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Chiral Calix[4]arene-Based Diphosphites as Ligands in the Asymmetric Hydrogenation of Prochiral Olefins

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Chiral calixarene-based diphosphite ligands **3a**–**d** have been obtained via lower-rim functionalisation of the *p*-*tert*-butylcalix[4]arene core. High enantiomeric excesses (up to 94 %) and good activities were obtained in the rhodium-catalyzed asymmetric hydrogenation of prochiral olefins with TADDOL-containing diphosphites **3c**,**d**. This is the first example of chiral calix[4]arene-modified ligands that induce high enantioselectivity in metal-catalysed asymmetric reactions.

Introduction

Asymmetric reactions catalysed by transition metals are among the most efficient methods for preparing a wide range of enantiomerically pure compounds.[1] The tremendous achievements in organometallic chemistry have resulted in fundamental understanding of elementary steps and consequently in many examples of rational ligand design.[2] Still, the rates and selectivity of enzymatic catalysis are seldom equalled by transition metal catalysis. Chemical transformations catalyzed by enzymes often operate via complicated mechanisms and require large and sophisticated protein structures that have been obtained after millions of years of evolution. Although nowadays enzymes are applied successfully in many chemical conversions, their substrate specificity can be too high in certain cases and the biological reaction conditions might be not wanted. This is why the majority of industrial processes is based on man-made catalysts. Many attempts are being made to obtain efficient catalysts that can compete with enzymes in substrate-selectivity and activity, such as incorporation of transition metal complexes in proteins and antibodies.[3] To bridge the gap between enzyme and transition metal catalysts it is important to develop new catalyst systems that, mimicking enzymes, impose steric confinement on metal and substrates in addition to the well-explored ligand effects.

Calixarenes form a suitable scaffold for the development of new bulky and structurally well-defined ligands.[4] The combination of calixarene cavities with catalytic centres might lead to shape-selective catalysts, adding this successfully exploited feature of biological systems to transition metal catalysis. Although the number of successful applications of the shape selectivity of calixarene-based catalysts is growing,[5] high selectivities in asymmetric catalysis have not been achieved so far.[6]

From the different functionalities that one can consider, phosphite ligands proved their adequacy in many transition metal-catalysed reactions such as hydrogenation, hydroformylation, hydrocyanation and allylic alkylation.[2]

Results and Discussion

Here we report on the asymmetric hydrogenation of prochiral olefins, as model reaction, using enantiopure calix[4],BINOL- and calix[4],TADDOL-containing diphosphites. The effective formation of a shape defined active site is achieved by directly attaching three of the hydroxy groups of the calix[4]arene through μ_3-bridging phosphorus atom. In this way, these new C1-symmetric bidentate ligands, which combine the intrinsic steric bulk of the calix[4]arene scaffold with a stereocentre located on a phosphite pendent arm linked to the lower rim of the calix[4]-cavity, represent the first class of chiral calix[4]arene-modified ligands to be reported in literature and successfully applied in metal-catalysed asymmetric reactions. In order to gain information about the potential of such type of ligands, we carried out some preliminary investigations on two different types of

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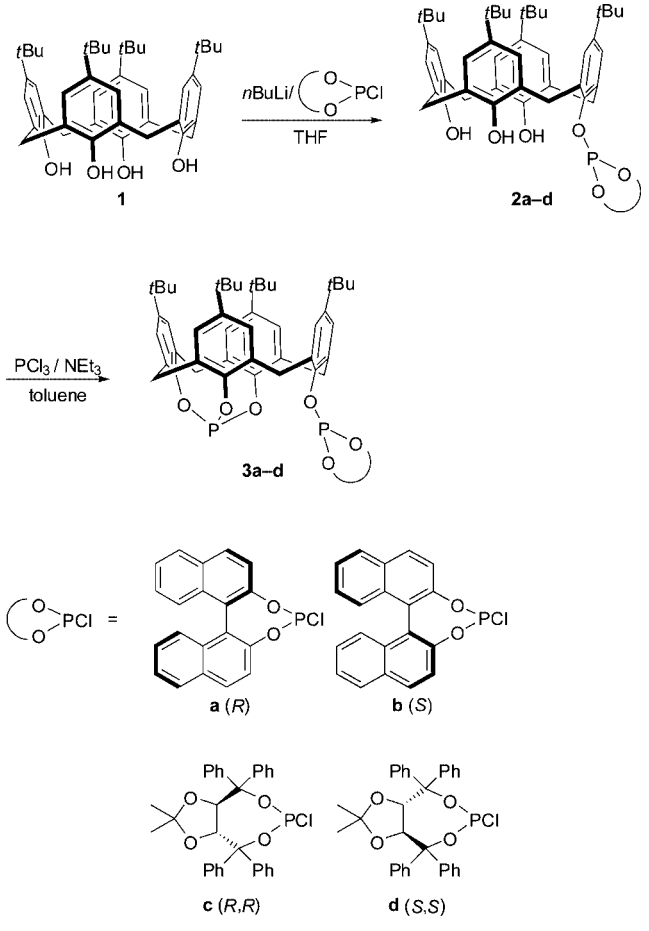
chiral moieties and by comparing the role of the stereocentre, we evaluated the efficacy of the ligand systems and their catalytic performances.

Chiral diphosphite ligands **3a**–**d** were prepared through a two-step synthesis according to reported calixarenes-phosphorylation procedures (Scheme 1).[5g] Since the sequence in which the two steps are followed is crucial in order to obtain diphosphites in the appropriate *cone* conformation,[5d,7] *p*-*tert*-butylcalix[4]arene **1** was firstly treated with one equivalent of *n*BuLi in THF at room temperature and then reacted with one equivalent of chiral phosphorochloridites (**a**–**d**),[8,9] affording the monofunctionalised calix[4]arene intermediates **2a**–**d**. In the present study, we focused our attention on chiral units derived from commercially available diols such as (*R*)- and (*S*)-BINOL [(*R*)-, (*S*)-2,2′-dihydroxy-1,1′-binaphthyl] and (*R*,*R*)- and (*S*,*S*)-TADDOL [(*R*,*R*)-, (*S*,*S*)-2,2-dimethyl-α,α,α′,α′-tetraphenyldioxolane-4,5-dimethanol] which allow an economically attractive preparative method of bidentate ligands and a fast and efficient preliminary investigation of the catalytic performances of the corresponding metal complexes.



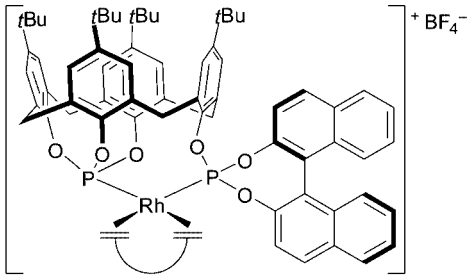
Scheme 1. Synthesis of chiral calix[4]arene-based diphosphites **3a**–**d**.

The first reaction step is not very selective towards monofunctionalisation and gives rise to the formation of by-products, like 1,3-disubstituted calix[4]arenes. We observed that the steric bulk of the phosphorochloridites strongly affects the product distribution. As expected, the more sterically hindered fragments (i.e. TADDOL-PCl **c**,**d**) afford mainly monofunctionalised products, while with the bare BINOL derivatives **a**,**b** the two fractions are obtained in a 1:1 ratio. Nevertheless, no further purification was carried out on the isolated crude products, which were treated in the second step with an excess of PCl_3/NEt_3 to give, after chromatographic separation, the pure chiral diphosphite products **3a**–**d**. Thus, the resulting calix[4],BINOL- (**3a**,**b**) and calix[4],TADDOL-based diphosphites **3c**,**d** are characterised by the presence of one phosphorus atom, acting as a triple μ_3-*O*,*O*,*O* bridge, at the lower rim of the calix[4]-cavity and a second phosphorus atom on a pendent chiral unit.

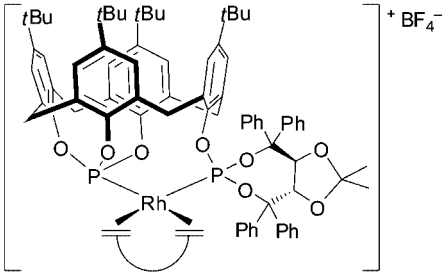
The ^{31}P NMR spectra show in all cases two distinctive singlets for the two non-equivalent phosphite moieties of each ligand: one at δ = 104 ppm for the μ_3-bridging phosphorus atom and one for the chiral fragment-containing phosphite (δ = 147 ppm for BINOL derivatives **3a**,**b**; δ = 140 ppm for TADDOL derivatives **3c**,**d** respectively). Both chemical shifts fall into the expected ranges for calix[4]-based μ_3-bridging phosphites,[5d,5g] and for TADDOL- or BINOL-based phosphite ligands.[10] Also in the corresponding ^1H NMR spectra, ligands **3a**–**d** show similar spectroscopic features. The four *tert*-butyl signals and the four AB patterns for the bridging methylene units (ArCH_2Ar), with AB separations larger than 1 ppm, clearly prove the C_1 symmetry of these structures and the overall *cone* conformation of the calix[4]arene backbone This geometry was further confirmed by the ^{13}C NMR spectra in which some of the signals for the ArCH_2Ar fall into the expected range for *syn*-oriented phenolic neighbours (ca. 35–36 ppm), while others fall in an intermediate range of values (ca. 36–37 ppm).[5g,11] It should be recalled that, due to the strain imposed by the very short μ_3-bridging phosphite unit, the observation of signals with an intermediate chemical shift might be interpreted in terms of partial flattening of the calixarene core.

Investigations have been carried out to define the coordination chemistry of diphosphites **3a**,**d** and assess their chelating abilities towards square planar Rh^I precursors. The complexation reaction of ligands **3a**,**c** with one equivalent of $[Rh(nbd)_2BF_4]$ (nbd = 2,5-norbornadiene) in dichloromethane solution proceeds rapidly. Displacement of one molecule of 2,5-norbornadiene occurs after 30 minutes at room temperature whilst stirring, affording complexes $[Rh(nbd)(P^1 \cap P^2)][BF_4]$ (**4a**,**c**). The corresponding ^{31}P NMR spectra showed two distinctive double doublets as a result of phosphorus–rhodium and phosphorus–phosphorus couplings [$^1J(Rh,P^1)$ = 274 Hz, $^1J(Rh,P^2)$ = 265 Hz and $^2J(P^1,P^2)$ = 83 Hz (**4a**); $^1J(Rh,P^1)$ = 265 Hz, $^1J(Rh,P^2)$ = 249 Hz and $^2J(P^1,P^2)$ = 81 (**4c**)].

The observed rhodium–phosphorus coupling constants are very similar to those reported for $[Rh(diolefin)(P^1 \cap P^2)]^+$ rhodium complexes with coordinated diphosphite ligands, while the coupling constants between the two non-equivalent phosphorus atoms are larger than expected.[12] Coupling constants between 27 and 50 Hz are generally observed



4a



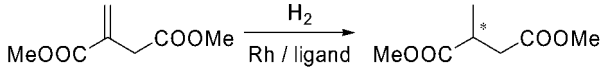
4c

between the two non-equivalent phosphorus atoms in relative *cis* positions. Lowering the temperature to 193 K did not result in any additional splitting of the ^{31}P NMR signals, which indicates that, for both rhodium complexes **4a**,**c**, only one isomer is present in solution. Clearly, this might represent an advantage in terms of enantioselectivity when these complexes are employed as catalysts in asymmetric transformations.

Chiral diphosphites **3a**–**d** were tested as ligands in the asymmetric rhodium-catalysed hydrogenation and of prochiral olefins using $[Rh(nbd)_2BF_4]$ as metal precursor. Catalytic experiments were run in a parallel manner using an autoclave equipped with 5, 8, or 15 mini-reactors (see Supporting Information for details). The catalyst precursors were formed in situ by mixing metal complexes with ligands **3a**–**d** under inert atmosphere. The autoclave was purged four times with hydrogen and then charged with the appropriate gas pressure.

The rhodium-catalysed hydrogenation, carried out under mild conditions (25 °C, 5 bar H_2), was examined as model reaction employing dimethyl itaconate (**A**) and α-(acylamino)acrylate (**B**) as representative substrates. Parallel experiments were run employing a standard substrate/rhodium ratio of 100 and using catalyst precursors formed in situ by mixing ligands **3a**,**c** with $[Rh(nbd)_2BF_4]$. The formation of the active species $[Rh(P^1 \cap P^2)(solvent)_2][BF_4]$, generated by removal of the diolefin, is generally faster when it involves the hydrogenation of the more reactive norbornadiene rather than that of cyclooctadiene.[13] Different outcomes have been observed, regarding both the activity and the selectivity of the catalytic process, depending on the nature of the substrate and of the diphosphite used.

The hydrogenation of dimethyl itaconate providing dimethyl methylsuccinate [**A**; Equation (1)], in dichloromethane, was chosen as the test reaction and the activity and the enantioselectivity of the catalyst precursors evaluated at different reaction conditions (Table 1). Initially the ligand to rhodium ratio was kept constant at 1.5 (entries 1 and 6), then the reaction time and the substrate/rhodium ratios were changed from 20 h to 4 h (entries 2 and 7) and from 100 to 1000 (entries 3 and 8), respectively.



A (1)

Table 1. Asymmetric hydrogenation of prochiral olefins with $[Rh(nbd)_2BF_4]$ and ligands **3a**–**d**.[a]

Entry	Ligand	Substrate	% Conv. (*t* [h])[b]	% *ee* (config.)[c]
1	**3a**	**A**	100 (20)	74 (*R*)
2	**3a**	**A**	100 (4)	74 (*R*)
3[d]	**3a**	**A**	100 (4)	76 (*R*)
4[e]	**3a**	**A**	60 (20)	20 (*S*)
5	**3a**	**B**	100 (20)	32 (*R*)
6	**3c**	**A**	100 (20)	92 (*R*)
7	**3c**	**A**	100 (4)	92 (*R*)
8[d]	**3c**	**A**	100 (4)	94 (*R*)
9[f]	**3c**	**A**	100 (20)	92 (*R*)
10	**3c**	**B**	100 (20)	94 (*R*)
11	**3b**	**A**	100 (20)	75 (*S*)
12	**3d**	**A**	100 (20)	92 (*S*)

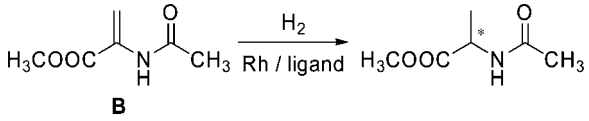
[a] Standard conditions: [Rh] = 1 mM; [ligand]/[Rh] = 1.5; [substrate]/[Rh] = 100; solvent = CH_2Cl_2 (2.0 mL); p = 5 bar; T = 25 °C; catalyst precursors prepared in situ. [b] Percent conversion measured by GC. [c] Percent enantiomeric excess measured by chiral GC. [d] [substrate]/[Rh] = 1000. [e] Solvent: CH_2Cl_2/toluene, 1:3. [f] [ligand]/[Rh] = 5.

The results summarised in Table 1 show that the catalytic systems obtained with diphosphites **3a**,**c** are very active in the hydrogenation of dimethyl itaconate (**A**) and, although a standard reaction time of 20 h was chosen, complete conversion was already reached after 4 h. The increase of the ligand to rhodium ratio or the substrate to rhodium ratio does not have a negative effect on the activity of the reported catalytic systems, which still afford high enantioselectivities (*ee* up to 94%) and full conversions after 4 h reaction time. In one case (entry 4) the solvent of the reaction was changed to a mixture of dichloromethane/toluene (1:3) showing that the efficiency of the process depends strongly on the nature of solvent employed, and that the catalyst performance, both in terms of activity and enantioselectivity, was best when pure dichloromethane was used. Interestingly, opposite stereoinduction was observed in this case. It should be noted that rhodium-catalysed asymmetric hydrogenation reactions are commonly performed in methanol, but since phosphite ligands are known to decompose in protic solvents,[14] further hydrogenation reactions were studied using dichloromethane.

Ligand **3c**, which contains the bulky TADDOL moiety, affords the best catalyst, reaching enantioselectivities around 92% in all experiments. The results obtained with

ligand **3a** follow the same trend as observed for ligand **3c**, but the enantioselectivities are somewhat lower. As it would be expected by less bulky ligands, the asymmetric inductions with precursors containing ligand **3a** are lower than those with ligand **3c**. Besides ligands **3a**,**c**, which were used extensively in these catalytic investigations, their enantiomers, namely ligands **3b**,**d**, were also employed in analogous hydrogenation experiments showing, as expected, identical results but with opposite stereoinduction (entries 11,12).

We also studied the hydrogenation of α-(acylamino)acrylates [Equation (2)] under standard reaction conditions. Hydrogenation of methyl α-acetamidoacrylate [**B**; Equation (2)] giving the alanine derivative afforded high enantioselectivity (*ee* = 94%) with ligand **3c**, while a low value of 32% was obtained with ligand **3a**. In both cases complete conversion was reached after 20 h reaction time (entries 5,10).



(2)

In general, the catalytic systems obtained with calix[4]-arene-based diphosphites **3a**–**d** were found to be comparable, in terms of performances, to the diphosphites previously reported in literature by Reetz et al. and by Claver et al., leading to excellent activities and high enantioselectivities in the hydrogenation of dimethyl itaconate and methyl α-acetamidoacrylate.[10a,12,15]

Conclusions

We have synthesized novel chiral diphosphite ligands built up on calix[4]arene backbones and characterised by a C_1 symmetry. We employed these ligands in the rhodium-catalysed hydrogenation of prochiral olefins, reaching excellent activities and enantioselectivities in the hydrogenation of dimethyl itaconate and methyl α-acetamidoacrylate. The best enantioselectivities have been obtained for both substrates with the same, most bulky, ligand. These preliminary investigations demonstrated for the first time that calix[4]-arene-based C_1-symmetric diphosphites can be successfully applied in metal-catalysed asymmetric transformations. Due to their ease of preparation, different classes of chiral bidentates can be generated, for example, by systematic variation of the steric and electronic properties of the stereocentre linked to the lower rim of the calix[4]-cavity. Thus, the results reported herein have to be considered as an important starting point and further study of this promising type of ligands in homogeneous catalysis is in progress.

Experimental Section

Experimental details for all compounds and procedures are given in the Supporting Information.

Supporting Information (see also the footnote on the first page of this article): Catalyst preparation, synthetic and catalytic procedures.

Acknowledgments

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