Selective hydroformylation of *N*-allylacetamide in an inverted aqueous two-phase catalytic system, enabling a short synthesis of melatonin†‡

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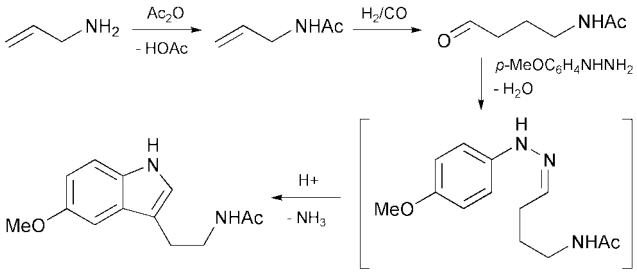
Water increases the selectivity in the Rh–phosphine catalysed hydroformylation of *N*-allylacetamide; an aqueous–organic biphasic system, containing a hydrophobic Rh-catalyst, provided facile catalyst/product separation, after which the aqueous product phase could be used in a one-pot synthesis of *N*-acetyl-5-methoxytryptamine (melatonin).

Olefin hydroformylation is one of the most commercially important reactions that makes use of a homogeneous catalyst.[1] Rh–phosphine complexes are active catalysts for this reaction with high selectivities towards linear aldehydes and a number of successful methods for the recycling of these catalysts have been developed.[2] Unfortunately, the feedstock is mainly restricted to linear, non-functionalised α-olefins, such as propene, styrene, *etc*.

Aldehydes bearing various functional groups are widely applied in the synthesis of, for example, flavours, fragrances and pharmaceuticals.[3] Their preparation by hydroformylation of a hetero-atom functionalised olefin, however, is not straightforward since these substrates react slowly, require high catalyst loadings and harsh reaction conditions, which leads to the formation of condensation products, such as acetals, hemiacetals, imines, *etc*.[4]

In connection with an alternative synthesis of *N*-acetyl-5-methoxytryptamine (melatonin), a human hormone which regulates sleep,[5] we required 4-acetamidobutanal. When combined with 4-methoxyphenylhydrazine this aldehyde affords an intermediate hydrazone, which in the presence of an acid undergoes a Fischer-indole reaction (Scheme 1).[6] 4-Acetamidobutanal was previously prepared by hydroformylation of *N*-allylacetamide in THF using 1% of $HRh(CO)(PPh_3)_3$.[7] After 18 h at 80 °C and 83 bar ($CO:H_2 = 1:1$), a conversion of 76% was reached with the product distribution: 4-acetamidobutanal (11%), 3-acetamido-2-methylpropanal (63%), *N*-acetylpyrrolidine (13%) and 2-formyl-*N*-acetylpyrrolidine (13%).

We found that the $Rh–PPh_3$ catalysed hydroformylation of *N*-allylacetamide gave the best results in a polar, protic solvent, such as methanol. Since *N*-allylacetamide is also soluble in water, we decided to carry out the hydroformylation in a one-phase aqueous medium, employing the water-soluble Rh–tppts catalyst (tppts = $P(C_6H_4$-*m*-$SO_3Na)_3$). To our surprise we found that the reaction proceeded smoothly under mild conditions. At 70 °C and a 10 bar pressure of a H_2–CO (1:1) mixture, the reaction was completed in 45 min using as little as 0.04% catalyst (Table 1, Exp. 2), with an initial rate of 3891 turnovers h^{-1}. The isomeric aldehydes were obtained in 99% selectivity. It was demonstrated by Mortreux and co-workers previously that the hydroformylation of acrylesters, such as methylacrylate, into their α- and β-formylesters also proceeds at a faster rate in a toluene–water two-phase system, employing the Rh–tppts catalyst, compared to the rate of $Rh–PPh_3$ in toluene alone (initial TOF = 545 *vs*. 225 h^{-1} (50 °C, 50 bar)).[8]



Scheme 1 Alternative synthesis of *N*-acetyl-5-methoxytryptamine.

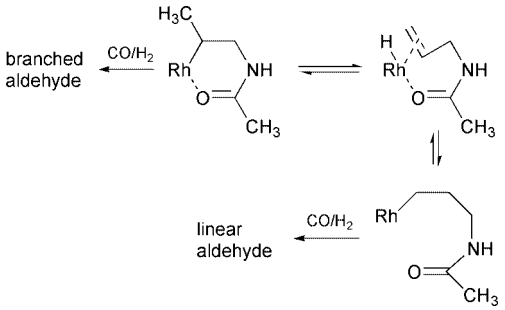
In a series of $MeOH–H_2O$ mixtures we found that both the reaction rate and the selectivity towards the aldehydes increased with the water content. A direct comparison of the two catalysts in neat MeOH showed that $Rh–PPh_3$ is slightly more active than Rh–tppts and yields a product mixture with a slightly higher linear/branched (l/b) ratio (1.15 *vs*. 1.05, Table 1). The rather low regioselectivity compared to non-functionalised linear olefins, such as propene (l/b = 23),[2] suggests that coordination of the amide may take place during the insertion of the olefin into the Rh–hydride bond. The possible formation of a 6-membered chelate ring (Scheme 2) is expected to enhance the formation of the branched aldehyde.

† Catalytic conversions in water, part 18. (Part 17: G. J. ten Brink, I. W. C. E. Arends and R. A. Sheldon, *Science*, 2000, **287**, 1636.)
‡ Experimental details are available as electronic supplementary information (ESI). See http://www.rsc.org/suppdata/cc/b0/b003715j/

Table 1 The hydroformylation of *N*-allylacetamide in organic, aqueous and biphasic media

Exp.[a]	Catalyst	Solvent	Time/min	Conv./%	Yield/%	1/b ratio	TOF[f]/h^{-1}
1	$Rh–PPh_3$	MeOH	180	98.6	92.3	1.15	1342
2	Rh–tppts	H_2O	45	98.9	97.9	1.30	3891
3	Rh–tppts	$MeOH–H_2O$[d]	120	99.9	95.3	1.09	1459
4	Rh–tppts	MeOH	180	99.9	93.4	1.05	1239
5	Rh–tppts	Toluene–H_2O[e]	60	97.4	96.8	1.34	2946
6	$Rh–PPh_3$	Toluene–H_2O[e]	270	81.6	80.2	1.54	578
7[b]	Rh–Xantphos	Toluene–H_2O[e]	1320	26.4	24.4	20.0	31
8[c]	Rh–Xantphos	Toluene–H_2O[e]	600	99.6	96.4	15.3	177

[a] Reaction conditions: 0.010 mmol $Rh(acac)(CO)_2$, 0.25 mmol ligand, 25 mmol *N*-allylacetamide, 70 °C, 10 bar H_2O–CO (1/1), 1000 rpm, 125 ml total reaction volume. [b] 0.010 mmol [$Rh(acac)(CO)_2$], 0.050 mmol Xantphos. [c] 0.050 mmol [$Rh(acac)(CO)_2$], 0.250 mmol Xantphos, 90 °C. [d] $MeOH–H_2O$ = 1/1 (v/v), 125 ml total. [e] 100 ml toluene, 100 ml H_2O. [f] TOF = initial turnover frequency in mol aldehyde per mol catalyst per hour.



Scheme 2 Proposed intermediates in the Rh/tppts catalysed hydroformylation of *N*-allylacetamide.

The high partition coefficients of 4-acetamidobutanal and 3-acetamido-2-methylpropanal in the water layers forestalled our attempts to extract them from the aqueous reaction mixtures with an organic solvent. Especially in the synthesis of pharmaceuticals the presence of traces of heavy metals is undesirable. In order to achieve efficient product/catalyst separation, we turned to an 'inverse two-phase catalyst system', containing the hydrophobic Rh–PPh_3 catalyst in a toluene–water mixture. In such a system the catalyst remains dissolved in the organic phase, while the products will move to the water layer; the opposite of standard aqueous biphasic catalysis.

In the biphasic system, the Rh–PPh_3 catalysed reaction (Exp. 6) proceeded considerably slower compared to Rh–tppts (Exp. 5), consistent with our observation (see above) that the reaction rate decreases when the hydroformylation is carried out in an apolar solvent, such as toluene. In addition, due to mass transfer limitations, the reaction rate decreased substantially after *ca.* 50% conversion (see Fig. 1). Such a decrease was less pronounced in the case of Rh–tppts, that operates in the aqueous layer, where the substrate concentration remains sufficiently high, resulting in a zero-order reaction profile until *ca.* 80% conversion. Nevertheless, due to the presence of water, the selectivity towards the aldehydes remained high (98%, Exp. 6) and the Rh–PPh_3 catalyst could conveniently be separated from the aqueous product phase.

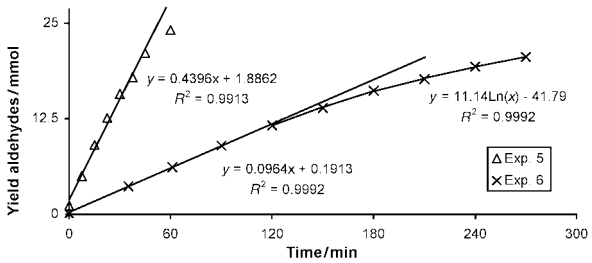


Fig. 1 Reaction profiles of Exp. 5 and Exp. 6.

To increase the regioselectivity towards the linear aldehyde, generally, rigid diphosphine ligands with a large bite angle are used.[9] We tested the Rh–Xantphos combination[10] (Xantphos = 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene) in our inverted two-phase system and, indeed, the l/b ratio increased to 20. The reaction rate, however, decreased dramatically to 31 h^{-1} (Table 1, Exp. 7). At 90 °C, in the presence of 0.2% catalyst, a nearly quantitative conversion was reached in 10 h reaction time with a small compromise in the l/b ratio. The organic catalyst phase could be recycled in 5 consecutive runs without loss in activity. Rh-analysis of the water layers by means of atomic absorption spectrometry confirmed a quantitative (> 99%) catalyst/product separation.

N-Acetyl-5-methoxytryptamine was subsequently prepared in a one-pot procedure starting from allylamine (see ESI). By successive acetylation of allylamine, selective hydroformylation, hydrazone formation with 4-methoxyphenylhydrazine (HCl salt) and a Fischer indole reaction, melatonin was isolated from the aqueous reaction mixture in 44% yield (not optimised).

In conclusion, we have demonstrated that the hydroformylation of *N*-allylacetamide proceeds smoothly in a one-phase aqueous medium, as well as in an aqueous–organic two-phase protocol under mild reaction conditions. Although we could not take full advantage of the rate accelerating effect of water in the inverted two-phase catalyst system, the linear aldehyde was obtained in high selectivity and efficient catalyst/product separation was achieved. The organic soluble catalyst was recycled and the aqueous product phase was applied without purification in the synthesis of *N*-acetyl-5-methoxytryptamine. Mechanistic details and the scope of the inverted two-phase system are currently under investigation.

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