Poly(benzyl ether) Dendrimers Functionalized at the Core with Palladium Bis(*N*-Heterocyclic Carbene) Complexes as Catalysts for the Heck Coupling Reaction

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Supporting Information

ABSTRACT: Bis(imidazolylidene)palladium complexes 9-12 containing a sterically hindered aryl group (mesityl or 2,6diisopropylphenyl) and a poly(benzyl ether) dendron as Nsubstituents of the NHC ligand are accessible up to the third generation by transmetalation of the corresponding silver complexes. Complexes 9-12 are soluble, active, and very stable catalysts under Heck reaction conditions. The NHC ligand appears to be stably coordinated to the Pd during catalysis. The catalytic activity increases with generation number, although irregularly. The palladium site is not significantly congested in the reaction solvent by the increasing size of the dendritic substituents, as corroborated by X-ray diffraction, fluorescence and DOSY-NMR spectroscopy, and MD simulation studies. This



is a consequence of the conformational semiflexibility of the poly(benzyl ether) dendrons and the benzylic link between these dendrons and the N-heterocyclic ligands.

INTRODUCTION

Advances in transition-metal-based homogeneous catalysis have provided well-defined and highly active and selective catalysts that can be tailored using ligand design as a key tool.¹ There is, however, an increasing need to increase the productivity of these fine catalysts in order to make them attractive for practical applications. Obviously, this requires the synthesis of catalysts that are able to operate without degradation—even under harsh conditions—and, therefore, are suitable for reuse. In terms of coordination versatility and stability, *N*-heterocyclic carbenes (NHCs) have proven to be a superb class of ancillary ligands in modern day organometallic chemistry and have allowed the synthesis of enhanced catalysts for a broad number of homogeneous processes.²

Dendritic architectures³ have been used as supports for active sites operating under homogeneous conditions.⁴ The bottomup approach to prepare this type of catalyst allows precise control of the metal environment, while the reaction microenvironment is progressively determined by the dendritic structure with increasing generation, rather than by the solvent. As a result, dendritic effects come into play in the catalytic process.⁵ Catalysts enclosed in the core of dendrimers are particularly appealing in this context since they mimic features of enzyme catalysts and have shown remarkable effects on catalytic activity, selectivity, and specificity in different reactions.⁶ Moreover, their size-enlarged (or nanosized) structure enables the possibility to run catalytic reactions in continuous-flow membrane reactors,^{7,8} while their nature can be tuned to meet the solubility requirements for the application of other separation methodologies.^{8,9}

Palladium dendrimers have already been tested in C–C coupling reactions, although metal leaching and catalyst deactivation, usually associated with the deposition of Pd black precipitates, have been a common problem for the recovery of the dendritic catalysts.¹⁰ We have previously studied the behavior in this and other types of reactions of poly(benzyl ether) or carbosilane dendrimers functionalized at the focal point or periphery with bis- or tris(pyrazol-1-yl)methane metal complexes.^{11–13} Unfortunately, the problems mentioned above prevented reuse of the dendritic catalysts. One of the advantages of the use of imidazole-derived NHC ligands in Pd-mediated reactions is the strong Pd–NHC bond and limited decomposition pathways.¹⁴ As such, we turned our attention to dendrimer NHC complexes containing the carbene as the anchoring ligand between the palladium center and the

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dendritic moiety. There are only a few examples of "formally" real dendrimers in the literature containing rhodium,¹⁵ iridium,⁶ ruthenium,¹⁶ or silver¹⁷ metal complexes anchored to the dendritic structure via a NHC ligand. In addition, Díez-Barra and co-workers have reported a star-shaped trimetallic NHC Pd complex that is more active than the corresponding monometallic catalyst in the Heck reaction between *p*-bromobenzaldehyde and *n*-butyl acrylate.¹⁸ Additionally, Haag and Meise have reported a highly active and water-soluble Suzuki cross-coupling catalyst based on hyperbranched polyglycerol decorated with bis(NHC)palladium complexes that was reused in five consecutive reactions without a loss in activity.¹⁹

Herein, we report the synthesis of new poly(benzyl ether) dendrimers (Fréchet dendrimers) of up to the third generation containing bis(imidazolylidene)palladium complexes at their core. The use of these macromolecules as precatalysts in a sample Heck-Mizoroki reaction is presented. Heck coupling usually requires high temperatures to proceed, even with activated substrates, and therefore Pd-NHC catalysts are particularly suitable for this reaction.^{20,21} The encapsulation of palladium centers within the dendrimer interior is often associated with enhanced stabilities,¹⁰ and even if the activity is lowered by the encapsulation effect of the substituent, this might be compensated by the longer durability of the catalyst. N-Mesityl (Mes) or N-2,6-diisopropylphenyl (ⁱPr₂Ph) imidazoles were selected as the building blocks for the NHC precursors because of the benefits observed in catalysis with bulky aryl substituents on the carbene ligand.^{22,23} The study is complemented with conformational and structural studies based on solid-state X-ray structures, fluorescence techniques, diffusion-ordered NMR spectroscopy, and molecular dynamics simulations.

RESULTS AND DISCUSSION

Synthesis of Dendronized (Aryl)imidazolium Salts 1-4 and Their Silver Derivatives 5–8. The asymmetrically $N_{\rm N}N'$ -substituted imidazolium salts 1-4 were prepared in good yields by N-alkylation of the corresponding 1-arylimidazole compounds with the appropriate benzylic bromide dendron (Gn-dend)Br in warm acetone (Scheme 1). The silver carbene complexes 5-8 were obtained, also in good yields, by reaction of the imidazolium salts with silver oxide in CH₂Cl₂, using Lin's procedure.²⁴⁻²⁶ In both synthetic steps, longer times were required for completion of the reaction as the dendron generation increased (see Scheme 1 and Supporting Information for details). The preparation of 1a and 1b and their silver derivatives 5a and 5b was previously reported using a similar procedure.²⁷ Compounds 1-8 were obtained as analytically pure solids and characterized by NMR and IR spectroscopy, and ESI mass spectrometry (see Supporting Information for details). In addition, the crystal structures of complexes 5a, 5b and 6b were determined by X-ray diffraction methods (see below). The imidazolium salts 1-4 are air stable, although hygroscopic, soluble in chlorinated and polar solvents, and insoluble in diethyl ether and in alkanes. The silver complexes 5-8 are also air stable, soluble in chlorinated and polar solvents, and insoluble in alkanes. The solubility of these compounds increases with the generation (e.g., compounds 1 are somewhat soluble in acetone whereas compounds 4 are readily soluble) and with the 'Pr₂Ph substituent (i.e., series b is slightly more soluble than a, which contains a Mes group).

Scheme 1. Preparation of Dendronized NHC Precursors and the Corresponding Silver Complexes a



^a(a) (Gn-dend)Br, acetone, 60 °C, from 4 h for G0 to 2 days for G3. (b) $1/2Ag_2O$, CH_2Cl_2 , room temperature, from 16 h for 5a to 8 days for 8b.

The ¹H and ¹³C resonances of the mesityl or diisopropylphenyl groups in 1-8 show the equivalence of the two halves defined by the plane perpendicular to the ring that contains the N-Carvi bond in solution, and the characteristic diastereotopicity of the two methyl groups of each isopropyl moiety in **1b–8b**. The ¹H resonances of the heterocycle shift to high field after deprotonation of the imidazolium salts (1-4) and formation of the silver complexes 5-8 (from ca. 7.0 and 7.5 to ca. 6.8 and 7.1 for H⁴ and H⁵, respectively; see Scheme 1 for numbering scheme). The protons of the N-bonded methylene are also shifted from ca. 5.8 to 5.3, whereas other protons of the dendritic moiety are rather insensitive to coordination of the NHC ligand and resonate in the three regions characteristic for this type of poly(benzyl ether) dendron.¹² With an increase in dendron generation, the resonances of the protons located within the dendritic core suffer a small, but steady and consistent, upfield shift that is especially notable for the Nbonded CH₂ and H⁴ imidazolic protons (between -0.09 and -0.18 ppm on going from G0 to G3 complexes). This shielding has been interpreted as a consequence of the increasing number of aryl groups surrounding the focal point of the dendritic wedge in poly(benzyl ether) dendrons.^{12,13}

The carbone carbons were not detected in the ¹³C NMR spectra of **5–8**. This has sometimes been associated with rapid intermolecular carbone ligand exchanges in solution via the equilibrium $[Ag(NHC) \text{ (halido)}] \leftrightarrow [Ag(NHC)_2][Ag(halido)_2]^{24-26,28,29}$ This finding, together with the observation of the $[Ag(NHC)_2]^+$ cation in the mass spectra of **5–8**, agrees with the ability of this type of complex to transfer NHC ligands. The existence of an intermolecular ligand exchange was also suggested by the different shapes found for the resonances of

the imidazolic H⁴ and H⁵ protons, depending on the dendritic generation and aryl substituent on the NHC ligand. These resonances were observed as doublets for the G0 to G3 series of complexes 5a-8a and for the G0 complex 5b (${}^{3}J_{\rm H,H} \approx 1.5$ Hz), whereas the appearance of an additional coupling to ¹⁰⁷Ag or ¹⁰⁹Ag in G1 to G3 complexes **6b**-**8b** (both with ${}^{4}J_{H,Ag} \approx 1.5$ Hz) resulted in triplets that were better resolved for higher generations. The triplets were converted into doublets when a sample of 7b in CDCl₃ was heated. These observations are in agreement with an intermolecular exchange of carbene ligands that should be expectedly slower for the most encumbered silver centers (i.e., compounds b) and larger dendrons. The bimolecular nature of the mechanism was supported by the disappearance of the ${}^{1}\text{H}{}^{-109/107}\text{Ag}$ coupling in more concentrated samples of 7b. The Imz- C^2 resonance in 7b was indirectly detected at 183.3 ppm by a ¹H-¹³C HMBC experiment. Interestingly, the observation of an approximate ${}^{1}J_{C,Ag}$ value of 250 Hz is in agreement with the predominance of mono- over bis-NHC species in solution.³⁰

The molecular structures determined for complexes 5a, 5b, and 6b are shown in Figures 1–3. The metal centers in dimer



Figure 1. ORTEP representation of **5a** (left; 50% probability ellipsoids, H omitted for clarity) and parameters for the $Ag_2(\mu-Br)_2$ core (right). Selected bond lengths [Å] and angles [deg] (symmetry transformation used to generate equivalent atoms A: -x, -y, -z + 1): Ag(1)-C(1) 2.119(4), Ag(1)-Br(1) 2.6098(10), Ag(1)-Br(1A) 2.7691(10), Ag(1)-..Ag(1A) 3.3403(10), C(1)-N(1) 1.352(5), C(1)-N(2) 1.352(5), C(3)-N(2) 1.394(5), C(2)-C(3) 1.342(7), C(2)-N(1) 1.388(6), C(4)-N(1) 1.482(5), C(11)-N(2) 1.438(5); Br(1)-Ag(1)-Br(1A) 103.29(2), C(1)-Ag(1)-Br(1) 135.60(11), C(1)-Ag(1)-Br(1A) 120.02(10), Ag(1)-Br(1)-Ag(1A) 76.71(2), N(1)-C(1)-N(2) 104.2(3).

5a are situated in a distorted triangular and nearly planar environment (bond angles ranging from 103° to 136°) and bridged by two bromide atoms, with the N-heterocycle approximately perpendicular to the Ag₂Br₂ plane (69°, Figure 1). The difference between the two Ag-Br bond distances (2.61 and 2.77 Å) is only 0.16 Å, thus reflecting the high symmetry of the bromido bridges in this complex compared with other $[\{(NHC)Ag\}_2(\mu-Br)_2]$ dimeric structures reported previously (with differences in bond distances of between 0.43 and 0.58 Å).^{29,31} Complex 6b is monomeric and shows a linear arrangement around the silver(I) center, with a bonding angle of 177.0° and an Ag-Br distance of 2.43 Å (Figure 3). The molecular structure of 5b might be considered as an almost frontier case between the monomeric and dimeric arrangements (Figure 2). Thus, the highly asymmetric bridge in this complex (with differences between Ag-Br distances of 0.65 Å) can be interpreted as the result of side-on Ag…Br



Figure 2. ORTEP representation of **5b** (left; 50% probability ellipsoids, H omitted for clarity) and mean parameters for the $Ag_2(\mu$ -Br)_2 core (right). Selected bond lengths [Å] and angles [deg] (values in brackets correspond to distances or angles in the A moiety of the dimer): Ag(1)–C(1) 2.119(6) [2.097(5)], Ag(1)–Br(1) 2.4678(7) [2.4385(7)], Ag(1)–Br(1A) 3.0306(8) [3.173(1)], Ag(1)···Ag(1A) 3.9729(8), C(1)–N(1) 1.349(7) [1.347(7)], C(1)–N(2) 1.342(6) [1.341(7)], C(3)–N(2) 1.385(7) [1.383(6)], C(2)–C(3) 1.299(8) [1.314(8)], C(2)–N(1) 1.392(7) [1.394(7)], C(4)–N(1) 1.459(6) [1.463(7)], C(1)–N(2) 1.455(6) [1.440(6)]; Br(1)–Ag(1)–Br(1A) 90.83(2) [88.07(3)], C(1)–Ag(1)–Br(1) 171.52(14) [169.98(14)], C(1)–Ag(1)–Br(1A) 97.60(14) [101.3(2)], Ag(1)–Br(1)–Ag(1A) 88.61(3) [92.51(2)], N(1)–C(1)–N(2) 105.1(4) [104.4(4)].



Figure 3. ORTEP representation of **6b** (50% probability ellipsoids, H omitted for clarity). Selected bond lengths [Å] and angles [deg]: Ag(1)-C(1) 2.089(5), Ag(1)-Br(1) 2.4288(8), C(1)-N(1) 1.341(6), C(1)-N(2) 1.340(6), C(2)-N(1) 1.384(7), C(2)-C(3) 1.376(8), C(3)-N(2) 1.418(7), C(4)-N(1) 1.454(7), C(11)-N(2) 1.547(6); C(1)-Ag(1)-Br(1) 176.95(13), C(1)-N(1)-C(2) 111.6(4).

intermolecular interactions at 3.10 Å between two almost linear (NHC)AgBr monomers, with coordination parameters (C–Ag–Br angle of 170.7° and Ag–Br distance of 2.45 Å) that are very close to those found in **6b**. The above structures are examples of the large variety of bonding motifs that the coordinative plasticity of silver(I) permits in the solid state with N-heterocyclic carbene ligands and halide anions.^{25,32} We recently highlighted that, even if sterically hindered NHC ligands favor the formation of monomeric structures, a uniform distribution of the ligand crowding around the silver-carbene axis is also important to prevent the formation of dimers and other aggregated structures.¹⁷ We defined the buried volume eccentricity to parametrize the uniformity of this axial distribution, finding a good correlation between the type of structure adopted by (NHC)Ag(halido) complexes and the percent buried volume (% $V_{\rm bur}$)³³ when the latter was used in conjunction with the eccentricity parameter. For eccentricities of around 1.45 (as in 5a, 5b, or 6b), we predicted the predominance of monomeric structures for NHC ligands with a $%V_{\rm bur}$ greater than ~30.¹⁷ The same tendency is observed in the structures reported here, since the complex with an Nbonded mesityl ring (5a, $\%V_{bur} = 29.4$) gives a dimer, whereas those with the most sterically demanding 2,6-diisopropylphenyl ligand (**5b** and **6b**, $%V_{\text{bur}} = 33.4$ and 32.6) form monomeric or strongly distorted dimeric structures. The similar or even slightly higher buried volume of the G0 complex 5b with respect to the G1 analogue **6b** is a consequence of the open conformation adopted by the N-benzylic substituent in both complexes, which moves the dendron arms away from the metal center in 6b. For comparison, the $%V_{bur}$ in complex [Ag{1,3-(G1-dend)₂-NHC)}Br], an analogue of complex 6b with a second G1 dendron replacing the N-mesityl substituent,¹⁷ is as high as 42.2 because, in this case, the two dendrons are folded around the metal center (the distance between silver and one of the outer benzyl CH₂ carbons is as short as 4.12 Å, compared with 6.90 Å in 6b.

Synthesis of Bis(carbene) Palladium(II) Complexes 9-12. Conventional syntheses of bis(NHC) palladium(II) complexes by deprotonation of an imidazolium salt with an external base and reaction with a Pd(II) source, or by direct metalation with $[Pd(OAc)_2]$, are sometimes inefficient³⁴⁻³⁶ or lead to unpredictable results, such as the formation of mesoionic complexes (NHC bonded via C^4 or C^5 instead of C^2) with ligands containing bulky *N*-substituents.³⁷ Conversely, silver NHC complexes have been shown to be excellent NHCtransfer agents to Pd(II) in straightforward reactions.^{23–26} We chose the latter as the better synthetic route to ensure formation of the full series of G0 to G3 complexes. The most common palladium precursors utilized for silver-mediated carbene transfer are dichlorido or chlorido(methyl)palladium-(II) complexes bearing weakly coordinated donor ligands such as acetonitrile or η^4 -1,5-cyclooctadiene (cod).^{23–26,34,35,38} The reaction of imidazolium bromides 5-8 with $[PdCl_2(cod)]$ in dichloromethane led to mixtures of the "expected" dichlorido complex combined with chloridobromido and dibromido bis(carbene) complexes (Scheme 2a). The exchange of halide between the palladium and silver centers was evidenced by the ¹H NMR and ESI+ mass spectra of the crude reaction mixtures and is favored by the higher lattice stability of AgCl versus AgBr. It should be noted that silver bromido carbenes have been reported to cleanly afford chloridopalladium complexes,^{24,34,39,40} although halide scrambling has also been described on some occasions.40-42

The mixture of palladium halide derivatives was converted into the dibromido complexes 9-12 by refluxing the crude reaction mixture in CH₂Cl₂ in the presence of an excess of LiBr or NaBr (Scheme 2b).⁴³ Alternatively, formation of the mixed halide was avoided by using [PdBr₂(cod)] as the metal precursor (Scheme 2c). The bis(NHC) palladium complexes were isolated in high yields (in general \geq 90%) as analytically pure white to pale yellow solids. They were characterized by NMR and IR spectroscopy and ESI mass spectrometry (see Supporting Information for details). The complexes are air stable; soluble in chlorinated and polar solvents such as acetone, DMF, or THF; and insoluble in alkanes. The higher generations are also somewhat soluble in aromatic solvents, particularly complexes 9b-12b containing the 2,6-diisopropylphenyl group.

Complexes 9–12 coexist in solution as a mixture of *trans-syn* (major) and *trans-anti* (minor) rotamers. The *trans* config-





^{*a*}(a) $1/2[PdCl_2(cod)]$, CH_2Cl_2 , room temperature. (b) Excess of LiBr or NaBr, refluxing CH_2Cl_2 , 3 h. (c) $[PdBr_2(cod)]$, CH_2Cl_2 , room temperature, 1 h for 9a and 10a, 2 h for 11a and 12a, from 3 h for 9b to 12 h for 12b. (d) Isomerization of *trans*-9a to *cis-anti*-9a by slow crystallization in CH_2Cl_2 .

uration is evidenced by the single ¹H resonance observed for the two N-bonded methylene protons of each rotamer, which contrasts with the diastereotopicity displayed by these protons in the *cis* isomers.^{40,42,44,45} The chemical shifts of around 170– 171 ppm for the C_{carbene} are also consistent with this assignment, since these resonances are expected at higher field for *cis* arrangements (157–165 ppm).^{34,40,42,44} The assignment of ¹H resonances to each rotamer was based on their relative integration and on the chemical shifts of the Nbonded methylene protons. These protons are shielded to high field in the *anti* conformation by the effect of the aromatic rings on the NHC ligand in *trans* (from 6.0–5.6 ppm in the *syn* to 5.5–5.4 ppm in the *anti* rotamers, Figure 4).^{40,44} In the *syn* conformation, shielding affects the *ortho*-CH₃ or isopropyl CH protons instead, which are shifted around 0.2 ppm upfield with respect to the *anti* rotamers. The *syn-anti* equilibrium is only slightly sensitive to the nature of the aryl substituent and,



Figure 4. Part of the ¹H NMR spectrum of the mixture of *syn* and *anti* rotamers in *trans-***9b**.

interestingly, to the size of the dendritic wedge (*syn/anti* ratio of around 1.9 for 9a-12a and from 2.2 to 3.0 for 9b-12b in CDCl₃ at room temperature).

Syn-anti exchange by rotation of the NHC ligand around the carbene-palladium bond is slow on the NMR time scale at 20 °C, as can be seen from the sharp ¹H resonances observed at this temperature in CDCl₃. Some broadening occurs at 55 °C, but there is no coalescence, in agreement with the free activation energies determined for this hindered rotation in related nickel,⁴⁰ palladium⁴⁴ ($\Delta G^{\ddagger} \approx 75$ kJ mol⁻¹), and platinum NHC complexes (~85 kJ mol⁻¹).45 Nevertheless, chemical exchange was observed between the N-bonded methylene protons and between the isopropyl protons of both rotamers in a NOESY-EXSY experiment performed for 9b in CDCl₃. Moreover, the original 2:1 mixture of rotamers was recovered immediately after the dissolution of pure samples of trans-anti-9a or trans-syn-10a, obtained by crystallization of the corresponding mixtures of rotamers from hexane/CH₂Cl₂, in CDCl₃.

*Cis-anti-***9a** was obtained by slow crystallization of the *trans* mixture of rotamers **9a** from CH_2Cl_2 (Scheme 2d). The *cis* configuration is deduced from the chemical shift of the carbenoid carbon at 163.7 ppm and the observation of two doublets, at 3.35 and 6.41 ppm with ${}^2J_{H,H} = 14.1$ Hz, for the benzyl CH₂ protons and two singlets, at 7.06 and 7.11 ppm, for the *meta*-protons of the mesityl substituent in CDCl₃ (Figure 5). The chemical inequivalence of these protons also confirms



the slow rotation of the NHC ligand around the palladiumcarbene bond and, as a consequence, the existence of only one rotamer in solution (probably the *anti* rotamer observed in the solid-state structure, see below). As noted by Herrmann et al., the rotation barrier for *cis*-Pd(II) complexes must be much higher than in the *trans* configuration.⁴⁶ These results suggest that the formation of **9–12** as *trans* isomers is kinetically controlled by the steric constraints of the bulky NHC ligands, while the strong *trans* influence of these ligands favors slow isomerization into the more thermodynamically stable *cis* structure observed in the case of **9a.**⁴⁷

The molecular structures of *trans-anti-***9a** and *trans-syn-***10a**, determined by X-ray diffraction methods, are shown in Figures 6 and 7. In addition, the structure of *cis-anti-***9a** is shown in Figure S1 of the Supporting Information. Although the refinement of this structure was poor due to the low quality of the crystal and collected data, the fundamental parameters could nevertheless be established. The *anti* conformation displayed by the NHC ligands in this *cis* complex is common to all the rare examples of *cis-*[(NHC)₂PdX₂] complexes characterized in the solid state with a sterically hindered *ortho*-substituted aryl in the NHC ring.^{48,49} Many of the features found in **9a** and **10a** are shared with other known structures of similar palladium dihalido complexes. Thus, the mesityl



Figure 6. ORTEP representation of *trans-anti-***9a** (50% probability ellipsoids, H omitted for clarity). Selected bond lengths [Å] and angles [deg] (symmetry transformation used to generate equivalent atoms A: -x, -y, -z): Pd(1)–C(1) 2.035(3), Pd(1)–Br(1) 2.4598(10), C(1)–N(1) 1.357(4), C(1)–N(2) 1.360(4), C(2)–N(1) 1.388(4), C(2)–C(3) 1.350(5), C(3)–N(2) 1.393(4), C(4)–N(1) 1.473(4), C(11)–N(2) 1.455(4); Br(1)–Pd(1)–Br(1A) 180.000(7), C(1)–Pd(1)–C(1A) 180.00(14), C(1)–Pd(1)–Br(1) 88.53(10), C(1)–Pd(1)–Br(1A) 91.47(10), N(1)–C(1)–N(2) 105.1(3).



Figure 7. ORTEP representation of *trans-syn-10a* (50% probability ellipsoids, H omitted for clarity). Selected bond lengths [Å] and angles [deg] (values between brackets correspond to distances or angles for the NHC ring B): Pd(1)–C(1) 2.023(3) [2.021(3)], Pd(1)–Br(1) 2.4525(7), Pd(1)–Br(2) 2.45360(7), C(1)–N(1) 1.348(4) [1.351(4)], C(1)–N(2) 1.356(4) [1.349(4)], C(2)–N(1) 1.382(4) [1.382(4)], C(2)–C(3) 1.345(6) [1.327(5)], C(3)–N(2) 1.400(5) [1.399(4)], C(4)–N(1) 1.459(4) [1.467(4)], C(11)–N(2) 1.436(5) [1.453(4)]; Br(1)–Pd(1)–Br(2) 171.68(2), C(1)–Pd(1)–C(1B) 177.61(14), C(1)–Pd(1)–Br(2) 90.29(10), C(1)–Pd(1)–Br(1) 90.39(10), C(1B)–Pd(1)–Br(1) 88.17(10), C(1B)–Pd(1)–Br(2) 91.40(10), N(1)–C(1)–N(2) 105.0(3) [104.5(3)].

substituents are arranged almost orthogonally to the NHC rings (72–79°), which are tilted relative to the square-planar metal coordination plane (66–85°) to minimize steric repulsions. The volume buried by each NHC ligand in the G1 complex **10a** (mean % $V_{\rm bur}$ of 28.1) is slightly smaller than in the *trans* isomer of **9a** (29.0), again reflecting the conformational flexibility of the G1 dendrons, which are fairly extended in **10a**, with average dihedral angles at the ether linkages (Ar–O–C–Ph) of 174°. The steric hindrance in the *syn* conformation of **10a** is higher in the hemispace in which the mesityl groups are located, and this probably produces the observed tilting of the bromido ligands to the side of the

dendritic substituents, with a Br–Pd–Br angle of 171.7° (while the C–Pd–C angle remains almost linear).

Evaluation of the Dendronized Pd NHC Complexes in the Heck Reaction. The catalytic performance of complexes 9–12 was analyzed in the model Heck reaction shown in Scheme 3 under the general conditions described in the

Scheme 3. Model Heck Reaction Tested Using the Palladium Complexes 9-12 as Catalysts^a

$$Me - H + O + NEt_3 \xrightarrow{9-12} Me - O + NEt_3 +$$

^{*a*}General conditions: methyl acrylate (0.12 M), 4-iodotoluene (0.1 M), NEt₃ (0.12 M) in acetonitrile or DMF (5 mL).

caption. (*E*)-Methyl 4-methylcinnamate was the only product detected by gas chromatography (GC) and ¹H NMR spectroscopy in all the tests performed. No formation of palladium black or metal nanoparticles was detected by visual or TEM analysis of the solutions after the reactions.

The reaction kinetics were quite reproducible (measured conversions at $\pm 5\%$). As shown in Figure 8a for experiments



Figure 8. Reaction profiles for the Heck coupling in acetonitrile at 80 °C in the presence of (a) 5 μ mol (1 mol %) of **9a–12a** or PdCl₂ and (b) 2.5, 0.5, or 0.05 μ mol (0.5, 0.1, or 0.01 mol %) of **10a**. Other conditions are summarized in Scheme 3. Conversions were determined by periodic GC monitoring.

performed in acetonitrile at 80 °C with catalyst loadings of 1 mol %, a positive dendritic effect on the reaction kinetics was observed on going from G0 (9a) to G3 (12a), with the exception of 11a (G2) which, intriguingly, was the least active. Similar activity patterns (G3 > G1 > G0 > G2) were observed for both series of complexes (9a–12a and 9b–12b) in DMF at 130 °C using reduced Pd loadings of 0.1 mol % (Table 1). Palladium dichloride (gray line in Figure 8a) afforded comparable initial rates to the most active dendritic precursor (G3); however, in contrast to 9a–12a, precipitation of copious amounts of Pd black occurred from the beginning of the

Table 1. Comparative Activities of Catalysts 9-12 in the Heck Reaction^{*a*}

	conversion (%) after reaction for 7 h				
catalyst (0.1 mol %)	9 (G0)	10 (G1)	11 (G2)	12 (G3)	
9a-12a	21	37	15	51	
9b-12b	61	81	20	86	

^aDMF at 130 °C. Other conditions as summarized in Scheme 3.

reaction. The reduction from 1 to 0.01 mol % in the loading of the G1 catalyst **10a** resulted in significant lowering of the conversion rates (Figure 8b). Of more interest, however, are the fairly similar turnover frequencies obtained at the different concentrations (4, 6, 4, and 17 h^{-1} , on average, after reaction for 23 h for 1, 0.5, 0.1, and 0.01 mol % (note that the last value is less accurate due to a higher relative error) or 13 and 12 h^{-1} at a fixed conversion of 20% for 1 and 0.5 mol %, respectively).

Since the reactions with complexes 9-12 occurred without apparent degradation of the catalysts, the longevity of the active species was assessed for the G3 complex 12a by repeated addition of fresh substrates to the reaction medium, thus restoring the initial concentrations once the previous catalytic cycle was completed (24 h in DMF at 130 °C). Parallel experiments were performed using palladium acetate under "ligand-free" conditions or mixed with imidazolium 4a in 1:1 and 1:2 ratios. The formation of catalysts in situ by mixing $Pd(OAc)_2$ and a NHC precursor is a widespread practice in similar reactions. The reactions using palladium acetate alone or mixed with 4a all proceeded quickly with almost complete conversion (90-100%) after 2 h in the initial reaction cycle (cycle 0). Formation of Pd black was observed in a few minutes for the three catalytic systems, with this formation being faster in the absence of 4a. The reloading runs were repeated five times for all the catalysts selected, with conversions after reaction for 24 h that were almost quantitative and showed only small differences between them. The conversions achieved at 2 h were more informative of the evolution of the reaction kinetics along the consecutive cycles (Figure 9). These



Figure 9. Catalytic conversions (%) after 2 h in successive cycles reloading the reaction media with fresh substrates. Pd loadings of 0.1 mol % (**12a**, Pd(OAc)₂, and **4a** + Pd(OAc)₂ in molar ratios of 1:1 and 2:1) in DMF at 130 °C. Other conditions are summarized in Scheme 3.

conversions were fairly constant for 12a (13–15% in the five runs, 35% in the initial one) with no detection of Pd(0) black precipitates or metal nanoparticles during the full series of cycles. The reactions using Pd(OAc)₂ or 4a and Pd(OAc)₂, in which Pd black is formed in the very early stages of the initial run, showed sharp differences depending on the catalyst composition. Thus, under ligand-free conditions or in the presence of 1 equiv of 4a, the rates at 2 h remained high in the first cycles but decayed more or less abruptly in the second or

third and subsequent cycles. Finally, the 2:1 mixture of $Pd(OAc)_2$ and 4a showed the fastest rate, with almost all consecutive runs completed after 2 h. At this point, it should be noted that the G3 complex 12b also showed a fairly constant performance in these reloading experiments (around 85% after reaction for 2 h).

It has been argued that Pd nanoparticles are formed in the Heck reaction under ligand-free conditions and that these soluble particles are in equilibrium with lower-order molecular species of high reactivity, while also being prone to aggregate further to form inactive Pd black.^{50,51} de Vries has extended this mechanistic consideration to Heck reactions catalyzed at high temperatures (120-160 °C) by precursors that are unstable under these conditions (e.g., palladacycles, phosphine or pincer complexes, different heterogeneous catalysts and colloids, etc.),⁵² which has also been supported by strong evidence from other groups.53 This model is consistent with the observations made above for the reactions involving $Pd(OAc)_2$. After several reloading cycles, and in the absence of 4a, or at a substoichiometric concentration thereof, the system must be reactivated by the leaching of soluble palladium species from larger metal particles to reach total conversion after about 24 h. de Vries and co-workers have demonstrated that these precipitates are readily reactivated by oxidation back to soluble Pd(II) by I₂ or Br₂, which then reset the system at virtually the same initial conditions of cycle 0.51 With Pd/4a mixtures at a ratio of 1:2, deactivation by aggregation must be hampered to some extent by the imidazolium salt, thus allowing the next cycle to be catalyzed. However, the results obtained with complexes 9-12 instead suggest the most likely involvement of molecular active species stabilized by coordinated carbene ligands, as proposed by Cavell et al. and Herrmann et al. for other bis(NHC) palladium complexes, ^{20,34,54} although undetected very low-order nanoparticles cannot be ruled out.55 This assumption is supported by several indicators: (a) Pdblack or nanoparticles are not observed; (b) the catalytic kinetics are clearly affected by the dendritic generation of the NHC ligand (as seen for the two series of complexes in two different solvents and temperatures); (c) the kinetics for 9-12are quite reproducible, with TOF values that correlate well with the concentration of Pd complex; and (d) the reactivity remains fairly constant in successive reloading cycles.

Fluorescence Measurements. As the discontinuity in the rate trend observed for the second-generation complexes 11a and 11b in the Heck reaction was intriguing, we performed several studies in an attempt to determine whether a structural congestion of the palladium site by the poly(benzyl ether) dendrons might be the source of this singularity. We started by analyzing solutions of complexes 9a-12a by fluorescence spectroscopy. The absorption spectra for these dendrimers (Figure S2 of the Supporting Information) exhibit a typical $\pi \rightarrow$ π^* aromatic phenyl group band, centered at approximately 265 nm for G0 (9a). This band is shifted slightly to the red by about ~ 10 nm for the other members of the series. Another weak band, which is only significant at relatively higher concentrations, also appears at approximately 360 nm. The latter band, which also becomes observable for PdBr₂(cod) but displaced to larger wavelengths (maximum at 425 nm), must be attributed to a transition that involves a metal-to-ligand chargetransfer state. As such, the mesitylene groups seem to exert a strong hypsochromic effect on the emission of the Pd core.

As depicted in Figure 10, the emission spectra for 9a-12a in CH_2Cl_2 upon excitation at 260 nm show a typical, and also

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Figure 10. Fluorescence emission spectra for G0 to G3 dendrimers 9a-12a in CH_2Cl_2 at 25 °C upon excitation at 260 nm (left) and 335 nm (right).

rather weak, phenyl monomer emission band centered at ~285 nm for 9a that shifts monotonically to the red with the generation number. The monomer band is broadened to the red for some of the members of the series (particularly for 10a). This broadening, which depends strongly on the dendrimer generation, is attributed to intramolecular excimers in the aromatic benzyl-ether groups of the dendrons. The amount of intramolecular excimers, as quantified by the ratio of excimers and monomer emission intensity bands $(I_E/I_M$ and other photophysical parameters in Table S3 of the Supporting Information), increases from 9a to 10a and decreases monotonically from 10a through 12a. Emission upon excitation at 335 nm for 9a-12a also exhibits a weak single fluorescence emission band centered at \sim 410 nm (Figure 10). This band is attributed to the Pd-carbene N-heterocyclic ligand core, which apparently behaves as a single chromophoric unit. Fluorescence quantum yields for this emission are rather similar and are low for all members of the series (Table S3). It seems that the size of the dendrons has very little influence on the rate of the deactivation processes of the Pd core. No emission at all is observed upon excitation at 260 nm for 9a-12a in acetonitrile or DMF, probably due to intramolecular energy transfer from the benzyl-ether groups to the Pd core.

The fluorescence intensity decay profiles for the Pd core emission ($\lambda_{\rm ex}/\lambda_{\rm em} = 335 \text{ nm}/420 \text{ nm}$) were fitted to three exponentials for any of the four **9a–12a** dendrimers in CH₂Cl₂ at 25 °C. Components in the 0.6–1.6, 3.0–5.3, and 15.4–31.6 ns ranges were found. This indicates that other processes more complicated than the simple radiative emission from a singlet state are involved. Table S3 also lists weighted lifetime averages for dilute **9a–12a**/CH₂Cl₂ solutions at 25 °C.

Quenching of the emission from the Pd core ($\lambda_{ex} = 335$ nm) by 2,3-butanedione (diacetyl) was also studied. The resulting Stern–Volmer plots (Figure S3 in the Supporting Information) of the intensity measured near the maximum of Pd core emission (420 nm) are rather linear throughout the range of concentrations used ([diacetyl] = 0–11.7 mM; quenching parameters obtained from the recorded plots can be found in Table S4 of the Supporting Information). The largest bimolecular quenching constant (k_q) is observed for the first member of the series **9a** ($k_q \approx 9 \times 10^{-9}$ M⁻¹ s⁻¹). However, k_q values are smaller and rather similar, being around 4–5 × 10⁻⁹ M⁻¹ s⁻¹, for the rest of the members (**10a**–**12a**). The Pd core seems to be more accessible to the quencher for **9a** than for the other members of the series (**10**–**12**). These findings also point

to a packing of dendrons around the core, which hardly varies for 10a-12a, as a similar quenching accessibility is observed for these compounds in CH₂Cl₂.

Diffusion-Ordered NMR Spectroscopy (DOSY) Measurements. As no emission was observed upon excitation at 260 nm in the solvents used in the catalytic experiments, we tried to obtain further information by measuring the hydrodynamic radii in DMF- d_7 by DOSY NMR.⁵⁶ The translational diffusion coefficients (*D*) measured at 25 °C for 9–12 in this solvent, and the hydrodynamic radii (r_h) derived from them using the Stokes–Einstein equation, are collected in Table 2,

Table 2. Diffusion Coefficients (D), Hydrodynamic Radii (r_h) , and Dendrimer Density (ρ) for 9–12 in Deuterated DMF or Acetone at 25 °C

2.35
5 26
3.30
2.16
5.43
11.7
12.5
12.7
12.3
0.94
0.75

^aMeasured by DOSY NMR spectroscopy at 25 °C in solutions containing 1.0 mg of complex in 0.75 mL of deuterated solvent. ^bHydrodynamic radii were determined from diffusion coefficients using the Stokes–Einstein equation for spherical rotors. ^cDetermined as the ratio between the hydrodynamic volume and the molar mass.

together with the values determined in acetone- d_6 for the same complexes. Acetone is considered a solvent of good quality for poly(benzyl ether) dendrons in which the branches do not tend to fold and collapse.⁵⁷ The radii obtained are of comparable magnitude in both deuterated solvents and increase by about 2.2 Å per generation. This generational increase is intermediate between the value of \sim 1.9 Å obtained from the radii of gyration determined for 9a-12a in a vacuum by molecular dynamics calculations (see below) and the increase of 2.9 Å predicted by molecular models for fully extended structures.⁵⁸ In addition, it is quite similar to that found in didendrons with a rubicene core in good solvents (2.3 Å per generation).⁵⁷ The hydrodynamic radii and molecular weights correlate linearly in a logarithmic scale, with R^2 coefficients for the linear regressions >0.993 (Figure 11). The slopes of the linear fits (0.50 to 0.56) are much greater than those calculated for uncharged spherical particles of uniform density (0.33).⁵⁹ Dendrimers are neither spherical in shape nor uniform in density; indeed, much larger slopes are to be expected for low-generation and lowmolecular-weight dendrimers, such as those reported here, which have a dense core, semiflexible arms, and are appreciably nonspherical.⁶⁰ In fact, similar slopes were found in poly(benzyl ether) monodendrons having a pyrene core (0.56),⁵⁸ or from the radii of gyration determined for 9a-12a in a vacuum by the molecular dynamic calculations studies described below (0.55). It should be noted that no irregularities are observed in the hydrodynamic radii of the second-generation dendrimers in



Figure 11. Logarithmic plots of the inverse hydrodynamic radius as a function of molecular weight for complexes 9a-12a and 9b-12b in deuterated acetone and DMF at 25 °C.

DMF or acetone. Dendrimer densities decrease monotonically, as expected for low-generation dendrimers adopting open conformations in good solvents (Table 2).

Molecular Dynamic (MD) Simulations. Five-nanosecond MD simulations in a vacuum at 300 K were performed for *trans-syn* and *trans-anti* rotamers of the four dendrimer generations (G0–G3) as models for dendrimers 9a-12a following the protocols described in the theoretical background section of the Supporting Information (Figure 12). Table 3 includes the van der Waals (V_{vdW}) and total dendrimer molecular volumes (V_{Rgyr}), as obtained from the van der Waals radii and the values of the average of the root-mean-



Figure 12. Most stable structures for the G3 *trans-syn* (upper) and *trans-anti* (bottom) forms obtained from the analysis of the 5 ns molecular dynamics trajectories. Pd and Br atoms are in magenta and green, respectively. Notice the accessibility of the Pd core.

Table 3. van der Waals Volume (V_{vdW}), Total Volume (V_{Rgy}), Hydrodynamic Volume (V_h) in DMF at 25 °C, and Free Volume Fraction ($V_{free,f}$) for 9a–12a

dendrimer (Gn)	$V_{\rm vdW} \ (\rm nm^3)^a$	$V_{\rm Rgyr} \ ({\rm nm}^3)^a$	$V_{\rm h} ({\rm nm}^3)^{b}$	$V_{\rm free,f}^{c}$
9a (G0)	0.57	0.39	0.66	0.14
10a (G1)	0.92	0.90	1.40	0.34
11a (G2)	1.63	2.05	2.91	0.44
12a (G3)	3.05	3.84	6.68	0.54

^{*a*}Determined from van der Waals radii and from the values of the average of the root-mean-square radius of gyration, respectively, obtained from the analysis of the 5 ns MD trajectories at 300 K under the assumption of a 2:1 mixture of *trans-syn* and *trans-anti* rotamers. ^{*b*}Determined from the hydrodynamic radii in Table 2. ^{*c*}Measured as the $(V_h - V_{vdW})/V_h$ ratio.

square radius of gyration calculated from an analysis of the trajectories of the *trans-syn* and *trans-anti* rotamers under the assumption of a 2:1 mixture. The quantitative values for both $V_{\rm vdW}$ and $V_{\rm Rgyr}$ are obviously smaller than the hydrodynamic volumes ($V_{\rm h}$) obtained experimentally in any solvent (Table 2), and their increase with the generation number is also smaller (see Figure S5 of the Supporting Information). This is due to the fact that, apart from the solvation effect, the dendrons fold more easily in a vacuum than in any solvent, thus providing more packed structures. However, this increase is parallel to the experimental trend obtained in good solvents for both parameters. The free volume was also determined by subtracting van der Waals from hydrodynamic volumes. As expected, the fraction of the free volume increases monotonically from G0 to G3 complexes.

The radial density profiles for the centers of mass of the phenyl ring from the dendrons and mesitylene groups (as the number of centers per Å³), with the distance being measured from the Pd core, were also obtained by analysis of the MD trajectories for the trans-anti and trans-syn rotamers of the four generations (results depicted in Figure S6 in the Supporting Information). The data reveal a decrease in radial density with distance to the core. The profile for G0 exhibits a maximum located at ~5 Å, which corresponds to the location of the center of mass of the mesityl and phenyl groups closest to the Pd core. The value for this maximum is smaller for the transanti isomer, and the distribution slightly wider, than for the trans-syn one. This feature also appeared for all other G1-G3 generations, with a maximum located at \sim 5 Å that is wider for the trans-anti isomers. However, another maximum was also observed at \sim 9 Å, followed by a monotonic decrease in density with an increase in the radial coordinate. Despite the larger steric hindrance and smaller flexibility of dendrons for the transsyn rotamers compared to the trans-anti ones, only a small difference in profiles is observed between the two rotamers.

CONCLUSIONS

The bis(imidazolylidene)dihalidepalladium complexes 9-12, containing a sterically hindered aryl group and a poly(benzyl ether) dendron as N-substituents on the NHC ligand, are easily accessible up to the third generation by transmetalation of the corresponding silver complexes. These complexes give rise to soluble, active, and very stable species under Heck reaction conditions. Several observations point to homotopicity⁶¹ of the homogeneous catalysts, with a stable coordination of the NHC ligands. Thus, the reaction profiles are reproducible and dependent on dendron size, the formation of Pd black or

nanoparticles is not observed, the turnover frequencies are constant at different catalyst concentrations, and their behaviors differ from that under "ligand-free" conditions or from mixtures of imidazolium salts and $Pd(AcO)_2$. In addition, the high molecular weight (up to 3875 Da) makes some of these dendritic catalysts suitable for recoverability studies using nanofiltration techniques.

The accessibility of substrates to the metal center is not significantly constrained by the increasing size of the dendritic substituents in complexes 9-12, as demonstrated by the activity of these catalysts, which even improves for the larger dendrimers. The lack of increased congestion around the palladium site can be explained by the conformational semiflexibility of the poly(benzyl ether) dendrons and the benzylic link between these dendrons and the N-heterocyclic ligands. Buried volumes determined from solid-state structures, hydrodynamic radii obtained in solution, or quenching experiments of fluorescence emission support this model. Interactions other than those occurring in the closest metal coordination sphere should, however, induce size-dependent effects in the reactivity of metal complexes situated at the core of dendrimers. Influences in the form of a better protection of active sites or an increased local concentration of substrates have been reported in the literature as one explanation for the better rates provided, on occasions, by larger dendrons, as is the case for those reported in this work. The discontinuity observed in the rate trend for the G2 complexes 11 is more difficult to explain and is not due to any particular irregularity in the accessibility to the metal or in the molecular density of these G2 dendrimers. As Tomalia has shown, dendritic effects are often dictated by concurring and interdependent factors that do not always render a property that varies regularly as a function of only the generation.

EXPERIMENTAL SECTION

The preparation of G3 compounds **4b**, **8b**, and **12b** is given as an example. Other experimental details can be found in the Supporting Information.

Synthesis of 4b. A mixture of $(G3-dend)Br^{63}$ (1.016 g, 0.6077 mmol) and 1-(2,6-diisopropylphenyl)-1*H*-imidazole (142 mg, 0.622 mmol) in acetone (20–25 mL) was introduced into an ampule equipped with a PTFE valve. The tube was sealed and the mixture stirred at 60 °C until completion of the reaction (2 days). The solvent was then removed under a vacuum and the residue washed with cold diethyl ether (2 × 15 mL) until **4b** precipitated as a beige solid, which was washed with pentane (yield: 1.110 g, 97%). Elemental analysis (%) calcd for C₁₂₀H₁₁₁BrN₂O₁₄ (1885.07): C, 76.46; H, 5.94; N, 1.49. Found: C, 75.89; H, 5.91; N, 1.48.

Synthesis of 8b. Ag₂O (43 mg, 0.19 mmol) was added to a Schlenk tube containing a solution of **4b** (700 mg, 0.371 mmol) in CH₂Cl₂ (20–30 mL) and the mixture stirred in the dark at room temperature for 8 days. An additional amount of Ag₂O (8 mg, 0.034 mmol) was added after 5 days of reaction. Once the reaction was complete, the excess of Ag₂O was separated by filtration. The solvent was subsequently evaporated to dryness under a vacuum, and the residue washed with hexane (3 × 20 mL) and diethyl ether (3 × 20 mL) to afford the silver complex **8b** as an off-white solid (500 mg, 67%). Elemental analysis (%) calcd for C₁₂₀H₁₁₀AgBrN₂O₁₄ (1991.93): C, 72.36; H, 5.57; N, 1.41. Found: C, 72.50; H, 5.89; N, 1.57.

Synthesis of 12b. $[PdBr_2(cod)]^{64}$ (52 mg, 0.139 mmol) and **8b** (550 mg, 0.276 mmol) were dissolved in CH₂Cl₂ (20–30 mL) in a Schlenk tube, and the mixture stirred at room temperature for 12 h. The solution was then filtered and evaporated to dryness under a vacuum. The residue was dissolved in CH₂Cl₂ (20 mL) and washed with water (3 × 15 mL). The organic layer was dried over MgSO₄ and

ASSOCIATED CONTENT

S Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.inorg-chem.5b02629.

General procedures and materials for the preparation of the compounds and catalytic studies, characterization data, data and background for the fluorescence measurements, and the theoretical MD simulations (PDF)

Crystallographic data for 5a, 5b, *trans-9a*, *cis-9a*, and 10a in CIF format (CIF)

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Notes

The authors declare no competing financial interest.

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