Sulfonated Xantphos Ligand and Methylated Cyclodextrin: A Winning Combination for Rhodium-Catalyzed Hydroformylation of Higher Olefins in Aqueous Medium

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The potential of sulfonated xantphos as ligand for a cyclodextrin-based hydroformylation process has been investigated. In addition to an activity enhancement, an increase in the linear to branched aldehydes ratio was measured when randomly methylated α- or β-cyclodextrins were used as inverse phase-transfer catalysts. The improvement of the selectivity was the result of two combined effects. First, contrary to what was observed with the TPPTS or TPPMS ligands, the interactions between the sulfonated xantphos and the methylated cyclodextrins were too weak to induce dissociation of the ligand from the complex under hydroformylation conditions. Second, concurrently to the constraint generated by the bulky sulfoxantphos ligand, the additional steric stress of the cyclodextrin cavity on the substrate compelled the latter to react preferentially by its terminal carbon, leading to very high regioselectivity toward linear aldehyde.

Introduction

In recent years, cyclodextrins have been successfully used as mass-transfer promoters in aqueous-phase organometallic catalysis.[1] The beneficial effect of these water-soluble host compounds on the mass transfer is ascribed to their complexing properties, and it is postulated that the cyclodextrins operate like inverse phase-transfer catalysts according to Figure 1.

In this mechanism, the receptor represented by a truncated cone forms a host/guest complex with the substrate at the liquid/liquid interface and transfers the water-insoluble substrate (**S**) into the aqueous phase, where it reacts with the water-soluble organometallic catalyst. After reaction, the product (**P**) is released in the organic phase and the subsequent transfer cycle can proceed. The efficiency of this process strongly depends on the nature of the CD. For example, methylation or hydroxyalkylation of the hydroxyl groups of β-CD gives rise to the most efficient CD in terms of rate enhancement.[2]

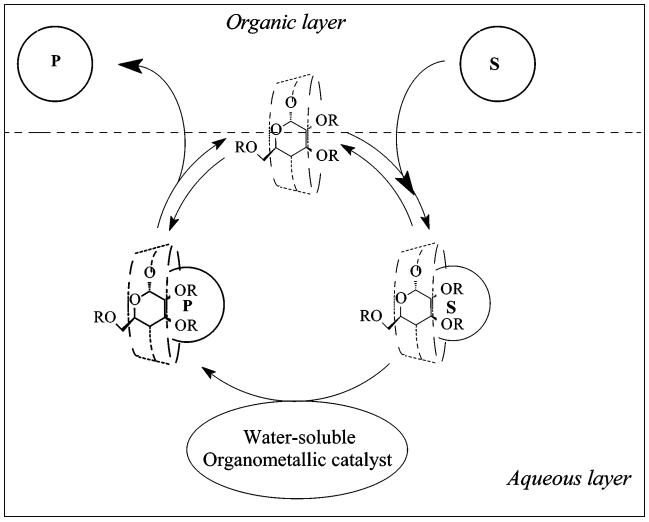

Figure 1. Concept of the inverse phase-transfer catalysis mediated by cyclodextrins.

We previously demonstrated that cyclodextrin can bind to the water-soluble phosphines used to dissolve

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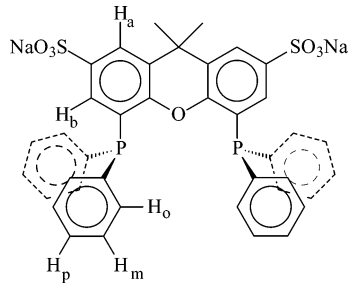
the organometallic catalyst in the aqueous phase,[3] and we have reported that the sodium salt of *meta*-substituted monosulfonated triphenylphosphine (*m*-TPPMS) and the sodium salt of the trisulfonated triphenylphosphine (TPPTS) form stable inclusion complexes with the β-cyclodextrin derivatives in water. For instance, the values of the association constants for the β-CD/*m*-TPPMS and β-CD/TPPTS inclusion complexes were estimated to be 12 000 and 1200 M^{-1} at 25 °C, respectively.[4] It was found that randomly methylated β-cyclodextrin (RAME-β-CD) exhibited a similar affinity for monodentate phosphines. Indeed, the values of the association constants for the RAME-β-CD/*m*-TPPMS and RAME-β-CD/TPPTS inclusion complexes were estimated to be 13 000 and 1000 M^{-1} at 25 °C, respectively.[5] The formation of inclusion complexes between the water-soluble ligand and the cyclodextrin derivatives has rather negative effects on the selectivity of the hydroformylation reaction.[6] For instance, the decrease in linear to branched aldehydes ratio observed in a cyclodextrin-based hydroformylation process (1.8 vs 2.7 without cyclodextrin) was recently attributed to the formation of inclusion complexes between RAME-β-CD and the TPPTS ligand.[7] In fact, by trapping the TPPTS ligand, the RAME-β-CD induces a displacement of the equilibria between the different rhodium species toward species having a low phosphine:rhodium ratio responsible for the formation of the branched aldehyde.[8]

In this context, bidentate phosphines based on xanthene-type backbones constitute particularly interesting ligands. Indeed, these diphosphines show a very high regioselectivity for the formation of linear aldehydes due to their large natural bite angle and are strongly bound to the metal center.[9] This last property allowed important developments in homogeneous catalysts recovery technology. Indeed, no leaching of the catalyst was observed when such catalysts were immobilized into liquids or on supports due to the high ligand-to-metal bond strength.[10]

Scheme 1. Sulfonated Xantphos



Scheme 2. Structure of Cyclodextrin Derivatives Used in This Work

Structure of cyclodextrin				
Abbreviations	n	R	Carbon bearing the OR group	OH group substituted per glucopyranose unit
β-CD	7	(-)	(-)	(-)
RAME-β-CD	7	-CH_3	2, 3, 6	1.8
RAME-α-CD	6	-CH_3	2, 3, 6	1.8

The high stability of these catalysts prompted us to evaluate the behavior of the rhodium complex of the disodium salt of 2,7-bisulfonate-4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (sulfoxantphos, Scheme 1) in the presence of cyclodextrin derivatives under hydroformylation conditions. Indeed, the strong chelating effect of this bidentate phosphine should counterbalance the possible formation of an inclusion complex between the ligand and the cyclodextrin. In addition to an activity enhancement, an increase in the selectivity of the hydroformylation of terminal alkenes could therefore be expected.

First, the interaction between sulfoxantphos and three cyclodextrin derivatives, the randomly methylated α-cyclodextrin (RAME-α-CD, Scheme 2), the native β-cyclodextrin (β-CD), and the randomly methylated

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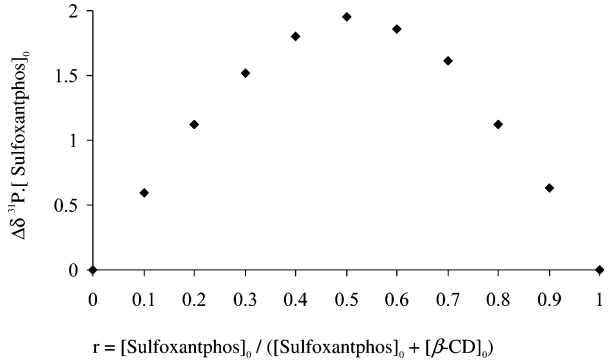

Figure 2. Continuous variation plot (Job's plot) derived from the $^{31}P\{^1H\}$ NMR data for β-CD and sulfoxantphos system.

β-cyclodextrin (RAME-β-CD, Scheme 2), has been investigated by ^1H and $^{31}P\{^1H\}$ NMR spectroscopy and by two-dimensional T-ROESY experiments. Second, the behavior of the in situ formed $HRh(CO)_2$(sulfoxantphos) complex was studied by high-pressure $^{31}P\{^1H\}$ NMR spectroscopy, and finally, the effect of the methylated cyclodextrins on the hydroformylation reaction rate and aldehydes selectivity was investigated.

Results and Discussion

First of all, interactions between sulfoxantphos and RAME-α-CD, β-CD, or RAME-β-CD were studied by ^1H and $^{31}P\{^1H\}$ NMR spectroscopy. Unlike RAME-α-CD, ^1H and $^{31}P\{^1H\}$ NMR spectra of mixtures of β-CD/sulfoxantphos or RAME-β-CD/sulfoxantphos denoted chemical shift variations for the phosphorus and protons of the phosphine and for most of the protons of the cyclodextrins, indicating that only the β-cyclodextrin derivatives interact with sulfoxantphos. The stoichiometry of these inclusion complexes was provided by the NMR continuous variation method.[11] A series of solutions was prepared in which the sum of β-cyclodextrin derivatives and sulfoxantphos concentrations was kept constant (5 mM in the present case), but in which the concentrations of cyclodextrins and sulfoxantphos were systematically varied. From the chemical shifts variations observed on the $^{31}P\{^1H\}$ NMR spectrum for the different cyclodextrin/phosphine mixtures, two Job plots were drawn, one for each supramolecular complex. As an example, the Job plot related to the β-CD/sulfoxantphos complex is depicted in Figure 2.

A maximum value of $r = 0.5$ and the highly symmetric shape of the curve revealed a 1:1 stoichiometry. The same type of curve was observed for the RAME-β-CD/sulfoxantphos complex, which was thus characterized by a 1:1 stoichiometry as well.

Binding constants of 80 and 440 M^{-1} at 25 °C were further calculated by the $^{31}P\{^1H\}$ NMR titration technique for the β-CD/sulfoxantphos and the RAME-β-CD/sulfoxantphos complexes, respectively. These constants are lower than those obtained with well-known water-soluble monodentate phosphines such as TPPMS and TPPTS (see above). The very low affinity of β-cyclodextrin derivatives for the sulfoxantphos ligand could be due to the closeness of the two diphenylphosphino groups. Actually, the complexation of the cyclodextrins with one of the two diphenylphosphino groups is probably hindered by the presence of the other.

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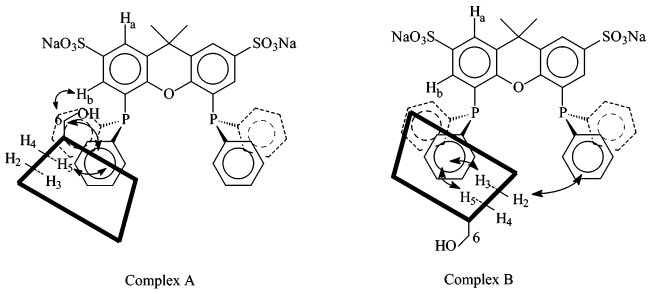

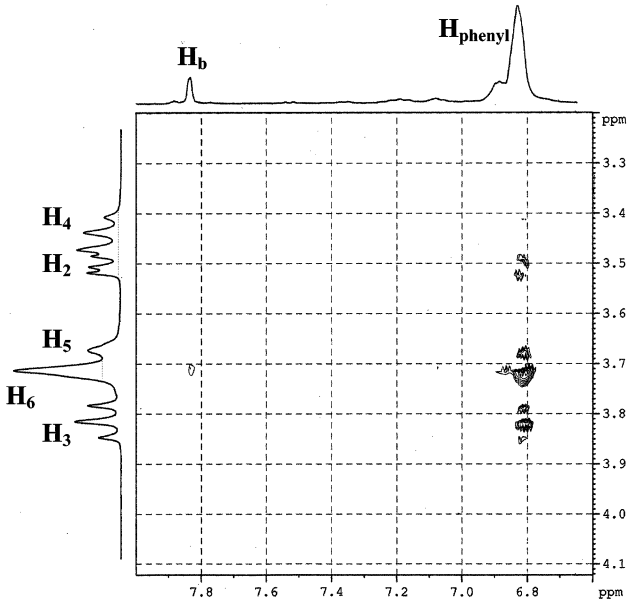

Figure 3. Partial contour plot of the T-ROESY spectrum of a solution containing β-CD (10 mM) and sulfoxantphos (10 mM) in D_2O at 298 K with a 300 ms mixing time. The structures deduced from this spectrum for the β-CD/sulfoxantphos complexes are presented over the spectrum. The interactions observed in the T-ROESY spectrum are also indicated on the structures.

To confirm this assumption, two-dimensional T-ROESY experiments have been performed. First, a mixture of sulfoxantphos and β-CD was prepared in a stoichiometric ratio. The corresponding spectrum is displayed in Figure 3.

The existence of cross-peaks between the nonsulfonated aromatic protons of the ligand and the protons situated inside the β-CD cavity (H_3 and H_5) fully proved the formation of inclusion complexes. Moreover, the strong cross-peak between the H_6 proton and the nonsulfonated phenyl ring of the sulfoxantphos indicates that the sulfoxantphos penetrated into the β-CD cavity from the primary OH group side as schematically represented in Figure 3 with complex A. In this complex, the phenyl group did not deeply penetrate in the cavity, as the contact between the H_6 proton and the H_b proton of the sulfoxantphos is very weak. It must be pointed out that such a penetration cannot explain the strong dipolar contact observed between the H_3 proton and nonsulfonated phenyl rings of the sulfoxantphos and suggests that another type of 1:1 inclusion complex is

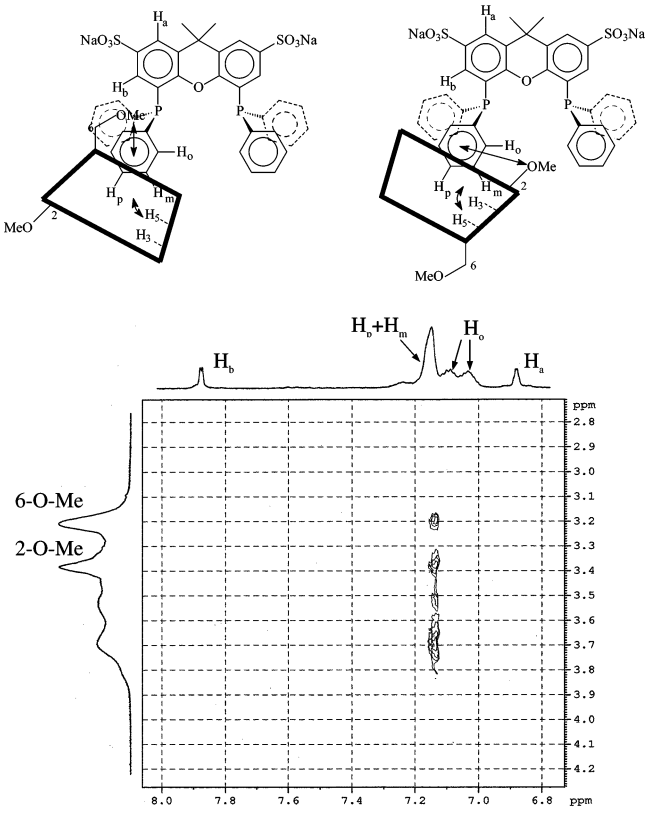

Figure 4. Partial contour plot of the T-ROESY spectrum of a solution containing RAME-β-CD (10 mM) and sulfoxantphos (10 mM) in D_2O at 298 K with a 300 ms mixing time. The structures deduced from this spectrum for the RAME-β-CD/sulfoxantphos complexes are presented over the spectrum. The interactions observed in the T-ROESY spectrum are also indicated on the structures.

present in solution. This second inclusion complex is obtained by penetration of a nonsulfonated ring by the secondary rim of the β-CD, as schematically represented in Figure 3 for complex B. Indeed, it is well known that a penetration into the β-CD cavity from the secondary OH group side induces strong dipolar contact between H_3 and the guest.[3,4] Interestingly, the cross-peak observed between the external proton H_2 of the cyclodextrin and the phenyl groups of the nonincluded diphosphine confirms that the phenyl groups of the nonincluded diphenylphosphino group were very close to the external surface of the cyclodextrin.

Second, the same experiment has been carried out with a stoichiometric mixture of sulfoxantphos and RAME-β-CD. The ^{1}H NMR spectrum revealed that the presence of RAME-β-CD induced a shift of the signals relative to the phenylic protons of the sulfoxantphos. Actually, COSY and HSQC NMR experiments showed that the eight *ortho*-protons of the phenyl groups were shifted to higher field (7.10 and 7.03 ppm) than the *meta*- and *para*-protons (7.17 ppm). It can also be noticed that the two H_a protons of the sulfonated rings now appeared distinctly (6.88 ppm). When looking at the T-ROESY spectrum (Figure 4), the interaction of sulfoxantphos with RAME-β-CD led to cross-peaks between the 2-methoxy or 6-methoxy groups of RAME-β-CD and the *meta*- and *para*-protons of the ligand.

The weak inclusion of the ligand in the cavity was then confirmed since no cross-peaks appeared between

Table 1. Hydroformylation of Higher Olefin Catalyzed by Rh/Sulfoxantphos System[a]

entry	olefin	cyclodextrin	conversion[b] (%)	selectivity[c] (%)	l/b ratio[d]
1	1-octene		19	94	14
2	1-octene	RAME-α-CD	74	>99	33
3	1-octene	RAME-β-CD	90	>99	20
4	1-decene		7	93	12
5	1-decene	RAME-α-CD	63	>99	32
6	1-decene	RAME-β-CD	71	>99	26

[a] Experimental conditions: Rh(acac)$(CO)_2$, 0.04 mmol; sulfoxantphos, 0.21 mmol; cyclodextrin, 0.48 mmol; water, 11.5 mL; olefin, 20.35 mmol; *n*-undecane (internal standard), 2.03 mmol; $P(CO/H_2, 1{:}1) = 50$ bar; $T = 120$ °C. [b] Olefin conversion after 24 h. [c] Aldehydes selectivity after 24 h. [d] Linear to branched aldehydes ratio after 24 h.

the *ortho*-protons of the phenyl groups and the protons of the RAME-β-CD. Furthermore, the existence of cross-peaks of similar intensity between the nonsulfonated phenyl ring of the sulfoxantphos and the 2-methoxy or 6-methoxy groups of the RAME-β-CD indicates that the inclusion of the ligand is possible by both sides of the cavity of RAME-β-CD as described above for β-CD.

Knowing that an interaction between the sulfoxantphos ligand and the β-CD derivatives was weak but possible, further NMR experiments have been performed with the RAME-β-CD and the RAME-α-CD under hydroformylation conditions. A solution of Rh(acac)$(CO)_2$, sulfoxantphos, and RAME-β-CD was pressurized under CO/H_2 (16 bar). Several ^{31}P NMR spectra were recorded at room temperature and 42, 48, 55, and 80 °C. Contrary to what has been observed in the case of the TPPTS ligand,[8] no dissociation of the bidentate ligand was observed at room temperature and the percentage of decoordinated sulfoxantphos ligand was very low at high temperature (5−10% at 80 °C vs 50% in the case of the TPPTS phosphane under similar conditions). Consequently, these HP NMR experiments suggest strongly that RAME-β-CD does not notably promote ligand dissociation. This assumption was fully supported by high-pressure NMR experiments conducted with the RAME-α-CD, which does not interact with the sulfoxantphos. Indeed, the ^{31}P{^{1}H} NMR spectrum of a solution of Rh(acac)$(CO)_2$, sulfoxantphos, and RAME-α-CD recorded at 80 °C under CO/H_2 pressure (18 bar) was similar to that obtained with the RAME-β-CD. Thus, it can be concluded that the affinity of the RAME-β-CD for the sulfoxantphos ligand is too weak to induce dissociation of the bidentate ligand from the Rh/sulfoxantphos complex.

The performances of the cyclodextrins/sulfoxantphos couple have been evaluated in the hydroformylation of 1-octene and 1-decene. The results obtained without any additive and in the presence of RAME-α-CD and RAME-β-CD are summarized in Table 1.

As can be deduced from the analysis of the experimental data of Table 1, the conversions after 24 h of reaction were always better when a cyclodextrin was used as a mass-transfer promoter. For example, a conversion of 19% was obtained for 1-octene without any cyclodextrin in the medium, whereas aldehyde conversions of 74% and 90% were reached with RAME-α-CD and RAME-β-CD, respectively. In the same manner, 1-decene gave a low aldehyde conversion (7%) without

cyclodextrin and rather good conversions with RAME-α-CD and RAME-*β*-CD (63% and 71%, respectively).

The chemoselectivity is already high in the absence of cyclodextrins (94%) but is better in the presence of RAME-α-CD or RAME-*β*-CD (99%). Compared to the TPPTS ligand, for which 23% of 2-octene isomers was obtained under the same experimental conditions, only 1% of byproducts was observed in the case of sulfoxantphos. Thus, at 120 °C, the supramolecular CD-sulfoxantphos-based catalyst complex was much more selective than the rhodium species based on the TPPTS ligands. The steric and electronic properties of the sulfoxantphos but also the position of the substrate/cyclodextrin complex in this hindered arrangement might be responsible for this high chemoselectivity.

Finally, the regioselectivity has also been examined through the evolution of the linear/branched (l/b) aldehydes ratio with the nature of the cyclodextrin. When RAME-α-CD was used as a carrier, both substrates gave regioselectivities that were about 2.5 times higher than those observed without cyclodextrin (33 vs 14 for 1-octene and 32 vs 12 for 1-decene). The bulkiness around the coordination sphere of the rhodium is proposed to be responsible for these results. In fact, in addition to the steric congestion related to the bulky diphosphine, it must also be mentioned that the substrate alkyl chain was restrained in the small cavity of RAME-α-CD, which forced the hydroformylation reaction rather on the terminal alkenyl carbon. Steric congestion of the substitutents at the phosphorus atoms also leads to wider bite angles, thus enhancing the steric effects.[12]

For RAME-*β*-CD, the increase in the regioselectivity was a little bit lower (only 1.4 times higher for oct-1-ene and 2.2 times higher for dec-1-ene). The decrease in the aldehydes ratio compared to that obtained with RAME-α-CD could be rationalized by considering that the wider cavity of RAME-*β*-CD gave to the substrate alkyl chain higher degrees of freedom. Consequently, with RAME-*β*-CD, the terminal unsaturated substrates might yield lower regioselectivity in the hydroformylation reaction on their alkenyl carbons.

Conclusion

The sulfoxantphos ligand appears to be a valuable ligand for a cyclodextrin-based hydroformylation process since no CD-induced dissociation of the bidentate ligand from the Rh/sulfoxantphos complex occurred under hydroformylation conditions in the presence of cyclodextrin derivatives. Furthermore, the results obtained in this study suggest that, concurrently to the constraint generated by the bulky sulfoxantphos ligand, the additional steric stress of the cyclodextrin cavity on the substrate compels the latter to react preferentially by its terminal carbon. Indeed, the effect is more pronounced if the size of the cavity of the cyclodextrin is small. Reduced available space around the metal results in a more selective approach of the substrate and therefore a higher selectivity for the normal aldehyde. Thus, the conjugated effects of the sulfoxantphos and the cyclodextrin/substrate complex on the bulkiness around the rhodium led to remarkable performances in terms of chemoselectivity and regioselectivity.

Experimental Section

General Methods. The ^{1}H and ^{31}P NMR spectra were recorded at 300.13 and 121.49 MHz on a Bruker Avance DRX spectrometer, respectively. ^{1}H and ^{31}P{^{1}H} chemical shifts are given in ppm relative to external references: sodium [D$_4$]3-(trimethylsilyl)propionate (98% atom D) in D$_2$O for ^{1}H NMR and H$_3$PO$_4$ in H$_2$O for ^{31}P{^{1}H} NMR. ^{1}H and ^{31}P{^{1}H} high-pressure NMR spectra were recorded on a Bruker DRX300 spectrometer. The 2D T-ROESY experiments were run using the software supplied by Bruker. T-ROESY experiments were preferred to classical ROESY experiments, as this sequence provides reliable dipolar cross-peaks with a minimal contribution of scalar transfer. Mixing times for T-ROESY experiments were set at 300 ms. The data matrix for the T-ROESY was made of 512 free induction decays, 1K points each, resulting from the co-addition of 32 scans. The real resolution was 1.5−6.0 Hz/point in F2 and F1 dimension, respectively. They were transformed in the non phase-sensitive mode after QSINE window processing. Gas chromatographic analyses were carried out on a Shimadzu GC-17A gas chromatograph equipped with a methyl silicone capillary column (25 m × 0.25 mm) and a flame ionization detector (GC:FID).

Materials. D$_2$O (99.95% isotopic purity) was obtained from Merck. Dicarbonylacetylacetonato rhodium(I) and organic compounds (undecane, 1-octene, 1-decene) were purchased from Strem Chemicals and Aldrich Chemicals in their highest purity and used without further purification. Randomly methylated *β*-cyclodextrin (RAME-*β*-CD) was purchased from Aldrich Chemicals. Randomly methylated α-cyclodextrin (RAME-α-CD) was prepared by adapting a procedure reported by Y. Kenichi et al.[13] These two cyclodextrins were partially methylated. Methylation occurred at position 2, 3, or 6 and 1.8 OH groups per glucopyranose unit were statistically modified. The disodium salt of 2,7-bisulfonate-4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (sulfoxantphos) was synthesized as previously reported.[14] Carbon monoxide/hydrogen mixtures (1:1) were used directly from cylinders (>99.9% pure; Air Liquide). Distilled deionized water was used in all experiments. All solvents and liquid reagents were degassed by bubbling nitrogen for 15 min before each use or by two freeze−pump−thaw cycles before use.

Continuous Variation Plot (Job's Plot). The NMR measurements for the Job's plot were taken on 11 samples. For each sample, the sum of *β*-cyclodextrin derivatives and sulfoxantphos concentrations was equal to 5 mM. This was obtained by appropriate additions into the corresponding 5 mm NMR tubes of increasing amounts of sulfoxantphos and decreasing amounts of cyclodextrin.

Calculation of Association Constants by NMR Spectroscopy. The phosphorus atom was chosen for evaluating the association constant. Assuming a 1:1 inclusion mechanism, the observed chemical shift of the phosphorus atom (δ_{OBS}) and the complex concentration [COMP] are described as follows:

$$\delta_{OBS} = (\delta_{Phos.}[\text{Phos.}] + \delta_{COMP}[\text{COMP}])/[\text{Phos.}]_T \quad (1)$$

$$[\text{COMP}] = -1/2[(1/K + [\text{CD}]_T + [\text{Phos.}]_T)^2 - 4[\text{CD}]_T[\text{Phos.}]_T]^{1/2} + 1/2(1/K + [\text{CD}]_T + [\text{Phos.}]_T) \quad (2)$$

where K and $[\ ]_T$ stand for association constant and total, respectively. For a given value of K, [COMP] is known and

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δ_{COMP} may be calculated from eq 1 for each $[CD]_T$. Standard deviation over δ_{COMP} is minimized relative to K to obtain the 1:1 association constant.[15]

High-Pressure NMR Experiments. In a typical experiment, the $Rh(acac)(CO)_2$ (0.104 mmol), sulfoxantphos (0.116 mmol), and cyclodextrin derivatives (0.126 mmol) were dissolved in 2.0 mL of degassed D_2O under nitrogen. The solution was placed into a high-pressure sapphire tube (ϕ = 10 mm) equipped with a titanium head. After the mixture had been pressurized with a 1:1 mixture of CO/H_2 to 16 bar NMR spectra were recorded at different temperatures (20, 42, 48, 55, and 80 °C).

Catalytic Experiments. All catalytic reactions were performed under nitrogen using standard Schlenk techniques. In a typical experiment, $Rh(acac)(CO)_2$ (0.04 mmol), sulfoxantphos (0.21 mmol), and the cyclodextrin (0.48 mmol) were dissolved in 11.5 mL of water. The resulting aqueous phase and an organic phase composed of olefin (20.35 mmol) and undecane (2.03 mmol, GC internal standard) were charged under an atmosphere of N_2 into the 50 mL reactor, which was heated at 120 °C. Mechanical stirring equipped with a multipaddle unit was then started (1500 rpm), and the autoclave was pressurized with 50 atm of CO/H_2 (1:1) from a gas reservoir connected to the reactor through a high-pressure regulator valve allowing to keep constant the pressure in the reactor throughout the whole reaction. The reaction medium was sampled during the reaction for GC analyses of the organic phase after decantation. For kinetic measurements the time corresponding to the addition of CO/H_2 was considered as the beginning of the reaction.

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