Rhodium-Catalysed Asymmetric Hydroformylation of Unsaturated Nitriles

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Abstract: Asymmetric hydroformylation of crotononitrile (**1**) and ally cyanide (**2**) was probed with the view to develop a synthesis for (*R*)-4-amino-2-methyl-butan-1-ol. Hydroformylation of **1** under a variety of conditions mainly led to hydrogenated product. Hydroformylation of **2** with Rh/tris(2,4-di-*tert*-butylphenyl) phosphite gave good selectivity to the formylated nitrile with an *n/iso* of 77:23. Asymmetric hydroformylation of **2** could be accomplished in 66% ee using Rh/(*R,S*)-BINAPHOS.

Keywords: aldehydes; asymmetric catalysis; homogeneous catalysis; hydroformylation; nitriles; P ligands; rhodium

Introduction

Hydroformylation converts olefins into the homologous aldehydes with 100% atom economy.[1] A mixture of terminal and internal olefins may result, the ratio of which can be influenced by the choice of catalyst. Early catalysts were based on cobalt, but nowadays rhodium catalysts are preferred because of lower pressures and higher chemo- and regioselectivity. A wide range of functional groups has been found to be compatible with hydroformylation conditions, such as aldehydes, free alcohols, carboxylic acids and alkyl halides. Nonetheless, despite these advantages, hydroformylation has not been used much in fine chemicals with the exception of applications in vitamins[2,3] and in flavours and fragrances.[4,5] This may be in part related to the difficulty in controlling chemo-, regio- and stereoselectivity in the course of the reaction. Whereas good solutions now exist for the highly selective formation of linear aldehydes upon hydroformylation of terminal alkenes, the exclusive formation of branched aliphatic aldehydes remains an unsolved problem. On top of this, asymmetric hydroformylation reactions also require control of stereoselectivity.[6] Successful asymmetric hydroformylations are hitherto largely restricted to the conversion of styrenes because of their high reactivity and high selectivity for *iso*-aldehydes. Best results in this field were obtained with rhodium complexes, particularly in combination with the BINAPHOS ligand.[7,8] Asymmetric hydroformylation of functionalised aliphatic alkenes has been recognised to be much more difficult than that of arylethenes.

For the development of a new route towards amino alcohol (*R*)-**4**, a building block for the new Tachykinin NK_1 receptor antagonist **5** developed by Takeda,[9] we envisaged a hydroformylation approach. Hydroformylation of unsaturated nitriles, particularly the readily available crotononitrile **1** or allyl cyanide **2** offers an entry to **4** (Scheme 1). However, thus far the hydroformylation of unsaturated nitriles has been restricted to the conversion of acrylonitrile.[1,10] From these publications it becomes obvious that use of $Co_2(CO)_8$ in the presence of methanol leads mainly to the β-formylated product as the acetal. Addition of N- or P-ligands ligands to this catalyst leads to formation of various by-products without changing the *n/iso* ratio. Few examples for the hydroformylation of crotononitrile and allyl cyanide are known from the literature. In the former case, these examples were limited to claims in the patent literature in which only hydroformylation of acrylonitrile using Rh_2O_3 and Rh/P(OPh)$_3$, respectively, is described.[11] Hydroformylation of allyl cyanide generally gave the unwanted *n*-aldehyde preferentially.[12] However, the branched aldehyde **3** was obtained in excess (ratio branched/linear 3:1) when formic acid was used as the hydrogen source under CO pressure in the presence of a rhodium-phosphine complex.[13] No reports exist of asymmetric hydroformylation reactions of unsaturated nitriles.

In this report the conversion of crotononitrile and allyl cyanide to aldehyde **3** with carbon monoxide and hydrogen is described. The influence of reaction parameters like CO/H_2 total pressure, CO/H_2 ratio, temperature and especially ligands on the regioselectivity and the enantioselectivity (for chiral ligands) was explored.

Results and Discussion

Initial attempts to synthesise aldehyde **3** started from **1**. Hydroformylation of **1** with Rh/triphenylphosphine as the catalyst at 100 °C afforded only butyronitrile (**6**), the

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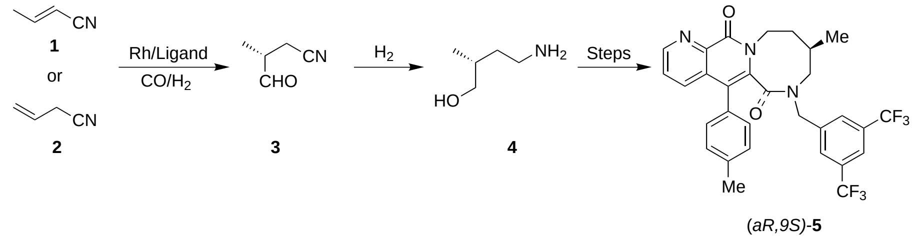
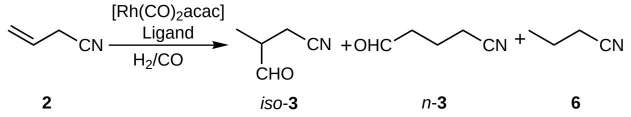


Scheme 1.

Table 1. Hydroformylation of allyl cyanide.



	Ligand[c]	Reaction conditions			Conversion[d]	Selectivity[d]		
		T [°C]	P [bar]	CO:H_2	[%]	% *iso*-**3**	% *n*-**3**	% **6**[e]
1[a]	PPh_3, 55 equiv.	100	50	1:1	100	45	47	8
2[a]	Xantphos, 2 equiv.	100	50	1:1	100	28	64	8
3[a]	$P(OPh)_3$, 5 equiv.	100	50	1:1	100	69	30	1
4[a]	$P(OPh)_3$, 5 equiv.	100	30	1:1	88[f]	51[f]	19 [f]	2
5[b]	$P(OPh)_3$, 5 equiv.	50	30	3:1	100	69	31	nd
6[b]	$P(OPh)_3$, 2 equiv.	50	30	3:1	97	70	30	nd
7[b]	$P(OPh)_3$, 10 equiv.	50	30	3:1	78	68	32	nd
8[b]	$P(ODBP)_3$,[g] 5 equiv.	50	30	3:1	100	76	24	0.2
9[a]	$P(ODBP)_3$, 5 equiv.	50	50	3:1	100	74	24	2
10[b]	$P(ODBP)_3$, 2 equiv.	50	30	3:1	100	76	24	nd
11[b]	$P(ODBP)_3$, 2 equiv.	40	30	1:1	100	77	23	nd
12[b]	$P(ODBP)_3$, 2 equiv.	60	30	1:1	100	75	25	0.5
13[b]	$P(ODBP)_3$, 2 equiv.	80	30	1:1	100	71	28	1
14[b]	–	50	30	3:1	9	81	19	nd
15[b]	TPPTS,[h] 2 equiv.	50	30	1:1	14	18	63	19
16[b]	TPPTS, 2 equiv.	80	30	1:1	25	7	58	35

[a] Reactions were performed on 30 mmol scale with toluene (50 mL) as the solvent and 0.2 mol % of $Rh(CO)_2acac$.
[b] Reactions were performed on 10 mmol scale with toluene (4 mL) as the solvent and 0.2 mol % of $Rh(CO)_2acac$.
[c] Number of equivalents with respect to rhodium.
[d] Conversion and selectivities were determined by GC analysis. The *iso*/*n* ratio was confirmed by NMR analysis and GC-MS.
[e] nd = not detected.
[f] The aldehydes proved to be unstable at ambient temperature: 28% of by-products were formed at ambient temperature overnight.
[g] DBP = 2,4-di-*tert*-butylphenyl.
[h] TPPTS = tri(m-sulfonyl)triphenylphosphine trisodium salt.

hydrogenation product. Similar results were obtained when 1,4-bis(diphenylphosphino)butane (dppb) or Xantphos were employed as ligand. The use of methanol as the solvent also gave exclusive hydrogenation of the double bond. As hydroformylation of internal olefins is rather slow,[1] hydrogenation becomes the main reaction of **1** under hydroformylation conditions. Moreover, it is generally known that α,β-unsaturated compounds (aldehydes, ketones, esters) are susceptible to hydrogenation under hydroformylation conditions.

Slightly better results were obtained when a cobalt catalyst was used. In the presence of $Co_2(CO)_8$ at 120 °C under 90 bar CO/H_2, a mixture of aldehydes, **1** and **6** (ratio 1:3:0.5) was obtained. Unfortunately, 3-formyl cyanide **3** was the minor aldehyde isomer.

Hydroformylation of allyl cyanide (**2**) proved to be more successful (Table 1). Conversion of **2** catalysed by rhodium in combination with phosphine or phosphite ligands at 100 °C and 50 bar of CO/H_2 was complete within 5 hours, giving aldehydes as the main product. The *n*/*iso* ratio depended on the ligand. Triphenylphosphine and Xantphos mainly gave the *n*-aldehyde, but *iso*-**3** was the main product when triphenyl phosphite was employed (*iso*/*n* 64:33).

The effect of several parameters on the stereoselectivity in the hydroformylation of allyl cyanide was

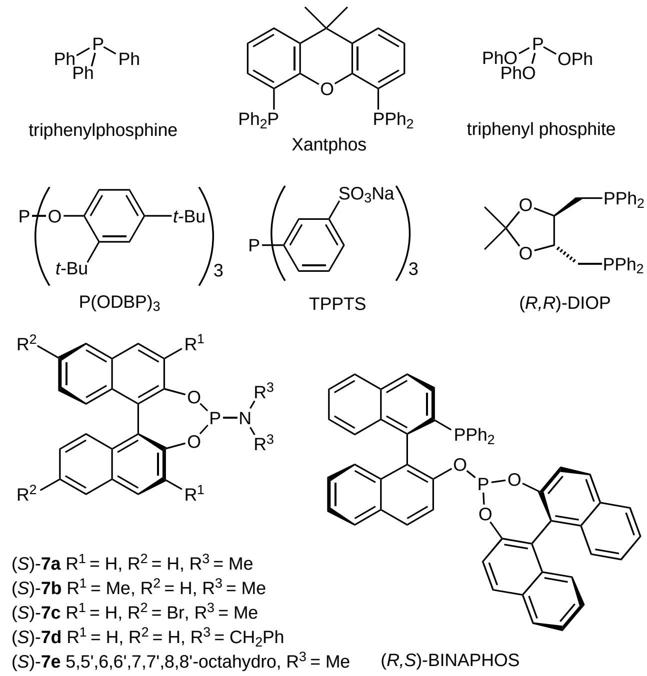


Figure 1. Phosphorus ligands used in the hydroformylation of allyl cyanide.

studied next. Lowering the pressure (entry 4) had a beneficial effect on the *iso*/*n* ratio. Moreover, intermittent sampling during the reaction revealed that the reaction started before the temperature of 100 °C was reached, so subsequent reactions were performed at lower temperatures. The reduction of temperature, as well as changing the CO/H_2 ratio from 1:1 to 3:1 had no effect on the selectivity of the hydroformylation reaction (entry 3 *versus* entry 5). The amount of ligand also had no effect on the regioselectivity of the reaction, but the rate of the gas uptake during the reaction revealed that highest reaction rate was obtained when 5 equivalents of ligand were used. This relation was confirmed by the lower conversions found when either 2 (entry 6) or 10 equivalents (entry 7) were used.

The selectivity of the reaction could be enhanced by using the bulky phosphite ligand tris-2,4-di-*tert*-butylphenyl) phosphite [$P(ODBP)_3$]. Again, no effect of pressure (entry 9) and amount of ligand (entry 10) was observed on the ratio between branched and linear aldehydes. Raising the pressure, however, favoured the hydrogenation reaction. Temperature, on the other hand, did affect the *iso*/*n*-ratio. Low temperatures promote the formation of *iso*-**3** (entries 11 – 13). In addition, hydrogenation of the C=C double bond increased with temperature.

Reactions without phosphite proceeded rather sluggishly (entry 14), though in good regioselectivity.

Attempts to use the water-soluble TPPTS ligand (allowing easy recovery of the catalyst) had no success (entries 15 and 16). Conversions were low, hydrogenation was a severe side-reaction especially at higher temperatures and, most importantly, the linear aldehyde was formed in surplus. When larger amounts of TPPTS were used, i.e., 40 equivalents instead of 2, the conversion was still negligible.

In conclusion, formation of the branched aldehyde is favoured by the use of bulky phosphite ligands. The chemo- and regioselectivity of the reaction decreases at higher temperatures. Total pressure and the amount of ligand with respect to rhodium had little or no effect on the *iso*/*n* ratio, but hydrogenation becomes a side reaction at higher pressures.

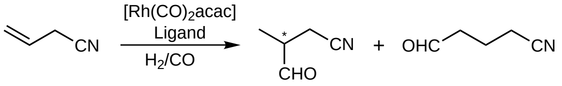
Ojima has established that the very high *iso/n* ratio in the hydroformylation of 3,3,3-trifluoropropene is related to the stabilisation of the branched rhodium-alkyl intermediate by the electron-withdrawing substituent.[14] Although the cyanomethylene substituent would seem to be much less electron-withdrawing its "group electronegativity" χ was rated as 2.48 whereas trifluoromethyl was rated as 3.10.[15]

Having established which parameters affect the regioselectivity of the reaction, further research was aimed at the asymmetric hydroformylation reaction. Although the focus is on high levels of enantioselection, regioselectivity remains an important variable in these reactions. The asymmetric hydroformylation of **2** was performed in toluene using rhodium in combination with a variety of chiral phosphorus ligands. After 3 hours at a temperature of 50 °C under a total pressure of 30 bar CO/H_2 (1:1, v/v), the reaction was stopped prematurely, to allow comparison of yields. The results are depicted in Table 2.

The use of the chiral bis-phosphine (−)-DIOP afforded mainly the linear aldehyde *n*-**3** (entry 1), which is in accordance with the results achieved with the non-chiral phosphine ligands. Because of the poor regioselectivity the use of chiral phosphines was abandoned.

We then turned to the use of phosphoramidite ligands. Phosphoramidites have been successfully employed in the copper-catalysed asymmetric diethylzinc addition to enones,[16] iridium-catalysed substitution of allylic acetates,[17] copper-catalysed allylic alkylations,[18] rhodium-catalysed asymmetric olefin hydrogenations,[19] palladium-catalysed asymmetric Heck reactions,[20] rhodium-catalysed asymmetric arylation of enones,[21] nickel-catalysed asymmetric hydrovinylations,[22] and palladium-catalysed asymmetric hydrosilylation of olefins.[23] The use of MonoPhos™ (**7a**) in the hydroformylation of allyl cyanide gave good results with respect to chemo- and regioselectivity. The *iso*/*n* ratio was comparable to that of $P(ODBP)_3$ (entry 2). The conversion rate, however, was considerable lower. More importantly, the ee of the branched aldehyde was only 7%. Changes in the substitution pattern of the phosphoramidite had little effect on the selectivity of the reaction (entries 3 – 6). The regioselectivity was quite similar in all cases, the ratio between *iso*-**3** and *n*-**3**

Table 2. Asymmetric hydroformylation of allyl cyanide.



2 *iso*-3 *n*-3

	Ligand[a]	Conversion[b]	Selectivity	
		[%]	*iso:n*[b]	ee [%][c]
1	(−)-DIOP, 3 equiv.	8	45:55	na
2	MonoPhos **7a** 4.0 equiv.	31	72:28	7
3	**7b**, 3.7 equiv.	40	76:24	18
4	**7c**, 3.9 equiv.	62	76:24	10
5	**7d**, 4.0 equiv.	55	66:34	2
6	**7e**, 3.9 equiv.	45	69:31	7
7	***(R,S)*-BINAPHOS, 4.0 equiv**.	73	72:28	66

[a] Reactions were performed on 10 mmol scale with toluene (4 mL) as the solvent and 0.2 mol % of $Rh(CO)_2acac$, pressure 30 bar ($CO/H_2 = 1/1$), temperature 50 °C.

[b] Conversion and selectivities were determined by GC analysis. The amount of butyronitrile was ≤ % in all cases.

[c] Absolute configuration not determined. na = not analysed.

being approximately 3:1. Unfortunately, all phosphoramidites showed only moderate chiral induction. The results, however, show that substituents on positions 3 and 3′ led to somewhat higher enantioselectivities, i.e., 18%.

Best results were obtained with the use of the phosphine-phosphite ligand (*R,S*)-BINAPHOS.[8] BINAPHOS is the most successful ligand in asymmetric hydroformylation reactions. Though most examples concern the hydroformylation of styrene (derivatives), promising results were obtained with aliphatic alkenes as well. Use of BINAPHOS also led predominantly to the branched aldehyde *iso*-**3**, which was obtained with 66% enantioselectivity.

Conclusions

3-Formyl cyanide, *iso*-**3**, is not accessible *via* hydroformylation of crotononitrile. Hydrogenation prevails, as the hydroformylation reaction is slow for internal olefins.

However, aldehyde *iso*-**3** is the major product in the hydroformylation of allyl cyanide in the presence of rhodium/phosphite catalysts. The regioselectivity of the reaction is favoured by the use of bulky phosphite ligands and low temperatures. Branched/linear ratios up to 77:23 could be achieved.

Thus far, a feasible asymmetric hydroformylation could only be accomplished using the BINAPHOS ligand. As both (*R,S*)-BINAPHOS and (*S,R*)-BINAPHOS are available, both enantiomers of *iso*-**3** are in principle accessible. No efficient asymmetric hydroformylation of allyl cyanide could be achieved with enantiopure phosphoramidite ligands. The use of more bulky phosphoramidites in asymmetric hydroformylation reactions might improve both enantioselectivity and reaction rates.

Experimental Section

Chemicals were purchased from Acros Chimica, Fluka, Aldrich or Strem and used as received. Solvents were of analytical grade and used without further purification. *S*-BINAPHOS was obtained from Takasago. Gas chromatography was performed on an HP-5 cross-linked 5% PH ME siloxane column.

Cobalt-Catalysed Hydroformylation of 1

A deoxygenated solution of $Co_2(CO)_8$ (112 mg, 0.33 mmol) in 40 mL of toluene was added to a Parr autoclave (125 mL) and subjected to three vacuum/nitrogen cycles. After flushing with CO/H_2 (1:1 v/v) three times the autoclave was pressurised to a final pressure of 70 bar and heated at 100 °C for 1 hour. A solution of **1** (2.4 mL, 29.5 mmol) in 10 mL of degassed toluene was pressure injected into the autoclave and the pressure brought to 90 bar. After stirring for 4 h at this pressure the autoclave was brought to ambient temperature and the contents analysed by GC and NMR.

General Autoclave Procedure for Rhodium-Catalysed Hydroformylation of 1 or 2

A deoxygenated solution of $Rh(CO)_2acac$ (15.6 mg, 0.06 mmol) and triphenyl phosphite (93 mg, 0.3 mmol) in toluene (10 mL) was added *via* syringe to a solution of **2** (2.013 g, 30 mmol) in deoxygenated toluene (40 mL) in a Parr autoclave (125 mL). The reaction mixture was stirred at 100 °C and 50 bar H_2/CO (1:1 v/v) pressure for 5 hours. After cooling to ambient temperature, the contents of the reactor were analysed by GC and NMR. See Table 1 for details of all experiments.

General Procedure for Hydroformylation in the Endeavor™

The experiments were performed in the Endeavor™, which contains 8 autoclaves with a working volume of 15 mL each. The same protocol as for the autoclave experiments was followed but on a scale of 10 mmol in a total volume of 4 mL of toluene. See Tables 1 and 2 for details.

Enantioselectivity Determination

The ee was determined by NMR, based on the ratio of the CH_3 signals of the diastereomeric Schiff bases of the aldehyde and L-methylbenzylamine. Accuracy ± 5%.

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