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Chemo- and Regioselective Homogeneous Rhodium-Catalyzed Hydroamidomethylation of Terminal Alkenes to *N*-Alkylamides

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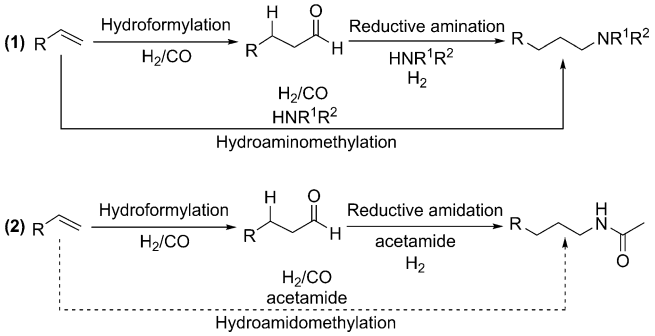
A rhodium/xantphos homogeneous catalyst system has been developed for direct chemo- and regioselective mono-*N*-alkylation of primary amides with 1-alkenes and syngas through catalytic hydroamidomethylation with 1-pentene and acetamide as model substrates. For appropriate catalyst performance, it appears to be essential that catalytic amounts of a strong acid promoter, such as *p*-toluenesulfonic acid (HOTs), as well as larger amounts of a weakly acidic protic promoter, particularly hexafluoroisopropyl alcohol (HOR^F) are applied. Apart from the product *N*-1-hexylacetamide, the isomeric unsaturated intermediates, hexanol and higher mass byproducts, as well as the corresponding isomeric branched products, can be formed. Under optimized conditions, almost full alkene conversion can be achieved with more than 80% selectivity to the product *N*-1-hexylamide. Interestingly, in the presence of a relatively high concentration of HOR^F, the same catalyst system shows a remarkably high selectivity for the formation of hexanol from 1-pentene with syngas, thus presenting a unique example of a selective rhodium-catalyzed hydroformylation–hydrogenation tandem reaction under mild conditions. Time-dependent product formation during hydroamidomethylation batch experiments provides evidence for aldehyde and unsaturated intermediates; this clearly indicates the three-step hydroformylation/condensation/hydrogenation reaction sequence that takes place in hydroamidomethylation. One likely role of the weakly acidic protic promoter, HOR^F, in combination with the strong acid HOTs, is to establish a dual-functionality rhodium catalyst system comprised of a neutral rhodium(I) hydroformylation catalyst species and a cationic rhodium(III) complex capable of selectively reducing the imide and/or ene–amide intermediates that are in a dynamic, acid-catalyzed condensation equilibrium with the aldehyde and amide in a syngas environment.

Introduction

The formation of carbon–nitrogen bonds is of great interest to synthetic chemists because nitrogen-containing molecules are important in bulk and fine-chemical building blocks, solvents, surfactants, dyes, pharmaceuticals, agrochemicals, and biologically active compounds.[1] Among the various catalytic methods known for the synthesis of amines, the hydroaminomethylation of alkenes is highly atom-economical and efficient. This cascade reaction consists of initial hydroformylation followed by reductive amination (Scheme 1),[2] and was originally discovered by Reppe and Vetter in the early 1950s at BASF by using $[Fe(CO)_5]$ in nearly stoichiometric amounts.[3] Research on this reaction up to the mid-1990s revealed that relatively harsh conditions (>150 °C) were required to give the desired amines in good yield.[4] The critical step in this sequence is the hydrogenation of intermediate imino compounds, which is generally hampered by the presence of carbon monoxide, but this can be overcome by using alcoholic and polar solvents.[5] However, hydroaminomethylation of alkenes is mostly limited to the use of secondary amines; for primary amines and ammonia, the selectivity is generally low because of over-alkylation.



Scheme 1. Hydroaminomethylation versus the hydroamidomethylation reaction.

In analogy with hydroaminomethylation, the thus far unknown hydroamidomethylation reaction would comprise of a cascade reaction of hydroformylation and catalytic reductive amidation (Scheme 1). The development of this new method for the synthesis of *N*-alkylamides using an amide as the substrate instead of an amine avoids the formation of over-alkylated side products due to the low nucleophilicity and steric encumbrance at the amide nitrogen atom of the initially formed mono-*N*-alkylamide. The low nucleophilicity of the primary

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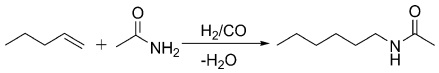
amide substrate generally makes the development of active and selective catalysts for the alkylation of a (primary) amide through hydroamidomethylation even more challenging than alkylation of (secondary) amines by hydroaminomethylation.

Inspired by our recent achievements concerning the catalytic reductive amidation of aldehydes,[6] we have undertaken an investigation into the catalytic synthesis of *N*-alkylamides, using acetamide and 1-pentene as example substrates, through a rhodium-catalyzed hydroamidomethylation reaction (Scheme 2).



Scheme 2. Hydroamidomethylation of 1-pentene with acetamide to form *N*-hexylacetamide.

Whereas we previously reported an efficient three-component homogeneous catalyst system consisting of rhodium/xantphos/*p*-toluenesulfonic acid (HOTs) for the selective reductive amidation of aldehydes under a pure H_2 atmosphere,[6] in the present study we aim to develop hydroamidomethylation catalyst systems that are not only effective in the hydroformylation of the alkenes, but also efficient in the reductive amidation of aldehydes formed in situ under a CO-containing atmosphere.

Results

General considerations

The products found after a typical hydroamidomethylation reaction of 1-pentene with acetamide are shown in Scheme 3 (full experimental details are given in the Supporting Information). Apart from the desired product, *N*-1-hexylacetamide (**3L**), depending on the efficiency and selectivity of the catalytic system, the reaction mixture may consist of the isomeric unsaturated intermediate compounds *N*-(1-hexylidene)acetamide and/or *N*-1-hexenylacetamide (**2L**), hexanal (**1L**), and hexanol (**4L**), as well as all corresponding branched products (**1B**, **2B**, **3B**, and **4B**). Additionally, various products with higher mass **5** (Figure 1), comprising self- or cross-aldol condensation products and the disubstituted product with two molecules of acetamide, may be formed.

The reactions were performed starting with 5 mmol of 1-pentene and an equivalent amount of acetamide; the product

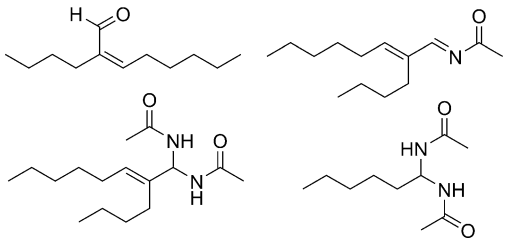
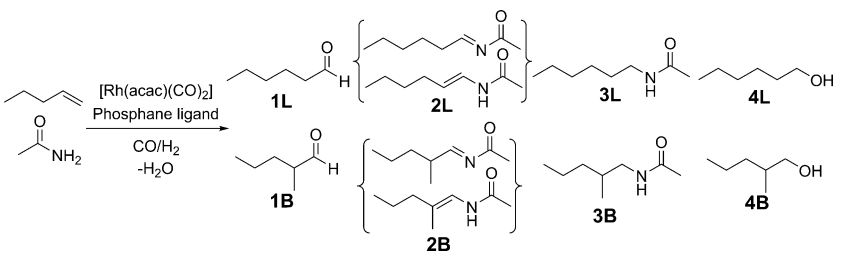


Figure 1. Products of higher molecular mass (**5**) observed in the hydroamidomethylation of 1-pentene with acetamide. Corresponding branched products are not shown.

distribution was determined by GC analysis. The conversion calculated for the reactions was based on the amount of 1-pentene found after the reaction. The amounts of linear and branched products **3L** and **3B**, unsaturated products **2L** and **2B**, hydroformylation products **1L** and **1B**, and alcohols **4L** and **4B** were determined by using calibration lines. In Tables 1–4, the selectivity for all products and intermediates is reported, as well as the linearity (%) of the aldehyde and *N*-hexylacetamide (**3L**). It is worth noting that the individual amounts of both types of unsaturated compounds **2** are generally small and present in an approximate 1:1 ratio; for clarity reasons, we have only indicated the total amount of compounds **2** in the product composition. The remainder consists of the higher mass products **5**, which were not individually quantified by GC, but rather lumped together and calculated from the mass balance of 1-pentene. Analytical product composition data of all experiments are given in the Supporting Information.

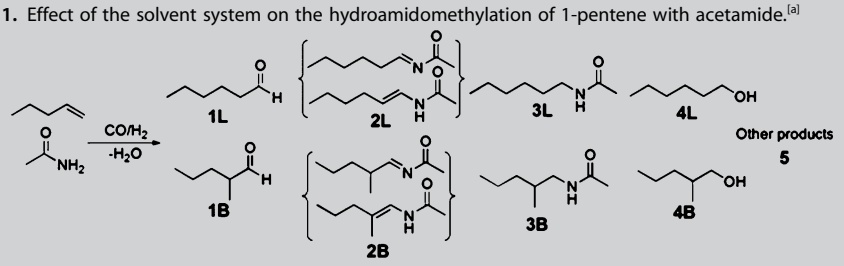
Catalytic hydroamidomethylation of 1-pentene with acetamide: Initial screening studies

Of the various rhodium precursors [{RhCl(cod)}$_2$] (cod = 1,5-cyclooctadiene), [Rh(acac)(CO)$_2$] (acac = acetylacetone), [Rh(cod)$_2$]BF$_4$, [Rh(CO)(H)(PPh$_3$)$_3$], and [Rh(cod)$_2$]OTf in combination with the 9,9-dimethyl-4,5-bis(diphenylphosphanyl)xanthene (xantphos) ligand, [Rh(acac)(CO)$_2$] gave the highest selectivity for **1L**, with only low amounts of condensation products **5** (Table S1 in the Supporting Information). HOTs was introduced as a cocatalyst to promote the coupling reaction of **1L** with acetamide;[6] however, next to a higher yield of **3L**, this resulted in strongly increased formation of products **5** (Table 1, entries 1 and 2). Although the use of trifluoromethanesulfonic acid (HOTf) resulted in higher selectivity for **3L**, large amounts of higher molecular weight products **5** were still produced (Table 1, entry 3). Increasing the amount of HOTs also led to some increased selectivity in favor of **3L**, but also resulted in high amounts of aldol condensation and di-coupled products (Table 1, entry 4). Finally, carrying



Scheme 3. Hydroamidomethylation of 1-pentene with acetamide: observed intermediates, products, and undesired byproducts.

Table 1. Effect of the solvent system on the hydroamidomethylation of 1-pentene with acetamide.[a]



Entry	Solvent (10 mL)	*t* [h]	Additive (0.05 mmol)	Conversion [%]	Selectivity [%][c] 1	2	3	4	acetal	5	Linearity [%] 1	3
1	diglyme	4	–	79	89	6	0	0	–	5	97	–
2	diglyme	4	HOTs	84	36	12	13	1	–	38	97	>99
3	diglyme	4	HOTf	89	26	11	19	3	–	41	92	>99
4	diglyme	4	HOTs (0.1)	89	24	12	23	1	–	40	94	>99
5	diglyme	8	HOTs	88	31	9	19	1	–	40	96	>99
6	diglyme[b]	8+4	HOTs	88	25	8	15	3	–	49	86	>99
7	MeOH	8	–	89	81	3	0	0	0	16	96	–
8	MeOH	8	HOTs	91	26	9	1	1	56	7	96	>99
9	1:1 MeOH/toluene	8	HOTs	89	35	19	2	0	34	9	92	>99
10	1:1 MeOH/diglyme	8	HOTs	90	31	17	1	0	40	11	93	>99
11	1:1 EtOH/diglyme	8	HOTs	82	45	22	0	0	20	13	93	–
12	1:1 *i*PrOH/diglyme	8	HOTs	85	43	20	7	2	16	12	92	>99
13	1:1 TFE/diglyme	8	HOTs	90	47	12	1	8	12	21	93	>99
14	1:1 HOR^F/diglyme	8	–	88	71	3	1	17	0	8	96	>99
15	1:1 HOR^F/diglyme	8	HOTs	85	52	6	14	16	6	6	96	99

[a] Reaction conditions: 0.01 mmol [Rh(acac)$(CO)_2$], 0.02 mmol xantphos, 5 mmol 1-pentene, 5 mmol acetamide (Rh/xantphos/1-pentene/acetamide = 1:2:500:500); P_{CO/H_2} = 50(1:2) bar; T = 100 °C; t = 4–12 h; solvent: 10 mL bis(2-methoxyethyl)ether (diglyme) or solvent/diglyme (*v*/*v*). [b] One-pot sequential reaction conditions; the reactor was charged with substrates in a similar fashion from the beginning of the reaction and then: 8 h at 100 °C hydroformylation under syngas P_{CO/H_2} = 50 (1:2) followed by depressurizing syngas- 3 pressurizing-depressurizing cycles with H_2- pressurizing with H_2-4 h, P_{H_2} = 80 bar at 80 °C reductive amidation. [c] The selectivity was determined by GC analysis with decane as an internal standard.

out the hydroamidomethylation reaction sequentially by first applying a syngas pressure followed by exposure to pure H_2 did not improve the yield of **3L** (Table 1, entry 6); this reaction sequence also resulted in the formation of large amounts of **5**.

A screening of various reaction solvents demonstrated that the product selectivity was highly dependent on solvent (Table 1, entries 7–15). The use of alcoholic solvents such as methanol, ethanol, isopropanol, *n*-butanol, isobutanol, and trifluoroethanol (TFE), as well as their combination with diglyme or toluene and with an acid cocatalyst, resulted mainly in acid-catalyzed acetal formation of **1L** with very low selectivity toward the desired product **3** (Table 1, entries 7–13; see also Table S2 in the Supporting Information). The use of the more acidic solvent 1,1,1,3,3,3-hexafluoroisopropyl alcohol (HOR^F, pK_a = 9.3) in combination with diglyme (1:1; even in the presence of HOTs) resulted in low acetal formation, but still only gave about 15% selectivity for the desired product **3** (Table 1, entry 15). Remarkably, a similar selectivity to **4L** (≈15%) was observed with the latter solvent combination, both in the absence and presence of HOTs (Table 1, entries 14 and 15).

It is worth noting that the overall regioselectivity for the linear products derived from 1-pentene (**1L**, **3L**, and **4L**) in nearly all cases is above 90%; this is in agreement with the intrinsically high linearity for hydroformylation of terminal alkenes with rhodium/xantphos catalysts reported in the literature.[7]

HOR^F as a cosolvent

Intrigued by the significantly deviating selectivity to alcohols in the experiment with a diglyme/HOR^F solvent mixture, we further examined the effects of HOR^F on the reaction characteristics. Thus, we investigated the effects of an increasing HOR^F/diglyme (*v*/*v*) ratio (at a constant total reaction volume) on the product composition. The results are depicted in Figure 2 (see also Tables S3 and S4 and Figures S2 and S3 in the Supporting Information).

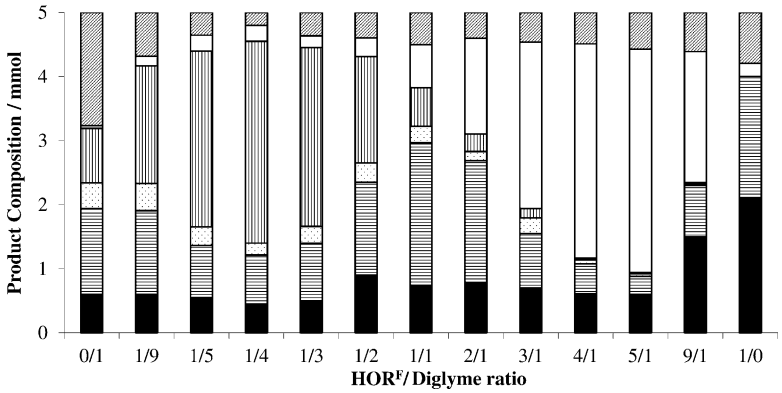


Figure 2. The effect of the ratio of HOR^F/diglyme on the product composition in the hydroamidomethylation of 1-pentene with acetamide catalyzed by the Rh/xantphos/HOTs system. Reaction conditions: 0.01 mmol [Rh(acac)$(CO)_2$], 0.02 mmol xantphos, 0.05 mmol HOTs, 5 mmol 1-pentene, 5 mmol acetamide (Rh/xantphos/HOTs/1-pentene/acetamide = 1:2:5:500:500); P_{CO/H_2} = 50(1:2) bar; T = 100 °C; t = 8 h; constant volume of reaction solvent: 10 mL; decane was used as an internal standard. ■ = 1-pentene, ▤ = aldehyde (**1**), ⊡ = unsaturated intermediate (**2**), ▥ = desired product (**3**), □ = alcohol (**4**), ▨ = other products (**5**); for more detailed information, see Table S3 and Figure S2 in the Supporting Information.

Gradually increasing the ratio of HOR^F/diglyme from 0:1 (pure diglyme) to 1:4 (*v*/*v*), did not considerably change the conversion of 1-pentene; the selectivity for the desired product **3**, however, increased spectacularly by almost a factor of five over this range of HOR^F concentration. Increasing the HOR^F concentration further to about 50% (HOR^F/diglyme = 1:1 *v*/*v*) surprisingly resulted in a drop of the selectivity to **3** with an increase in selectivity to aldehyde **1**. Moving to a HOR^F-richer regime of 5:1 resulted in a high selectivity (>80%) to alcohol **4**, which was clearly at the cost of the aldehydes. The use of pure HOR^F resulted in a decrease in the conversion of 1-pentene with a steep decrease in selectivity to alcohol **4**; the main products were aldehyde **1** and condensation products **5**. Thus, it appears that the 1:4 ratio of HOR^F/diglyme (≈20 mmol of HOR^F) gives the highest selectivity to the desired product **3**. As shown in Table S3 in the Supporting Information, acetal formation of **1L** with HOR^F appeared to be undetectable, when the applied HOR^F/diglyme ratio was smaller than 1:2.

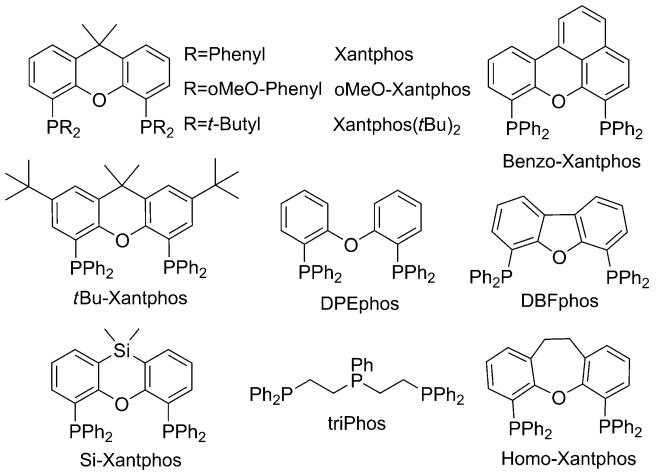


Figure 3. Selected ligands used in the hydroamidomethylation of 1-pentene with acetamide.

Optimization and scope of the hydroamidomethylation reaction in HOR^F/diglyme (1:4 *v*/*v*)

Effect of temperature and ligands

It appeared that the highest selectivity (≈70%) for product **3** was obtained at a reaction temperature of 100 °C (Figure S3 and Table S7 in the Supporting Information). At 120 °C, the selectivity for hydroamidomethylation decreased, particularly due to the formation of higher amounts of higher-mass products **5** (Figure S4 and Table S7 in the Supporting Information). Upon lowering the reaction temperature to 60–80 °C, the conversion of 1-pentene dropped with the build up of a significant concentration of unsaturated intermediates **2**; this indicated a progressively lower rate of reduction of intermediates **2** relative to their rate of formation.

A selection of ligands with different stereoelectronic properties as potential substitutes for xantphos were also tested under the same optimal reaction conditions. An overview of the ligands is shown in Figure 3. The catalytic results obtained with in situ generated rhodium/ligand/HOTs catalysts are summarized in Table 2.

In the absence of any phosphane ligand (Table 2, entry 1) full conversion of 1-pentene was observed, but with a low chemoselectivity (≈10%) to **3L**. Most striking is the low regioselectivity (≈70%) for **3L**, and only 30% for aldehyde product **1L**. The use of monodentate ligands, such as PPh_3 (Table 2, entry 2), resulted in nearly full conversion of 1-pentene after 4 h; however, again the linearity of the aldehyde (≈50%) and the selectivity to the desired product was very low (≈3%). Remarkably, the use of DPEphos (Table 2, entry 3), which is considered to be a more flexible analogue of xantphos, gave a low-performance catalyst with low chemoselectivity to **3** (≈35%). The high regioselectivity for linear product **3L** (97%) combined with a low regioselectivity of aldehyde clearly indicates that the subsequent reductive amidation of the linear aldehyde occurs preferentially over its branched isomer.

Among the various different xantphos-type ligands, the best results were obtained with xantphos (Table 2, entry 5), Si-xantphos (Table 2, entry 7), and *t*Bu-substituted xantphos (Table 2, entry 6) with selectivity to **3** of 53–59% (at 4 h reaction time)

Table 2. Effect of various ligands on the hydroamidomethylation of 1-pentene with acetamide.[a]

Entry	Ligand	Conversion [%]	Selectivity [%][b]					Linearity [%]	
			1	**2**	**3**	**4**	**5**	**1**	**3**
1	none	99	46	23	10	1	21	30	71
2	PPh_3	96	42	20	3	0	36	51	>99
3	DPEphos	70	37	13	34	3	14	67	97
4	triPhos	10	67	0	0	0	33	70	–
5	xantphos	83	27	9	57	4	4	95	>99
6	*t*Bu-xantphos	80	26	8	59	3	4	96	>99
7	Si-xantphos	77	31	7	53	5	4	72	99
8	*o*MeO-xantphos	11	71	8	3	0	17	58	>99
9	benzoxantphos	82	52	13	16	0	19	53	>99
10	DBFphos	46	44	25	23	3	5	97	98
11	homoxantphos	28	17	12	61	4	6	70	95
12	xantphos(tBu)$_2$	97	50	24	9	1	16	28	82

[a] Reaction conditions: 0.01 mmol [Rh(acac)(CO)$_2$], 0.02 (bidentate) or 0.04 mmol (monodentate) ligand, 0.05 mmol HOTs, 5 mmol 1-pentene, 5 mmol acetamide (Rh/L/HOTs/1-pentene/acetamide = 1:2 (bidentate) or 4 (monodentate):5:500:500); T = 100 °C; t = 4 h; P_{CO/H_2} = 50 bar (1:2); solvent: 10 mL HOR^F/diglyme (1:4). DPEphos = bis(2-diphenylphosphinophenyl)ether, triPhos = bis(2-phenylphosphinoethyl)phenylphosphane, *t*Bu-xantphos = 2,7-di-*tert*-butyl-9,9-dimethyl-4,5-bis(diphenylphosphanyl)xanthene, Si-xantphos = 4,6-bis(diphenylphosphanyl)-10,10-dimethyl-10*H*-dibenzo[*b*,*e*][1,4]oxasilane, *o*MeO-xantphos = 9,9-dimethyl-4,5-bis(di-*ortho*-methoxyphenylphosphanyl)xanthene, benzoxantphos = 6,8-bis(diphenylphosphino)benzo[*k*,*l*]-xanthene, DBFphos = 1,1′-(4,6-dibenzofurandiyl)bis(1,1-diphenylphosphane), homoxantphos = 4,6-bis(diphenylphosphino)-10,11-dihydrodibenzo[*b*,*f*]oxepine, xantphos(tBu)$_2$ = 9,9-dimethyl-4,5-bis(di-*tert*-butylphosphino)xanthene. [b] The selectivity was determined by GC analysis with decane as an internal standard.

and a combined selectivity, including potential precursors **1** and **2**, of up to 90–95%. In particular, catalytic systems with these ligands show a relatively low accumulation of unsaturated intermediates **2**, thus showing the importance of the rigid P–O–P backbone for selective hydrogenation.[6] The use of *o*MeO-xantphos (Table 2, entry 8) gave a low-activity catalyst with low chemoselectivity to **3** and surprisingly low regioselectivity (≈60%) to the aldehyde. Apparently, the bulky *o*MeO-phenyl substituents not only prevent binding of the aldehydes and intermediates **2**, but also that of 1-pentene.

Remarkably, low selectivity (≈15%) for **3** is also obtained with benzoxantphos (Table 2, entry 9). This ligand gave high alkene conversion, but low regioselectivity (50%) for linear aldehyde **1L**, and thus, exemplifies that low regioselectivity for hydroformylation can be accompanied by low selectivity for reductive amidation of the aldehydes. This is also reflected by a significant accumulation (≈15%) of unsaturated intermediates **2**, which eventually may result in increased amounts of **5** (Table S11 in the Supporting Information). It is surprising that the presence of a naphthyl fragment in this ligand can have such a decisive stereoelectronic influence at the rhodium center. A similar observation was made with DBFphos (Table 2, entry 10) as the ligand with a build up of intermediate **2** of up to 25%; this is indicative of a low hydrogenation activity for these intermediates, even though heavy-end formation remained low. This latter observation suggests that not only the Brønsted acid component of the catalyst system is responsible for the formation of aldol-type higher mass products, but that the metal complex can also play an activating role for the formation of these products.

It is interesting to note that the highest selectivity for the formation of **3L** (>60%) was obtained with homoxantphos as a ligand (Table 2, entry 11), albeit at a relatively low overall activity. This catalyst combines moderate hydrogenation activity of the intermediates **2** with low heavy-end formation.

Finally, the results with xantphos(tBu)$_2$ (Table 2, entry 12) are remarkable: high activity for hydroformylation was observed, with almost full 1-pentene conversion, but, at the same time, this ligand afforded a catalyst with almost the worst performance for hydroamidomethylation with a selectivity for **3** of less than 10% and highest accumulation (≈25%) of the intermediates **2**; this indicates very low activity for the hydrogenation of these intermediates. The very similar product distribution to that obtained when no ligand is applied (Table 2, entry 1) suggests that this ligand fails to form stable complexes with rhodium.

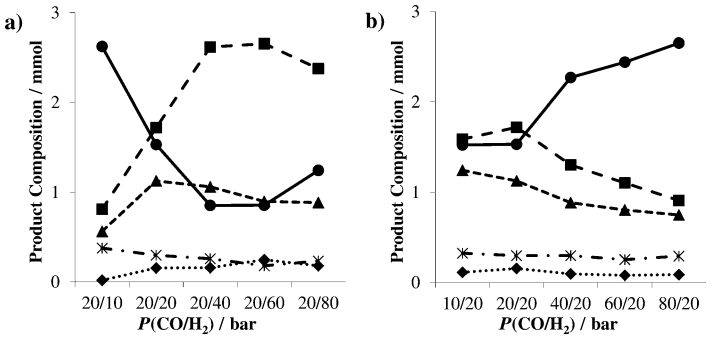


Figure 4. The effect of the syngas ratio on the hydroamidomethylation of 1-pentene with acetamide catalyzed by the Rh/xantphos/HOTs system: A) effect of H_2 and B) effect of CO. Reaction conditions: 0.01 mmol [Rh(acac)(CO)$_2$], 0.02 mmol xantphos, 0.05 mmol HOTs, 5 mmol 1-pentene, 5 mmol acetamide (Rh/xantphos/HOTs/1-pentene/acetamide = 1:2:5:500:500); T = 100 °C; t = 4 h; solvent: 10 mL HOR^f/diglyme (1:4 *v/v*); decane as an internal standard. ○ = 1-pentene, ▲ = aldehyde (**1**), * = unsaturated intermediates (**2**), ■ = desired product (**3**), ◆ = alcohol (**4**).

Effect of H_2/CO ratio on the hydroamidomethylation of 1-pentene

In the next set of experiments, the effect of the H_2/CO ratio on the hydroamidomethylation reaction was investigated (Figure 4 and Table S5 in the Supporting Information). Increasing the pressure of H_2 gas (with a constant pressure of 20 bar CO) from 10 to 40 bar (Figure 4A) resulted in an increased conversion of 1-pentene as well as a steep increase in selectivity to **3**, with only a slight increase in the yield of **1** and **4**. The use of pressures higher than 40 bar of H_2 did not further improve the reaction efficiency to **3**. The use of CO pressures in excess of a hydrogen pressure of 20 bar resulted in a significant drop in the conversion of 1-pentene and yields of both **3** and **1** (Figure 4B).

Alternative promoter compounds as a substitute for HOR^F

The finding that HOR^F acted as a promoter for hydroamidomethylation catalysis prompted us to search for other compounds with similar or better performance. We hypothesized that the acidic properties of HOR^F, perhaps in addition to polarity, was a decisive parameter for its effect on catalysis. Thus, a selected number of compounds characterized by acid strength were screened in diglyme in the molar quantity that proved optimally effective with HOR^F. The results of this screening study are summarized in Table 3 (see also Table S13 in the Supporting Information). Some phenol-type compounds, such as phenol, 2-fluorophenol, 3-fluorophenol, 4-fluorophenol, 2-chlorophenol, and 4-chlorophenol, show similar catalyst promoter performance to that of HOR^F (see Table 3, entries 2, 4, 6, 7, 8, 9, and 11). In particular, with 3-fluorophenol, 4-fluorophenol, and 4-chlorophenol (Table 3, entries 7, 6, and 9, respectively), the reactions seem to show comparable product compositions as those observed with HOR^F, with low accumulation of **2** and low heavy-ends **5**. All compounds that induce selectivity for **3** above 50% have a pK_a value between ≈8.5 and 10, whereas the probed compounds with pK_a > 10 generally have poor promoter performance. It is however clear from the general features displayed in Table 3 that acid strength as a sole criterion for promoter performance is not well validated. Unfortunately, insufficient data on polarity/dielectric constant/dipole moment are available to identify a correlation with promoter performance and a more complete survey needs to be

Table 3. Effect of various additives in combination with diglyme on the hydroamidomethylation of 1-pentene with acetamide.[a]

Entry	Cosolvent (20 mmol)	Dielectric constant	pK_a	Conversion [%]	Selectivity [%][b] 1	2	3	4	5	Linearity [%] 1	3
1	–	–	–	88	31	9	19	1	40	96	>99
2	HOR^F	16.8	9.2	90	19	2	68	5	5	93	>99
3	TFE	27.7	12.37	89	16	6	34	2	42	98	>99
4	PhOH	2.95–3.1	9.99	82	23	8	46	4	19	88	>99
5	4-CF_3-PhOH	–	8.68	95	34	15	22	4	25	59	91
6	4-F-PhOH	–	9.89	86	25	3	59	4	9	92	>99
7	3-F-PhOH	–	9.29	90	22	3	66	5	4	91	>99
8	2-F-PhOH	–	8.73	88	19	4	42	2	32	93	>99
9	4-Cl-PhOH	11.2	–	91	21	3	67	6	4	90	>99
10	3-Cl-PhOH	6.26	9.12	90	61	15	8	0	16	56	>99
11	2-Cl-PhOH	7.4	8.56	88	20	3	52	3	21	92	>99
12	4-Br-PhOH	–	9.37	84	23	11	9	2	55	>99	>99
13	2,6-di-Me-PhOH	–	10.36	88	17	4	30	2	46	90	>99
14	2,6-di-*i*Pr-PhOH	–	11.1	89	22	7	9	2	60	94	>99
15	2,6-di-*t*Bu-PhOH	–	13.6	86	23	9	14	0	54	98	>99
16	2,6-di-Me-PhCOOH	–	3.25	88	34	5	7	2	52	96	>99
17	AcOH	6.2–6.5	4.76	89	10	9	25	1	56	98	>99
18	di-Ph-CHOH	–	13.4	87	41	14	22	2	21	95	>99
19	di-*i*Pr-CHOH	–	≈14.5	89	32	10	15	1	42	95	>99
20	H_2O	80	15.7	89	88	3	0	1	7	97	–
21	2-naphthol	4.95	9.63	85	16	8	12	1	62	99	>99

[a] Reaction conditions: 0.01 mmol [Rh(acac)$(CO)_2$], 0.02 mmol xantphos, 0.05 mmol HOTs, 5 mmol 1-pentene, 5 mmol acetamide (Rh/xantphos/HOTs/1-pentene/acetamide = 1:2:5:500:500); T = 100 °C; t = 8 h; P_{CO/H_2} = 50 bar (1:2); solvent: 10 mL diglyme; 20 mmol of cosolvent. [b] The selectivity was determined by GC analysis with decane as an internal standard.

accomplished to shed more light on this matter. This and possible further optimization studies on some promising compounds are subjects of further study.

Hydroamidomethylation product development with time

Figure 5 shows the product-development curves with time for the rhodium/xantphos/HOTs catalytic system in HOR^F/diglyme (1:4). These curves were constructed from reaction product compositions of separate identical experiments carried out during the respective residence times. The product composition development clearly shows that aldehydes and unsaturated compounds **2** exist as reaction intermediates to ultimately form **3L** as well as the other final products, **4L** and heavy ends. Clearly, it can be deduced from Figure 5 that the rate- and selectivity-determining step in the overall hydroamidomethylation reaction with the present catalytic system involves the reductive amidation of aldehydes.

Scope of the hydroamidomethylation reaction

Various olefins and a number of different amides were used as substrates in the hydroamidomethylation reaction under the optimized reaction conditions (Table 4 and Table S12 in the Supporting Information). The use of 1-hexene or 1-octene in the reaction with acetamide gave the desired *N*-alkylamide with similar conversion, selectivity, and linearity as that for 1-pentene (Table 4, entries 1–3). The use of styrene resulted in high conversion, however, with decreased selectivity to the desired product **3*** (Table 4, entry 4) due to the accumulation of more stable unsaturated linear intermediate **2***. Whereas hydroformylation produces significant quantities of the branched aldehyde, this aldehyde is more reluctant to undergo reductive amidation. The use of amides with more electron-donating carbonyl groups, such as propanamide, 2-methylpropanamide and pentanamide, resulted in higher selectivity to the *N*-hexylamides (Table 4, entries 1, 5, 6, and 8). Applying an amide with a bulkier carbonyl group, such as 2,2-dimethylpropanamide (pivalamide), resulted in only slightly lower selectivity to the desired product (Table 4, entry 7). Application of an amide with an electron-withdrawing fluoromethylcarbonyl group caused a drastic drop in the selectivity to *N*-hexylfluoroacetamide (Table 4, entry 9); the main product of this reaction was **1L**. The use of benzamides resulted in lower selectivity to **3*** compared with acetamide. Applying a benzamide with an electron-donating *p*-methoxy substituent again gave significantly higher selectivity to **3***, whereas *p*-trifluoromethylbenzamide with an electron-withdrawing group again resulted in lower selectivity. These results show a correlation between the efficiency of hydroamidomethylation and the nucleophilic character of

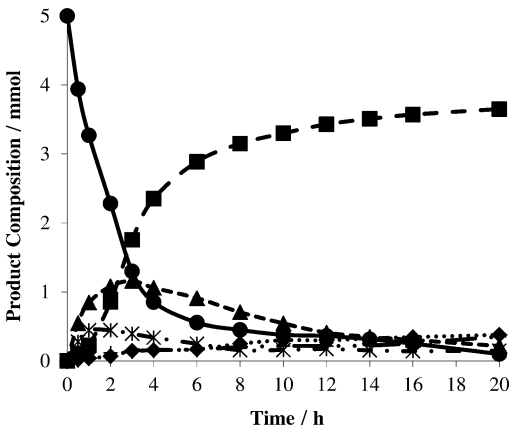
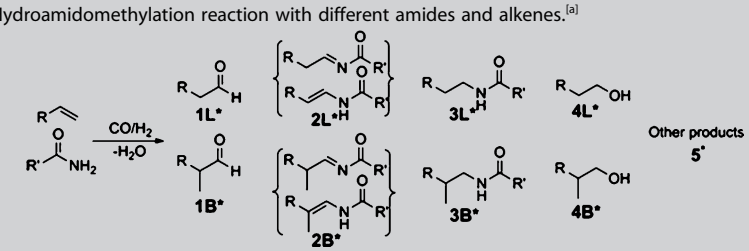


Figure 5. Product development with time for the hydroamidomethylation of 1-pentene with acetamide. Reaction conditions: 0.01 mmol [Rh(acac)$(CO)_2$], 0.02 mmol xantphos, 0.05 mmol HOTs, 5 mmol 1-pentene, 5 mmol acetamide (Rh/xantphos/HOTs/1-pentene/acetamide = 1:2:5:500:500); T = 100 °C; P_{CO/H_2} = 50 bar (1:2); solvent: 10 mL (*v*/*v*) HOR^F/diglyme (1:4); decane as an internal standard. ● = 1-pentene, ▲ = **1L**, ■ = **3L**, ◆ = **4L**, * = other products (**5**). For clarity only the linear products are depicted (details are given in Figure S8 and Table S10 in the Supporting Information).

Table 4. Hydroamidomethylation reaction with different amides and alkenes.[a]



Entry	Alkene (5 mmol)	Amide (5 mmol)	Conversion [%]	Selectivity [%][b]					Linearity [%]	
				1*	2*	3*	4*	5*	1*	3*
1	1-pentene	acetamide	91	17	4	69	6	4	92	>99
2	1-hexene	acetamide	89	20	3	67	6	4	90	>99
3	1-octene	acetamide	88	24	2	62	6	7	93	>99
4	styrene	acetamide	86	20	36	33	4	8	51	>99
5	1-pentene	propanamide	90	14	5	74	3	4	96	>99
6	1-pentene	2-Me-propanamide	89	18	4	71	3	4	88	>99
7	1-pentene	pivalamide	87	25	6	61	3	5	91	>99
8	1-pentene	valeramide	93	10	2	83	4	1	90	>99
9	1-pentene	F-acetamide	90	77	12	4	4	3	96	>99
10	1-pentene	benzamide	69	38	8	24	0	30	99	>99
11	1-pentene	*p*-MeO-benzamide	90	38	3	48	1	10	99	>99
12	1-pentene	*p*-CF_3-benzamide	57	29	31	21	0	18	90	>99

[a] Reaction conditions: 0.01 mmol [Rh(acac)$(CO)_2$], 0.02 mmol xantphos, 0.05 mmol HOTs, 5 mmol alkene, 5 mmol amide (Rh/xantphos/HOTs/alkene/amide = 1:2:5:500:500); $T = 100\,^{\circ}C$; $t = 8$ h; $P_{CO/H_2} = 50$ bar (1:2); solvent: 10 mL (*v*/*v*) HOR^F/diglyme (1:4). [b] The selectivity was determined by GC analysis with decane as an internal standard.

the N atom of the amide; the same correlation was observed earlier with the reductive amidation of aldehydes with pure H_2 and is a clear indication of the tandem character of hydroformylation–reductive amidation in the hydroamidomethylation reaction.[6]

Influence of HOR^F in the separate steps: Hydroformylation and reductive amidation

Because we observed that the reductive amidation of **1L** in pure diglyme was severely inhibited by the presence of CO,[6] the separate reaction steps, hydroformylation and reductive amidation with the rhodium/xantphos catalyst system, were studied in more detail.

Hydroformylation of 1-pentene

The hydroformylation of 1-pentene with the rhodium/xantphos catalytic system in pure diglyme, as well as in a mixture of HOR^F/diglyme (1:4 *v*/*v*), was studied. The results given in Figure 6A and B show that the conversion of 1-pentene in the HOR^F/diglyme mixture was generally lower than that in pure diglyme. The lower conversion was particularly distinct when HOTs was present as a catalyst component [HOTs/Rh = 5 (mol/mol)], giving about 90% conversion in pure diglyme, but only 30% in the HOR^F/diglyme 1:4 (*v*/*v*) mixture. Remarkably, hydroformylation with HOTs as a catalyst component resulted in both solvent systems in detectably higher amounts of **4L** as well as heavy-end byproducts. To simulate the presence of the weakly basic amide under actual hydroamidomethylation conditions, hydroformylation was also carried out in the presence of DMA (in an equimolar amount to 1-pentene). For the pure diglyme solvent system this resulted in lower conversion (from 70 to 55%), whereas hardly any effect of DMA was discernible for the HOR^F/diglyme solvent system; the weak basicity of DMA seems to be neutralized by the excess (by about factor 4) of HOR^F. When both DMA and HOTs [DMA/HOTs = 100 (mol/mol)] were applied in the catalytic reaction mixture, the catalyst activation effect of HOTs in pure diglyme appeared to be virtually unaffected, albeit with reduced alcohol formation. In contrast, the activity-reducing effect in the HOR^F/diglyme mixture was virtually absent; this suggested a neutralizing effect between DMA

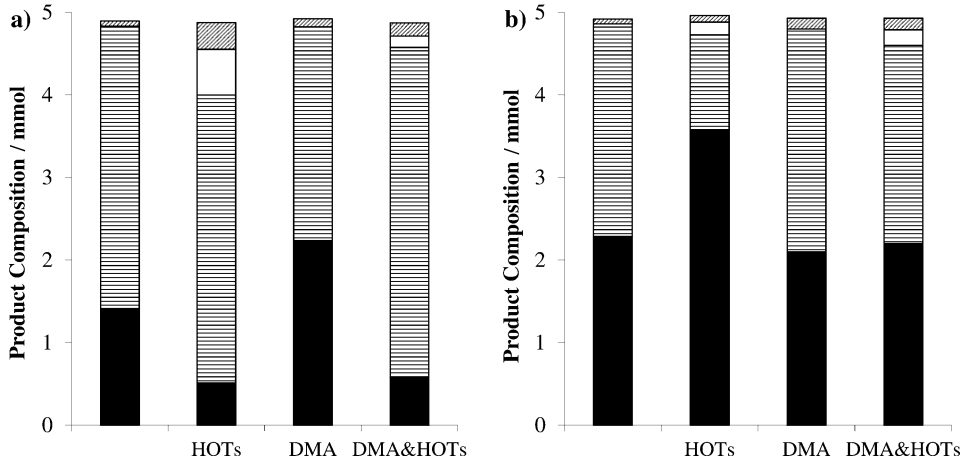


Figure 6. The effect of acid and base on the hydroformylation of 1-pentene catalyzed by the Rh/xantphos catalytic system: A) in diglyme and B) in HOR^F/diglyme 1:4 (*v*/*v*). Reaction conditions: 0.01 mmol [Rh(acac)$(CO)_2$], 0.02 mmol xantphos, 0.05 mmol HOTs (if acid was used), 5 mmol 1-pentene, 5 mmol *N*,*N*-dimethylacetamide (DMA; if DMA was used); Rh/xantphos/1-pentene = 1:2:500; $P_{CO/H_2} = 50$ bar (1:2); $t = 2$ h; solvent: 10 mL diglyme or 10 mL HOR^F/diglyme = 1:4 (*v*/*v*); decane as the internal standard. ■ = 1-pentene, ▤ = aldehyde (**1**), □ = alcohol (**4**), ▨ = heavy-end products (**5**).

and HOTs in HOR^F. Small amounts of **4L** were still formed in both cases (selectivity ≈3 and ≈7% for, pure diglyme and HOR^F/diglyme mixed solvent systems, respectively (Table S8-1 and Figure S5 in the Supporting Information).

The effect of different amounts of HOR^F on the hydroformylation reaction in the presence of HOTs was also investigated. The amounts of DMA and HOTs were kept constant in the series of experiments depicted in Figure 7A to simulate the presence of amide under hydroamidomethylation conditions.

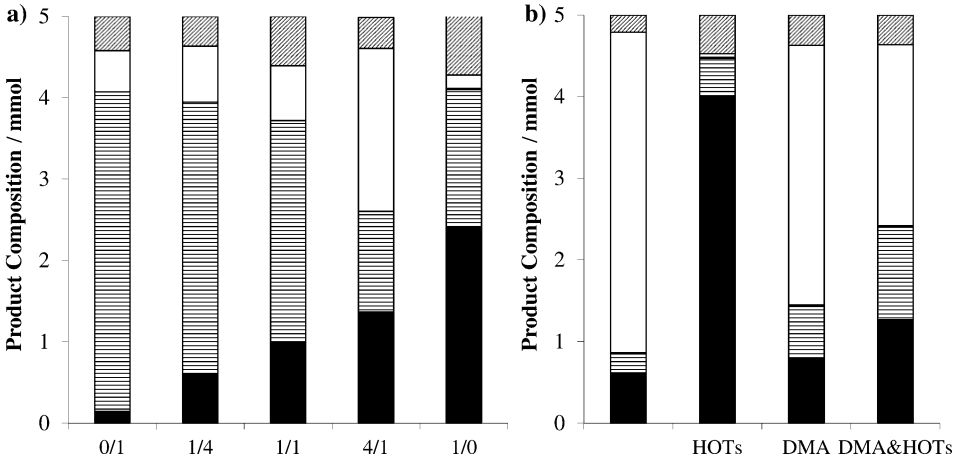


Figure 7. The effect of HOR^F in the absence and presence of acid on the hydroformylation of 1-pentene catalyzed by the Rh/xantphos system: A) different ratio (*v*/*v*) of HOR^F/diglyme in the presence of HOTs and DMA, and B) in HOR^F/diglyme 5:1 (*v*/*v*). Reaction conditions: 0.01 mmol [$Rh(acac)(CO)_2$], 0.02 mmol xantphos, 5 mmol 1-pentene; Rh/xantphos/1-pentene = 1:2:500; 0.05 mmol HOTs (if acid was used), 5 mmol DMA (if DMA was used); P_{CO/H_2} = 50 bar (1:2); *t* = 8 h; solvent: 10 mL HOR^F/diglyme(*v*/*v*); decane as an internal standard. ■ = 1-pentene, ▤ = aldehyde (**1**), □ = alcohol (**4**), ▨ = heavy-end products (**5**).

Increasing ratios of HOR^F/diglyme (*v*/*v*) in this series of experiments revealed that, the higher the HOR^F/diglyme ratio, the higher selectivity to **4L** observed (Figure 7A). However, the catalytic activity dropped gradually; the 1-pentene conversion fell from >95% in pure diglyme to about 50% in pure HOR^F. Remarkably, when applying pure HOR^F as a solvent, the selectivity to **4L** dropped again to about 10% from 55% at 80 vol% of HOR^F. This observation is consistent with those observations under real hydroamidomethylation conditions depicted in Figure 2, which show a quantitatively very similar effect at high HOR^F/diglyme ratios.

In the experiments shown in Figure 7B, a constant HOR^F/diglyme ratio of 5:1 (*v*/*v*) was applied, both in the absence and presence of HOTs and DMA. In this HOR^F-rich reaction medium in the absence of HOTs, the selectivity to **4L** was boosted dramatically to 90%, while reaching a high alkene conversion of about 90%. When HOTs was present, both the alkene conversion and selectivity to **4L** decreased dramatically. However, in the presence of DMA [DMA/HOTs = 100 (mol/mol)], HOTs seemed to be at least partly neutralized and restoration of the hydroformylation activity as well as selectivity to **4L** became apparent (Figure 7B and Table S8-2 in the Supporting Information). Again, this observation is consistent with the observations depicted in Figure 2 at the same HOR^F/diglyme ratio under real hydroamidomethylation conditions, thus giving confidence that the addition of DMA (in amounts equimolar to 1-pentene) in the individual reaction steps truly approaches hydroformylation conditions that prevail in hydroamidomethylation reactions.

Reductive amidation of hexanal

The effects of the presence of HOR^F as a cosolvent in rhodium/xantphos/HOTs-catalyzed reductive amidation of **1L** with acetamide are shown in Figure 8. When the reductive amidation of **1L** with acetamide was carried out in diglyme, the selectivity to **3L** dropped from about 40% in pure H_2 to only about 10% with the addition of only 5 bar of CO (45 bar H_2). At higher CO pressure, this selectivity further decreased to below 10%, while an increased amount (>15%) of unsaturated **2** became visible (Figure 8A).

Amazingly, a strongly positive effect of CO on the selectivity of the reductive amidation of **1L** was revealed when a HOR^F/

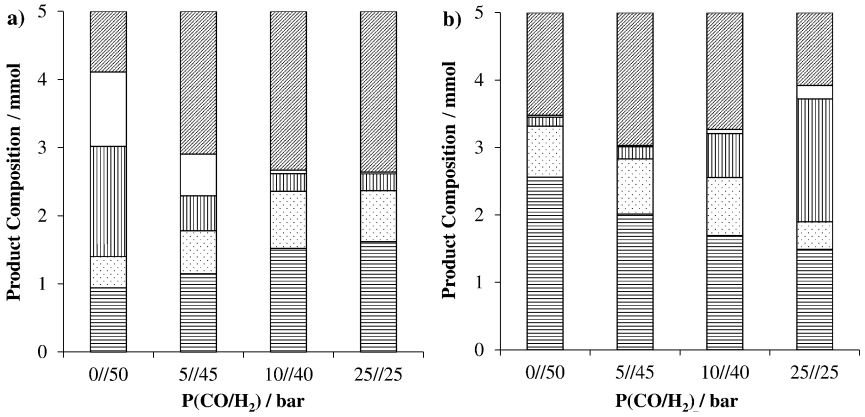
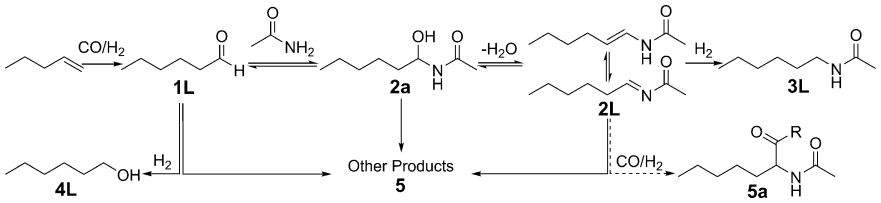


Figure 8. The effect of CO/H_2 partial pressures on the reductive amidation of **1L** with acetamide catalyzed by the catalytic system Rh/xantphos/HOTs: A) in pure diglyme and B) in HOR^F/diglyme 1:4 (*v*/*v*). Reaction conditions: 0.01 mmol [$Rh(acac)(CO)_2$], 0.02 mmol xantphos, 5 mmol **1L**, 5 mmol acetamide; Rh/xantphos/HOTs/**1L**/acetamide = 1:2:5:500:500; *P* = 50 bar; *t* = 2 h; solvent: 10 mL diglyme or 10 mL (*v*/*v*) HOR^F/diglyme = 1:4; decane as an internal standard. ▤ = **1L**, ⊡ = unsaturated imide or enamide (**2L**), ▥ = **3L**, □ = **4L**, ▨ = other products (**5**).

diglyme [1:4(*v*/*v*)] solvent mixture was applied (Figure 8B).[8] Application of syngas ($CO/H_2 = 1$) even led to an increase in the selectivity to **3** by an order of magnitude from less than 5% at 50 bar of pure H_2 to 50% at 50 bar of syngas. The yield of **3** (and to a lesser extent also of **4L**) increased gradually with increasing CO pressure, whereas the amount of intermediate product **2** and heavy-end products **5** simultaneously decreased, thus indicating not only an increase in the general hydrogenation activity of the catalyst, but also indicating an increase in substrate specificity for the hydrogenation of intermediates **2** over **1L**.



Scheme 4. Catalytic hydroamidomethylation of 1-pentene: a one-pot synthesis of **3L** through the formation of **1L** and intermediate **2L**; **4L** and heavy-ends **5** are undesired byproducts (for clarity only the linear products are depicted). R in **5a** can be H (CHO) or OH (COOH).

It is worth noting that the use of different amounts of HOR^F for the rhodium/xantphos/HOTs-catalyzed reductive amidation of **1L** with acetamide in a pure hydrogen atmosphere showed that HOR^F strongly retarded reductive amidation by inhibiting the hydrogenation of unsaturated **2**, which was shown to accumulate in the reaction mixture (Figure S6 in the Supporting Information). The presence of progressively more HOR^F resulted in lower conversion of **1L** (Figure S6 and Table S9 in the Supporting Information). In the absence of HOTs, the rhodium/xantphos catalyst system in pure HOR^F led to almost exclusive hydrogenation of **1L** (Figure S7 in the Supporting Information), a result similar to that in diglyme.[6] However, when HOTs was applied in the rhodium/xantphos catalytic system, a significant difference between the role of the solvents diglyme and HOR^F again became apparent. Whereas in diglyme both the reductive amidation product **3** and **4L** were coproduced, in HOR^F hardly any **4L** or product **3** was formed, thus revealing that the catalytic system in HOR^F under a pure H_2 atmosphere had very poor hydrogenation activity (Figure S7 and Table S9 in the Supporting Information). All observations reported in this section thus suggest that different rhodium/xantphos complexes are operative as imide/enamide or aldehyde hydrogenation catalysts under different conditions, for example, in different solvent systems; with different reducing gas environments; and in the presence or absence of potential catalyst promoter compounds, such as HOTs and HOR^F.

Discussion

General considerations

All experimental results concerning the hydroamidomethylation reaction, but, in particular, the development of the reaction products with time (Figure 5) prominently indicate that the hydroamidomethylation of 1-pentene with acetamide comprises three sequential steps, which are shown schematically in Scheme 4. The first step is hydroformylation of 1-pentene to aldehyde **1**. The second step consists of two equilibrium reactions: the nucleophilic addition of acetamide to **1L** forming **2a** followed by dehydration to form the two isomeric unsaturated intermediates **2L**.[6] Hydrogenation of these unsaturated intermediates results in the formation of the desired product **3** in the third step. The formation of **4** by the direct hydrogenation of **1L** constitutes a competing reaction of **1L**, resulting in lower selectivity for **3**.

The unsaturated intermediates (**1** as well as **2**) may undergo various side reactions, most pronounced of which are aldol condensation and double addition reactions, resulting in the higher mass products **5** that are indeed observed in varying amounts. Other reported reactions of intermediates **2** are hydroformylation and hydrocarbonylation reactions, which are also shown in Scheme 4;[9] however, products **5a** (aldehyde or carboxylic acid) were not observed in our reactions (see Figures S1 and S23 in the Supporting Information).

Finding active and selective alkene hydroamidomethylation catalysts will thus involve developing catalyst systems that are not only active for the hydroformylation of alkenes, but, under the prevailing syngas conditions, also possess the ability to selectively hydrogenate the unsaturated intermediates **2** in the presence of aldehyde **1**; compounds that are mutually involved in the condensation equilibrium shown in Scheme 4. In this way, intermediates **2** are removed selectively from the condensation equilibrium and the reaction is drawn to completion by catalytically forming the *N*-alkylamide product. If, on the other hand, the catalyst system has preference for hydrogenation of the aldehyde substrate **1** over **2**, the condensation equilibrium can be drawn to completion to alcohol **4**.

Considerations on the roles of catalyst promoters HOTs and HOR^F in Rh/xantphos-catalyzed hydroamidomethylation of alkenes

Our studies on the catalytic reductive amidation of **1L** with acetamide by using pure H_2 revealed that the optimal catalytic system comprised a rhodium precursor with a xantphos-type ligand and a catalytic amount of a strong acid promoter, such as HOTs, in diglyme as the reaction solvent. The addition of a catalytic amount of strong acid [HOTs/Rh $\approx$5 (mol/mol)] is necessary to catalyze the addition equilibrium reaction of the amide with the aldehyde.[6] In this respect, the mechanism is different from that of reductive amination of an aldehyde, in which case the addition of an amine N–H bond to the aldehyde occurs spontaneously, without the involvement of any acid.[5a–d] However, a strong acid such as HOTs also modifies the catalytic system.

The first acid–base reaction that would take place is protonation of $[Rh(acac)(CO)_2]$ to form the $[Rh^I(CO)_2(xantphos)]OTs$

species with the release of Hacac; this rhodium/xantphos species then can be feasibly converted into the well-known alkene hydroformylation catalyst [Rh^{I}(CO)(H)(xantphos)]. Additionally, the presence of HOTs may induce equilibria between neutral Rh^{I} hydroformylation and cationic Rh^{III} hydrogenation species. One of our most prominent observations, however, is that the additional presence of a weakly acidic promoter compound, such as HOR^{F} [in solvent-like quantities, typically HOR^{F}/Rh $\approx$2000 (mol/mol) at HOR^{F}/diglyme = 1:4 (*v*/*v*)], also has a strong impact on the course of the catalytic hydroamidomethylation reaction, as shown in Figure 2, creating an active hydrogenation catalyst in the CO-containing atmosphere. Similar effects are observed in the separate hydroformylation and reductive amidation reactions (Figures 6–8).

Hydroformylation

Clearly, the addition of HOR^{F} leads to a lower hydroformylation rate of 1-pentene (Figure 6). Interestingly, the rate of hydroformylation even further decreases when HOTs is added to this system; the formation of **4L** becomes visible. A remarkable observation is the recovery of catalyst performance to a level achieved before HOTs addition upon the addition of DMA in a stoichiometric quantity relative to 1-pentene. However, a decrease in hydroformylation activity due to the presence of HOR^{F} remains, even if DMA is added. This is likely to be due to the large (fourfold molar ratio) excess of HOR^{F} over DMA under the given conditions.

The high acidity of HOTs ($pK_a \approx -2.7$) combined with a large excess of weakly basic DMA (DMA/HOTs $\approx$100) accounts for a likely complete deprotonation of HOTs and formation of the salt. The resulting protonated $HDMA^{+}$ cation of course still behaves as quite a strong acid and is responsible for the formation of cationic Rh^{III} species, as suggested from the formation **4L** (Figure 6B), lowering the concentration of the neutral Rh^{I} hydroformylation catalyst. It is thought that the distinct decrease in hydroformylation activity due to the addition of the weakly acidic HOR^{F} (pK_a in water of $\approx$9) is due to its very large excess over Rh, which thus may contribute to the generation and stabilization of Rh^{III} species, similar to HOTs. Again a neutralization effect is observed when DMA [HORF/DMA $\approx$4–20 (mol/mol)] is added to the reaction ($DMA + HOR^{F} \rightleftarrows HDMA^{+} + OR^{F-}$; for which the equilibrium constant would be much lower than that for the strong acid HOTs). The decreasing rate of hydroformylation with increasing concentration of HOR^{F}, while the product composition changes from **1L** to **4L** (Figure 7A), is fully consistent with a dual catalyst species model, in which cationic Rh^{III} hydrogenation species gradually replace neutral Rh^{I} hydroformylation species.

Remarkably, hydroformylation in pure HOR^{F} not only results in a low hydroformylation rate, but also in a low selectivity for alcohol formation (Figure 7A). Similarly, the addition of HOTs at a high concentration of HOR^{F} leads to a severe drop in hydroformylation and hydrogenation activity (Figure 7B). This could be a consequence of the stronger electrophilic nature of the Rh^{III} center in pure HOR^{F}, due to relatively easy dissociation of the associated OTs^{-} anions in this polar medium and the unavailability of OR^{F-} anions due to protonation. This stronger electrophilicity would cause O-coordination of the aldehyde to the Rh^{III} center rather than π-carbonyl coordination required for hydrogenation. When DMA is added, OR^{F-} anions are generated by the deprotonation equilibrium. These OR^{F-} anions coordinate more strongly to the Rh^{III} center and the original situation is substantially restored; the electrophilicity of the Rh^{III} metal center is reduced, as diagnosed by increasing alcohol formation.

Reductive amidation

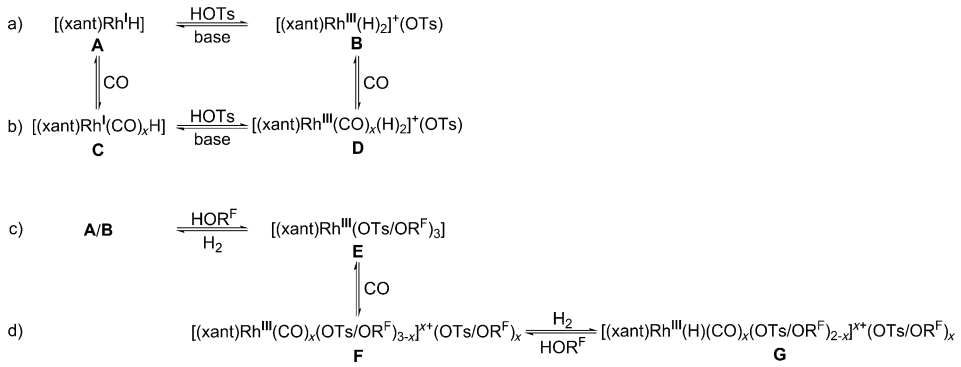
The reductive amidation of **1L** with acetamide in the presence of HOTs and with pure H_2 as the reductant is strongly inhibited by the addition of HOR^{F} (Figure S6 in the Supporting Information). Not only the hydrogenation of intermediates **2**, but also hydrogenation of aldehydes is severely suppressed by the presence of HOR^{F}. This could suggest that the [$Rh^{III}(H)_2$(xantphos)](OTs) species proposed to be the active Rh hydrogenation species in reductive amidation under pure H_2 pressure[6] is converted by protonation at the hydride with HOR^{F} to the species [$Rh^{III}(OTs/OR^{F})_3$(xantphos)], which has no intrinsic activity for hydrogenation under pure H_2 pressure.

The effects of HOR^{F} and HOTs on reductive amidation with the rhodium/xantphos catalyst system under pure H_2 pressure are further illustrated in Figure S7 in the Supporting Information; in diglyme and diglyme/HOR^{F} ($\approx$1:4 *v*/*v*), the introduction of HOTs is required for the establishment of the aldehyde–amide addition equilibrium.[6] The acidity of HOR^{F} is not sufficiently strong to catalyze this equilibrium under the applied reaction conditions. It also appears that, in the absence of HOTs, but in the presence of HOR^{F}, the rhodium/xantphos catalyst is highly active for the hydrogenation of **1L** to **4L** (Figure S7 in the Supporting Information). This could be a consequence of the fact that aldehyde coordination to a metal center only requires one free coordination site, whereas a catalyst for hydrogenation of compounds **2** is likely to have two adjacent positions to allow for the selective bidentate binding of **2** in the presence of aldehyde.

The effect of CO on the reductive amidation in diglyme is as expected: with increasing CO pressure, a strongly negative effect is observed on the yield of **3L** as well as **4L** (Figure 8A), and consequently, the yields of unsaturated compounds **2** and higher condensation products increase. In contrast, when the same experiments are carried out in diglyme/HOR^{F}, the yield of **3L** and **4L** strongly increases with CO pressure, thus a strongly increased general hydrogenation activity is manifested by the presence of CO. This implies that, in the presence of HOR^{F}, a catalytic hydrogenation system other than the one present under pure H_2 pressure must be operative. We thus arrive at the conclusion that the cationic [$Rh^{III}(H)_2$(xantphos)]$^{+}$ species is likely to operate as a hydrogenation catalyst under pure H_2 in an aprotic solvent such as diglyme,[6] but does not exist in the presence of HOR^{F} under syngas conditions. Instead, a cationic [$Rh^{III}(CO)_x(H)(OTs/OR^{F})$(xantphos)]$^{+}$ catalyst species with a mixture of OR^{F-} and OTs^{-} anions will arise in addition to neutral Rh^{I} hydroformylation species. The observed increase in reduc-

tive amidation product, with associated decrease in intermediates **2**, is approximately first-order in CO pressure (Figure 8B), which is consistent with necessary binding of CO to a cationic Rh^{III} center as the catalyst in the overall rate-determining step of hydroamidomethylation, that is, hydrogenation of the unsaturated intermediates **2**. The relative occupation of coordination sites in this Rh^{III} species by CO and the OR^{F-}/OTs^- anions will depend on the relative quantities of HOR^F, HOTs, and base (amide and *N*-alkylamide) as well as CO/H_2 pressure, as suggested by the separate results on hydroformylation and reductive amidation.

As implied by the effects of added amide (such as DMA) on hydroformylation with the rhodium/xantphos/HOTs catalyst system, we may conclude that under hydroamidomethylation conditions the amide reactant (and *N*-alkylamide product) also plays an important controlling role in the observed catalytic performance. It is likely that partial deprotonation of HOTs and HOR^F occurs, thus providing anions of which the reaction-medium-dependent coordinating properties to Rh^{III} may control some of the catalyst's attributes, such as specificity of hydrogenation of unsaturated substrates.



Scheme 5. Generation of various hydrogenation catalysts under reductive amidation conditions (xant = xantphos): a) in pure diglyme with a H_2 atmosphere; b) in diglyme with a H_2/CO atmosphere; c) in HOR^F/diglyme with a H_2 atmosphere; and d) in HOR^F/diglyme with a H_2/CO atmosphere.

Hydroaminomethylation versus hydroamidomethylation

The reaction conditions for hydroamidomethylation can be compared to those for well-known hydroaminomethylation of alkenes with amines. Under the strongly basic conditions with amines as substrates, acetal formation cannot occur. Several studies of hydroaminomethylation applied simple alcohols (such as methanol) in this reaction.[5a–d] In general, higher hydroaminomethylation reaction rates are observed in the presence of alkanols, thus also indicating a promoting effect of protic cosolvents in hydroaminomethylation. Although a mechanistic study into the nature of this promoting effect has not been published, it has been postulated that the protic solvent could somehow serve to stabilize cationic rhodium hydrogenation species.[10] We wish to suggest that the simple alcohols in hydroaminomethylation serve a similar purpose to that of HOR^F in hydroamidomethylation.[11] The difference is that associated alkoxide anions are formed due to deprotonation of the alcohol by the strongly basic amine substrate and product. Because hydroamidomethylation involves much weaker basic amide substrates and products, a stronger acidic alcohol needs to be applied to successfully generate alkoxide anionic species to stabilize the cationic Rh^{III} center.[12]

Synthesis of the overall mechanistic proposal

In our study concerning the reductive amidation of **1L** with acetamide in a pure hydrogen atmosphere, we postulated the formation of a neutral Rh^I–hydride species **A** to be responsible for the hydrogenation of aldehyde to alcohol, whereas a cationic Rh^{III}–dihydride species **B** would be active in the hydrogenation of the unsaturated intermediates **2** (Scheme 5a).[6] These two species are related through an acid/base equilibrium; the addition of acid resulted in higher selectivity for **3L**, whereas the addition of base resulted in the formation of **4L**.

When reductive amidation is carried out in diglyme with a partial pressure of CO, both the hydrogenation of aldehyde and intermediate **2** is poisoned (Figure 8A); remarkably the hydrogenation of **1L** seems to be the most sensitive to the presence of CO. This observation can be rationalized by the coordination of CO to both species **A** and **B**, forming **C** and **D**, respectively (Scheme 5b). Species **C** is a hydroformylation catalyst that is known to have low hydrogenation activity. Carbon monoxide binds more strongly to Rh^I than to Rh^{III}, making it plausible that the hydrogenation activity of species **B** is partially retained.

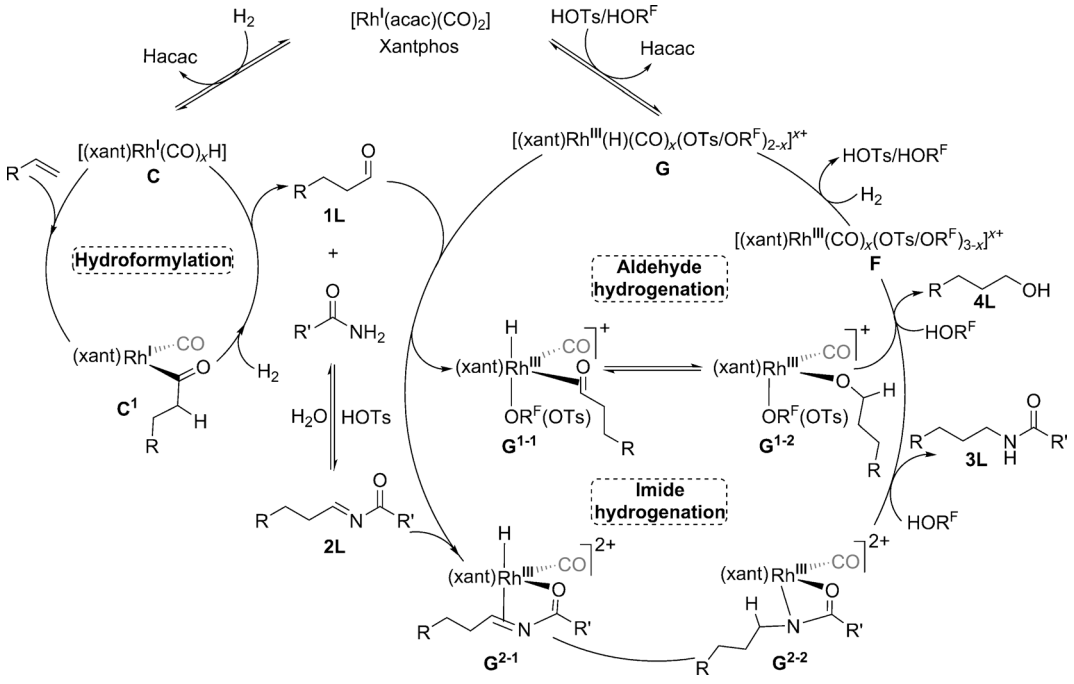
The effect of the addition of HOR^F on the hydrogenation activity of the catalytic system in reductive amidation in a pure hydrogen atmosphere is even more detrimental (Figure 8B); in HOR^F/diglyme (1:4) only a small amount of **3L** is formed. This may be rationalized by protonation of both species **A** and **B**, forming the inactive species [(xantphos)Rh^{III}(OTs/OR^F)$_3$] (**E**; Scheme 5c). Remarkably, the hydrogenation activity of the system is restored with the addition of a partial pressure of CO; apparently carbon monoxide is able to compete with OR^{F-} anions for coordination sites at the Rh^{III} center in 'neutral' species **E**, resulting in the formation of cationic species **F**. This allows for the activation of hydrogen by heterolytic splitting, resulting in the formation of HOR^F and the cationic Rh^{III}–hydride species **G** (Scheme 5d), which again may be an active hydrogenation catalyst.

In the hydroformylation of 1-pentene in diglyme, the equilibrium shown in Scheme 5b is also operative; by the addition of HOTs, hydroformylation catalyst **C** is partially converted into the Rh^{III}–hydride species **D**; this is apparent from the formation of **4 L** (Figure 6 A). This conversion is reversed by the addition of the base DMA, resulting in the formation of species **C** to give **1 L** as the major product. The catalytic hydroformylation system in a mixture of HOR^F/diglyme (1:4) behaves almost the same, indicating that similar catalytic species are operative, albeit with lower overall activity (Figure 6 B). The activity of the hydroformylation catalyst is inversely related to the amount of HOR^F added (Figure 7 A); with increasing amounts of HOR^F the hydroformylation activity decreases, whereas the hydrogenation activity increases up to a HOR^F/diglyme ratio of 5:1 (Figure 7 B). This phenomenon again may be attributed to the formation of species **D** by the weakly acidic HOR^F, lowering the concentration of hydroformylation catalyst **C**. In the presence of HOTs, but in the absence of base (DMA), the hydroformylation catalyst **C** is virtually nonexistent (Figure 7 B) and most likely species **E** and/or **F** are prevalent.

Now we are ready to consider the overall picture of the hydroamidomethylation reaction by considering the results most prominently illustrated in Figure 2. From these results, five different regimes seem to be present upon changing from a pure diglyme to a pure HOR^F solvent system. The overall picture is complicated by the different acid/base equilibria induced by the presence of base (acetamide and **3 L**, at a constant concentration), strong acid (HOTs, only in relatively small amounts), and weak acid (HOR^F, in increasing amounts).

Our view of the general mechanism of hydroamidomethylation is shown in Scheme 6. Hydroformylation of alkenes catalyzed by a neutral Rh^I species is followed by an acid-catalyzed aldehyde–amide condensation equilibrium that involves both aldehyde and imide substrates. This equilibrium is coupled through two hydrogenation cycles that involve either the imide or aldehyde as the substrate, both catalyzed by a cationic Rh^{III} species. Competition between the last two substrates involved in the respective catalytic cycles, thought to the governed by anion coordination to the cationic Rh^{III} center, is the basis for the chemoselectivity of the overall hydroamidomethylation process.[13]

In pure diglyme, an active hydroformylation catalyst is formed, but the catalytic system in the presence of CO lacks hydrogenation activity; the most prominent catalytic compound present in solution is most likely to be species **C**. Any Rh^{III}–hydride species present in solution is possibly blocked by coordination of CO, forming species **D** (Scheme 5). Addition of more of the strong acid HOTs is not an option because it results in the formation of more aldol condensation products. However, the addition of weakly acidic and polar HOR^F as a cosolvent results in the formation of an active hydrogenation catalyst (such as species **G**) that is capable of hydrogenating the intermediate products **2** or aldehyde **1**, depending on the relative amount of HOR^F. A HOR^F/diglyme ratio of 1:4 (*v*/*v*) generates a more polar environment, in which the OTs^- anions become less coordinating, and thus, are likely to provide two binding sites for imide intermediate **2** (species $\mathbf{G}^{2-1}$), resulting in an active catalytic system for hydroamidomethylation with the highest selectivity for *N*-alkylamides. Upon increasing the HOR^F/diglyme ratio to 1:1, the hydroformylation activity is retained, but the hydrogenation activity of the catalytic system is severely inhibited; this may be due to the formation of a higher concentration (relative to [Rh]) of relatively strongly coordinating OR^{F-} anions. Upon increasing the HOR^F/diglyme



Scheme 6. Proposed overall mechanism for the hydroamidomethylation of 1-alkenes.

ratio to 5:1, the hydroformylation activity is retained, but now **4L** is the major hydrogenation product. In this HOR^F-rich medium, the OR^{F-} anions become more readily solvated to allow binding of the monodentate substrate aldehyde, via species $\mathbf{G}^{1-1}$. Finally, it is important to note that we believe that the hydroformylation reaction concerns a neutral catalytic species that activates H_2 by oxidative addition, shuttling between Rh^I and Rh^{III}. The hydrogenation cycles proceed via cationic Rh^{III} species; the intermediate products are protonated in the acidic medium to form species **F**. Through the CO-assisted heterolytic splitting of hydrogen proposed above, species **G** is then restored.

Both HOR^F and HOTs can provide anions to the cationic Rh^{III}–hydride species, by protonation of the weakly basic amide reactant. Depending on their relative amounts, the relative acidic strength, and coordinative properties to the Rh center, it can thus be rationalized that the immediate anionic environment around a cationic $[(xantphos)Rh^{III}H]^{2+}$ species plays an important role in the hydrogenation substrate specificity of the intermediate **2** relative to the aldehyde, which are both involved in a dynamic condensation equilibrium. Such a model can rationalize the dramatic change in selectivity from **3L** as a product (>80%) at a relatively low HOR^F concentration to **4L** as the product (>90%) at a high concentration of HOR^F. At low HOR^F concentrations, the weakly coordinating OTs^- anions render the Rh^{III} species receptive to binding of the bidentate substrate **2**, even in the presence of the monodentate aldehyde. The aldehyde substrate is less hindered by the anions around the rhodium center, which is likely to be because of its monodentate binding: even with the intrinsically more strongly coordinating OR^{F-} anions, the aldehyde's carbonyl functionality succeeds in approaching the Rh^{III} center and can become hydrogenated, in particular, when immersed in a high concentration of polar HOR^F molecules. The relatively sharp decline in hydrogenation activity, now accompanied with a significant decrease in hydroformylation activity at very high concentration of HOR^F (>90%) may be attributed to an increased presence of species **E**, but now associated almost exclusively with the relatively strongly coordinating OR^{F-} anions, thus behaving more as a neutral Rh^{III} species. It is thought that this process may proceed to the extent that heterolytic activation of H_2 (producing active cationic species **F** and **G**) becomes rate determining and relatively slow.

Herein, we have proposed plausible catalytic events occurring in the hydroamidomethylation (hydroformylation–reductive amidation) reaction that can rationalize most of our observations. To the best of our knowledge, in studies reporting the related hydroaminomethylation (hydroformylation–reductive amination) reaction, no clear mechanistic proposals have been provided specifically for the second step (reductive amination) of the reaction. However, it has been proposed that the hydrogenation step benefits from the presence of protic solvents because of the formation of cationic rhodium species.[4c, 5c, d] The role of alcohol as a protic cosolvent in the tandem hydroformylation–hydrogenation reaction, in which alcohols are formed directly from alkenes, has also been explained by a mechanism based on the formation of a rhodium–carbenoid species.[14] In this proposed mechanism, the intermediate Rh–acyl species formed in hydroformylation is directly hydrogenated (by a proton-assisted isomerization to a Rh–hydroxycarbenoid) without intermediate formation of an aldehyde. However, we have shown that with the rhodium/xantphos/HOTs catalytic system, the hydroamidomethylation and related alcohol formation reactions occur through sequential steps that involve aldehyde–amide adducts and free aldehyde, respectively, as indicated by the build up of intermediates **2** and aldehydes, depending on the reaction conditions. A high selectivity for one over the other can be obtained by adjusting the competitive hydrogenation of the respective molecules. We believe that one interesting aspect of the present work is the revelation of the selectivity-controlling ability of the amide substrate, presumably by acting as a weak base, on the amount and type of anions associated with the cationic rhodium species as part of the overall catalyst system.

Conclusions

We have successfully developed a novel catalytic system that comprised of rhodium/xantphos/HOTs in the presence of HOR^F as a cosolvent for the atom-economic hydroamidomethylation of terminal alkenes to form *N*-alkylamides. It appeared that the presence of both strong acid (HOTs) and a polar acidic solvent (HOR^F) was crucial in determining the reaction selectivity and efficiency. The strong acid was necessary to establish the equilibrium addition/condensation reaction between the aldehyde formed in situ and the amide. The presence of the polar, weakly acidic cosolvent was necessary for the generation and solvation of cationic Rh^{III}–hydride species that were active as hydrogenation catalysts in the presence of carbon monoxide. By choosing the right circumstances, this catalytic system could be fine-tuned to make either an alcohol or an *N*-alkylamide from terminal alkenes. The novel hydroamidomethylation reaction has potential in the synthesis of a wide range of secondary amides, as shown by its applicability to different olefins and different aliphatic and aromatic amides. We are currently seeking to utilize this catalytic system for the hydroamidomethylation reaction of internal alkenes with an amide to form linear *N*-alkylamides, for which the isomerization step is, of course, highly challenging.

Experimental Section

Chemicals: The phosphane ligands PPh_3, DPEphos, bis(diphenylphosphinoethyl)phenylphosphane, and xantphos were purchased from Strem Chemicals, Germany. The bidentate phosphane ligands benzoxantphos, homoxantphos, and DBFphos were purchased from Innovative Catalyst Technologies (InCatT B.V.), the Netherlands. Other phosphorous ligands, such as *t*Bu-xantphos, Si-xantphos, *o*MeO-xantphos, and 4,5-bis[di(*tert*-butyl)phosphanyl]-9,9-dimethylxanthene (di-*t*Bu-xantphos), were generously provided by Shell Global Solutions Amsterdam B.V., and were synthesized according to literature procedures.[7a, 15] All other chemicals, solvents, acids, and bases were purchased from Acros Organics or Sigma Aldrich, the Netherlands.

Instruments: The stainless-steel autoclave reactors (100 mL) from HEL Ltd, UK, were equipped with a magnetic stirrer, pressure transducer, and temperature controlling thermocouple. A Hewlett Packard HP6890 Series auto-sampler GC system was used for regular GC analysis. GC–MS analysis were carried out on an Agilent technologies 7820A GC system series coupled with an Agilent technologies 5975 series GC-MSD system. A glove box from M. Braun Inertgas-System GmbH, Germany, was used for storing and handling air-sensitive phosphane ligands. NMR spectra were recorded on Bruker DPX300 (300 MHz) or Bruker DMX400 (400 MHz) spectrometers.

Catalytic high-pressure reaction: All preparations and manipulations were performed by using standard Schlenk techniques under an argon atmosphere. The solvent diglyme was distilled from CaH_2, deoxygenated, and used immediately after the purification process. The catalytic reactions were carried out under varying syngas pressures and reaction temperatures. For all catalytic experiments, the active catalyst precursor was formed in situ in the autoclave by transferring the metal precursor and selected phosphane ligands. In the preparation of a typical catalytic reaction mixture, 0.01 mmol of [Rh(acac)$(CO)_2$] (2.58 mg) and 0.02 mmol of bidentate phosphane ligand or 0.04 mmol of monodentate phosphane ligand were weighed and transferred into an autoclave. The autoclave was tightly closed and subsequently filled with argon through the use of a Schlenk line that was connected to one of the valves of the autoclave. Through another valve under a continuous flow of argon, dried and degassed diglyme (8 mL) was subsequently added along with HOR^F (2 mL), decane (0.605 mL, 3.125 mmol) as an internal standard, 1-pentene (0.548 mL, 5 mmol), and acetamide (0.295 g, 5 mmol) followed by HOTs (9.51 mg, 0.05 mmol). Then the reactor was inserted into the heating block and pressurized with 50 bar ($CO/H_2 = 1:2$) syngas. This reaction mixture was stirred at 500 rpm for 30 min to ensure that complex formation was complete. The reaction mixture was heated to 100 °C (within 30 min) under stirring at 500 rpm. All reaction conditions of the catalytic process were controlled by computerized software panels. After standing for 2, 4, or 8 h at this temperature, the autoclave was cooled to room temperature over about 1 h. The autoclave was then carefully vented to atmospheric pressure.

After each catalytic run, the reaction mixture was taken from the reactor and immediately analyzed by gas chromatography. Calibration lines for each analyte were used to determine the conversion of the substrates and yields of the various products. The two isomeric unsaturated intermediates **2a** and **2L** are lumped together as **2**; generally these two isomeric compounds are present in only low amounts. The assignments of the products were confirmed by GC–MS and compared with authentic and pure commercial samples.

The products in Table 4,[16] *N*-heptylacetamide,[1a,17] *N*-nonylacetamide,[18] *N*-(3-phenylpropyl)acetamide,[19] *N*-hexylpropanamide,[16b,20] *N*-hexylisopropylamide,[16b,21] *N*-hexyl-2,2-dimethylpropionamide (*N*-hexylpivalamide),[16c,21,22] *N*-hexylpentanamide,[23] *N*-hexylbenzamide,[16b,24] *N*-hexyl-4-methoxybenzamide,[16b] *N*-hexyl-4-trifluoromethylbenzamide,[16b] *N*-hexyl-2-fluoroacetamide,[25] *N*-(2-methylpentyl)acetamide, and *N*-benzylacetamide[16a,c] are known compounds and were identified by ^1H and ^{13}C NMR spectroscopy and GC–MS (see Figures S11–S18 in the Supporting Information).[6]

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Keywords: chemoselectivity · homogeneous catalysis · hydroamidomethylation · regioselectivity · rhodium

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[12] It is worthwhile briefly commenting on the results of our search for alternative catalyst promoter compounds to HOR^F for hydroamidomethylation (Table 3). The fact that some phenolic compounds with pK_a values of around 9–10 show similar performances to HOR^F; this suggests that the promoting effect depends upon the acidity of the pro-

moter compounds. Only a rather narrow pK_a range of potential promoters can be applied; acids that are too strong cannot be used because this will lead to high rates of aldol condensation, whereas weaker acids, such as simple alkanols, cannot be used because of aldehyde acetal formation.

[13] To explain why neither carbonylation nor hydroformylation of intermediates **2** occurs in our reaction, it is thought that hydrogenation may proceed through insertion of one of the compounds **2**, that is, via *N*-hexylideneacetamide. The insertion of C=N into a cationic Rh^{III}–H species can selectively give the intermediate Rh^{III}–imido species (Rh–N-CHR), which is immediately converted into the Rh^{III} species and **3 L** through protonation in the acidic medium. If hydride migration were to result in a Rh–C-NHR intermediate, it seems quite likely that CO insertion into Rh–C might occur to give Rh–C(O)–C-NHR, which may then be terminated by hydrogenolysis to give the α-amidoaldehyde.

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