ORGANIC LETTERS

2000
Vol. 2, No. 11
1621−1624

Synthesis of Periphery-Functionalized Dendritic Molecules Using Polylithiated Dendrimers as Starting Material

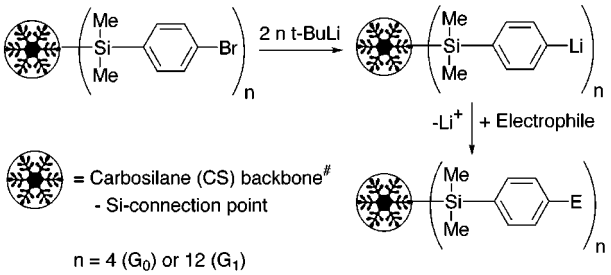
Peter Wijkens,[†] Johann T. B. H. Jastrzebski,[†] Paul A. van der Schaaf,[‡] Roman Kolly,[‡] Andreas Hafner,[‡] and Gerard van Koten*,[†]

Debye Institute, Department of Metal-Mediated Synthesis, Utrecht University, Padualaan 8, 3584 CH Utrecht, The Netherlands, and Ciba Specialty Chemicals, Building K-420, CH-4002 Basel, Switzerland

g.vankoten@chem.uu.nl

Received April 7, 2000

ABSTRACT



A general method for the functionalization of Si–Cl terminated carbosilane dendritic molecules via organolithium or organomagnesium reagents is described. Quantitative exchange of the bromine atoms of 4-bromophenyl-functionalized dendrimers affords polylithiated species that are valuable starting materials for further functionalization, e.g., into pyridyl alcohols. The latter were successfully applied as catalyst precursors in a ruthenium-mediated ring-closure metathesis reaction.

Among the many potential applications[1] of dendrimers, the immobilization of catalytically active sites at the periphery of these molecules is of current interest. The first example was the successful use of an arylnickel-functionalized carbosilane as a homogeneous catalyst in the Kharasch addition of polyhalogenoalkanes to C═C double bonds.[2]

Today, a number of dendritic molecules are known that contain ligand systems at their periphery to which metal atoms may be bound covalently or via heteroatom donor bonds. This topic has been reviewed recently.[3,4] So far, only a few examples of such metallo-dendrimers have been applied as immobilized catalysts. A recent development is the use of metallo-dendrimers as low-conversion catalysts in continuous membrane-reactor processes. An example is the selective hydrovinylation of styrene with an in situ prepared palladium catalyst immobilized on a carbosilane (CS) dendrimer.[5] Similar examples are palladium-catalyzed C−C bond formation reactions using bisphosphine-containing CS-dendrimers[6] or diaminopropyl-type dendrimers.[7]

Peripheral functional groups are often connected to the dendrimer core via heteroatom-containing linkers such as

[†] Utrecht University.
[‡] Ciba Specialty Chemicals.

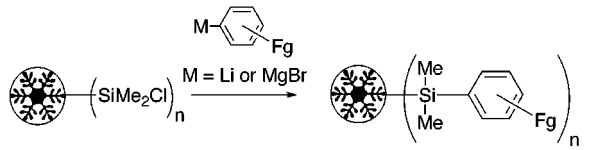
(1) Bosman, A. W.; Janssen, H. M.; Meijer, E. W. *Chem. Rev.* **1999**, *99*, 1665.
(2) Knapen, J. W. J.; van der Made, A. W.; de Wilde, J. C.; van Leeuwen, P. W. N. M.; Wijkens, P.; Grove, D. M.; van Koten, G. *Nature* **1994**, *372*, 659.
(3) Majoral, J.-P.; Caminade, A.-M. *Chem. Rev.* **1999**, *99*, 845.
(4) Newkome, G. R.; He, E.; Moorefield, C. N. *Chem. Rev.* **1999**, *99*, 1689.
(5) Hovestad, N. J.; Eggeling, E. B.; Heidbüchel, H. J.; Jastrzebski, J. T. B. H.; Kragl, U.; Keim, W.; Vogt, D.; van Koten, G. *Angew. Chem., Int. Ed.* **1999**, *38*, 1655.
(6) De Groot, D.; Eggeling, E. B.; de Wilde, J. C.; Kooijman, H.; van Haaren, R. J.; van der Made, A. W.; Spek, A. L.; Vogt, D.; Reek, J. N. H.; Kamer, P. C. J.; van Leeuwen, P. W. N. M. *Chem. Commun.* **1999**, 1623.
(7) Brinkman, N.; Giebel, D.; Lohmer, G.; Reetz, M. T.; Kragl, U. *J. Catal.* **1999**, *183*, 163.

10.1021/ol0059100 CCC: $19.00
Published on Web 05/10/2000

esters, carbamates, amides, or Si−O bonds. The presence of such reactive groups hampers or even precludes further derivatization using organolithium or Grignard reagents. We here present a preparative route to functionalized CS-dendrimers in which ligand moieties are bound to the carbosilane core via σ Si−C bonds, which are inert under most catalytic conditions.

Previously we have shown that 4-[(dimethylamino)methyl]-phenyl- and 3,5-[bis(dimethylamino)methyl]phenyl-functionalized CS-dendrimers are easily accessible by reaction of Me_2SiCl-terminated carbosilane dendrimers with the corresponding organolithium or Grignard reagents.[8] To further explore the scope of this method we have reacted Me_2SiCl-terminated carbosilanes **1a** and **1b**,[9] (Scheme 1; the

Scheme 1



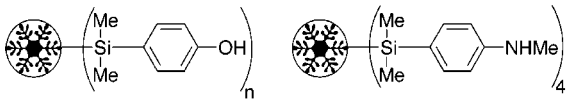
1a; $Si[(CH_2)_3SiMe_2Cl]_4$
1b; $Si\{(CH_2)_3Si[(CH_2)_3SiMe_2Cl]_3\}_4$

2a; n = 4, Fg = 4-$OSiMe_2t$-Bu
2b; n = 12, Fg = 4-$OSiMe_2t$-Bu
2c; n = 4, Fg = 4-$N(Me)SiMe_2t$-Bu
2d; n = 4, Fg = 4-Br
2e; n = 12, Fg = 4-Br
2f; n = 4, Fg = H

encircled "snowflake" symbol is introduced by the authors to represent a dendritic support), with various (protected) functionalized arylmagnesium or aryllithium reagents.

When **1a** or **1b** is reacted with a slight excess of the Grignard reagent derived from Me_2t-BuSi-protected 4-bromophenol or 4-bromo-*N*-methylaniline, the silyl-protected functionalized dendrimers **2a**, **2b**, and **2c** are formed quantitatively.[10] After workup, the products were obtained in pure form and were characterized by ^1H and ^{13}C NMR spectroscopy, as well as MALDI-TOF MS and elemental analysis (see Supporting Information).

The 4-hydroxyphenyl- and 4-*N*-methylaminophenyl-functionalized CS-dendrimers **3** and **4** were obtained by deprotection with Et_3NHF in THF. These CS-dendrimers can be



3a; n = 4
3b; n = 12

4

easily converted into further functionalized molecules using straightforward organic reactions such as esterification or amide formation.[11]

In particular, the 4-bromophenyl-functionalized CS-dendrimers **2d** and **2e** are valuable starting materials that allow the easy introduction of a variety of functional groups. This may be realized by substitution of the bromine atoms in **2d** and **2e** by lithium.

It is well known that the aryl groups in *o*-aminoarene-functionalized CS-dendrimers can be quantitatively lithiated via heteroatom-assisted lithiation reactions. The lithiation products may then be easily converted by transmetalation into a wide variety of other organometallic derivatives.[8] Accordingly, a synthetic protocol was developed to substitute all bromine atoms in **2d** and **2e** by lithium atoms. These 4-lithiophenyl-functionalized CS-dendrimers appear to be excellent starting materials for the synthesis of a variety of periphery-functionalized dendrimers using suitable electrophiles.

Reaction of **2d** or **2e** with 4 or 12 equiv, respectively, of *n*-BuLi, gave sticky insoluble materials, which were not further analyzed but directly converted into products (see Scheme 2).

The lithiation reaction, i.e., the exchange of bromine for lithium, is quantitative, as was shown by hydrolysis of freshly prepared **5a**. The phenyl-functionalized derivative **2f** (see Scheme 1) was the only product obtained. Analysis of the product by MALDI-TOF showed the complete absence of bromine-containing products.

Reaction of in situ prepared **5a** or **5b** with Ph_2PCl afforded the corresponding diphenylphosphino derivatives **6a** and **6b** in high yield. Because these materials are rather susceptible to oxidation, for analytical purposes (elemental analysis and MALDI-TOF MS) **6a** and **6b** were converted to the corresponding phosphinoxide compounds **6a′** and **6b′** via a H_2O_2 oxidation reaction. (Note that the CS-dendrimer backbone remained unaffected.) The dicyclohexylphosphino compound **6c** was prepared similarly from c-Hex_2PCl.

The feasibility of this approach for the introduction of acyl-, hydroxy-, or amino-functionalized groups at the periphery of CS-dendrimers was tested by reacting **5a** with DMF, acetone, or *N*-*tert*-butyl(phenyl)imine to give the corresponding derivatives **7**, **9**, and **8** (see Scheme 2). Whereas **7** and **9** were isolated analytically pure after workup, **8** contained about 20% material resulting from partial protolysis of aryl-Li groups present in **5a**. A separate experiment demonstrated that reaction of 4-(trimethylsilyl)-phenyllithium with *N*-*tert*-butyl(phenyl)imine, under various reaction conditions, also produced considerable amounts (20−25%) of the protolysis product trimethylsilylbenzene.

Previously it has been shown that the heteroatom-assisted *ortho*-lithiation of *N*-alkyl(phenyl)imines is a competing reaction during the addition of organolithium compounds to the imine bond, especially when bulky N-substituents are present.[12] We believe that in our case a comparable Li−H exchange occurs between the Li atoms in **5a** and one of the *ortho*-H atoms in *N*-*tert*-butyl(phenyl)imine.

(8) Kleij, A. W.; Kleijn, H.; Jastrzebski, J. T. B. H.; Smeets, W. J. J.; Spek, A. L.; van Koten, G. *Organometallics* **1999**, *18*, 268.

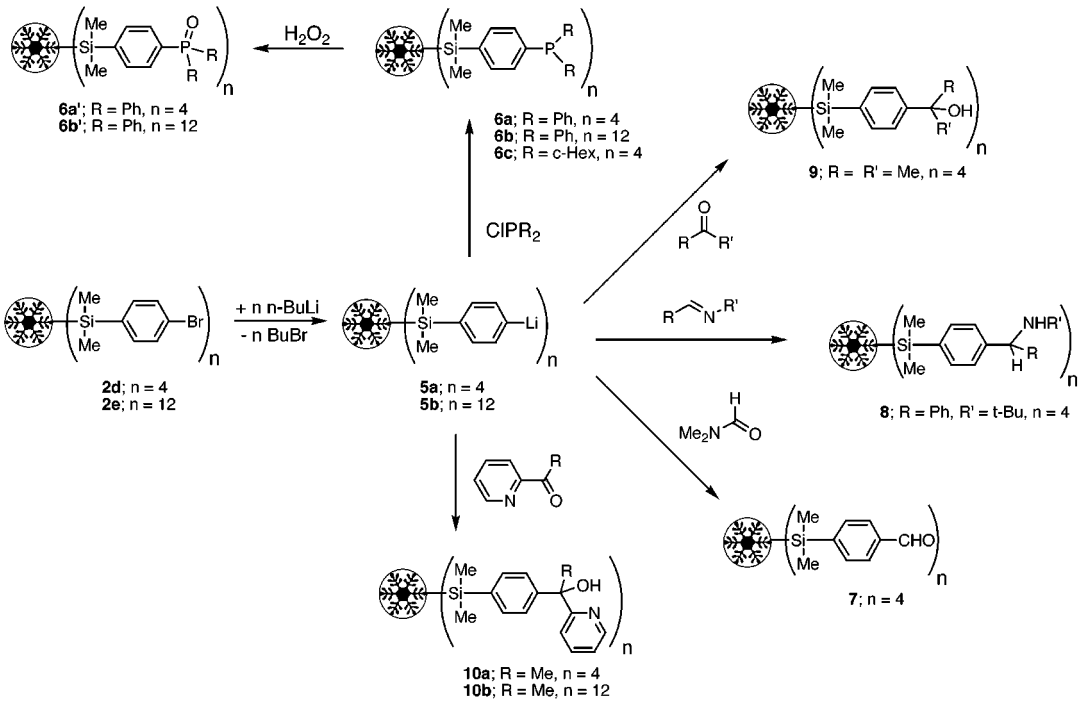
(9) Van der Made, A. W.; van Leeuwen, P. W. N. M. *J. Chem. Soc., Chem. Commun*. **1992**, 1400.

(10) As a result of the excess Grignard reagent Me_2t-BuSi-protected phenol or *N*-methyl aniline was also formed.

(11) Recently we reported the synthesis of 4-(hydroxymethyl)phenyl-substitued CS-dendrimers and their subsequent conversion into phosphino carboxylic esters; see ref 5.

(12) Cliffe, I. A.; Crossley, R.; Shepher, R. G. *Synthesis* **1985**, 1138.

Scheme 2

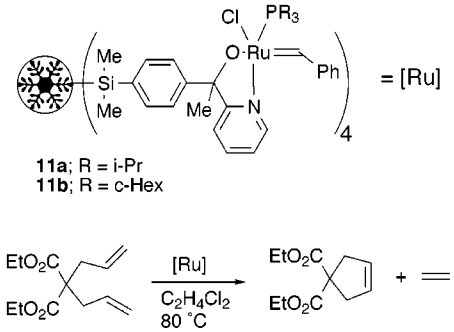


2-Pyridylcarbinol has been well-established as a ligand for catalyst precursors, e.g., for ring-opening metathesis polymerization (ROMP) reactions.[13] Also, the application of 2-pyridylcarbinol-containing ruthenium carbene catalysts for the ring-closure metathesis (RCM)[14] reaction of bifunctional olefins, e.g., diethyl diallyl malonate to diethyl-3-cyclopentene dicarboxylate, has recently been disclosed.[15]

To obtain the dendrimeric equivalent of this useful ligand, we have reacted **5a** and **5b** with 2-acetylpyridine. The 2-hydroxyalkylpyridyl-functionalized dendritic compounds **10a** and **10b** (see Scheme 2) were obtained in excellent yield. Deprotonation of **10a** with 4 equiv of *n*-BuLi and subsequent transmetalation with $PhC(H)=RuCl_2(PR_3)_2$ (R = *i*-Pr or *c*-Hex) afforded after workup, **11a** and **11b**, as dark-green solids.

Both **11a** and **11b** were applied as catalysts under homogeneous conditions in the RCM reaction of diethyl diallyl malonate (see Scheme 3). To a solution containing 2 mmol of diethyldiallylmalonate in 20 mL of 1,2-dichloroethane was added 1 mol % (based on ruthenium) of catalyst **11a** or **11b**. The reaction mixture was heated to 80 °C, and the conversion of the substrate into diethyl-3-cyclopentene dicarboxylate was monitored by GC. After 30 min 100% conversion was reached, a value comparable to that of the unimolecular catalyst.[15]

Scheme 3



A similar experiment was carried out[16] in which the catalyst solution was separated from the solution containing the substrate and the products by a membrane (SelRO-nanofiltration membrane MPS-60; stated molecular weight cutoff, 400). In this case, the conversion to diethyl-3-cyclopentene dicarboxylate stopped after about 20% conversion while extensive decomposition of the catalyst occurred (a black precipitate was formed in the vessel containing the catalyst). A possible explanation for this phenomenon may be deactivation of the metathesis catalyst by the membrane surface.

In this respect it should be noted that the currently available membranes with the proper pore size are in most cases not compatible with the applied reaction conditions, in particular the use of organic solvents. However, it was shown that leaching of the catalyst through the membrane into the vessel containing the substrate does not occur, because this solution remained clear and colorless.

(13) van der Schaaf, P. A.; Abbenhuis, R. A. T. M.; van der Noort, W. P. A.; de Graaf, M.; Grove, D. M.; Smeets, W. J. J.; Spek, A. L.; van Koten, G. *Organometallics* **1994**, *13*, 1433.

(14) Fürstner, A. *Top. Catal.* **1998**, *4*, 285.

(15) Van der Schaaf, P. A.; Mühlebach, A.; Hafner, A.; Kolly, R. Heterocyclic ligand containing ruthenium and osmium catalysts. WO 99/29701 (prio. date 4/12/1997).

(16) Albrecht, M., Hovestad, N. J., Boersma, J., van Koten, G., submitted for publication.

The development of membranes that are compatible with both the applied reaction conditions and organic solvents and that have varying cutoff properties is an important challenge for the future. When such membranes become available, homogeneous catalytic processes in membrane reactors can be developed that are characterized by a continuous compartmentalization of the dissolved catalyst. Various aspects of this research are currently under investigation.

Supporting Information Available: Experimental procedures and characterization data for compounds **2a**−**f**, **3a**−**b**, **4**, **6a**−**c**, **7**−**9**, and **10a**−**b**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0059100