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A Liquid-Phase Approach to Functionalized Janus Dendrimers: Novel Soluble Supports for Organic Synthesis

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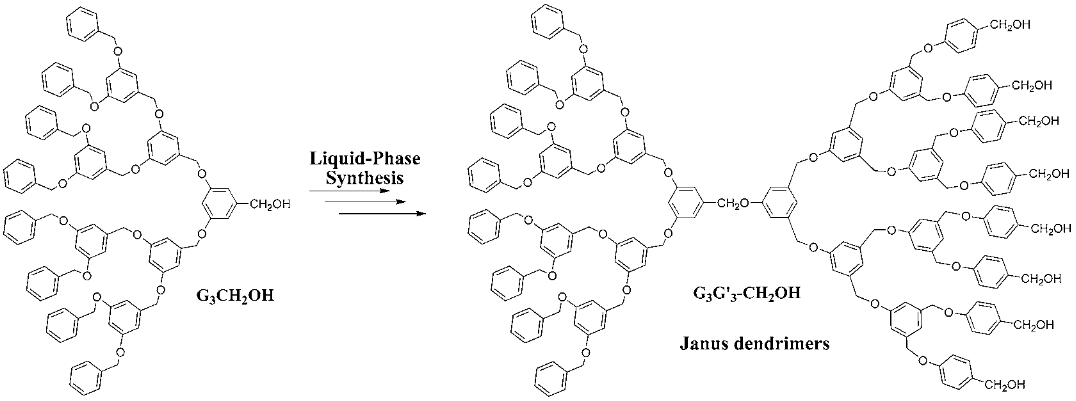
ABSTRACT



A new kind of functionalized Janus dendrimer has been synthesized via a liquid-phase approach, which could easily be purified using a simple precipitation method without the need for chromatographic separation. Their use for liquid-phase organic synthesis has been achieved in the Pd-catalyzed Suzuki coupling reactions, giving biaryl products in excellent yields after cleavage.

Dendrimers are well-defined, highly branched, three-dimensional macromolecules with a large number of reactive end groups.[1] Dendrimers are therefore receiving great interest as new polymeric materials for applications in areas such as molecular light harvesting,[2] molecular encapsulation,[3] drug-delivery systems,[4] and catalysts.[5] Divergent and convergent approaches are two general routes for the synthesis of dendrimers.[6] However, these two methods both involve multiple steps and time-consuming purifications, which often

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result in low yields, thereby limiting their potential practical applications. In this regard, the solid-phase synthesis of dendrimers appears to be a promising alternative.[7] Although solid-phase synthesis techniques have been applied successfully in the synthesis of a number of dendrimers,[8] the heterogeneous reaction nature of this strategy might result in some problems, such as relatively low reactivity, extended reaction time, and difficulty in characterization of dendritic hybrids.

As an alternative, soluble supports have recently been used in liquid-phase organic synthesis (LPOS).[9] In this case, the similar reaction conditions of classic orgainic chemistry are reinstated, and yet product purification is still facilitated through application of macromolecular properties. Over the past decade, this methodology has achieved great success in organic synthesis.[10] To the best of our knowledge, however, only two research groups reported the synthesis of dendrimers or dendritic hybrids via LPOS by using linear polymer or oligomer as supports. Fréchet and co-workers first reported the synthesis of dendritic linear hybrids using linear poly(ethylene glycols) (PEGs) as the support via LPOS.[11] Most recently, Ahn et al. reported the synthesis of alphatic ester dendrimers on linear polystyrene support.[12] To date, synthesis of codendrimers by using dendron support via LPOS has not been reported in the literature.

The concept of codendrimer was first established by Hawker and Fréchet in the synthesis of segmented and layed codendrimers based on ester and ether monodendrons.[13] Due to their unique structures and properties, codendrimers have been attracting great attention.[14] So far, a number of diblock codendrimers have been reported. However, almost all these dendrimers were synthesized step by step via conventional solution synthesis and therefore suffered from time-consuming purifications and low yields. In relation to our interest in applications of functionalized organometallic dendrimers as homogeneous catalysts,[15] we wish to report here a new kind of codendrimers via LPOS by using the third-generation Fréchet-type poly(aryl ether) dendron[6c] as the support.[16] These dendrimers combine two functionally different surface, nonpolar benzyl ether moieties and polar benzyl alcohol units, resulting in two-faced Janus dendritic molecules (Figure 1). In addition, these Janus dendrimers and reaction intermediates were purified by simple solvent precipitation without the need for column chromatography. Their potential use as a novel soluble support for LPOS has been demonstrated with the Pd-catalyzed Suzuki coupling reaction.

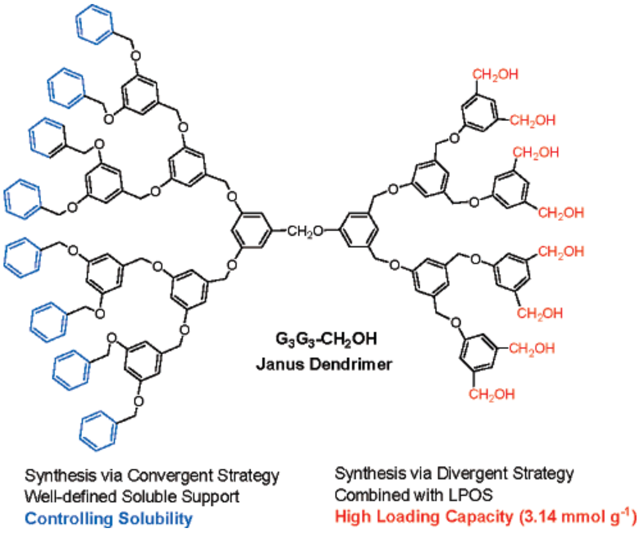

Figure 1. Structure of the third-generation Janus dendrimer.

The Fréchet-type poly(aryl ether) dendron was chosen as support because of its high inertness toward organic reagents and good accessibility. Synthesis and structure of the Janus dendrimers are outlined in Scheme 1. The third-generation Fréchet's dendron **1** was prepared according to the reported convergent approach.[6c] Commercially available dimethyl 5-hydroxylisophthalate **2** was used as the growth unit for the esterification with the hydroxy group of **1** under standard Mitsunobu reaction conditions. The resulting dendritic ester was then reduced by LiAlH$_4$ to provide the **G$_3$G$_1$-CH$_2$OH**

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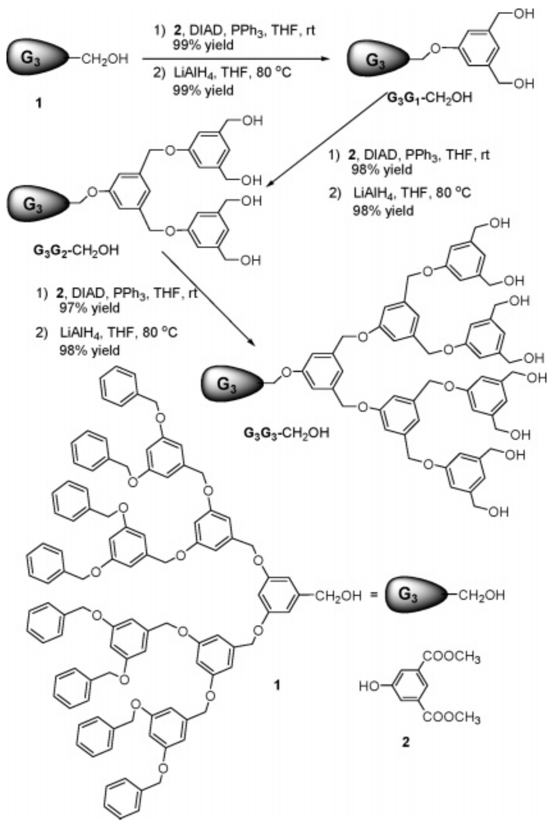
Scheme 1. Synthesis of Janus Dendrimers



in quantitative yield. Repetitive Mitsunobu coupling and ester reduction sequence led to the formation of higher generation dendrimers, **G_3G_2-CH_2OH** and **G_3G_3-CH_2OH**, in almost quantitative yields. Unlike solid-phase synthesis,[8d,8e] the reaction progress could be easily monitored by thin layer chromatography (TLC). The purity and structure of all these Janus dendrimers were confirmed by using ^{1}H and ^{13}C NMR and TOF mass spectrometry (see Supporting Information).

In contrast to the classical solution-phase synthesis, during the growth and reduction steps, there was no need for purification by column chromatography. Usually, there is difficulty during the product purification in Mitsunobu reactions,[17] in which separation of the reagent-derived byproducts often need careful chromatography. In our case, the resulting dendrimer was purified by a simple solvent precipitation at the end of reaction, utilizing the difference in solubility between the insoluble dendrimer and highly soluble byproducts and excess growth units. Obviously, high efficiency of this approach was exemplified in the product purification of the synthesis of **G_3G_2-COOMe**. According to the ^{1}H NMR shown in Figure 2, precipitation of the crude product in ether and methanol removed all the byproducts [triphenylphosphine oxide (TPPO) and diisopropoxycarbonylhydrazine (DICH)] and excess reagents [**2**, diisopropyl azodicarboxylate (DIAD) and triphenylphosphine (TPP)].

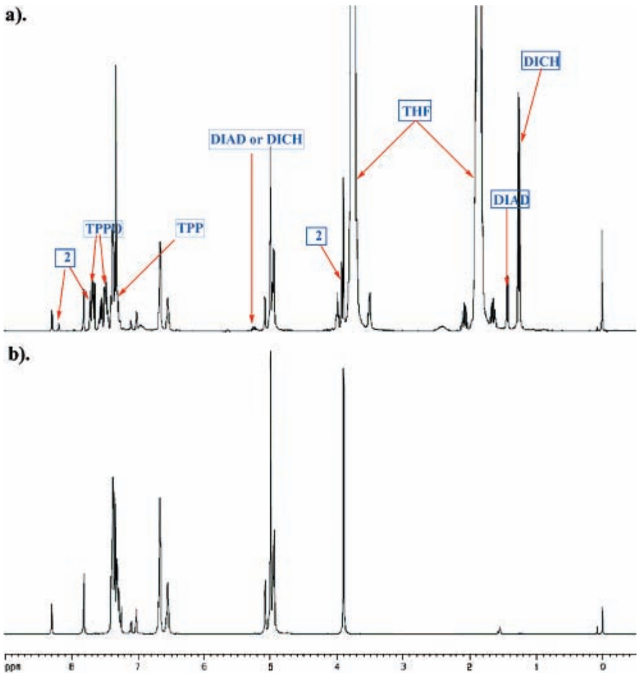
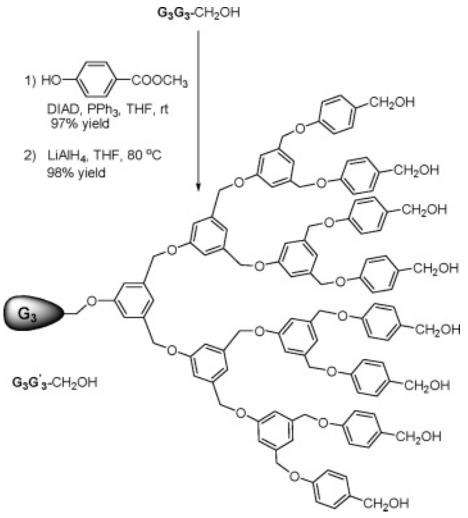


Figure 2. ^{1}H NMR of **G_3G_2-COOMe**: (a) reaction mixture after removal of most of organic solvent and (b) after purification by precipitation in ether and methanol.

To prove the versatility of these new Janus dendrimers, the peripheral functional groups were further modified by Wang-linkers. As shown in Scheme 2, standard Mitsunobu condensation of **G_3G_3-CH_2OH** with methyl *p*-hydroxylbenzoate gave the dendritic ester in 97% yield. Reduction of the ester groups with LiAlH$_4$ afforded **$G_3G'_3$-CH_2OH** in 98% yield. This dendrimer was well characterized by ^{1}H and ^{13}C NMR and TOF mass spectrometry as reported in Supporting Information.

Scheme 2. Synthesis of Janus Dendrimer with Wang-Linkers



With these Janus dendrimers in hand, we investigated their potential use for LPOS[18] by choosing the Pd- catalyzed

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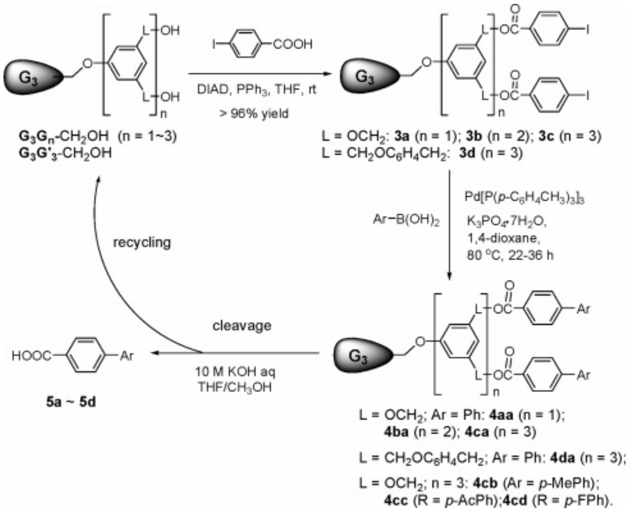
[17] Dandapani, S.; Curran, D. P. *Chem.−Eur. J.* **2004**, *10*, 3130.

Suzuki coupling as a standard reaction. This choice was based on the following facts:[19, 20] (a) this reaction provides a powerful tool for the synthesis of biaryls, which are found in many natural and synthetic products; (b) the coupling reactions are generally carried out at high temperature and in the presence of a base, which can be used to demonstrate the chemical stability of these dendritic supports; and (c) separation of the homogeneous Pd-catalyst after the reaction is often problematic.

The Pd-catalyzed Suzuki coupling of dendrimer-supported *p*-iodo benzoate **3a**∼**3d** with aromatic boronic acids was then studied (Scheme 3).

Scheme 3. Janus Dendrimers as Soluble Supports for the Pd-Catalyzed Suzuki Coupling Reactions



The dendritic supports of **G_3G_1-CH_2OH, G_3G_2-CH_2OH**, **G_3G_3-CH_2OH**, and **$G_3G'_3$-CH_2OH** were loaded with *p*-iodobenzoic acid under standard Mitsunobu reaction conditions respectively, followed by Suzuki coupling with different aromatic boronic acids. The reaction progress was monitored by TLC. Both steps were demonstrated to give quantitative conversions and excellent purity according to the ^{1}H NMR and TOF−MS spectra for every dendrimer support, giving high isolated yields (Table 1). The Pd content in the product **4ba** was measured by ICP−MS and found to be 6.11 ppm (0.004%). It was noted that complete conversion could be achieved at prolonged time for higher generation dendrimers. The dendrimer-supported coupling products **4** were cleaved by using aqueous KOH in THF/methanol solvent system at refluxing temperature. After concentration, the dendrimer support was quantitatively recovered upon addition of diethyl ether and filtration. This result indicates that these dendritic supports are very stable under these relatively harsh reaction conditions. Finally, the products were separated by ether extraction in high yields after the filtrate was acidified (Table 1). Unlike common dendrimer-supported organic synthesis, separation of these dendrimer products did not require time-consuming techniques, such as size exclusion chromatography (SEC), dialysis, or even column chromatography.[18] All products in every step were purified by a simple solvent precipitation and the product purity in each step is excellent as confirmed by ^{1}H NMR, ^{13}C NMR, and MALDI-TOF (see Supporting Information).

Table 1. Janus Dendrimers as Soluble Supports for the Pd-Catalyzed Suzuki Coupling Reactions[a]

entry	dendrimer	Ar (sub.)	**4** (%)[b]	**5** (%)[b]
1	**G_3G_1-CH_2OH**	Ph	97 (**4aa**)	98 (99)[c]
2	**G_3G_2-CH_2OH**	Ph	98 (**4ba**)	97 (98)[c]
3[d]	**G_3G_2-CH_2OH**	Ph	96 (**4ba**)	96 (97)[c]
4	**G_3G_3-CH_2OH**	Ph	98 (**4ca**)	98 (98)[c]
5	**$G_3G'_3$-CH_2OH**	Ph	98 (**4da**)	97 (97)[c]
6	**G_3G_3-CH_2OH**	*p*-MePh	96 (**4cb**)	96 (98)[c]
7	**G_3G_3-CH_2OH**	*p*-AcPh	98 (**4cd**)	98 (98)[c]
8	**G_3G_3-CH_2OH**	*p*-FPh	97 (**4ce**)	98 (97)[c]

[a] Arylboronic acid/aryl iodide = 1.15 (mol/mol), $K_3PO_4 \cdot 7H_2O$/aryl iodide = 2.0 (mol/mol), 1.0 mol % $Pd[(P(p\text{-}C_6H_4CH_3)_3]_3$, dioxane, reflux, 22∼36 h. [b] Isolated yield. [c] Data in brackets are recovered yields of dendrimer supports. [d] Recovered **G_3G_2-CH_2OH** was used.

In conclusion, we have established for the first time a liquid-phase approach for the synthesis of new kind of functionalized Janus dendrimers. Dendrimers were grown from the benzyl alcohol focal point of the Fréchet's dendron and were purified using a simple precipitation method without the need for chromatographic separation. The potential application of these Janus dendrimers as well-defined support for LPOS has been demonstrated in the Pd-catalyzed Suzuki coupling reactions. Their uses as chiral catalyst supports are in progress in the same laboratory. Furthermore, this method may provide insight into design of other codendrimers such as diblock codendrimers composed of two extremely different dendrons[14e] without the need for time and labor consuming purification steps.

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Supporting Information Available: General experimental methods, preparation and characterization data for Janus dendrimers, and ^{1}H and ^{13}C NMR and TOF−MS spectral data for the Janus dendrimers and dendritic intermediates. This material is available free of charge via the Internet at http://pubs.acs.org.

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