Towards golf ball shaped reagents: dendrimer fixed concave pyridines

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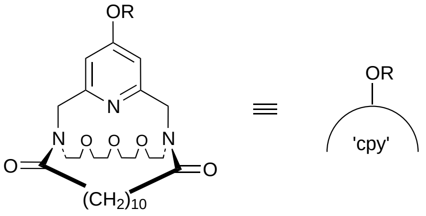
Two first generation dendrimers 5 and 7 carrying four and six concave pyridines on their surface have been synthesized by convergent synthesis; they have been applied as catalysts in selective acylations, and 7 can be separated from smaller molecules by nanofiltration.

According to the concept of concave reagents,[1] a variety of bimacrocyclic concave acids and bases such as pyridines **1**, 1,10-phenanthrolines, carboxylic acids, sulfinic acids and bridged calixarenes have been synthesized by incorporation of an appropriate functional group into a concave environment.[2] The concave reagents have been investigated in a variety of model reactions and increases in selectivity by the use of these reagents have been achieved. As the synthesis is rather tedious and the recovery of these concave reagents has not yet been solved satisfactorily, larger scale application has not been realized up to now. The recovery problem can be avoided by using polymeric reagents.



1a R = Me
b R = CH_2CH_2OH
c R = CH_2CH_2I
d R = CH_2CH_2–Merrifield polymer
e R = CH_2CH_2–poly(vinylbenzyl chloride)

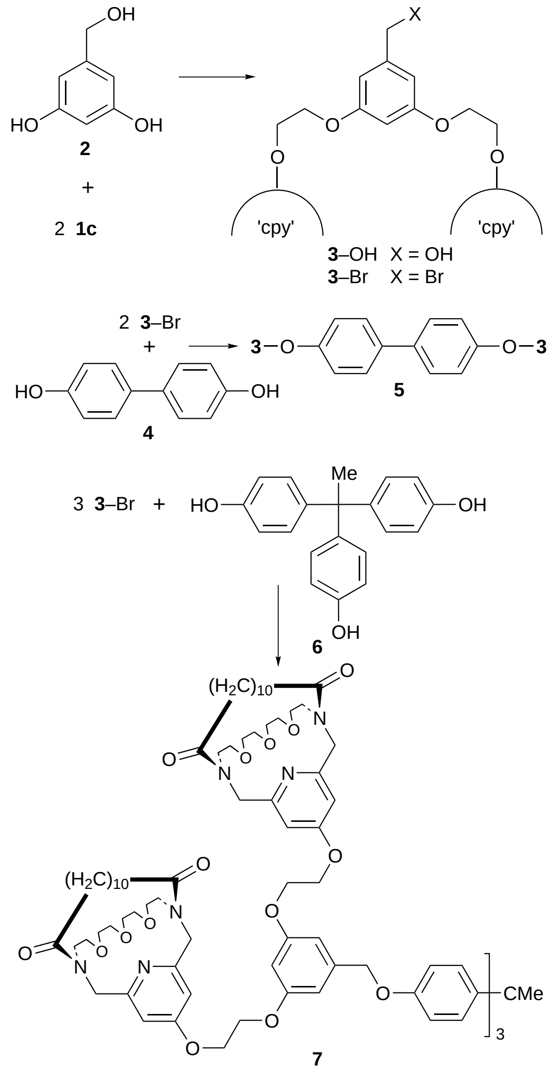
Here we describe the synthesis of the first generation of dendrimer fixed concave pyridines **1**. The fixation of a concave pyridine **1b** to a Merrifield polymer resin giving **1d** has been described.[3] Because of the insolubility of this functionalized resin, **1d** could only be used as a heterogeneous reagent or catalyst. Soluble polymers combine the advantages of common soluble reagents with attributes of solid phase reagents. Soluble polymers can be separated from the reaction products by ultrafiltration. In the case of linear polymers the problem of reptation through the semipermeable membrane must be overcome. It should be avoided by the use of soluble branched polymers.

These reflections consequently lead to dendrimer-fixed concave pyridines. Dendrimers are highly branched macromolecules with well-defined structures[4] which are rather easy to characterize because they possess a single molecular weight. We chose the poly(aryl alkyl ether) dendrimers developed by Frechet and Hawker[5] as the main frame, which are synthesized by a convergent route. The concave pyridine **1c** was fixed on the dendritic structure *via* its convex back side by a spacer.

In contrast to the polymers **1d** and **1e**, the fractional coverage of the dendrimers functionalized by concave pyridines (**5** and **7**) is 100% (83 wt%) [Merrifield polymer **1d**: 9% (20 wt%); linear soluble polymer **1e**: 29% (60 wt%)]. This guarantees the absence of other functional groups on the surface, and optimizes these fixed concave pyridines **5** and **7** for applications.[6]

The products **5** and **7**† were synthesised according to Scheme 1 and characterized by ^1H NMR spectroscopy. Because of the large number of aliphatic protons in the side chains of the concave pyridines, the important portion of the spectra is between 4.5–8.5 ppm and contains the absorbtions of the aromatic and benzylic protons. The ratio between the aromatic pyridine protons and the aromatic phenyl protons, as well as the ratio between the aromatic (6.5–7.5 ppm) and benzylic protons (4.5–5.4 ppm), was diagnostic. These results and the ^{13}C NMR spectra elucidated the structures of **5** and **7**.

The functionalized dendrimers **5** and **7** showed the same behaviour as the analogous unfixed concave pyridines **1a**, **1b** and **1c**. Three different amide conformers could be observed in the ^1H NMR spectra of **5** and **7**, in the same ratio as it had been observed in solutions of the unfixed concave pyridines **1a**, **1b** and **1c**.[8] Because the dendrimer-fixed concave pyridines **5** and



Scheme 1

Table 1 Selectivity increase in the base-catalysed acylation of primary, secondary and tertiary alcohols with diphenylketene[a]

	Selectivity		
Catalyst	EtOH	Pr^iOH	Bu^tOH
Pyridine	4.7	1	0
Lutidine	7.1	1	0
1a	12.0	1	0
1e	9.5	1	0
1d	7.4	1	0
5	11.6	1	0
7	11.4	1	0

[a] Conditions have been described previously (ref. 6).

7 showed the same conformer ratio, it might be expected that the selectivity increase in the model reaction would also be the same. This assumption was checked in the base catalysed acylation of primary, secondary and tertiary alcohols with diphenylketene in an intermolecular competition reaction.[6] As Table 1 shows, the selectivity increase was the same as found for the unfixed concave bases, such as **1a**, but better than the increase produced by the use of concave pyridines fixed on linear polymers **1e**, and much better than that produced by the use of concave pyridines fixed on the Merrifield polymer resin **1d**.

With **5** and **7**, the first two dendrimers loaded with concave reagents with molecular weights of 2557 (**5**) and 3863 (**7**), respectively, have been synthesized. Compound **7** is large enough to be filtered off by nanofiltration. Retention and permeation have been checked gravimetrically. It can be recovered in good yield (70–90%) from a CH_2Cl_2 solution using a nanofiltration membrane. Therefore dendrimer-fixed concave pyridines can be recycled from batch reaction mixtures by nanofiltration. For a continuous process, however, the retention needs to be optimized. This should be possible with higher generations of dendrimer-fixed concave pyridines. In these higher generations the coverage of the surface by concave reagents will increase, finally reaching an overall geometry which resembles a golf ball.

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Footnotes and References

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† *Synthesis:* The reaction of the concave pyridine **1c**[7] (2.1 equiv.) with 3,5-dihydroxybenzyl alcohol **2** (1 equiv.) in dry THF in the presence of K_2CO_3 (2.5 equiv.) and 18-crown-6 (0.4 equiv.) gave the first generation dendron **3**-OH as a colourless glassy solid with mp 105–108 °C in 76% yield. The conversion of the benzylic alcohol **3**-OH to the benzylic bromide **3**-Br succeeded with an excess of CBr_3 and PPh_3 in dry THF in 90% yield and gave a colourless glassy solid with mp 98–101 °C. This dendron **3**-Br (2.2 equiv.) reacted with the two-directional core **4** (1 equiv.) in the presence of K_2CO_3 (3 equiv.) and 18-crown-6 (0.4 equiv.) in dry THF yielding 67% of a colourless glassy solid **5** with mp 117–119 °C. The reaction of the three-directional core **6** (1 equiv.) with the dendron **3**-Br (3.3 equiv.) in the presence of K_2CO_3 (4 equiv.) and 18-crown-6 (0.4 equiv.) in dry acetone yielded 81% of a colourless glassy solid **7** with mp 118–120 °C.

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