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Phosphorus Functionalized Dendrimers and Hyperbranched Polymers: Is There a Need for Perfect Dendrimers in Catalysis?

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Abstract. In this paper we describe the facile and straightforward covalent functionalization of commercially available dendritic poly(propylenimine) and hyperbranched poly(ethylenimine) with P-containing functional groups. The P-functionalized macromolecules have been applied as multivalent ligands in the Pd-catalyzed allylic substitution reactions (batch and continuous process) using either morpholine or thiophenol as nucleophile. Palladium complexes of all described molecules are active in allylic substitution reactions. The PEI functionalized polymers appear more sensitive to small changes in the P/Pd ratio than the PPI analogues, but form catalysts that are more active. When used in a continuous flow process the macromolecules are completely retained by the nanofiltration membrane, while the catalytic activity decreases with time because of palladium depletion. This is more severe for the allylic thiolation, probably because of the stronger affinity of sulfur for palladium, facilitating palladium leaching.

INTRODUCTION

In the last decades several synthetic procedures have been developed for the large-scale preparation of (almost) perfect dendritic and hyperbranched polymers. Vögtle, and later Mülhaupt and Meijer, described the divergent synthesis of poly(propylenimine) dendrimers from the diaminobutane core.[1] This type of dendritic scaffold has already been used for covalent functionalization with appropriate functional groups that can act as ligands in transition metal catalysis. Reetz et al. functionalized commercially available DAB-dendrimers with diphenylphosphine groups at the periphery via double phosphination of the amines with diphenylphosphine and formaldehyde.[2] The corresponding Pd complexes have been prepared (Fig. 1) and used as catalyst for the Heck coupling reaction between bromobenzene and styrene.

Brinkmann et al. reported the use of these phosphine-containing dendritic catalysts for allylic substitution reactions in a Continuous Flow Membrane Reactor.[3] Retention factors up to 0.999 were reported for the 3rd generation dendrimer (calculated molecular weight = 10212 Da). Although the dendrimer remained in the reactor, leaching of palladium was observed. Better results were obtained by using in-situ prepared palladium complexes of a 4th generation dendrimer (calculated molecular weight 20,564 Da for 100% palladium loading of the 32 diphosphines). After 100 residence times, the conversion had decreased from 100% to approximately 75%. The formation of inactive $PdCl_2$ was proposed to account for an additional drop in conversion, besides the small amount that leaches.

Kaneda and coworkers used similar components to prepare phosphinated dendrimer-bound Pd(0) complexes that were applied in allylic amination reactions.[4] The catalysts showed high stereoselectivity due to the surface congestion of the dendrimers and could be efficiently recycled without loss of activity under thermomorphic conditions.

The structural perfection that may be present in a dendritic support might not be required for every application in catalysis, and hyperbranched polymers provide interesting and cheap alternatives as catalyst supports. These hyperbranched polymers are obtained from a simple one-pot synthesis, yielding globular polymeric structures with broader molecular weight distributions

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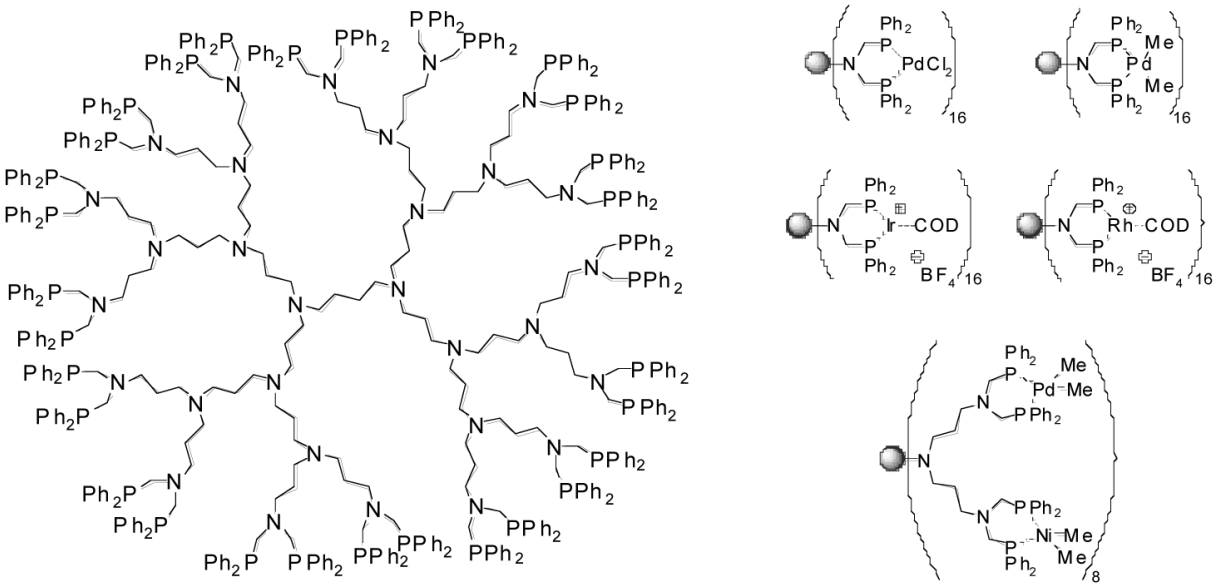


Fig. 1. Metal complexes of phosphane-functionalized poly(propylenimine) dendrimers.

compared to their dendritic analogues. Poly(ethyleneimine) in particular is prepared by cationic ring-opening polymerization of aziridine (ethylenimine), and it can be prepared at large scale. This compound has already been known for decades but recently new synthetic procedures have been developed that lead to polymers with a high degree of branching (~65%) and (relatively) narrow polydispersity (ca. 1.3 for the commercial PEI-5, polyethylenimine with MW ~5000).[5] From a chemical point of view these polymers are closely related to the PPI-dendrimers as their backbones are only made of C and N. Importantly, the nature of the N atoms is different; only tertiary and primary nitrogen atoms are found for the PPI-dendrimer, whereas the hyperbranched PEI also contains secondary amine groups. Another difference with respect to PPI dendrimers is the number of C atoms in the spacer of the repetitive unit, being 3 for PPI dendrimers and 2 for hyperbranched PEI. It is unknown if and how the different pattern of branching and the smaller repetitive unit will affect their properties as supports for catalysts. This class of polymers has been used for antimicrobial properties, coating preparation, and gene delivery,[6] but reports on applications as supports for transition metal catalysis are still limited.[7] Frey and coworkers used modified hyperbranched poly(ethylenimine) as macroligand for the copper-mediated atom transfer radical polymerization (ATRP) of methyl methacrylate (MMA).[8] This system appeared to be catalytically efficient, providing polymers with narrow molecular weight distributions (M_w/M_n < 1.4) even at high conversions (96%). Haag and coworkers prepared hyperbranched polyethylenimine with carbohydrate terminal groups (glycidol, gluconolactone, or lactobionic acid) and used them as stabilizing support materials for colloidal metal nanoparticles (i.e., Cu, Ag, Au, and Pt) in water.[9] The platinum nanoparticles stabilized with PEI derivatives proved to be as effective and robust for the selective hydrogenation of isophorone in water as the dendrimer derivatives.

It is clear from the contributions of many groups that dendrimers and hyperbranched polymers are suitable supports for transition metal catalysts. The two main aspects related to the use of dendritic supports in catalysis are the so-called "dendritic effect" and recycling. The special properties that may result from catalyst incorporation onto these macromolecules can be described as a "dendrimer effect". This term has been generally invoked in the literature to explain phenomena that arise as the generation of the dendrimer increases. At this stage it is important to note that there is no general trend observed in the many reports concerning catalysis with periphery-functionalized dendrimers. In some cases the activity of the catalysts decreases with the dendrimer generation, while in other examples it does not. As already mentioned, the synthesis of (perfect) dendrimers can be very time-consuming and costly. While the highly symmetric dendrimers give beautiful pictures that have often served as covers for many journals, one might wonder if the efforts to prepare these macromolecules are justified by the added value

they have in catalysis. Cheaper materials like the hyperbranched polymers represent interesting alternatives to be used as supports for recyclable catalysts. The price per active site of this type of materials competes with other supports such as polystyrene and silica. In this paper we describe new strategies for the covalent functionalization of dendritic poly(propylenimine) and hyperbranched poly(ethylenimine). Their application in transition metal catalysis in batch and continuous processes is investigated and the results are discussed and compared to shine light on the effect of the support on catalysis. It is, to the best of our knowledge, the first time that dendrimers and hyperbranched polymers are directly compared in this type of application.

RESULTS AND DISCUSSION

Synthesis

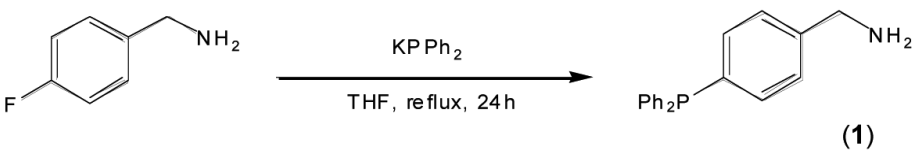
The periphery of the commercially available poly(propylenimine) dendrimer was functionalized with *p*-(Diphenylphosphino)benzylamine groups via urea linkage formation. First an appropriate ligand moiety bearing a reactive amino function was prepared for further functionalization of the dendritic scaffolds. *p*-(Diphenylphosphino)benzylamine **1** has been prepared (Scheme 1) following a slightly modified literature procedure.[10]

The coupling of **1** to the dendrimer via urea moieties was accomplished following an adapted literature procedure using 1,1′-carbonyldiimidazole (CDI).[11] This reaction was first optimized using a diamine that resembles the peripheral diamino end-groups present on the DAB dendrimers (Scheme 2) before application of the synthetic strategy to the larger systems.

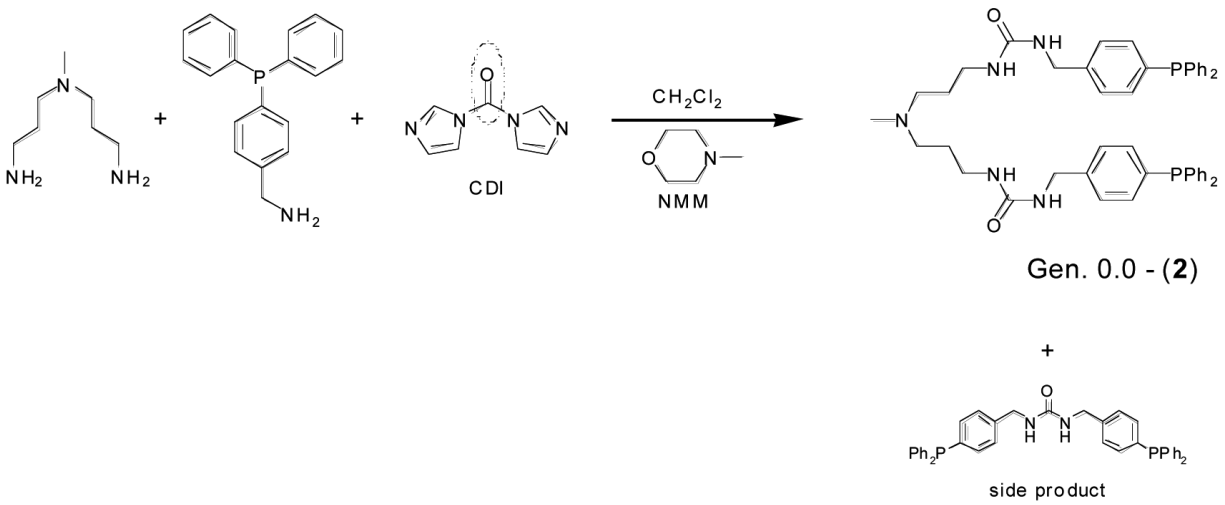
Product **2** was obtained in 79% yield after precipitation from *i*-PrOH and was characterized with ^{1}H, ^{13}C, and ^{31}P NMR and mass spectrometry. This model compound was obtained in at least 97% purity as judged from GC analysis. NMR spectroscopy does not give conclusive information on the purity of the product because both in ^{1}H and ^{31}P NMR spectrometry the signals of the desired and the byproduct overlap. In the GC-MS spectrum it is possible to distinguish two peaks corresponding to MW = 779 (desired product) and 608 (byproduct). The impurities are thus likely the result of bis(phosphine)urea formation, as this corresponds to the MW of 608 Da.

The scope of the reaction was first extended to the smallest member of the poly(propylenimine) dendrimer family, bearing 4 end-groups, giving product **3** (Fig. 2).

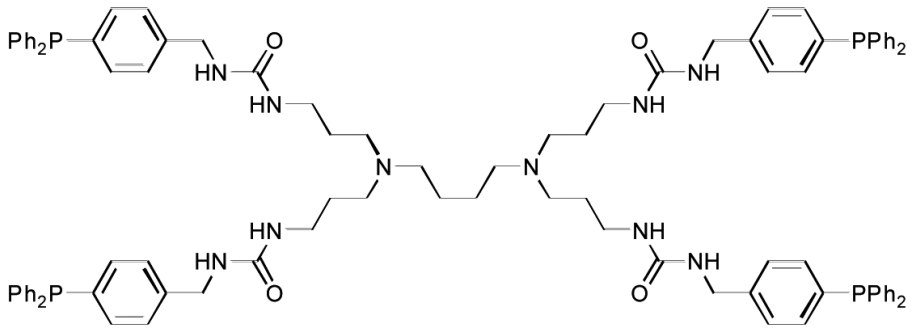
Also in this case the product was obtained in high yield (82%) and purity (98%) as judged from ^{1}H, ^{13}C, and ^{31}P NMR and mass spectrometry. The only impurity present appears to be phosphine oxide, detectable



Scheme 1. Synthesis of p-(Diphenylphosphino)benzylamine: Nucleophilic phosphinylation of fluoro aromatic compounds.



Scheme 2. CDI-coupling of *p*-(diphenylphosphino)benzylamine via urea linkage to a polyamine scaffold.



Gen. 1.0 - (**3**)

Fig. 2. Phosphine-functionalized 1st generation DAB-PPI-dendrimer.

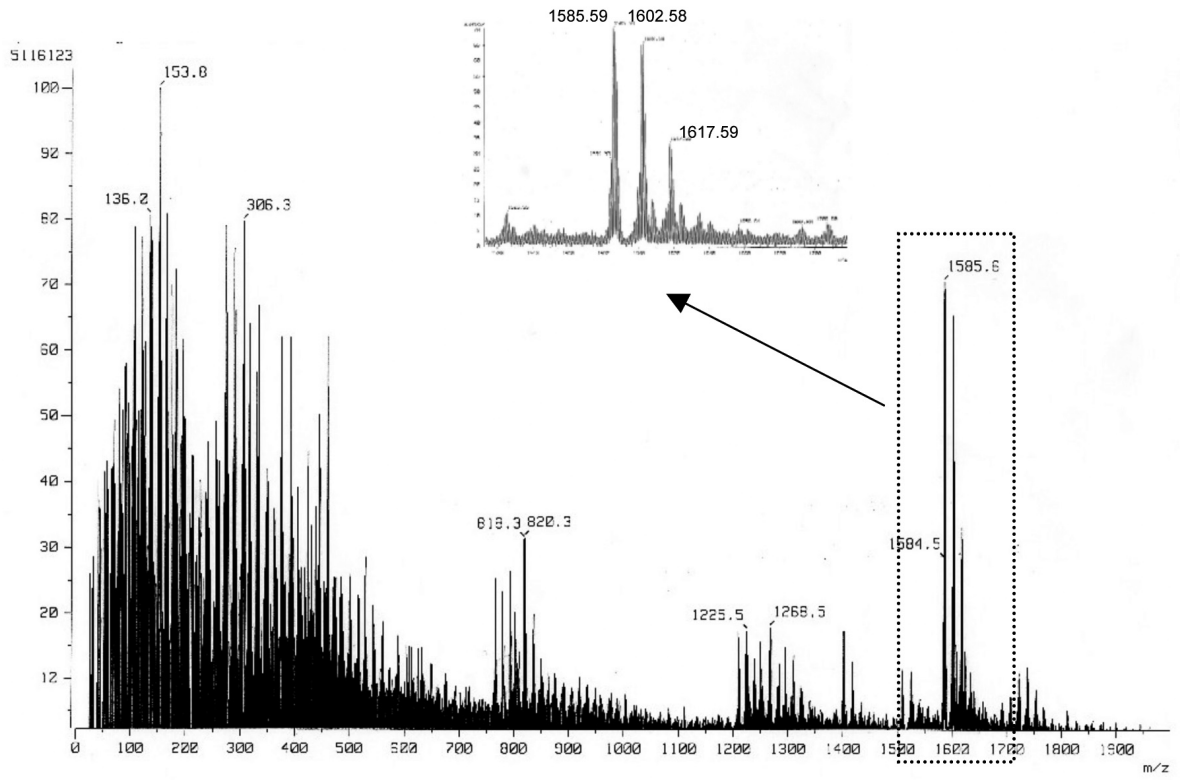


Fig. 3. FAB-MS spectrum of the phosphine-functionalized 1st generation DAB-PPI-dendrimer.

both in ^{31}P NMR and FAB MS. The mass spectrum of **3** (Fig. 3) clearly shows the molecular peak at *m*/*z* = 1586 Da, as well as its oxidized analogues. Most of the oxidation takes place during the mass analysis experiment.

The peaks at 820, 1225, and 1268 Da are due to fragmentations typically observed for this type of dendrimers (Fig. 4).[12]

Encouraged by these results, the synthetic procedure was applied to the 5th generation of the poly(propylenimine) dendrimer family, which has a MW of 7168. The phosphine-functionalized compound **4** is depicted in Fig. 5.

Thanks to the well-defined structure of the parent dendrimer, it is possible to dose accurately the amounts of reagents. The addition of exact stoichiometric amounts of CDI and phosphine with respect to the polyamine makes the work-up and purification very simple.

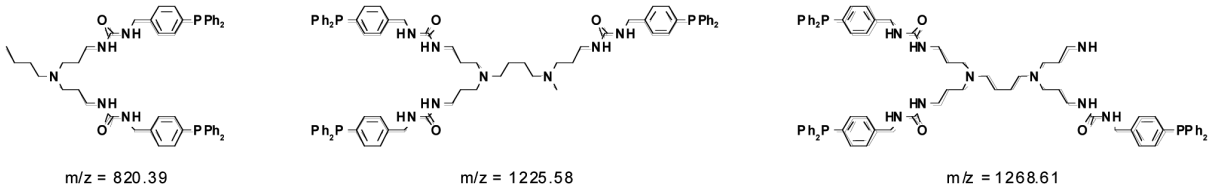


Fig. 4. Molecular fragments observed in the FAB-MS for Phos-PPI-G1.0 (3) (Fig. 3).

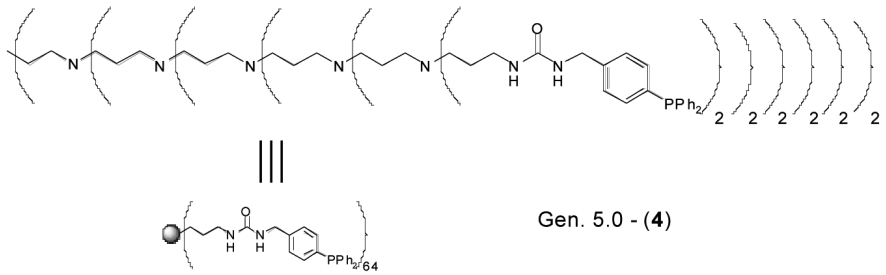


Fig. 5. Schematic depiction of the phosphine-functionalized 5th generation DAB-PPI-dendrimer.

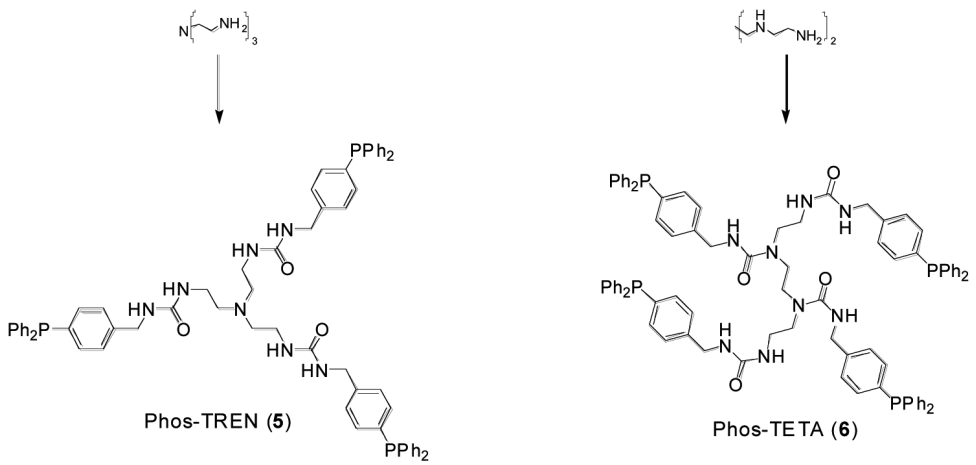


Fig. 6. Phosphine-functionalized model polyamine compounds mimicking structural elements of hyperbranched PEI.

Also in this case the product was obtained in high purity (95%) as judged from ^{1}H, ^{13}C, and ^{31}P NMR analysis. The impurities are a consequence of partial oxidation of the phosphorous moieties, similar to that observed for **3**. It was not possible to obtain satisfactory MALDI-TOF spectra as additional evidence for the formation of the product, which is not uncommon for molecules of this type and size.[12]

A similar procedure for functionalization has been applied to two hyperbranched poly(ethylenimine) polymers, PEI-5 and PEI-25, with average molecular weights (M_n) of, respectively, ca. 5000 and ca. 25,000, corresponding to, respectively, ~180 and ~580 monomer units. They both show a degree of branching of ~70% and a polydispersity of 1.3 and 2.5, respectively.

Two model "monomeric" compounds were first prepared, consisting respectively of primary/tertiary and primary/secondary amino groups only. These were used as model compounds for the preparation of the functionalized hyperbranched poly(ethylenimine) and were also used as reference compounds in catalysis. The products (along with the respective precursors) are displayed in Fig. 6.

The compounds Phos-TREN (**5**) and Phos-TETA (**6**) were characterized using ^{1}H, ^{13}C, and ^{31}P NMR and mass spectrometry. According to these measurements **5** and **6**

were very pure (96% in both cases); the impurities derive again from partial oxidation (2%) of the P moieties and bis(phosphine)urea formation (2%). The overall yields were 83% and 89%, respectively.

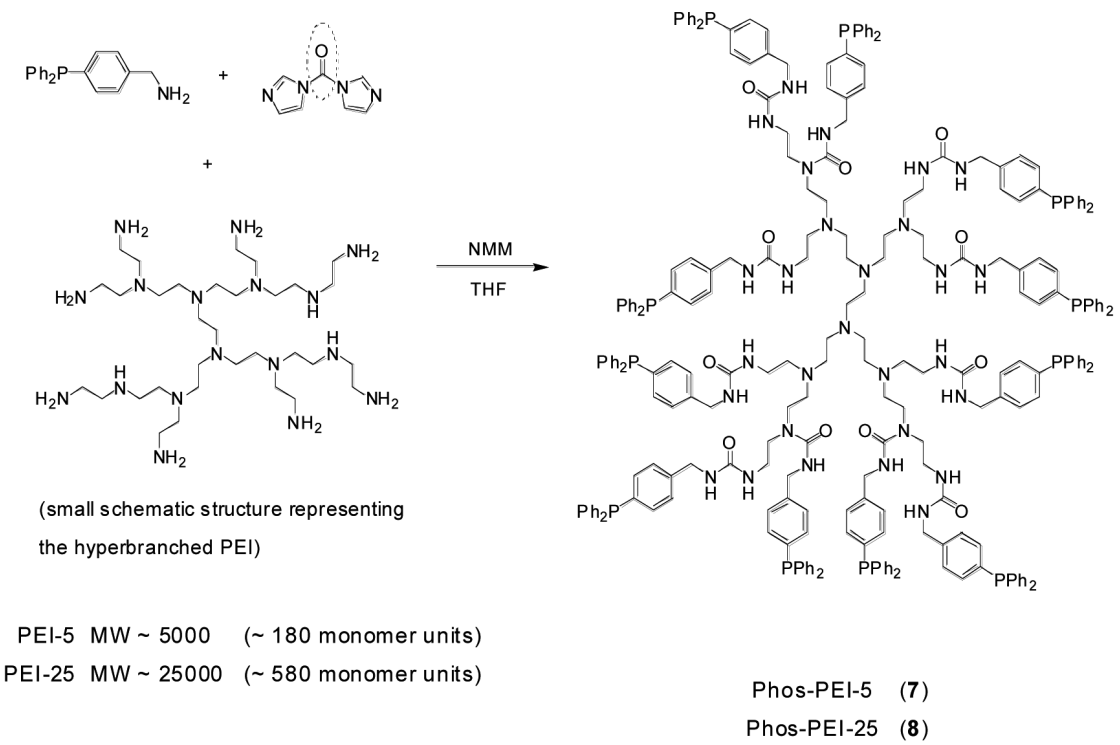
The covalent functionalization of hyperbranched poly(ethylenimine) has been achieved using a similar synthetic procedure (Scheme 3).

The less defined structure of the hyperbranched polymer requires the use of a slight excess (5–10% excess) of *p*-(diphenylphosphino)benzylamine and 1,1′-carbonyldiimidazole with respect to the calculated number of –NH and $–NH_2$ groups (40 and 35, respectively, for PEI-5, 200 and 180 for PEI-25). The excess of reactants can be easily removed by precipitating the solid crude product from boiling isopropanol (see Experimental section for details). At room temperature the macromolecular products appear to be soluble only in a small number of solvents, which does not include *i*-PrOH. The products **7** and **8** have been characterized with ^{1}H, ^{13}C, and ^{31}P NMR. It was not possible to obtain satisfactory MALDI-TOF spectra as additional evidence for the formation of the products, which is not uncommon for molecules of this type and size.[13] The coupling was quantitative and according to ^{1}H NMR there were no free amino ($–NH_2$ or –NH) groups left. From ^{31}P NMR we observed that 5% of the P ligands were oxidized after the work-up procedure. The content of P in the functional hyperbranched polymers was determined by means of calibration versus a (simple) known phosphine molecule (tri-*o*-tolyl phosphine) that is structurally related to the compounds under investigation but whose chemical shift in the ^{31}P NMR is sufficiently separated from those of the polymer, thus allowing a good comparison of the two integral signals (Fig. 7).

The functional Phos-PEI-5 and Phos-PEI-25 show a phosphorus content of, respectively, 2.620 mmol/g and 2.622 mmol/g; these values correspond to, respectively, 77 and 390 P atoms per molecule, which is in good agreement with the number of reactive (that is, primary and secondary) amino groups per molecule (75 and 380, respectively) reported by the producer. This confirms that all primary and secondary amine groups of the polymer were converted into a urea-phosphine moiety.

Catalysis

The phosphorus-functionalized dendritic molecules (**2**–**8**) have been studied as multivalent ligands in transition metal catalysis. We focused our attention on the Pd-catalyzed allylic substitution reactions (i.e., amination and thiolation). Other researchers in our group have



Scheme 3. Schematic depiction of the synthetic procedure used for the covalent attachment of *p*-(diphenylphosphino)benzylamine to hyperbranched PEI via urea linkage (CDI coupling).

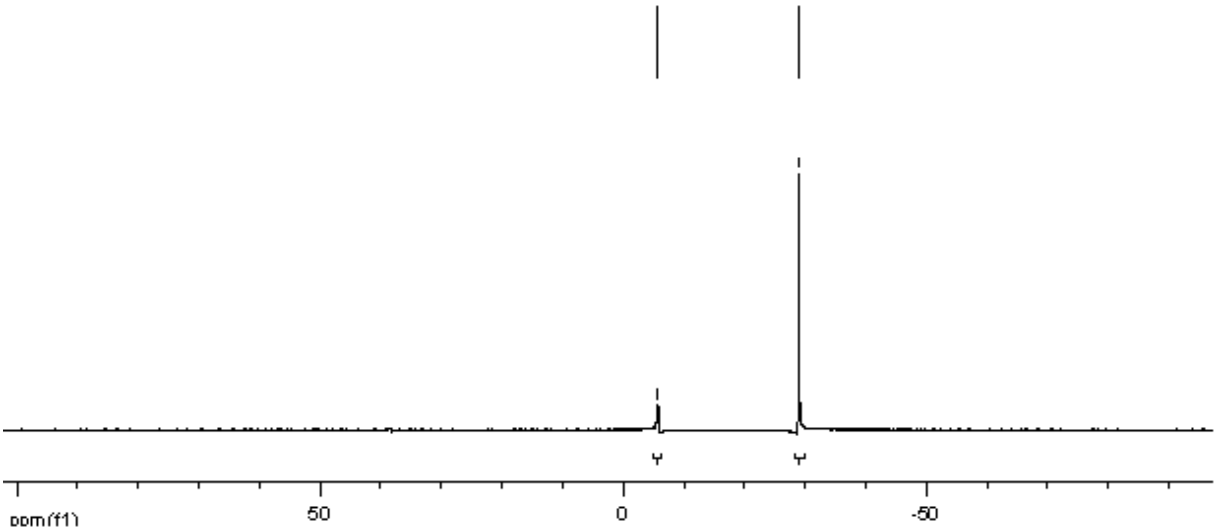
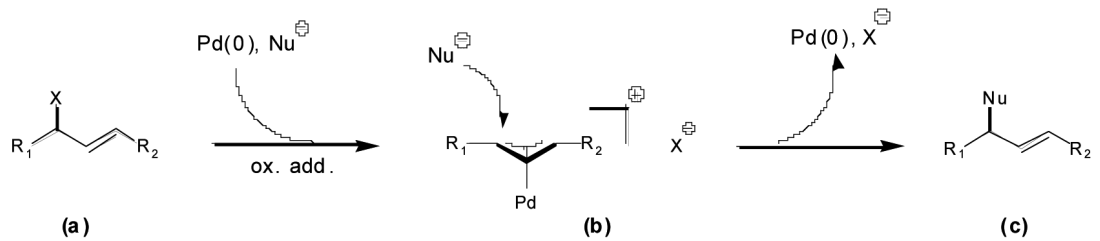


Fig. 7. ^{31}P NMR spectrum of Phos-PEI-5 **7** (–5.7 ppm) vs. tri-*o*-tolyl phosphine (–18.9 ppm).



Scheme 4. General mechanism for palladium catalyzed allylic subsitution.

previously studied different phosphorus-functionalized dendrimers for applications in transition metal catalysis, in batch and continuous flow systems.[14,15] It was demonstrated that the position of the catalytic sites and their spatial separation are determined by the geometry of the dendrimer, which is very important for the performance of the catalyst. For the allylic substitution reaction it was found that periphery-functionalized systems have activities comparable to those of monomeric systems, but application in a continuous-flow membrane reactor showed that these catalyst systems can be very unstable. In contrast, the core-functionalized dendrimers gave slower but very stable catalysts. Moreover, using these dendritic catalysts the selectivity was controlled by the apolar microenvironment created by the dendrimer. We now apply the functionalized dendritic molecules ("perfect" dendrimers and hyperbranched polymers) in transition metal catalysis (batch and continuous flow) and compare the results with the ones previously obtained from core- and periphery-functionalized dendrimers. The larger dendritic ligands (**4**, **7**, and **8**) have also been used in a continuous-flow membrane reactor. The catalytic sites located (mainly) at the periphery of the functional macromolecules are readily accessible to the substrate and the dendritic supports are sufficiently large to be retained in the reactor when a membrane with molecular weight cutoff of 700 Da is used.

Batch Processes; Pd-Catalyzed Allylic Substitution

Transition metal complexes with unsaturated hydrocarbons that are π-bonded to the metal have long been the focus of organometallic chemistry. The transition metal catalyzed allylic substitution reaction using a variety of nucleophilic reagents is now a well-established methodology in organic synthesis and is widely used to construct complex organic molecules.[16]

The mechanism of the palladium-catalyzed allylic substitution (Scheme 4) proceeds via a cationic (or neutral) palladium π-allyl complex **(b)**, which is formed after oxidative addition of **(a)** to palladium. In the sec-

ond step, the nucleophile attacks directly at the allylic ligand to form the product **(c),** and a palladium(0) species forms that re-enters the catalytic cycle.

Allylic Amination

We studied palladium–crotyl complexes (crotyl = but-2-enyl) of the P-functionalized dendritic species as catalysts in the allylic substitution reaction using morpholine as the nucleophile and methyl crotyl carbonate as the substrate (Scheme 4).[17] In a typical experiment the catalyst was formed by dissolving crotylpalladium chloride dimer and dendritic ligand in CH_2Cl_2 (unless otherwise stated). According to the ^{31}P NMR spectrum of the complex Pd·**7** (P/Pd ratio = 2.20) in $CDCl_3$ (Fig. 8) two major species are formed. The peak around 30 ppm is attributed to the mono-ligated species, whereas the one at ~22 ppm is attributed to the bidentate *syn* complex.

After ~120 min of incubation time the reaction was started by the addition of a CH_2Cl_2 solution containing crotyl methyl carbonate (reactant), morpholine (reactant and base) and *n*-decane (internal standard) to the catalyst solution. The reaction was monitored by gas chromatography.

In Tables 1 and 2 the results are displayed. The monomeric modular ligands **2**-**3**-**5**-**6** appear to form effective palladium catalysts for the allylic amination of crotyl methyl carbonate. All reactions went to completion within 1 h using 3 mol % of catalyst; this relatively high catalyst loading was chosen to compare the results with previous work. Their activities are all comparable to the activity of the catalyst formed by PPh_3. The activity of **5** (Phos-TREN) increases upon increasing the P/Pd ratio; a similar trend has already been observed by other authors.[14c,18] The selectivity is in all cases in favor of the branched product. The proposed *syn* stereochemistry of the Pd complex formed is not sufficient to explain the observed product distribution though.[19] In fact, this might be the consequence of a late transition state[20] (favored in presence of a weak nucleophile such as an amine) and the interaction of the counterion ($^-O_2COMe \rightarrow MeO^-$) with the palladium center, which is known to increase the rate of dynamic behavior of the allyl moiety.[21] This all results in an isomerization of the *syn* complex to the *anti* complex and vice versa. The resulting regioselectivity of the catalytic reaction is dependent on the relative rates of *syn–anti* isomerization and nucleophilic attack[22] (Scheme 6). In the case under investigation the isomerization is probably fast enough to favor the formation of (preferentially) the branched product.

We anticipated that, due to its non-uniform nature, the catalytic activity of the metal complexes of the macromolecular ligand **7** (Phos-PEI-5) might be sensitive to the metal loading (Table 2 and Fig. 9).

The curves displayed in the graph (Fig. 9) show the conversion of substrate (crotyl methyl carbonate) into the various products (allylamine isomers) as a function of time; each curve corresponds to a different metal loading. The catalytic activity of the "perfect" dendritic ligand **4** is also displayed. Indeed very small changes in P/Pd ratio (from 1.99 to 2.10) resulted in substantial changes in activity.

Ligand **4** provides palladium catalysts that show activity comparable to the catalyst based on PPh_3 (entries 1–3). Large changes in phosphorus/palladium ratio for ligand **4** gave much smaller differences of activity and opposite than the hyperbranched polymer derivative; an excess of phosphorus units leads to a decrease in activity. On the other hand, only a slight excess of ligand moieties (2.06 vs. 2) is necessary for the hyperbranched derivative **7** to equal the performance of the dendritic analogue (entries 4–7). This is attributed to the non-perfect structure of the polymer compared to the dendrimer. Some P atoms are concealed in the bulk of the core of the macromolecule and are therefore not

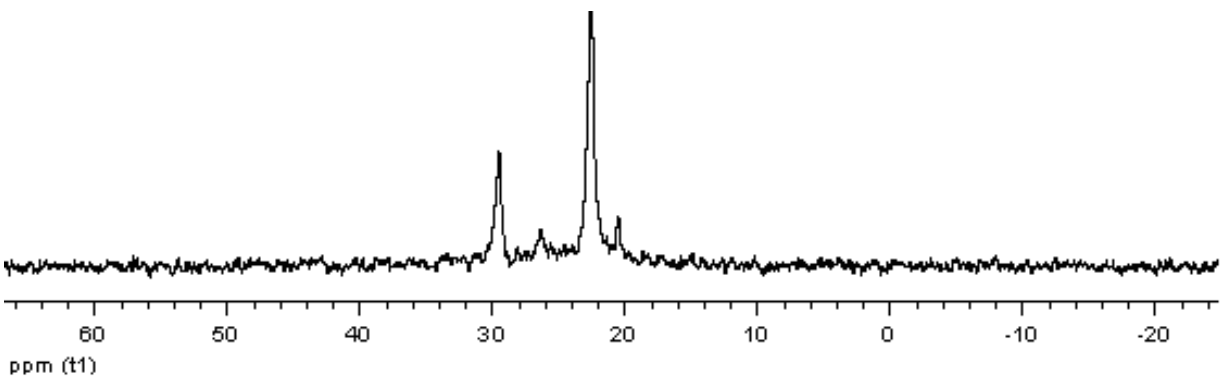


Fig. 8. Part of the ^{31}P NMR spectrum in chloroform-*d* (25 ºC) of the complex between Phos-PEI-5 (**7**) and $[Pd(crotyl)Cl]_2$.

Table 1. Pd-catalyzed allylic amination of crotyl methyl carbonate and morpholine using "model" ligands P[a]

ligand	P / Pd (molar ratio)	TOF[b]	product distribution (%) branched/ linear *trans*/linear *cis*
PPh_3	2	286	65/30/5
Phos-G0.0 (**2**)	2	229	64/32/4
Phos-G1.0 (**3**)	2	277	64/31/5
Phos-TREN (**5**)	2	180	60/35/5
Phos-TREN (**5**)	3	299	58/38/4
Phos-TETA (**6**)	2	387	64/30/6

[a]Room temperature, solvent CH_2Cl_2, vol 3 mL, [substrate] = 0.11 M, [amine] = 0.12 M, [Pd] = 3 mM. [b]mol mol^{-1} h^{-1}; average turnover frequency measured after 5 min.

Table 2. Pd-catalyzed allylic amination of crotyl methyl carbonate with morpholine using dendritic ligands **4**-**7**-**8**[a]

entry	ligand	P / Pd ratio	TOF[b]	product distribution (%) branched/ linear *trans*/linear *cis*
1	Phos-G5.0 (**4**)	2.00	299	61 / 36 / 3
2	**4**	2.21	238	62 / 36 / 2
3	**4**	2.46	211	60 / 36 / 4
4	Phos-PEI-5 (**7**)	1.99	114	65 / 33 / 2
5	**7**	2.03	216	65 / 32 / 3
6	**7**	2.06	321	66 / 32 / 2
7	**7**	2.10	365	65 / 31 / 4
8	Phos-PEI-25 (**8**)	1.89	308	63 / 35 / 2
9	**8**	2.01	348	63 / 34 / 3
10	**8**	2.39	387	62 / 35 / 3

[a]Room temperature, solvent CH_2Cl_2, vol 3 mL, [substrate] = 110 mM, [amine] =120 mM, [Pd] = 3 mM. [b]mol mol^{-1} h^{-1}; average turnover frequency measured after 5 min.

accessible to form a bis-ligated palladium complex. It is interesting to note that in absolute terms the hyperbranched polymer-supported catalyst outperformed the dendritic analogue. The activity is about 1.2 times higher (entry 7 vs. entry 1). The back-folding phenomenon often observed with this class of compounds provides an additional and complementary explanation for the opposite trends shown by dendrimer **4** and hyperbranched polymer **7**. In the first case, due to the uniform well-defined structure of dendrimer **4**, the back-folding of the peripheral arms (in conditions of excess of phosphorus vs. palladium) hampers the approaching of substrate molecules towards the catalytic centers. In the case of the hyperbranched polymer **7**, the back-folding is, on the other hand, beneficial as it provides stabilization of the metal centers, thus increasing the catalytic activity. Comparing the catalytic activities of ligands **2**, **3** (Table 1), and **4** (Table 2), a small positive dendritic effect on the TOF can be noted, which is presumably a consequence of the increasing bulk around the catalytic metal center. A similar effect was observed by de Groot et al. in the catalytic activity exhibited by different phosphine-functionalized carbosilane dendrimers in the Pd-catalyzed allylic amination.[14c] A more pronounced effect was reported by Gade and coworkers, who followed the activity of different generations of Pyrphos-functionalized PPI and PAMAM dendrimers.[23] These effects are often observed in palladium catalyzed allylic substitutions, which are known to be particularly sensitive to small changes in the chemical environment of the active catalyst site.[16d,17a,24] Experiments performed with the larger member of the hyperbranched poly(ethylenimine) derivatives, i.e., Phos-PEI-25 (**8**), exhibited a

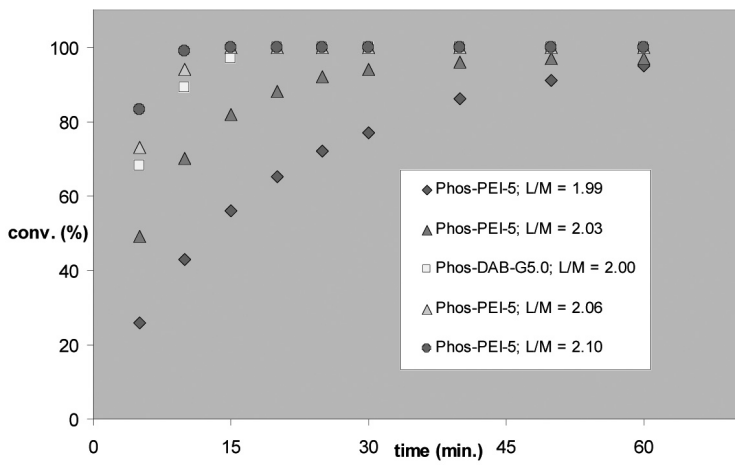
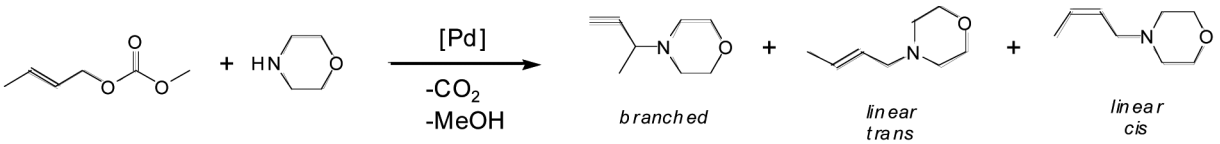
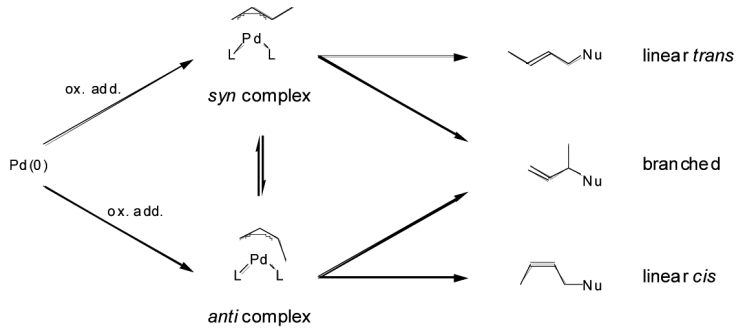


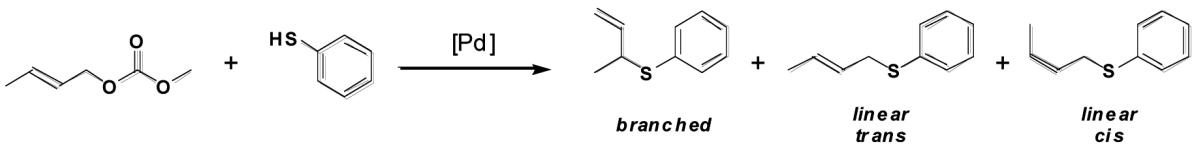
Fig. 9. Pd-catalyzed allylic amination of crotyl methyl carbonate with morpholine using dendritic ligands Phos-DAB-G5.0 (**4**) and Phos-PEI-5 (**7**).



Scheme 5. Pd-catalyzed allylic amination reaction of crotyl methyl carbonate with morpholine.



Scheme 6. Formation of regioisomers in the allylic substitution of (crotyl)Pd(bisphosphine) complexes.



Scheme 7. Allylic thiolation reaction of crotyl methyl carbonate with thiophenol.

similar trend as for macroligand **7** (entries 8–12), that is, an increase of activity upon increase of the P/Pd ratio. The experiments were carried out in CH_2Cl_2 as solvent but the results suffered from inadequate reproducibility (±30%), probably due to limited solubility of the catalyst system in this solvent. The reactions were also performed in CH_3CN and THF, achieving clear solutions, but they showed low conversion values, possibly as a result of the coordinating properties of the aforementioned solvents.

Allylic Thiolation

Transition metal-catalyzed synthetic reactions using sulfur-containing compounds are not straightforward, since these compounds can act as catalyst poisons because of the strong coordinating properties[25–27] of sulfur. Recently, a palladium-catalyzed S-allylation of aromatic and heteroaromatic thiols with allylic carbonates has been reported.[28,29] Allylic rearrangements consistent with a π-allyl palladium intermediate are observed. Regioisomeric allylic carbonates gave identical mixtures of regio- and stereoisomeric sulfides in which the substitution occurred at the less hindered allylic terminus of the π-allyl system.

We were interested to see if our dendritic catalysts were also active in the allylic thiolation and therefore studied the current system in this reaction (Scheme 7). Indeed, palladium–crotyl complexes (crotyl = but-2-enyl) of the dendritic species were active catalysts in the allylic substitution reaction performed using thiophenol as the nucleophile and crotyl methyl carbonate as the substrate. In a typical experiment the catalyst was formed by dissolving crotylpalladium chloride dimer and dendritic ligand in CH_2Cl_2 (unless otherwise stated). After an incubation time of ~ 120 min, the reaction was started by addition of a CH_2Cl_2 solution containing crotyl methyl carbonate (reactant), thiophenol (reactant), 4-methylmorpholine = *N*-methylmorpholine (NMM) (auxiliary base) and *n*-decane (internal standard) to the catalyst solution. The reaction was monitored by gas chromatography.

All reactions went to completion within 1 h except the experiment carried out with macroligand **7** applied at low P/M ratio; in Table 3 the turnover frequency after 5 min is displayed to compare activities.

The ligands under study appear to form effective palladium catalysts for the allylic thiolation of crotyl methyl carbonate, although the reaction rates are lower

Table 3. Pd-catalyzed allylic thiolation of crotyl methyl carbonate with thiophenol using dendritic ligands **2**-**4**-**7**[a]

ligand	P/Pd (molar ratio)	TOF P[b]	product distribution (%) branched/linear trans/ linear *cis*
$PPhB_{3B}$	2	198	67/30/3
Phos-G0.0 (**2**)	2	224	36/60/4
Phos-G5.0 (**4**)	2	216	47/50/3
Phos-PEI-5 (**7**)	1.99	75	40/55/5
7	2.03	154	42/53/5
7	2.06	233	38/57/5

[a]Room temperature, solvent CH_2Cl_2, vol 3 mL, [substrate] = 0.11 M, [thiol] = 0.12 M, [base] = 0.02 M, [Pd] = 3 mM. [b]mol mol^{-1} h^{-1}; average turnover frequency measured after 5 min.

than those of the allylic amination reaction. Their activities are all comparable with the activity of the simple PPh_3-based catalyst, while the selectivity is in this case in favor of the linear isomers, unlike for the allylic amination. The trends in catalytic activity and selectivity are consistent with the "late" nature of the transition state, which is more pronounced for S than for N.[20,22] The sulfur nucleophile, which can be considered a "soft" nucleophile, attacks preferentially at the less substituted termini of the π-allyl intermediate.[28a,b,P]

In analogy with the allylic amination, very small changes in P/Pd ratio (from 1.99 to 2.06) result in substantial changes in TOF. Again, it may be inferred that a slight excess of ligand moieties is necessary for the hyperbranched derivative to approach the performances of the dendritic analogue, probably due to the non-perfect structure of the polymer compared to the dendrimer; some P atoms are concealed in the core of the macromolecule, which are less accessible for formation of bis(phosphine)palladium complexes.

Continuous Processes

Reactor setup

A continuous-flow membrane reactor (CFMR) previously developed in our group was used for various catalytic reactions (Fig. 10a). The reactor consists of a stainless steel autoclave in which the catalyst solution can be injected via a two-way valve. The membrane is located at the bottom of the autoclave and kept in place by a Viton O-ring. The Koch/SelRO MPF-50 nanofiltration membrane (MW cutoff = 700 Da)[30] was chosen for the filtration experiments since it previously gave good results with similar dendritic ligands in transition metal-catalyzed reactions.[14] For similar reasons CH_2Cl_2 was used to prepare all solutions because it proved to be the best solvent so far.[14] A vessel containing the substrate solution (usually under inert atmosphere) is connected to the membrane reactor via an HPLC-pump that pushes the substrate solution into the reactor and through the membrane. The product stream is collected and samples are taken at regular time intervals; these are analyzed by GC to obtain the conversion in the product phase as a function of time.

Commonly, dendritic transition metal catalysts applied in a CFMR can suffer from two forms of leaching: depletion of the dendritic catalyst through the membrane and metal dissociation from the dendrimer resulting in further leaching of the unsupported metal through the membrane. In Fig. 10b the theoretical retention of

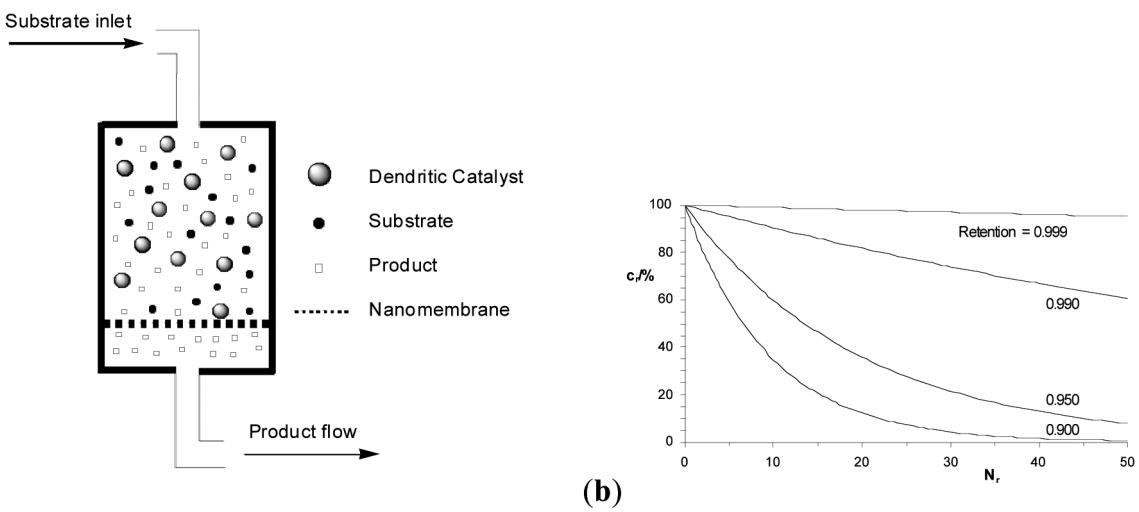


Fig. 10. Schematic presentation of a membrane reactor (*left*, **a**) and theoretical relative concentrations (C_r) of the dendritic species vs. the substrate flow (expressed in number of reactor volumes pumped through N_r) calculated for various retention coefficients (*right*, **b**).

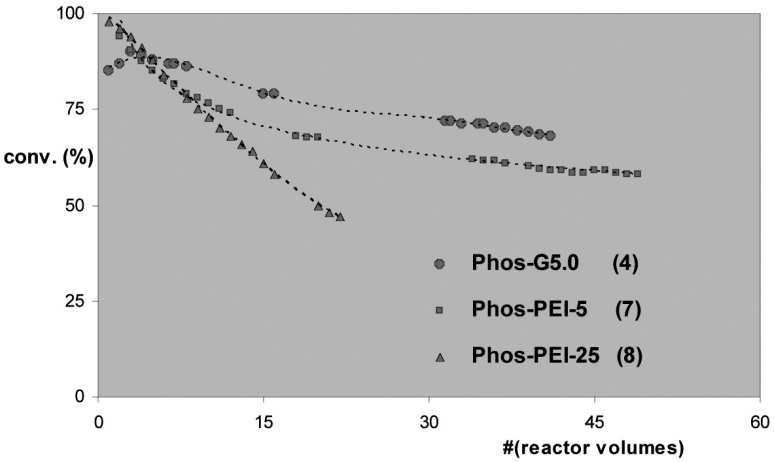


Fig. 11. Product yield in the allylic amination of crotyl methyl carbonate with morpholine in the CFMR as a function of the substrate flow (expressed as no. of reactor volumes) using different dendritic ligands (**4**), (**7**), and (**8**). {Reaction conditions: [substrate] = 0.11 M, [amine] = 0.12 M, [*n*-decane] = 0.10 M, [Pd] = 5 mM, 6 mL CH_2Cl_2, room temperature, flow rate = 9 mL h^{-1} (150 μL min^{-1})}.

catalysts are plotted for dendritic systems with various retention coefficients. For example, if a dendritic catalyst has a retention factor of 0.95, only 25% of the catalyst would remain in the reactor after the reactor had been flushed with 30 times its volume. For practical applications, the overall retention of the dendritic catalyst must be very high (typically, >99.9%) to maintain the material in a CFMR for long reaction times.

Allylic amination

The macromolecular ligands Phos-DAB-G5.0 (**4**), Phos-PEI-5 (**7**) and Phos-PEI-25 (**8**) were applied in a CFMR for the allylic amination of crotyl methyl carbonate. A CH_2Cl_2 solution of the ligand under study (**4**, **7**, or **8**) and crotylpalladium chloride dimer was stirred at room temperature for 3 h and then 3 mL was injected into the membrane reactor (vol 6 mL). At the same time the reactor was fed with a solution of crotyl methyl carbonate, morpholine, and *n*-decane (internal standard). All experiments performed resulted in a pressure buildup in the membrane (up to 10–11 bar), as a consequence of the production of CO_2 as one of the reaction byproducts. The product stream of the reaction was sampled at regular intervals of time and analyzed by means of GC; the conversion values are plotted as a function of the number of cycles performed by the reactor. The curves displayed show the product yield as a function of the substrate flow, indicated as number of reactor volumes:

#(reactor volumes) = (flow rate × time)/(reactor volume)

A comparative view (Fig. 11) of the catalytic performances shown by the three ligands under investigation displays the differences between the various supports.

The recycling with macroligand **4** was performed using Pd catalyst (5 mol % catalyst vs. substrate, P/Pd ratio = 2). The reaction started immediately after addition of the catalyst solution and reached its maximum conversion (~90%) after approximately two cycles. The yield gradually started decreasing during the next thirty-eight cycles, after which the reaction was stopped because all substrate solution was consumed. The observed decrease in catalyst activity was ascribed to loss of the palladium compound from the reactor; this was also confirmed by the slight yellow color of the product stream[3,14a,c,15,31] (a similar though far more dramatic phenomenon was also observed with dendritic Ni catalysts[32]). Loss of the dendritic ligand as a possible reason for the drop in activity was excluded by analysis of the reactor content at the end of the reaction. ^{31}P NMR of the solution in the reactor, vs. tri-*o*-tolylphosphine as a standard, showed that the P-functionalized macromolecule was completely retained in the reactor (within the experimental error), as expected on the basis of its size. Interestingly, the stereoselectivity observed during the continuous recycling experiment is similar to that of the batch processes, in favor of the branched product. When applying ligand **7**, the Pd catalyst was used in 5% molar ratio vs. substrate and a P/Pd ratio of 2.3 was applied (slightly higher than the "optimum" found in the corresponding batch reaction). The reaction starts immediately after addition of the catalyst solution with very high conversion (~94%). The yield gradually decreased dur-

ing the next thirty-two hours (forty-eight cycles). Also in this case the observed decrease in catalyst activity was ascribed to loss of palladium from the reactor[3,14a,c,31] (the outgoing solution was slightly yellow). Similarly to the case of the perfect dendritic ligand **4**, ^{31}P NMR of the solution in the reactor vs. tri-*o*-tolylphosphine showed that the P-functionalized macromolecule was completely retained in the reactor. The observed selectivity is again similar to that of the corresponding batch process (predominantly branched product). In spite of the difficulties encountered during the batch experiments (solubility), we chose to investigate the performance of ligand **8** in CFMR. The Pd catalyst was used in 5% molar ratio vs. substrate and P/Pd ratio of 2.39 was applied (slightly higher than the "optimum" found in the corresponding batch reaction). The curve shows that the reaction starts immediately after addition of the catalyst solution with very high conversion (~98%). The yield immediately decreased with a steep slope during the next fourteen hours (twenty-two reactor cycles). The observed decrease in catalyst activity was again attributed to loss of palladium from the reactor;[3,14a,c,31] this was confirmed by the yellow color of the product stream and total retention of the dendritic ligand within the nano-membrane reactor.

The structure and stability of the metal complexes of the phosphine-functionalized molecules, which is crucial for the application in a continuous process, appear to be very sensitive to changes in the dendritic structure. This was also previously found for carbosilane-based dendrimers. When using dendrimer ligands with $Si(CH_2PPh_2)_2$ end-groups, the yield for allylic substitution reactions dropped rapidly during continuous flow experiments, whereas a stable catalyst was obtained in a CFMR when dendrimer ligand with $SiCH_2CH_2PPh_2$ end-groups was used.[14c,15]

Importantly, the behavior displayed by the "perfect' dendritic ligand Phos-G5.0 (**4**) and the smaller hyperbranched Phos-PEI-5 (**7**) is quite similar. This was supported by the small amount of black Pd metal deposited on the membrane in both cases. The curves of the mentioned ligands (represented in the diagram by circles and squares, respectively) diverge in the initial part but then assume a very similar declining trend; likely the Pd-complexes formed (the active catalysts) are very similar in nature. The clearly faster loss in activity shown by the Phos-PEI-25 (lig. **8**) compared to the smaller analogue Phos-PEI-5 (lig. **7**) can be attributed to the lower stability of the Pd complexes formed, as can be deduced from the more intense yellow color of the outgoing stream and the distinctly larger amount of Pd metal accumulated on the membrane. The aforementioned solubility issues and the structural characteristics of the macromolecule might be responsible for the fast loss of activity shown by Phos-PEI-25. It has been shown that the globular and, perhaps more important, shape-persistent structures of the dendrimers are fundamental for effective application in membrane filtration recycling; a high degree of rigidity in the backbone of macromolecular complexes leads indeed to more efficient retentions of multimetallic materials by nanofiltration membranes.[33] A number of experimental[34,35] and theoretical[38] approaches show that dendrimers and hyperbranched polymers in good solvent conditions[37] are best described as flexible macromolecular aggregates[38] with their maximum density in the center of the molecule (dense-core structure)[39] and fluctuating monomer groups.[40] The higher flexibility of Phos-PEI-25 compared to Phos-PEI-5 could contribute to the formation of less stable catalysts and therefore cause faster loss of activity of the system when applied in the CFMR.

Allylic thiolation

The macromolecular ligand Phos-PEI-5 (**7**) was applied in a continuous-flow membrane reactor for the allylic thiolation of crotyl methyl carbonate. A CH_2Cl_2 solution of the ligand and crotylpalladium chloride dimer was mixed at room temperature and then injected into the membrane reactor. Subsequently the reactor was fed with a solution of crotyl methyl carbonate (reactant), thiophenol (reactant), NMM (auxiliary base) and *n*-decane (internal standard). The setup of the recycling system is done in a similar way as for the allylic amination. The product stream of the reaction was sampled at regular intervals of time and analyzed by means of GC; the conversion values are plotted as a function of the number of cycles performed by the reactor in Fig. 12.

The reaction started immediately after addition of the catalyst solution with high conversion (~83%) and reached its maximum value (~96%) after approximately three cycles. The conversion then decreased during the next twelve cycles. It is reasonable to assume that, in analogy with the allylic amination reaction, structural features lead to a drop in catalytic activity. In this experiment the product stream appeared much more intensely colored (yellow) than found for the allylic amination reactions; this phenomenon is probably a consequence of the strong affinity of Pd metal centers for S ligands (reactant and products, in this case) that would eventually wash out the metal catalyst.[26,31] P NMR of the solution in the reactor vs. tri-*o*-tolyl phosphine showed that the P-functionalized macromolecule was completely retained in the reactor. The observed selectivity is similar to that of the corresponding batch process, i.e., the linear isomers prevail.

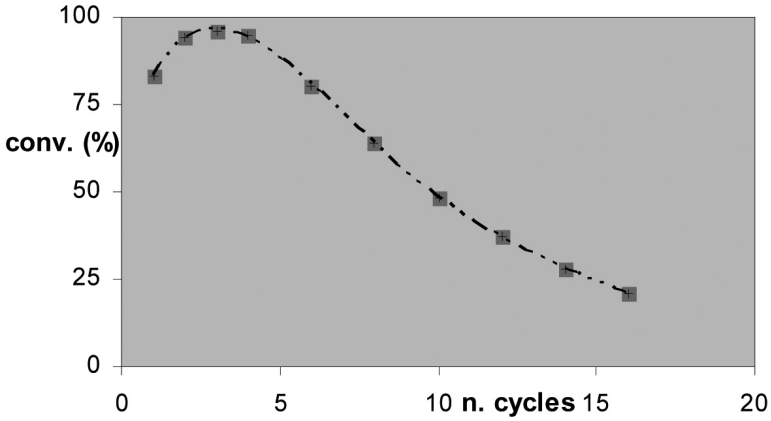


Fig. 12. Product yield in the allylic thiolation of crotyl methyl carbonate with thiophenol in the CFMR as a function of the substrate flow (expressed as no. of cycles) using dendritic ligand **7**. {[substrate] = 0.11 M, [thiol] = 0.12 M, [base] = 0.02 M, [*n*-decane] = 0.12 M, [Pd] = 5 mM, P/Pd = 2.31, 6 mL CH_2Cl_2, room temperature, flow rate = 6 mL h^{-1} (100 μL min^{-1})}.

CONCLUSIONS

In this paper we have described the facile and straightforward covalent functionalization of commercially available dendritic poly(propylenimine) and hyperbranched poly(ethylenimine) with P-containing functional groups. The P-functionalized macromolecules have been applied as multivalent ligands in the Pd-catalyzed allylic substitution reactions (batch and continuous process) using either morpholine or thiophenol as nucleophile. Palladium complexes of all described molecules are active in allylic substitution reactions. The PEI-functionalized polymers appear more sensitive to small changes in the P/Pd ratio than the PPI analogues, but form catalysts that are more active. In the allylic amination, Pd complexes of Phos-PEI-5 show selectivities comparable with PPh_3, whereas in the allylic thiolation, the use of Phos-PEI-5 reverses the selectivity (predominantly linear allylic sulfides). When the dendritic ligands are used in a continuous-flow process, the macromolecules are completely retained by the nanofiltration membrane, while the catalytic activity decreases with time because of palladium depletion. Palladium leaching is not associated with the nature of the dendrimers or macromolecules, but it is an intrinsic problem of palladium-catalyzed coupling reactions. Palladium depletion is more severe for the allylic thiolation, probably because of the stronger affinity of sulfur for palladium, facilitating palladium leaching. Unexpectedly, the larger PEI-25 derivative loses activity more quickly than the smaller Phos-PEI-5 ligand, showing that this is not a suitable support for this reaction. In contrast, Phos-PEI-5 shows a very similar behavior to the perfect DAB-dendrimer derivative when applied in the CFMR. Indeed, the cheap PEI polymer was successfully used as catalyst support and outperformed the PPI dendrimer.

EXPERIMENTAL SECTION

General Remarks

All reactions were carried out in flamed-dried glassware and under a dry nitrogen atmosphere using Schlenck techniques unless mentioned otherwise. Solvents were dried and distilled under nitrogen; Et_2O and THF from sodium/benzophenone, hexane from sodium/benzophenone/triglyme, CH_2Cl_2 and EtOAc from CaH_2. Dendritic poly(propylenimines) (DAB dendrimers, DSM products) were purchased from Aldrich Chemical Company, hyperbranched poly(ethylenimine) PEI-5 and PEI-25 were purchased from HyperPolymers GmbH, other chemicals were purchased from Acros Organics or Aldrich Chemical Company and used without further purification unless otherwise stated. The *N*-methyl morpholine and morpholine were distilled prior to use, respectively, from KOH and sodium. Crotyl methyl carbonate was prepared using a slightly modified literature procedure.[41] Silica 60 (SDS Chromagel, 70–200 μm) was used for column chromatography. ^1H, $^{13}C\{^1H\}$ and $^{31}P\{^1H\}$ NMR spectra were recorded using the following spectrometers: Varian Mercury 300 (^1H 300 MHz, ^{31}P 121 MHz, and ^{13}C 125 MHz) and Varian Inova 500 (^{13}C 125 MHz). The spectra were recorded in $CDCl_3$ unless stated otherwise and the chemical shifts are given in ppm versus TMS (^1H, ^{13}C) or 85% H_3PO_4 (^{31}P). FAB MS experiments were performed on a Joel JMS SX/SX 102A four sector mass spectrometer coupled to a Joel MS-MP7000 data system, using 3-nitro benzyl alcohol as matrix. GC analyzes were performed on an Interscience HRGC Mega 2 (J&W Scientific DB-1 30 m × 0.32 mm × 3.0 μm). All catalytic experiments were performed at least in duplicate.

***p*-(Diphenylphosphino)benzylamine (1)**.[10] A 250 mL flame-dried three-necked round bottom flask equipped with a nitrogen inlet and a reflux condenser was charged with 5 mL of 4-fluorobenzylamine (43.95 mmol) and 88 mL of a 0.5 M solution of $KPPh_2$ in THF (Aldrich). After heating the reaction mixture at reflux for 20 h the possible unreacted phosphido anion was quenched with 5 mL of MeOH, then the solvent

was evaporated under reduced pressure, redissolved in CH_2Cl_2 (75 mL), and washed with degassed water (2 × 40 mL). The organic phase was dried over Na_2SO_4, filtered, and the solvent removed under reduced pressure. The crude product was purified using two methods different from the one reported in the reference. Method A: the crude product was purified by column chromatography over silica using $CHCl_3$/MeOH (9:1) as an eluent (R.F. = 0.3). Method B: the crude product was purified by reprecipitation from boiling hexane. Total yield: 8.96 g (70%), white product. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.4–7.2 (m, 14 H, Ar*H*), 3.8 (s, 2 H, CH_2), 2.2 (s (br), 2 H, NH_2); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 46.3, 127.9, 128.9, 129.3, 134.0, 134.7, 136.0, 137.8, 143.9; ^{31}P{^{1}H} NMR (121 MHz, $CDCl_3$) δ –5.63 (s).

Phos-MA-Am-2 (2). A 50 mL flame-dried Schlenck flask equipped with a 25 mL dropping funnel was charged with a solution of 1,1′-carbonyl diimidazole (CDI, 0.487 g = 3.00 mmol) and NMM, 0.11 mL = 0.101 g = 1.00 mmol, ~1/3 equiv) in 5 mL of CH_2Cl_2. A solution of *p*-(Diphenylphosphino)benzylamine (0.795 g = 2.73 mmol) in CH_2Cl_2 (17 mL) was transferred into the dropping funnel and subsequently slowly dropped into the flask and allowed to react for ~15 min. A solution of 3,3′-diamino-*N*-methyldipropylamine (0.200 mL = 0.180 g = 1.24 mmol, ~1/2 equiv) in CH_2Cl_2 (3 mL) was then added in one portion and left stirring overnight at room temperature. The reaction mixture was washed with degassed water (2 × 20 mL) and then dried over Na_2SO_4. Filtration and evaporation of the solvent under reduced pressure left a white solid that was purified by reprecipitation from boiling *i*-PrOH. The filtered product was further washed with pentane and/or Et_2O to remove traces of solvent and give 0.764 g of white product (yield 79% vs. starting material MA-Am-2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.57 (t, 4 H, NCH$_2$CH_2CH$_2$N), 2.22 (s, 3 H, CH_3N), 2.34 (t, 4 H, NCH_2CH$_2$CH$_2$NHCO), 3.12 (m, 4 H, NCH$_2$CH$_2$CH_2NHCO), 4.16 (d, 4 H, ArCH_2NHCO), 6.08–6.47 (br., 4 H, N*H*CON*H*), 7.11–7.45 (m, 28 H, Ar*H*); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 27.0, 38.8, 43.6, 44.3, 52.7, 127.5, 128.6, 128.8, 133.6, 134.1, 136.2, 137.3, 140.1, 158.2; ^{31}P{^{1}H} NMR (121 MHz, $CDCl_3$) δ –5.41; GC-MS [M]$^+$ 779.

Phos-DAB-Am-4 (3). A 100 mL flame-dried Schlenck flask equipped with a 50 mL dropping funnel was charged with a solution of CDI, 0.952 g = 5.87 mmol, and NMM, 0.2 mL = 0.184 g = 1.82 mmol, ~1/3 equiv) in 8 mL of CH_2Cl_2. A solution of *p*-(Diphenylphosphino)benzylamine (1.555 g = 5.34 mmol) in CH_2Cl_2 (20 mL) was transferred into the dropping funnel and subsequently slowly dropped into the flask and allowed to react for ~15 min. A solution of DAB-Am-4 (0.400 mL = 0.384 g = 1.21 mmol, ~1/4 equiv) in CH_2Cl_2 (7 mL) was then added in one portion and left stirring overnight at room temperature. The reaction mixture was washed with degassed water (2 × 20 mL) and then dried over Na_2SO_4. Filtration and evaporation of the solvent under reduced pressure left a white solid that was purified by reprecipitation from boiling *i*-PrOH. The filtered product was further washed with pentane and/or Et_2O to remove traces of solvent and give 1.58 g of white product (yield 82% vs. starting material DAB-Am-4). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.39 (m, 4 H, NCH$_2$CH_2CH_2CH$_2$N) 1.64 (m, 8 H, NCH$_2$CH_2CH$_2$N), 2.29–2.34 (m, 12 H, NCH_2CH$_2$CH$_2$NHCO + NCH_2CH$_2$CH$_2$CH_2N), 3.10 (m, 8 H, NCH$_2$CH$_2$CH_2NHCO), 4.17 (d, 8 H, ArCH_2NHCO), 6.10–6.50 (br., 8 H, N*H*CON*H*), 7.13–7.49 (m, 28 H, Ar*H*); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 26.0, 26.6, 39.9, 46.1, 51.1, 53.9, 127.5, 128.6, 128.8, 133.6, 134.1, 136.2, 137.3, 140.1, 158.2; ^{31}P{^{1}H} NMR (121 MHz, $CDCl_3$) δ –5.27; FAB-MS [M]$^+$ 1586.

Phos-DAB-Am-64 (4). A 100 mL flame-dried Schlenck flask equipped with a 50 mL dropping funnel was charged with a solution of CDI, 0.476 g = 2.94 mmol, and NMM, 0.1 mL = 0.092 g = 0.91 mmol, ~1/3 equiv) in 5 mL of $CHCl_3$ (fractionally distilled from $CaCl_2$). A solution of *p*-(Diphenylphosphino)benzylamine (0.778 g = 2.67 mmol) in $CHCl_3$ (15 mL) was transferred into the dropping funnel and subsequently slowly dropped into the flask and allowed to react for ~15 min. A solution of DAB-Am-64 (0.272 g = 37.94 μmol, ~1/64 equiv) in THF (20 mL) was then added in one portion and left stirring for 2 ½ days at room temperature. The solvent was evaporated and the crude product redissolved in CH_2Cl_2 (40 mL). The solution was then washed with degassed water (2 × 20 mL) and dried over Na_2SO_4. Filtration and evaporation of the solvent under reduced pressure left a white solid that was purified by reprecipitation from boiling *i*-PrOH (40 mL). The filtered product was crushed and further washed with pentane and/or Et_2O to remove traces of solvent and give 0.826 g of white product (yield 79% vs. starting material DAB-Am-64). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.39 (m, 4 H, NCH$_2$CH_2CH_2CH$_2$N), 1.55 (br., 248 H, NCH$_2$CH_2CH$_2$N),2.11–2.48(br.,372H,NCH_2CH$_2$CH$_2$NHCO + NCH_2CH$_2$CH_2N + NCH_2CH$_2$CH$_2$CH_2N), 2.98–3.18 (br., 128 H, NCH$_2$CH$_2$CH_2NHCO), 3.97–4.36 (br., 128 H, ArCH_2NHCO), 6.08–6.57 (br., 128 H, N*H*CON*H*), 6.91–7.69 (m, 896 H, Ar*H*); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 24.4, 27.7, 37.5, 45.7, 51.1, 51.7, 127.5–140.1, 158.2; ^{31}P{^{1}H} NMR (121 MHz, $CDCl_3$) δ –5.32 (br.).

Phos-TREN (5). A 50 mL flame-dried Schlenck flask equipped with a 25 mL dropping funnel was charged with a solution of CDI, 0.476 g = 2.94 mmol, and NMM, 0.1 mL = 0.092 g = 0.091 mmol, ~1/3 equiv) in 5 mL of CH_2Cl_2. A solution of *p*-(Diphenylphosphino)benzylamine (0.778 g = 2.67 mmol) in CH_2Cl_2 (20 mL) was transferred into the dropping funnel and subsequently slowly dropped into the flask and allowed to react for ~10 min. A solution of TREN (tris(2-aminoethyl)amine) (0.120 mL = 0.120 g = 0.822 mmol, ~1/3 equiv) in THF (3 mL) was then added in one portion and left stirring overnight at room temperature. The reaction mixture was washed with degassed water (2 × 15 mL) and then dried over Na_2SO_4. Filtration and evaporation of the solvent under reduced pressure left a white solid that was purified by reprecipitation from boiling Et_2O. The filtered product was further washed with pentane to remove traces of solvent and give 0.831 g of white product (yield 92% vs. starting material TREN). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.57 (t., 6 H, NHC(O)NHCH$_2$CH_2N), 3.29 (t., 6 H, NH(O)CNHCH_2CH$_2$N), 4.32 (s., 6 H, ArCH_2NHCO), 6.05–6.61 (br., 6 H, N*H*CON*H*), 7.24–7.63 (m., 42 H, Ar*H*); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 40.7, 43.2, 51.3, 127.3, 128.8, 129.2, 133.3, 134.5, 136.7,

138.0, 140.1, 157.3; $^{31}P\{^{1}H\}$ NMR (121 MHz, $CDCl_3$) δ –5.47; FAB-MS $[M]^+$ 1098.

Phos-TETA (6). A 50 mL flame-dried Schlenck flask equipped with a 25 mL dropping funnel was charged with a solution of CDI, 0.479 g = 2.95 mmol, and NMM, 0.1 mL = 0.092 g = 0.091 mmol, ~1/3 equiv) in 5 mL of CH_2Cl_2. A solution of *p*-(Diphenylphosphino)benzylamine (0.782 g = 2.69 mmol) in CH_2Cl_2 (20 mL) was transferred into the dropping funnel and subsequently slowly dropped into the flask and allowed to react for ~10 min. A solution of TETA (triethylenetetramine) (0.100 mL = 0.098 g = 0.672 mmol, ~1/4 equiv) in CH_2Cl_2 (3 mL) was then added in one portion and left stirring overnight at room temperature. The reaction mixture was washed with degassed water (2 × 15 mL) and then dried over Na_2SO_4. Filtration and evaporation of the solvent under reduced pressure left a white solid that was purified by reprecipitation from boiling Et_2O. The filtered product was further washed with pentane to remove traces of solvent and give 0.884 g of white product (yield 93% vs. starting material TETA). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.35 (br. m., 12 H, NH(O)CNHCH_2CH_2NC(O)NH + NHC(O)NCH_2CH_2NC(O)NH), 4.27 (s., 8 H, ArCH_2NHCO), 6.09–6.47 (br., 6 H, NCON*H* + N*H*CON*H*), 7.21–7.59 (m., 56 H, Ar*H*); $^{13}C\{^{1}H\}$ NMR (75 MHz, $CDCl_3$) δ 39.2, 43.5, 47.2, 50.5, 126.9, 127.9, 128.3, 132.9, 133.7, 135.8, 137.1, 141.2, 159.0; $^{31}P\{^{1}H\}$ NMR (121 MHz, $CDCl_3$) δ –5.61; FAB-MS $[M]^+$ 1416.

Phos-PEI-5 (7). A 100 mL flame-dried Schlenck flask equipped with a 50 mL dropping funnel was charged with a solution of CDI, 0.773 g = 4.77 mmol, and NMM, 0.15 mL = 0.14 g = 1.36 mmol, ~1/3 equiv) in 8 mL of THF. A solution of *p*-(Diphenylphosphino)benzylamine (1.389 g = 4.77 mmol) in THF (22 mL) was transferred into the dropping funnel and subsequently slowly dropped into the flask and allowed to react for ~ 20 min. A solution of PEI-5 (0.298 g = 59.6 μmol, ~1/80 equiv) in THF (25 mL) was then added in one portion and left stirring for 4 dd at room temperature. The solvent was evaporated and the crude product purified by reprecipitation from boiling *i*-PrOH (60 mL); the solid was isolated and the last procedure repeated 2 more times to remove all impurities. The filtered product was crushed and further washed with pentane to remove traces of solvent and give 1.081 g of off-white product (yield 63% vs. starting material PEI-5). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.36–2.78 (br., $CH_2NCH_2CH_2NCH_2$), 2.96–3.47 (br., $CH_2N(CO)CH_2CH_2NHCO$), 3.87–4.49 (br., ArCH_2NHCO), 6.06–6.62 (br., N*H*CON*H*), 6.97–7.72 (m, Ar*H*); $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$) δ 38.5, 45.7, 50.5, 51.7, 127.5, 128.6, 128.8, 133.6, 134.1, 136.2, 137.3, 140.1, 158.2; $^{31}P\{^{1}H\}$ NMR (121 MHz, $CDCl_3$) δ –5.32 (br.).

Phos-PEI-25 (8). A 100 mL flame-dried Schlenck flask equipped with a 50 mL dropping funnel was charged with a solution of CDI, 0.485 g = 2.99 mmol, and NMM, 0.11 mL = 0.101 g = 1.0 mmol, ~1/3 equiv) in 5 mL of THF. A solution of *p*-(diphenylphosphino)benzylamine (0.872 g = 2.99 mmol) in THF (20 mL) was transferred into the dropping funnel and subsequently slowly dropped into the flask and allowed to react for ~20 min. A solution of PEI-25 (0.187 g = 7.48 μmol, ~1/400 equiv) in THF (30 mL) was then added in one portion and left stirring for 5 dd at room temperature. The solvent was evaporated and the crude product purified by reprecipitation from boiling *i*-PrOH (60 mL); the solid was isolated and the last procedure repeated 2 more times to remove all impurities. The filtered product was crushed and further washed with pentane to remove traces of solvent and give 0.751 g of off-white product (yield 69% vs. starting material PEI-25). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.29–2.73 (br., $CH_2NCH_2CH_2NCH_2$), 2.98–3.42 (br., $CH_2N(CO)CH_2CH_2NHCO$), 3.91–4.37 (br., ArCH_2NHCO), 5.97–6.52 (br., N*H*CON*H*), 6.95–7.75 (m, Ar*H*); $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$) δ 38.7, 46.2, 50.3, 51.2, 127.3, 128.3, 129.1, 133.2, 134.8, 136.5, 137.7, 140.2, 158.4; $^{31}P\{^{1}H\}$ NMR (121 MHz, $CDCl_3$) δ –5.32 (br.).

Crotyl methyl carbonate. A solution of 50.0 mL (42.25 g = 0.586 mol) crotyl alcohol (97% *trans*) and 71.0 mL (69.44 g = 0.878 mol) pyridine in 60 mL CH_2Cl_2 was cooled to 0 ºC with an ice/water bath, after which 54.0 mL (66.04 g = 0.699 mol) methyl chloroformate was added dropwise. The reaction mixture was left to warm to room temperature and was-stirred overnight, after which it was poured into 500 mL 10% NH_4Cl solution. The organic layer was separated, washed with 250 mL brine, dried over Na_2SO_4, and concentrated in vacuo. The crude product was purified by distillation under reduced pressure to give 63.29 g of colorless liquid (yield = 83%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.71 (d, CH_3CH = CHCH$_2$, 3 H), 3.67 (s, OCH_3, 3 H), 4.67 (d, CH = CHCH_2O, 2 H), 5.63 (m, CH_3CH = C*H*CH$_2$, 1 H), 5.73 (m, CH_3C*H* = CHCH$_2$, 1 H); $^{13}C\{^{1}H\}$ NMR (75 MHz, $CDCl_3$) δ 18.4, 55.4, 69.8, 125.3, 131.5, 155.7.

Batchwise Allylic Amination Catalysis

A solution of ligand (18 μmol of "P" units, P/Pd = 2) and $[Pd(crotyl)Cl]_2$ (1.773 mg = 9 μmol of "Pd") in CH_2Cl_2 (2 mL) was stirred for 2 h at R.T. Substrate solution was prepared by dissolving 0.0716 g crotyl methyl carbonate (0.55 mmol), 0.0523 g morpholine (0.6 mmol) and 0.0712 g *n*-decane (0.5 mmol) in 5 mL CH_2Cl_2. Addition of 1 mL of substrate solution started the catalysis. Samples of 50 μL were taken at t = 5, 10, 15, 20, 25, 30, 40, 50, 60 min, diluted in 3 mL Et_2O, filtered over Celite, and analyzed by GC.

Batchwise Allylic Thiolation Catalysis

A solution of ligand (18 μmol of "P" units, L/M = 2) and $[Pd(crotyl)Cl]_2$ (1.773 mg = 9 μmol of "Pd") in CH_2Cl_2 (2 mL) was stirred for 2 h at R.T. Substrate solution was prepared by dissolving 0.0716 g crotyl methyl carbonate (0.55 mmol), 0.0661 g thiophenol (0.6 mmol), 0.0101 g NMM (0.1 mmol) and 0.0712 g *n*-decane (0.5 mmol) in 5 mL CH_2Cl_2. Addition of 1 mL of substrate solution started the catalysis. Samples of 50 μL were taken at t = 5, 10, 15, 20, 25, 30, 40, 50, 60 min, diluted in 3 mL Et_2O, filtered over Celite, and analyzed by GC.

Continuous Allylic Amination Catalysis

A piece of Koch/SelRO MPF-50 membrane (stored in EtOH) was cut to the correct size and pretreated by bathing it in acetone overnight and subsequently in MeOH overnight. The membrane was then installed in the reactor and flushed overnight with CH_2Cl_2 and then with substrate solution (approx. two reactor volumes). The substrate solution was pre-

pared by mixing 5.726 g crotyl methyl carbonate (0.044 mol), 4.182 g morpholine (0.048 mol) and 5.692 g *n*-decane (0.04 mol) in 400 mL CH_2Cl_2, transferred into the storage chamber of the CFMR, and pumped through the reactor with a flow rate of 9 mL h^{-1} (150 μL min^{-1}). The catalyst solution was prepared by dissolving $[Pd(crotyl)Cl]_2$ (7.880 mg = 40 μmol of "Pd") and dendritic ligand (80 μmol of "P" if P/Pd = 2) in 4 mL CH_2Cl_2 and stirring for 3 h. The reaction was started by the injection of 3 mL of catalyst solution into the membrane reactor. Samples of 100 μL were taken at regular intervals (generally after one cycle = 40 min), quenched in 3 mL DBA/Et_2O, filtered over Celite, and analyzed by GC.

Continuous Allylic Thiolation Catalysis

A piece of Koch/SelRO MPF-50 membrane (stored in EtOH) was cut to the correct size and rinsed in acetone overnight and subsequently in MeOH overnight. The membrane was then fit in the reactor and flushed overnight with CH_2Cl_2 and then with substrate solution (approx. two reactor volumes). The substrate solution was prepared by mixing 2.290 g crotyl methyl carbonate (0.0176 mol), 2.115 g thiophenol (0.0192 mol), 0.324 g NMM (3.2 mmol) and 2.277 g *n*-decane (0.016 mol) in 160 mL CH_2Cl_2 and was pumped through the reactor with a flow rate of 6 mL h^{-1} (100 μL min^{-1}). The catalyst solution was prepared by dissolving $[Pd(crotyl)Cl]_2$ (7.880 mg = 40 μmol of "Pd") and dendritic ligand (80 μmol of "P" if P/Pd = 2) in 4 mL CH_2Cl_2 and stirring for 3 h. The reaction was started by the injection of 3 mL of catalyst solution into the membrane reactor. Samples of 100 μL were taken at regular intervals in time (generally after one cycle = 60 min), quenched in 3 mL DBA/Et_2O, filtered over Celite, and analyzed by GC.

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