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COMMUNICATION

Construction of Janus Dendrimers through a Self-Assembly Approach Involving Chiral Discrimination at a Focal Point

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A strategy to build Janus dendrimers via the chirality-directed self-assembly of heteroleptic Zn(II) BOX complexes is reported. The method allows quantitative synthesis of Janus dendrimers in situ without the need for purifications. Each dendritic domain of the Janus dendrimers can be recycled upon disassembly at the focal point.

A Janus dendrimer[1] is an unsymmetric dendrimer having two dendritic domains on both sides of a core with different functionalities.[2] Due to their unique properties and functions, Janus dendrimers have a wide range of applications in various fields, including materials, catalysis, and medicine.[3] Among various synthetic approaches developed thus far,[4] a straightforward preparation of Janus dendrimers involves an independent preparation of dendron halves followed by a convergent reaction to connect the dendrons through complementary functional groups at the focal point of each dendron. Various coupling reactions,[4d] for example click chemistry,[5] have been reported to proceed with high selectivity to form structurally distinct Janus dendrimers.[4d,6] However, many of these coupling processes often require long reaction time and tedious isolation/purification processes to remove reaction by-products.[7] To this end, a self-assembly approach[8] is an attractive alternative to the chemical coupling methods as it can provide: 1) easier generation of large libraries of unique Janus dendrimers in short period of time. 2) faster and quantitative assembly of Janus dendrimers *in situ* without a need for isolation/purification, 3) better functional group tolerance on the dendron subunits by eliminating the often harsh reaction conditions associated with the chemical coupling step, 4) an advantage in recycling dendron subunits by disassembly of the Janus dendrimer at the reversible focal point.

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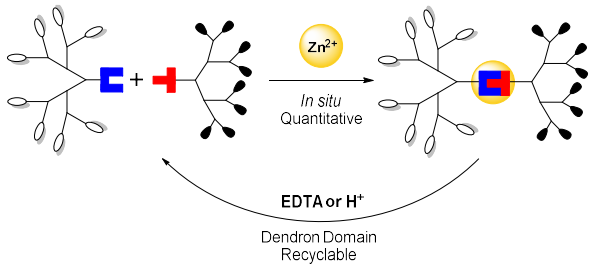
The process of self-assembly involves discrete components spontaneously organized into ordered aggregates through their mutual recognition properties.[8] The precise assembly of superstructures relies on a highly selective non-covalent recognition of units typically under thermodynamic equilibrium. Amongst the various modes of reversible self-assembly in constructing supramolecular structures, hydrogen bonding,[9] metal-ligand bonding,[10] π-donor/acceptor interactions,[11] and host-guest chemistry,[12] the metal-ligand approach is an attractive one due to the comparatively higher bond strength of the metal-ligand interactions rendering this strategy applicable



Scheme 1 The construction of Janus dendrimers via reversible chirality-directed self-assembly.

even at elevated temperatures.[13] Toward this end, Takacs, et al. developed a system utilizing ligand pairs with complemental chirality for self-assembly with a high level of chiral discrimination.[14] This approach has been employed to construct novel heteroleptic chiral bidentate ligands for several catalytic asymmetric reactions.[15] Hence, we introduce a new versatile approach to generate Janus dendrimers *in situ* through the use of chiral self-discrimination at the focal point of dendrimers (Scheme 1). This is the first example utilizing metal-ligand interaction to construct Janus dendrimer which enables fast building of large library as well as recycling of each dendron subunits.

As reported previously,[14,15] treatment of an equimolar mixture of enantiomeric chiral methylene bis-(oxazolines) with diethylzinc ($(Et)_2Zn$) affords, to the level of NMR detection, exclusive formation of the heterochiral Zn(II) complex (*SS*,*RR*)-Zn(II)-BOX through chiral self-discrimination. The ligand

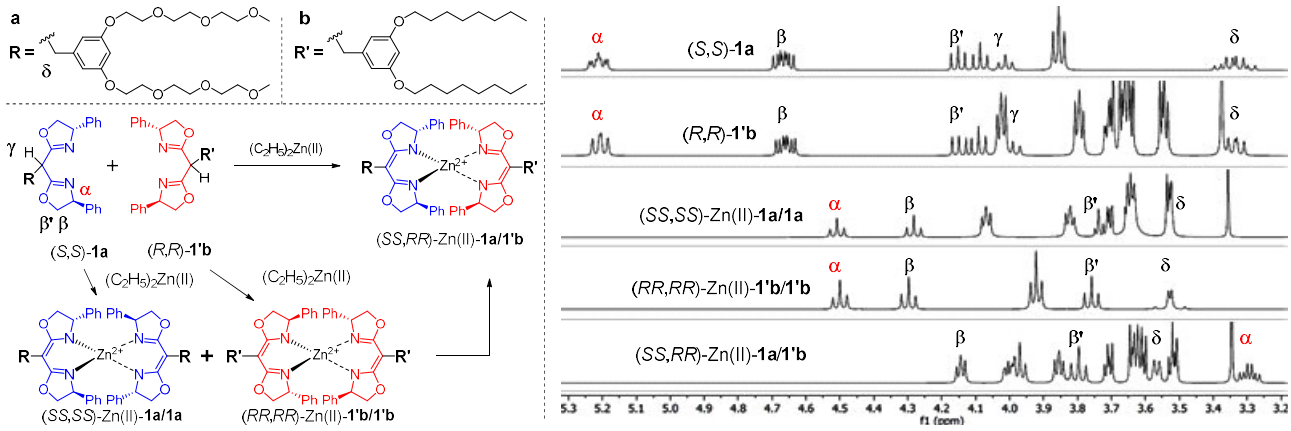
exchange process is quantitative leaving no free ligands or homochiral Zn(II) complexes in solution as judged by ^{1}H NMR analysis. Alternatively, heterochiral Zn(II) BOX complexes can be prepared through a rapid ligand exchange between both enantiomers of homochiral Zn(II) complexes. The lower thermodynamic stability of homochiral Zn(II) complexes relative to the heterochiral Zn(II) complex can be explained by steric crowding of the phenyl substituents on the BOX subunits, which forces the Zn(II) center to adopt a distorted tetrahedral geometry.[14]

At the outset, we have prepared chiral BOX ligands with generation 1 (G1) dendrons possessing hydrophobic or hydrophilic chains as peripheral groups (Scheme 2). Dendrons were attached to the BOX subunit via an alkylation reaction using n-butyllithium and the benzyl bromide derivative of each dendron. Symmetric dendrimers with homochiral Zn(II) complex core ((*SS*,*SS*)-Zn(II)-**1a/1a** and (*RR*,*RR*)-Zn(II)-**1'b/1'b**) are prepared by mixing 2 equivalents of the dendron halves, either (*S*,*S*)-**1a** or (*R*,*R*)-**1'a**, in the presence of one equivalence of diethylzinc. The quantitative formation of the symmetric full dendrimer with homochiral Zn(II) core was apparent from ^{1}H NMR analysis, (Scheme 2 right) where the protons at the chiral center on the oxazoline ring of the free ligand shifted from 5.21 to 4.51 / 4.50 ppm (Scheme 2 right, (*SS*,*SS*)-Zn(II)-**1a/1a** / (*RR*, *RR*)-Zn(II)-**1'b/1'b**). High resolution mass spectrometric analysis showed peaks at 1503.683 and 1367.793 m/z for (*SS*,*SS*)-Zn(II)-**1a/1a** and (*RR*,*RR*)-Zn(II)-**1'b/1'b**, respectively, matching their theoretical values.[16]

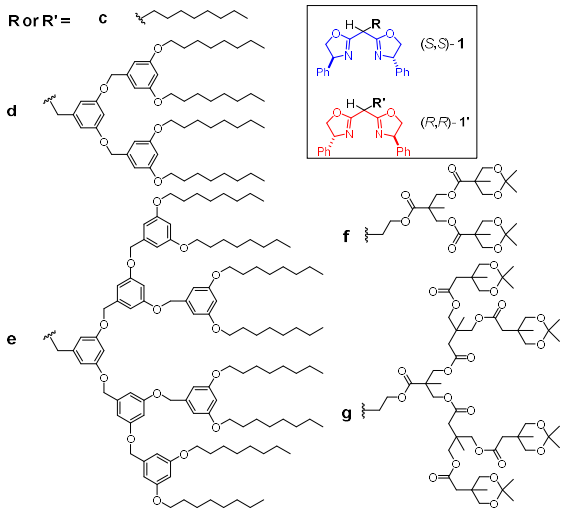
The Janus dendrimer (*SS*,*RR*)-Zn(II)-**1a/1'b** can be generated by two alternative methods: (i) mixing equimolar amounts of dendron halves ((*S*,*S*)-**1a** and (*R*,*R*)-**1'b**) in the presence of diethylzinc or (ii) by simply mixing symmetric dendrimers with homochiral Zn(II) cores ((*SS*,*SS*)-Zn(II)-**1a/1a**/ (*RR*,*RR*)-Zn(II)-**1'b/1'b**) (Scheme 2, left). Through both approaches, the exclusive formation of Janus dendrimers possessing a heterochiral Zn(II) core was confirmed by ^{1}H NMR spectroscopy through the upfield shift of the chiral proton (Scheme 2, 3.30 ppm) and by mass spectrometry yielding a molar mass of 1435.794 m/z, matching its theoretical value. Although the latter approach, which uses a combination of symmetric dendrimers with homochiral Zn(II) cores ((*SS*,*SS*)-Zn(II)-**1a/1a** / (*RR*,*RR*)-Zn(II)-**1'b/1'b**), requires an extra step in preparation of two symmetric dendrimers, it enables independent optimization of each dendritic functions as full dendrimer prior to assembling them into a dual functional Janus dendrimer. The resulting Janus dendrimer, (*SS*,*RR*)-Zn(II)-**1a/1'b**, remain intact for long period of time in solution at ambient temperature, and even for hours at elevated temperatures (no free dendritic ligands were observed after 8 hours at 135°C in TCE-*d*2/1% CD_3OD measure by VT NMR). In addition, the Janus dendrimer (*SS*,*RR*)-Zn(II)- **1a/1'b** remains intact with no ligand exchange when excess amount of free unsubstituted (*S*,*S*)-BOX ligand or its homochiral non-dendritic (*SS*,*SS*)-Zn(II)-BOX complex was added to the solution.[17] In contrast, the Janus dendrimer (*SS*,*RR*)-Zn(II)-**1a/1'b** disassembled into free dendron halves, (*S*,*S*)-**1a** and (*R*,*R*)-**1'b**, in 3 hours upon treatment with excess TFA or EDTA. Disintegration of Zn(II) complex was measured by ^{1}H NMR, and is apparent from downfield shift of chiral protons on the BOX ligand (α in Scheme 2) from 3.3 ppm (Zn(II) complex) to 5.2 ppm region (free dendritic BOX ligands). It is noteworthy to mention that the resulting dendron halves, ((*S*,*S*)-**1a** and (*R*,*R*)-**1'b**), having differences in their polarity, can be recycled upon separation and purification through column chromatography (CH_2Cl_2:CH_3OH = 10:1).

Encouraged by these results, several dendrons of various generations with different internal/external polarities were prepared (Scheme 3). The preparation of dendron halves via alkylation of chiral BOX all went efficiently. For instance, chiral BOX ligands with a hydrocarbon chain **c** were synthesized in high yield. Similarly, aromatic dendrons G2 to G3 with hydrophobic peripheral chains (**d** and **e**) were prepared, and their steric bulkiness did not affect the efficiency in the alkylation reaction. In addition, chiral BOX ligands with hydrophilic dendrons based on ester frameworks (**f** and **g**) were also synthesized efficiently using the same approach. The influences of dendron size/polarity on forming Janus dendrimer with heterochiral Zn(II) core complexes were investigated using various combinations of dendron halves listed in Scheme 3.

First, the selectivity toward formation of heterochiral Zn(II)



Scheme 2 Left: Self-assembly of Janus dendrimer via chirality discrimination at focal dendrimer point. (*S,S*) BOX ligand **1** (Blue) and (*R,R*) BOX ligand **1'** (Red). Right: ^{1}H NMR spectra of free, homochiral, and heterochiral Zn(II) complexes. Proton peaks corresponding to side chains of dendrons are not labelled. Each chiral proton α is labelled in red.

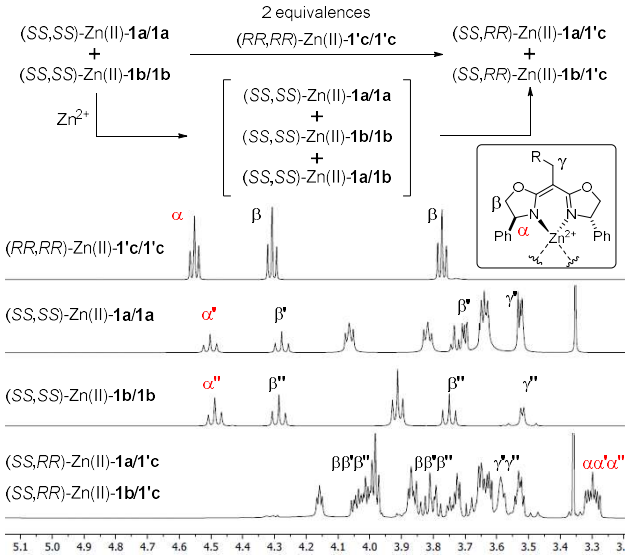


Scheme 3 Various dendrons attached to the chiral BOX ligands (*S,S*)-**1** and (*R,R*)-**1'**.[19]

core was not affected by the difference in size of dendrons attached to the chiral BOX.

For instance, the amphiphilic Janus dendrimer (*SS,RR*)-Zn(II)-**1g/1'c** was formed exclusively through ligand exchange of the corresponding symmetric homochiral dendrimer Zn(II) complexes, (*SS,SS*)-Zn(II)-**1g/1g** and (*RR,RR*)-Zn(II)-**1'c/1'c**. The ligand exchange was completed within 60 minutes, yielding the dendrimer (*SS,RR*)-Zn(II)-**1g/1'c** in quantitative yield. None of the symmetric dendrimers with homochiral Zn(II) core nor free dendrons were present in solution. An identical result was obtained by the combination of the G3 dendron (*R,R*)-**1'e** and hydrophilic G1 dendron (*S,S*)-**1c** which were used to generate (*SS,RR*)-Zn(II)-**1c/1'e**. No free ligands or symmetric dendrimers were observed in solution. The selectivity and yield toward the formation of heterochiral Zn(II) core were not altered by the overall steric bulkiness of resulting Janus dendrimers. For instance, the G3-heterochiral (*SS,RR*)-Zn(II)-**1e/1'g** was obtained in quantitative yield when an equimolar amount of (*RR,RR*)-Zn(II)-**1'e/1'e** and (*SS,SS*)-Zn(II)-**1g/1g** were mixed in solution. However, the rate of ligand exchange was influenced by the size of the overall steric bulkiness of dendrimers. For example, under the same condition, the formation of heterochiral (*SS,RR*)-Zn(II)-**1e/1'g** was 6 times slower (approx. 4h) as compared to the formation of a smaller (*SS,RR*)-Zn(II)-**1a/1'b** dendrimer from the homochiral (*RR,RR*)-Zn(II)- **1'b/1'b** and (*SS,SS*)-Zn(II)-**1a/1a** (approximately 40 min).[20,21] The thermal stability of the large Janus dendrimer, G3-heterochiral (*SS,RR*)-Zn(II)-1e/1'g, was checked using VT NMR and no disintegration of Zn(II) complex was observed at temperature we tested (8h in TCE-*d*2/1% CD_3OD, 135 °C).

Finally, the high selectivity toward the formation of heterochiral Zn(II) complex core over the homochiral Zn(II) complex led us to develop a methodology for the generation of a specific set of two structurally distinct Janus dendrimers *in situ* using a mixture of 3 symmetric dendrimers with homochiral Zn(II) cores. When three symmetric dendrimers with homochiral Zn(II) complexes ((*SS,SS*)-Zn(II)-**1a/1a**, (*SS,SS*)-Zn(II)-**1b/1b,** and phenyl (*RR,RR*)-Zn(II)-**1'c/1'c**) were mixed in a ratio of 1:1:2 respectfully, all symmetric dendrimers were subject to



Scheme 4 ^{1}H NMR spectroscopic results of selective *in situ* generation of two dendrimers with heterochiral Zn(II) complexes Proton peaks corresponding to dendrons are not labelled. Each chiral protons α, α', α" is labelled in red.

ligand exchange, leaving only the Janus dendrimers with heterochiral Zn(II) cores ((*SS,RR*)-Zn(II)-**1a/1'c** and (*SS,RR*)-Zn(II)-**1b/1'c**, with 1201.597, 1133.617 m/z) dendrimers were formed which can be confirmed by both ^{1}H NMR and MOLDI-TOF analysis.[16] Identical results were obtained when the free dendron ligands (*S,S*)-**1a** (*S,S*)-**1b,** and (*R,R*)-**1'c** were mixed with a molar ratio of 1:1:2 in the presence of 2 molar equivalences of diethylzinc(II). Stepwise analysis showed that when the (*SS,SS*)-Zn(II)-**1a/1a** and (*SS,SS*)-Zn(II)-**1b/1b** complexes were mixed, three dendrimers homochiral Zn(II) complexes, (*SS,SS*)-Zn(II) **1a/1a**, (*SS,SS*)-Zn(II)-**1b/1b**, and (*SS,SS*)-Zn(II)-**1a/1b** were formed in solution. Once the dendrimer complex with opposite enantiomeric core, (*RR,RR*)-Zn(II)-**1'c/1'c**, was added to this mixture, all dendrons homochiral Zn(II) core complexes were subject to ligand exchange by (*RR,RR*)-Zn(II) **1'c/1'c** to form heterochiral Zn(II) complexes, yielding (*SS,RR*)-Zn(II)-**1a/1'c** and (*SS,RR*)-Zn(II)-**1b/1'c**. This approach does not generate any reaction by-product and can be a powerful tool to generate supramolecular structures such as hybrid bilayer systems *in situ*, readily co-assembled from multiple amphiphilic dendrimers.

In summary, a strategy to build Janus dendrimers via the chirality-directed self-assembly of heteroleptic Zn(II) BOX complexes is reported. Our methodology can be used to build a large library of structurally/functionally unique dendrimers in a short period of time by simply mixing different pairs of dendron halves, each having opposite enantiomers of BOX ligands in the presence of Zn(II). Further studies, including the generation of various dual functional dendrimers as well as the investigation on various dendritic aggregates are currently in progress.

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Conflicts of interest

There are no conflicts to declare.

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16. See ESI for MALDI-TOF results.
17. In contrast, a dendrimer having homochiral Zn(II) complex at focal point was subject to ligand exchange with unsubstituted homochiral (*SS*,*SS*)-Zn(II)-BOX. For instance, mixing equimolar amount of (*SS*,*SS*)-Zn(II)-BOX and (*SS*,*SS*)-Zn(II)-**1a**/**1a** yielded (*SS*,*SS*)-Zn(II)-**1a**/**1a**, (*SS*,*SS*)-Zn(II)-**1a**/BOX, (*SS*,*SS*)-Zn(II)-BOX in approximately 1:2:1 ratio.
18. Representative experiments using TFA and EDTA is described in ESI pg 6-7.
19. List of prepared compounds and their synthetic procedures: see schemes (pg 8-11) on ESI
20. The ligand exchange of unsubstituted Zn(II) BOX complex was faster than for the dendritic Zn(II) BOX complexes (< 5 min vs. 40 min).
21. The same trend was observed using symmetric dendrimer with heterochiral Zn(II) complexes. For instance, formation of bulkier G3 (*SS*,*RR*)-Zn(II)-**1e**/**1'e** was 3.8 times slower than that of G1 (*SS*,*RR*)-Zn(II)-**1b**/**1'b**.

