalyst for the same purpose failed.[3]

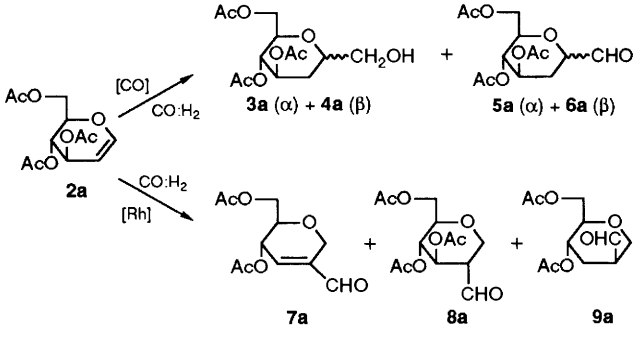
The high efficiency of rhodium catalysts in the hydroformylation of functionalized alkenes is well known.[5] However, cyclic and internal alkenes are much less reactive than terminal alkenes in rhodium catalysed hydroformylation reactions.[6,7] Recently, the use of bulky phosphites has allowed the hydroformylation of hindered alkenes.[7,8] In this paper we show that the use of $[Rh_2\{\mu\text{-}S(CH_2)_3NMe_2\}_2(cod)_2]$[9] **1** (cod = cycloocta-1,5-diene) as precursor catalyst and tris(*ortho-tert*-butylphenyl) phosphite[7] $[P(O\text{-}o\text{-}Bu^tC_6H_4)_3]$ as auxiliary ligand allows the hydroformylation of glucal derivatives in good yields and selectivities, giving principally the 2-α-formyl derivative.

First, we evaluated different rhodium catalytic systems for the hydroformylation of tri-*O*-acetyl-D-glucal **2a**. The reaction conditions and the results are reported in Table 1. When $[RhH(CO)(PPh_3)_3]$ (entries 1 and 2) or **1** + 10PPh_3 (entry 3) were used, poor conversions were obtained. Compound **7a** was principally obtained from the introduction of a formyl group at position 2 of the sugar ring and the elimination of acetic acid (Scheme 1). Only when the system **1** + $P(O\text{-}o\text{-}Bu^tC_6H_4)_3$ was used were good conversions achieved (entries 4–6, Table 1), In this case, compound **7a** was also obtained, together with compound **8a**.† Appreciable amounts of compound **9a** (Scheme 1) and of the hydrogenation compound were also detected in the reaction mixture. The CO : H_2 ratio or the addition of NEt_3 to the reaction mixture does not modify the results. The three compounds **7a**, **8a** and **9a** come from the introduction of the formyl group at the C-2 of the substrate, the alkenic carbon with highest electron density.[10] This regioselectivity is opposite to that obtained when a cobalt catalyst was used.[3]

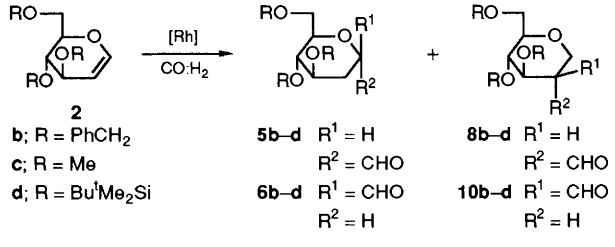
On the other hand, it seems that the allylic acetate group determines the stereoselectivity of the reaction leading to compound **8a**, and the obtention of the elimination product **7a**. Furthermore, the coordination of the allylic acetate to the metal could explain the formation of **9a**. These results prompted us to extend the investigation to other non-participative protecting groups.

When tri-*O*-benzyl-D-glucal **2b** was hydroformylated using the system **1** + 10 $P(O\text{-}o\text{-}Bu^tC_6H_4)_3$ as catalyst in the conditions shown in Table 2, only aldehydes were obtained. The ^1H NMR spectrum shows the presence of the three protecting groups in all cases. Compounds **5b**, **8b** and **10b**‡ were identified (Scheme 2); **8b**, the 2-formyl equatorial derivative was obtained in highest yield.

Starting from tri-*O*-methyl-D-glucal **2c**, high conversions were obtained and three aldehydes detected. The only aldehyde identified, **8c**,§ is also obtained in highest yield in



Scheme 1 Hydroformylation of tri-*O*-acetyl-D-glucal **2a** with Co and Rh catalysts



Scheme 2 Hydroformylation of compounds **2b**, **2c** and **2d**, with the catalytic system $[Rh_2\{\mu\text{-}S(CH_2)_3NMe_2\}_2(cod)_2]$ **1** + $P(O\text{-}o\text{-}Bu^tC_6H_4)_3$ (denoted as [Rh])

† *Spectroscopic data* for **7a** ^1H NMR: δ 9.50 (s, 1H, CHO), 6.72 (td, *J* 3, 3, 1.6 Hz, 1H, H-3), 5.50 (dd, *J* 9, 8 Hz, 1H, H-4), 4.58 (dd, *J* 19, 3 Hz, 1H, H-1), 4.35 (dd, *J* 19, 3 Hz, 1H, H-1'), 4.25–4.15 (m, 2H, H-6e, H-6a), 3.70 (td, *J* 8, 8, 4 Hz, 1H, H-5). ^{13}C NMR: δ 190.6, 170.6, 169.9, 142.5, 141.6, 73.9, 65.2, 63.4, 62.8, 20.7, 20.6.

Spectroscopic data for **8a** (as 2,4-dinitrophenylhydrazone) ^1H NMR: δ 11.12 (s, 1H, NH), 9.10, 8.36, 8.20 (Ar), 7.57 (d, *J* 3.3 Hz, 1H, CH=N), 5.12 (td, *J* 10, 10, 4 Hz, 1H, H-4), 4.0–4.2 (m, 3H, H-1e, H-6e, H-6a), 3.79 (dd, *J* 12, 3.3 Hz, 1H, H-1a), 3.59 (dt, *J* 10, 10, 5.3 Hz, 1H, H-5), 2.91 (td, *J* 5.4, 3.3, 3.3 Hz, 1H, H-2), 2.72 (broad d, *J* 11 Hz, 1H H-3e), 1.16 (td, *J* 11, 11, 5.4 Hz)

‡ *Spectroscopic data* for **8b** (as 2,4-dinitrophenylhydrazone) ^{1}NMR: δ 10.60 (s, 1H, NH), 9.10, 8.25, 7.75, 7.50–7.10 (15H, Ph), 6.85 (d, *J* 5.3 Hz, 1H, CH=N), 4.50–4.90 (6H, CH_2Ph), 4.08 (dd, *J* 11, 5.3 Hz, 1H, H-1e), 3.72 (m, 2H, H-6a, H-6e), 3.66 (t, *J* 10.3 Hz, 1H, H-3), 3.45 (m, 2H, H-4, H-5), 3.44 (dd, *J* 11, 10.5 Hz, 1H, H-1a), 2.85 (m, 1H, H-2); ^{13}C NMR: δ 148.7, 144.7, 138.1, 138.0, 137.9, 137.8, 130.1, 129.0, 128.7, 127.7, 123.5, 116.5, 82.1, 79.7, 79.3, 75.1, 74.8, 75.5, 68.7, 67.7, 45.9.

Spectroscopic data for **10b**: ^1H NMR: δ 9.70 (s, 1H, CHO), 7.60–7.10 (15H, Ph), 4.8–4.6 (m, 8H, CH_2Ph, H-3, H-4), 4.0–3.6 (m, 3H, H-5, H-6e, H-6a), 3.83 (dd, *J* 12.5, 2.5 Hz, 1H, H-1), 2.42 (td, *J* 12.5, 5, 2.5 Hz, 1H, H-2e), 1.54 (dt, *J* 12.5, 12.5, 11.5 Hz, 1H, H-2a); ^{13}C NMR: δ 201.2, 137.0–139.0, 128.7–127.0, 80.2, 79.4, 79.1, 75.1, 73.5, 73.4, 71.4, 69.2, 31.4.

§ *Spectroscopic data* for **8c** ^1H NMR: δ 9.75 (d, *J* 1 Hz, 1H, CHO), 4.00 (dd, *J* 14, 10 Hz, 1H, H-1a), 3.60–3.10 (m, 6H), 3.55 (s, 3H, Me), 3.50 (s, 3H, Me), 3.45 (s, 3H, Me), 2.80 (td, *J* 10, 10.7 Hz, 1H, H-2). ^{13}C NMR: δ 202.0, 83.0, 81.0, 78.5, 77.5, 72.0, 65.0, 61.0, 58.5, 55.8.

Table 1 Hydroformylation of tri-*O*-acetyl-D-glucal **2a**[a]

Entry	Catalyst	Pressure/ 10^5 Pa	Conversion (%)[b]	**7a**[c]	**8a**[c]	**9a**[c]
1	$RhH(CO)(PPh_3)_3$[d]	9	6	60	—	—
2	$RhH(CO)(PPh_3)_3$[e]	115	10	70	—	—
3	**1** + 10 PPh_3	75	—	—	—	—
4	**1** + $P(O\text{-}o\text{-}Bu^tC_6H_4)_3$	35	36	19	23	31
5	**1** + $P(O\text{-}o\text{-}Bu^tC_6H_4)_3$	75	82	32	17	36
6	**1** + $P(O\text{-}o\text{-}Bu^tC_6H_4)_3$	75[f]	71	45	8	23

[a] [Substrate]/[Rh] = 100, [phosphite]/[Rh] = 5, 1,2-dichloroethane, CO/H_2 = 1, 120 °C, 24 h. [b] Tri-*O*-acetyl-D-glucal converted. Determined by GC and ^1H NMR. [c] Values expressed as the percentage of total products formed. [d] 90 °C. [e] 100 °C. [f] Toluene.

Table 2 Hydroformylation of compounds **2b**, **2c** and **2d**, using **1** + 10 $P(O\text{-}o\text{-}Bu^tC_6H_4)_3$ as catalyst[a]

Entry	Substrate	Conversion (%)[b]	**5**[c]	**6**[c]	**8**[c]	**10**[c]
1	**2b**	88	12	—	71	5
2	**2c**	94	—	—	68	—
3	**2d**	35	40	23	37	—

[a] [Substrate]/[Rh] = 100, [phosphite]/[Rh] = 5, 1,2-dichloroethane, 75 × 10^5 Pa, 120 °C, CO/H_2 = 1, 24 h. [b] Determined by GC and ^1H NMR. [c] Values expressed as the percentage of total products formed.

this case. When bulkier protective groups were used, such as in tri-*O*-*tert*-butyldimethylsilyl-D-glucal **2d**, the conversion fell strongly and three aldehydes were detected in the reaction mixture. Significantly, in this case the introduction of a formyl group at position 1 of the sugar was preferential (compounds **5d** and **6d**) but the stereoselectivity was very low. However, when the formyl group was introduced at position 2 of the sugar, only compound **8d** was obtained.

In conclusion, the use of the catalytic precursor **1** and $P(O\text{-}o\text{-}Bu^tC_6H_4)_3$ as auxiliary ligand has allowed the hydroformylation of glucal derivatives for the first time using rhodium catalysts. Compounds **8b** and **8c** could be prepared in an overall yield of 62 and 64%, respectively. The observed regioselectivity seems related to the polarization of the alkene,[10] and the steric hindrance of the protective group at position 3 of the sugar ring, resulting in the preferential introduction of an equatorial formyl group at position 2 of the sugar. The different regioselectivity observed when cobalt catalysts were used can be explained by taking into account the different size and polarizability of the rhodium with regard to cobalt.[10] The stereoselectivity of the reaction is apparently determined by the stereochemistry of the allylic substituent (position 3 of the carbohydrate ring) when the formyl group enters at carbon 2. However, when the formyl group is introduced at carbon 1, stereoselectivity is almost absent, as has been already observed for cobalt catalyst.[3]

This methodology offers easy access to branched carbohydrates. Further work in this field is in progress.

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