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Rhodium-Catalyzed Homogeneous Reductive Amidation of Aldehydes

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Abstract: The catalytic reductive amidation of an aldehyde (hexanal) with an amide (acetamide) is reported. Apart from the desired *N*-hexylacetamide, the two isomeric unsaturated intermediates as well as hexanol are produced together with higher mass products that arise from aldol condensation and diamide coupling of the aldehyde. Screening of different catalyst precursor salts, ligands and reaction conditions led to the finding that the catalytic system based on the (cyclooctadiene)rhodium chloride dimer, $[Rh(cod)Cl]_2$, in combination with the ligand xantphos and an acid co-catalyst results in high selectivity for the desired product. Under optimized conditions nearly full conversion is reached with high selectivity to the desired *N*-alkylamide and with a very high *N*-alkylamide/alcohol ratio, while producing only small amounts of by-products. The scope of the reaction has been investigated using different amides as well as aldehydes; the results show the general applicability of this novel reaction, but with electron-withdrawing amides the selectivity to *N*-alkylamide is lower. NMR studies showed that the nucleophilic addition of acetamide to hexanal is acid catalyzed, forming *N*-(1-hydroxyhexyl)acetamide in equilibrium with both hexanal and the dehydrated unsaturated imides. A catalytic mechanism is proposed in which a strong acid such as HOTs acts as a co-catalyst by establishing a rapid chemical equilibrium between the aldehyde, acetamide and the intermediates. Furthermore, it is proposed that the presence of acid causes a change in catalytic species, enabling a cationic Rh/xantphos hydrogenation catalyst to selectively hydrogenate the intermediates to *N*-hexylacetamide in the presence of hexanal.

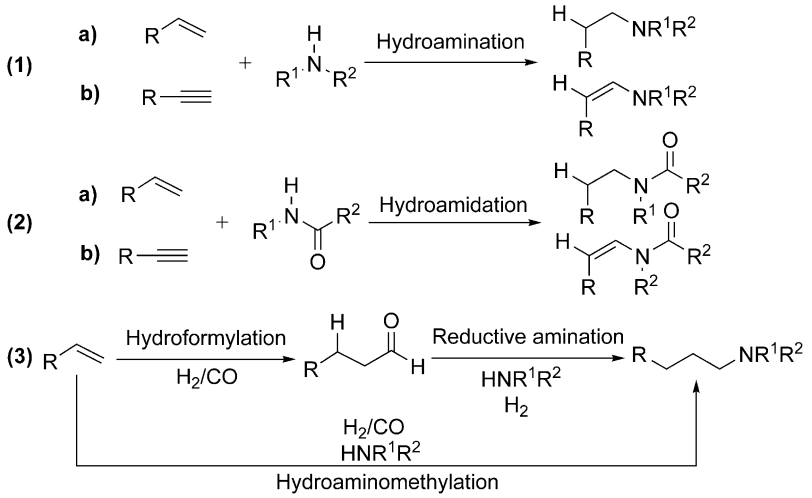
Keywords: homogeneous catalysis; phosphane ligands; reductive amidation; rhodium

Introduction

The reductive amidation of aldehydes with amides affording alkylated amides is a reaction with tremendous synthetic potential for application in academia as well as industry. The amide bond is one of the most significant functionalities found in many natural products. The catalytic formation of carbon-nitrogen bonds is highly attractive in organic chemistry, as well as in the bulk and fine chemical industries for the production of solvents, pharmaceutical intermediates and also in the synthesis of bioactive compounds such as amino acids.[1] In this respect, catalytic conversions to *N*-alkylamides definitely offer potential advantages over conventional methods of C–N coupling reactions, where large quantities of salts are produced stoichiometrically as by-products.

Among the different methods of carbon-nitrogen bond formations (Scheme 1), the most studied and challenging methods are hydroamination of alkenes and alkynes with amines,[2] hydroamidation of alkenes and alkynes[2f,3] and the reductive amination of carbonyl compounds.[4] In principle, these reactions can be performed with 100% atom efficiency, without or with very limited waste formation, fulfilling the requirement of green chemistry.

The intermolecular hydroamination of alkenes or alkynes is defined as the addition of an $H–NH_2$, $H–NHR^1$ or $H–NR^1R^2$ bond across an alkene or alkyne providing a next higher substituted alkyl- or alkenylamine, respectively [Scheme 1, reaction (1) a-b]. This reaction, which can be catalyzed both by transition metal complexes or by strong base, has been mostly studied with secondary amines rather than ammonia or primary amines; due to the subsequent reactivity of the primary reaction product, doubly and triply alk(en)ylated products are also formed when the latter substrates are being used.[2f,5] The catalytic hy-



Scheme 1. Hydroamination; hydroamidation; hydroaminomethylation and reductive amination reactions.

droamination reaction of olefins is hampered by low rates and low catalyst turnover numbers, while the thermodynamic driving force for the intermolecular version of hydroamination is close to zero or even negative at the elevated temperatures generally required for the reaction to proceed.[5b]

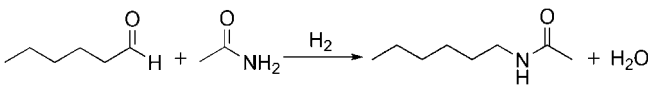
The related hydroamidation reaction, involving the addition of an amide's N–H bond to an alkene[2f] or alkyne[3] [Scheme 1, reaction (2) a-b] has also been studied; application of this reaction in an intermolecular fashion suffers from very similar problems as mentioned for intermolecular hydroamination, in particular with alkenes as substrate.[2f]

As a possible atom-economical efficient synthesis of amines the hydroaminomethylation of alkenes has also attracted considerable attention [Scheme 1, reaction (3)]. The (exothermic) hydroaminomethylation of alkenes is a tandem reaction consisting of three steps: initial hydroformylation of alkene, followed by the condensation of the aldehyde with a primary or secondary amine to form an enamine or imine, and a final hydrogenation to give the saturated secondary or tertiary amine.[1,6]

The most challenging step of hydroaminomethylation, i.e., the metal-catalyzed reductive amination of aldehydes with ammonia, primary amines or secondary amines, has been extensively studied.[4,7] Because of the high reactivity of the imine intermediates, reductive amination of aldehydes generally is accompanied by significant build-up of heavy, oligomeric byproducts, in particular with catalysts and under conditions such that hydrogenation of the imine intermediates is too slow. For ammonia and primary amines as substrates, over-alkylation of the desired primary or secondary amines is a general issue of concern. This is a consequence of the high reactivity of the primary or secondary amines, which will act as competing substrates in the course of the reductive amination process. Separation of the reaction products is usually difficult due to small differences in the boiling points of the products. In attempts to reach higher selectivity toward the desired product, the reductive amination reaction is often carried out using a large excess of the amine substrate; however, in a commercial application this would require costly (energy intensive) amine recycle processes.

The development of a new method for the synthesis of *N*-alkylamides using an amide as the substrate instead of an amine could be attractive as we reasoned that such a reductive amidation most likely would avoid the formation of over-alkylated amide side-products, due to a combination of relatively low nucleophilicity of the amide and increased steric encumbrance in the *N*-alkylated amide. This lower reactivity would allow application of an aldehyde/amide substrate ratio close to unity. Moreover, subsequent hydrolysis of the resulting *N*-alkylamide may yield a primary amine; the recovered carboxylic acid can be recycled to the corresponding amide with ammonia. Thus, the catalytic reductive amidation reaction would be a means to make primary amines, avoiding the difficulties of reductive amination with ammonia.

Herein, we report our studies towards the catalytic reductive amidation reaction of hexanal with acetamide (Scheme 2). The ultimate goal of our research is to combine the reductive amidation reaction with *in situ* formation of the aldehyde by hydroformylation of alkenes (hydroamidomethylation).

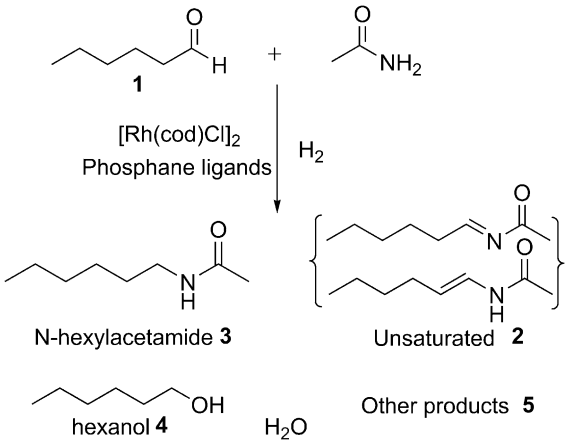


Scheme 2. Reductive amidation of hexanal with acetamide to form *N*-hexylacetamide.

Results

General Considerations

The products found in a typical reductive amidation experiment with hexanal **1** and acetamide as the substrates, are shown in Scheme 3. Apart from the desired *N*-hexylacetamide **3**, the two isomeric unsaturated compounds *N*-(1-hexylidene)acetamide or *N*-(1-hexenyl)acetamide **2** as well as hexanol **4** were observed with GC analysis. Additionally, formation of various products with higher mass (Figure 1), comprising aldol condensation products **5a** and the condensation product of hexanal with two molecules of acetamide **5b** was confirmed by both ^{1}H and ^{13}C NMR and mass spectroscopic analysis.



Scheme 3. Reductive amidation of hexanal with acetamide: observed products.

The reductive amidation experiments were performed starting with 5 mmol of hexanal **1** and a small excess of acetamide (6 mmol); a quantitative product distribution was determined from GC analysis. The hexanal conversions shown in the tables were calculated from the amount of hexanal found in the reaction mixtures after the reaction. Amounts of desired product **3**, unsaturated products *N*-(1-hexylidene)acetamide or *N*-(1-hexenyl)acetamide **2**, and hexanol **4** were determined using calibration lines.

The remainder consisted of the higher mass products **5**, which were not generally individually quantified from GC, but rather calculated as a lumped-together-number from the uneven mass balance of hexanal-derived GLC-measurable products. In the tables the selectivity for **2** as well as for the sum of **3**+**4** are reported. The specificity of the catalysts for reductive amidation *versus* hydrogenation of hexanal **1** is given as the ratio **3**/**4**. Full analytical data of all reaction mixtures are given in the Supporting Information.

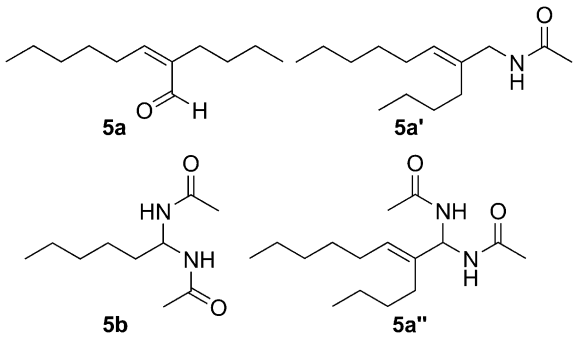


Figure 1. Products of higher molecular mass (**5**) observed in the reductive amidation reaction.

Catalytic Reductive Amidation: Initial Screening Studies

To investigate reductive amidation of aldehydes, we started our exploratory studies by testing various rhodium precursors. As shown in Table 1, the precursors $[Rh(cod)Cl]_2$, $[Rh(cod)_2]BF_4$ and $[Rh(cod)_2]OTf$ turned out to yield the highest hexanal **1** conversion with only moderate differences in the **3**/**4** ratio and **3**+**4** selectivity. It appeared, however, that neither of the tested rhodium complexes showed a high hydrogenation activity nor good selectivity to the desired *N*-hexylacetamide **3**. High specificity for reductive amidation *versus* hydrogenation of hexanal **1** is lacking, as is apparent from the relatively low **3**/**4** ratio. In addition, a significant conversion of hexanal to heavier products **5** (~35% selectivity) is apparent from the uneven hexanal-derived product balance as derived from GLC analysis. Because of its low sensitivity to air and moisture and because this precursor showed the highest product specificity **3** *versus* **4**, $[Rh(cod)Cl]_2$ was selected as the catalyst precursor for further studies.

Table 1. Reductive amidation of hexanal with acetamide.[a]

	Rhodium precursor	Conv. [%]	**2** Sel. [%]	**3**/**4** Ratio	**3**+**4** Sel. [%]
1	$[Rh(cod)Cl]_2$	56	35	14.7	30
2	$Rh(acac)(CO)_2$	25	42	3.1	12
3	$[Rh(cod)_2]BF_4$	47	29	1.9	46
4	$RhCl_3 \cdot x H_2O$	53	29	8.7	20
5	$Rh(CO)(H)(PPh_3)_3$	27	6	0.0	57
6	$[Rh(cod)_2]OTf$	58	16	2.7	54

[a] *Reaction conditions:* 0.01 mmol Rh precursor, 5 mmol hexanal, 6 mmol acetamide (Rh:hexanal:acetamide = 1:500:600); P_{H_2} = 80 bar; T = 100 °C; t = 4 h; solvent: 25 mL diglyme; decane as internal standard.

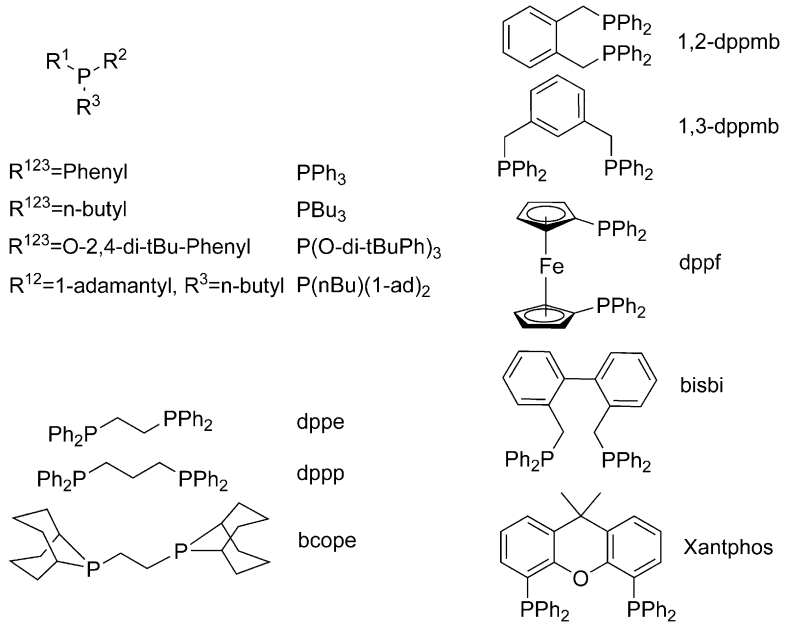


Figure 2. Ligands used in reductive amidation studies of hexanal.

In the following screening studies $[Rh(cod)Cl]_2$ was combined *in situ* with a large number of monodentate or bidentate phosphane ligands.

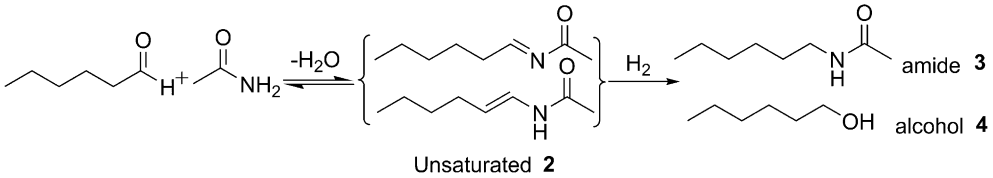
Variation in the stereoelectronic properties of the ligands was achieved by changing the P-substituent for monodentate ligands (aryl, alkyl, aryloxy or alkyloxy), while for bidentate ligands also the length and structure of the backbone spacer between the P donor atoms was varied. A selection of the ligands that were tested is shown in Figure 2.

The catalytic results of the screening studies using the different ligands are summarized in Table 2. The addition of various monodentate ligands to $[Rh(cod)Cl]_2$ resulted in lower conversion of the substrate relative to that obtained with the metal complex precursor alone (*cf.* entries 1, 3, 5, 7, 9). More importantly, these catalytic systems are quite active in hexanal **1** hydrogenation as shown by the low **3/4** ratio. Introducing a 5-fold molar excess on Rh of *p*-toluenesulfonic acid (HOTs) as additive appeared to have a pronounced impact on conversion and selectivity; however, in most cases the selectivity to the desired product remained low, as for example for the ligand PPh_3 (entries 3 and 4). The use of the more basic ligand P(*n*-Bu)$_3$ resulted in a catalytic system with high selectivity for hexanol **4** formation (80%) while here addition of acid did not have a significant effect on the **3/4** ratio (*cf.* entries 5 and 6). A higher product ratio **3/4** was observed with the catalytic systems containing the acid additive and the monodentate ligands P(ad)$_2$(*n*-Bu) or P(O-di-*t*-BuPh)$_3$ (entries 7–10), but the selectivity for the total amount of hydrogenated products **3**+**4** is still modest. The use of catalytic systems based on the bidentate ligands generally gave higher hexanal **1** conversion.The use of the bidentate phosphane ligands dppe and dppp, however, gave only moderate overall results with a low selectivity to **3** (entries 11–14), while the addition of acid again gave rise to higher conversion, but with only a slightly higher **3/4** product ratio and formation of larger amounts of **5**.

Use of the strongly electron-donating bidentate ligand bcope resulted in full conversion of hexanal **1** yielding exclusively hexanol **4** as the hydrogenation product together with small amounts of **5**; the addition of acid merely resulted in formation of more **5**. Better results were obtained when ligands with larger bite angle are used (entries 17–26). With the ligands 1,2-dppmb and 1,3-dppmb fairly high **3/4** product ratios were achieved, but with poor total hydrogenation selectivity to **3**+**4**. On the other hand, use of dppf or bisbi resulted in catalytic systems with higher selectivity to **3**+**4**, but with only moderate **3/4** product ratios. Much better yields of **3** were achieved with the xantphos ligand in combination with an added catalytic quantity of the acid HOTs (cf. entries 25 and 26). The addition of the acid dramatically improved the **3/4** product ratio from 0.3 to 17.5 with 80% combined hydrogenation selectivity to **3**+**4** at a high conversion of hexanal **1** (90%). At a lower reaction temperature (80 °C), the **3/4** product ratio and **3**+**4** selectivity increased to, respectively, ~21 and ~95% with only a slightly lower hexanal **1** conversion (entry 27).

In a next set of catalytic experiments in the presence of HOTs, the rhodium/xantphos ratio was varied (Table 3); the results show that increasing the rhodium/xantphos ratio from 1:1 to 1:3 leads to lower conversions but only slightly lower selectivity for hydro-

Table 2. Reductive amidation of hexanal with acetamide catalyzed by $[Rh(cod)Cl]_2$ in combination with different ligands.[a]



	Ligand	HOTs [mmol]	Conversion [%}	**2** Selectivity [%]	**3/4** Ratio	**3+4** Selectivity [%]
1	–	–	56	35	14.7	30
2	–	0.05	80	15	4.3	30
3	PPh_3	–	14	57	0.0	6
4	PPh_3	0.05	79	16	1.0	16
5	P(*n*-Bu)$_3$	–	36	0	0.0	78
6	P(*n*-Bu)$_3$	0.05	52	0	0.3	73
7	P(O-di-*t*-BuC_6H_3)$_3$	–	24	8	2.5	58
8	P(O-di-*t*-BuC_6H_3)$_3$	0.05	78	3	20.0	43
9	P(*n*-Bu)(1-ad)$_2$	–	28	7	2.3	71
10	P(*n*-Bu)(1-ad)$_2$	0.05	82	2	6.5	37
11	dppe	–	21	21	0.4	49
12	dppe	0.05	73	7	10.7	22
13	dppp	–	55	42	0.6	47
14	dppp	0.05	80	5	1.9	37
15	bcope	–	100	0	0.0	92
16	bcope	0.05	100	0	0.0	78
17	1,2-dppmb	–	47	34	7.6	35
18	1,2-dppmb	0.05	75	13	5.3	36
19	1,3-dppmb	–	48	37	14.4	33
20	1,3-dppmb	0.05	78	18	18.1	22
21	dppf	–	53	14	1.5	74
22	dppf	0.05	89	5	3.0	60
23	bisbi	–	64	35	0.4	40
24	bisbi	0.05	81	12	1.1	43
25	xantphos	–	82	2	0.3	85
26	xantphos	0.05	90	0	17.5	82
27	xantphos[b]	0.05	84	1	20.6	93

[a] *Reaction conditions:* 0.005 mmol $[Rh(cod)Cl]_2$, 5 mmol hexanal, 6 mmol acetamide [Rh:L:hexanal:acetamide = 1:1.25 (bidentate) or 2.5 (monodentate):500:600]; P_{H_2} = 80 bar; T = 100 °C; t = 4 h; solvent: 25 mL diglyme; decane as internal standard.
[b] T = 80 °C

Table 3. The effect of Rh/xantphos ratio on the reductive amidation of hexanal with acetamide.[a]

	Rh/L Ratio	Conversion [%]	**3/4** ratio	**3+4** Sel. [%]	**3** Sel. [%]
1	1/1	82	17.5	90	85
2	1/1.25	84	20.6	93	88
3	1/1.5	76	21.4	82	78
4	1/2	74	22.3	81	78
5	1/3	70	22.5	80	77

[a] *Reaction conditions:* 0.005 mmol $[Rh(cod)Cl]_2$, 5 mmol hexanal, 6 mmol acetamide (Rh:hexanal:acetamide = 1:500:600); HOTs (0.05 mmol); P_{H_2} = 80 bar; T = 80 °C; t = 4 h; solvent: 25 mL diglyme; decane as internal standard.

genated products. The use of 1.25 equivalents of xantphos on rhodium appears to give the best overall yield of *N*-hexylacetamide **3** (entry 2).

For the Rh/xantphos/HOTs catalytic system the use of different ratios of acetamide/hexanal (1/1 up to 2/1) did not result in large changes in hexanal conversion; it appeared that a small excess of acetamide (ratio of 1.2) gave the highest conversion of hexanal and selectivity to **3** and no over-alkylation was observed (see the Supporting Information, Table S4).

Screening of various reaction solvents revealed that for the Rh/xantphos/HOTs catalytic system diglyme is the most suitable solvent; the use of tetrahydrofuran (THF) gave comparable results with slightly lower selectivity to **3**. Use of other solvents like toluene, mesitylene, dichloromethane and *N*-methylpyrrolidone re-

sulted in significantly lower specificity to **3** as well as lower combined hydrogenation selectivity **3**+**4**, thus leading to rather mediocre overall selectivity to **3**. When methanol was used as solvent, full conversion of hexanal **1** was obtained, however hexanal **1** was mainly (~90%) converted to the dimethyl acetal and **3** was not obtained (see the Supporting Information, Table S5).

The effect of the reaction temperature on the hexanal conversion and product distribution is shown in Figure 3. Lowering of the reaction temperature from 120 °C to 80 °C leads to a pronounced increase in selectivity for **3**, from 70% up to 90%. At 80 °C, the formation of the heavy aldol condensation and diamide coupled products is suppressed. Upon further lowering of the reaction temperature, however, the conversion of hexanal **1** becomes lower, while the relative amount of unsaturated intermediates **2** and other heavier products **5** increases, thus indicating that hydrogenation activity to **3**+**4** decreases with temperature below 80 °C. It thus appears that a reaction temperature of 80 °C is the optimal temperature for this catalytic system.

The effect of the hydrogen pressure on the reductive amidation was also determined. When lowering the hydrogen gas pressure from 100 to 20 bar the overall hydrogenation activity of the catalytic system significantly decreases, thus resulting in increased formation of **5**. For the remaining studies a pressure of 80 bar was applied, as this resulted in relatively high hexanal **1** conversion combined with good selectivity to **3** (see the Supporting Information, Table S7 and Figure S1).

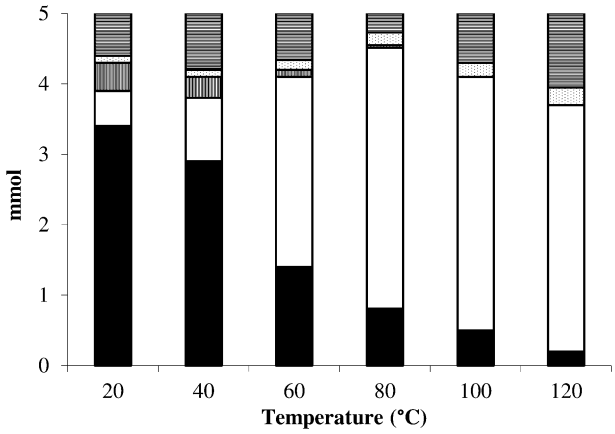


Figure 3. The effect of reaction temperature on product distribution in the reductive amidation reaction using the Rh/xantphos/HOTs catalytic system. *Reaction conditions:* 0.005 mmol $[Rh(cod)Cl]_2$, 0.0125 mmol xantphos, 0.05 mmol HOTs, 5 mmol hexanal, 6 mmol acetamide (Rh:xantphos:HOTs:hexanal:acetamide = 1:1.25:5:500:600); P_{H_2} = 80 bar; t = 4 h; solvent: 25 mL diglyme; decane as internal standard. ■ = hexanal (**1**), □ = *N*-hexylacetamide (**3**), ▥ = unsaturated *N*-(1-hexylidene)acetamide or *N*-(1-hexenyl)acetamide (**2**), ⁝⁝ = hexanol(**4**), ▤ = other products (**5**).

As it seemed that the xantphos ligand could play a unique role in the hydroamidation of an aldehyde to produce *N*-alkylamides in good selectivity, a variety of other xantphos-type ligands shown in Figure 4 were applied under the same acidic conditions as applied with xantphos. Catalytic results are collected in Table 4.

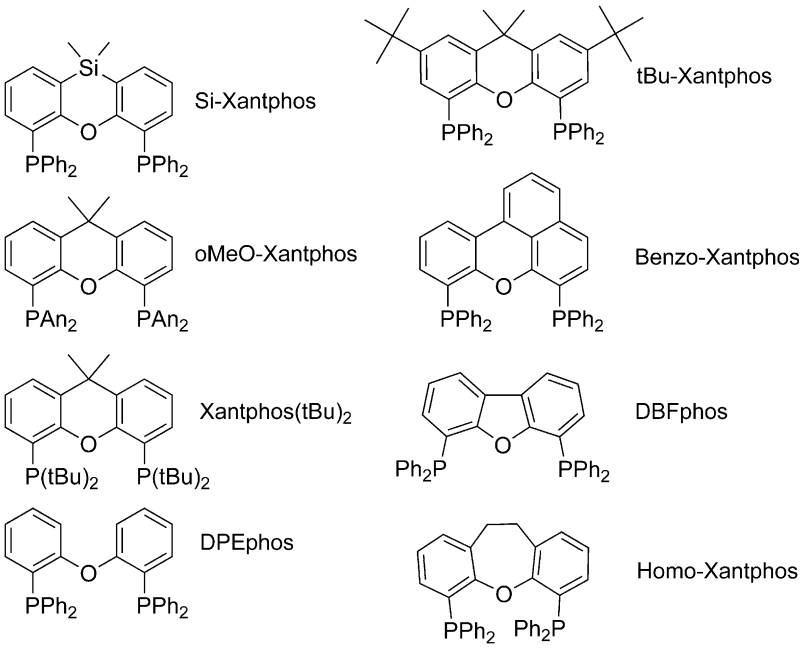


Figure 4. Selected xantphos-type ligands used in the reductive amidation of hexanal (An = *ortho*-anisole).

Table 4. Reductive amidation of hexanal with acetamide catalyzed by $[Rh(cod)Cl]_2$ in combination with different xantphos-type ligands.[a]

	Ligand	Conv. [%]	**2** Sel. [%]	**3/4** Ratio	**3+4** Sel. [%]
1	xantphos	84	1	20.6	93
2	*t*-Bu-xantphos	80	4	16.9	88
3	Si-xantphos	78	11	4.1	74
4	*o*MeO-xantphos	60	31	6.2	12
5	xantphos(*t*-Bu)$_2$	59	28	10.2	19
6	DPEphos	64	28	6.3	34
7	DBFphos	50	29	8.8	27
8	homoxantphos	60	24	1.1	39
9	benzoxantphos	47	28	5.9	26

[a] *Reaction conditions:* 0.005 mmol $[Rh(cod)Cl]_2$, 0.0125 mmol ligand, 0.05 mmol HOTs, 5 mmol hexanal, 6 mmol acetamide (Rh:L:hexanal:acetamide = 1:1.25:500:600); P_{H_2} = 80 bar; T = 80 °C; t = 4 h; solvent: 25 mL diglyme; decane as internal standard.

The best results were obtained with xantphos and *t*-Bu-xantphos (Table 4, entries 1 and 2). Remarkably, even relatively small modifications, such as the use of Si-xantphos or Benzo-xantphos instead of xantphos, in the catalytic system already resulted in a very significantly lower **3/4** ratio and lower selectivity to **3** (entry 3). Using the other xantphos-type ligands also resulted in significant suppression of the **3/4** ratio and selectivity to **3+4**. Apparently this is mainly due to a lower hydrogenation activity of these catalytic systems as also reflected by a significant increase in formation of unsaturated intermediates **2**; accumulation of these intermediates also results in increased amounts of **5** (entries 4–9).

Effect of Acid and Base Additives

As shown above the addition of HOTs to the reductive amidation reaction mixture has a significant effect on the selectivity of the catalytic system based on rhodium/xantphos. This prompted us to investigate the effect of acids or bases as additives in the reaction in more detail (Table 5).

Increasing the amount of HOTs from 0.025 to 0.05 mmol positively affects the **3/4** product ratio and the selectivity in favour of **3** (entries 2 and 3). Addition of a larger amount of HOTs (e.g., 8 mM; HOTs/Rh ~ 20) leads only to a slight decrease in selectivity predominantly due to the formation of more aldol condensation products **5** (entries 4 and 5). With the addition of the same amounts of significantly weaker acids such as acetic acid, phosphoric acid and phenylphosphonic acid, hexanol **4** becomes the dominant hydrogenation product (entries 7–9), quite similar to the experiment in which no acid is added. The use of

Table 5. Effect of the addition of various acids or bases on the reductive amidation of hexanal with acetamide using Rh/xantphos catalytic system.[a]

	Additive (0.05 mmol)	pK_a[b]	Conv. [%]	**3/4** Ratio	**3+4** Sel. [%]	**3** Sel. [%]
1	no acid		76	0.3	84	21
2	HOTs[c]	−2.7	78	2.4	84	60
3	HOTs	−2.7	84	20.6	93	88
4	HOTs[d]	−2.7	92	24.5	87	83
5	HOTs[e]	−2.7	98	30.8	84	81
6	HOTs[f]	−2.7	86	4.4	88	72
7	AcOH	4.8	70	0.1	86	9
8	H_3PO_4	2	68	0.4	76	21
9	PhH_2PO_3	1.8	68	0.7	76	32
10	TFA	−0.3	74	1.6	78	49
11	HBF_4	−4	66	12.5	82	76
12	HCl	−7	70	20.8	80	76
13	HOTf	−5.1	90	26.0	87	84
14	NMP		72	0.0	86	3
15	NEt_3		90	0.0	91	0

[a] *Reaction conditions:* 0.005 mmol $[Rh(cod)Cl]_2$, 0.0125 mmol xantphos, 5 mmol hexanal, 6 mmol acetamide Rh:xantphos:hexanal:acetamide = 1:1.25:500:600); P_{H_2} = 80 bar; T = 80 °C; t = 4 h; solvent: 25 mL diglyme; decane as internal standard.

[b] The pK_a values are determined in water as solvent (see ref.[8]).

[c] 0.025 mmol HOTs.

[d] 0.1 mmol HOTs.

[e] 0.2 mmol HOTs.

[f] HOTs 12% in acetic acid.

stronger acids leads to progressively higher selectivity to **3** (entries 10–13); with triflic acid (HOTf) excellent conversion with high **3/4** ratio and high selectivity is obtained (entry 13). Conversely, the use of the weak base *N*-methylpyrrolidone (NMP) or stronger base triethylamine (NEt_3) both result in the formation of hexanol **4** as the exclusive hydrogenation product, remarkably with a similar hexanal **1** conversion rate as obtained under acidic conditions (entries 14 and 15).

Effect of Acid on Hydrogenation of Aldehyde

To elucidate the selectivity-improving role of acid addition in reductive amidation as apparent from the spectacular increase of the **3/4** product ratio with the rhodium/xantphos catalytic system the influence of acid addition on the hydrogenation of hexanal **1** to hexanol **4** was separately investigated, both in the absence and presence of an inert amide model compound, *N*,*N*′-dimethylacetamide (Table 6).

In the absence of HOTs and acetamide, the rhodium/xantphos catalytic system hydrogenates hexanal **1** to hexanol **4** with about 50% conversion after 4 h at 80 °C (entry 1). Addition of a catalytic amount of

Table 6. Hydrogenation and reductive amidation of hexanal with and without acetamide.[a]

	Amide (6 mmol)	HOTs [mmol]	Conv. [%]	**3/4** Ratio	**3+4** Sel. [%]	**4** Sel. [%]
1	–		52	–	–	85
2	–	0.05	14	–	–	9
3	DMA[b]		54	–	–	81
4	DMA[b]	0.05	26	–	–	62
5	acetamide		76	0.3	84	63
6	acetamide	0.05	84	20.6	93	4

[a] *Reaction conditions:* 0.005 mmol $[Rh(cod)Cl]_2$, 0.0125 mmol xantphos, 5 mmol hexanal, in some cases 6 mmol amide (Rh:xantphos:hexanal = 1:1.25:500); P_{H_2} = 80 bar; T = 80 °C; t = 4 h; solvent: 25 mL diglyme; decane as internal standard.

[b] *N*,*N*′-Dimethylacetamide.

HOTs causes a significant drop in conversion; assuming first order reaction kinetics one can calculate a decrease in hydrogenation rate constant of about a factor 5 by the presence of acid.[9] The effect on the selectivity of hydrogenation is even more dramatic, due to a competing acid-catalyzed aldol condensation of hexanal **1** giving **5** (entry 2). The use of *N*,*N*′-dimethylacetamide, added to the reaction mixture to simulate a similar reaction medium as applied in actual reductive amidation, gives a qualitatively similar result (*cf.* entries 3 and 4). However, likely due to the weak basicity of *N*,*N*′-dimethylacetamide the addition of HOTs now leads to a decrease in hydrogenation rate constant only by a factor of about 2.5, while maintaining a reasonably good selectivity for hydrogenation to **4**. For comparison, the data for the hexanal reduction in the presence of acetamide are summarized (entries 5 and 6): without acid almost exclusively **4** is formed as the reduction product, while in the presence of a catalytic quantity of HOTs, **3** is the almost exclusive reduction product.

Influence of Added Water

As in the reductive amidation of an aldehyde one equivalent of water is formed, the effect of added water in the reaction media was also investigated. Addition of 2.5 mmol of water, theoretically corresponding to about 50% conversion of hexanal **1**, already has a significant impact on the reaction; still ~75% conversion is reached, but the selectivity to **3** drops to about 70%. Increasing the amount of water to 5 mmol has a more dramatic effect, in particular on selectivity to **3**. The addition of molecular sieves (3 Å) to the reaction does not have a significant effect on the conversion, but seems to have a slightly positive effect on the **3**/**4** ratio (see the Supporting Information, Table S12).

Catalyst Systems other than those Based on Rh

Under the optimized reaction conditions shown above, we tested various other transition metal precursors (based on Ru, Pd, Pt, Ir and Co) in combination with xantphos – with or without HOTs – in the reductive amidation reaction (see the Supporting Information, Table S13). None of the used complexes showed a performance comparable with the Rh catalysts. The catalytic system containing Rh/xantphos/HOTs turned out to be by far the most active and selective catalytic system for reductive amidation.

Product Evolution in Time

The product development over the time for the Rh/xantphos/HOTs catalytic system is depicted in Figure 5. After ten hours at 80 °C nearly full conversion (98%) (TON ~ 500) is reached with about 88% selectivity to **3**. It is shown that the unsaturated intermediates **2** do not build up to any significant extent in this experiment, while the aldehyde concentration monotonously decreases according to an approximately first-order reaction. This could indicate that formation of the unsaturated amide adducts is rate-

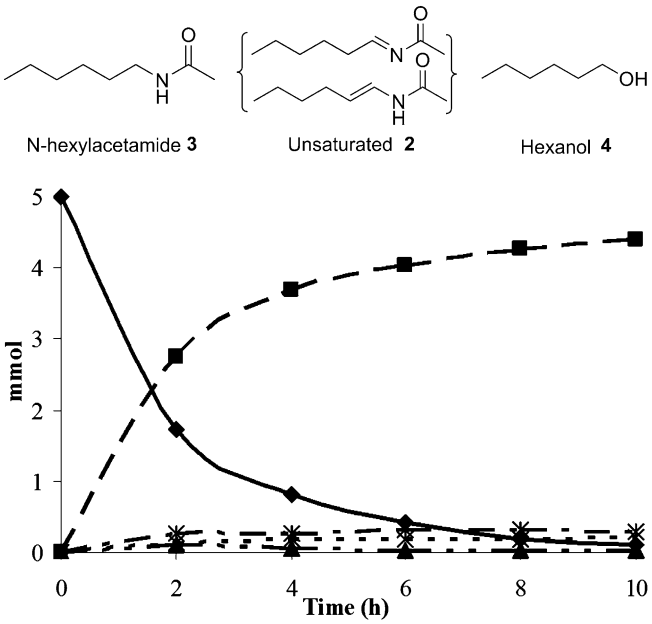


Figure 5. Product development in time in the reductive amidation of hexanal with acetamide; Reaction conditions: 0.005 mmol $[Rh(cod)Cl]_2$, 0.0125 mmol xantphos, 0.05 mmol HOTs, 5 mmol hexanal, 6 mmol acetamide (Rh:xantphos:HOTs:hexanal:acetamide = 1:1.25:5:500:600); P_{H_2} = 80 bar; T = 80 °C; solvent: 25 mL diglyme; decane as internal standard. ◆ = hexanal (**1**), ■ = *N*-hexylacetamide (**3**), ▲ = unsaturated *N*-(1-hexylidene) acetamide or *N*-(1-hexenyl)acetamide (**2**), × = hexanol (**4**), * = other products (**5**) (the exact data are given in the Supporting Information, Table S14)

determining under the prevailing conditions, and that hydrogenation of these intermediates is a relatively fast reaction.

The robustness of the catalytic system in the optimized reaction conditions was investigated using 10 mmol of substrate with 0.0025 mmol of rhodium precursor in combination with xantphos and HOTs at 80 °C. After 10 h 75% conversion of hexanal **1** was reached with 60% overall selectivity to **3**. The cumulative turnover number thus obtained was about 1800, i.e., quite an acceptable number considering the scale, water build-up and low catalyst concentration applied in this experiment.

Scope of Reductive Amidation; Applying Different Amide and Aldehyde Substrates

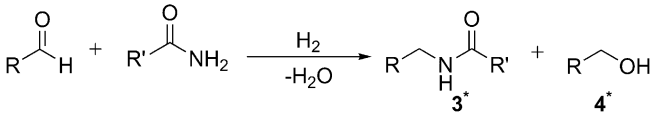
A number of different N-nucleophiles were applied in the reductive amidation of hexanal **1** (Table 7). The use of amides with one electron-donating alkyl group at the alpha C of the amide such as propanamide and pentanamide, results in higher conversion and selectivity (entries 1, 2, 5). The use of amides with two or three alpha-C alkyl substituents leading to bulkier alkylamides, such as isopropylamide and *tert*-butylamide, results in a somewhat lower efficiency of the reaction (entries 3 and 4). For comparison, application of the electron-withdrawing fluoroacetamide results in a very significant drop in the selectivity to **3*** (entry 6). The use of benzamide also results in lower conversion and selectivity compared to acetamide. Applying *p*-methoxybenzamide with an electron-donating group gives higher selectivity and conversion, whereas *p*-trifluoromethylbenzamide with an electron-withdrawing group again results in considerably lower selectivity and conversion. Clearly, the nucleophilicity of the N atom in the amide plays a decisive role in a successful reductive amidation of aldehyde.

The branched aldehyde 2-methylpentanal and the electronically different benzaldehyde, (entries 10 and 11) are considerably less reactive in reductive amidation with acetamide; not only the conversion is lower, but also the hydrogenation activity and substrate specificity (ratio **3*/4***) quite drastically decreases.

NMR Study of the Hexanal/Acetamide Mixture in the Absence of Rh Catalyst

The adduct formation of hexanal **1** with acetamide was studied by following the time evolution of ^{1}H NMR spectra of a 1:1 mixture hexanal/acetamide in THF-d_8 at 60 °C in the absence of the rhodium/ligand catalytic system. It appears that condensation of hexanal **1** with acetamide in THF-d_8 does not proceed in the absence of HOTs (see the Supporting Information). However, as shown in Figure 6, in the presence of only 1 mol% of HOTs already after 10 min adduct formation between hexanal **1** and acetamide is observed, as indicated by the simultaneous formation of proton resonances at 5.25 ppm attributed to -C**H**(OH) (**2a***) and at 7.65 ppm attributed to N**H** of **2a** (Figure 6).

Table 7. Scope of reductive amidation using various amides and aldehydes.[a]



	Aldehyde	Amide	Conversion[b] [%]	**3*/4*** Ratio	**3*+4*** Sel. [%]	**3*** Sel. [%][c]
1	hexanal	acetamide	84	21	92	88
2	hexanal	propanamide	90	24	93	90
3	hexanal	isopropylamide	77	13	85	79
4	hexanal	*tert*-butylamide	75	12	87	81
5	hexanal	pentanamide	92	31	95	92
6	hexanal	fluoroacetamide	32	2	51	35
7	hexanal	benzamide	58	8	81	72
8	hexanal	*para*-methoxybenzamide	72	14	85	80
9	hexanal	*para*-trifluoromethylbenzamide	38	4	73	58
10	2-methylpentanal	acetamide	57	3	41	31
11	benzaldehyde	acetamide	42	0.1	63	9

[a] Reaction conditions: 0.005 mmol $[Rh(cod)Cl]_2$, 0.0125 mmol xantphos, 0.05 mmol HOTs, 5 mmol aldehyde, 6 mmol amide (Rh:xantphos:HOTs:hexanal:amide = 1:1.25:5:500:600); P_{H_2} = 80 bar; T = 80 °C; t = 4 h; solvent: 25 mL diglyme;

[b] The conversion was determined by GC analysis based on the amount of aldehyde found in the reaction mixtures after the reaction.

[c] The selectivity was determined by GC analysis using decane as an internal standard.

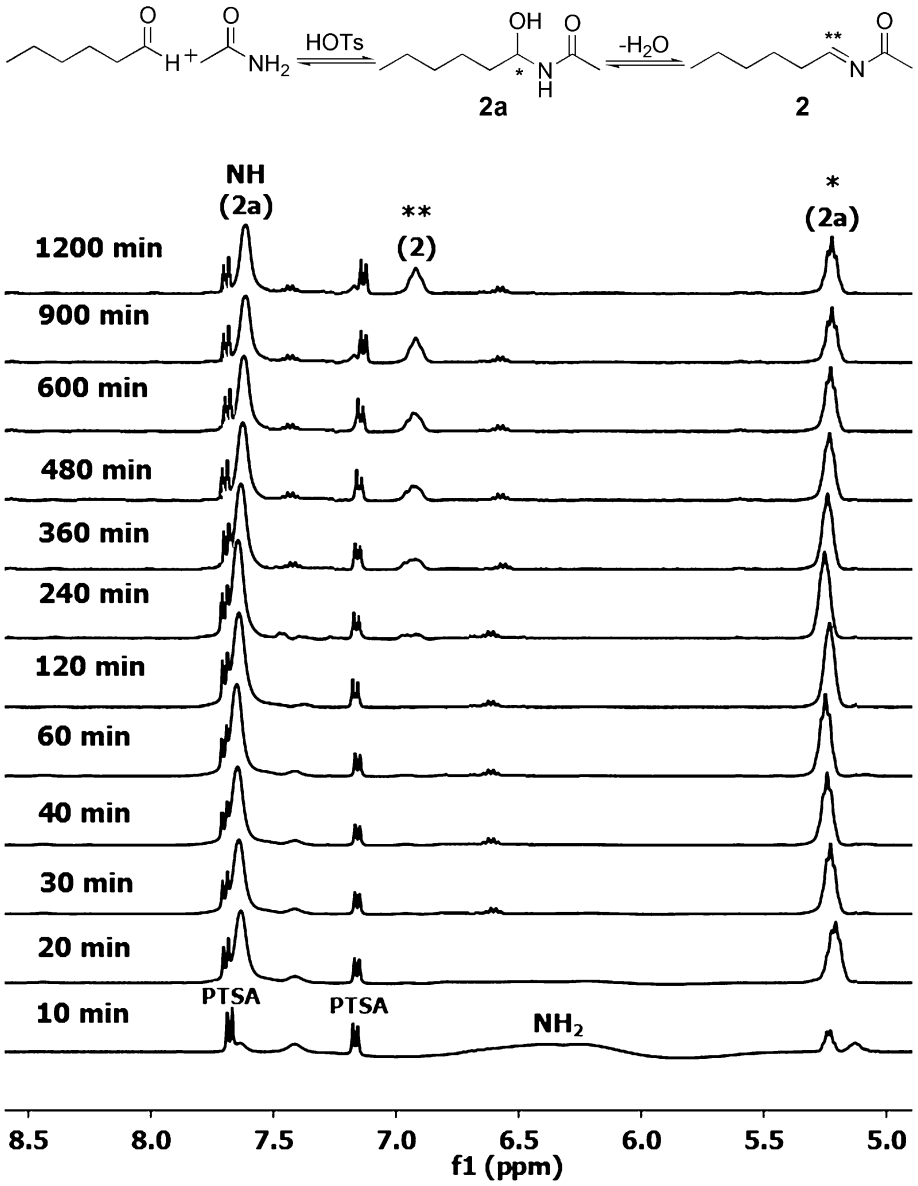


Figure 6. ^{1}H NMR time evolution of part of the ^{1}H NMR spectra relevant for the condensation reaction of hexanal with acetamide; hexanal:acetamide:PTSA = 1:1:0.01 ratio in THF-d_8; T = 60 °C.

The intensity of these resonances keeps growing up to about 150 min; after this time resonances attributed to the dehydrated product **2** appear [the peak at 6.95 ppm can be assigned to the imide functionality-C**H**=N (**2****)].[10] The evolution of the proton resonances is thus consistent with a two-stage addition process of the acetamide's N–H bond to hexanal **1**, initially forming the nucleophilic addition product **2a** followed by dehydration to give **2**. Small proton resonances at 5.10 and 6.70 ppm can be assigned to the other isomeric dehydration product, *N*-(1-hexenyl)-acetamide **2**;[10] however, the integrals of these resonances remain relatively small under our conditions.[11]

From the time evolution of the proton resonances representative for hexanal, acetamide, **2a** and **2** the time-dependent concentration of these compounds has been constructed and is graphically depicted in Figure 7. From this it is immediately clear that the two stages in the acetamide–aldehyde addition process both involve equilibrium processes. Two separate equilibrium constants can be calculated from these data. The first equilibrium constant ($K_1 = 2.701\ M^{-1}$) shows that in the presence of a catalytic amount of HOTs, addition of acetamide to hexanal forming **2a** is an equilibrium reaction that proceeds under the prevailing conditions (hexanal:acetamide = 1:1; THF solvent; 60 °C) to slightly less than 50% hexanal conversion. The subsequent dehydration reaction forming **2**

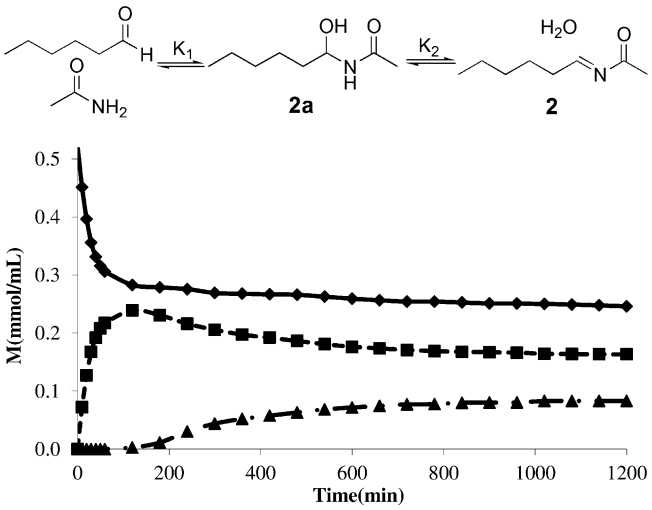


Figure 7. Development of the relative intensities of resonances assigned to hexanal (9.72 ppm), *N*-(1-hydroxyhexyl)acetamide (5.25 ppm and 7.65 ppm) and *N*-(1-hexenylidene)-acetamide (6.95 ppm) in time. Hexanal:acetamide:HOTs = 1:1:0.01 ratio in THF-d_8; $T = 60\,°C$. Measuring in the first hour every 10 min and then every 60 min until 20 h. ◆ = hexanal (**1**), ■ = **2a**, ▲ = **2**.

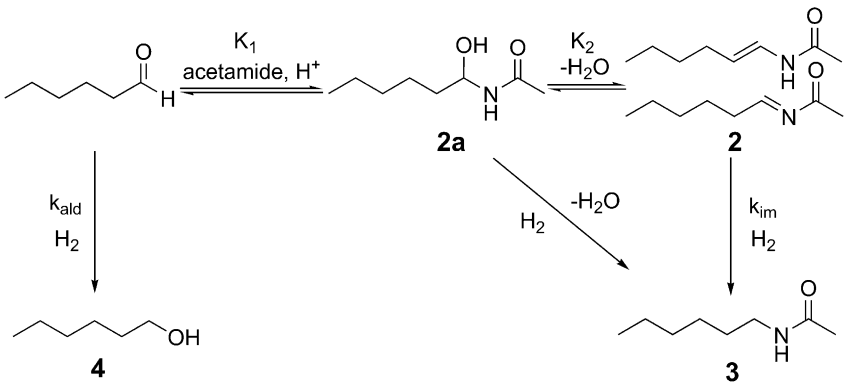
proceeds only to a limited extent, as shown by the apparent low value of the second equilibrium constant ($K_2 = 0.042\,M^{-1}$) which implies that only relatively low concentrations of **2** can be present in the reaction mixture at equilibrium.

However, it must be noted that for this model study, a low reaction temperature of 60 °C was applied for practical reasons. One may expect the dehydration equilibrium (K_2) to shift to higher conversion at the higher temperatures used in the catalytic experiments (80–100 °C). We conclude from this model study that the addition of an acetamide's N–H to the aldehyde proceeds in two consecutive stages catalyzed by (strong) acid. In this respect the addition of acetamide strongly deviates from addition of a more nucleophilic amine to aldehyde which generally involves a thermally spontaneous addition of the amine to aldehyde, forming imines (or carbinolamines) under very mild conditions. Clearly, a reduced nucleophilicity of the N atom of amides relative to amines must be responsible for this difference.

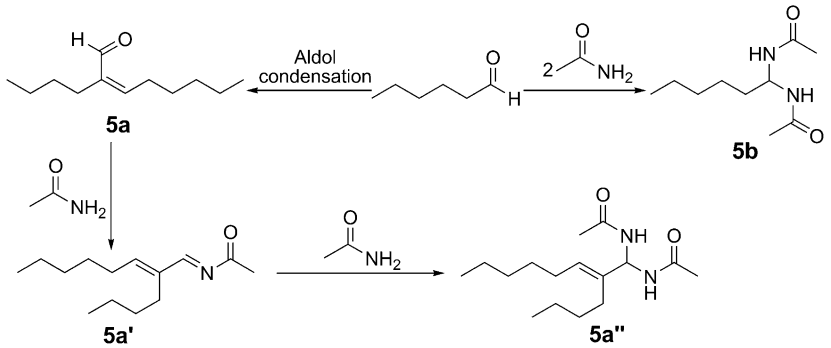
Discussion

The reductive amidation of hexanal **1** with acetamide comprises two sequential steps as shown in Scheme 4. The first step consists of two consecutive equilibrium reactions: the nucleophilic addition of acetamide to hexanal **1** yielding the intermediate **2a** which may undergo dehydration to form the two isomeric unsaturated intermediates **2**, i.e-, *N*-(1-hexylidene)acetamide and to a lesser extent *N*-(1-hexenyl)acetamide. Irreversible hydrogenation of these unsaturated intermediates will subsequently result in the formation of desired product **3**. Direct hydrogenolysis of **2a** to give **3** may also occur, as has also been suggested for intermediate *N*-carbinolamines in the reductive amination of aldehyde with secondary amines.[4a,12] Formation of **4** by the hydrogenation of hexanal **1** constitutes a loss of starting material, thus resulting in lower selectivity for reductive amidation.

An efficient catalytic system for the reductive amidation reaction thus comprises a catalyst that has a significantly higher rate of hydrogenation of the unsaturated intermediates **2** (k_{im}) (and/or hydrogenolysis of **2a**) relative to hydrogenation of the aldehyde (k_{ald}) in combination with rapid establishment of the equilibrium addition reaction of the aldehyde with the amide. The water formed in the dehydration step in the second equilibrium eventually will have an adverse effect on this equilibrium. Applying an active and selective catalytic system for the hydrogenation of the unsaturated intermediates **2** (or hydrogenolysis of **2a**) not only advances the reductive amidation reaction by irreversibly removing these intermediates from the equilibria, but also avoids accumulation of the unsatu-



Scheme 4. Catalytic reductive amidation of hexanal; formation of *N*-hexylacetamide **3** *via* *N*-(1-hydroxyhexyl)acetamide **2a** and imide or enamide intermediates **2**. Hexanol **4** is a by-product of the reaction.



Scheme 5. Catalytic reductive amidation; formation of other products characterized by NMR, GC and GC-MS.

rated intermediates that eventually may form heavier by-products. Possible routes to the higher-mass coupling products are shown in Scheme 5. In the absence of an active hydrogenation catalyst the intermediates **2** may react with a second molecule of acetamide to form the di-coupled product **5b**. The other competing side-reactions proceed *via* the aldol condensation of hexanal **1** yielding product **5a**; this aldol product can also undergo nucleophilic attack of acetamide to form **5a′** and the di-coupling reaction with acetamide giving **5a″**.

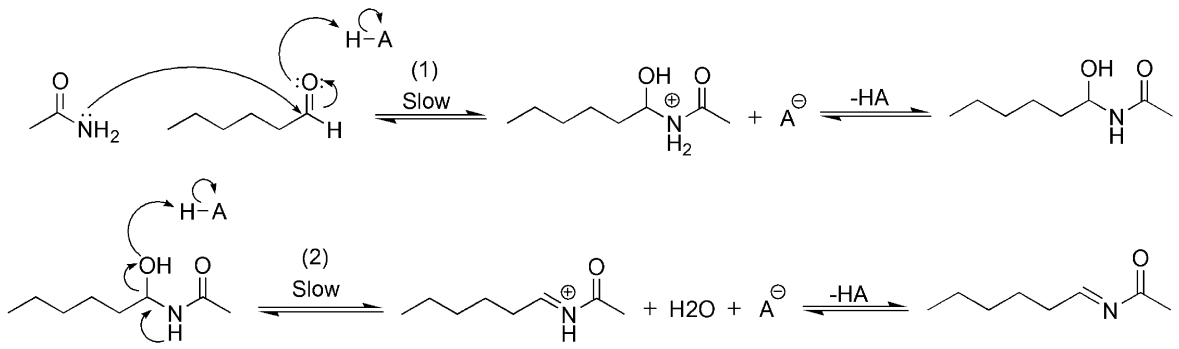
Influence of Acid

For nearly all catalytic systems that have been screened in our study, the addition of a catalytic amount of acid results in higher conversion of hexanal **1** and improved selectivity to **3**. The formation of aldol condensation and di-coupling products is also promoted by the introduction of acid, as is clearly observed for those catalytic systems that have low hydrogenation activity.

The results of the NMR study show that the nucleophilic addition of acetamide's N–H to hexanal clearly is promoted by acid (Scheme 6); in absence of acid (and hydrogenation catalyst) the addition reaction does not proceed at all, whereas in the presence of acid the reaction to **2a** and the dehydrated products **2** reaches equilibrium at 60 °C in about 10 h. At a practical temperature of 80–100 °C of the catalytic reductive amidation reaction, this process will be faster. The proposed mechanism is consistent with the acid-catalyzed nucleophilic addition of inactivated amines to a carbonyl functionality as described in the literature.[13] The dehydration of the intermediate *N*-1-carbinolamide **2a** to form the unsaturated acetamides **2** should also be acid catalyzed, but only occurs to a relatively small extent ($K_2 = 0.042\,M^{-1}$) at 60 °C.

Influence of Ligands, Reagents and Reaction Conditions

The use of different rhodium precursor complexes in the absence of ligand results in catalytic systems with reasonable conversion of hexanal **1**, but low selectivity. Notably, the use of rhodium precursors with carbonyl ligands results in lower conversions. The addition of various monodentate or bidentate phosphorus ligands to $[Rh(cod)Cl]_2$ generally leads to higher conversion of hexanal. The use of electron-donating alkylphosphane ligands results in catalytic systems that are highly selective for hydrogenation of hexanal to **3**. The use of xantphos results in a catalytic system that shows high conversion to **4** and only a very small amount of **3**, while the intermediates **2** are observed only in trace amounts. Remarkably, upon the addition



Scheme 6. Proposed mechanism for the acid-catalyzed condensation reaction of hexanal with acetamide.

of a catalytic amount of HOTs the desired reductive amidation product **3** is obtained with high selectivity of about 90% and a **3/4** product ratio > 20. This shows that the addition of HOTs not only leads to a more rapid establishment of the equilibrium between aldehyde and enamide/imide as shown by our NMR study, but apparently also leads to significant changes of the relative rates of hydrogenation of the unsaturated amides **2** (giving **3**) and aldehyde (giving **4**, Scheme 4).

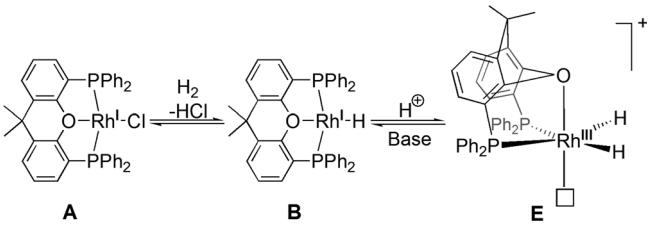
Generally, the conversion is strongly affected by the choice of the N-substrates, which supports the idea that the coupling reaction is dependent on the nucleophilicity and bulkiness around nitrogen of the substrates. Lowering of the reaction temperature from 120 °C to 80 °C results in formation of less aldol condensation products, and thus in higher overall (**3**+**4**) hydrogenation selectivity. However, at temperatures lower than 80 °C the hydrogenation activity of the catalysts is also drastically decreased, which lowers the overall hexanal **1** conversion as well as the hydrogenation selectivity; a higher aldehyde concentration profile during the reaction period will generally lead to higher amounts of heavy aldol products. Also, lower hydrogen gas pressures in the reaction lead to lower hydrogenation activity, consequently resulting in the accumulation of intermediates that eventually yields higher amounts other products **5**.

Mechanistic Considerations

The catalytic system based on rhodium/xantphos in the absence of added acid, but in the presence of the amide, predominantly hydrogenates hexanal **1** to **4**; intermediates **2** are observed only in trace amounts. However, upon the addition of a catalytic amount of HOTs the desired product **3** is obtained with high selectivity.

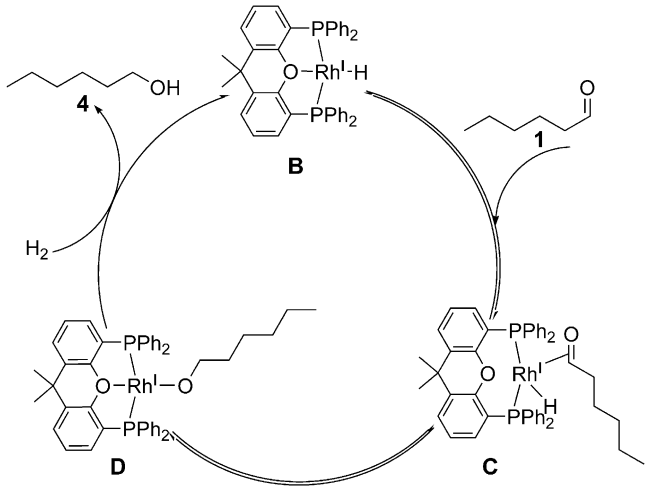
One reason for the high specificity in the hydrogenation of unsaturated amides (or hydrogenolysis of **2a**) lies in the intrinsically lower activity for aldehyde hydrogenation of the Rh/xantphos species generated in the presence of acid as shown in Table 7 (*cf.* entries 1 *vs.* 2 and 3 *vs.* 4).

In Scheme 7 a proposed pathway is given for the formation of the different catalytic species in the presence or absence of acid. Starting from $[Rh(I)(cod)Cl]_2$ and xantphos, the complex [Rh(I)(xantphos)Cl] **A** is initially formed. In the absence of acid, heterolytic splitting of dihydrogen may result in the formation of the neutral mono-hydride species [Rh(I)(xantphos)H], **B**. In the presence of acid the cationic dihydride species $[Rh(III)(xantphos)(H)_2]^+$ **E** may be formed by protonation of the monohydride Rh(I) compound.[14]



Scheme 7. Proposed pathways for the formation of the different catalyst precursors for the reductive amidation reaction in the presence or absence of acid; □ = open site or solvent molecule.

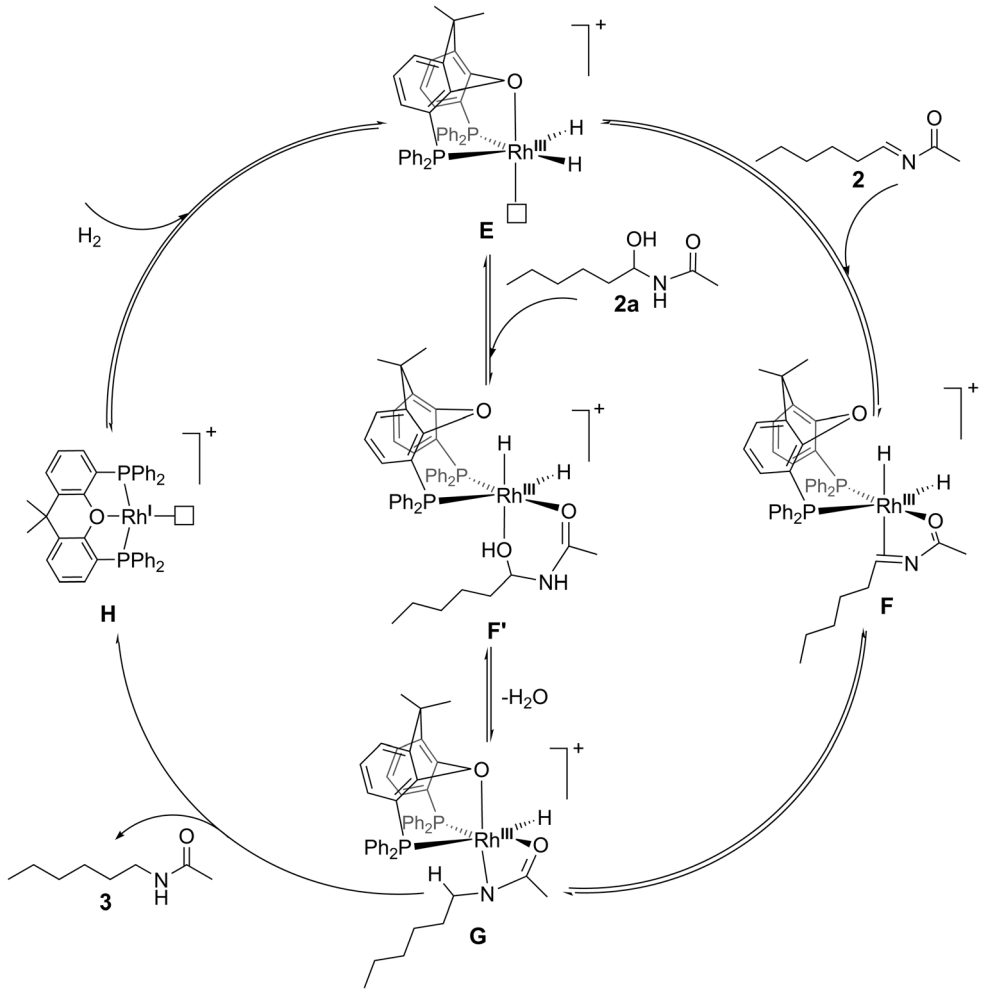
It is our hypothesis that species **B** is a selective catalyst for the hydrogenation of hexanal (Scheme 8). The neutral, low-valent Rh(I) compound would favour the binding of the aldehyde *via* its π electrons, with subsequent migration of the hydride resulting in



Scheme 8. Proposed catalytic cycle for hydrogenation of hexanal.

the formation of the Rh(I) alkoxide species **D**. In the final step, heterolytic activation of dihydrogen yields **4** with the regeneration of mono-hydride species **B**. In this mechanism, the xantphos ligand may bind in a meridional fashion, stabilizing the catalytic species in its Rh(I) state throughout the catalytic cycle.

On the other hand, the cationic, high-valent species **E**, $[Rh(III)(xantphos)(H)_2]^+$ would favour binding of the imido intermediate **2** through both the carbonyl oxygen and the imide double bond over the π-bond of the aldehyde's carbonyl, forming species $[Rh(xantphos)(H)_2(imide)]^+$ **F** (Scheme 9). A similar reasoning could hold for possible *N*-(1-hexylidene)acetamide. Then, hydride migration to the imide carbon atom results in the formation the *N*-hexylacetamido species **G**. Finally, *N*-hexylacetamide **3** is released *via* reductive elimination to form the Rh(I) species **H**;



Scheme 9. Proposed catalytic cycle for the hydrogenation of intermediate *N*-(hexenylidene)acetamide **2** or *N*-(1-hydroxyhexyl)acetamide **2a**; □ = open site or solvent molecule.

subsequent oxidative addition of dihydrogen recovers species **E**. In this mechanism, the rhodium center is cationic and shuttling between the Rh(I) and Rh(III) oxidation state. The selective binding and subsequent H-migration involving the *N*-(1-hexylidene)acetamide and *N*-(1-hexenyl)acetamide intermediates **2** is thought to contribute to the unusually high substrate specificity for hydrogenation of **2** that at all times during the reaction is present in only relatively low concentrations in equilibrium with the aldehyde. An additional factor disfavouring the hydrogenation of aldehyde could be that, in contrast with the Rh(I) center in the absence of acid as proposed in Scheme 8, the now strongly electrophilic cationic dihydride Rh(III) center would favour coordination of the hard carbonyl oxygen over π-coordination of the carbonyl bond. This carbonyl oxygen binding mode is not a suitable configuration for hexanal **1** hydrogenation, as in this case hydride migration to the carbonyl carbon is not easily possible.

From the NMR studies it is clear that in the presence of an acid (and at relatively low temperatures), instead of one of the unsaturated intermediates **2** the addition product, carbinolamide **2a**, is predominantly present in solution. Thus, alternatively, this bifunctional carbinolamide may also bind selectively to species **E** in the presence of aldehyde, effectively giving selective direct dehydrative hydrogenolysis of the alcohol group *via* a species **F′**.

The POP-pincer structure in xantphos-type ligands has been shown to be important for the stabilization of catalytic intermediates in different reactions such as intramolecular hydroamination,[15] methanol carbonylation,[16] and intermolecular hydroacylation of alkenes and alkynes.[17] Structural studies have also shown the importance of the flexibility of this ligand, with the possible *trans* bidentate and *fac* or *mer* tridentate coordination modes.[17,18] Moreover, the crystal structure of a Rh(III) compound containing a 4-

membered imidocarbonyl chelate similar to our proposal for species **G** has recently been reported.[19]

Conclusions

We have successfully developed a highly selective catalytic system comprising rhodium/xantphos/HOTs for the reductive amidation of an aldehyde with an amide to form *N*-alkylamides in high yield and under mild conditions. We have achieved a promising TON of 1800 with use4 of only a small excess of amide substrate. The use of an acid co-catalyst appears to be important for both the nucleophilic addition of the amide to the aldehyde as well as the substrate specificity in the hydrogenation step. The selective reductive amidation of aldehydes bears resemblance with the well-known transition metal-catalyzed reductive amination of aldehydes, but which often suffers from the formation of substantial amounts of side-products originating from (base-catalyzed) aldol condensation and over-alkylation.

We are currently seeking to utilize our reductive amidation catalytic system for a 'hydroamidomethylation' reaction, comprising a tandem hydroformylation–reductive amidation process of an alkene with syngas and an amide. For this purpose the reductive amidation catalyst must of course be able to tolerate the presence of carbon monoxide necessary for the hydroformylation step. Preliminary investigations have shown that the presence of traces CO in the reductive amidation reaction results in quenching of the hydrogenation activity and selectivity of the catalyst. Further studies are directed at ways to reduce or eliminate the CO sensitivity of the catalytic system.

Experimental Section

Chemicals

Hexanal, acetamide, propionamide, isopropylamide, *tert*-butylamide, fluoroacetamide, valeramide, benzamide, *p*-methoxybenzamide, *p*-trifluoromethylbenzamide, 2-methylpentanal, benzaldehyde, decane (internal standard), hexanol, *para*-toluenesulfonic acid, chlorido(1,5-cyclooctadiene)rhodium(I) dimer, bis(1,5-cyclooctadiene)rhodium(I) trifluoromethanesulfonate, (acetylacetonato)dicarbonylrhodium(I), carbonylhydridotris(triphenylphosphane)rhodium(I), bis(cycloocta-1,5-diene)rhodium(I) tetrafluoridoborate, bis(2-methoxyethyl) ether (diglyme) and other solvents, acids and bases were purchased from Acros Organics and Sigma Aldrich, the Netherlands. The monodentate ligands triphenylphosphane (PPh_3), tri-*n*-butylphosphane [P(*n*-Bu)$_3$], *n*-butyldi-1-adamantylphosphane [P(*n*-Bu)(1-ad)$_2$], tris(2,4-di-*tert*-butylphenyl)phosphite [P(O-di-*t*-BuC_6H_3)$_3$], the bidentate ligands 1,2-bis(diphenylphosphanyl)ethane (dppe), 1,3-bis(diphenylphosphanyl)propane (dppp), 1,1′-bis(diphenylphosphanyl)ferrocene (dppf), 1,2-bis(diphenylphosphanylmethyl)benzene (1,2-dppmb), 1,3-bis(diphenylphosphanylmethyl)benzene (1,3-dppmb), 9,9-dimethyl-4,5-bis(diphenylphosphanyl)xanthene (xantphos) and 2,2′-bis(diphenylphosphanylmethyl)biphenyl (bisbi) were purchased from Strem Chemicals, Germany. The other phosphorus ligands such as 1,2-bis(cyclooctylphosphanyl)ethane (bcope) and 2,7-di-*tert*-butyl-9,9-dimethyl-4,5-bis(diphenylphosphanyl)xanthene (*t*-Bu-xantphos), 4,6-bis(diphenylphosphanyl)-10,10-dimethyl-10*H*-dibenzo[*b,e*][1,4]oxasilane (Si-xantphos), 9,9-dimethyl-4,5-bis(di-*ortho*-methoxyphenyl-phosphanyl)xanthene (*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., where they were synthesized according to literature procedures.[20]

Apparatus

The stainless steel autoclave reactors (100 mL) of HEL Limited, UK, were equipped with 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 analyses were carried out on an Agilent technologies 7820 A GC system series coupled with an Agilent technologies 5975 series GC-MSD system. Nuclear magnetic resonance spectra were recorded on a Bruker DPX300 (300 MHz) or a Bruker DMX400 (400 MHz) spectrometer. A glovebox of M. Braun Inertgas-System GmbH, Germany, was used for storing and handling of air-sensitive phosphane ligands.

Procedures

All preparations and manipulations were performed using standard Schlenk techniques under an argon atmosphere. The solvent bis(2-methoxyethyl) ether (diglyme) was distilled from CaH_2, deoxygenated and then saturated with argon and used immediately after the purification process. The catalytic reactions were carried out under varying hydrogen pressures and reaction temperatures. For all the catalytic experiments the catalyst precursor was formed *in situ* in the autoclave by transferring the metal precursor and the selected phosphane ligands into the reactor.

In the preparation of a typical catalytic reaction mixture containing solid ingredients that are not air sensitive, 0.005 mmol of [Rh(cod)Cl]$_2$ (2.46 mg, 0.01 mmol of Rh) and 0.0125 mmol of bidentate phosphane ligand or 0.025 mmol of monodentate phosphane ligand were weighed in air and transferred into an autoclave. The autoclave was closed and subsequently filled with argon using a Schlenk line connected to one of the valves of the autoclave. Through another valve under a continuous flow of argon subsequently were added: 25 mL of dried and degassed diglyme as solvent, 3.125 mmol (0.605 mL) decane as an internal standard, 5 mmol (0.615 mL) hexanal and 6 mmol (0.354 g) acetamide (for selected experiments acid or another additive was added, dissolved in the diglyme). Then the reactor was inserted into the heating block and connected to the gas line of the reactor block with a continuous flow of N_2 gas through the gas line of autoclave to remove the air inside the gas line. The autoclave reactor was flushed three times

with N_2 and one time with H_2 and finally pressurized with hydrogen gas. The reaction mixture was stirred at 500 rpm for 20–30 min to ensure complex formation.

In the set of experiments using air-sensitive ligands such as P(*n*-Bu)$_3$, P(*n*-Bu)(1-ad)$_2$, bcope and di-*t*-Bu-xantphos, in a glove box the metal precursor complex and ligand (for some experiments with other additives like acid), were weighed into a Schlenk flask and dissolved in 10 mL of dried and degassed diglyme; dissolution generally was complete in about 2–3 min as was visible by the formation of a transparent yellowish solution. The flask was then connected to a Schlenk line and the solution was transferred through the valve of a reactor under a continuous flow of argon into the 100 mL stainless steel autoclave reactor. The procedure for gas intake in the autoclave was carried out as described above.

The reaction mixtures were heated up to 80 °C, 100 °C or 120 °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 two, four or ten hours at this temperature, the autoclave was cooled down to room temperature over about one hour. The autoclave was then slowly vented to atmospheric pressure.

After each catalytic run the reaction mixture was taken from the reactor and immediately analyzed with gas chromatography. Calibration lines for each analyte were used to determine the conversion of the substrates and yields of the various products. The assignments of the products were confirmed with GC-MS and comparison with authentic and pure commercial samples. The products in Table 7 comprising *N*-hexylacetamide,[21] *N*-hexylpropanamide,[21b,22] *N*-hexylisopropylamide,[21b,23] *N*-hexyl-*tert*-butylamide,[21c,23,24] *N*-hexylpentanamide,[25] *N*-hexylbenzamide,[21b,26] *N*-hexyl-4-methoxybenzamide,[21b] *N*-hexyl-4-trifluoromethylbenzamide,[21b] *N*-hexyl-2-fluoroacetamide,[27] *N*-(2-methylpentyl)acetamide and *N*-benzylacetamide[21a,c] are known compounds and were identified by ^{1}H and ^{13}C NMR and GC-MS (see the Supporting Information Figure S15 to Figure S36).

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[9] $\ln(1-\text{conv}/100) = -kt \rightarrow k$ (without acid) = 0.18, while k (with acid) = 0.038, assuming first-order kinetics in

hexanal. In the presence of *N,N'*-dimethylacetamide (entries 3 and 4) these numbers are respectively, 0.19 and 0.075.
[10] The NMR assignment and chemical shift were determined by compering with NMR predictors of ChemOffice and NMRDB simulator.
[11] Unlike NMR analysis of the equilibrium hexanal/acetamide mixtures at low temperatures, the intermediate **2a** was never observed in GLC analysis. It is expected that any amount present in the reaction medium would be detected in the GLC diagram as unsaturated intermediates **2**, as dehydration is likely a rapid thermal process at 250 °C prevailing in the injection port of the GLC.
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