13398 *J. Am. Chem. Soc.* **1998,** *120,* 13398−13404

Rhodium-Catalyzed Hydroformylation in Supercritical Carbon Dioxide

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Received March 5, 1998

Abstract: Supercritical carbon dioxide ($scCO_2$) is an environmentally benign reaction medium for highly efficient rhodium-catalyzed hydroformylation reactions. Olefinic substrates can be hydroformylated in $scCO_2$ at 40−65 °C to give the corresponding aldehydes in practically quantitative yields. The reaction course of the hydroformylation of 1-octene in $scCO_2$ was analyzed in detail by online-GC monitoring. The influence of reaction parameters such as temperature, synthesis gas pressure, and [P]/Rh ratio on reaction rates and selectivities is grossly similar to the effects observed in conventional solvents. Maximum turnover frequencies of 1375, 500, and 115 h^{-1} were determined as lower limits for the catalytic activities under the present conditions for the unmodfied, phosphine-modified, and phosphite-modified systems, respectively. With unmodified catalysts, the hydroformylation rates are considerably higher in $scCO_2$ than in organic solvents or liquid CO_2 under otherwise identical conditions. Modified catalytic systems formed with perfluoralkyl-substituted triarylphosphine and triaralyphosphite ligands lead to higher regioselectivities than those found in conventional solvents. A constant overall *n/iso* ratio of 5−6 was achieved with "CO_2-philic" triarylphosphines, whereas it increased in an apparent linear fashion during the reaction from approximately 6 to over 9 with the phosphite ligand. Olefin isomerization, which is a typical side reaction for phosphite-modified systems in conventional solvents, was effectively suppressed in $scCO_2$.

Introduction

Many of the numerous advantages associated with the use of supercritical carbon dioxide ($scCO_2$; $T_c = 31$ °C, $p_c = 73.75$ bar, $d_c = 0.468$ g cm^{-3}) as an environmentally benign reaction medium for metal-catalyzed chemical synthesis arise from the "gaslike" properties of the supercritical fluid, i.e., (i) high miscibility with reactant gases, (ii) absence of a liquid/gas phase boundary, (iii) high diffusivity/low viscosity, and (iv) high compressibility.[1,2] The first example for the utilization of these properties in homogeneous catalysis appears to be the hydroformylation of propene using $[Co_2(CO)_8]$ as a catalyst precursor.[3] The original study by Rathke and Klingler was largely devoted to the detection of catalytically active intermediates by ^{59}Co NMR spectroscopy in $scCO_2$, but an enhanced selectivity for the linear *n*-aldehyde at comparable catalytic activity was also noted.[3a] However, this hydroformylation reaction still suffers from the typical drawbacks of the cobalt carbonyl catalyst,[4] in particular high catalyst loading and high reaction temperatures (≥75 °C, generally >90 °C).[3]

In the present work, we introduce $scCO_2$ as a generally applicable reaction medium for rhodium-catalyzed hydroformylation.[5,6] We demonstrate that *unmodified rhodium catalysts* can be used with high efficiency for hydroformylation of various unsaturated substrates in $scCO_2$ as the reaction medium, whereby considerably higher reaction rates are obtained than in conventional solvents. *Rhodium catalysts modified with phosphorus donor ligands* can also be adopted for hydroformylation in $scCO_2$, if the ligands provide sufficient solubility of the active species in the supercritical fluid.[5a] A comparative study was carried out on the hydroformylation of 1-octene (**1a**) using the catalyst precursor [(cod)Rh(hfacac)] (**4**) without any modifiers, with the phosphine ligands **5a,b**, and with the new phosphite

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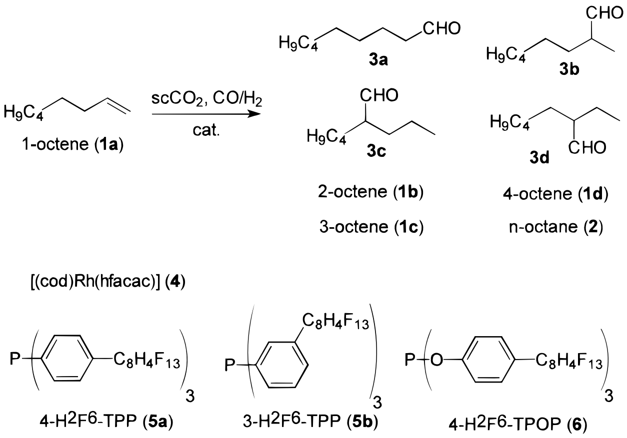
10.1021/ja980729w CCC: $15.00

Scheme 1. Rhodium-Catalyzed Hydroformylation of 1-Octene (**1a**) in $scCO_2$



ligand **6** (Scheme 1).[7] In this study, reaction rates and product distribution were monitored in situ using a high-pressure reactor with online-GC analysis. This technique provides detailed insight into the reaction course and allows convenient and rapid comparison of different catalytic systems and/or optimization of reaction conditions in supercritical fluid catalysis.

Experimental Section

Solvents and all olefins were dried, purified, and degassed according to literature protocols[8] and stored under argon. The gases CO/H_2 (1:1), argon (99.995%), and CO_2 (99.9995%) were purchased from Messer Griesheim and used without further purification. The compounds $[(CO)_2Rh(acac)]$, $[Rh_2(CO)_6]$, and $RhCl_3 \cdot nH_2O$ were commercial products and used as received. [(cod)Rh(hfacac)] (**4**) was synthesized according to a modified literature procedure.[9] The synthetic route to tri[4-(1*H*,1*H*,2*H*,2*H*-perfluorooctyl)phenyl]phosphine (**5a**) and tri[3-(1*H*,1*H*,2*H*,2*H*-perfluorooctyl)phenyl]phosphine (**5b**) has been reported briefly[5,10] and will be described in detail together with the preparation of tri[3-(1*H*,1*H*,2*H*,2*H*-perfluorooctyl)phenyl]phosphite (**6**) elsewhere.[11] NMR spectra were recorded on Bruker AC200 and AM300 spectrometers. Offline-GC measurements were carried out on Carlo Erba instruments (Series 6000 with 30-m DB-1; series 5300 with 44-m CW-20M). Rhodium contents in the products were determined by atomic absorption spectroscopy (AAS). Activity and selectivity data of catalytic runs are outside the uncertainty of the analytical methodes, and all discussed differences and trends are significant under the general limits of reproducibility of catalytic reactions.

Online-GC Configuration. As shown in Figure 1, a window-equipped high-pressure reactor (V = 225 mL) was connected via an automatic sampling device[12] to a Carlo Erba 4100 gas chromatograph with a flame ionization detector (FID). Nitrogen was used as carrier gas, and argon was used as makeup gas for the FID. The automatic sampling and injection system consists of two pneumatic valves: a three-port valve (Valco AC3UW, p_{max} = 350 bar, T_{max} = 75 °C) for controlling the purging of the injection system and a six-port valve (Valco A6C6W, p_{max} = 350 bar, T_{max} = 75 °C) which contains a sample loop (20 μL) and is directly connected to the injection block of the chromatograph. Both pneumatic valves are controlled by programmable timers (Legrand 49585). The GC conditions (25-m OV-1; injector, 220 °C; column, 80 °C; FID, 320 °C) allow identification and quantification (via calibration curves) of all primary reaction components **1a**−**d**, **2**, and **3a**−**d**. Secondary products arising from aldol condensation or oxidation of the aldehydes are also detectable but were never observed during online monitoring.

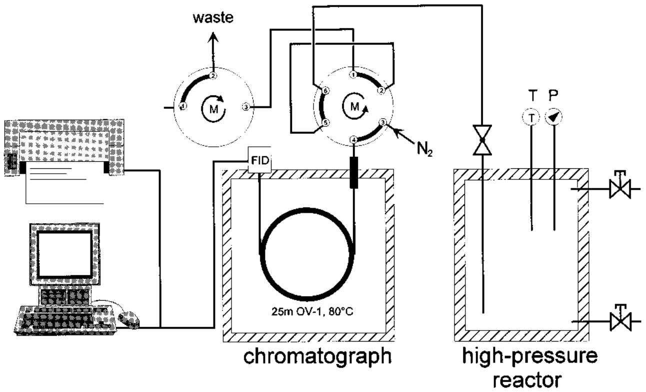


Figure 1. Layout of the online-GC reactor.

General Procedure for the Rhodium-Catalyzed Hydroformylation of Olefins in $scCO_2$. In a typical experiment, a small window-equipped stainless steel reactor (V = 25 mL) was charged with the catalyst components and the substrate (4.0−6.0 mmol) under an argon atmosphere. The mixture was pressurized at room temperature with CO/H_2 (1:1), and CO_2 was introduced using a compressor to adjust the desired density of the reaction medium. The reactor was heated to the desired reaction temperature (measured at the outer wall of the reactor) for a standard reaction time of approximately 20 h. Products were collected for NMR or offline-GC analysis by careful venting through cold traps.

Online-GC Monitoring of the Hydroformylation of 1-Octene (1a). A window-equipped stainless steel reactor (V = 225 mL) was charged with the catalyst components and **1a** (10.0 mL, 63.0 mmol) under an argon atmosphere. The mixture was pressurized at room temperature with CO/H_2 (1:1), and CO_2 was introduced using a compressor to adjust the desired density of the reaction medium. The reactor was connected to the sampling system for online-GC analysis (Figure 1), and heating was started immediately. The final reaction temperature as measured by a thermocouple directly in the reaction medium was reached within less than 10 min. All mixtures were fully homogeneous at or around the critical temperature of pure CO_2 (31 °C). Online-GC monitoring showed that conversion was negligible before temperature equilibration.

Results and Discussion

Supercritical CO_2 as a Reaction Medium for Homogeneous Rhodium-Catalyzed Hydroformylation. During our investigations on the development of “CO_2-philic” ligands for homogeneous catalysis in $scCO_2$,[5] we noticed that complex **4** was a highly efficient catalyst precursor for the hydroformylation of olefins in this medium *even in the absence of any additives*. The reaction was found to be quite general and allowed the hydroformylation of various unsaturated substrates under a typical set of mild, but not yet optimized standard conditions (Table 1). Terminal and internal double bonds with alkyl and aryl substitutents were hydroformylated in $scCO_2$ almost quantitatively at 40 °C at substrate/catalyst ratios of approximately 800:1. Quarternary carbon centers were not reactive under these conditions, as expected for Rh catalysts from Keuleman’s rule.[4] Allylic acetate was converted to the isomeric oxo-esters quantitatively at 60 °C, whereas ethyl acrylate gave only small amounts of the corresponding aldehydes under identical conditions (NMR analysis). The ratios of linear to branched aldehydes were in the typical range observed with

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[7] The following abbreviations are used: cod = 1,5-cyclooctadiene; acac = acetylacetonate; hfacac = hexafluoroacetylacetonate; tpp = PPh_3; tppts = $P(m\text{-}C_6H_4SO_3Na)_3$; tpop = $P(OPh)_3$; for the nomenclature of the substituted phosphorus ligands, see ref 5.

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[9] Leipoldt, J. G.; Grobler, E. C. *Trans. Met. Chem.* **1986**, *11*, 110.

[10] Kainz, S.; Luo, Z.; Curran, D. P.; Leitner, W. *Synthesis* **1998**, 1425.

[11] Kainz, S.; Koch, D.; Wittmann, K.; Leitner, W. Manuscript in preparation.

[12] Similar equipment was used for heterogeneous Fischer−Tropsch catalysis in supercritical hexane: Snavely, K.; Subramaniam, B. *Ind. Eng. Chem. Res.* **1997**, *36*, 4413.

Table 1. Hydroformylation of Various Olefins in $scCO_2$ Using [(cod)Rh(hfacac)] (**4**) as the Catalyst Precursor[a]

olefin	d (g mL^{-1})	T (°C)	cv^c (%)	aldehyde distribution (%)
1-octene (**1a**)	0.55	40	>97	**3a** (57), **3b** (39), **3c** (3), **3d** (1)
1-octene (**1a**)	d	40	54	**3a** (58), **3b** (42)
trans-3-hexene	0.54	40	>97	2-methylhexanal (14), 2-ethylpentanal (86)
trans-3-hexene	d	40	23	2-methylhexanal (4), 2-ethylpentanal (96)
2,3-dimethyl-2-butene	0.55	35	0	
styrene	0.51	60[b]	>97	2-phenylpropanal (85), 3-phenylpropanal (15)
allyl acetate	0.58	60[b]	>97	4-oxobutyl acetate (28), 3-oxo-2-methylpropyl acetate (78)

[a] Conditions: substrate (4.0−6.0 mmol), **4** (5.7−6.7 μmol), $V_{reactor} = 25$ mL, $p(CO/H_2) = 45$ bar at room temperature, $t = 20$ h. [b] $p(CO/H_2) =$ 40 bar at room temperature; all data from ^1H NMR analysis. [c] Total conversion to aldehydes. [d] Control experiment in toluene (25 mL, $V_{reactor} = 50$ mL).

unmodified rhodium catalysts also in conventional solvents. The chemoselectivity for aldehyde formation was remarkably high in all cases, and the amount of hydrogenation products was below 2% according to NMR and GC analysis.

The phase behavior of complex reaction mixtures consisting of the compressed gases CO_2, CO, and H_2 together with the substrate and the (by-)products in varying amounts is neither known nor predictable from standard equations of states. Similarily, predictions of the solubility of metal species in such multicomponent systems are difficult, and current solubility data are restritced to a limited range of complexes in pure CO_2.[13] Although the combination of a single homogeneous reactant phase *and* high solubility of the transition metal complex is by no means always a necessary prerequisite for effective catalysis in $scCO_2$,[2,14] it is in many cases a decisive factor for its practical utility[3,5,15] and is, of course, crucial for spectroscopic investigations[3,5] related to our fundamental understanding of catalysis in this medium. In the present study, fully homogeneous mixtures[16] were obtained at or just above the critical temperature of pure CO_2 for all substrates listed in Table 1, and no residual solid material could be detected by visual inspection. No phase separation was observed under the reaction conditions, and the initially colorless solution turned pale yellow during the course of the reaction. The online-GC experiments discussed below prove unambiguously that the substrate and all products remain homogeneously distributed in this supercritical phase throughout the reaction in case of **1a**.

As mentioned above, the overall reactivity and selectivity of **4** in $scCO_2$ is similar to the established behavior of typical unmodified rhodium catalysts in conventional solvents.[4] To allow for a more direct comparison, control experiments with the substrates **1a** and *trans*-3-hexene were conducted using catalyst **4** in toluene as a typical organic solvent for hydroformylation processes. Reactions were carried out with identical amounts of substrate and catalyst in the same volume of the reaction medium (25 mL) using a 50-mL reactor. Although we did not measure exact reaction rates in this case, it can be seen from Table 1 that olefin conversion was remarkably lower for **1a** and *trans*-3-hexene in toluene after identical reaction times, even with optimum agitation under the given technical limitations (magnetic stirring bar). This clearly indicates that aldehyde formation is considerably slower in toluene than in $scCO_2$, the effect being most pronounced for internal double bonds: *trans*-3-hexene was quantitatively hydroformylated within the standard reaction time of 20 h in $scCO_2$, whereas only 23% conversion was achieved in the organic solvent under identical conditions. Thus, the reaction rate increases *at least* 5-fold upon changing the reaction medium from toluene to $scCO_2$. The presence of internal aldehydes **3c**,**d** in the hydroformylation of **1a** in $scCO_2$ compared to the remaining of 10% of internal olefins in toluene manifests again the higher activity for hydroformylation of the internal double bonds in $scCO_2$ as a reaction medium.

The influence of the reaction conditions on the hydroformylation in $scCO_2$ was investigated for substrate **1a** using the hexafluoroacetonate complex **4** as a catalyst precursor without any additional modifier (Table 2). Again, all reaction mixtures were fully homogeneous by visual inspection at reaction temperatures above 31 °C, and conversion of **1a** to aldehydes **3a−d** was quantitative in all these cases. Most notably, however, only 5% conversion of **1a** was achieved at room temperature (i.e., *below* the critical temperature of pure CO_2), although **4** was apparently completely soluble in the liquid phase consisting of the substrate and liquified CO_2. The low conversion may reflect a lower concentration and/or slower mass transfer of the gaseous reactants in liquid CO_2 compared to that in the supercritical phase, but the high sensitivity of the hydroformylation reaction toward the reaction temperature[4] (see also Table 3) prevents a definite conclusion.

Variation of the density of the homogeneous reaction mixture had very little influence on the product ratio at temperatures above T_c of pure CO_2. At constant density, the amount of internal aldehydes **3c** + **3d** showed a significant increase with increasing temperature and decreasing synthesis gas pressure (Figure 2). This effect can be attributed to the different influences of these reaction parameters on the relative rates of the catalytic cycles responsible for isomerization and hydroformylation, respectively (vide infra).[4]

As can be seen from Table 2, the related Rh(I) complex $[(CO)_2Rh(acac)]$ (acac = acetylacetonate) gave also rise to a soluble and highly active unmodified catalyst for the hydroformylation of **1a** in $scCO_2$. Similarly, the Rh(0) cluster $[Rh_6(CO)_{16}]$ was found to be an efficient precursor, whereby fewer internal aldehydes resulting from isomerization prior to hydroformylation were formed.[17] The low activity of $RhCl_3\cdot 3H_2O$ reflects most likely its poor solubility in the reaction mixture, because Rh(III) would be expected to be at least partly

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[13] (a) Smart, N. G.; Carleson, T.; Kast, T.; Clifford, A. A.; Burford, M. D.; Wai, C. M. *Talanta,* **1997**, *44*, 137. (b) Kreher, U.; Schebesta, S.; Walther, D. *Z. Anorg. Allg. Chem.* **1998**, *624*, 602.

[14] For example: (a) Kröcher, O.; Köppek, R. A.; Baiker, A. *J. Chem. Soc., Chem. Commun.* **1996**, 1497. (b) Kröcher, O.; Köppek, R. A.; Baiker, A. *Chem. Commun.* **1997**, 453. (c) Mistele, C. D.; Thorp, H. H.; DeSimone, J. M. *Pure Appl. Chem.* **1996**, *A33*, 953. (d) Darensbourg, D. J.; White Stafford, N.; Katsurao, T. *J. Mol. Catal. A: Chem.* **1995**, *104*, L1.

[15] For example: (a) Jessop, P. G.; Hsiao, Y.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1996**, *118*, 344. (b) Burk, M. J.; Feng, S.; Gross, M. F.; Tumas, W. *J. Am. Chem. Soc.* **1995**, *117*, 8277. (c) Xiao, J.; Nefkens, S. C. A.; Jessop, P. G.; Ikariya, T.; Noyori, R. *Tetrahedron Lett.* **1996**, *37*, 2813. (d) Super, M. E.; Berluche, E.; Costello, C.; Beckman E. *Macromolecules* **1997**, *30*, 368. (e) Wu, X.-W.; Oshima, Y.; Koda, S. *Chem. Lett.* **1997**, 1045. (f) Jeong, N.; Hwang, S. H.; Lee, Y. W.; Lim, J. S. *J. Am. Chem. Soc.* **1997**, *119*, 10549. (g) Pesiri, D. R.; Morita, D. K.; Glaze, W.; Tumas, W. *Chem. Commun.* **1998**, 1015.

[16] These mixtures are commonly referred to as “supercritical” in order to distinguish them from liquified or multiphase systems.

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Table 2. Influence of the Reaction Parameters on the Hydroformylation of 1-Octene (**1a**) in $scCO_2$ Catalyzed by Different Rhodium Precursors in the Absence of Any Phosphorus Modifiers[a]

cat. (μmol of Rh)	d^b (g/mL)	T (°C)	$p_{syn}{}^c$ (bar)	$p_{tot}{}^d$ (bar)	C_8 composition (%),[e] **1a−d + 2**	aldehyde composition (%)[f] **3a**	**3b**	**3c + 3d**	cv^g (%)	TON[h]
4 (6.7)	0.53	80	45	235	0.3	52	35	13	>99	720
4 (7.4)	0.52	60	45	195	0.5	56	36	8	>99	650
4 (7.7)	0.55	40	45	160	0.7	58	39	3	>99	625
4 (7.4)	liq.	23	45	115	95	60	40		5	30
4 (6.7)	0.57	60	30	175	0.6	53	36	11	>99	720
4 (7.4)	0.56	60	60	245	<0.25	58	38	4	>99	650
4 (6.7)	0.72	60	30	220	0.7	54	36	10	>99	720
$[Rh_6(CO)_{16}]$ (36)	0.52	60	45	200	6	63	34	3	94	130
$[(CO)_2Rh(acac)]$ (23)	0.50	60	60	210	0.2	53	37	10	>99	420
$RhCl_3 \cdot 3H_2O$ (25)[i]	0.53	60	45	200	94	60	40		6	10

[a] Conditions: **1a** (4.8 mmol), $V_{reactor} = 25$ mL, $t = 20$ h. [b] Amount CO_2 per reactor volume. [c] $p(CO/H_2)$ at room temperature. [d] Total initial pressure at reaction temperature *T*. [e] From offline GC analysis. [f] From ^1H NMR analysis. [g] Total conversion to aldehydes. [h] Total amount of aldehydes **3a−d** per mole of rhodium. [i] **1a** (9.6 mmol).

Table 3. Hydroformylation of 1-Octene (**1a**) in $scCO_2$ Using Various Modified and Unmodified Rhodium Catalysts Based on Precursor **4**[a]

cat.	**1a**/Rh	[P]/Rh	T (°C)	$p_{syn}{}^b$ (bar)	$p_{tot}{}^c$ (bar)	t^d (h)	product composition (%)[e] **1a−d**	**2**	**3a**	**3b**	**3c + 3d**	cv^f (%)	TON[g]
4	2650		65	20	200	20	5	3	59	29	7	92	2440
4/5a	2100	10:1	65	20	200	21.5	1	0	81	18	0	99	2080
4/5b	2100	10:1	65	20	200	18	7	0	79	14	0	93	1950
4/6	2175	10:1	65	20	200	88	5	0	85	10	0	95	2065
4/5b[h]	290	4:1	60	45	210	20	3	0.1	74	23	0	97	280
4/5b[i]	235	6:1	62	60	235	19	10	0	74	16	0	90	210
4/5b[h]	300	13:1	60	45	210	20	87	0	11	2	0	13	40

[a] Conditions: **1a** (63.0 mmol), $V_{reactor} = 225$ mL, $d = 0.62$ g mL^{-1}. [b] $p(CO/H_2)$ at room temperature. [c] Total initial pressure at reaction temperature *T*. [d] Reaction time. [e] GC analysis. [f] Total conversion to aldehydes. [g] Total amount of aldehydes **3a−d** per mole of rhodium. [h] **1a** (4.8 mmol), $V_{reactor}$ = 25 mL. [i] **1a** (9.6 mmol), $V_{reactor} = 25$ mL.

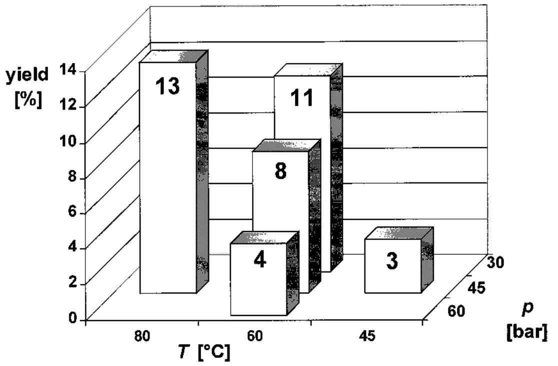

Figure 2. GC yield of aldehydes **3c** + **3d** as a function of reaction temperature *T* and CO/H_2 pressure *p* at density $d = 0.52{-}0.57$ g mL^{-1}.

reduced to active hydroformylation species under the present reaction conditions.[18]

Triarylphosphorus compounds are the most important class of ligands in the so-called *modified hydroformylation catalysts*. Triphenylphosphine (tpp) and its trisulfonated analogue (tppts) have already found industrial application in hydroformylation processes, and triaryl phosphites have received considerable attention, especially for hydroformylation of long-chain olefins.[4] Like most arylphosphines, tpp is very badly soluble in $scCO_2$ and cannot be used as ligand for the hydroformylation of **1a** under these conditions (26% conversion).[5a,c] As a possible solution to this problem, we have recently suggested the use of perfluoralkyl groups as solubilizers in the periphery of the corresponding catalyst. These substituents can be attached to the aryl moiety of the ligand in a flexible synthesis,[5ab,10,11,19] whereby a proper choice of the substitution pattern makes it possible to keep structural and electronic changes at the active center to a minimum compared to those of the unsubstituted parent complexes.[5a] The high solubility of catalysts containing such ligands allows their NMR spectroscopic investigation in $scCO_2$ using high-pressure sapphire tubes.[5b]

Table 3 compiles hydroformylation results for **1a** using **4** either without any modifiers or in the presence of the "CO_2-philic" phosphines **5a**,**b** and phosphite **6**. Up to 99% conversion of the olefin to the aldehydes **3a−d** was achieved after appropriate reaction times at substrate/Rh ratios up to 2650:1. The time required for quantitaive conversion and the overall chemo- and regioselectivity for aldehyde formation increased in the order **4** < **4/5a** ≈ **4/5b** < **4/6** (see below for details). The combination of high chemo- *and* regioselectivity in the case of ligand **6** is noteworthy, as the unsubstituted triphenyl phosphite (tpop) ligand leads to fast competing isomerization in conventional solvents.[20]

Using ligand **5b**, the regioselectivity for the formation of the linear aldehyde **3a** increased from an *n*/*iso* ratio **3a**/**3b** = 3.2 to 5.6 upon increasing the ligand-to-metal ratio [P]/Rh from 4:1 to 10:1. A higher ratio of **5b**/Rh led to a drastic decrease in rate without further improvement of the *n/iso* ratio. This influence of ligand excess parallels the effects observed with the unsubstituted parent compound in conventional solvents[4] and substantiates further that the catalytic cycle is carried by a ligand-modified species which is homogeneously dissolved in the supercritical reaction mixture.

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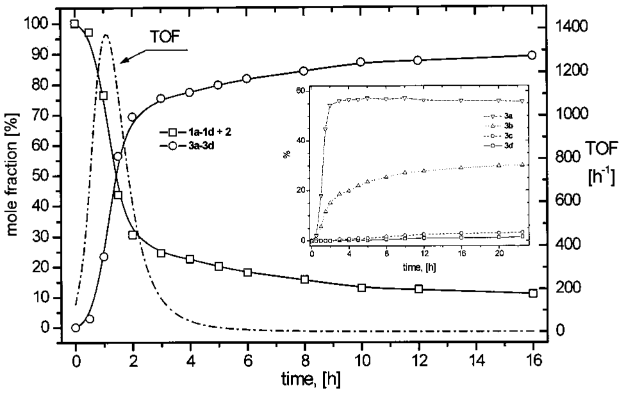

Figure 3. Online-GC data and TOF (h^{-1}) for the aldehyde formation in the hydroformylation of **1a** with the unmodified precursor **4** as catalyst. The inset shows the selectivity toward the individual aldehydes **3a**−**d**.

Separation of Products and Catalysts. The extractive properties of $scCO_2$[21] can provide a simple and straightforward methodolgy for the separation of products and catalysts in metal-catalyzed reactions.[2] Using **4** together with any of the perfluorinated ligands **5a**,**b** or **6**, we were, indeed, able to selectively extract the aldehydes **3a**−**d** from the reaction mixture by changing the pressure and temperature after complete conversion. The aldehydes were collected as colorless liquids and contained less than 1 ppm Rh under optimum conditions. The catalyst remaining in the high-pressure reactor was reused in five catalytic runs (overall number of catalytic turnovers ca. 1×10^4) without any noticeable change in selectivity and activity (complete conversion within the standard reaction time of 20 h).

Monitoring the Rhodium-Catalyzed Hydroformylation in $scCO_2$ by Online-GC Analysis. The present results and related recent research demonstrate the large potential of $scCO_2$ as an environmentally benign reaction medium with unique properties for various types of metal-catalyzed reactions.[1,2,14,15] Hence, there is an increasing need for efficient tools to monitor such processes. Such a monitoring device should ideally provide an efficient methodology for optimizing the reaction parameters for a given system and allow at the same time mechanistic insight by investigation of the reaction kinetics and product distribution. Exploiting the "gaslike" properties of $scCO_2$ in a practical way, we have used the online-GC reactor described in the Experimental Section for a comparative study of the unmodified, phosphine-modified, and phosphite-modified rhodium catalysts in the hydroformylation of **1a** (Scheme 1).

Figure 3 illustrates the reaction course for the hydroformylation of **1a** using complex **4** as a catalyst precursor without modifier in $scCO_2$ at a reaction temperature of 65 °C and 20 bar initial synthesis gas pressure. Olefin conversion to aldehydes (cv) was over 75% after 3.0 h and reached almost completion within less than 20 h; i.e., the total number of catalytic turnovers (TON) for aldehyde formation in this experiment was approximately 2400 (see Table 3, entry 1). The first derivative of the aldehyde formation curve provides direct information on the activity of the catalyst in the hydroformylation cycle at any time of the reaction, given as the turnover frequency (TOF, moles of aldehyde per mole of Rh and hour). As can be seen from Figure 3, the TOF of catalyst **4** depends strongly on the course of reaction with a distinct induction period during the early stages of reaction and a maximum value of 1375 h^{-1} after 1.1 h ($cv \approx 30\%$).

Table 4. Characteristic Activity Data for Various Rhodium Catalysts in the Hydroformylation of 1-Octene (**1a**) in $scCO_2$ and in Toluene[a]

cat.	**1a**/Rh	[P]/Rh	TOF_{max} (h^{-1})	t_{max} (h)	cv_{max} (%)
4	2650		1375	1.1	32
4/tpp[b]	2010	10:1	320	2.2	30
4/**5a**	2100	10:1	430	2.0	25
4/**5b**	2100	10:1	500	1.5	25
4/**6**	2175	10:1	115	7.0	26

[a] Maximum turnover frequency TOF_{max} for the fomation of aldehydes **3a**−**d** at corresponding time t_{max} and olefin conversion cv_{max} as revealed by online GC. Reaction conditions are given in Table 3. [b] In toluene under otherwise identical conditions. Data from offline ^1H NMR analysis.

Similar reaction profiles were observed for the modified rhodium catalysts **4**/**5a**,**b** and **4**/**6**, and characteristic data for the "catalytic activity" of all systems are summarized in Table 4 (see also Supporting Information). Although the rate law of the rhodium-catalyzed hydroformylation in $scCO_2$ has yet to be determined, the decrease in rate at higher conversions can reasonably be attributed to a decrease of the reactant concentrations.[22] Since the maximum TOF values were reached at $\geq 25\%$ conversions in all cases, they represent only a *lower limit* for the optimum turnover rate under the given conditions, and the intrinsic hydroformylation activities of all catalytic systems under scrutiny must be considerably higher than the data derived from these measurements. The relative activities confirm the conclusion drawn form preparative experiments. The unmodified catalyst has by far the highest activity, with the TOF_{max} being an order of magnitude larger than that for the phosphite-modified system **4**/**6**, which is the least active catalyst investigated in this series. The activity of **4** in the presence of para-substituted **5b** is slightly larger than that with meta-substituted **5a**.

A TOF of approximately 150 h^{-1} can be estimated from published kinetic data for the rhodium-catalyzed hydroformylation of **1a** with tpp as a ligand in toluene under related conditions.[23] However, published activity data for this ligand vary widely with the experimental conditions, and TOF values as high as 5000 h^{-1} have been reported for benzene solutions ($[P]/Rh = 10$, $T = 90$ °C, $p(CO/H_2) = 20$ bar).[27] We have therefore carried out a control experiment with **4**/tpp in toluene under the conditions typically applied in the supercritical medium, and the reaction profile was found to be again similar to the one shown in Figure 3. The maximum turnover frequency for **4**/tpp (Table 4) in the conventional solvent was somewhat lower than that with **4**/**5** in $scCO_2$, although the rate increase is less pronounced than that for the unmodified systems (see above).

In addition to the activity data, detailed analysis of the online-GC traces also makes it possible to determine the chemoselectivity (hydrogenation/isomerisazion vs hydroformylation) and the regioselectivity (linear vs branched isomers) of the various catalytic systems over the whole course of the reaction. As can be seen from the online-GC trace depicted in Figure 4, the hydroformylation of **1a** using the unmodified catalyst **4** produced

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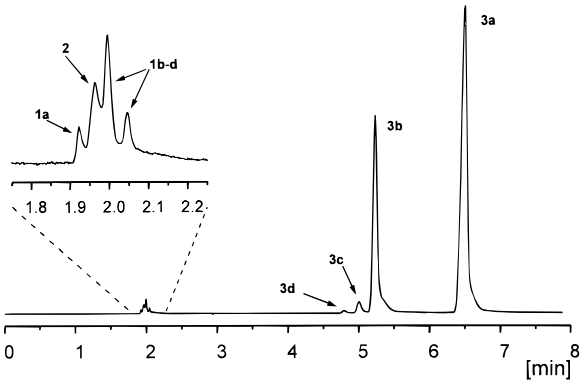

Figure 4. Online-GC trace of a hydroformylation of **1a** using catalyst **4** (total conversion to aldehydes = 92%).

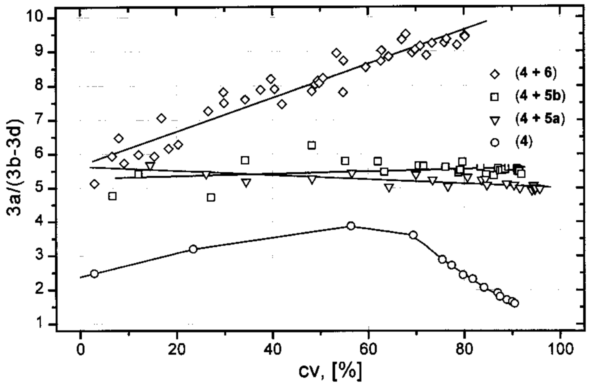

Figure 5. Ratio of linear aldehyde **3a** to branched isomers **3b**−**d** as a function of total conversion to aldehydes (*cv*) during the hydroformylation of **1a** with different catalysts.

almost exclusively the aldehydes **3a**−**d.** The hydrogenation product **2** was formed very slowly, amounting to less than 12% of the total mixture at the end of the reaction. The ratio of linear to branched aldehydes observed with catalyst **4** exhibited a significant increase in the first part of the reaction, reaching a maximum ratio of **3a**/(**3b**−**d**) = 3.8 after approximately 1.5 h ($cv \approx 50\%$), but decreased subsequently to a final value of 1.6 (Figure 5).

The marked dependence of the regioselectivity on the course of the reaction in the case of unmodified **4** may reflect (i) the formation of different catalytically active species with different selectivities (induction period!), (ii) the complex interplay of different catalytic cycles sharing identical or at least closely related intermediates, and (iii) the dependence of the regioselectivity on the variation in substrate, CO, and H_2 concentrations. Although all these effects are related and can occur at the same time under the present conditions, the following mechanistic information can be deduced by analysis of the individual chromatograms even at this early stage of our investigations. Migration of the double bond to form the isomeric olefins **1b**−**d** occurs slowly in a catalytic cycle parallel to the formation of **3a**,**b**. Although the hydroformylation of substituted double bonds is more efficient in $scCO_2$ than in organic solvents (vide supra), the internal olefins **1b**−**d** are still less reactive than the terminal alkenes **1a** in $scCO_2$. Accordingly, the aldehydes **3c**,**d** are formed only at very late stages of the reaction (>2.5 h), when consumption of **1a** exceeds 75% and the final amounts of **3c** and **3d** are low, with 3.3% and 1.5% of the total mixture, respectively.

Using **4** together with the "CO_2-philic" phosphorus modifiers **5a**,**b** and **6** led to even higher overall chemo- and regioselectivities. In all three cases, only the two isomeric aldehydes **3a**,**b** were detectable in appreciable amounts by GC summing up to 99% (**5a**), 93% (**5b**), and 95% (**6**) of the final reaction mixture (Table 3, entry 2−4). As can be seen from Figure 5, the linear-to-branched ratio remained almost constant between 5 and 6 over the whole course of reaction with the perfluoroalkyl-substituted arylphosphines **5a** and **5b**, respectively. This regioselectivity is considerably higher than that with **4**/tpp in toluene, where a ratio of **3a**/**3b** = 2.7 was observed in the control experiment described in Table 4. It is also higher than the *n*/*iso* ratio reported for **1a** under industrial hydroformylation conditions (**3a**/**3b** = 2.6 at [P]/Rh = 13:1, $p(H_2/CO, 1{:}2) = 33$ bar, $T = 107$ °C).[24]

A steady increase of the *n*/*iso* ratio **3a**/**3b** from 5 to over 9 was observed with the new phosphite ligand **6**. The apparent linear increase of the *n/iso* ratio can be best rationalized by analysis of the product distribution rather than product ratios as a function of conversion. Numerical analysis of the GC data revealed that the product distribution is only slightly in favor of **3a** in the initial part of the reaction ($cv < 10\%$), corresponding to a ratio of **3a**/**3b** ≈ 5:1. Subsequently, the mole fractions of *both* aldehydes **3a** and **3b** show a *linear* increase over the whole course of reaction (see Supporting Information). The active species resulting from **4**/**6** in $scCO_2$ must therefore operate with a *constant* and remarkably high intrinsic selectivity at this stage. From the slopes of the two linear product formation curves, this intrinsic *n*/*iso selectivity* can be determined to be **3a**/**3b** = 12:1. The observed linear increase of the *n*/*iso ratio* in Figure 5 therefore does not correspond to a continuous change in selectivity, but merely reflects the increasing overall ratio of **3a**/**3b** resulting from the short initial period of less selective aldehyde formation.

Another striking feature of the hydroformylation of **1a** with catalyst **4**/**6** in $scCO_2$ is the almost complete suppression of olefin isomerization. Phosphite rhodium complexes in general[25] and tpop complexes in particular[26] are highly active isomerization catalysts under hydroformylation conditions in conventional solvents. It has been argued that this behavior is largely due to mass-transfer limitations[25] and can be suppressed by faster rates for CO addition to the catalyst.[27] In accord with these arguments, it was previously found that the amount of isomerization decreased from 56% to 29% upon increasing the synthesis gas pressure from 5 to 10 bar in the hydroformylation of **1a** using tpop ([P]/Rh = 8:1) in toluene at 80 °C.[20] Using **6** in $scCO_2$, isomerization products were not observed, even at very late stages of the reaction, corresponding to low partial CO pressures. Although a final conclusion must await a detailed quantification of this effect, the beneficial lack of isomerization can reasonably be attributed to the absence of mass transport limitations and to the high diffusion rates in the homogeneous supercritical phase.

Conclusion

Taken together, the results of this study demonstrate the general applicability of $scCO_2$ as a highly promising reaction medium for the rhodium-catalyzed hydroformylation of olefinic substrates using unmodified, phosphine-modified, or phosphite-modified systems. Online-GC monitoring was introduced as a highly efficient and useful monitoring technique for catalysis in $scCO_2$ and revealed maximum turnover frequencies for the hydroformylation of **1a** of 1375, 500, and 115 h^{-1} for the unmodified, phosphine-modified, and phosphite-modified systems, respectively. These data correspond to the lower limits for the catalytic activities under the present conditions, and the performance of all three systems is therefore well in the range of potential technical utility (TOF > 200 h^{-1}).[28] The results also provide clear experimental evidence that hydroformylation with *unmodified* rhodium catalysts is considerably faster in $scCO_2$ than in toluene as a typical organic solvent. Internal olefins, which are notoriously unreactive in conventional solvents, are hydroformylated with high rates and excellent chemo- and regioselectivity.

The results obtained in $scCO_2$ with catalysts containing the "CO_2-philic" phosphorus ligands also compare favorably with related systems[29] for hydroformylation of long-chain olefins in other reaction media, as was already discussed for the Rh/tpp system in toluene. Hydroformylation of 1-decene using either tpp or $P[CH_2CH_2(CF_2)_6F]_3$ as ligand in the fluorous biphasic system (FBS) introduced recently by Horváth et al. gave *n/iso* ratios of 3.2 and 8−9% isomerization, whereby the internal olefins were not hydroformylated further.[30] The bulky monodentate phosphite ligand tris(2-*tert*-butyl-4-methylphenyl)phosphite developed by van Leeuwen and co-workers has been reported to allow extremely fast hydroformylation of **1a** in organic solvents (TOF up to 12 500 h^{-1}), but the *n/iso* ratio was only 1.5, and 8.8% of the products were due to double bond isomerization.[31]

Owing to their very low solubility in water, long-chain olefins cannot be hydroformylated with the industrially used Rh/tppts system in aqueous biphasic systems at temperatures comparable to that of the $scCO_2$ system. A mixed tpp/tppts system has been described to allow hydroformylation of **1a** in aqueous solution with TOFs up to 800 h^{-1}, but the system operates at much higher temperature (100 °C), and no selectivity data were reported.[32] Using cyclodextrine as a phase-transfer catalyst, a TOF of 300 h^{-1} and an *n/iso* ratio of 1.9 was obtained for 1-decene as substrate.[33] Reetz and Waldvogel reported 95% conversion of **1a** after 18 h under 100 bar synthesis gas with an *n/iso* ratio of 3.2 employing a cyclodextrine-bound diphosphine.[34] Water-soluble polymeric Rh catalysts have recently been described to be active for the hydroformylation of **1a** in the absence of additional ligands or additives, but only 89% conversion of the substrate was achieved after 22 h at 100 °C.[18a] An *n/iso* ratio of 2.5 was reported for the aldehydes, and 37% isomerization to **1b** was observed, which was not hydroformylated in this system.

These examples illustrate that hydroformylation using rhodium catalyst occurs in $scCO_2$ in general at rates and selectivities that are comparable and in many cases superior to those of closely related catalytic systems operating in other solvents. Furthermore, we have proven the potential for an effective and simple separation of product and catalysts using supercritical fluid extraction. We therfore believe that $scCO_2$ represents an attractive and environmentally benign alternative reaction medium for rhodium-catalyzed hydroformylation reactions on laboratory and technical scales. Future work is clearly needed to allow a detailed comparison of the various catalytic systems in terms of mechanisms and practical utility. In particular, it will be interesting to see how the physical and chemical properties of CO_2 relate to the now established effects in detail.[35,36] An improvement of our fundamental understanding of catalysis in $scCO_2$ is urgently required for the devolpment of more efficient catalytic systems, and current efforts in our laboratory are devoted to such investigations.

Acknowledgment. This work was supported by the Max-Planck-Gesellschaft, the Deutsche Forschungsgemeinschaft (Gerhard-Hess-Programm), and the Fonds der Chemischen Industrie. We thank Celanese GmbH, Werk Ruhrchemie, for financial support and for the AAS measurements. Generous loans of chemicals by Clariant GmbH, Werk Gendorf, and Degussa AG are gratefully acknowledged. Special thanks are due to U. Häusig, A. Iländer, and W. Grothe for their skillful assistance in assembling the online-GC reactor. This paper is dedicated to Prof. Helmut Werner on the occasion of his 65th birthday.

Supporting Information Available: Plots of the data revealed from online-GC monitoring of hydroformylation of **1a** with **4**/**5a,b** and **4**/**6** in $scCO_2$ and from NMR analysis for **4**/tpp in toluene (6 pages, print/PDF). See any current masthead page for ordering information and Web access instructions.

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