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PAPER

SCS-pincer palladium-catalyzed auto-tandem catalysis using dendritic catalysts in semi-permeable compartments

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Novel monometallic and dendritic SCS-pincer palladium complexes **2**, **3** and **4** have been synthesized in good yields (60–89%) and high purity (palladium loading >97%). These complexes were successfully used as catalysts in the stannylation of cinnamyl chloride with hexamethylditin and in the catalytic auto-tandem reaction consisting of this stannylation followed by an electrophilic addition with 4-nitrobenzaldehyde, showing similar reaction rates and selectivities for all complexes. Dendritic complex **4** has furthermore been used in the compartmentalized catalysis of single and auto-tandem reactions, allowing catalyst reuse for four consecutive runs.

Introduction

Immobilization of homogeneous catalysts on a solid or macromolecular soluble support[1–7] allows for the separation of catalysts from reaction mixtures by (membrane) filtration techniques and enables catalyst recycling and continuous catalytic processes, *e.g.* in membrane reactors. The use of dendrimers as support permits control over the number of catalyst units on each single macromolecular entity. Dendrimers have excellent solubility properties and tend to dissolve better in organic solvents than their linear and cross-linked polymeric analogues.[8] The controlled, molecular synthesis of dendrimers provides access to monodisperse materials, which further enhances their solubility and separation properties. The first example of a functionalized dendrimer containing multiple peripheral metal catalysts was published in 1994 by Van Koten and Van Leeuwen[9] and since then the field of dendrimer catalysis has further developed. Several comprehensive reviews on dendritic catalysts, their use in synthesis and their separation and reuse have been reported.[1,2,4,10–18]

The possibility of performing sequential or tandem catalysis, *i.e.* a sequence of chemical reactions in which every transformation is catalyzed, with a single or several dendritic catalysts has been pointed out in an early stage,[15] but no experimental reports on this topic have been published so far. We are interested in such systems, because the ability to carry out multiple sequential catalyzed reaction steps in combination with the possibility of separating and recycling the costly catalysts creates an interesting reaction setup in view of process intensification. The various aspects of tandem catalysis are nicely compiled in a review by Fogg and Dos Santos.[19]

One approach towards tandem catalysis using multiple catalysts is the use of compartmentalized catalysts that prohibit disadvantageous effects between different types of catalysts and in which catalytic activity is linked to location. Recent publications by Rothenberg and Vogt report on dendritic catalysts in combination with solution-phase compartmentalized catalysis in tailor-made membrane reactors.[20–22] Also in heterogeneous[23] and enzyme catalysis[24] similar systems have been described. We have chosen to investigate a reaction setup that does not require sophisticated membrane reactors. We therefore set out to investigate the use of closed membrane dialysis bags filled with dendritic catalysts. Catalytic (tandem) reactions can be performed using such semi-permeable compartments by inserting one or several of these compartments in a single reaction mixture. After reaction the dialysis bag(s) can be easily removed from the reaction mixture and in principle be placed into a fresh reaction solution. Proofs of concept for such a 'teabag' approach have been reported earlier by us[25,26] and more recently by Gade.[27]

A prerequisite for the separation and recycling of dendritic catalysts is that the active catalytic centers should be tightly bound to the dendritic support to prevent catalyst leaching. Because of its robust metal-carbon bond, dendritic ECE-pincer complexes are good catalyst candidates in this respect. Many studies on ECE-pincer metal complexes (ECE = $C_6H_3(CH_2E)_2$-2,6]$^-$; E = NR_2, PR_2, SR, *etc.*, see Fig. 1) in which the metal ions are bound to the pincer ligand *via* a covalent M–C bond and two coordinative M–E bonds have been reported.[28–31] Amongst others, we have shown that dendritic ECE-pincer complexes can indeed be separated by membrane separation techniques and reused without significant metal leaching for several runs.[25,32]

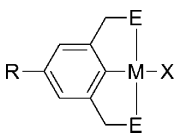

Fig. 1 A pincer metal complex. M = metal (Ni, Pd, Pt, *etc.*), X = co-ligand (*e.g.* Cl, Br, I, NCMe, OH_2), E = electron donating groups (NMe_2, PPh_2, SPh, *etc.*).

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In a recent collaboration with the group of Szabó, we have found that two independent reactions that are catalyzed by two different pincer metal complexes[33,34] (Fig. 2, *reaction 1 and 2*), can in fact be catalyzed in a consecutive, one pot manner by a single, different pincer metal complex[35,36] (Fig. 2, *reaction 3*). The stannylation of cinnamyl chloride with hexamethylditin to form cinnamyl trimethylstannane (*reaction 1*) is typically catalyzed by NCN-pincer Pd-complexes and the homoallylation of 4-nitrobenzaldehyde by cinnamyl trimethylstannane to form 1-(4-nitrophenyl)-2-phenyl-3-buten-1-ol (*reaction 2*) is typically catalyzed by PCP-pincer Pd-complexes. In contrast, monometallic SCS- and PCS-pincer palladium-complexes are able to catalyze both of those mechanistically different reactions. In this catalytic auto-tandem reaction (*reaction 3*) all three starting materials are present in the reaction mixture from the offset of the reaction and the reaction is carried out in one pot. In the presence of 5 mol% SCS-pincer palladium-catalyst, the homoallylic alcohol products are formed in 74% yield after 16 h at 40 °C.[35] A diastereomeric product ratio of 9 : 1 favoring the *anti* diastereomers was observed.

Here, we present our investigations on a dendrimer supported version of the SCS-pincer Pd auto-tandem catalyst and have explored its use in a compartmentalized set-up. The objectives of our investigations were twofold. First, a first generation dendritic catalyst was to be tested in solution and its activity compared to those of its monometallic and its zeroes generation dendritic analogues. For this purpose a series of four catalysts was prepared (Fig. 3). This series consists of two monometallic analogues (**1** and **2**) and two dendritic SCS-pincer palladium-complexes

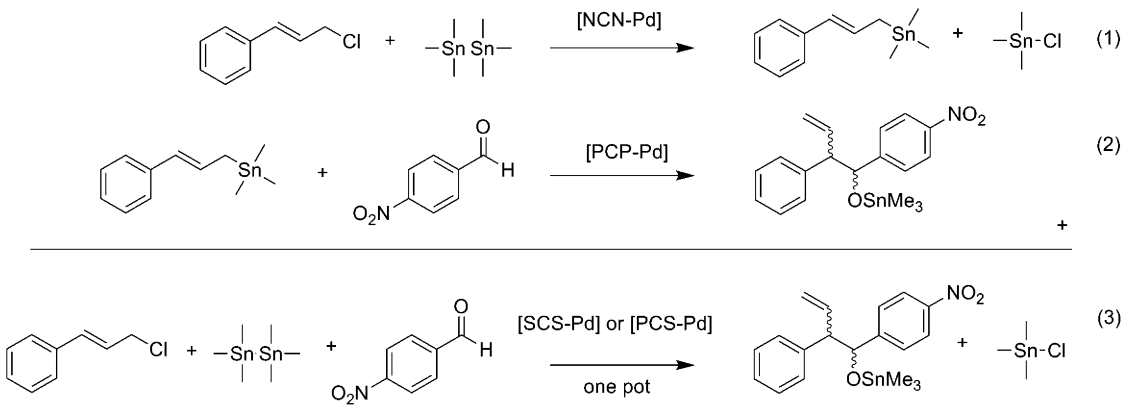

Fig. 2 The NCN-pincer palladium-catalyzed stannylation of cinnamyl chloride to cinnamyl trimethylstannane (reaction 1) and the PCP-pincer palladium-catalyzed electrophilic cross-coupling of cinnamyl trimethylstannane and 4-nitrobenzaldehyde to 1-(4-nitrophenyl)-2-phenyl-3-buten-1-ol (reaction 2) can be combined to a SCS- or PCS-pincer palladium-catalyzed auto-tandem reaction where all substrates are present from the beginning of the reaction (reaction 3).

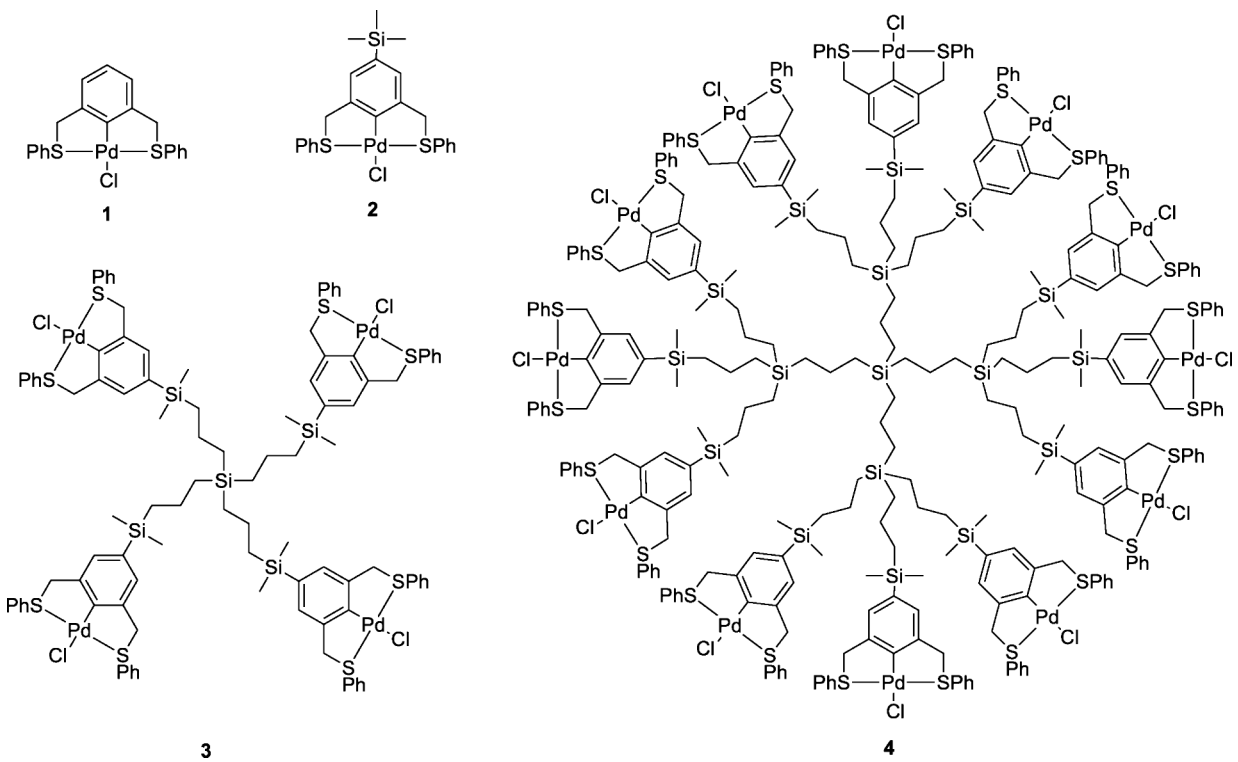

Fig. 3 Monomeric and dendritic SCS-pincer palladium-complexes **1–4** used as catalyst in the tandem reaction.

(**3** and **4**). Compound **2** contains a *para*-functionalized trimethylsilyl group that resembles the connectivity of the pincer moieties to the dendritic scaffold. As a second objective, dendritic catalyst **4** was tested in a compartmentalized set-up and reused several times to evaluate its stability and recyclability.

Synthesis of compound 1–4

Parent SCS-pincer palladium complex **1** has been reported by Sillanpää and co-workers and was synthesized as described.[37] The trimethylsilyl-functionalized complex **2** was synthesized starting from the *para*-bromo functionalized pincer ligand precursor **5** in a two-step synthetic protocol (Fig. 4). Ligand precursor **5** was lithiated *via* lithium-halogen exchange by addition of 2 equiv. of *t*BuLi at –80 °C and subsequent treatment with trimethylsilyl chloride. After workup this procedure gave pincer ligand precursor **6** in 96% isolated yield. Palladation of **6** was achieved *via* direct C–H-activation with $[Pd(MeCN)_4](BF_4)_2$ in refluxing acetonitrile. The resulting cationic acetonitrile complex was treated with a saturated aqueous sodium chloride solution to replace the acetonitrile ligand by the stronger chloride ligand. Although cationic SCS-pincer Pd(MeCN)-complexes have shown to be very reactive in the stannylation reaction[33] and in the tandem reaction,[35] our catalytic studies have been performed with the neutral SCS-pincer Pd-Cl-complexes, because of the poor solubility properties of the polycationic SCS-pincer Pd(MeCN) dendrimers and the improved storage properties of the Pd-Cl dendrimers.

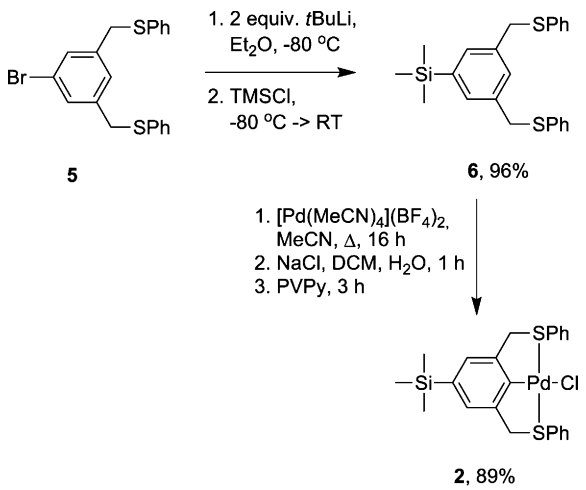

Fig. 4 Synthesis of trimethylsilyl functionalized SCS-pincer palladium complex **2**.

The resulting SCS-pincer Pd-complex was purified by column chromatography, and further treated with 100 equiv. of poly(vinylpyridine) (PVPy) in dichloromethane for 3 h. PVPy is known to intercept free palladium particles in solution and is regularly used in catalyst poisoning experiments.[38,39] By doing so, minute amounts of potentially catalytically active Pd(0) species were excluded from palladium complexes that were subsequently used in catalysis experiments. After this workup, **2** was obtained as an air and moisture stable orange–yellow solid in 89% yield.

Dendritic complexes **3** and **4** were synthesized *via* a similar protocol as trimethylsilyl-pincer complex **2**. Instead of using trimethylsilyl chloride as the quenching agent for lithiated **5**, chloro-terminated carbosilane dendrimers **7** and **8** were used (Fig. 5). These dendritic scaffolds where synthesized according to a standard literature procedure *via* a repetitive Grignard/hydrosilylation reaction sequence starting from tetrachlorosilane and allylbromide.[40]

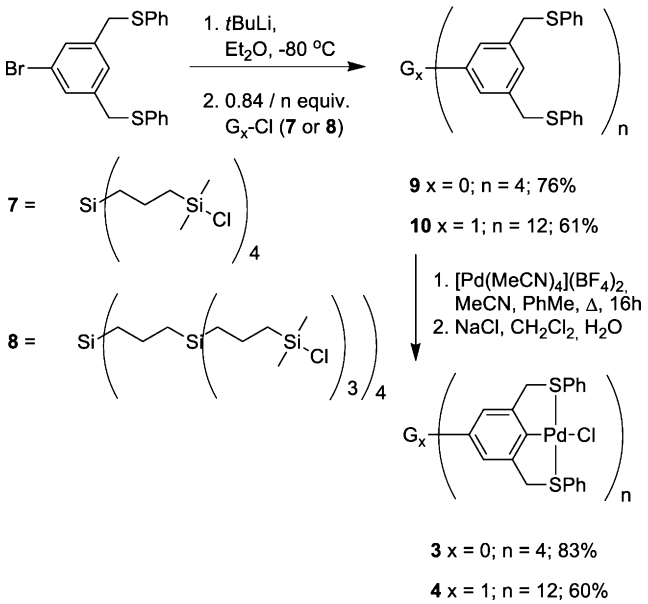

Fig. 5 Synthesis of carbosilane-based dendritic SCS-pincer palladium–complexes **3** and **4**.

An excess of lithiated **5** (1.2 equivalents per Si–Cl moiety) was used to ensure a complete conversion of all chlorosilyl groups in order to yield monodisperse dendritic materials. The excess of pincer ligand precursor (and eventual other low molecular weight contaminants) was removed by passive dialysis. After three dialysis cycles, the dendritic ligand precursors were isolated in good yields (76% for dendrimer **9**, and 61% for dendrimer **10**) and high purity (*vide infra*).

Dendrimers **9** and **10** were palladated by using an excess of $[Pd(MeCN)_4](BF_4)_2$ (1.2 equivalents per dendritic arm) in a refluxing mixture of acetonitrile and toluene. This solvent combination was used to improve the solubility of the dendritic ligands. A treatment with NaCl resulted in the chloride complexes. After passive dialysis and PVPy treatment, orange–yellow powders were obtained in reasonable to good yields (83% for G0 dendrimer **3**, 60% for G1 dendrimer **4**).

The integrity and purity of palladium complexes **1–4** was verified by means of a combination of analytical techniques. ^{1}H NMR analysis of the complexes showed a single characteristic signal for the benzylic protons around 4.6 ppm. The introduction of the palladium center caused a large downfield shift for this signal compared to the corresponding pre-ligands, which show this resonance at 4.0 ppm. Besides the chemical shift of this signal, also its line width differs significantly for the palladium complexes compared to the pre-ligands. A sharp singlet was observed for the ligand precursors **6**, **9** and **10**, whereas a broad to very broad singlet was seen for the corresponding SCS-pincer palladium-complexes **2–4**. This observation is in agreement with observations in the literature, and is caused by the flexible structure of SCS-pincer Pd-complexes due to a combination of inversion of the conformation

of the sulfur atoms, and puckering of the S–Pd–C chelate.[41,42] A similar shift of the benzylic signals was observed in the ^{13}C NMR spectra; for all reported species the signal corresponding to the benzylic carbon shifts from 39 ppm for the ligand precursor to 52 ppm for the palladium complex. ^{1}H as well as ^{13}C NMR spectra of complexes **7–10** did not show any residual ligand precursor signals. The dendritic ligands and complexes show broad signals for all observed protons, in agreement with their macromolecular nature.

G0 ligand precursor **9** and complex **3** were successfully analyzed by MALDI TOF MS. For **9**, a parent peak at $m/z = 1714.69$ was observed (theoretical value for $[M+H]^+$ is $m/z = 1714.94$). Analysis of complex **3** showed a distinct signal at $m/z = 2478.73$ for a tetra-palladium species (theoretical value for $[M+Na]^+$ is 2479.19). No signals corresponding to species of lower palladium content or to the free ligand were observed. For the G1 ligand **10** and G1 complex **4** the conditions for a good mass analysis were not found. Changing to ESI-MS also did not result in a proper analysis.

Besides the absorption around 250 nm that is typical of compounds that contain aromatic groups, SCS-pincer palladium complexes show a characteristic UV absorption at 330 nm. The corresponding pre-ligands do not show an absorption in this region ($\varepsilon_{330} < 0.001$). This specific optical feature was therefore used to determine the Pd content of the isolated dendritic materials. Analytically pure trimethylsilyl functionalized complex **2** was used as a calibrant. Separate dilution series of monometallic complex **2** and dendritic complexes **3** and **4** in CH_2Cl_2 were prepared by using an equal concentration of palladium centers (theoretical value). The absorption at 330 nm for these dilution series was plotted against their theoretical Pd-concentration. The ratio of the slopes of these straights for **3** and **4** to the slope of the straight of **2** were taken as a measure of the percentage of palladium centers in the dendritic complexes. These experiments showed an average of 3.9 and 11.9 metalated arms per molecule, respectively, thus showing a full palladium loading of both **3** and **4** (Table 1). Metalations of identical dendritic compounds bearing NCN-type pincer ligands were performed *via* stepwise lithiation of the pincer ligands with *t*-BuLi followed by transmetalation with a metal(II) precursor.[32] Although these reactions appeared to be high yielding for momomeric pincer complexes, for dendritic complexes no complete metal loading was achieved due to partial hydrolysis of the extremely sensitive lithio-intermediate. Metalation percentages around 80–90% were generally observed for these NCN-pincer dendrimers. To the best of our knowledge, the present SCS-pincer dendrimers are the first to show full metalation for these types of structures.

Table 1 Determination of the palladium content of complexes **3** and **4** based on absorption intensities (330 nm) of dilution series[a]

Catalyst	Slope of dilution series	R^2 value of dilution series	% of palladated arms	Calc. nr. of palladated arms
2	0.0074700	0.9972	100	1
3	0.0072627	0.9988	97.22	3.9
4	0.0074227	0.9991	99.37	11.9

[a] The dilution curve of complex **2** was used as a standard and the Pd-content of **3** and **4** were calibrated accordingly.

Table 2 Formation of cinnamyl trimethylstannane (%) in the stannylation of cinnamyl chloride as catalyzed by complexes **1–4**[a]

Catalyst	1 h, CH_2Cl_2	5 h, CH_2Cl_2	1 h, THF	5 h, THF
1	58	99	83	100
2	71	100	82	100
3	69	100	83	100
4	55	99	82	100

[a] Conditions: 0.80 mmol cinnamyl chloride, 0.80 mmol hexamethylditin and 2 mol% Pd catalyst in 6 mL CH_2Cl_2 or THF, ambient temperature, N_2 atmosphere.

Catalysis with 1–4 in solution

Dendrimers **3** and **4** and their mononuclear counterparts **1** and **2** were tested as catalysts in the stannylation reaction (*reaction 1*) and in the two-step tandem reaction (*reaction 3*). In both reactions, the substrates were combined in either THF or CH_2Cl_2 in equimolar amounts. These solutions were found to be stable for a prolonged time without catalyst: no blank reactions took place. The catalysts were added at 2 mol% palladium (*i.e.* 2 mol% of **1** or **2**, 0.5 mol% of **3** or 0.167 mol% of **4**). A nitrogen atmosphere was necessary because of the sensitivity towards hydrolysis of hexamethylditin, and due to the lability of the intermediate cinnamyl trimethylstannane.

Both the monometallic and the dendritic complexes were found to be excellent catalysts for the stannylation of cinnamyl chloride (Table 2). Complete conversion was obtained in all cases in less than 5 h, showing very similar reaction kinetics. In CH_2Cl_2 the reactions were complete in 5 h, with a conversion of 55–71% in the first hour. In THF a similar trend was observed, although after 1 h the conversion is significantly higher (~83%).

In the tandem reaction (*reaction 3*) in THF, it was found that the overall activity after 24 and 72 h was very similar for compounds **1–4** (Table 3). Initially, a fast decrease of cinnamyl chloride was observed within 5 h (Fig. 6), next to a fast increase of cinnamyl trimethylstannane. The second reaction step was much slower and reached full conversion only after several days. The dendritic catalysts **3** and **4** proved to be more effective than the monomeric catalysts in the first reaction step. For the overall tandem reaction, the 'head start' of the dendritic catalysts was averaged out due to the much longer reaction time that was required for the second reaction step. Overall, monomeric catalyst **1**, which lacks a trimethylsilyl group on the *para*-position with respect to the palladium center, appeared to be slightly slower than the other catalysts used. The ratio between *anti* and *syn* products at the end of the reaction showed a slight dependence on the catalyst, with the dendritic catalysts being somewhat more selective for the *anti* 1-(4-nitrophenyl)-2-phenyl-3-buten-1-ol products. The *anti*/*syn* ratio varies from 5 for the monometallic species to 6 for the dendritic catalysts.

Compartmentalized catalysis with dendritic complex 4

Next, the catalytic performance of first generation metallodendritic catalyst **4** was investigated in a compartmentalized setting. For this purpose, catalyst **4** was placed inside a semi-permeable compartment and tested in the stannylation reaction 1 and in tandem reaction 3. As the semi-permeable compartment a

Table 3 Substrate conversion, intermediate built-up, and product formation in tandem reaction 3 catalyzed by **1–4** in THF[a]

	Cinnamyl chloride (%)			Cinnamyl trimethylstannane (%)			Homo-allyl alcohol (%)			
	1 h	24 h	72 h	1 h	24 h	72 h	1 h	24 h	72 h	*Anti*/*Syn* ratio
1	37	1	0	38	61	21	25	38	79	5.0
2	44	1	0	36	50	6	20	49	94	5.2
3	29	0	0	39	58	12	32	42	88	5.7
4	15	0	0	53	56	6	32	44	94	6.0

[a] Conditions: 0.80 mmol cinnamyl chloride, 0.80 mmol hexamethylditin, 0.80 mmol 4-nitrobenzaldehyde and 2 mol% Pd catalyst in 6 mL THF at ambient temperatures, N_2 atmosphere.

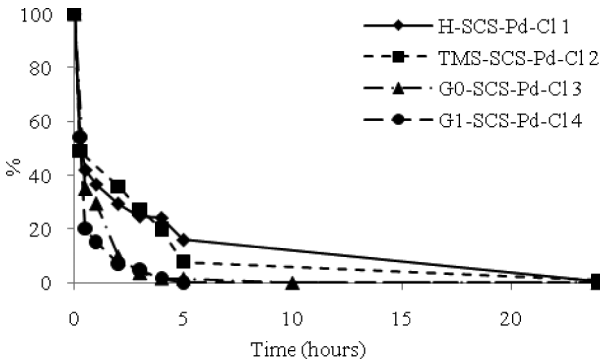

Fig. 6 Conversion of cinnamyl chloride to cinnamyl trimethylstannane catalyzed by Pd-catalysts **1–4** in the tandem setup.

membrane dialysis bag (benzoylated regenerated cellulose dialysis tubing) was used. The mass weight cut-off (MWCO) of this membrane is 1000 Da, whereas the molecular weight of the dendritic catalyst is 7593 Da. As shown by UV/Vis analysis, no detectable dendrimer leaching took place in CH_2Cl_2 or THF for a week when the dendritic catalyst was placed inside such a membrane dialysis bag. For these studies a reaction vessel was used that is equipped with a glass raster at approximately 1 cm above the bottom of the reactor in order to protect the membrane dialysis bag from being damaged by the rotating stirring bar at the bottom of the reactor (Fig. 7).

Fig. 7 Reactor used for compartmentalized (tandem) catalysis experiments. A dialysis membrane bag closed by two white clamps contains the catalyst solution.

Stannylation of cinnamyl chloride with hexamethylditin (reaction 1)

Initial studies with compartmentalized dendritic catalyst **4** were performed in the palladium-catalyzed stannylation reaction of cinnamyl chloride. To this end, a membrane dialysis bag containing a solution of dendritic catalyst **4** in THF was placed into a solution containing the substrates. After 24 h of reaction, the membrane dialysis bag was removed and placed into a second vessel containing a new batch of substrates in THF. The presence of the semi-permeable barrier had a large effect on the reaction rate. Not only was a significant lag phase in substrate conversion observed, the reaction also took considerably longer to go to completion (24 h) compared to the reaction under standard homogeneous conditions (5 h). Diffusion of substrates into the membrane bag and of products out of the membrane bag driven by osmotic pressure seems an obvious reason why a lower reaction rate was observed under compartmentalized conditions, as product sampling was carried out from the outer membrane phase.

The same catalyst batch was used in four consecutive runs by removal of the membrane dialysis bag from the reaction solution after 24 h and placement of the bag into a new batch of substrates. The compartmentalized catalyst remained active over the four runs, although the reaction rate steadily decreased in every run. Substrate conversions of 100%, 95%, 72%, and 61%, respectively, were observed for the four runs. The fourth run was prolonged to 72 h of reaction time and a conversion of 99% was observed at this time, indicating the endured activity of the dendritic catalyst.

The palladium contents of the outer membrane solution of these four runs were analyzed *via* ICP mass spectroscopy in order to probe possible palladium leaching from the membrane bag. Various amounts of palladium were found in all four runs (Table 4). In the first run 13 ppm Pd was detected, corresponding to 5.2% of the total starting amount of palladium. In the second, third and fourth runs lower amounts of palladium were found. In these

Table 4 Pd ICP MS analysis of the outer membrane solution in the consecutive formation of cinnamyl trimethylstannane using compartmentalized catalyst **4**

	Palladium (ppm)	Leaching (%)
Run 1	13	5.2
Run 2	10	4.0
Run 3	5	2.0
Run 4	3	1.2

Table 5 Substrate conversion, intermediate built-up, and product formation in tandem reaction 3 catalyzed by dendritic catalyst **4** inside a membrane dialysis bag in THF[a]

	Cinnamyl chloride (%)			Cinnamyl trimethylstannane (%)			Homo-allyl alcohol (%)			
	1 h	24 h	168 h	1 h	24 h	168 h	1 h	24 h	168 h	*Anti*/*Syn* ratio
Run 1	48	0	0	39	56	36	13	44	64	4.2
Run 2	47	0	0	36	54	49	17	46	51	3.8
Run 3	88	14	4	5	59	43	7	29	53	1.9
Run 4	83	44	45	11	33	23	6	23	32	1.9

[a] Conditions: 8.0 mmol cinnamyl chloride, 8.0 mmol hexamethylditin, 8.0 mmol 4-nitrobenzaldehyde and 2 mol% Pd catalyst inside a membrane dialysis bag in 60 mL THF at ambient temperatures and N_2 environment.

four runs, a total of 12.4% of the starting amount of palladium had leached through the membrane into the outer solution.

After the fourth run, complex **4** was regained from the dialysis bag in 89% yield. NMR analysis showed that **4** was not regained unmodified. Analysis of the peaks corresponding to the benzylic protons showed that a significant amount of the SCS-pincer moieties (approximately 30%) no longer contained a palladium center and had been transformed in a preligand form. Apparently, significant amounts of palladium were released from the pincer ligand manifold during catalysis *via* overall protonolysis. The difference between the amount of Pd leaching as determined by ICP MS and by NMR analysis (12.4% and 30% respectively) might be caused by agglomeration of released palladium into larger clusters inside the membrane dialysis bag or by adsorption of Pd by the membrane itself.

Possible leaching of dendritic catalyst **4** itself from the membrane bag was tested in the presence of each individual substrate in THF under catalytic conditions (*i.e.* 2 mol% Pd per substrate and identical concentration). In none of these experiments any palladium leaching was observed ([Pd] < 0.1 ppm). This leads to the conclusion that only under true catalytic conditions, *i.e.* in the presence of both substrates, palladium leaching took place.

Tandem stannylation and electrophilic addition (reaction 3)

After the single step stannylation reaction, the compartmentalized dendritic catalyst **4** was investigated in the tandem stannylation/homo-allylation reaction. The compartmentalized tandem reaction was found to progress more slowly than the stannylation reaction: NMR-monitoring of the reaction was carried out for one week whereupon the dialysis bag was transferred into a new batch of substrates.

In the first run, the stannylation reaction took place readily and went to completion within 24 h (Table 5). The second step of the tandem reaction, *i.e.* the electrophilic substitution of nitrobenzaldehyde and cinnamyl trimethylstannane was found to progress at a much lower rate: noticeable amounts of cinnamyl trimethylstannane were still present after 2 days of reaction. In fact, also after a prolonged reaction time of one week the reaction had not gone to completion. At that point a steady state mixture of tandem products (60%) and cinnamyl trimethylstannane (40%) was observed. An *anti*/*syn* product ratio of 4.2 : 1 was found in this mixture, which is a somewhat lower ratio than for the homogeneous reaction (6.0 : 1).

Upon further use of the same compartmentalized catalyst in three additional consecutive runs by replacing the contents of the reaction vessel by a fresh batch of substrates after 1 week, it was found that the catalyst was active in all of these runs. This might be somewhat surprising taking into account that the electrophilic addition of the first run did not reach complete conversion. Actually, a very similar reaction profile was found for the second run as for the first run. The rate of conversion and of product formation were almost identical in the first two runs (Table 5). The amount of tandem products found in the second run was even slightly higher compared to the first run, which is most probably caused by the remaining amount of product in the dialysis bag present after the first run. The *anti*/*syn* ratio of the products in run 1 (4.2 : 1) and 2 (3.8 : 1) was found to be similar.

In the third run, the first step of the tandem reaction was considerably slower than in the first two runs. Consequently, the second step showed a reduced reaction rate in the initial stage. However, after one week the same amount of tandem product had formed as compared to the second run. In the fourth run a considerable decrease in reaction rate for both reaction steps was observed: half of the starting amount of cinnamyl chloride was still present after one week, and tandem product formation proceeded to only 37%. The *anti*/*syn* product ratio in run 3 and run 4 (1.9 : 1) differed significantly from that in the previous runs.

ICP MS analysis was again carried out to probe the palladium concentration in the outer solutions after 1 week of reaction (Table 6). The amount of palladium observed in these cases was higher than for the single step stannylation reaction, which might be caused by the longer reaction times that are necessary for the tandem catalysis reaction. In the first run a considerable 35.8 ppm of palladium leached out of the membrane bag, which corresponds to 14.3% of the total amount of palladium centers. Pd-leaching in the three subsequent runs decreased to 1.6 ppm in run 4.

Table 6 Pd-analysis (ICP MS analysis) of the outer membrane solution for four consecutive compartmentalized runs of reaction 3 using complex **4**

	Palladium (ppm)	Leaching (%)
Run 1	35.8	14.3
Run 2	23.1	9.3
Run 3	5.7	2.3
Run 4	4.1	1.6

Table 7 Formation of secondary product and Pd ICP MS analysis of the outer membrane solution for the compartmentalized tandem catalysis experiment after 2 h under optmised conditions[a]

	Product formation (%)	*Anti*/*Syn* ratio	Palladium (ppm)	Observed leaching (%)
Run 1	89	3.9	0	0
Run 2	96	4.0	0	0
Run 3	96	3.8	3	1
Run 4	92	3.7	8	3

[a] Conditions are equal to those used in Table 5, except that 3 equiv. of cinnamyl chloride (24 mmol) and 3 equiv. of hexamethylditin (24 mmol) have been used.

Optimization of reaction conditions

Preliminary results from mechanistic studies aimed at optimizing the conditions to perform compartmentalized auto-tandem catalysis showed a very fast tandem reaction takes place when three (or more) equivalents of cinnamyl chloride and hexamethylditin are used compared to 4-nitrobenzaldehyde.[43] Using these reagent excess conditions, dendritic SCS-pincer palladium complex **4** (2 mol% Pd) was investigated in a compartmentalized setup to explore the possibility of performing recyclable auto-tandem catalysis. This modification led to a dramatic improvement in reaction time: an almost full conversion to 1-(4-nitrophenyl)-2-phenyl-3-buten-1-ol was obtained in only two hours (Table 7), whereas only 50% of product was synthesized in a week by using just one equivalent of cinnamyl chloride and hexamethylditin.

The subsequent second, third and fourth runs also yielded almost quantitative amounts of 1-(4-nitrophenyl)-2-phenyl-3-buten-1-ol in the same amount of time. When the contents of the (outer) reaction solutions were analyzed for palladium leaching by ICP/MS analysis (Table 7), palladium leaching was found to be significantly diminished. No detectable amounts of palladium leaching were observed in the first two runs, whereas starting in the third run palladium leaching was observed to a very minor extent. Furthermore a constant *anti*/*syn* product ratio was observed for four consecutive runs. These optimized reaction conditions and their mechanistic implications will be the subject of a forthcoming manuscript.

Conclusions

In this paper, the synthesis of novel SCS-pincer palladium dendrimers is described. For the first time, full metal loadings were obtained for this type of dendritic carbosilane compound. Since the palladation of the SCS-pincer ligands in the present study was performed by a direct C–H activation in absence of reactive intermediates, a full metal loading for both the G_0 and the G_1 dendritic complexes could be achieved in a synthetic route that also contains less reaction steps than in the earlier report on NCN-pincer Pd-dendrimers.

The new dendritic SCS-pincer palladium complexes appear to be efficient catalysts for the stannylation of allyl chlorides by hexamethylditin (reaction 1) and for the auto-tandem reaction between cinnamyl chloride, hexamethylditin and 4-nitrobenzaldehyde to form 1-(4-nitrophenyl)-2-phenyl-3-buten-1-ol (reaction 3). This particular auto-tandem reaction was studied in a standard batch manner as well as in a compartmentalized manner. We found that compartmentalized tandem catalysis is indeed possible using simple commercially available dialysis bags in a tea-bag approach. These studies provide the first example for compartmentalized auto-tandem catalysis using a semi-permeable compartment in which a molecularly enlarged catalyst is retained. Upon reuse of a catalyst-loaded membrane bag, the catalytic reaction was found to take place with a similar reaction profile. However, upon further reuse, *i.e.* in a third and fourth catalytic run, the reaction rate slowed down, while still significant amounts of products were formed. On the other hand, complex **4** was used for one month in this recycling experiment, which shows an overall stability of the organometallic complex.

In addition, these studies showed an anticipated drawback of the membrane bag setup. When relying on passive diffusion for substrate and product transport, overall reaction rates tend to be low. The use of excess amounts of only two of the reaction substrates, however, was found to considerably speed up the compartmentalized tandem reaction.

For the particular palladium-catalyzed tandem reaction studied here, palladium leaching through the membrane was also observed. Obviously, this possesses a serious drawback in view of recyclability and reproducibility of the system. For further research more robust catalytic systems and/or different reaction conditions would have to lead to an improved recyclability. We will, furthermore, investigate other dendritic catalyst systems in order to further develop the concept of compartmentalized catalysis and compartmentalized tandem reactions. At the same time, we are looking into the SCS-pincer palladium-catalysts discussed here. These complexes have earlier been found to be instable at high temperatures (>120 °C) in the presence of strong bases and are used in these conditions among others as precursor for Pd(0)-catalyzed Heck reactions.[44–46] In the current reactions, however, neither high temperatures nor strong bases were used, so palladium leaching from the pincer manifold was rather unexpected. To the best of our knowledge, this is the first example in which it has been found that SCS-pincer palladium-complexes are instable under mild conditions, *i.e.* ambient temperature and non-acidic or non-basic conditions.

We are currently carrying out further mechanistic studies on this particular catalytic tandem reaction in which palladium is combined with ditin and tin halide species. These studies have already led to an optimized and very promising compartmentalized auto-tandem system that performs fast catalysis for this tandem reaction with very minor Pd(0) leaching.

Experimental

General

All reactions were carried out using standard Schlenk techniques under an inert dinitrogen atmosphere unless stated otherwise. All solvents were carefully dried and distilled prior to use. All standard reagents were purchased commercially and used without further purification. Carbosilane dendrimers **7** and **8**,[40] SCS-pincer ligand **5**[47,48] and $[Pd(MeCN)_4](BF_4)_2$[49] were prepared according to literature procedures. All other reagents were purchased from Acros Organics and Sigma–Aldrich Chemical Co. Inc. and used as

received. ^{1}H (300 MHz), ^{13}C (100 MHz) and ^{29}Si (60 MHz) NMR spectra were recorded on a Varian 400 MHz spectrometer at 25 °C, chemical shifts are given in ppm referenced to residual solvent resonances. UV-vis spectra were recorded on a Cary 50 Scan UV-visible spectrophotometer. MALDI-TOF MS spectra were acquired using a Voyager-DE Bio-Spectrometry Workstation mass spectrometer equipped with a nitrogen laser emitting at 337 nm. High resolution mass spectroscopy (HRMS) has been performed on a Waters LCT Premier XE Micromass instrument using the electrospray ionization (ESI) technique. Elemental analyses and ICP-MS analyses were carried out by Kolbe Mikroanalytisches Laboratorium (Mülheim a.d. Ruhr, Germany).

3,5-bis(phenylthiomethyl)phenyl)trimethylsilane 6 (TMS-SCS-H)

A solution of **5** (2.49 mmol, 1.00 g) in Et_2O (30 mL) was cooled to −80 °C whereupon a 1.6 M *t*BuLi solution in pentane (2.0 eq., 4.98 mmol, 3.11 mL) was added slowly in 5 min. The solution immediately turned dark red. After stirring for another 5 min. at −80 °C trimethylsilyl chloride (1.1 eq., 2.74 mmol, 348 µL) was added in one portion. The cooling bath was removed and the reaction mixture was allowed to reach ambient temperature. The solution turned pale yellow. After 30 min, all volatiles were evaporated and dichloromethane was added to the residue. This solution was washed with water (2 × 50 mL) and a saturated NaCl solution (2 × 50 mL), dried over $MgSO_4$ and concentrated, yielding **6** as a colorless syrup in 0.90 g (92%).

^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.32–7.21 (m, 13H, CH_{arom}), 4.10 (s, 4H, CH_2), 0.21 (s, 9H, SiMe_3). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 141.1, 137.3, 136.5, 133.0, 130.7, 130.3, 129.1, 126.7, 39.5, −0.8. ^{29}Si NMR ($CDCl_3$, 60 MHz): δ −3.76. ESI-HRMS for $C_{23}H_{26}S_2Si$ (*m*/*z*): $[M+Na]^+$ 417.1143 (calc. 417.1108).

para-TMS SCS-pincer Pd-complex 2

To a solution of **6** (1.27 mmol, 500 mg) in acetonitrile (30 mL) was added $[Pd(MeCN)_4](BF_4)_2$ (1.2 eq., 1.52 mmol, 674 mg). The reaction mixture was stirred for 16 h at reflux temperature followed by filtration over Celite and evaporation of the solvent. A biphasic solution consisting of dichloromethane (10 mL) and a saturated aqueous solution of NaCl (10 mL) was added. The resulting mixture was stirred for 1 h. Subsequently, the organic phase was separated and the aqueous phase was washed with dichloromethane (2 × 20 mL). The combined organic fractions were washed with water, dried over $MgSO_4$ and evaporated to dryness. Column chromatography (CH_2Cl_2) was used for further purification of the product. Finally, the product is dissolved in dichloromethane and a large excess (~100 eq.) of PVPy was added. After the solution has stirred for 2 h, the solution was filtered over Celite. After evaporation of the dichloromethane, the product was obtained as yellow powder. Yield: 605 mg (89%).

^{1}H NMR (CD_2Cl_2, 300 MHz): δ 7.86 (m, 4H, C SPh$_{ortho}$), 7.41 (m, 6H, SPh$_{meta+para}$), 7.13 (s, 2H, C$H_{arom.pincer}$), 4.64 (br.s, 4H, SCH_2), 0.24 (s, 9H, SiMe_3). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 149.7, 136.9, 132.8, 131.7, 130.0, 129.8, 127.2, 125,1, 52.1, −1.1. ^{29}Si NMR ($CDCl_3$, 60 MHz): δ −3.67. UV/Vis (CH_2Cl_2): λ_{max} = 331.0 nm. ESI-HRMS for $C_{23}H_{25}ClPdS_2Si$ (*m*/*z*): $[M-Cl]^+$ 499.0239 (calc. 499.0210).

G_0 dendritic SCS-pincer ligand 9

A solution of **5** (4.4 eq., 1.87 mmol, 0.75 g) in Et_2O (40 mL) was cooled to −80 °C and a 1.6 M *t*BuLi solution in pentane (8.6 eq., 3.65 mmol, 2.28 mL) was added dropwise in 5 min. The solution immediately turned dark red. The reaction was stirred for another 5 min at −80 °C. Next, carbosilane dendrimer **7** (1 eq., 0.425 mmol, 0.242 g) was added in one portion. The cooling bath was removed and the reaction mixture was allowed to reach ambient temperature. The color turned to red/orange. Subsequently, MeOH (5 mL) was added to quench the excess lithio-pincer. Immediately, the solution turned pale yellow. After 30 min, all volatiles were evaporated and dichloromethane was added to the residue. This solution was washed with water (2 × 50 mL) and brine (2 × 50 mL), dried over $MgSO_4$ and concentrated. The resulting orange syrup was dissolved in 5 mL of a CH_2Cl_2:MeOH mixture (1 : 1, v/v) and placed into a dialysis bag. This bag was placed into a beaker containing a mixture of CH_2Cl_2:MeOH (500 mL; 1 : 1 *v*:*v*) and dialyzed for 2 h. This procedure was repeated twice. Finally, the contents of the dialysis bag were evaporated, yielding **9** as a pale orange syrup in 0.57 g (76%).

^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.30–7.16 (m, 48H, CH_{arom}), 4.06 (s, 16H, SCH_2), 1.31 (m, 8H, SiCH$_2$CH_2), 0.74 (t, 8H, *J* = 6.2 Hz, SiMe$_2$CH_2), 0.56 (t, 8H, *J* = 6.2 Hz, Si$_{core}$CH_2), 0.17 (s, 24H, SiMe_2). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 140.5, 137.1, 136.5, 133.1, 130.4, 130.1, 129.0, 126.7, 39.4, 20.7, 18.8, 17.7, −2.7. ^{29}Si NMR ($CDCl_3$, 60 MHz): δ 0.73, −3.82. MALDI-TOF MS for $C_{100}H_{116}S_8Si_5$ (*m*/*z*): $[M+H]^+$ 1714.69 (calc. 1714.94).

G_0 dendritic SCS-pincer Pd-complex 3

To a solution of compound **9** (0.32 mmol, 550 mg) in an acetonitrile/toluene mixture (20 mL, 1 : 1 *v*:*v*) was added $[Pd(MeCN)_4](BF_4)_2$ (5 eq., 1.6 mmol, 740 mg). The reaction mixture was stirred for 16 h at reflux temperature. After removal of the solvent *in vacuo* a biphasic system consisting of dichloromethane (10 mL) and brine was added. The reaction mixture stirred for 1 h. Subsequently, the organic phase was separated and the aqueous phase was washed with dichloromethane (2 × 20 mL). The combined organic fractions were washed with water, dried over $MgSO_4$ and evaporated to dryness. The product was purified with column chromatography (CH_2Cl_2:EtOAc 4 : 1 *v*:*v*). Finally, the product is dissolved in dichloromethane and a large excess (~100 eq.) of PVPy was added. After the solution has stirred for 2 h, the solution was filtered over Celite. After evaporation of the dichloromethane, the product was obtained as yellow powder. Yield: 650 mg (83%).

^{1}H NMR (CD_2Cl_2, 300 MHz): δ 7.83 (d, 16H, SPh$_{ortho}$), 7.39 (m, 24H, SPh$_{meta+para}$), 7.07 (s, 8H, CH_{pincer}), 4.62 (br. s, 16H, SCH_2), 1.31 (m, 8H, SiCH$_2$CH_2), 0.74 (t, 8H, *J* = 6.3 Hz, CH_2SiMe$_2$), 0.53 (t, 8H, *J* = 6.3 Hz, Si$_{core}$CH_2), 0.18 (s, 24H, SiMe_2). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 149.2, 136.3, 132.8, 132.4, 131.4, 130.4, 127.9, 125,9, 52.3, 20.7, 18.8, 17.6, −2.9. ^{29}Si NMR ($CDCl_3$, 60 MHz): δ 0.62, −3.82. UV-VIS: 330.1 nm. MALDI-TOF MS for $C_{100}H_{112}Br_4Pd_4S_8Si_5$ (*m*/*z*): $[M + Na]^+$ 2478.73 (calc. 2479.19).

G_1 dendritic SCS-pincer ligand 10

The used procedure of the synthesis of dendritic ligand **10** was similar to the one described for the compound **9**. For **10** 14 equiv.

of **5** and 27 equiv. of *t*BuLi have been used. An orange-brown syrup was obtained in 61% yield (0.94 gram).

^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.29–7.17 (m, 144H, CH_{arom})., 4.03 (s, 48H, SCH_2), 1.33 (m, 32H, $SiCH_2CH_2$ (inner and outer)), 0.72 (bt, 24H, CH_2SiMe_2), 0.58 (m, 40H, $SiCH_2$), 0.13 (s, 72H, $SiMe_2$). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 140.5, 137.2, 136.7, 132.7, 130.8, 129.7, 128.7, 126.3, 39.4, 20.5, 20.2, 19.5, 18.9, 18.4, 17.8, –2.7. ^{29}Si NMR ($CDCl_3$, 59.6 MHz): δ 0.80 (core), 0.57 (middle), –3.75 (periphery).

G_1 dendritic SCS-pincer Pd-complex 4

The used procedure for the synthesis of **4** was similar to the one described for the synthesis of **3**, but now 15 equivalents of $[Pd(MeCN)_4](BF_4)_2$ were used. The product appeared as an orange–yellow foam. Yield: 110 mg (60%).

^{1}H NMR (CD_2Cl_2, 300 MHz): δ. 7.86 (m, 48H, SPh_{ortho}), 7.45 (m, 72H, $SPh_{meta+para}$), 7.12 (bs, 24H, $CH_{arom,pincer}$), 4.61 (br. s, 16H, CH_2S), 1.37 (m, 32H, $SiCH_2CH_2$), 0.79 (m, 24H, CH_2SiMe_2), 0.60 (m, 40H, $SiCH_2$), 0.21 (s, 72H, $SiMe_2$). ^{13}C NMR ($CDCl_3$, 75 MHz): δ. 149.2, 136.0, 132.8, 131.9, 131.8, 130.1, 129.7, 127.0, 52.3, 20.7, 20.0, 19.7, 18.8, 18.4, 17.6, –2.8. ^{29}Si NMR ($CDCl_3$, 59.6 MHz): δ 0.77 (core), 0.57 (middle), –3.64 (periphery). UV-VIS: 330.1 nm

General protocol for the stannylation reaction with the catalyst present in solution

In a representative experiment, the appropriate catalyst (2 mol% [Pd], 0.016 mmol), was added to a solution of cinnamyl chloride (0.80 mmol, 122.1 mg, 113 µL), hexamethylditin (1.05 eq., 0.84 mmol, 275 mg, 174 µL) and hexamethylbenzene (internal standard, 0.088 mmol, 14.4 mg) in 6 mL dry THF or CH_2Cl_2. The reaction stirred at room temperature in a nitrogen environment. Aliquots of 50 µL for NMR/GC analysis were regularly taken with an airtight syringe.

General protocol for the tandem coupling reaction with the catalyst present in solution

In a representative experiment, the appropriate catalyst (2 mol% [Pd], 0.016 mmol), was added to a solution of cinnamyl chloride (0.80 mmol, 122.1 mg, 113 µL), hexamethylditin (1.05 eq., 0.84 mmol, 275 mg, 174 µL), 4-nitrobenzaldehyde (1.05 eq., 0.84 mmol, 126.9 mg) and hexamethylbenzene (internal standard, 0.088 mmol, 14.4 mg) in 6 mL dry THF. The reaction stirred at room temperature in a nitrogen environment. Aliquots of 50 µL for NMR/GC analysis were regularly taken with an airtight syringe.

General protocol for the compartmentalized stannylation reaction with dendritic catalyst 4 present inside a membrane dialysis bag

In a tailor-made reaction vessel, which is equipped with a stirring bar, a NS50 joint and a nitrogen inlet, dry THF (60 mL) was added. To the solvent were subsequently added cinnamyl chloride (8.0 mmol, 1.22 g, 1.13 mL), hexamethylditin (8.0 mmol, 2.75 g, 1.74 mL), and hexamethylbenzene (internal standard, 0.89 mmol, 144 mg). A dialysis bag (Aldrich, benzoylated cellulose membranes, MWCO = 1000 Da.) with 2.5 mL THF and 0.0133 mmol (2 mol% Pd) **4** was added to this solution. In regular intervals, samples of the outer solution were taken and analyzed by ^{1}H NMR.

General protocol for the compartmentalized tandem coupling reaction with dendritic catalyst 4 present inside a membrane dialysis bag

In a tailor-made reaction vessel, which is equipped with a stirring bar, a NS50 joint and a nitrogen inlet, dry THF (60 mL) was added. To the solvent were subsequently added cinnamyl chloride (8.0 mmol, 1.22 g, 1.13 mL), hexamethylditin (8.0 mmol, 2.75 g, 1.74 mL), 4-nitrobenzaldehyde (8.0 mmol, 1.21 g) and hexamethylbenzene (internal standard, 0.89 mmol, 144 mg). A dialysis bag (Aldrich, benzoylated cellulose membranes, MWCO = 1000 Da.) with 2.5 mL THF and 0.0133 mmol (2% Pd) **4** that was closed by plastic clamps was added to this solution. In regular intervals, samples of the outer solution were taken and analyzed by ^{1}H NMR.

After the reaction has finished, the dialysis bag was directly placed reused in a fresh batch of substrates to start a new catalytic run.

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