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Solid-Phase Catalysis: A Biomimetic Approach toward Ligands on Dendritic Arms to Explore Recyclable Hydroformylation Reactions

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The hydroformylation reaction is extensively used, on a commercial basis, to obtain linear and branched aldehydes from the reaction of alkenes with hydrogen and carbon monoxide in the presence of a catalyst (i.e., Rh, Co, etc.).¹ Although homogeneous catalysis has been widely practiced in the past, in most cases, the separation of the products from the reaction mixtures is a nontrivial undertaking. Over the years, several promising Rh- and Co-derived catalysts have been developed for hydroformylation reactions, but the lack of a recycling process severely limits their potential.² Due to the high costs involved in the syntheses of ligands that exhibit high reactivity and high selectivity, and the use of costly metals (i.e., Rh) in catalysis, there is a growing interest to explore the heterogenization of the ligands in developing heterogeneous catalytic reactions.

With the objectives of the heterogenization of Rh-based metal catalysts, we initiated a program to explore the applications of immobilized dendritic ligands anchored onto silica gel³ and onto polystyrene-based beads⁴ for hydroformylation reactions. These systems could be recycled easily, a desired requirement when it comes to using expensive metals.⁵ Reasons to explain the observed reactivity with the heterogenized, dendritic ligands are not clear at this stage. Due to multiple copies of ligands on dendritic surfaces, cooperative nature may be one of the several factors, but it remains to be confirmed.^{6,5d} In addition, to address the issue of recycling potential of heterogenized catalysts, leaching of the metals (e.g., Rh in particular) is one of the serious drawbacks that needs attention. In this communication, we outline a novel strategy that is targeted to address “the leaching problem” and

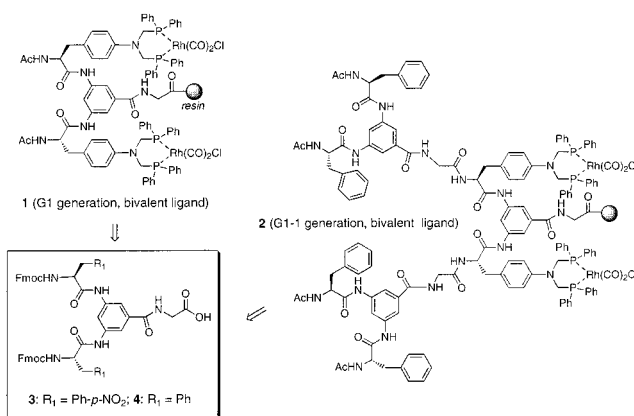


Figure 1. Retrosynthetic analysis: heterogenized catalytic systems with ligands on arms.

its applications to study heterogeneous catalysis derived-hydroformylation reactions.

Cognizant of the knowledge that several proteins and enzymes possess their key functional moieties in the inner core, we decided to use heterogenized, dendritic systems in which the ligands could be placed on the inner arms. The plan was to develop a modular approach that allows the incorporation of ligands at different interior sites in a highly controlled manner. We relied upon solid-phase methodology to achieve this goal.⁷ To place ligands on arms, we utilized a building block, **3**, having two Fmoc-protected N-terminal NH₂ groups required for the growth of the dendritic macromolecule. In addition, it has two NO₂ groups on the side chain that were converted to ligands via the reduction of NO₂ to NH₂ on solid phase, followed by phosphinomethylation.

Heterogenized catalytic systems, **1** and **2** (Figure 1) were selected to test our *biomimetic-based hypothesis that ligands immersed in dendritic architectures may exhibit a prolonged reactivity by preserving the catalytic sites from the outer environment, and it may prevent the leaching of the metal, etc.*⁸ Both of them bear the same number of ligands (i.e., bivalent) on the arms but are exposed to very different surroundings. For example, it is possible to envision that the two catalytic sites in system **1** are perhaps more exposed when compared to system **2**. It was postulated that, due to its nature, system **2** should have a sustained effect on the recycling behavior, provided it is not too hindered to exhibit any reactivity. To our surprise, no reduction in reactivity was observed in system **2** in comparison to **1**. However, in some cases, system **2** was found to have a prolonged reactivity over several cycles in hydroformylation reactions.

Interest in the design and synthesis of functional, dendritic macromolecules is growing constantly with applications in materials and biological sciences.⁹ Several publications describe the synthesis of dendritic macromolecules having functional groups in the interior core.¹⁰ However, a modular approach to place ligands on arms to explore the effect on the leaching of the metal has not been investigated. To our surprise, it was observed that the heterogenized dendritic catalysts with ligands on arms are very reactive in hydroformylation reactions. Moreover, as anticipated, the two heterogenized catalytic systems **1** and **2** exhibited very different behavior in their recyclable abilities. The

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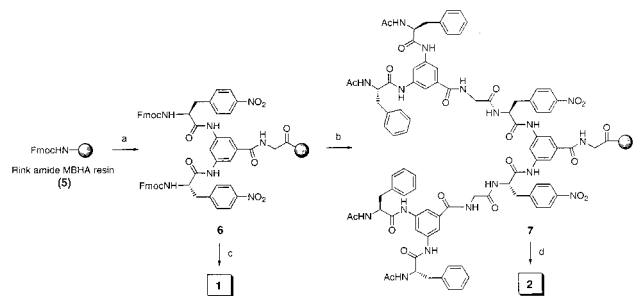
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(8) We termed our approach as “biomimetic” because several proteins and enzymes possess their functional sites in the interior of the macromolecular architectures, and in several cases it has been shown that the macromolecular environment play important roles in modulating specific biological responses.

Scheme 1. Solid-Phase Synthesis of Heterogenized Ligands on Dendritic Arms^a

^a (a) (i) 20% piperidine, DMF; (ii) 4.0 equiv **3**, 4.0 equiv HBTU, 8.0 equiv DIPEA, DMF, 20h. (b) (i) 20% piperidine, DMF; (ii) 10.0 equiv **4**, 10.0 equiv HBTU, 16.0 equiv DIPEA, DMF, 48 h; (iii) 20% piperidine, DMF; (iv) Ac₂O, DIPEA; (c) (i) 20% piperidine, DMF; (ii) Ac₂O, DIPEA; (iii) 12.0 equiv SnCl₂·H₂O, DMF, 10 h; (iv) 20.0 equiv phosphinomethanol prepared in situ from *p*-formaldehyde and Ph₂PH in degassed MeOH, ref 2 h, stirred rt 12 h; (v) 1.0 equiv [Rh(CO)₂Cl]₂ per NH₂ group, CH₂Cl₂, rt, 14 h. (d) repeat steps in (c).

effect of the surroundings on their ability to function as different catalytic systems is highly intriguing and could have impact on other applications in the area of functional dendritic macromolecules.

Building blocks **3** and **4**⁴ were required for the synthesis of the two heterogenized catalytic systems **1** and **2**. Compound **3** was obtained from a Fmoc-protected *p*-NO₂-phenylalanine derivative (Scheme 1).¹¹

To examine the recycling behavior of the two heterogenized catalysts **1** and **2** in hydroformylation reactions, styrene, *p*-methoxystyrene (see, Table 1), vinyl acetate, and vinyl benzoate (see Table 2) were selected as substrates. In a typical reaction, 2.0 mmol of the olefin in 10 mL of CH₂Cl₂ with 25 mg of the catalyst was treated with CO (500 psi) and H₂ (500 psi) gas mixture in a 1:1 ratio at 45 °C. Catalysts **1** and **2** were found to be highly reactive for the hydroformylation of styrene. For example, both catalysts exhibited >99% conversion to the product (branch:linear ratio ranged from 14:1 to 19:1) even up to the sixth cycle. With *p*-methoxystyrene, the catalyst **1** was found to be very reactive up to the fourth cycle (>99%, ratio, B:L, 17:1) but the conversion to the product decreased to 56% (B:L, 30:1) for the fifth cycle. Catalyst **2** was found to be equally reactive (> 99% for the fourth cycle, B:L, 17:1) and a continued reactive behavior was observed for the fifth cycle (>85%, B:L, 30:1). Similar observations were made with vinyl benzoate as the substrate. With catalyst **1**, the third cycle exhibited >99% conversion to the product (B:L, 20:1). The reactivity was significantly reduced for the fourth (43%, B:L, 30:1) and for the fifth cycles (20%, B:L, 30:1). However, once again the heterogenized catalyst **2** exhibited a better recycling response. For example, the third cycle with catalyst **2** gave the product with >99% (B:L, 25:1). Contrary to

Table 1. Hydroformylation of Styrene (*p*-Methoxystyrene) Using Rhodium Complexed Heterogenized Catalytic Systems, **1** and **2**^a

catalyst	cycle	time (h)	temp (°C)	conversion (%)	branched:linear ^b
1	1st	1	45	18	19:1
1	2nd	1	45	12	19:1
1	3rd	2	45	14	19:1
1	1st	5	45	97	15:1
1	2nd	20	45	>99 (>99)	18:1 (16:1)
1	3rd	20	45	>99 (>99)	17:1 (17:1)
1	4th	20	45	>99 (>99)	15:1 (17:1)
1	5th	20	45	>99 (56)	14:1 (30:1)
2	1st	1	45	23	16:1
2	2nd	1	45	13	15:1
2	3rd	2	45	9	16:1
2	1st	5	45	96 (>99)	16:1 (19:1)
2	2nd	20	45	>99 (>99)	18:1 (16:1)
2	3rd	20	45	>99 (>99)	18:1 (18:1)
2	4th	20	45	>99 (>99)	17:1 (17:1)
2	5th	20	45	>99 (85)	19:1 (30:1)

^a Reaction conditions: Styrene or *p*-methoxystyrene (2.0 mmol), CO (500 psi), H₂ (500 psi), catalyst (25 mg). ^b Ratio of branched:linear aldehydes was determined by ¹H NMR.

Table 2. Hydroformylation of Vinyl Acetate (Vinyl Benzoate) Using Heterogenized Catalytic Systems, **1** and **2**^a

catalyst	cycle	time (h)	temp (°C)	conversion (%)	branched:linear ^b
1	1st	5	45	73 (78)	19:1 (20:1)
1	2nd	20	45	99 (>99)	17:1 (27:1)
1	3rd	20	45	90 (>99)	17:1 (20:1)
1	4th	20	45	88 (43)	18:1 (30:1)
1	5th	20	65	85 (20)	19:1 (30:1)
2	1st	5	45	77 (85)	20:1 (30:1)
2	2nd	20	45	97 (>99)	17:1 (30:1)
2	3rd	20	45	95 (>99)	19:1 (25:1)
2	4th	20	45	92 (91)	18:1 (20:1)
2	5th	20	65	88 (83)	17:1 (19:1)

^a Reaction conditions: Vinyl acetate or vinyl benzoate (2.0 mmol), CO (500 psi), H₂ (500 psi), catalyst (25 mg). ^b Ratio of branched:linear aldehydes was determined by ¹H NMR.

catalyst **1**, complex **2** was appreciably more reactive in the fourth (91%, B:L, 20:1) and the fifth cycles (83%, B:L, 19:1).

To summarize, we have shown that it is possible to design heterogenized, dendritic catalytic systems that could exhibit a better response to the recycling behavior. Our approach is highly modular and allows for the placement of ligands on arms in a highly controlled manner. Although the potential of this approach has only been shown in heterogenized catalytic studies, one may envision several other applications that may require a precise positioning of functional moieties in a highly controlled manner. As observed earlier, the common notion that heterogenized catalysts exhibit poor reactivities is not true with our present systems. No reduction in reactivity was observed with the heterogenized catalyst **2** that bear the two ligands on arms. In fact, this system exhibited the enhanced recycling potential that was originally hypothesized. Although results with catalyst **2** clearly indicate a better recycling potential when compared to system **1**, one can only speculate at the moment to explain this behavior. It is also hoped that the successful outcome with the present systems may benefit further by applying combinatorial approaches, thus obtaining even better catalysts with high reactivities and an everlasting, true catalytic behavior!¹²

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Supporting Information Available: Experimental details (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>. JA003854S

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(11) See Supporting Information for the synthesis of the building block **3** and for the heterogenized catalytic systems **1** and **2**.