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Dendronized piperidine: highly effective and recyclable catalysts for Henry reaction

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ABSTRACT

Two types of dendronized tertiary amines were synthesized by attaching piperidine to the core of a Fréchet-type dendrimer or to the end of an alkyl chain that is linked to the dendritic core. The relationship between structure and property of the catalysts in the Henry reaction of 2-nitrobenzaldehyde and nitromethane was established. It was observed that the attachment of piperidine to the dendritic sector by using a hexamethylene chain effectively avoids the scenario of dendritic shell encapsulation. And the **4**-G_3' catalyst of third-generation with dendritic link exhibits excellent catalytic performance, and can be recycled ten times without a significant loss of activity.

The development of well-defined catalysts that enable rapid and selective chemical transformation, and can be completely separated from the product is a paramount challenge.[1] The recent success of homogeneous catalysis is reflected in the number of applications that is known today both in laboratory and industrial practices; but so far there is not a single solution for effective catalyst-product separation. A widely studied approach to tackle the problem is the attachment of homogeneous catalysts to insoluble organic, inorganic, or hybrid supports.[2–6] However, there are difficulties that are intrinsic, such as (i) nonuniformity and the partially unknown structure of the heterogenized catalysts, (ii) mass transport limitation due to slow diffusion of reactants, and (iii) the lower activity compared to the homogeneous analogue. It is envisaged that the use of a soluble support can lead to a recyclable catalyst that does not suffer from mass transfer limitation, and therefore showing activity similar to that of the monomeric analogues.[7,8]

In the past three decades, the use of dendrimers as scaffolds received much attention. The well-defined macromolecular structure of a dendrimer enables the synthesis of a catalyst with its structure precisely controlled. For a catalytic system of high performance, it is essential to define the position of the catalytic sites as well as the spatial separation of the catalysts. Moreover, the globular shape and special solubility of dendrimers of higher generations can be utilized in nano-filtration or solvent-precipitation methods. Since the pioneering work of van Koten and co-workers,[9] it is reckoned that the gap between homogeneous and heterogeneous catalysis can be bridged by dendritic catalysts. So far, a number of dendrimer-supported catalysts with catalytic sites at either the core or the periphery were reported.[10–15]

Nonetheless, there are drawbacks in the dendrimer systems. In the cases of core-functionalized dendrimers, the steric shielding or blocking effect of the specific microenvironment created by the dendritic structure results in change of catalytic behavior of the core. For example, the effect of site isolation can be beneficial for some reactions,[16,17] but the dendrimer catalysts of higher generation often suffer from deactivation caused by the steric shielding effect of the dendritic shell.[18–22] Furthermore, the multistep synthesis of dendritic catalysts is tedious and time-consuming, and the recyclability of dendritic catalysts is not satisfactory.[23–27]

In the past decade, we developed several kinds of dendritic catalysts to study the relationship between dendrimer structure and catalytic property.[28–30] We designed dendrimer catalysts that are high in activity and reusability, and applied them for the Henry reaction to meet the related challenges.[31,32] In this article, we report two types of dendronized tertiary amines synthesized by attaching piperidine to the core of Fréchet-type dendrimers or to the end of alkyl chains that are linked to the dendritic core. The practicality of them as a recyclable homogeneous catalyst is demonstrated in Henry reactions.

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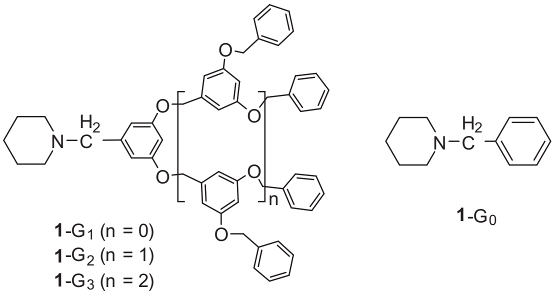
The core-functionalized dendritic piperidine catalysts **1**-G$_1$, **1**-G$_2$, and **1**-G$_3$ were facilely synthesized in high yields through the coupling of polyether dendritic benzyl bromides[33] with piperidine in the presence of triethyl amine in CH_2Cl_2 at room temperature (Supporting Information). A polyether dendrimer was chosen to ensure catalyst stability under optimized reaction conditions. Similarly, the reference compound **1**-G$_0$ was prepared in good yield by coupling benzyl chloride with piperidine (Fig. 1). The synthesized compounds were purified by flash column chromatography and characterized by ^1H and ^{13}C NMR spectroscopy as well as by HRMS techniques. The results of characterization are consistent with the known spectra of the target compounds (Supporting Information).

Initial studies were performed using the Henry reaction of 2-nitrobenzaldehyde and nitromethane at room temperature (20–30 °C) as model reaction. To evaluate the efficiency of the dendritic piperidine catalysts, we selected piperidine, *N*-methylpiperidine, *N*-butylpiperidine, *N*-hexylpiperidine, *N*-octylpiperidine, and **1**-G$_0$ for benchmarking. The results are shown in Table 1. High catalytic activity was observed over **1**-G$_1$, and the isolated yield of product is 90% (entry 7), which is only slightly lower than that of **1**-G$_0$ (entry 6) and far or slightly higher than that of piperidine, *N*-methylpiperidine, *N*-butylpiperidine, *N*-hexylpiperidine, or *N*-octylpiperidine (entries 1–5). The results well demonstrate the effectiveness of the piperidine catalysts with a well-defined dendritic wedge. Nonetheless, there is significant decrease of activity over the **1**-G$_3$ catalyst of third generation (entry 9). It was reckoned that the profound 'generation effect' could be due to the inadequate solubility of **1**-G$_3$ in CH_3NO_2. We would like to point out that the solubility of high-generation dendronized piperidines (i.e. **1**-G$_3$ and **4**-G$_3$′) is poor in polar solvents such as CH_3NO_2. Because CH_3NO_2 serves as a substrate as well as a solvent in this study, it is necessary to add another solvent to enhance homogeneity. We tested CH_2Cl_2, THF, H_2O, and toluene, and found that the solvent effect follows the order of $CH_3NO_2–CH_2Cl_2 > CH_3NO_2–THF > CH_3NO_2–H_2O > CH_3NO_2$–Toluene. We hence adopted the binary $CH_3NO_2–CH_2Cl_2$ system and observed yield improvement from 52% to 64% over **1**-G$_3$ (entries 9 and 13), whereas that over **1**-G$_0$, **1**-G$_1$, or **1**-G$_2$ shows little change. Despite the moderate to excellent yields over the **1**-G$_0$, **1**-G$_1$, and **1**-G$_2$ catalysts (entries 10–12), the product yield is inferior to that observed by Fan et al. over dendrimer BINAP.[34] It is deduced that the inferiority is due to the encapsulation of active species by the dendrimers of higher generation, which hinders the diffusion of the substrates into the catalytically active core.[28,35]

The phenomena of amines being encapsulated by dendrimers in Henry reaction was reported before.[36–38] Considering the negative steric shielding effect of the dendritic shell on the catalytic center, we perceived that extending the chain length between the catalytic site and dendron would result in relief of the steric shielding effect. It is known that the third-generation dendronized piperidine can be better recovered and reused than the first- or second-generation counterpart through the addition of methanol into the reaction medium. Indeed, **1**-G$_3$ is better than **1**-G$_1$ and **1**-G$_2$ in terms of recyclability. With such consideration, despite **1**-G$_3$ suffered more severely from the 'dendrimer negative effect', it was chosen for improvement of activity. We designed the new dendrimer-linked catalyst **4**-G$_3$′ by grafting piperidine onto the third generation Fréchet-type dendritic wedges using a hexamethylene chain (Scheme 1). To the best of our knowledge, this is the first example of an alkyl chain being deployed as a linker in a dendrimer to distance the catalytically active core from the dendron. It was expected that the dendritic **4**-G$_3$′ can act as an efficient and recyclable homogeneous catalyst for the Henry reaction.

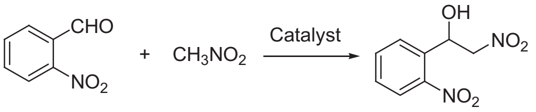


1-G$_1$ (n = 0)
1-G$_2$ (n = 1)
1-G$_3$ (n = 2)

1-G$_0$

Figure 1. Schematic of the core-functionalized dendritic catalysts **1**-G$_1$, **1**-G$_2$, and **1**-G$_3$ and the reference compound **1**-G$_0$.

Table 1
Henry reaction catalyzed by different catalysts[a]



Entry	Catalyst	Solvent	Time (h)	Yield[b] (%)
1	Piperidine	CH_3NO_2	24	65
2	*N*-Methylpiperidine	CH_3NO_2	6	75
3	*N*-Butylpiperidine	CH_3NO_2	6	84
4	*N*-Hexylpiperidine	CH_3NO_2	6	84
5	*N*-Octylpiperidine	CH_3NO_2	6	85
6	**1**-G$_0$	CH_3NO_2	6	94
7	**1**-G$_1$	CH_3NO_2	6	90
8	**1**-G$_2$	CH_3NO_2	6	88
9	**1**-G$_3$	CH_3NO_2	6	52
10	**1**-G$_0$	$CH_3NO_2–CH_2Cl_2$	6	94
11	**1**-G$_1$	$CH_3NO_2–CH_2Cl_2$	6	90
12	**1**-G$_2$	$CH_3NO_2–CH_2Cl_2$	6	89
13	**1**-G$_3$	$CH_3NO_2–CH_2Cl_2$	6	64
14	*N*-Butylpiperidine	$CH_3NO_2–CH_2Cl_2$	6	82
15	*N*-Hexylpiperidine	$CH_3NO_2–CH_2Cl_2$	6	81
16	*N*-Octylpiperidine	$CH_3NO_2–CH_2Cl_2$	6	83
17	**4**-G$_3$′	$CH_3NO_2–CH_2Cl_2$	6	91
18[c]	**4**-G$_3$′	$CH_3NO_2–CH_2Cl_2$	6	95
19[d]	**4-G$_3$′**	$CH_3NO_2–CH_2Cl_2$	6	83
20[e]	**4**-G$_3$′	$CH_3NO_2–CH_2Cl_2$	6	78

[a] Reaction conditions: 2-nitrobenzaldehyde (0.3 mmol) in solvent of 1.5 mL CH_3NO_2 (entries 1–9) and 1.5 mL $CH_3NO_2–CH_2Cl_2$ (3:2, v/v, entries 10–19), 50 mol % catalyst (entries 1–17), room temperature, under nitrogen unless otherwise noted.

[b] Isolated yields.

[c] 10 mol % catalyst.

[d] 5 mol % catalyst.

[e] 1 mol % catalyst.

The synthesis of dendrimer-linked catalyst **4**-G$_3$′ is outlined in Scheme 1. First, the intermediate 1-(6-bromohexyl)-piperidine was quantitatively prepared through *N*-alkylation reaction from commercially available piperidine and 1,6-dibromohexane. Then the *N*-alkylation reaction of 1-(6-bromohexyl)piperidine **2** with the third generation dendritic benzyl alcohol **3** in the presence of sodium hydride (NaH) affords **4**-G$_3$′ in 78% isolated yield. The synthesis condition, purity and structure of **4**-G$_3$′ as determined by standard spectroscopic methods are described in Supporting Information.

We then probed the catalytic efficiency of **4**-G$_3$′ in the Henry reaction between 2-nitrobenzaldehyde and nitromethane. The experimental data are also depicted in Table 1. As expected, the dendrimer-linked catalyst **4**-G$_3$′ exhibits catalytic activity as high as that of 1-G$_1$ (entry 17 vs 11). Notably, the **4**-G$_3$′ catalyst is highly effective even the catalyst loading is reduced from 50 to 10 mol % (entries 17 and 18). Between 10 and 1 mol % loading, there is gradual decline of product yield. At 5 and 1 mol %, the product yield is 83% and 78% (entries 19 and 20), respectively. We also studied the catalysts that were prepared using butamethylene