Hyperbranched chiral catalysts for the asymmetric reduction of ketones with borane

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Received (in Liverpool, UK) 28th July 1999, Accepted 6th September 1999

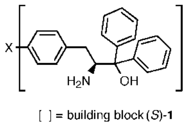
Optically active dendritic amino alcohols catalyse the enantioselective borane reduction of ketones with good yields and high enantiomeric excesses.

Dendrimers represent a new class of polymeric compounds which are distinguished from traditional polymers by their unusual fractal-like architecture.[1] Due to their unique characteristic features they appear attractive for applications in the fields of biology and materials sciences as well as for use in homogeneous catalysis.[2,3] For enantioselective catalysis chiral dendrimers[4] are required; as yet, however, very few dendritic chiral catalysts have been described.[5–11] In a recent study we reported on the synthesis of chiral dendrimer-bound pyridyl alcohols and their application in the asymmetric addition of diethylzinc to benzaldehyde.[11] Various generations of these hyperbranched chiral catalysts (hccs) were tested, and gratifyingly, no significant loss of catalyst activity and enantioselectivity was observed, when compared to catalysis with the parent pyridyl alcohol. Thus, even in reactions with higher hcc generations the resulting secondary alcohols were obtained in satisfying yields, having ees of up to 86%. Considering possible applications of dendritic chiral catalysts in continuously operated membrane reactors,[3e,12] we also envisioned other strategies for the synthesis of optically active alcohols. Here, we report the first use of dendritic catalysts for the enantioselective borane reduction of prochiral ketones leading to the desired products with up to 96% ee.

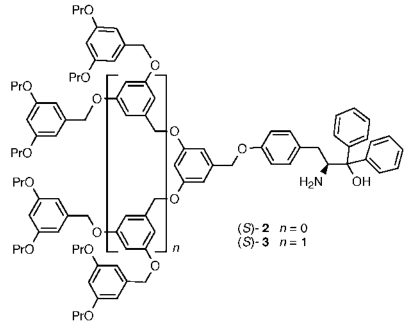
Readily available building block (*S*)-**1** was chosen as a chiral unit, since high catalytic efficiency and convenient applicability of various compounds containing **1** had been elegantly demonstrated by Itsuno *et al.*[13,14] In addition, results of catalyses with polymer-supported **1** under homogeneous[12a] and heterogeneous[14] conditions could serve as reference points. Chiral dendrimers (*S*)-**2** to (*S*)-**5** were synthesised in good yields by the convergent-growth approach introduced by Hawker and Fréchet[15] using (*S*)-2-amino-3-(*p*-hydroxyphenyl)-1,1-diphenylpropan-1-ol (**1b**) and appropriate polyether wedges derived from 3,5-dihydroxybenzyl alcohol or 4,4-bis(4′-hydroxyphenyl)pentanol, respectively.[16]

The asymmetric borane reductions[17] were studied under the following conditions: 10 mol% of dendritic amino alcohol (*S*)-**2** to (*S*)-**5**, $BH_3 \cdot SMe_2$ as reductant, THF as solvent, at room temperature. Various prochiral substrates were used, and the results are summarised in Table 1.

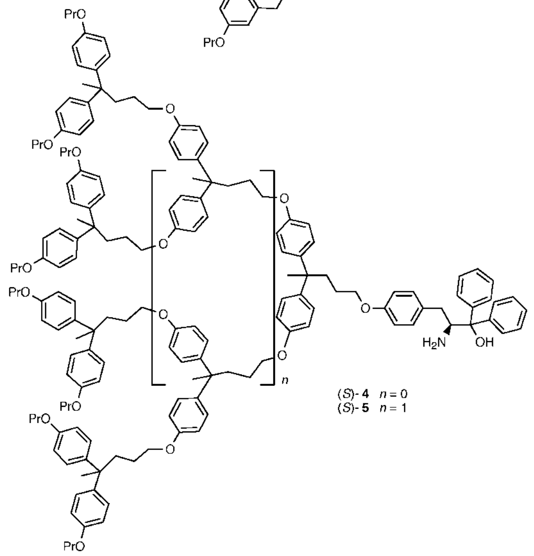
In general, excellent ketone conversion was achieved, and the corresponding optically active alcohols were obtained in good yields (> 75%). The enantioselectivities were high (81–96% ee), and reductions of alkyl aryl ketones led to the predominant formation of the (*R*)-configured products. Compared to the parent systems containing **1**, all hccs performed well. For example, even with stoichiometric amounts of **1a** only 87% ee had been achieved in the reduction of acetophenone.[13] Here, with 10 mol% of catalyst (*S*)-**4**, (*R*)-1-phenylethanol was obtained with 91% ee. Among all hccs evaluated in this reaction (Table 1, entries 1–4), (*S*)-**4** was the best catalyst in terms of yield and ee. Presumably, the higher rigidity of the dendritic backbone in **2** and **3** and the increased steric crowding in the



[ ] = building block (*S*)-**1**
(*S*)-**1a** X = H
b X = OH
c X = O-polymer
d X = O-dendrimer

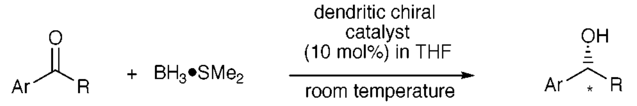


(*S*)-**2** *n* = 0
(*S*)-**3** *n* = 1



(*S*)-**4** *n* = 0
(*S*)-**5** *n* = 1

Table 1 Enantioselective borane reduction of various ketones using hccs **2**–**5**



Entry	Ketone	Dendritic amino alcohol	Yield (%)[a]	Alcohol ee (%)[b]	Abs. config.[c]
1	PhC(O)Me	**2**	80	89	(*R*)
2	PhC(O)Me	**3**	78	88	(*R*)
3	PhC(O)Me	**4**	80	91	(*R*)
4	PhC(O)Me	**5**	79	89	(*R*)
5	PhC(O)Et	**2**	82	84	(*R*)
6	PhC(O)Et	**3**	80	82	(*R*)
7	Tetralone	**4**	80	86	(*R*)
8	Tetralone	**5**	78	81	(*R*)
9	$PhC(O)CH_2OTBDPS$	**4**	76	91	(*S*)
10	$PhC(O)CH_2OTBDPS$	**5**	75	91	(*S*)
11	$PhC(O)CH_2Cl$	**4**	82	96	(*S*)
12	$PhC(O)CH_2Cl$	**5**	80	94	(*S*)

[a] After column chromatography. [b] Determined by HPLC using a chiral stationary phase. [c] Determined by comparison of optical rotations with literature values.

higher-generation catalyst **5** led to product formation with slightly reduced enantioselectivity.

The highest ee values were found in reductions of α-chloroacetophenone giving the corresponding alcohol with up to 96% ee (Table 1, entries 11 and 12). These results are particularly important because α-(chloromethyl)benzyl alcohol is a valuable precursor for the synthesis of phenyloxirane.[18]

The potential of these new dendritic catalysts which operate homogeneously is also highlighted by the fact that under heterogeneous conditions with polymeric **1c** significantly lower enantioselectivities were achieved (*cf.* acetophenone: 76% ee; propiophenone: 79% ee; α-chloroacetophenone: 84% ee).[14,19]

In summary, we have demonstrated the feasibility of performing highly enantioselective borane reductions of prochiral ketones using dendritic catalysts (hccs), and we are currently investigating their possible applications in continuously operating reactor systems.[20,21]

We are grateful to the Bundesministerium für Forschung und Technologie (BMFT) and the Fonds der Chemischen Industrie for financial support of this work. We thank the Degussa-Hüls for the generous donation of chemicals.

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Communication 9/06258K