Highly effective and recyclable dendritic BINAP ligands for asymmetric hydrogenation†

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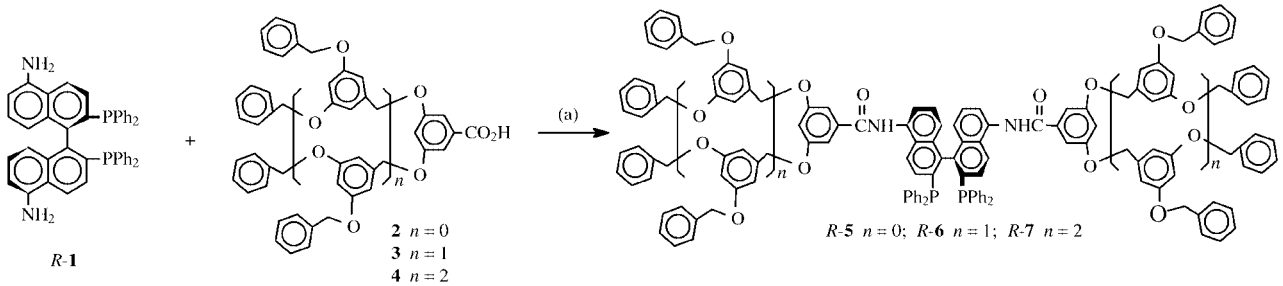
A series of dendritic BINAP ligands have been synthesised and their ruthenium complexes used as catalysts in asymmetric hydrogenation.

In recent years, the attachment of homogeneous catalysts to soluble polymer supports has been attracting considerable attention owing to its potential combination of the advantages, and minimization of the disadvantages, of homogeneous and heterogeneous catalysis.[1–3] Unlike traditional cross-linked polymer-supported catalysts in which the structure is usually not clear, soluble polymer-supported catalysts also offer opportunities for the study of polymer–catalyst interactions to fine-tune both catalytic activity and stereoselectivity through systematically adjusting the microstructure of the catalytic sites in the polymer supports. Recently, we have developed a soluble chiral polyester-supported Ru(BINAP) catalyst which offered a higher rate of reaction than the corresponding monomeric homogeneous catalyst while retaining high stereoselectivity.[4] Most recently, dendritic organometallic catalysts have become a very active field of research.[5–7] The dendrimer architecture might offer a means of better controlling the disposition of the catalytic species in soluble polymer-based catalysts. Such novel catalysts are well defined and highly branched three-dimensional macromolecules on the nano-scale size, which may aid the recycling of catalysts simply by supra-filtration or solvent precipitation methods.‡ For asymmetric catalysis, chiral dendrimers are required, however, so far, very few dendritic chiral catalysts have been described.[8–14] Two general strategies for the construction of chiral dendritic catalysts can be applied: multiple chiral metal complexes employed at the periphery of the dendrimer, or chiral metal complexes incorporated in the core of the dendrimer. For the second strategy the space-filling nature of the dendritic wedges near the metal center would alter the structure of the metal complex, and thus possibly influence the reactivity of the catalyst and/or the substrate selectivity of the catalytic reaction with increasing generations. This kind of dendritic catalyst has been thus termed 'dendrizyme'.[6] For chiral diphosphine-containing catalysts, such as Ru(BINAP), chiral information is transferred from the ligand to the catalytically active center *via* the arrangement of the four phenyl rings of the diphenylphosphino groups.[15] Therefore, upon incorporation of a chiral diphosphine-containing catalyst into the core of a dendrimer, the chiral information might be enhanced by the steric bulk of the dendritic wedges and forced towards the pocket of the catalyst, in which the enantioselective reaction takes place.

Here, we report the first use of chiral diphosphine ligands bearing dendritic wedges for asymmetric hydrogenation.[16] BINAP was chosen as a model ligand for this study, since it is probably the most versatile and effective ligand among all the chiral phosphine ligands which have been studied for asymmetric catalysis.[15] Both rhodium and ruthenium BINAP complexes have been extensively studied and several commercial processes based on these catalysts have been developed.[17] BINAP itself cannot be easily attached to a dendrimer so (*R*)-5,5′-diamino-BINAP (*R*-**1**) was synthesized according to the literature.[18] A polyether dendrimer was chosen owing to its inertness to catalytic reaction. Polyether dendritic wedges **2**–**4** with carboxyl groups located at the focal point were synthesised by the convergent-growth approach introduced by Hawker and Fréchet.[19] The chiral dendritic BINAP ligands **5**–**7** were synthesised in > 85% yield by condensation of the wedges **2**–**4** with *R*-**1** in the presence of triphenylphosphite, pyridine and calcium chloride in *N*-methyl-2-pyrrolidone (NMP) at 100 °C (Scheme 1). These ligands were purified by fast column chromatography and characterized by ^{1}H and ^{31}P NMR spectroscopy, MALDI-TOF mass spectrometry and elemental analysis. All results are in full agreement for the proposed structures.

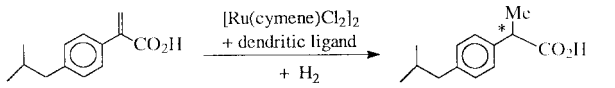
Asymmetric hydrogenation of 2-[*p*-(2-methylpropyl)phenyl]acrylic acid **8** was used as the model reaction for the investigation of the catalytic activity and enantioselectivity of these dendritic Ru(BINAP) catalysts. *In situ* catalyst preparation was attained by mixing a dendritic BINAP ligand with $[Ru(cymene)Cl_2]_2$ in methanol–toluene (1 : 1, v/v) and stirring for *ca.* 40 min at 50 °C. Various generations (**5**–**7**) of these dendritic Ru(BINAP) catalysts were tested, and complete conversions of **8** were obtained with high enantioselectivities in 24 h with preliminary results summarised in Table 1. For

† Electronic supplementary information (ESI) available: (A) characterisation of dendritic ligands and *in situ* catalysts; (B) time-dependent conversion of **8** catalysed by dendritic catalysts. See http://www.rsc.org/suppdata/cc/b0/b001503m/



Scheme 1 Synthesis of BINAP ligands with polyether dendritic wedges. *Reagents and conditions:* (a) NMP, $CaCl_2$, $P(OPh_3)$, pyridine, 100 °C, 2 h.

Table 1 Activity and enantioselectivity in the asymmetric hydrogenation of **8** catalyzed by dendritic Ru(BINAP) complexes[a]



8 ibuprofen

Entry	Ligand	*t*/h	Conv.[b] (%)	TOF[c]/ h^{-1}	Ee[d] (%)	Abs. config.[e]
1	(*S*)-BINAP	2	10.2	6.3	89.8	(*S*)
2	**5**	2	10.4	6.5	91.8	(*R*)
3	**6**	2	13.2	8.3	92.6	(*R*)
4	**7**	2	34.3	21.4	91.6	(*R*)
5	**7**	5	69.3	17.3	91.6	(*R*)
6	**7** (cycle 1)[f]	5	67.3	16.8	91.4	(*R*)
7	**7** (cycle 2)[f]	5	68.9	17.2	91.8	(*R*)
8	**7** (cycle 3)[f]	5	66.6	16.6	90.9	(*R*)

[a] Hydrogenations were carried out using a 0.06 M solution of **8** in methanol–toluene (1:1, v/v) as solvent under the following reaction conditions: *in situ* catalyst = $[Ru(cymene)Cl_2]_2$ + dendritic ligand or (*S*-BINAP); substrate/catalyst = 125 (mol/mol); NEt_3/substrate = 3:2 (mol/mol); H_2 = 80 atm, room temperature. [b] Based on GC analysis and ^1H NMR; all catalytic reactions reached 100% conversion in 24 h. [c] Average TOFs calculated over the quoted reaction time. [d] Ee values at 100% conversion of **8** were determined by GC with a Chrompack Chirasil-dex column (25 m × 0.25 mm). [e] Determined by comparison of optical rotations with literature values. [f] Recovered catalyst used.

example, with 0.8 mol% Ru(*R*-**6**) catalyst, hydrogenated product (ibuprofen) was obtained with 92.6% ee and 100% conversion in 20 h. Confirming the worth of designing Ru(BINAP) catalysts with dendritic wedges, all of the dendritic catalysts performed better compared to the parent BINAP complex. These catalysts showed higher ee values than Ru(BINAP), although the highest-generation catalyst Ru(*R*-**7**) gave slightly lower enantioselectivity (Table 1, entries 1–4).§ Most interestingly, the size of the dendritic wedges influenced the reactivity of these catalysts. Unlike common dendritic catalysts,[7a] the rate of the reaction increased using higher generation catalysts. This effect is most pronounced when going from generation 1 to 2 (Table 1, entries 2–4). The profound size effect is probably due to the steric bulk of the dendritic wedges which affects the dihedral angle of the two naphthalene rings in the Ru(BINAP) complex, and thus leads to a faster rate and/or better enantioselectivity of reaction. Similar acceleration effects have been observed in the asymmetric hydrogenation of unsaturated carboxylic acids catalyzed by Ru(II) catalysts containing polyester-supported BINAP,[4] H_8-BINAP[20] or a bis-steroidal phosphine,[21] which possess a larger steric bulk than BINAP itself.

The large molecular size and different solubilities of the dendritic Ru(BINAP) catalysts in various solvents provided a convenient and reliable method for the separation and reuse of the catalysts. For example, upon completion of the reaction, methanol was added to the reaction mixture and the catalyst Ru(*R*-**7**) was quantitatively precipitated and recovered *via* filtration. The recovered catalyst was reused for at least three cycles with the same activity and enantioselectivity (Table 1, entries 5–8).

In summary, we have demonstrated the importance of the dendritic wedges on the catalytic activity and enantioselectivity of dendritic Ru(BINAP) complexes. This study opens up a new frontier for the development of highly effective and easily separable chiral catalysts. Current work is aiming at a detailed insight of the nature of the dendritic effect and the exploration of these catalysts in other reactions.

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Notes and references

‡ Supra-filtration or solvent precipitation methods are suitable procedures for small scale high-value processes, but are not viable options for larger scale lower cost processes.

§ In three-times repeated experiments, the catalysts showed very similar ee values [experimental error (on a computer-controlled VISTA 6000 gas chromatograph) is ≤ ±0.5%]. Further demonstration of the 'dendrimer effect' on enantioselectivity is under way in our laboratory, by using higher generation dendritic BINAP ligands and exploring the catalysts in other reactions in which Ru(BINAP)-type catalysts are less effective.

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