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Dendritic phosphoramidite ligands in Rh-catalysed asymmetric hydrogenations

Peter N. M. Botman,[a] Alessia Amore,[a] Rieko van Heerbeek,[a] Jaap Willem Back,[b] Henk Hiemstra,[a] Joost N. H. Reek[a,*] and Jan H. van Maarseveen[a,*]

[a]*Van 't Hoff Institute of Molecular Sciences, University of Amsterdam, Nieuwe Achtergracht 129, 1018 WS Amsterdam, The Netherlands*
[b]*Swammerdam Institute for Life Sciences, Mass Spectrometry Group, University of Amsterdam, Nieuwe Achtergracht 166, 1018 WV Amsterdam, The Netherlands*

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Abstract—The axially chiral BICOL backbone was functionalised with two third generation carbosilane dendritic wedges and further elaborated to a phosphoramidite ligand. High enantioselectivities were obtained when these monodentate ligands were applied in the rhodium-catalysed asymmetric hydrogenation of methyl 2-acetamidocinnamate.

Over the last few years, the field of asymmetric hydrogenation of prochiral olefins has witnessed a remarkable change of opinion. Ever since the introduction of the diphosphine DIOP by Dang and Kagan,[1a] the use of enantiopure bidentate ligands seemed to be a necessity for obtaining excellent enantioselectivities. Some famous examples are DIPAMP,[1b] BINAP[1c] and DuPHOS,[1d] which all contributed to the outstanding level the field has reached nowadays.[2] Pioneering studies from the groups of Pringle,[3a] Reetz[3b] and Feringa[3c] and more recently Chan[3d] and Zhou[3e] showed that chiral monodentate phosphonite, phosphoramidite or phosphate ligands also yield highly active and selective rhodium catalysts for the hydrogenation of a variety of alkenes, giving comparable or sometimes better results than obtained with bidentate ligands. Interestingly, most monodentate ligands use C_2-symmetric BINOL as the chiral element of the ligand. Unfortunately, this commercially available diol is not readily amenable for further functionalisation. Here, we present a new BICOL[4] (**1**) based chiral monodentate phosphoramidite ligand **3**. The nitrogens in the bicarbazole skeleton allow easy introduction of functional groups, which is clearly demonstrated by the synthesis of dendrimer functionalised ligands **5** and **6**, which are to the best of our knowledge, the first dendrimer supported phosphoramidite ligands.[5]

For the selective *N*,*N*-difunctionalisation of BICOL, the hydroxyl groups were first protected as *t*-butyldimethylsilyl ethers to give **2**. After methylation of the carbazole nitrogens of **2** and TBAF desilylation to liberate the diol, reaction with hexamethylphosphorous triamide (HMPT) yielded **3** in excellent yield (Scheme 1).

The introduction of two anchoring moieties for the dendritic wedges was carried out via *N*,*N*-dialkylation of **2** with $BrCH_2CO_2Me$ followed by saponification (Scheme 2). A standard peptide-coupling between the two carboxylic acid groups and the third generation carbosilane dendritic wedges equipped with a primary amine in the focal point (**4a**)[6] gave BICOL embedded in an apolar dendritic environment. Removal of the silyl-protecting groups followed by reaction with HMPT,[7] yielded dendrimer supported phosphorous amidite **5** in 78% yield over five steps. Ligand **5** was purified by flash chromatography and characterised by ^1H and ^{31}P NMR, MALDI-TOF and elemental analysis.[8]

The dendritic wedges could also be attached to **2** via a double alkylation of the carbazole nitrogens with iodide functionalised carbosilane wedges (**4b**),[6] using sodium

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* Corresponding authors. Tel.: +31-20-5255671; fax: +31-20-5255670; e-mail: jvm@science.uva.nl

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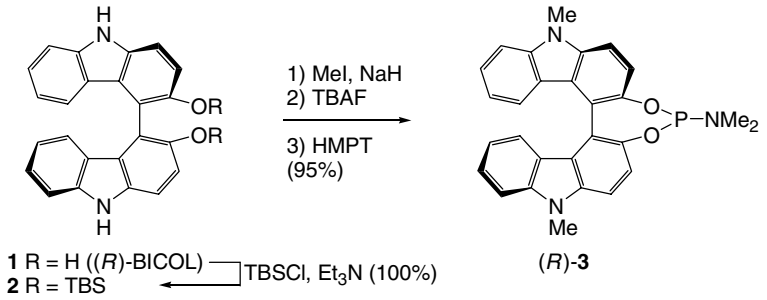
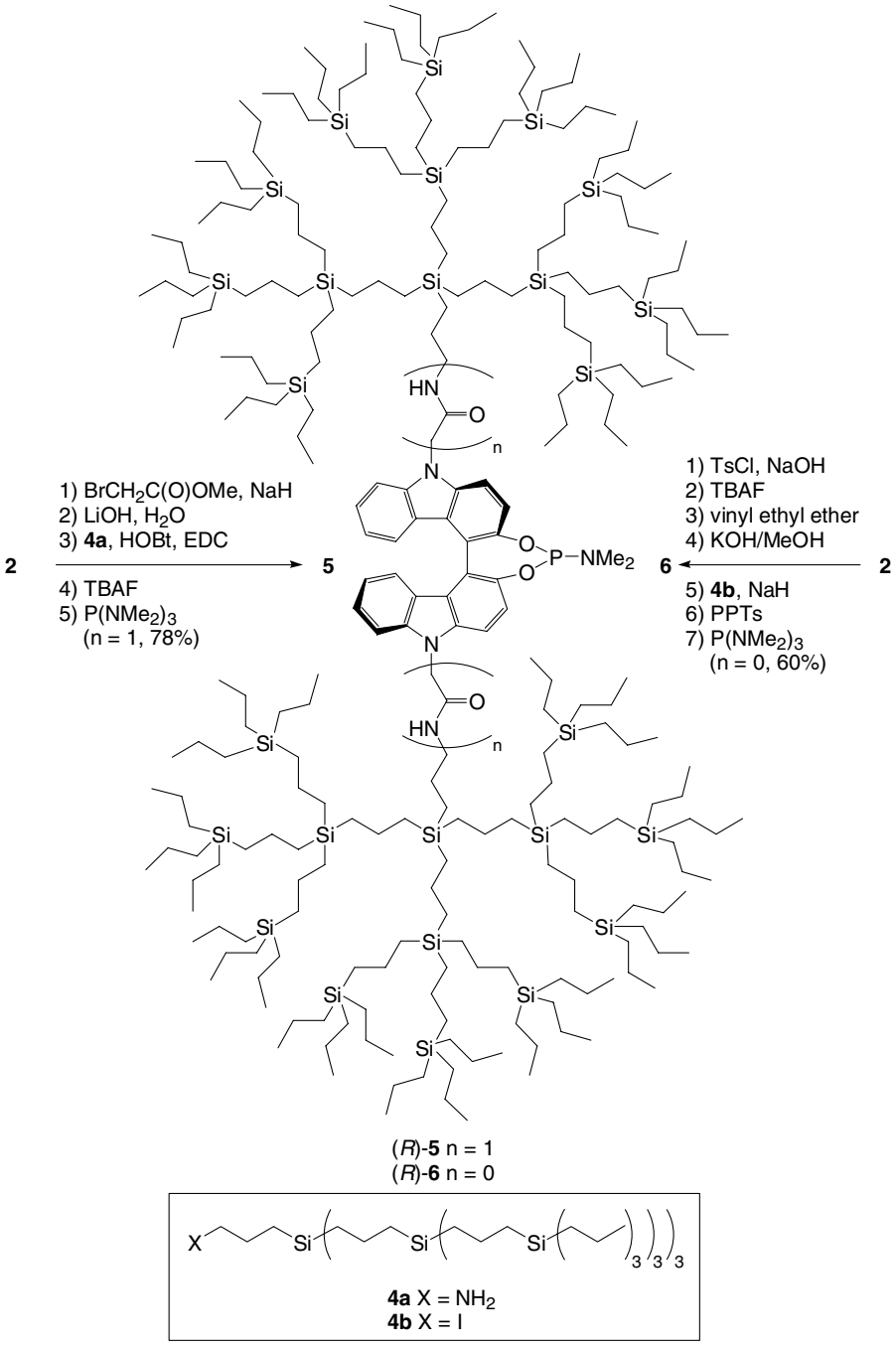
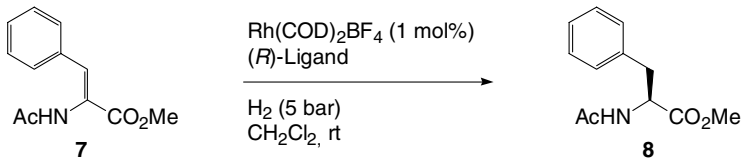


Scheme 1. Synthesis of phosphoramidite ligand **3** from (*R*)-BICOL.



Scheme 2. Synthesis of dendritic ligands.

Table 1. Asymmetric hydrogenation of methyl 2-acetamido cinnamate **7**



Entry	Ligand	Ratio L/Rh	*t* (h)	Conv. (%)[a]	Ee (%)[b]
1	MonoPhos[c]	2.2	2.0	100	95
2	MonoPhos[c]	3.0	2.0	0	—
3	**3**	2.2	2.5	100	93
4	**5**	2.2	2.5	100	95
5	**5**	3.2	2.5	100	95
6	**5**	4.2	2.5	~30	90

[a] Determined by ^{1}H NMR.
[b] Determined by chiral HPLC (Diacel OD, heptane–isopropanol = 9:1).
[c] Taken from Ref. 9.

hydride as a base at a reaction temperature of 120 °C for 72 h (Scheme 2). Since partial removal of the silyl-protecting groups was observed, the TBS groups were exchanged for more base-stable ethoxy ether (EE) groups. To prevent unwanted *N*-alkylation during the EE-protection step intermediate *N*-protection as a tosylate was required. After the dendritic wedges had been introduced, the diol was liberated with PPTs/EtOH, followed by subsequent introduction of the phosphoramidite moiety. Dendritic ligand **6** was synthesised in a seven step sequence starting from **2** in an overall yield of 60%, demonstrating the versatility of the carbazole nitrogens towards functionalisation of the BICOL backbone. Ligand **6** could be purified by flash chromatography and was fully characterised. However, we observed unexpectedly rapid decomposition of the phosphoramidite part of the molecule, making this ligand unsuitable for catalysis. The exact reason for the instability is not known, but we believe that the steric bulk of the two dendritic wedges forces the BICOL backbone to adopt a conformation that induces strain opening up the phosphoramidite moiety.

The rhodium-catalysed asymmetric hydrogenation of methyl 2-acetamidocinnamate **7** was used as the model reaction to study the catalytic behaviour of the new ligands **3** and **5** (Table 1). When a ligand to rhodium ratio of 2.2 was used, the enantioselectivity induced by the rhodium complex based on ligand **3** (entry 3) was 93% (at full conversion), which is comparable to the results obtained by Feringa and co-workers using BINOL derived monodentate phosphoramidite MonoPhos (entry 1).[3c,9] This shows the ability of the bicarbazole skeleton to induce high enantioselectivity. The catalytic behaviour of the dendritic analogue **5** was similar; in 2.5 h product **8** was obtained quantitatively with an enantiomeric excess of 95% (entry 4). This result shows that the BICOL derived phosphoramidite ligand can be immobilised without sacrificing activity and selectivity.[10]

Interestingly, when the dendrimer-encapsulated ligand **5** was used with ligand to rhodium ratios higher then three (entries 5 and 6), the catalytic system remained active, which is in contrast to the results obtained with MonoPhos (entry 2). Feringa and co-workers explained this lack of catalytic activity by the formation of inactive rhodium species with three or more ligands coordinated to the metal.[8] The formation of RhL_3 and RhL_4 complexes was observed during the hydrogenation of similar substrates with $[Rh(nbd)_2]BF_4$/MonoPhos (1:2). We believe that the steric dendritic bulk of ligand **5**, suppresses the formation of unwanted higher ligated rhodium species during the hydrogenations.

In conclusion, a novel enantiopure monodentate phosphoramidite ligand based on BICOL is presented. The straightforward synthesis of dendritic ligands **5** and **6** shows that the carbazole nitrogen is an excellent handle for the diversification of the BICOL backbone. The new BICOL based phosphoramidite ligands prove to be highly effective in the asymmetric hydrogenation of a dehydroamino acid. We are currently exploring the applications of dendritic ligand **5** in different catalytic asymmetric transformations.

Acknowledgements

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