

Dialyzable Carbosilane Dendrimers as Soluble Supports for the Functionalization of Pyridine Fragments via Palladium-Catalyzed Coupling Reactions

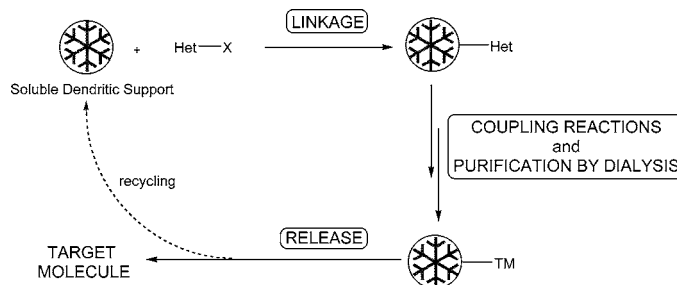
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ABSTRACT



The use of carbosilane (CS) dendrimers as soluble supports in liquid phase organic synthesis (LPOS) is described. Control of the three key steps is perfectly achieved by covalently binding a pyridine fragment to the soluble support, modifying it via coupling reactions, and releasing it at the end. Nanofiltration (dialysis) allows facile purification of the supported molecules after each step.

Among the many applications of solid-phase chemistry, the use of insoluble resins as supports for substrate modification has become a powerful tool in organic syntheses, especially within a pharmaceutical setting and using high throughput experimentation.¹ Advantages of this methodology include the high conversions obtained by the use of large reagent excesses and the easy purification of the supported products

by filtration and washings. Some limitations exist, however, to the use of insoluble resins in solid-phase organic chemistry (SPOS). Some supports can present total incompatibility with certain reagents, such as polystyrene beads with strongly basic reagents.² Monitoring of reaction progress in these heterogeneous systems using standard spectroscopic techniques can furthermore be cumbersome.

As an alternative, soluble supports have recently been used in so-called liquid-phase organic synthesis (LPOS).³ Linear polymeric materials such as poly(ethylene glycol) (PEG)

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have first been developed.⁴ Due to the low loading capacity of these polymers, hyperbranched polymers and dendrimers appear to be more suitable supports.⁵

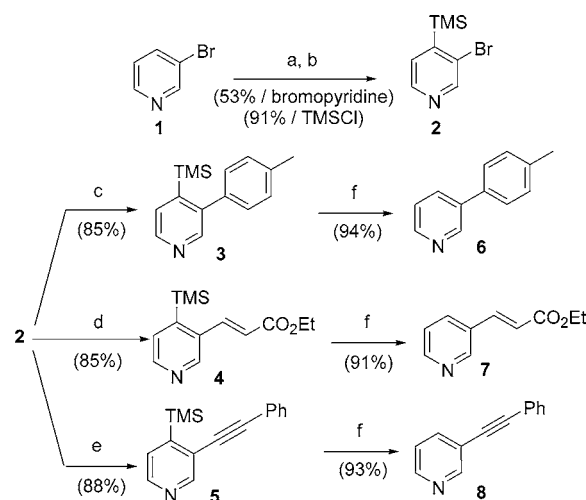
In relation to our interest in applications of functionalized dendrimers as homogeneous catalysts,⁶ we recently showed that soluble carbosilane (CS) dendrimers are suitable supports to allow classical organic reactions at their periphery.⁷ Among the variety of dendritic backbones, CS dendrimers present several advantages such as high thermal stability, high inertness toward organic reagents, good accessibility, good solubility in classical organic solvents, and a size that makes these supports separable via nanofiltration.⁸

To further explore the scope and the multipurpose aspects of this type of support, we present here the multistep modification of pyridine derivatives via palladium-catalyzed coupling reactions at the periphery of a soluble carbosilane dendritic support. We have used a simple process based on three key steps,^{1a} including (1) attachment of the organic fragment to the support, without linker, via a covalent bond; (2) modification of this fragment by coupling reactions; and (3) release of the target molecule from the support by a simple and clean procedure. To complete the overall methodology, the effective nanosize of the dendritic scaffolding allows the facile purification of the synthesized, supported intermediates by means of dialysis.

Pyridine structures have been selected because these are known to belong to numerous natural product skeletons and pharmacophores, such as (–)-nicotine derivatives.⁹ Substituted pyridines are also used as ligands in organometallic and coordination chemistry,¹⁰ and for the study of cross-coupling reactions in classical solution-phase chemistry.¹¹

They, furthermore, represent a model substrate for the study of selective activation of C–H bonds in the presence of halogen–carbon bonds via lithiation chemistry. This regio- and chemoselective lithiation step constitutes the key step of substrate attachment to the dendritic support.¹² As a test substrate, a substituted pyridine, such as 3-bromopyridine **1**, was chosen in which the presence of the 3-Br–C bond allowed the introduction of an organic fragment on the supported pyridine; see Scheme 1.

Scheme 1^a



^a (a) LDA/THF/–100 °C; (b) TMSCl; (c) Pd(PPh₃)₄ (1 mol %), *p*-MeC₆H₄B(OH)₂, Na₂CO₃ (2 M), toluene/EtOH (5/1), 100 °C, 16 h; (d) Pd(OAc)₂ (2.5 mol %), PPh₃ (5 mol %), ethyl acrylate, Et₃N, DMF, 130 °C, 16 h; (e) PdCl₂(PPh₃)₂ (5 mol %), PPh₃ (10 mol %), CuI (10 mol %), phenylacetylene, Et₃N, THF, 70 °C, 16 h; (f) *n*-Bu₄NF, THF, rt, 16 h.

As a simplified model system, a trimethylsilyl (TMS) group was used as a mimic of the dendritic support. Selective additions of electrophiles via lithiation of bromopyridines are well-known, and controlled ortho- and para-lithiation of 3-bromopyridine has been reported.^{12b,12c} Para-lithiation using LDA at low temperature (–100 °C) in tetrahydrofuran and subsequent quenching with TMSCl afforded the corresponding 3-bromo-4-trimethylsilylpyridine **2** in 53% yield, based on the pyridine starting material. Because the TMS group is used as a mimic of the dendritic support it should in consequence be considered as the determining factor of the reaction. Thus, an excess of the lithiated pyridine (2 equiv) was employed which improved the yield to 91%, based on the starting TMSCl.

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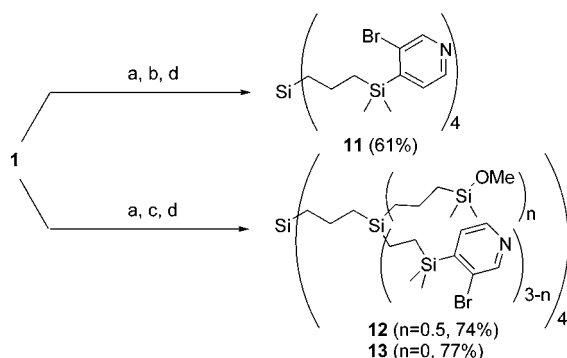
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Palladium-catalyzed coupling reactions were then tested on the silylated bromopyridine **2** using standard procedures. A Suzuki coupling reaction was first tested and after 16 h in refluxing THF a complete conversion into the 3-*p*-tolyl-4-trimethylsilylpyridine **3** was observed (isolated yield 85%); see Scheme 1. This result shows that the mutual ortho-positioning of the TMS and bromide groups on the pyridine ring does not affect reaction at the C–Br bond and also that desilylation, which would cause unwanted release of the organic fragment from the dendritic support, does not take place. In a similar way, a Heck coupling reaction was successfully tested using ethyl acrylate. After an overnight heating at 130 °C, the 3-(4-trimethylsilylpyridin-3-yl)acrylic acid ethyl ester **4** was obtained in 85% yield. A Sonogashira coupling reaction afforded the formation of 3-phenylethynyl-4-trimethyl-silylpyridine **5** in high yield without any desilylation.

Classical desilylation conditions were then employed using tetrabutylammonium fluoride to “release” the modified pyridine fragment from the TMS group.¹³ Desilylated compounds **6**, **7**, and **8** from the corresponding palladium-catalyzed coupling reaction products were obtained in 94%, 91%, and 93% yield, respectively, by purification using a simple filtration through a plug of silica. Using a TMS group as a mimic of the carbosilane dendrimer established the synthetic principle of our methodology and showed that the presence of the silicon substituent does not interfere with the modification of the other positions at the pyridine ring.

Our strategy was then applied to the G₀ and G₁ carbosilane dendrimers **9** and **10** that carry, respectively, 4 and 12 peripheral chlorosilane groups. For the G₀-dendrimer **9** the linkage procedure using 2 equiv of lithiated pyridine per Si–Cl moiety afforded a complete conversion into the fully substituted dendrimer **11**, which was readily purified by column chromatography on silica using ethyl acetate as eluent (61% yield), see Scheme 2.

Scheme 2^a



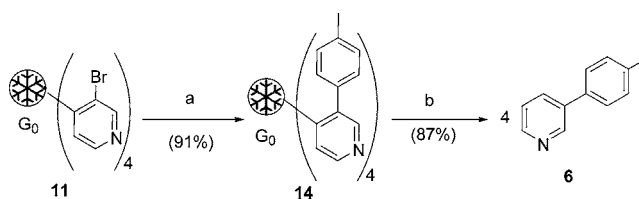
^a (a) LDA/THF/–100 °C; (b) dendrimer G₀-Cl **9**; (c) dendrimer G₁-Cl **10**, –100 to 0 °C; (d) Et₃N/MeOH, rt.

Similarly, using 2 equiv of lithiated bromopyridine **1**, a high level of substitution on the G₁-dendrimer was reached according to ¹H, ¹³C, and ²⁹Si NMR analyses. The eventually

unreacted Si–Cl groups were converted into unreactive Si–OMe functions by a quench reaction with dry methanol and dry triethylamine. Compound **12**, obtained from a preliminary experiment, showed approximately 80% of substitution, i.e. 10 of the 12 chlorosilane functions had reacted with lithio-bromopyridine and two of them had not. Following experiments presented higher levels of substitution (>95%) by allowing the temperature to reach 0 °C before the addition of methanol and triethylamine (see compound **13**, Scheme 2).

The supported 3-bromopyridines were then used in the different palladium-catalyzed cross-coupling reactions. Concerning the G₀-dendrimer **11**, complete conversions to the coupling compounds were observed, and in the case of the Suzuki coupling reaction, the corresponding modified dendrimer **14** was isolated after chromatography in 91% yield (Scheme 3).

Scheme 3^a



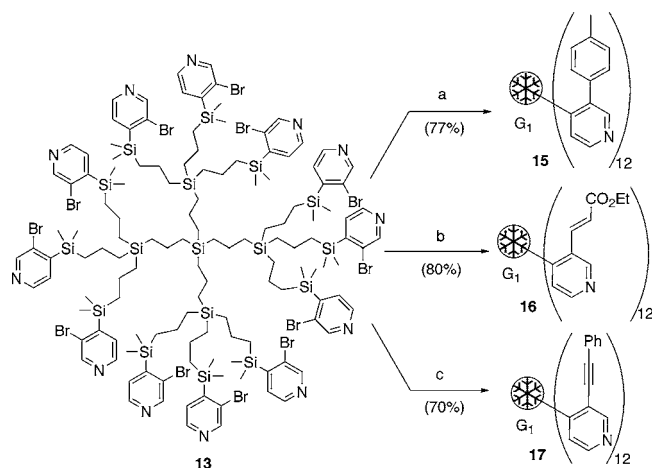
^a (a) Pd(PPh₃)₄ (4 × 1 mol %), *p*-MeC₆H₄B(OH)₂, Na₂CO₃ (2 M), toluene/EtOH (5/1), 100 °C, 16 h; (b) *n*-Bu₄NF, THF, rt, 16 h.

With the G₁-dendrimers, compound **12** presenting 10 bromopyridines moieties at its periphery was first employed in a Suzuki coupling reaction using 1 mol % of palladium catalyst per bromine atom. A complete conversion was observed, which indicates that both the supported nature of one of the cross-coupling partners as well as the presence of Si–OMe moieties did not interfere with the catalytic reaction. The G₁-dendrimer **13** bearing 12 3-bromopyridines was then successfully used in different cross-coupling reaction procedures (Scheme 4).

In all of the steps dealing with the G₁-dendrimer as support, the crude reactions were purified using passive dialysis⁸ over commercially available dialysis tubing (recycled benzoylated cellulose) with a cutoff mass of 1200 g/mol (MW of **13**, 3395.5 g/mol).

Passive dialysis purification of the crude mixture of the linkage procedure afforded the compounds **12** and **13** in 74% and 77% yield, respectively. Without any refreshment of the solvent, compounds **12** and **13** were obtained in high purity to allow subsequent cross-coupling reactions (see Supporting Information for experimental details). The crude mixtures of the cross-coupling reactions were again treated by passive dialysis and the supported compounds **15**, **16** and **17** were isolated in 77%, 80%, and 70% yield, respectively.

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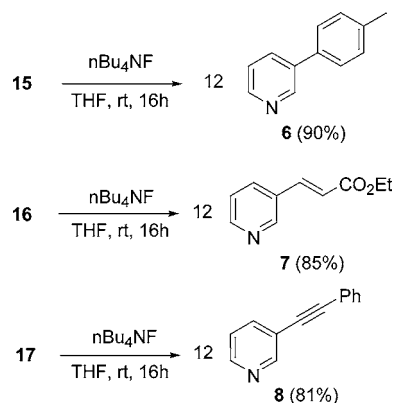
Scheme 4^a

^a (a) $\text{Pd}(\text{PPh}_3)_4$ (12×1 mol %), $p\text{-MeC}_6\text{H}_4\text{B}(\text{OH})_2$, Na_2CO_3 (2 M), toluene/EtOH (5/1), 100 °C, 16 h; (b) $\text{Pd}(\text{OAc})_2$ (12×2.5 mol %), PPh_3 (12×5 mol %), ethyl acrylate, Et_3N , DMF, 130 °C, 16 h; (c) $\text{PdCl}_2(\text{PPh}_3)_2$ (12×5 mol %), PPh_3 (12×10 mol %), CuI (12×10 mol %), phenylacetylene, Et_3N , THF, 70 °C, 16 h.

The release reaction of the modified pyridine fragments was performed using tetrabutylammonium fluoride solution at room temperature. From the supported Suzuki coupling compound **11** on the G_0 -dendrimer, an overnight reaction afforded the desilylated substituted pyridine **6** in 87% yield after filtration over a short plug of silica (Scheme 3). Similar release reactions of cross-coupling compounds from G_1 -dendrimer support were performed with complete conversion. The desilylated coupling compounds **6**, **7**, and **8** were separated from the degraded dendritic fragments by means of chromatography and were isolated in 90%, 85%, and 81% yield, respectively (Scheme 5).

By controlling the three steps of our dendrimer-supported pyridine model system, we have shown that carbosilane dendrimers are suitable and robust supports for LPOS which are compatible with organolithium and Grignard (ref 7a) reagents. In addition, relatively small generation dendrimers

Scheme 5



(G_1) allow easy control of the efficiency of reactions on supported fragments and, furthermore, allow the purification of (modified) fragments via filtration techniques (dialysis).

Studies on the use of this type of soluble synthesis support for other classical organic reactions and for the total synthesis of natural products and analogues are currently under investigation, as is the potential to recycle the support.

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Supporting Information Available: Experimental procedures and characterization data for compounds **2**–**17**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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