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Rhodium catalyzed hydroformylation of β-isophorone: An unexpected result

Stefano Paganelli [a,*], Federica Battois [a], Mauro Marchetti [b], Raffaello Lazzaroni [c], Roberta Settambolo [d], Silvia Rocchiccioli [c]

[a] *Dipartimento di Chimica, Università Ca' Foscari di Venezia, Calle Larga S. Marta 2137, I-30123 Venezia, Italy*
[b] *Istituto di Chimica Biomolecolare, CNR, Sez. di Sassari, traversa La Crucca 3, Località Baldinca, Li Punti, I-07049 Sassari, Italy*
[c] *Dipartimento di Chimica e Chimica Industriale, via Risorgimento 35, I-56126 Pisa, Italy*
[d] *ICCOM-CNR, Sez. di Pisa, Dipartimento di Chimica e Chimica Industriale, via Risorgimento 35, I-56126 Pisa, Italy*

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Abstract

The rhodium catalyzed hydroformylation of β-isophorone (**1a**) should afford, as only oxo-product, the aldehyde 4-formyl-3,5,5-trimethylcyclohexan-1-one (**2a**), an important intermediate for the preparation of δ-Damascone, a floral woody fragrance used for soaps, shampoos, foam baths, etc. Surprisingly, under the reaction conditions adopted by us, we obtained two isomeric aldehydes, namely the expected **2a**, formed in a small amount, and the (3,3-dimethyl-5-oxo-cyclohexyl)acetaldehyde (**5a**), that resulted to be the preponderant oxo-product. The chemoselectivity of the reaction was strongly affected by the substrate isomerization to α-isophorone (**3a**) and by the extensive formation of the corresponding saturated ketone **4a**, so lowering the efficiency of the whole process. However, by perfoming the hydroformylation on a β-isophorone derivative without the possibility of conjugation of the two double bonds, namely the ketal 7,9,9-trimethyl-1,4-dioxa-spiro[4.5]dec-7-ene (**1b**), the chemoselectivity of the reaction strongly increased and the amount of the hydrogenation product was rather low. In any case the predominant oxo-product was the acetaldehyde derivative **5b**, while the aldehyde **2b**, deriving from the attack of the formyl group on the less substituted carbon atom of the olefinic double bond, was produced in a very small amount.

Keywords: Hydroformylation; β-Isophorone; Rhodium catalyst; Biphasic hydroformylation; Fragrances

1. Introduction

The hydroformylation of olefins is one of the most important reactions catalyzed by homogeneous cobalt and rhodium complexes for the industrial production of aldehydes [1,2]. In particular, rhodium compounds, generally modified with phosphorous ligands, give rise to high reaction rates and good selectivities to the desired products [2–5]. The rhodium-catalyzed hydroformylation of olefins containing different functions is a useful tool for the preparation of numerous compounds having biological activity [2–5]. In the last years we have assisted to a remarkable expansion of the oxo-methodology towards fine chemicals to produce several valuable intermediates and hence to substitute old preparative methods, based on conventional organic chemistry, with new economical methods for C–C bond formation.

The fragrance and flavour industry is, i.e., a field in which both heterogeneous and homogeneous catalysis play an important role and have grown extensively over the last few decades [6]. In this view hydroformylation is a well-known example of catalytic reaction that allows access to a large number of aldehydes, useful for perfumery, from simple olefinic precursors [6].

In this area BASF has a long experience with hydroformylation of highly substituted alkenes or isomerization sensitive alkenes such as α-pinene [7], *tert*-butyldihydrodioxepine [8] or β-isophorone (**1a**) [9]. In particular, the hydroformylation of β-isophorone (**1a**) (3,5,5-trimethylcyclohex-3-enone), can represent a powerful tool for the synthesis of 4-formyl-3,5,5-trimethylcyclohexan-1-one (**2a**), an important intermediate for the preparation of δ-Damascone, a floral woody fragrance pro-

* Corresponding author.
E-mail address: spag@unive.it (S. Paganelli).

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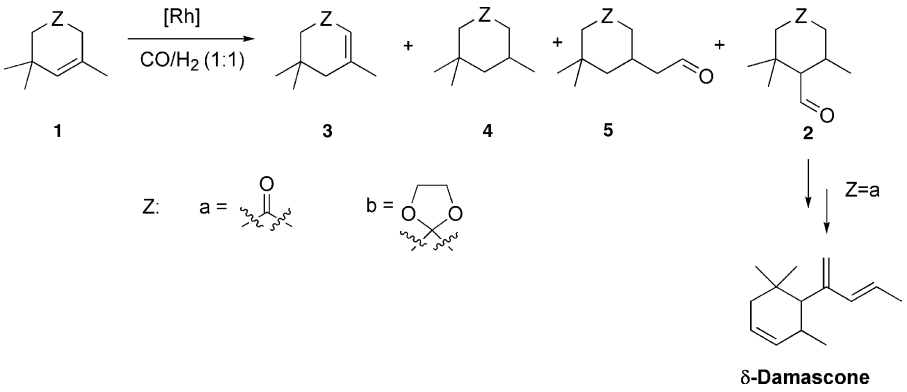


Scheme 1.

duced by IFF and used for soaps, shampoos, foam baths, etc. [9,10] (Scheme 1).

Indeed, β-isophorone, characterized by a trisubstituted double bond, is expected to give, under hydroformylation conditions, only one carbonylic product, namely the aldehyde 4-formyl-3,5,5-trimethylcyclohexan-1-one (**2a**), as described in a BASF patent [9]. Nevertheless the reported chemoselectivity of β-isophorone hydroformylation is very low, due to the extensive substrate isomerization to α-isophorone (**3a**) and to the formation of the saturated ketone **4a** deriving from the hydrogenation of **1a** and/or **3a** [9] (Scheme 1).

In this frame, since the reaction conditions adopted by BASF are extremely drastic (up to 600 atm of syngas and 150 °C) and the chemoselectivity is almost unsatisfactory [9], we decided to study this oxo-process with the aim to enhance the aldehyde **2a** yield and to perform the reaction under milder conditions. Moreover, to avoid the formation of the isomerization product **3a**, we decided to investigate the hydroformylation of the ketal 7,9,9-trimethyl-1,4-dioxa-spiro[4,5]dec-7-ene (**1b**) (Scheme 1).

2. Experimental

2.1. General remarks

β-Isophorone (**1a**) was purchased from BASF. $HRh(CO)(PPh_3)_3$, $Rh(CO)_2(acac)$, DPPB and $P(C_6H_5O)_3$ were Strem products. TPPTS was used as obtained from Fluka AG. Flash chromatographies were carried out on silica gel Merck 60, 230–400 mesh. NMR spectra were recorded on a Bruker Advance 300 and on a Varian Unity 400, using $CDCl_3$ as solvent. GC analysis were carried out on an Agilent 6850A instrument, using an HP1 column (30 m × 0.32 mm × 0.25 μm). GC–MS analysis were performed by using an Agilent MS Network 5937 using an HP-5MS column (30 m × 0.25 mm × 0.25 μm). Solvents were purified as described in the literature [11].

2.2. General procedure for β-isophorone (*1a*) hydroformylation

A 150 ml stainless steel reaction vessel was charged under a nitrogen purge with 0.0144 mmol of rhodium complex, 7.2 mmol of β-isophorone and 5 ml of anhydrous toluene. The autoclave was then pressurized to 100–180 atm of syngas ($CO/H_2 = 1$) and heated at 60–120 °C for the due time (see Table 1). For analytical purposes the two isomeric aldehydes **5a** and **2a** were isolated from the reaction mixture by flash silica gel chromatography (*n*-hexane/ether 8/2).

Compound **5a**. ^1H NMR (400 MHz, $CDCl_3$) δ: 9.76 (t, 1H, $J = 1.8$ Hz), 2.5 (m, 1H, C**H**), 2.48 (m, 2H, C$\mathbf{H}_2$CHO), 2.4 (m, 1H$_{eq.}$, C$\mathbf{H}_2$), 2.1 (q, 2H, C$\mathbf{H}_2$, $J = 13.3$ Hz), 1.9 (t, 1H$_{ax.}$, C$\mathbf{H}_2$, $J = 13.3$ Hz), 1.7 (m, 1H$_{eq.}$, C$\mathbf{H}_2$), 1.3 (t, 1H$_{ax.}$, C$\mathbf{H}_2$,

Table 1
Rhodium catalyzed hydroformylation of β-isophorone (**1a**)

Run	Catalytic precursor	*T* (°C)	*P* (atm)	*t* (h)	Conversion (%)	**2a** yield (%)	**5a** yield (%)	**4a** yield (%)	**3a** yield (%)
1	$HRh(CO)(PPh_3)_3$	100	100	48	>99	4.5	1.5	87.0	7.0
2	$Rh(CO)_2acac$	100	100	48	>99	8.5	25.2	46.4	19.8
3	$Rh(CO)_2acac$	120	100	24	>99	–	12.0	73.0	15.0
5[a]	$Rh(CO)_2acac/P(C_6H_5O_3)_3$	120	100	24	>99	–	1.7	85.0	13.3
6	$Rh(CO)_2acac$	120	130	24	>99	2.0	18.6	71.8	7.6
7	$Rh(CO)_2acac$	80	150	72	89.0	7.4	17.7	31.6	32.3
8	$Rh(CO)_2acac$	100	150	24	90.4	4.1	24.7	32.3	29.3
9[b]	$Rh(CO)_2acac$/DPPB	100	150	41	>99	3.7	5.0	45.2	46.1
10[c]	$Rh(CO)_2acac$/TPPTS	100	100	72	91.7	3.1	23.8	43.4	21.4

Substrate = 7.2 mmol; solvent (toluene) = 5 ml; substrate to catalyst (molar ratio) = 500.
[a] P/Rh (molar ratio) = 5.
[b] DPPB = 1,4-*bis*(diphenylphosphino)butane; P/Rh (molar ratio) = 6/1.
[c] TPPTS = triphenylphosphine-3,3′,3″-trisulfonic acid trisodium salt; P/Rh (molar ratio) = 6/1; solvent: H_2O (3 ml) + toluene (2 ml).

J = 12.7 Hz), 1.1 (s, 3H, C**H**$_3$), 0.9 (s, 3H, C**H**$_3$). ^{13}C NMR δ: 210, 200, 54, 51, 47, 45, 35, 32, 29, 25. MS: *m*/*e* 168 (M^+), 153, 125, 83, 69, 55, 41.
Compound **2a**. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.75 (d, 1H, C**H**O, J = 4.2 Hz), 2.6–1.5 (m, 6H, cyclohexyl ring), 1.14 (s, 3H, C**H**$_3$), 1.01 (s, 3H, C**H**$_3$), 1.0 (s, 3H, C**H**$_3$). ^{13}C NMR δ: 209, 205, 65, 56, 48, 39, 30, 29, 23, 21. MS: *m*/*e* 168 (M^+), 153, 111, 83, 69, 55, 41.

2.3. β-Isophorone (*1a*) hydroformylation in aqueous biphasic medium

In a Schlenk tube $Rh(CO)_2(acac)$ (3.7 mg, 0.0144 mmol) and TPPTS (49.0 mg, 0.0864 mmol) were dissolved under nitrogen in H_2O (3 ml). A solution of β-isophorone (1.0 g, 7.2 mmol) in toluene (2 ml) was then added to the aqueous solution. The Schlenk tube was transferred to a 150 ml stainless steel autoclave under nitrogen, pressurized to 100 atm with syngas (CO/H_2 = 1) and heated at 100 °C for 72 h. The reactor was then cooled to RT and the residual gases released. The organic phase was separated, dried on Na_2SO_4 and toluene removed in vacuo: the two isomeric aldehydes **2a** and **5a** were recovered and identified as previously described.

2.4. Preparation of 7,9,9-trimethyl-1,4-dioxa-spiro[4.5]dec-7-ene (*1b*)

A mixture containing α-isophorone (**3a**) (5.53 g, 40 mmol), diethylen glycol (7 ml, 125.5 mmol) and *p*-toluensulphonic acid monohydrate (250 mg) in toluene (100 ml), was heated at reflux for 16 h with continuous removal of water by means of a Dean-Stark trap [12]. The mixture was cooled to room temperature, washed with saturated aqueous sodium bicarbonate and saturated brine and dried over anhydrous magnesium sulfate. After removal of the solvent under reduced pressure, a mixture of the two ketals 7,9,9-trimethyl-1,4-dioxa-spiro[4.5]dec-7-ene (**1b**) and 7,9,9-trimethyl-1,4-dioxa-spiro[4.5]dec-6-ene (**3b**) was obtained by flash chromatography on silica gel (*n*-hexane/ether 9/1) in 54% yield. The molar ratio between **1b** and **3b**, determined by GC, resulted to be 3/2. This mixture (21.6 mmol), dissolved in 150 ml of 95% methanol, was then treated with oxalic acid dihydrate (74.3 mmol) at room temperature for 10 min. The reaction mixture was poured into 400 ml of cold saturated aqueous sodium bicarbonate, diluted with saturated brine, and extracted with ether. Pure ketal **1b** was obtained by flash chromatography on silica gel (*n*-hexane/ ether 9/1) in 64% yield.

Compound **1b**. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 5.18 (bs, 1H, C**H**), 3.97 (s, 4H, –OC**H**$_2$–C**H**$_2$O–), 2.15 (s, 2H, C**H**$_2$–C=CH), 1.69 (s, 2H, C**H**$_2$), 1.62 (s, 3H, C**H**$_3$), 1.06 (s, 6H, C(C**H**$_3$)$_2$). MS: *m*/*e* 182 (M^+), 167, 139, 127, 113, 86.

2.5. General procedure for 7,9,9-trimethyl-1,4-dioxa-spiro[4.5]dec-7-ene (*1b*) hydroformylation

A 150 ml stainless steel reaction vessel was charged under a nitrogen purge with 0.0144 mmol of rhodium complex, 7.2 mmol of 7,9,9-trimethyl-1,4-dioxa-spiro[4.5]dec-7-ene (**1b**) and 5 ml of anhydrous toluene. The autoclave was then pressurized to 90–150 atm of syngas (CO/H_2 = 1) and heated at 100 °C for the due time (see Table 2). The mixture of the two oxo-aldehydes **5b** and **2b** was isolated from the crude by flash silica gel chromatography (*n*-hexane/ether 8/2).

Mixture of compound **5b** and **2b**. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 9.77 (t, 1H, C**H**O, J = 2.7 Hz), 9.66 (d, 1H, C**H**O, J = 7.5 Hz), 3.99 (m, 4H, –OC**H**$_2$–C**H**$_2$O–), 2.38 (m, 2H, C**H**$_2$CHO), 2.20–1.18 (complex multiplets due to the protons of the cyclohexyl ring), 1.18 (s, 3H, C**H**$_3$), 1.10 (s, 3H, C**H**$_3$), 0.98 (s, 3H, C**H**$_3$).
Compund **5b**. MS: *m*/*e* 212 (M^+), 197, 184, 169, 153, 141, 127, 113, 86, 69, 55, 41.
Compund **2b**. MS: *m*/*e* 212 (M^+), 197, 184, 167, 155, 141, 127, 113, 86, 69, 55, 41.

3. Results and discussion

As already mentioned, the hydroformylation of β-isophorone (**1a**), previously carried out by BASF under almost drastic reaction conditions, affords rather low chemoselectivity into aldehyde [9]. With the aim to perform the hydroformylation of β-isophorone (**1a**) under milder reaction conditions and to improve the chemoselectivity of the oxo-process, we carried out some hydroformylation experiments at 60–120 °C under a syngas pressure of 100–180 atm, in the presence of different rhodium based catalytic precursors (Table 1). In all cases, even at low temperature, the chemoselectivity was very disappointing because of the extensive substrate isomerization to α-isophorone

Table 2
Rhodium catalyzed hydroformylation of 7,9,9-trimethyl-1,4-dioxa-spiro[4.5]dec-7-ene (**1b**)

Run	Catalytic precursor	P (atm)	t (h)	Conversion (%)	**5b** yield (%)	**2b** yield (%)	**4b** yield (%)	By-prod. (%)
1	$HRh(CO)(PPh_3)_3$	90	72	53.4	44.8	5.9	2.7	–
2	$Rh(CO)_2(acac)$	90	72	52.2	40.4	6.3	5.5	–
3	$Rh(CO)_2(acac)$	90	120	71.2	53.9	10.7	2.2	4.4
4[a]	$Rh(CO)_2(acac)$/DPPB	90	120	86.2	40.0	20.5	19.7	6.0
5	$Rh(CO)_2(acac)$	100	52	36.4	29.7	6.2	–	0.5
6	$Rh(CO)_2(acac)$	150	48	51.7	44.9	5.2	1.2	0.4

Substrate = 7.2 mmol; substrate to catalyst (molar ratio) = 500; temperature = 100 °C; $p(CO) = p(H_2)$; solvent (toluene) = 5 ml.
[a] DPPB = 1,4-*bis*(diphenylphosphino)butane; P/Rh (molar ratio) = 4/1.

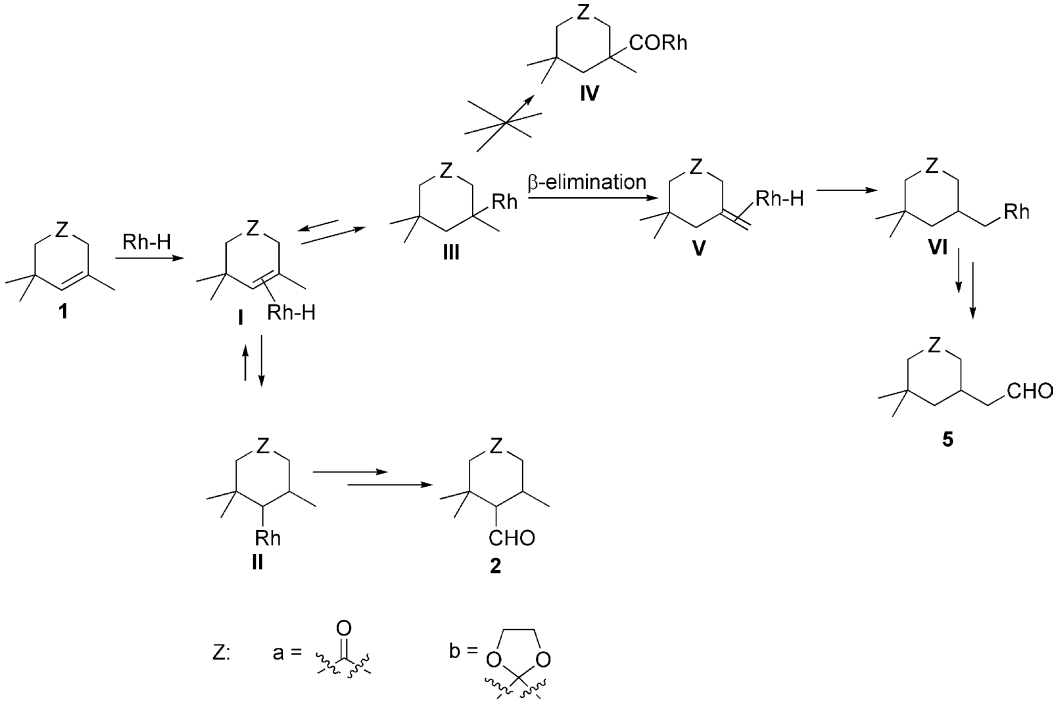
(3,5,5-trimethylcyclohex-2-en-1-one) (**3a**) and to the formation of the corresponding saturated ketone **4a**. In spite of we did not succeed in improving the chemoselectivity of the process, we obtained a very surprising and intriguing result: in fact, we observed the formation of two isomeric oxo-aldehydes instead of only one, as expected. After separation of these two isomers from the reaction mixture by flash chromatography and careful GC–MS, ^{1}H NMR and ^{13}C NMR analysis we were able to conclude that the preponderant oxo-product resulted to be the (3,3-dimethyl-5-oxo-cyclohexyl)acetaldehyde (**5a**), while the expected 4-formyl-3,5,5-trimethylcyclohexan-1-one (**2a**) was the aldehyde formed in the minor amount (Scheme 1).

From the data depicted in Table 1 we can observe that the aldehyde yield was always very low and the best result was obtained carrying out the reaction in the presence of $Rh(CO)_2(acac)$ at 100 atm of syngas and 100 °C for 48 h, with a substrate to catalyst molar ratio = 500; the conversion was practically complete but the total aldehyde yield was about 34%, with the formation of 25% of the acetaldehyde derivative **5a** and 8.5% of aldehyde **2a**. Also in this case, the main product was the saturated ketone **4a** (run 2 of Table 1).

We also tried to carry out the hydroformylation reaction in an aqueous biphasic system: accordingly, we subjected β-isophorone (**1a**) to the oxo-process, at 100 °C and 100 atm of syngas ($CO/H_2 = 1$), in the presence of $Rh(CO)_2(acac)$ modified with the water soluble phosphino ligand TPPTS. Also under this reaction conditions we obtained the two isomeric aldehydes **2a** and **5a** and the main oxo-product was again the acetaldehyde derivative **5a**; in any case the chemoselectivity of the process was very low due to the formation of the α-isophorone (**3a**) and of the corresponding saturated ketone **4a** (run 10 of Table 1).

Under all the reaction conditions adopted we did not succeed in avoiding both the undesired substrate isomerization to the α,β-unsaturated ketone **3a** and the formation of the corresponding saturated compound **4a**. The chemoselectivity of the reaction resulted strongly effected by this concurrent phenomena so lowering the efficiency of the whole process. At this point it was necessary to use a device which allowed us to increase the chemoselectivity of the oxo-process. Therefore, we decided to prepare a β-isophorone derivative where the possibility of conjugation of the two double bonds were prevented. Our choice falled on the ketal 7,9,9-trimethyl-1,4-dioxa-spiro[4.5]dec-7-ene (**1b**). This substrate, prepared by acetalyzation of α-isophorone (**3b**) with diethylen glycol [12], was subjected to some hydroformylation experiments catalyzed by rhodium carbonyl compounds at 100 °C and 90–150 atm of syngas (Scheme 1) and the results are reported in Table 2.

In all the experiments the chemoselectivity of the reaction resulted to be strongly increased and the amount of the hydrogenation product **4b** was rather low; only in the presence of the phosphino ligand DPPB (1,4-bis-diphenylphosphinobutane) compound **4b** was formed in almost 20% at a substrate conversion of 86%. The formation of the saturated ketal **4b** was completely suppressed for quite low substrate conversion (36.4%) (run 5 of Table 2). In all cases the predominant oxo-product was the acetaldehyde derivative **5b**, while the aldehyde **2b**, deriving from the attack of the formyl group on the less substituted carbon atom of the olefinic double bond, was produced in a quite small amount. Nevertheless we can note that the reaction rate was much slower than that observed with β-isophorone, probably because of the presence of the sterically hindered acetal group. In fact, almost high conversions (71–86%) were obtained only by prolonging the reaction time for 120 h at



Scheme 2.

100 °C under 80 atm of syngas ($CO/H_2 = 1$) (runs 3 and 4 of Table 2).

A plausible explanation of the unexpected results obtained in the hydroformylation of **1a** and **1b**, namely the formation of the aldehydes **5**, can be given on the basis of the generally accepted mechanism of the rhodium-catalyzed hydroformylation [3], by supposing the initial formation of the π rhodium complex **I** that generates not only the secondary but also the tertiary alkyl rhodium intermediates **II** and **III**, respectively. Nevertheless, the tertiary alkyl rhodium intermediate **III**, as it formed, cannot give the migratory insertion on a CO bound to the rhodium atom to form the acylrhodium specie **IV**, because of the steric hindrance. As a consequence, it undergoes a β-hydride elimination involving the methyl group which brings to the π complex **V**. This complex, then, quickly evolves to the primary Rh-alkyl specie **VI** by an anti Markovnikov addition of Rh-H; the subsequent migratory insertion on a coordinated CO followed by oxidative addition of H_2 gives rise to the formation of aldehyde **5a** (Scheme 2). An analogous behaviour can be assumed for the ketal derivative **1b**.

In order to explain the prevailing formation of the aldehyde **5** with respect to **2** we can take into account the hypothesis that, for steric reasons, the secondary intermediate **II** is preferentially formed with respect to the tertiary one **III**. However, the migratory insertion for **II**, precursor of the aldehyde **2**, could be slow for steric hindrance while the isomerization of **III** to **VI** and the successive migratory insertion on CO could be very fast. An other hypothesis, i.e., a preferential formation of the tertiary alkyl with respect to the secondary one, is less attractive because it is known that the steric hindrance play a crucial role into the alkyl formation step, at least when all groups bonded to the Rh-C carbon atom are aliphatic [13,14].

4. Conclusive remarks

In conclusion, the rhodium catalyzed hydroformylation applied to the ketal **1b** instead of keton **1a** strongly increases the aldehydes chemoselectivity and surprisingly, the unexpected acetaldehyde derivative **5b** is the prevailing oxo-product. Interestingly, in order to explain the formation of the aldehyde products **2** and **5**, the formation of a tertiary, secondary and primary alkyl rhodium intermediates arising from the same substrate **1** can be hypothesized. The reversible formation of the above alkyl species together with the different rate of the step concerning the migratory insertion are likely responsible for the regioselectivity of the reaction.

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