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Formation of Acetals under Rhodium-Catalyzed Hydroformylation Conditions in Alcohols

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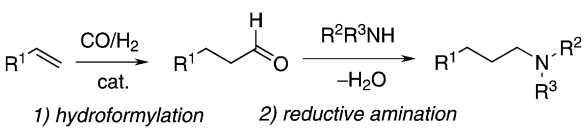
Abstract: Hydroformylation of terminal alkenes in alcohol solvents leads to the selective formation of the corresponding acetals. The Xantphos ligand gave the best results as well as acetal selectivities higher than 99% and linear/branched ratios of up to 52 were obtained. The scope of the reaction was studied. Acetals were found to be unreactive under hydroaminomethylation conditions.

Keywords: acetals; alcohols; alkenes; hydroformylation; phosphorus ligands; rhodium

Introduction

The last 40 years have seen considerable progress in the field of rhodium-catalyzed hydroformylation.[1] Many catalytic systems have been reported and nowadays excellent selectivities and turnover frequencies can be achieved under mild reaction conditions. Representing a potential atom efficient route to amines, we are interested in the hydroaminomethylation (HAM),[2,3] a cascade reaction involving hydroformylation and a reductive amination step (see Scheme 1).[4] This reaction proceeds faster and with better selectivities using alcohols as co-solvent.[4a] In order to understand the role of the alcohol in the catalytic cycle, we decided to investigate in the first place the hydroformylation reaction in alcohol solvents.

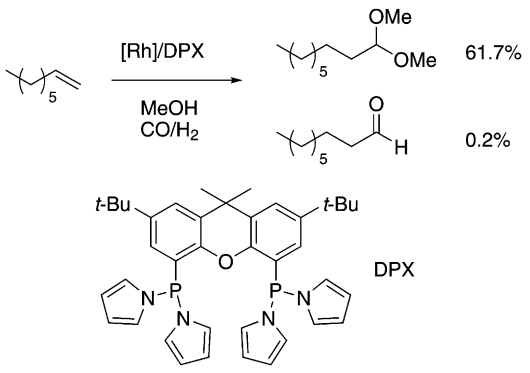


Scheme 1. Hydroaminomethylation reaction.

Results and Discussion

Ligand and Parameter Screening

We reported recently on the excellent activities and selectivities obtained in hydroaminomethylation using a combination of a rhodium source and the DPX ligand (Scheme 2).[4a] Ethanol and methanol were the most suitable solvents for this transformation. Hence, the hydroformylation of 1-octene using a DPX-modified rhodium catalyst was carried out in methanol. A new product was formed in high selectivity which was identified as the acetal 1,1-dimethoxynonane (see Scheme 2). The amount of aldehyde in the final mixture composition was only 0.2% (Table 2 entry 6).



Scheme 2. Acetal formation in methanol.

Table 1. Hydroformylation of 1-octene in methanol using monodentate ligands.[a]

Entry	L	Cone angle	χ[b]	Conversion[c]	% Octane	Acetal selectivity [%][d]	l/b ratio acetal
1	none (CO)	–	–	49.7	15.2	95.6	1.5
2	$P(pyrrolyl)_3$	145	–	97.9	1.1	96.3	4.4
3	phosphabenzene[e]	–	24.0[h]	95.7	0.1	95.5	2.1
4	$P(OAr)_3$[f]	175	30.0	99.2	31.6	91.9	1.4
5	$P(OAr)_3$[g]	175	30.0	100	10.4	60.3	2.0
6	$P(OPh)_3$	128	29.2	96.9	2.9	95.6	4.3
7	$P(OPh)_3$[g]	128	29.2	22.6	0.8	0.0	n.d.
8	$P(O\text{-}o\text{-}tolyl)_3$	141	28.0	99.0	12.1	91.1	2.4
9	PPh_3	145	12.8	93.9	0.2	81.8	4.5
10	PBu_3	132	4.2	91.7	0.4	0.7	1.5
11	PCy_3	170	0.3	96.8	44.4	65.1	2.8

[a] *Reaction conditions:* in a 10 mL autoclave were placed 1-octene (1 mmol), dodecane (0.2 mmol, internal standard for GC), methanol (20 mmol), $[Rh(cod)_2]BF_4$ (10 μmol, S/Rh = 100), ligand (30 μmol, L/Rh = 3), CO/H_2 (30 bar, 1:2 ratio), 110 °C, 1 h. For full details on final mixture composition, see Supporting Information, Table S1.
[b] Tolman electronic parameter. $\chi[P(t\text{-}Bu)_3] = 0$ (see ref.[8]).
[c] Conversion based on octenes consumption.
[d] Selectivities calculated amongst C_9 products.
[e] 2,4,6-Triphenylphosphabenzene.
[f] Ar = 2,4-$(t\text{-}Bu)_2C_6H_3$.
[g] P/Rh = 10.
[h] Based on the complex *trans*-[$\mathbf{L}_2$Rh(CO)Cl] (see ref.[9]).

Table 2. Hydroformylation of 1-octene in methanol with bidentate ligands.[a]

Entry	L	Bite angle β_n (°)	Conversion[b]	% Octane	Acetal selectivity [%][c]	l/b ratio acetal
1	dppm	72	3.2	3	n.d.	n.d.
2	dppe	85	1.0	0.9	n.d.	n.d.
3	(*R*)-Binap	93	4.3	1	71.9	2.3
4	dppf	99	29.2	11.5	32.2	9.3
5	*rac*-bidentate phosphite	101	91.3	7	97.9	4.1
6	DPX	111	84.5	22.6	99.7	14.9
7	Xantphos	111	78.8	4	97.6	42.3

[a] *Reaction conditions*: in a 10 mL autoclave were placed 1-octene (1 mmol), dodecane (0.2 mmol, internal standard for GC), methanol (20 mmol), $[Rh(cod)_2]BF_4$ (10 μmol, S/Rh = 100), ligand (30 μmol, L/Rh = 3), CO/H_2 (30 bar, 1:2 ratio), 110 °C, 1 h. For full details on final mixture composition, see Supporting Information.
[b] Conversion based on octenes consumption.
[c] Selectivities calculated amongst C_9 products.

The formation of acetals from alkenes under hydroformylation conditions has been already described in the literature.[5] This reaction has been reported to be catalyzed by various metal precursors including cobalt, palladium, platinum and rhodium in alcohol media[6] or by using orthoformate derivatives.[7] We report here on a systematic study of the influence of different reaction parameters (ligand, alcohol, substrate, etc.) on the acetal selectivity in the rhodium-catalyzed reaction. To understand the formation of acetals, the same reaction was conducted using monodentate ligands with different steric and electronic properties (see Table 1).[8]

When performing the reaction without any phosphorus ligand, the acetal selectivity was high but the l/b ratio was expectedly poor. Moreover the reaction was slow, 50% octene being left unreacted (entry 1). The very π-accepting 2,4,6-triphenylphosphabenzene[9] and $P(pyrrolyl)_3$[10] ligands gave excellent acetal selectivies, the latter leading to a better l/b ratio (entries 2 and 3). The more significant steric bulk of 2,4,6-triphenylphosphabenzene appeared deleterious for the regioselectivity. The same trend was observed with phosphite ligands, the cone angle having a considerable impact on both yields and linearities (entries 4, 6 and 8). Increasing the ratio P/Rh had an important effect on the acetal formation (entries 5 and 7). In the case of $P(OAr)_3$, known to lead selectively to monocoordinated rhodium species,[11] similar hydroformylation activities were observed. However, high P/Rh ratios reduced the acetalization activity (entry 5). Increasing the amount of $P(OPh)_3$, known to form di-

and tri-coordinated complexes with rhodium, led to a dramatic decrease of both hydroformylation and acetalization activities (entry 7). This effect was already observed by El Ali et al.[6f] Surprisingly PPh_3 gave mainly acetals, but with lower acetal selectivity than with π-acceptor ligands (entry 9). The highly σ-donating PBu_3 and PCy_3 ligands gave lower acetal yields (entries 10 and 11). Interestingly, PBu_3 hardly allowed the formation of acetal and a significant amount of alcohols was formed instead (28.8% with l/b ratio of 6.9).[12] It is important to note that no unsaturated ethers were detected in this case by gas chromatography.[6f] From this monodentate ligand study it appears clear that the more π-accepting the ligand, the better the acetal selectivity (Figure 1).

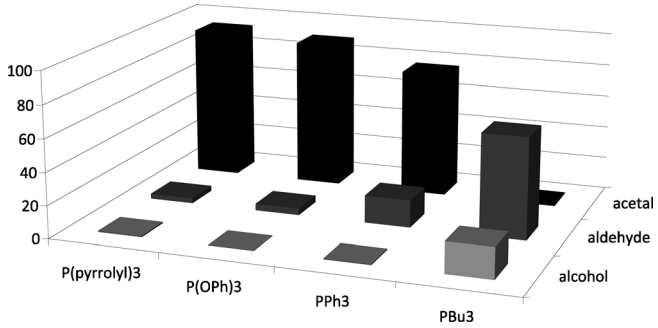
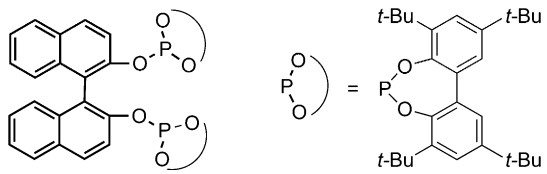


Figure 1. Electronic effect on selectivity.

Next, bidentate ligands of increasing bite-angle β_n[13] and π-accepting character were tested. Large bite-angle ligands are known to give high regioselectivties for the linear products.[14] The results are shown in Table 2. Small bite angle ligands (dppm, dppe and binap, entries 1 to 3) gave very low conversions. The dppf ligand ($\beta_n = 99°$) led to a more active catalytic system, but the conversion was only 29% after 1 h of reaction with low acetal selectivity (Table 2, entry 4). The bidentate phosphite[15]



***rac*-bidentate phosphite**

Figure 2. *rac*-Bidentate phosphite used.

(Figure 2) gave a very good selectivity to the acetal but relatively low l/b ratio (Table 2, entry 5). The best results were obtained with the large bite-angle ligands DPX[4a,16] and Xantphos[17] (Table 2, entries 6 and 7).

Although the DPX ligand gave 22.6% octane and a low l/b ratio, it gave an excellent acetal selectivity. Xantphos produced only a small amount of octane, a good acetal selectivity and an excellent l/b ratio of 42. This is why Xantphos was chosen for further investigations. It is important to note that the l/b ratio of the acetals was always higher than that of the remaining aldehyde, strongly suggesting that acetalization of linear aldehydes is preferred (also see Supporting Information).

Different parameters were then changed (see Table 3). Increasing the S/Rh to 200 and 300 ratio did not significantly affect the final mixture composition (Table 3, entries 2 and 3). The following experiments have been conducted with an S/Rh ratio of 200. Using syngas with a ratio CO/H_2 1:1, the reaction was slightly faster but significantly less selective towards acetal formation (85.5% instead of 92.1% with CO/H_2 1:2). Moreover, the regioselectivity dropped, the l/b ratio being 34.6 in this case (Table 3, entry 4). Decreasing the reaction temperature only led to lower activities and lower linearities (Table 3, entries 5 and 6). Decreasing the reaction pressure to 20 bar did not significantly affect the product distribution, though the l/b ratio decreased to 46.3 (Table 3, entry 7).

Table 3. Hydroformylation of 1-octene using Xantphos as ligand.[a]

Entry	Reaction parameters	Conversion [%][b]	% Octane	Acetal selectivity [%][c]	l/b ratio acetal
1	S/Rh = 100	78.8	4	97.6	42.3
2	S/Rh = 200	86.3	2.4	92.1	52.4
3	S/Rh = 300	84.2	2.0	91.9	51.1
4	CO/H_2 30 bar 1:1	96.6	2.6	85.5	34.6
5	$T = 95\,°C$	78.8	2.5	94.2	26.0
6	$T = 80\,°C$	65.9	4.5	95.9	13.6
7	$P = 20$ bar	82.2	2.1	94.1	46.3

[a] *Reaction conditions:* in a 10 mL autoclave were placed 1-octene, dodecane (0.2 mmol, internal standard for GC), methanol (20 mmol), $[Rh(cod)_2]BF_4$ (10 μmol), ligand (30 μmol, L/Rh = 3), CO/H_2 (P = 30 bar, 1:2), 110 °C, 90 min. For full details on final mixture composition, see Supporting Information.
[b] Conversion based on octenes consumption.
[c] Acetal selectivities based on C_9 products.

Reaction Profile

The reaction was then set up using a substrate/rhodium ratio of 400 in a 75-mL autoclave equipped with a capillary sampling system (Figure 3). Linear aldehyde was the main intermediate product, reaching 53% of the product composition after 40 min of reaction. The acetal formation from the aldehyde appeared to be slower.

The TOF of the reaction at 50% conversion of 1-octene (after 12 min) was estimated to 1000 h^{-1}. The acetal formation was slower: one mole of catalyst produced 120 moles of acetal per hour (at 20% acetal yield).

As can be seen in Figure 4, during this reaction, the l/b ratio of both aldehyde and acetal decreased in time. But gratifyingly, the l/b ratio of the acetal is always higher than the one of the aldehyde, suggesting again that the acetalization of the linear aldehyde is strongly preferred.

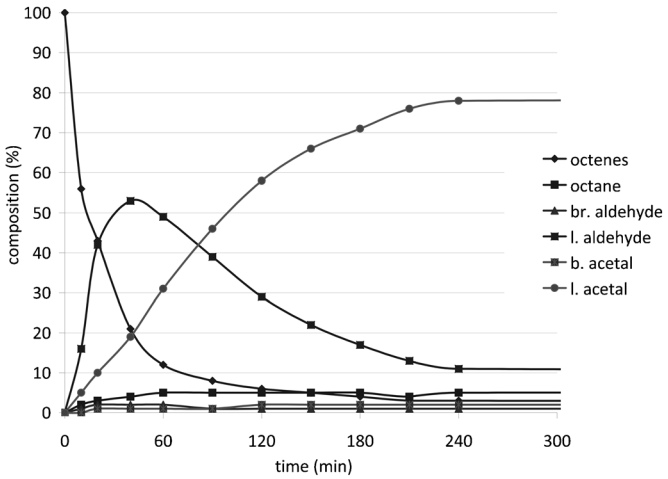


Figure 3. Reaction profile of the 1,1-dimethoxynonane formation. 1-octene (10 mmol), $[Rh(cod)_2BF_4]$ (S/Rh = 400), Xantphos (L/Rh = 3), MeOH (200 mmol), CO/H_2 (30 bar, 1:2), 110 °C.

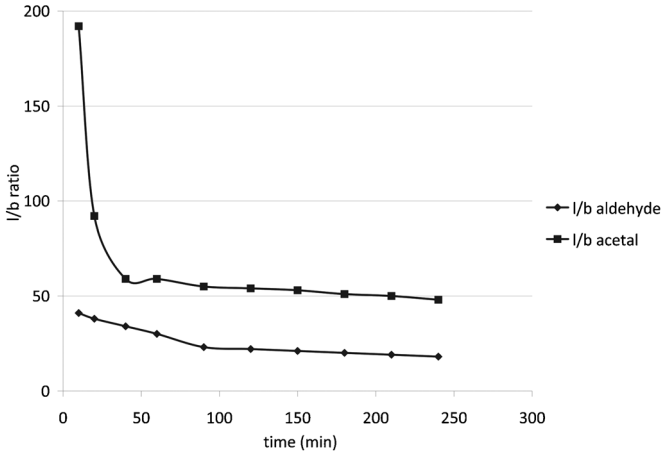
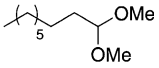
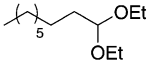
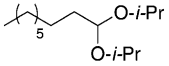
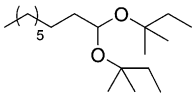
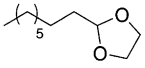
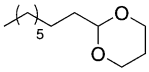


Figure 4. Evolution of l/b ratio in time. 1-octene (10 mmol), $[Rh(cod)_2BF_4]$ (S/Rh = 400), Xantphos (L/Rh = 3), MeOH (200 mmol), CO/H_2 (30 bar, 1:2), 110 °C.

Scope of the Reaction

Different alcohols were used as solvent (see Table 4). The acetal selectivity decreases from primary alcohols

Table 4. Scope of the reaction; different alcohols.[a]

Entry	Product	Conversion [%][b]	% Octane	Acetal selectivity [%][c]	l/b ratio acetal
1		86.3	2.4	92.1	52.4
2		87.7	12.1	85.2	53.9
3		88.2	2.2	68.7	89.2
4		83.6 93.5[d]	8.4 5.6	6.9 <0.5	16.6 n.d.[e]
5		70.1	9.6	99.3	25.6
6		92.1	3.7	93.6	9.1

[a] *Reaction conditions:* in a 10 mL autoclave were placed 1-octene (2 mmol), alcohol or diol (20 mmol), $[Rh(cod)_2]BF_4$ (10 μmol), Xantphos (30 μmol), CO/H_2 (30 bar, 1:2 ratio), 110 °C, 90 min. For full details on final mixture composition, see Supporting Information.
[b] Conversion based on octenes consumption.
[c] Acetal selectivities based on C_9 products.
[d] Reaction conducted at 140 °C.
[e] Not determined. Mainly aldehydes, aldol condensation products and alcohols were obtained.

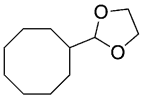
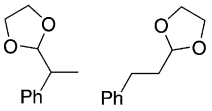
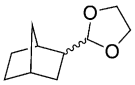
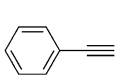
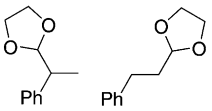
to tertiary alcohols (Table 4, entries 1 to 4). The tertiary 2-methylbutan-2-ol gave only 6.9% acetal selectivity (Table 4, entry 4). In this case, the major product was the linear aldehyde. Increasing the temperature led to a mixture of various C_9 and C_{18} products and no acetal was detected. Diols are widely used as protecting agents for aldehydes. Thus our attention was focussed on the use of ethylene glycol and propylene glycol (Table 4, entries 5 and 6). Gratifyingly, the acetal selectivities were very high (up to 99.3% for ethylene glycol). This reaction can thus find interesting application in synthesis since the produced aldehyde can be changed to a 2-alkyldioxolane or 2-alkyl-1,3-dioxane in the same pot. Interestingly, technical grade diols could be used in this case, showing that the presence of traces of water was not deleterious for the reaction.

The scope was then further investigated by using different alkenes in ethylene glycol, producing 2-alkyldioxolanes (Table 5). With internal alkenes (*cis*-cyclooctene here), the reaction was very slow (Table 5, entry 1). Even after 63 h, the conversion was only 27%. However, a very good acetal selectivity was obtained and only little octane was formed (0.5%). As only one product can be formed, the reaction was performed using $P(OPh)_3$ as ligand. In this case, excellent conversion and selectivities were obtained in a short reaction time. We then moved to styrene (Table 5, entry 2). The conversion was very high, and the selectivity towards acetal was 91.4%. However, the l/b ratio was 1.0 and a significant amount of ethylbenzene (hydrogenation product) was produced (24.0%).[18] A screening of ligands showed that the linear product is difficult to form and that the regioselectivity is very different than in toluene.[19] Triphenylphosphine proved to be the most selective towards the branched product, the l/b ratio being 0.31 in this case. Norbornene (Table 5, entry 3) was also a suitable substrate for this transformation and 92.0% acetal selectivity was obtained (5% alcohol and 3% aldehyde were obtained as side products). Phenylacetylene was submitted to the same reaction conditions (Table 5, entry 4). In this specific case, the saturated acetals are obtained, suggesting a cascade hydroformylation–acetalization–hydrogenation reaction. The reaction was followed over time and saturated and unsaturated aldehydes were detected. However, no trace of unsaturated acetal was observed, suggesting that the acetalization of the unsaturated aldehyde is not favored (see Scheme 3).

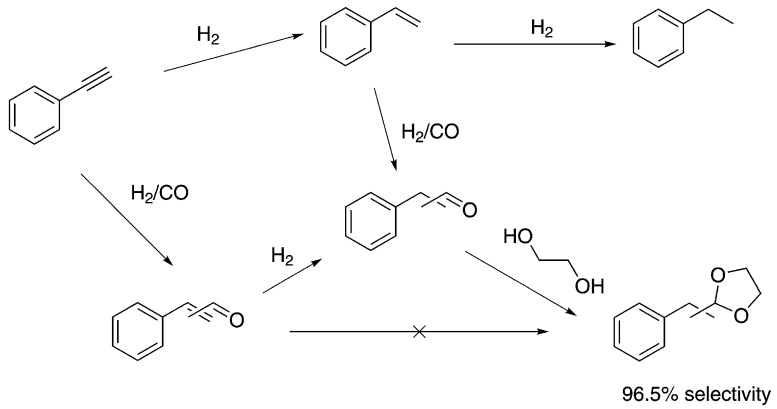
Tolerance to Ketone Functionalities

The reaction described above allows the direct formation of protected aldehydes from an alkene or alkyne source. It appeared interesting to check whether ketones were also protected under our reaction conditions. We decided then to focus our attention on the hydroacetalization of a ketoalkene. As a simple and

Table 5. Scope of the reaction; different alkenes.[a]

Entry	Substrate	Product	Conversion [%]	% Alkane	Acetal selectivity [%]	l/b ratio acetal
1			6.6	0.4	8.9	–
			27.0[b]	0.5	94.7	–
			97.8[c]	0.5	98.9	–
2			95.3	24.0	91.4	1.0
			96.8[d]	19.9	96.8	1.0
			94.8[e]	14.3	94.9	1.34
			100[f]	5.4	96.8	0.31
			100[g]	4.8	98.2	0.55
3			>99.5	<0.5	92.0	8.6[h]
4			91.1	<0.5	96.5	2.5

[a] *Reaction conditions:* in a 10 mL autoclave were placed alkene (2 mmol), ethylene glycol (20 mmol), $[Rh(cod)_2]BF_4$ (10 μmol), Xantphos (30 μmol), CO/H_2 (30 bar, 1:2 ratio), 110 °C, 90 min.
[b] Reaction time was 63 h.
[c] $P(OPh)_3$ (30 μmol) used as ligand.
[d] No ligand was used.
[e] Bidentate phosphite was used as ligand; P/Rh = 6. See ref.[19]
[f] Using PPh_3 as ligand; P/Rh = 3.
[g] Using $P[O\text{-}2,4\text{-}(t\text{-}Bu)_2C_6H_3]_3$ as ligand; P/Rh = 3.
[h] The *endo/exo* ratio, determined by GC.



Scheme 3. Reaction with phenylacetylene.

commercially available substrate, 5-hexen-2-one (allylacetone), was chosen and was subjected to hydroacetalization conditions in methanol and in ethylene glycol (see Table 6). When using methanol as solvent, no trace of the diacetals was detected, showing that the acetalization reaction selectively affects aldehydes in this case (Table 6, entries 1 and 2).[6g] In ethylene glycol, as expected, the acetal formation was fast, leaving only traces of the intermediate ketoaldehyde (Table 6, entry 3). Both the ketoacetal[20] and diacetal were produced in a 2.1:1 ratio. The l/b ratios were significantly lower in that case.

Understanding the Acetal Formation

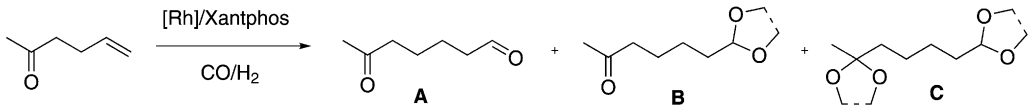
In order to get more insight in the *in situ* acetal formation, nonanal was submitted to our "standard reaction conditions".[21] Expectedly, nonanal is converted into 1,1-dimethoxynonane (in methanol) or into 2-nonyldioxolane (in ethylene glycol) in excellent yields (see Table 7, entry 1). Without rhodium present, very little acetal was formed (Table 7, entry 2). Interestingly, running the reaction without H_2 (reaction pressurized only with 10 bar of CO), the acetal formed in only 4.6% yield (Table 7, entry 3). These results suggest that the rhodium precursor and molecular hydrogen are required to get good acetal selectivity. Suspecting that the formation of tetrafluoroboric acid from $[Rh(cod)_2BF_4]$ and dihydrogen, the reaction was conducted using $[Rh(acac)(CO)_2]$ as precursor. In this case, only 44.5% acetal was formed (Table 7, entry 4).

The effect of the rhodium precursor on the selectivity was already observed in the hydroaminomethylation reaction.[4b] Finally, nonanal was reacted using only HFB_4 as catalyst which showed good acetalization ability (Table 7 , entries 6 and 7) but did not outperform $[Rh(cod)_2BF_4]$. These experiments suggest that the good acetal selectivities obtained above are due to a cooperative effect between the rhodium species and the *in situ* formed acid HBF_4.

Acetal as Intermediate in HAM?

As described above, alcohol co-solvents have appeared necessary for good activity in rhodium-catalyzed hydroaminomethylation (HAM).[4] In the absence of amine reactant (present catalytic system), acetals are formed selectively.[3b] However, acetals were never detected during HAM processes.[2,3,4] We decided then to investigate whether acetals could be

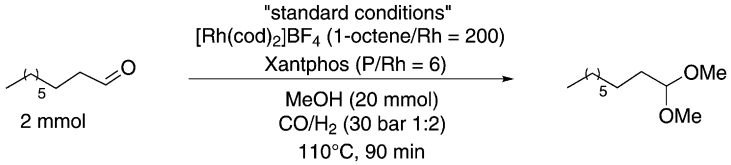
Table 6. Tandem hydroformylation-acetalization of 5-hexen-2-one (allylacetone).[a]



Entry	Solvent	Conversion [%]	% Alkane	B selectivity [%]	% A (l/b ratio)	% B (l/b ratio)	% C (l/b ratio)
1	methanol	96.2	8.6	85.6	12.6 (9.8)	74.8 (20.2)	<0.2 (n.d.[b])
2	methanol[c]	99.8	8.5	85.2	13.4 (10.3)	77.2 (21.1)	<0.2 (n.d.[b])
3	ethylene glycol[d]	83.7	19.2	49.3	0.6 (n.d.[b])	35.2 (6.7)	16.5 (6.5)

[a] *Reaction conditions:* in a 10 mL autoclave were placed alkene (2 mmol), alcohol (20 mmol), $[Rh(cod)_2]BF_4$ (10 μmol), Xantphos (30 μmol), CO/H_2 (30 bar, 1:2 ratio), 110 °C, 1 h.
[b] Not determined.
[c] Reaction time is 5 h.
[d] 19.1% of the substrate was acetalized at the ketone position without hydroformylating the alkene.

Table 7. Acetalization of nonanal.



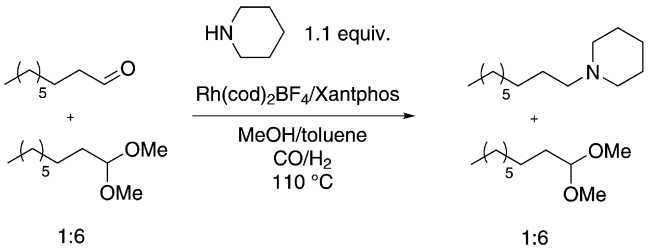
Entry	Deviation from "standard conditions"	Acetal yield [%]
1	none	93
2	no Rh	1.4
3	no H_2	4.6
4	$[Rh(acac)(CO)_2]$ instead of $[Rh(cod)_2BF_4]$	44.5
5	acacH[a,b]	0
6	no Rh, no Xantphos, HBF_4 0.5 mol%	71.1
7	no Rh, no Xantphos, HBF_4 10 mol%	87.1

[a] acacH: acetylacetone, 0.5 mol%.
[b] Aldol condensation product was formed (*ca.* 50%).

reaction intermediates in hydroaminomethylation reactions. When a mixture of nonanal/1,1-dimethoxynonane (1:6) was subjected to the hydroaminomethylation conditions described by Beller[3b] using piperidine as amine source, nonanal was quantitatively converted to 1-nonylpiperidine and 1,1-dimethoxynonane was left unreacted. Moreover, the ratio 1-nonylpiperidine/1,1-dimethoxynonane was still 1:6 showing that nonanal was not converted to 1,1-dimethoxynonane in the presence of an amine (see Scheme 4). This result shows that acetals are not an intermediate in HAM.

Conclusions

Hydroformylation of terminal and internal alkenes with a rhodium/Xantphos system in alcohols as solvent led to the highly selective formation of the corresponding acetals. Especially in methanol and ethylene glycol, good to excellent selectivites were obtained. Small amounts of water were tolerated, so technical grade alcohols could be used without the need of dessicating agents. An autoclave equipped with a capillary sampling device permitted to draw the reaction profile which showed the aldehyde formation to be fast (TOF = *ca.* 1000 h^{-1}) and the acetalization to be the limiting step. The rate of acetal formation was estimated at 120 h^{-1}. Acetals do not undergo reductive amination under typical HAM conditions. Hence they can be ruled out as, however short lived, intermediates. Nevertheless, the exact role of alcohol co-sovlents in HAM reactions remains unclear. There is still the possibility of hemiaminal participation as suggested by Börner.[22]



Scheme 4. Acetal is not an intermediate in HAM.

Performing the reaction with 5-hexen-2-one showed that the aldehyde group was selectively acetalized in methanol. However the selectivity dropped when moving to ethylene glycol. Finally we could show that the good acetal selectivities are due to a cooperative effect of the rhodium species and HBF_4 formed *in situ* from the catalyst precursor.

Experimental Section

General Procedure

Reactions were performed in home-made 10 mL autoclaves. The autoclave was charged with $[Rh(cod)_2]BF_4$ (10 μmol; cod = 1,5-cyclooctadiene), alkene (2 mmol) and ligand (30 μmol) in 20 mmol of solvent (alcohol or diol) under an argon atmosphere. The autoclave was purged three times with H_2 ($P = 10$ bar) to remove the remaining argon from the autoclave. Subsequently, the autoclave was pressurized with CO and H_2 to the desired pressure and heated to reaction temperature using a preheated oil bath. After a certain reaction time, the autoclave was cooled to room temperature and the mixture was removed from the autoclave, filtered and analyzed by GC.

Reaction Profile

The reaction profile (Figure 3) was obtained using a home-made 75-mL autoclave equipped with a high pressure sampling system. A solution containing all the ingredients was prepared in a Schlenk flask under argon and injected into the autoclave which was purged three times with H_2 ($P =$

10 bar) to remove the remaining argon. Subsequently, the autoclave was pressurized with CO and H_2 to the desired pressure and heated to the reaction temperature. Samples were taken regularly and analyzed by GC.

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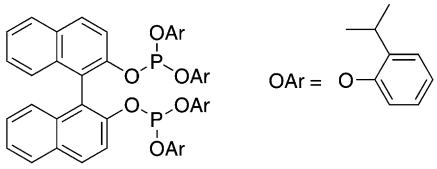

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