Highly regio- and enantio-selective rhodium-catalysed asymmetric hydroformylation without organic solvents

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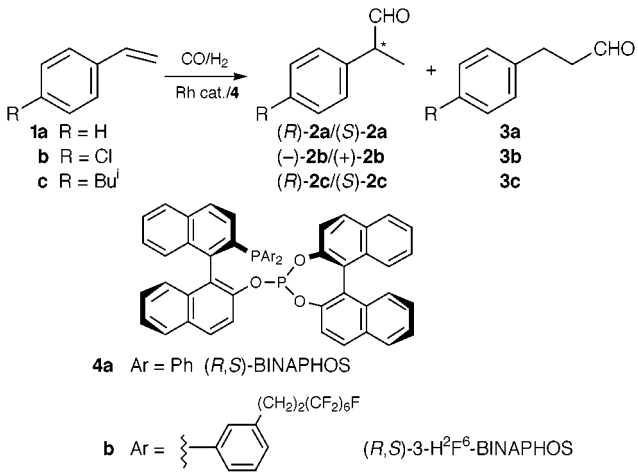
High enantioselectivity and unprecedented high regioselectivity without the need for hazardous organic solvents are achieved in rhodium-catalysed asymmetric hydroformylation with the perfluoroalkyl-substituted ligand (*R,S*)-3-H^{2}F^6-BINAPHOS, whereby the substitution pattern of the ligand is crucial for its successful use in compressed carbon dioxide and for the increased regioselectivity.

Asymmetric hydroformylation using chiral transition metal catalysts is an efficient and well established strategy for the synthesis of functionalised non-racemic organic compounds, providing for example viable routes to important anti-inflammatory drugs starting from simple vinyl arenes.[1] The chiral phosphine/phosphite ligand (*R,S*)-BINAPHOS **4a** allows rhodium-catalysed asymmetric hydroformylation of vinyl arenes **1a**–**c** with outstanding levels of enantiocontrol (Scheme 1).[2] However, the regioselectivity towards the chiral branched aldehydes **2a**–**c** is less satisfactory (88% for **2a**) even under carefully optimised conditions, leading to considerable amounts of linear aldehydes **3a**–**c** as undesired by-products. Furthermore, the established protocols require the use of ecologically and toxicologically hazardous organic solvents, especially benzene, representing another major drawback in light of the potential practical application of the methodology.

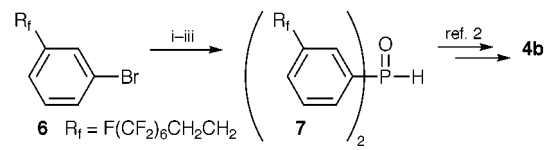


Scheme 1

We now report that the use of the new perfluoroalkyl-substituted derivative (*R,S*)-3-H^{2}F^6-BINAPHOS **4b**[3] allows rhodium-catalysed hydroformylation of vinyl arenes (Scheme 1) to be carried out in compressed (liquid or supercritical) carbon dioxide as a solvent with similar catalytic activity and the same level of enantiocontrol as **4a**, resulting at the same time in unprecedented high regioselectivity for the branched aldehydes. The high regioselectivity originates from the ligand substitution pattern and is retained also during hydroformylations in other solvents or even in the neat substrate.

Supercritical carbon dioxide ($scCO_2$) has gained increasing interest as an environmentally friendly solvent with unique properties for chemical synthesis in general[4] and metal-catalysed reactions in particular.[5] Non-enantioselective hydroformylation has been achieved in $scCO_2$,[6–10] and there are also examples of highly enantioselective catalytic reactions in this medium.[11,12] These promising results encouraged us[9] and others[10c] to apply $scCO_2$ as a reaction medium for asymmetric hydroformylation as well. However, it soon became apparent that **4a** cannot be used efficiently in $scCO_2$, owing to its low solubility in this medium.[9]

We have shown recently that the low solubility of aryl-phosphorous ligands and their metal complexes in $scCO_2$ can be overcome by fixation of perfluoroalkyl substituents $(CH_2)_x(CF_2)_yF$ at the aryl rings.[8a] Following this approach, we set out to synthesise the fluoroalkyl-substituted (*R,S*)-3-H^{2}F^6-BINAPHOS **4b** and its rhodium complex [(**4b**)Rh(acac)] **5b**. The fluoroalkyl substituents were introduced *via* the bisaryl phosphonic acid **7**, which was obtained in a one-pot procedure from the *meta*-substituted aryl bromide **6**[13] (Scheme 2). Crystallisation from pentane provided **7** as a white solid in 63% yield.[14] The remaining route to **4b** was a modified version of the original synthesis of **4a** giving a similar overall yield. The $^{31}P\{^1H\}$ NMR data of the phosphine/phosphite ligand **4b** and its rhodium complex **5b** are almost identical to those reported for the unsubstituted parent compounds **4a** and **5a**.[2,14]



Scheme 2 *Reagents and conditions*: i, BuLi, Et_2O, −30 °C, then 30 min at 0 °C; ii, $(NEt_2)PCl_2$, Et_2O, −30 °C; iii, conc. HCl.

In contrast to **4a**, the perfluoroalkyl-substituted ligand **4b** allows highly efficient asymmetric hydroformylation of styrene **1a** using compressed CO_2 as the reaction medium (Table 1, entries 5–9).‡ The isomer (*R*)-**2a** was formed preferentially with ees between 90 and 94% under various reaction conditions. Quantitative conversion (> 98%) of **1a** could be achieved in less than 16 h at a substrate-to-rhodium ratio of 1000 : 1 and a reaction temperature of 60 °C. Somewhat longer reaction times were required at lower temperatures or lower catalyst loadings. Most remarkably, a very high regioselectivity of 93–96% was achieved consistently for the formation of **2a**.

Similar results were obtained using **4b** in the asymmetric hydroformylation of the substituted vinyl arenes **1b**,**c**. Substrate **1b** bearing an electron-withdrawing chloride substitutent in the *para* position was hydroformylated with a modest enantiomeric excess of 88% ee, but the regioselectivity was again high (92%, entry 12). Substrate **1c**, the precursor for the hydroformylation route to ibuprofen, was hydroformylated with excellent enantioselectivities of up to 93% and an unprecedented high regioselectivity of 96% for **2c** (entries 13, 14).

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Table 1 Rhodium-catalysed asymmetric hydroformylation of vinyl arenes **1a–c**[a]

Entry	Substrate	S/Rh	Ligand	L/Rh	Solvent	d (CO_2)[b] /g cm^{-3}	T/°C	$P_{H_2/CO}$ /bar	P_{tot} /bar	t/h	Conversion (%)	Regioselectivity[c] (%)	Ee (%)
1[d]	**1a**	2000	**4a**	4	Benzene	—	60	100	—	43	> 99	88	94 (*R*)
2	**1a**	2000	**4b**	4	Benzene	—	60	100	—	17	> 99	92.7	90.6 (*R*)
3	**1a**	1000	**4b**	4	Hexane	—	40	100	—	46	42.0	95.7	90.0 (*R*)
4	**1a**	2000	**4b**	4	Neat	—	60	100	—	12	> 99	94.1	90.6 (*R*)
5	**1a**	2000	**4b**	3	CO_2	0.681	40	40	178	66	75.4	94.8	93.6 (*R*)
6	**1a**	1000	**4b**	2	CO_2	0.596	60	20	156	16	> 99	92.5	90.4 (*R*)
7	**1a**	1000	**4b**	2	CO_2	0.596	60	60	242	16	97.6	93.0	92.0 (*R*)
8	**1a**	1000	**4b**	2.4	CO_2	0.460	36	40	123	62	91.6	94.8	91.8 (*R*)
9	**1a**	1000	**4b**	2.4	CO_2	0.80	31	40	115	62	96.5	95.6	91.8 (*R*)
10[d]	**1b**	2000	**4a**	4	Benzene	—	60	100	—	34	> 99	87	93 (−)
11	**1b**	1000	**4b**	2	CO_2	0.580	40	40	150	15	89.0	91.9	88.4 (−)
12[d]	**1c**	300	**4a**	4	Benzene	—	60	100	—	66	> 99	88	92 (*R*)
13	**1c**	1000	**4b**	2	CO_2	0.531	40	40	146	16	> 99	95.5	90.1 (*R*)
14	**1c**	1000	**4b**	2	CO_2	0.81	29	40	115	43	61.2	96.1	92.8 (*R*)

[a] See note ‡. [b] Density derived from weighed amount of CO_2 and reactor volume for $T > T_c$. [c] Defined as **2**/(**2** + **3**); hydrogenation or other side reactions were insignificant. [d] Data taken from ref. 2(*a*) for comparison.

It is important to note that the positive results achieved with ligand **4a** are *independent* of the phase behaviour of the reaction mixture. At temperatures ≥40 °C and CO_2 densities of $d \geq 0.59$ g cm^{-3}, the reaction mixtures with substrate **1a** were homogeneous by visual inspection and no phase separation was observed throughout the reaction. At T = 36 °C and d = 0.46 g cm^{-3}, *i.e.* in close vicinity to the critical point of pure CO_2 (T_c = 31.1 °C, d_c = 0.466 g cm^{-3}) the formation of small droplets was detected during the latter stages of the reaction. A liquid phase was present throughout the reaction at T = 31 °C. With substrate **1c**, the reaction occurred smoothly and with high selectivity at temperatures above or below T_c of pure CO_2.

The most striking feature of Table 1 is clearly the remarkably increased regioselectivity observed with **4b** as compared to **4a**. In order to distinguish solvent effects[6a,8b] from ligand effects,[15] we carried out control experiments with **4b** in typical organic solvents and in the neat substrate. Excellent regio- and enantioselectivities were observed in all cases (entries 2–4) demonstrating that the higher regioselectivity of the system **4b**/CO_2 compared to **4a**/benzene is mainly due to the ligand substitution pattern rather than the reaction medium.

In summary, we have accomplished the first synthesis of a highly complex ligand containing perfluoroalkyl substituents. The ligand (*R*,*S*)-3-H^{2}F^6-BINAPHOS **4b** allows for the first time efficient and highly regio- and enantio-selective hydroformylation of vinyl arenes using compressed CO_2 as an environmentally and toxicologically benign solvent. Particularly in the case of the practically most important substrate **1c**, the selectivities and reaction rates with ligand **4b** in compressed CO_2 compare favourable to those reported previously using **4a** in benzene under similar conditions. The successful use of CO_2 as a reaction medium raises the attractive possibility of applying our recently developed protocols for catalysis and extraction using supercritical carbon dioxide (CESS process).[8b,12,16] The evaluation of the scope and limitations of this approach and spectroscopic investigations of the rhodium complexes under catalytic conditions are under way.

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Notes and references

‡ Hydroformylation experiments were carried out in a window-equipped stainless-steel high-pressure reactor (V = 10 cm^{-3}). Complex **5b** and the ligand **4b** were charged as THF solutions in the reactor under argon. After stirring for 5 min, the solvent was removed *in vacuo* and the substrate was introduced. The reactor was pressurised with a 1:1 mixture of CO and H_2 and then filled with a weighed amount of CO_2 by means of a compressor. The reaction mixture was heated and stirred with a PTFE stirring bar for the desired reaction time. After cooling to 0 °C, the reactor was carefully vented and the products were collected by extraction of the reactor content with toluene for NMR and GC analysis.

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