Highly Stereoselective Hydroformylation of Olefins Possessing Chiral Sugar Templates

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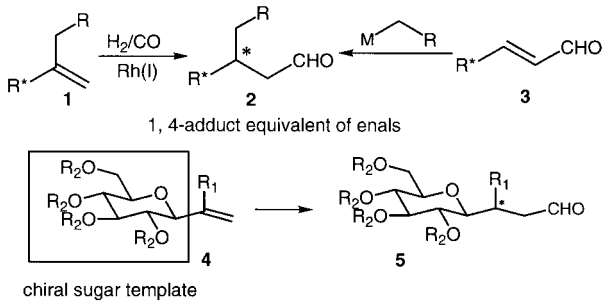
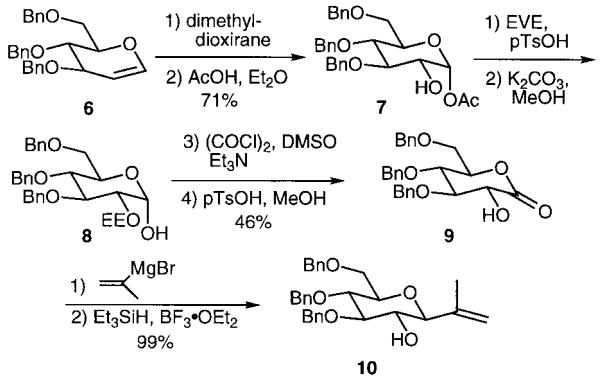
Abstract: Hydroformylation of 1,1-disubstituted olefins possessing chiral sugar templates gave β-substituted aldehydes in good to excellent yields with up to 99% diastereoselectivity.

The stereoselective introduction of a formyl group to olefins is an important goal in synthetic organic chemistry, as the formyl group can be used for further functionalization of the molecule. Many methods have been developed for the stereoselective synthesis of β-substituted aldehydes **2** as chiral building blocks for several important classes of natural products.[1] Many of these syntheses involve 1,4-addition of nucleophiles to α,β-unsaturated aldehydes **3** or their equivalents.[2] In devising a new catalytic process for the stereoselective and facile synthesis of β-substituted aldehydes **2**, hydroformylation[3] of 1,1-disubstituted olefins **1** should provide an effective alternative approach.[4] It has been reported that the diastereoselective hydroformylation of 1,1-disubstituted allylic alcohols gave *threo*- and *erythro*-hydroxyalkanals in a ratio of up to 82 : 18.[5] However, it is generally difficult to achieve high stereoselectivity in the hydroformylation without introducing a catalyst directing group into the substrates.[6] It was conceived that 1,1-disubstituted olefins **4** possessing a sugar moiety might be very useful substrates for the stereoselective hydroformylation, as the stereochemical outcome of the hydroformylation would be controlled by the bulky sugar substituent adjacent to the olefin and sugar derivatives have been extensively used as chiral synthons in the synthesis of natural products.[7] Herein, we report that the hydroformylation of 1,1-disubstituted olefins **4** possessing a chiral sugar template is an effective method for the highly diastereoselective, catalytic synthesis of β-substituted aldehydes **5**.



Scheme 1

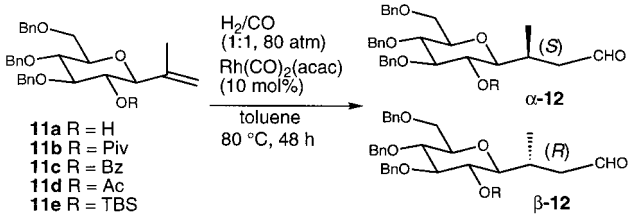
At first, we examined the hydroformylation of 1,1-disubstituted olefins possessing a methyl group and a glucose moiety with various protective groups at the C-2 position in glucose. The substrates for the hydroformylation were prepared as shown in Scheme 2. Epoxidation of D-(+)-glucal tribenzylether **6**, which was obtained from commercially available D-(+)-glucal triacetate in two steps, with dimethyldioxirane in acetone at 0 °C,[8] followed by acetolysis of the resulting epoxide gave the acetate **7** in 71% yield. Protection of the C-2 alcohol with ethyl vinyl ether and deacetylation of the resulting product with K_2CO_3 in MeOH afforded the lactol **8**. Swern oxidation of **8**, followed by removal of the ethoxy ethyl group with p-TsOH gave the lactone **9** in 46% overall yield from **7**. Addition of isopropenylmagnesium bromide to **9** and subsequent reduction of the ketol with triethylsilane[9] in the presence of $BF_3{\cdot}Et_2O$ gave the C-glycosylated olefin **10** in 99% yield. Protection of the C-2 alcohol afforded the substrates **11b** - **e** in 30%, 48%, 52% and 50%, respectively.



Scheme 2

The resulting substrates **11a** - **e** were subjected to hydroformylation using 10 mol% of $Rh(CO)_2(acac)$ as the catalyst. A toluene solutions of the Rh catalyst and substrates **11a** - **e** were heated in an autoclave under 80 atm of syn gas (H_2 / CO = 1) at 80 °C for 48 h. The hydroformylation proceeded smoothly to give the corresponding aldehydes **12** in excellent yields and with high (*S*)-selectivities of up to 99%.[10] The results are shown in Table 1. It was found that the protecting group at the C-2 hydroxyl group exerted an influence on the diastereoselectivities of the hydroformylation. When **11a** without protective group was employed, α-12a and β-12a were formed in an 83 : 17 ratio. Protection of the alcohol with pivalate **11b**, benzoate **11c**, and acetate **11d** improved the diastereomeric ratios to 90 : 10, 97 : 3 and 98 : 2, respectively, favoring the (*S*) configuration. The hydroformylation of the TBS ether **11e**, in which only α-12e[11] was obtained, is extremely noteworthy.

Table 1



Substrates	Yield (%)	α-12 : β-12
11a	81	83 : 17
11b	91	90 : 10
11c	99	97 : 3
11d	99	98 : 2
11e	99	> 99 : < 1

The relative stereochemistries were assigned for the products **12** by transformation to the lactone **13**[11] and subsequent NOE experiments (Figure 1). The observed independence of the diastereoselectivity on the nature of protective group at C-2 seemed to indicate that a conformational preference inherent to the 1,1-disubstituted olefin might be the origin of the observed stereoselectivity. A plausible explanation for the hydroformylation of **11** is shown in Figure 1. The compounds **11** have two preferred conformations **11A** and **11B** where there is overlap of σ^*_{CO} orbital with the alkene π-orbitals. The compounds **11** prefer conformation **11A** over than **11B** in order to relieve the steric repulsions between the vinyl methyl group and the anomeric hydrogen. If we

assume coordination of the rhodium catalyst from a less hindered *Re*-face of the olefin, hydroformylation would provide the α-12, which was found experimentally.

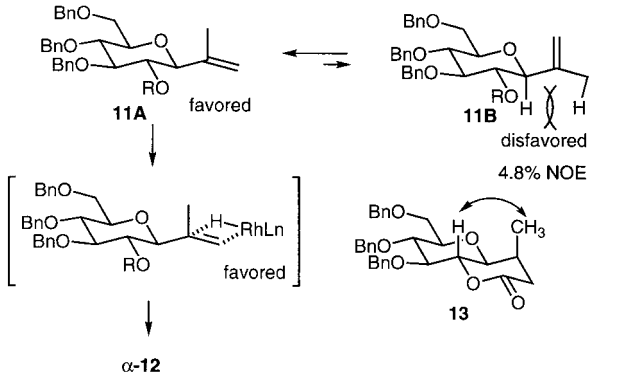
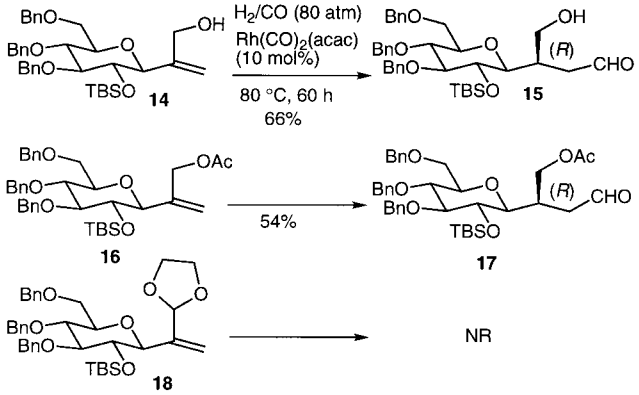


Figure 1

To test the versatility of the olefins bearing a sugar moiety as substrates for hydroformylation, we examined the hydroformylation of 1,1-disubstituted olefins possessing hydroxy methyl **14**, acetoxy methyl **16** and acetal **17** moieties. Hydroformylation of **14** under 80 atm of syn gas at 80 °C for 60 h gave the aldehyde **15**, in which the (*R*) isomer was obtained exclusively in 66% yield. While the acetoxy methyl derivative **16** was less reactive than **14**, only the (*R*) isomer **17** was obtained in 54% yield. When the acetal **18** was subjected to hydroformylation, starting material was recovered quantitatively. It seems that the reaction did not proceed due to steric hindrance of the acetal group.



Scheme 3

In conclusion, we have demonstrated that 1,1-disubstituted olefins bearing a sugar moiety undergo hydroformylation in good to excellent yields and with high stereoselectivities to provide the corresponding aldehydes.

References and Notes

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10. The ratio was determined by HPLC analysis after conversion of the aldehydes **12** to the corresponding diols.
11. Spectral data for α-**12e** ^{1}H NMR (270 MHz, $CDCl_3$) δ -0.01 (s, 3H), 0.04 (s, 3H), 0.88 (s, 9H), 1.15 (d, *J* = 6.60 Hz, 3H), 2.18-2.53 (m, 2H), 3.13 (d, *J* = 7.72 Hz, 1H), 3.42-3.57 (m, 7H), 4.54-4.69 (m, 4H), 4.79 (d, *J* = 11.55 Hz, 1H), 5.05 (d, *J* = 11.88Hz, 1H), 7.06-7.34 (m, 15H), 9.81 (brs); IR (neat) 2922, 1726, 1494, 1452, 1360, 1254, 1066, 861, 836, 778, 734, 698 cm^{-1}; for **13** ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.12 (d, *J* = 6.60 Hz, 3H), 2.41-2.52 (2H, m), 2.72-2.82 (m, 1H), 3.51-3.81 (m, 6H), 4.24 (dd, *J* = 9.24, 9.90 Hz, 1H), 4.48-5.05 (m, 6H), 7.14-7.44 (m, 15H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 14.5, 28.1, 36.8, 69.0, 73.5, 74.2, 75.4, 77.3, 77.4, 79.6, 84.3, 127.7-128.4 (aromatic), 138.0, 138.2, 170.0; IR (neat) 2920, 1741, 1452, 1204, 1095, 789, 753, 699 cm^{-1}.