Hydroformylation by Mechanosynthesis

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Hydroformylation of Alkenes in a Planetary Ball Mill: from Additive-Controlled Reactivity to Supramolecular Control of Regioselectivity

*Kévin Cousin, Stéphane Menuel, Eric Monflier, and Frédéric Hapiot**

Abstract: *The Rh-catalyzed hydroformylation of aromatic-substituted alkenes is performed in a planetary ball mill under CO/H_2 pressure. The dispersion of the substrate molecules and the Rh-catalyst into the grinding jar is ensured by saccharides: methyl-α-D-glucopyranoside, acyclic dextrins, or cyclodextrins (CDs, cyclic oligosaccharides). The reaction affords the exclusive formation of aldehydes whatever the saccharide. Acyclic saccharides disperse the components within the solid mixture leading to high conversions of alkenes. However, they showed typical selectivity for α-aldehyde products. If CDs are the dispersing additive, the steric hindrance exerted by the CDs on the primary coordination sphere of the metal modifies the selectivity so that the β-aldehydes were also formed in non-negligible proportions. Such through-space control via hydrophobic effects over reactivity and regioselectivity reveals the potential of such solventless process for catalysis in solid state.*

Transition-metal-catalyzed hydroformylation of alkenes represents one of the most important approaches to aldehydes. Since the seminal studies from Roelen,[1] a range of improvements have been made to produce aldehydes in excellent yields at operatively convenient conditions of pressures and temperatures.[2] Over the years, research has focused on the design of catalysts consisting of transition metals stabilized by specialized ligands, to increase chemo-, regio-, and enantioselectivities.[3] Countless first-sphere ligands are now available for regioselective control in hydroformylation of terminal and internal alkenes.[4–7] Concurrently, a supramolecular approach has been developed aiming at controlling site-selective reactions via secondary interactions.[8] Cooperative ligand systems have thus demonstrated that supramolecular interactions between substrate and ligand can result in non-covalent substrate preorganization around the active catalytic site. In this context, one of the most developed approach relies on hydrogen bonding between the ligand and the substrate.[9–13] However, the substrate preorganization in hydroformylation reactions could also be achieved through hydrophobic effects. For example, we showed that bidentate ligands and cyclodextrins (CDs, cyclic oligosaccharides consisting of glucopyranose units) supramolecularly interact to compel terminal alkenes to react preferentially by their terminal carbon, leading to very high regioselectivity toward linear aldehyde.[14]

Recently, focus has been in controlling selectivity of organic reactions under solventless ball-milling conditions.[15] Concurrently with works of Cravotto et al.,[16,17] we showed that regioselective mono-2-*O*-tosylation of the secondary face of CDs proceeds quantitatively upon grinding on very short reaction times (ca. 1 min) via supramolecular means, the reactant (tosylimidazole) being included into the CD cavity.[18] Similarly, highly selective processes were identified in the mechanically-activated Au-catalyzed reduction of nitroarenes in the presence of CDs.[19] On the basis of the aforementioned results, we sought to assess the potential of CDs to control both the chemo- and regioselectivity of the hydroformylation reaction under CO/H_2 pressure under mechanochemical activation. To our knowledge, nothing has been published so far on the hydroformylation of alkenes in the solid state under ball-milling conditions. In fact, very few has been reported so far on the mechanochemical activation of catalytic reactions using a pressurized ball mill.[20,21] Reported herein is the ball-milled Rh-catalyzed hydroformylation of alkenes to the corresponding aldehydes under CO/H_2 pressure in the presence of saccharide additives such as methyl-α-D-glucopyranoside (**1a**), acyclic dextrins (**1b**, maltodextrins 6D, degree of polymerization = 20)[22] and CDs of different cavity size (**1c**–**e**, Figure 1). The saccharides have been chosen for their high temperature of fusion (168 °C for

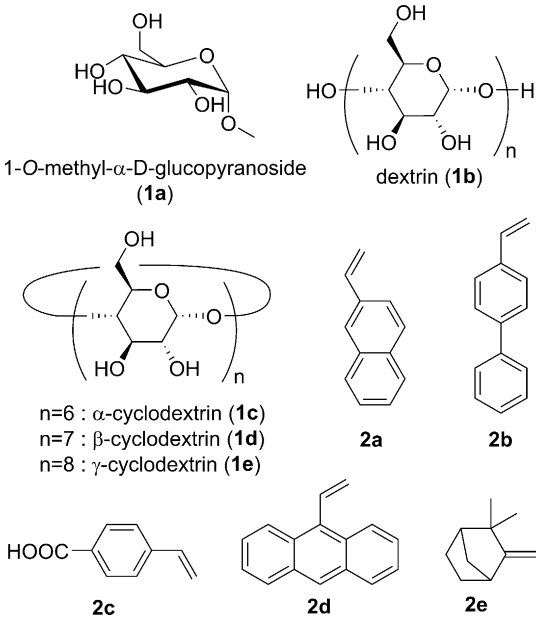

Figure 1. Selected saccharides and substrates.

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1a, and >250 °C for **1b** and CDs) which ensures that the catalytic process takes place at the solid state. The role of saccharides in favoring and orienting the course of the mechanically activated hydroformylation reaction is especially highlighted.

To begin with, we demonstrated that the hydrido-Rh precursor could be synthesized under mechanochemical conditions. As described for many other organometallic complexes,[23] ball milling allowed for the straightforward synthesis of the $HRh(CO)(PPh_3)_3$ complex, as confirmed on the basis of ^1H and ^{31}P NMR spectroscopy (Figure 2 and Figure 3). The hydrido-Rh species was identified at −9.8 ppm on the ^1H NMR spectrum and the Rh-P bond was revealed by

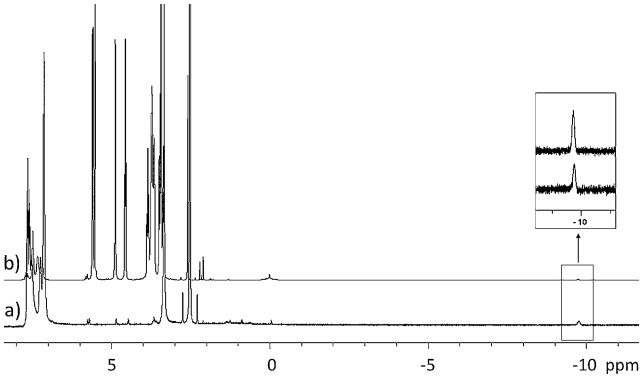


Figure 2. ^1H NMR spectra of a) commercial $HRh(CO)(PPh_3)_3$ and b) a mixture of $Rh(CO)_2(acac)$ (0.16 mmol), PPh_3 (0.78 mmol), and α-CD (2.06 mmol) after 1 h ball-milling under 15 bar CO/H_2 (1:1) in $[D_6]$DMSO at 25 °C.

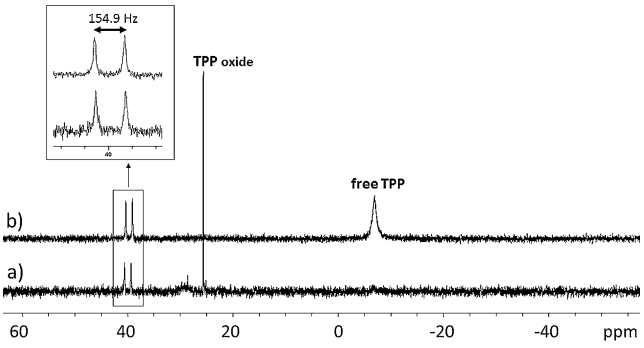
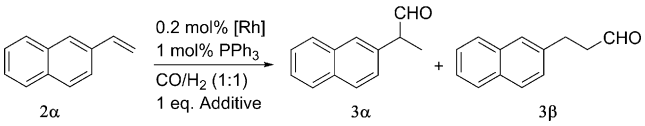


Figure 3. ^{31}P NMR spectra of a) commercial $HRh(CO)(PPh_3)_3$ and b) a mixture of $Rh(CO)_2(acac)$ (0.16 mmol), PPh_3 (0.78 mmol), and α-CD (2.06 mmol) after 1 h ball-milling under 15 bar CO/H_2 (1:1) in $[D_6]$DMSO at 25 °C. TPP = PPh_3.

the doublet at 40.0 ppm ($^1J_{Rh\text{-}P} = 154.9$ Hz) in the ^{31}P NMR spectrum. The chemical shift and coupling constant values were in line with those of the commercial product. Note that the formation of hydrido-Rh complex in solution during the NMR analysis should be discarded in that the medium was free of H_2 in the NMR tube.

The first catalytic test began with the Rh-catalyzed hydroformylation of 2-vinylnaphtalene (**2a**) as a model substrate in a planetary ball mill rotating at 850 rounds per minute (rpm) for 4 h. The $HRh(CO)(PPh_3)_3$ catalyst was generated in situ by mixing $Rh(CO)_2(acac)$ (acac = acetylacetonate) with 5 equiv PPh_3 under 220 psi CO/H_2 (1:1) pressure in the presence of saccharide. Considering **1a** as an additive led to remarkable 100 % conversion of **2a** (Table 1, entry 1) and 100 % chemoselectivity in aldehydes, as deter-

Table 1: Optimization of the reaction conditions.[a]



Entry	Additive	Conv. [%][b]	Aldehyde sel. [%][b]	**3α/3β**[b]
1	**1a**	100	100	10.0
2	**1b**	79	100	10.0
3	**1c**	38	100	4.5
4	**1d**	54	100	2.0
5	**1e**	67	100	3.2

[a] Reagents and Conditions: $Rh(CO)_2(acac)$ (3.7 μmol), PPh_3 (18.5 μmol), **2a** (1.8 mmol), additive (1.8 mmol), CO/H_2 (1:1) (220 psi), rotation speed (850 rpm), 4 h. [b] determined by NMR spectroscopy.

mined by ^1H NMR spectroscopy. The α-aldehyde (**3α**) was mainly formed (10 times more than the β-aldehyde (**3β**), Table 1), in line with what was typically observed in solution for the hydroformylation of aromatic-substituted alkenes.[24,25] The preference for **3α** resulted from the formation of a rhodium α-arylalkyl intermediate stabilized by π-benzyl interaction.[26] Thus, the high proportion of **3α** suggested that the in situ formation of the rhodium α-arylalkyl intermediate also took place at the solid state under ball-milling conditions. This experiment alone validated the approach of hydroformylation under ball-milling conditions.

The same reaction was then carried out by using the acyclic dextrin **1b** as additive. Because of its helicoidal structure and extended binding site,[27] **1b** can bind to **2a** resulting in a reduced diffusion of **2a** and lower 79 % conversion (entry 2). Here again, **2a** was exclusively converted into aldehydes and the **3α/3β** ratio remained unchanged (Table 1). Grinding **2a** in the presence of α-CD (**1c**) gave 38 % conversion and 100 % chemoselectivity towards aldehydes (entry 3). The moderate conversion likely resulted from the formation of host-guest complexes between the naphthyl moiety of **2a** and the CD cavity,[28] which slowed down the diffusion of **2a** within the solid mixture. This result was in line with our previous observations about the poor ability of **1c** to diffuse aromatic substrates in AuNP-catalyzed reduction under ball-milling conditions.[19] Interestingly, while the conversion was negatively affected by **1c**, significant effects were measured on the regioselectivity. The proportion of **3β** significantly increased (Table 1, entry 3), suggesting that the cyclic structure of **1c** slightly affected the rhodium α-arylalkyl intermediate in the solid state. However, the cavity of **1c** being too narrow to include the entire naphthalene ring,[29] the discriminating effect to **3β** was limited. The negative effect on the conversion of **2a** was

less pronounced using β-CD (**1d**) as an additive (54%, Table 1) probably because of better dynamics of exchange between **2a** and the larger cavity of **1d** compared to **1c**.[30]

In terms of regioselectivity, a deeper penetration of **2a** into the cavity of **1d** explained the lower **3α/3β** ratio of 2.0 (33% of **3β**). Upon inclusion of **2a**, the bulky rigid structure of **1d** repelled the Rh-catalyst to the less hindered β-position (Figure 4). The formation of the rhodium α-arylalkyl intermediate was then disfavored, resulting in higher proportion of **3β**. These observations were substantiated by experiments carried out with γ-CD (**1e**) as additive. Compared to **1c** and **1d**, the conversion was higher (67%, Table 1, entry 5) using **1e** as its wider cavity promoted higher dynamics of exchange of **2a** and its corresponding aldehydes throughout the solid mixture. However, the percentage of **3β** decreased (24%) compared to that obtained for **1d**. Indeed, as **2a** was less constrained by the more flexible structure of **1e**, the imperfect preorganization of **2a** around the active catalytic site resulted in lower percentage of **3β**.

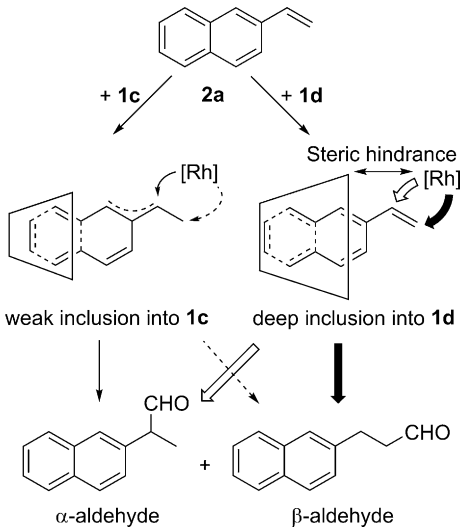


Figure 4. Schematic representation of the influence of the molecular recognition between **2a** and the CD cavity of **1c** and **1d** on the regioselectivity of the hydroformylation under ball-milling conditions.

We then conducted a comparative study to determine the contribution of amorphization and complexation under ball milling conditions. To do so, differential scanning calorimetry (DSC) analysis was performed on co-grinded mixtures of **2a** and saccharides (Supporting Information) to assess the encapsulation efficiency (EE%).[31] While EE% is based on thermodynamic data (especially enthalpy, see Supporting Information), its variation with time gives indications on the rate of the amorphization and/or encapsulation processes. More precisely, from the variations of EE% values at different grinding times, we estimated the ability of **1a** to amorphize **2a** (no inclusion complex in that case), and the ability of **1b**, **1c**, **1d**, or **1e** to form inclusion complexes with **2a** in the solid state. Hypothesizing that the amorphization contribution was similar for all saccharides, the higher EE% measured at a given grinding time for CDs with respect to **1a** and **1b** illustrated the formation of CD/substrate inclusion complexes. Upon inclusion into the CDs' cavity, the diffusion of the substrate throughout the solid mixture slowed down, which logically resulted in lower catalytic activity.

We then tried to intensify the discriminating effect of **1d** by optimizing the catalytic parameters. Varying the CO/H_2 pressure from 75 to 220 psi did not significantly change the conversion. The rotation speed, for its part, affected both the catalytic activity and the regioselectivity. By increasing the rotation speed from 350 to 850 rpm under 220 psi CO/H_2, the conversion increased from 6% to 54% and the percentage of β-aldehyde increased from 9% to 36%.[32] This clearly indicated that the energy transfer resulting from friction and shocks of the balls onto the reactor walls favored the inclusion process of **2a** into the cavity of **1d**. In terms of regioselectivity, the Rh-catalyst was more prone to react favorably on the less hindered position of the vinyl group upon inclusion, resulting in higher proportion of **3β**. Changing the nature of the ligand (Figure 5) also gave interesting results (Table 2). The best conversion was obtained using TPFP (Table 2, entry 5). The electron-withdrawing effects of the F atoms probably allowed for a rapid de-coordination of TPFP from the Rh-center to form catalytically active low-phosphine coordinated Rh-complexes.

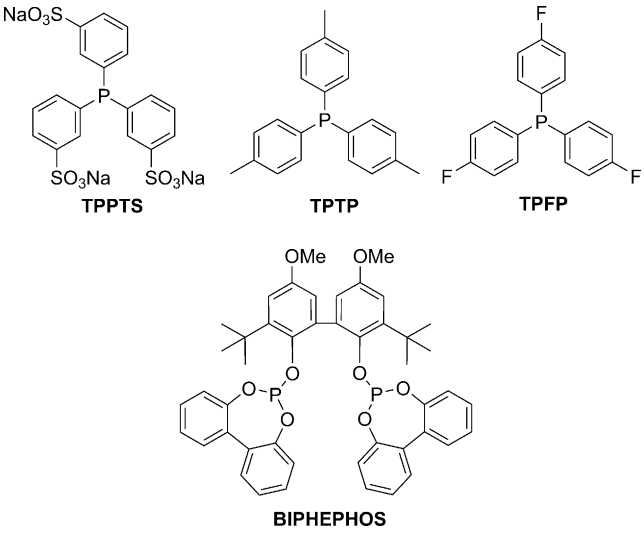


Figure 5. Selected phosphines and phosphite.

Table 2: Influence of the ligand on the hydroformylation of **2a** under ball-milling conditions in the presence of **1d**.[a]

Entry	Phosphine	Conv [%][b]	Aldehyde sel. [%][b]	**3α/3β**[b]
1	–	0	100	–
2	PPh_3	54	100	2
3	TPPTS	4	100	10
4	TPTP	38	100	3.3
5	TPFP	67	100	2.5
6	BIPHEPHOS	35	100	1.1

[a] Reagents and Conditions: $Rh(CO)_2(acac)$ (3.7 μmol), PPh_3 (18.5 μmol), **2a** (1.8 mmol), additive (1.8 mmol), CO/H_2 (1:1) (220 psi), rotation speed (850 rpm), 4 h. [b] determined by NMR spectroscopy.

In terms of regioselectivity, the best regioselectivities were obtained using BIPHEPHOS, a bidentate ligand BIPHEPHOS well-known to favor the reactivity of terminal alkene carbons.[3,12]

In that case, **3α** and **3β** were obtained in almost equal proportions (Table 2, entry 6). The low **3α**/**3β** ratio reflected the tendency of the bulky BIPHEPHOS-based Rh-catalyst to orient the hydroformylation towards the two vinyl carbons in a balanced way. Actually, the steric effects of both **1d** and BIPHEPHOS probably operate in conjunction (Figure 4). The formation of the bidentate Rh-complex derived from BIPHEPHOS under ball-milling conditions was unambiguously demonstrated by NMR measurement (Supporting information).

Once the proof-of-concept was complete with **2a** as a model substrate, we examined the substrate scope of the reaction, and the results are shown in Table 3. Compared to **2a**, similar trends were observed for 4-vinyl biphenyl (**2b**), 4-vinylbenzoic acid (**2c**), and 9-vinylanthracene (**2d**). Acyclic saccharides always led to high dispersion of the substrate within the solid mixture with beneficial effects on the catalytic activity. CDs, for their part, were less effective in terms of catalytic activity, but significantly modified the regioselectivity. Note that, as already mentioned in the literature,[12] the aldehydes resulting from hydroformylation of **2c** reacted in the aldol condensation under acidic conditions (inherent to **2c**), as revealed by the disappearance of the formyl signal on the ^{1}H spectra.

Table 3: Substrate scope of the hydroformylation reaction.[a]

Entry	Substrate	Additive	Conv[b] [%]	Aldehyde sel. [%][b]	α/β[b]
1	**2b**	**1a**	82	100	6.2
2	**2b**	**1b**	100	100	10
3	**2b**	**1c**	24	100	5
4	**2b**	**1d**	27	100	2
5	**2b**	**1e**	24	100	3.3
6	**2c**	**1a**	100	100	n.d.
7	**2c**	**1b**	100	100	n.d.
8	**2c**	**1c**	27	100	3.3
9	**2c**	**1d**	24	100	2
10	**2c**	**1e**	23	100	3.3
11	**2d**	**1a**	9	100	100
12	**2d**	**1b**	20	100	100
13	**2d**	**1c**	10	100	10
14	**2d**	**1d**	4	100	5
15	**2d**	**1e**	3	100	2

[a] Conditions: $Rh(CO)_2$(acetylacetonate) (3.7 μmol), TPP (18.5 μmol), substrate (1.8 mmol), additive (1.8 mmol), CO/H_2 (1:1) (200 psi), rotation speed (850 rpm), 4 h. [b] determined by NMR spectroscopy; n.d. = not determined.

In conclusion, Rh-catalyzed hydroformylation of alkenes was reported for the first time under ball-milling conditions. The reaction proceeded under CO/H_2 pressure in a planetary ball mill in the presence of saccharides as additives. The activity and selectivity of Rh-catalyzed hydroformylation of vinyl derivatives were controlled by a judicious choice of the saccharide. Excellent chemoselectivity was observed whatever the nature of the saccharide, as aldehydes were exclusively formed during the course of the reaction. Acyclic saccharides greatly favor the diffusion of the substrate within the solid mixture while cyclic saccharides, such as CDs, act as transient second-sphere ligand around the catalyst center with noncovalent structure-directing effects. They modify the regioselectivity via through-space control and favor hydroformylation at the less-hindered position of the vinyl function. The effect could be amplified by using bulky bidentate ligands, such as BIPHEPHOS. This is the first example of saccharide-assisted selectivity control under solvent-free ball-milling conditions. These unprecedented results pave the road to further developments of catalytic processes with high catalytic activity and unusual selectivity in the solid state.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: cyclodextrins · hydroformylation · mechanosynthesis · regioselectivity · supramolecular chemistry

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Communications

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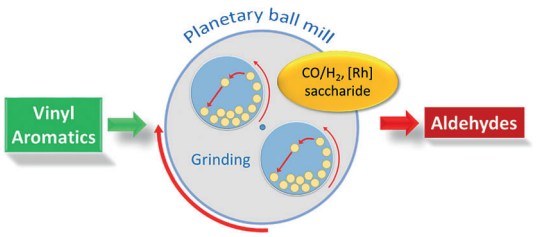

Ground sugar: The rhodium-catalyzed hydroformylation of aromatic-substituted alkenes is efficiently performed in a planetary ball mill under CO/H_2 pressure. It gives aldehydes in high chemoselectivity and with modification of the regioselectivity to the less-preferred β-aldehydes.