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Journal of Organometallic Chemistry 691 (2006) 4054–4057
Journal of Organometallic Chemistry
www.elsevier.com/locate/jorganchem

Substrate-directed asymmetric induction in the rhodium catalyzed hydroformylation of C-allyl-sugars: The influence of the glycoside-moiety on the selectivity of the reaction

Raffaello Lazzaroni [a,*], Silvia Rocchiccioli [a], Anna Iuliano [a], Laura Cipolla [b]

[a] *Dipartimento di Chimica e Chimica Industriale, Università di Pisa, Via Risorgimento 35, 56126 Pisa, Italy*
[b] *Dipartimento di biotecnologie e Bioscienze, Università di Milano-Bicocca, P.za Della Scienza 2, 20126 Milano, Italy*

Received 9 May 2006; received in revised form 6 June 2006; accepted 6 June 2006
Available online 15 June 2006

Abstract

α- and β-C-allylgalactopyranosides **1c** and **1d**, α-C-allylazaglucopyranoside **1e** and α-C-allylfruttofuranoside **1f** were hydroformylated at low temperatures affording a mixture of linear and branched aldehydes in regioisomeric and diastereoisomeric ratios depending on the starting alkene. The results obtained have allowed us to study the influence of the different structural features of the sugar moiety on the regio- and diastereoselectivity of the hydroformylation reaction.

Keywords: Hydroformylation; C-allylglicosides; Asymmetric induction; Rhodium

1. Introduction

The hydroformylation of chiral olefins represents an elegant approach to the stereoselective formation of a C–C bond [1]. The extent of stereoselectivity depends on the stereochemical features of the starting alkene and is generally high in the case of cyclic substrates bearing an endocyclic double bond [2]. Sugars are good chiral auxiliaries for this reaction: not only high level of asymmetric induction have been reached with sugars having an endocyclic double bond [3], but also vinylidenic glucoside derivatives have been hydroformylated with very good diastereoisomeric excesses [4]. Recently we demonstrated that glucosides are suitable chiral synthons to obtain good levels of 1,3-asymmetric induction [5]. In fact, the Rh-catalyzed hydroformylation of α- and β-C-allyl glucosides **1a** and **1b** (Chart 1) gave the corresponding branched aldehydes with diastereoisomeric excess up to 70% [5]. The extent of asymmetric induction as well as the regioselectivity depended both on the stereochemistry of the sugar moiety and on the reaction conditions [5]. The most critical reaction parameter was the temperature, the highest diastereomeric excesses being obtained at 0 °C. As far as the substrate stereochemistry is concerned, the best results were reached with α-C-allyl glucoside. The sense of asymmetric induction depended on the absolute configuration of the C anomeric centre and the newly formed stereogenic centre was *S* configurated in the case of α-C-allyl glucoside, whereas a prevalence of the *R* diastereoisomer was obtained in the case of β-C-allylglucoside.

The high level of 1,3-asymmetric induction obtained prompted us to investigate the influence of the glycoside structure on the selectivity of the reaction namely the change of the stereochemistry of a remote stereogenic centre (**1c** and **1d**) [6], or the substitution of the endocyclic heteroatom (**1f**) [7] or the different size of the sugar ring (**1e**) [8].

* Corresponding author. Tel.: +39 0502219227; fax: +39 0502219260.
E-mail address: lazza@dcci.unipi.it (R. Lazzaroni).

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doi:10.1016/j.jorganchem.2006.06.008

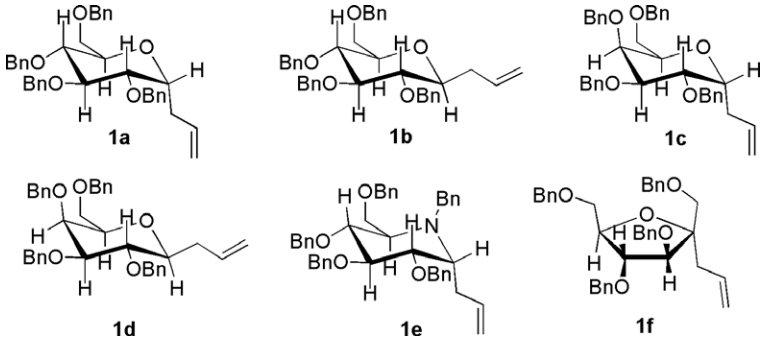


Chart 1.

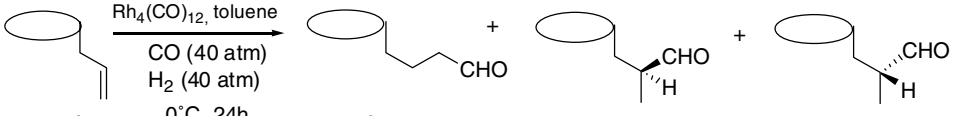
2. Results and discussion

2.1. Hydroformylation

Screening of the reaction conditions performed upon **1a** and **1b** showed that the best results in terms of selectivity (regio- and diastereo-) were obtained by performing the hydroformylation at low temperature (0 °C) with $Rh_4(CO)_{12}$ at 80 atm of CO and H_2 (1:1), and in toluene as solvent [5]. Therefore we used these optimized conditions, which afforded complete conversion of the starting alkene in 24 h, for C-allylglycosides **1c**, **1d** and **1f**: only **1e** was reacted at 25 °C, as no conversion took place at lower temperatures. Both regio- and diastereomeric ratios were determined by ^{1}H NMR analysis performed on the crude products in $CDCl_3$ solutions, on the basis of the integral value of aldehydic proton signals, which appear as three well separated resonances. The regioisomeric and diastereoisomeric ratios, the chemical shifts of isomeric aldehydic protons as well as the absolute configuration of the prevailing diastereoisomer are reported in Table 1 in comparison with the values concerning the hydroformylation of **1a** and **1b**. The absolute configuration of the newly formed stereogenic centre of **3a**, **3b**, **4a** and **4b** was obtained by NOE measurements on the PGME derivatives of the corresponding acids [5]. Interestingly, we have observed that the CHO proton of the diastereoisomer having *S* absolute configuration of the newly formed stereogenic centre resonates at lower NMR frequencies, independently of the absolute configuration at the C-anomeric centre [5]. This means that the relative position of the formyl proton signals in the two diastereoisomeric aldehydes is only affected by the absolute configuration of the stereogenic centre in α position to the formyl group: the change of stereochemistry even in proximity of this position (C-anomeric centre) having no influence. On the basis of this consideration and taking into account that the signal pattern is similar for the hydroformylation products of **1a**–**f**, we assigned the absolute configuration of the newly formed stereogenic centre on the basis of the chemical shifts of the branched aldehyde CHO protons.

The hydroformylation of α-C-allyl galactoside **1c** (entry 2) shows a moderate regioselectivity toward the branched aldehydes, which were obtained in a 70:30 diastereomeric ratio. We previously observed that the hydroformylation of **1a** gave no regioselectivity but higher diastereoselectivity, affording the branched aldehydes in a 85:15 ratio (entry 1). Since the only difference between **1c** and **1a** is the

Table 1
Hydroformylation of alkenes **1a**–**f**



1 2 3 4

Entry	Alkene	2%	3%	4%	3/4[a]	δ (ppm) CHO[a]		
						2	3	4
1	**1a(α)**[c]	50	43	7	85/15	9.74	9.64	9.66
2	**1c(α)**	40	42	18	70/30	9.79	9.69	9.73
3	**1b(β)**[c]	34	20	46	30/70	9.72	9.59	9.62
4	**1d(β)**	32	16	52	24/76	9.69	9.54	9.59
5[b]	**1e(α)**	80	5	15	25/75	9.60	9.52	9.55
6	**1f(α)**	30	39	31	56/44	9.80	9.51	9.65

[a] Determined by ^{1}H NMR analysis on $CDCl_3$ solutions.
[b] This reaction was carried out at 25 °C.
[c] Results already published[5].

absolute configuration of the C4 stereogenic centre, these results suggest that the change of stereochemistry far from the reaction site affects the selectivity of the reaction. The influence of the C4 has been observed also in the hydroformylation of β-C-allylglycosides **1b** and **1d**, where both regio- and diastereoselectivity slightly improve in passing from gluco derivative to galacto derivative (entries 3 and 4): it is worthy of note that, in the galacto derivatives, the diastereisomeric ratio is higher in the β-anomer than in the α-anomer (entries 2 and 4) [9]. The sense of asymmetric induction is still determined by the absolute configuration of the C-anomeric centre, the prevailing diastereoisomer being (***S***)-**3** for both α-gluco and α-galacto derivatives (entries 1 and 2) and (***R***)-**4** for both the β-C-anomers (entries 3 and 4).

The hydroformylation of the α-C-allyl azagluco derivative **1e** gave a very high prevalence of the linear aldehyde (entry 5) and a good diastereoisomeric excess in favour of (***R***)-**4**. It is noteworthy that **1a**, which possesses the same α-gluco structure also showed a high diastereoselectivity but in favour of (***S***)-**3**, but did not show any regioselectivity. The extent of regio- and diastereoselectivity, observed for **1e**, point out a high steric hindrance near the alkene moiety, which both disfavours the formation of the branched products [10] and allows a high diastereoisomeric excess to be obtained [11]. Both the higher steric hindrance near the reaction site and the sense of asymmetric induction can be explained taking into account that **1e** assumes a $^3C_6$ conformation (Fig. 1) [7], in which the allyl moiety is in a pseudo-β disposition and the *N*-benzyl substituent is located near the reaction site.

C-allylfruttofuranoside **1f** showed an unusual behaviour because it gave the highest regioselectivity towards the branched aldehydes (70/30 ratio) and the lowest value of diastereoselectivity (entry 6) among the examined substrates. A prevalence of branched isomer had been previously observed in the hydroformylation of allyl-ethers [10] and could be interpreted taking into account an interaction of the Rh-catalyst with ethereal oxygen [12]. A similar situation can be envizaged in the case of **1f**, where the C1 benzyloxy group is endowed with a conformational freedom that could allow its oxygen atom to interact with the Rh-catalyst coordinated at the double bond. The low asymmetric induction can be explained taking into account the different disposition of the C2 *O*-benzyl group in **1f**, due both to the different size of the ring and the stereochemistry of this centre; thus, on the contrary of which happens in the case of α-gluco derivative **1a** (Fig. 2), the C2 *O*-benzyl does

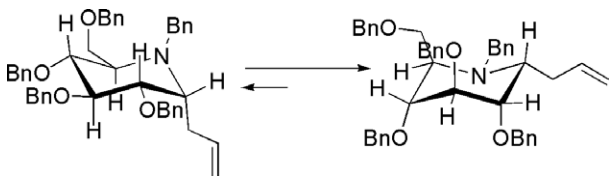


Fig. 1. Conformational equilibrium in **1e**.

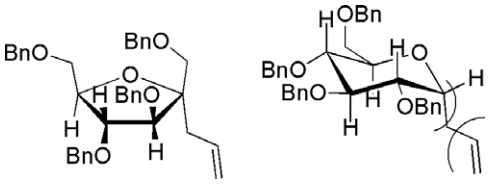


Fig. 2. Structure of **1f** and **1a**.

not sterically interact with the reaction site, giving rise to a random Rh catalyst attack upon the two diastereotopic faces of the **1f** double bond [1].

3. Conclusions

The results obtained in the hydroformylation of **1a**–**f** allows us to reach some conclusions about the effect of different structural parameters upon the selectivity of the reaction. The change of absolute configuration of a stereogenic centre far from the reaction site improves the regioselectivity and affects the extent of the asymmetric induction. The replacement of the endocyclic oxygen atom with a nitrogen engenders a conformational change in the sugar moiety, which gives unexpected results both in terms of regio- and diastereoselectivity. As far as diastereoselectivity is concerned, the presence of a sterically demanding group near the reaction site seems to be mandatory to obtain satisfactory levels of asymmetric induction: as a matter of fact, the hydroformylation of **1f**, which does not possess this structural requirement, proceeds with a very low diastereoselectivity, whereas starting from **1a** and **1e** good asymmetric induction is obtained. No general conclusions can be drawn about the regioselectivity, which depends not only on steric but also on electronic effects [12]. From a synthetic point of view the low regioselectivity does not represent a serious drawback, since linear and branched aldehydes can be easily separated by flash chromatography [5]. Finally, the sense of the asymmetric induction depends only on the absolute configuration of the C-anomeric centre, which induces a *R* configuration when is β and a *S* configuration when is α. This is true also when the α or β disposition of the allylic appendage is the result of a conformational equilibrium, as in **1e**.

4. Experimental

4.1. General

^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ on a Varian Gemini-200 MHz or on a Varian Inova-600 MHz NMR spectrometers, using TMS as an internal standard. The following abbreviations are used: s, singlet; d, doublet; dd, double doublet; t, triplet; m, multiplet; br s, broad signal. TLC analyses were performed on silica gel 60 Macherey-Nagel sheets. Toluene was dried over molecular sieves and distilled under nitrogen. $Rh_4(CO)_{12}$ was prepared according to the well-known procedure [13]. *C*-allyl glyco-

sides were prepared as described elsewhere and matched the reported characteristics [6–8]. Unless otherwise stated, the reagents were used without any further purification.

4.1.1. Hydroformylation of C-allyl-glycosides: general procedure

A solution of $Rh_4(CO)_{12}$ in toluene (5 ml) was introduced by suction into an evacuated 25 ml stainless steel reaction vessel. Carbon monoxide (40 atm) and H_2 (40 atm) were introduced, the autoclave was then rocked and kept at 40 °C for 30 min. The reaction mixture was then freezed at 0 °C and the C-allylglycoside (ratio substrate/Rh = 100/1) was introduced at that temperature. The reaction was monitored by TLC (SiO_2, CH_2Cl_2/aceton = 98:2) and the conversion was complete in 24 h. After removing the solvent at reduced pressure the crude products were filtered on a pad of silica gel (SiO_2, CH_2Cl_2/aceton = 98/2) affording the aldehyde mixtures (80% yield).

*4.1.2. Characterization of **2c**, **3c** and **4c***

^{1}H NMR (600 MHz, $CDCl_3$, δ): 1.05 (d, $J = 7.2$ Hz, 3H, **4c**-CH_3), 1.11 (d, $J = 7.2$ Hz, 3H, **3c**-CH_3), 1.52–1.75 (m, 4H, **2c**-CH_2), 1.82 (m, 2H, **3c** + **4c** *CH–C*H*H), 2.35 (m, 2H, **3c** + **4c** *CH–CH*H*), 2.42 (t, $J = 6.6$ Hz, 2H, **2c**-C*H*$_2$–CHO), 2.43 (m, 1H, **4c**-*C*H*–CH_3), 2.48 (m, 1H, **3c**-*C*H*–CH_3), 3.62–3.87 (m, 12H, **2c** + **3c** + **4c** CH_{ring}), 3.92 (m, 1H, **4c**-anomeric H), 3.99 (m, 1H, **2c**-anomeric H), 4.01 (t, $J = 4.2$ Hz, 6H, **2c** + **3c** + **4c** $^6CH_2$), 4.07 (m, 1H, **3c**-anomeric H), 4.50–4.72 (m, 24H, **2c** + **3c** + **4c** CH_2–Ph), 7.32 (m, 60H, **2c** + **3c** + **4c** Ar), 9.59 (d, $J = 0.6$ Hz, 1H, **3c**-CHO), 9.64 (d, $J = 0.6$ Hz, 1H, **4c**-CHO), 9.70 (t, $J = 1.2$ Hz, 1H, **2c**-CHO).

^{13}C NMR (50 MHz, $CDCl_3$, δ): 13.1, 14.1, 18.7, 26.5, 28.8, 31.7, 42.9, 43.6, 67.5, 67.7, 71.2, 71.3, 73.1, 73.4, 74.5, 76.5, 76.8, 77.9, 78.3, 127.6–128.5, 138.4–138.6, 202.7, 204.8.

*4.1.3. Characterization of **2d**, **3d** and **4d***

^{1}H NMR (600 MHz, $CDCl_3$, δ): 1.04 (d, $J = 6.0$ Hz, 3H, **4d**-CH_3), 1.06 (d, $J = 7.2$ Hz, 3H, **3d**-CH_3), 1.51–1.73 (m, 4H, **2d**-CH_2), 1.83 (m, 2H, **3d** + **4d** *CH–C*H*H), 2.18 (m, 2H, **3d** + **4d** *CH–CH*H*), 2.31 (m, 1H, **3d**-*C*H*–CH_3), 2.40 (t, $J = 6.6$ Hz, 2H, **2d**-C*H*$_2$–CHO), 2.53 (m, 1H, **4d**-*C*H*–CH_3), 3.20 (m, 1H, **3d**-anomeric H), 3.30 (m, 1H, **4d**-anomeric H), 3.46–3.70 (m, 13H, **2d**-anomeric H and **2d** + **3d** + **4d** CH_{ring}), 3.98 (br s 6H, **2d** + **3d** + **4d** $^6CH_2$), 4.40–4.95 (m, 24H, **2d** + **3d** + **4d** CH_2–Ph), 7.32 (m, 60H, **2d** + **3d** + **4d** Ar), 9.54 (d, $J = 0.6$ Hz, 1H, **3d**-CHO), 9.59 (d, $J = 0.6$ Hz, 1H, **4d**-CHO), 9.69 (t, $J = 1.1$ Hz, 1H, **2d**-CHO).

^{13}C NMR (50 MHz, $CDCl_3$, δ): 13.5, 18.4, 18.6, 31.0, 33.1, 42.9, 43.5, 43.7, 68.7, 69.0, 72.2, 73.3, 73.5, 73.6, 74.4, 75.4, 78.8, 79.3, 84.7, 84.9, 127.6–128.4, 138.3–138.7, 202.7, 204.7.

*4.1.4. Characterization of **2e**, **3e** and **4e***

^{1}H NMR (300 MHz, $CDCl_3$, δ): 0.61 (d, $J = 6.9$ Hz, 3H, **4e**-CH_3), 0.82 (d, $J = 7.5$ Hz, 3H, **3e**-CH_3), 0.95–1.45 (m, 4H, **2e**-CH_2), 1.60 (m, 2H, **3e** + **4e** *CH–C*H*H), 2.12 (m, 2H, **3e** + **4e** *CH–CH*H*), 2.80 (t, $J = 5.7$ Hz, 2H, **2e**-C*H*$_2$–CHO), 3.08 (m, 1H, **4e**-*C*H*–CH_3), 3.30 (m, 1H, **3e**-*C*H*–CH_3), 3.67–4.96 (m, 45H, **2e** + **3e** + **4e**-anomeric H, $^6CH_2$, CH_2–Ph and CH_{ring}), 7.32 (m, 60H, **2e** + **3e** + **4e** Ar), 9.52 (d, $J = 0.9$ Hz, 1H, **3e**-CHO), 9.55 (d, $J = 1.8$ Hz, 1H, **4e**-CHO), 9.60 (t, $J = 1.5$ Hz, 1H, **2e**-CHO).

^{13}*C NMR* (50 MHz, $CDCl_3$, δ): 11.1, 19.3, 29.8, 43.5, 52.7, 56.1, 56.8, 69.1, 72.1, 72.8, 74.3, 74.7, 75.2, 78.3, 80.0, 84.6, 127.7–128.5, 138.2–140.9, 175.9, 202.8.

*4.1.5. Characterization of **2f**, **3f** and **4f***

^{1}H NMR (600 MHz, $CDCl_3$, δ): 1.04 (d, $J = 6.6$ Hz, 3H, **3f**-CH_3), 1.06 (d, $J = 7.2$ Hz, 3H, **4f**-CH_3), 1.57–1.74 (m, 4H, **2f**-CH_2), 2.25 (m, 2H, **3f** + **4f** *CH–C*H*H), 2.35 (m, 2H, **3f** + **4f** *CH–CH*H*), 2.39 (t, $J = 7.2$ Hz, 2H, **2f**-C*H*$_2$–CHO), 2.46 (m, 1H, **3f**-*C*H*–CH_3), 2.55 (m, 1H, **4f**-*C*H*–CH_3), 3.45–3.60 (m, 12H, **2f** + **3f** + **4f** $^1CH_2$ and $^6CH_2$), 3.85–4.13 (m, 9H, **2f** + **3f** + **4f** CH_{ring}), 4.13–4.60 (m, 24H, **2f** + **3f** + **4f** CH_2–Ph), 7.32 (m, 60H, **2f** + **3f** + **4f** Ar), 9.41 (d, $J = 3.6$ Hz, 1H, **3f**-CHO), 9.56 (d, $J = 3.0$ Hz, 1H, **4f**-CHO), 9.71 (br s, 1H, **2f**-CHO).

^{13}C NMR (50 MHz, $CDCl_3$, δ): 15.6, 16.2, 33.4, 35.7, 36.3, 41.8, 42.2, 44.2, 66.0, 69.8, 70.6, 70.8, 71.2, 71.3, 72.2, 72.3, 72.5, 72.7, 73.4, 77.2, 79.8, 80.7, 81.0, 84.6, 85.3, 85.5, 85.8, 86.6, 87.1, 87.6, 127.7–128.5, 138.4–138.5, 202.7, 204.2, 205.0.

Acknowledgements

Financial support by MIUR – Programma di Ricerca Scientifica di Rilevante Interesse Nazionale – is gratefully acknowledged. We thank Prof. F. Nicotra for helpful discussions.

References

[1] B. Breit, Acc. Chem. Res. 36 (2003) 264.
[2] H. Siegel, W. Himmele, Angew. Chem., Int. Ed. Eng. 19 (1980) 178.
[3] E. Fernandez, A. Ruitz, C. Claver, S. Castillon, A. Polo, J.F. Piniella, A. Alvarez-Larena, Organometallics 17 (1998) 2857.
[4] T. Takahashi, S. Ebata, H. Yamada, Synlett (1998) 381.
[5] R. Lazzaroni, S. Rocchiccioli, A. Iuliano, L. Cipolla, F. Nicotra, Tetrahedron: Asymmetry 16 (2005) 3661.
[6] D.M. Lewis, J. Kun Cha, Y. Kishi, J. Am. Chem. Soc. 104 (1982) 4976.
[7] F. Nicotra, L. Panza, G. Russo, J. Org. Chem. 52 (1987) 5627.
[8] L. Cipolla, A. Palma, B. La Ferla, F. Nicotra, J. Chem. Soc., Perkin Trans. 1 (2002) 2161.
[9] The different selectivity found in the case of galacto derivatives **1c** and **1d** could be tentatively attributed to a different coordination mode of the 4-OBn group to the Rh centre depending on its axial disposition.
[10] P.W.N.M. Van Leeuwen, C. Claver, Rhodium Catalyzed Hydroformylation, Kluwer Academic Publishers, 2000.
[11] I. Ojima (Ed.), Catalytic Asymmetric Synthesis, second ed., Wiley Publisher, 2000.
[12] M. Halmann, O. Walter, J. Organomet. Chem. 689 (2004) 3117.
[13] (a) J.A. McCleverty, G. Wilkinson, Inorg. Synth. 8 (1966) 211; (b) P.E. Cattermole, G.A. Osborne, Inorg. Synth. 17 (1977) 115.