

Copper-free, recoverable dendritic Pd catalysts for the Sonogashira reaction

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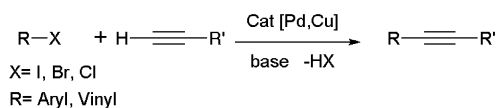
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Three generations of bidentate phosphinated Pd(II) dendrimers are efficient catalysts in the absence of copper co-catalyst for the Sonogashira reaction and are, with two cyclohexyl substituents on the phosphorus atoms, recovered by precipitation and re-used.

Metallo-dendrimers¹ have been known since the early 90's, and one of their most attractive applications is in catalysis.² They might be extremely useful in this area, because they are well-defined and appropriate for classic mechanistic studies typical of homogeneous catalysts. Yet, their nanoscopic size should allow their removal from the reaction medium using methods known for biomolecules. This key property will allow their re-use, an essential perspective in green chemistry involving both ecological and economical reasons. The first example of a recoverable metallo-dendritic catalyst was reported in 1997 by Reetz for the Heck reaction using Pd dendrimers derived from the dendritic phosphines DAB-dendr-[N(CH₂PPh₂)₂]_x obtained by double phosphinomethylation of the commercial DSM polyamino dendrimers DAB-dendr-(NH₂)_x (x = 4, 8 or 16 for generation 1, 2 or 3 respectively).³ There has recently been a strong focus on specific techniques aiming at the recovery of metallo-dendritic catalysts which now need to be applied.^{2,4}

Therefore, we report three generations of new pallado-dendritic complexes **2a–f** based on dendritic phosphine ligands **1a–f** closely related to Reetz's dendrimers that serve as copper-free recoverable catalysts for the Sonogashira coupling between aryl halides and alkynes. These two families of pallado-dendrimers (Scheme 1, R = Cy vs. *t*-Bu) show impressively distinct reactivities and recoverabilities, but a rather similar dendritic effect in the Sonogashira reaction.

The Sonogashira-type carbon–carbon coupling reaction is a very convenient and useful methodology for the preparation of arylalkynes or conjugated enynes, and it is of crucial importance in the synthesis of numerous biologically active compounds.⁵ Generally, this coupling is achieved by a palladium–copper catalyzed reaction of aryl or vinyl halide and terminal alkyne.⁶

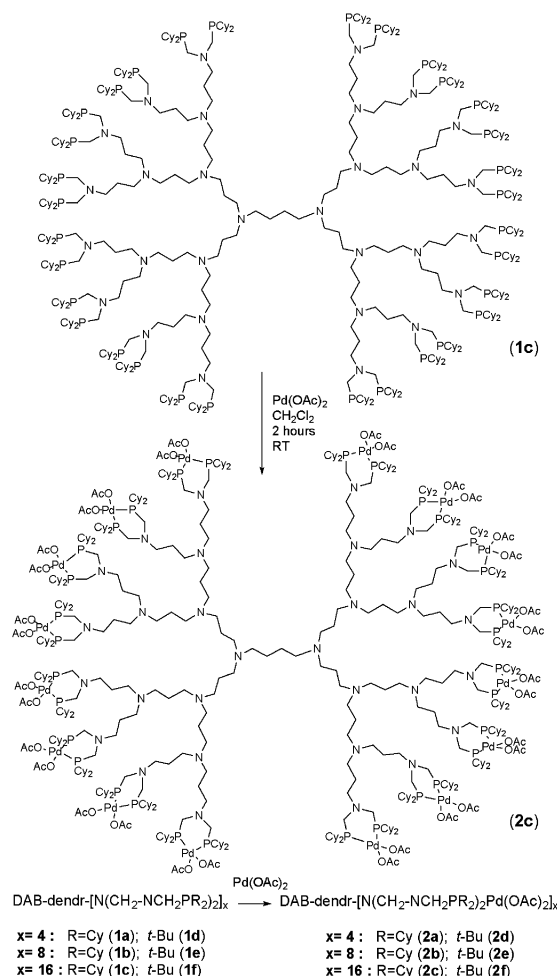


The presence of the copper co-catalyst is an obstacle, however, towards the metallo-dendritic approach of the catalytic system. In addition, it favors the oxidative homocoupling (Glaser coupling)⁷ of the terminal alkyne to the corresponding diyne by-product which is also difficult to separate. Only very few examples of copper-free procedures have been recently reported,⁸ involving for instance *in situ* Pd(0) complex formation with bulky phosphines.⁹

As the monomers,¹⁰ the Pd(II) dendrimers **2a–f** were readily obtained by treatment of the aminophosphines **1a–f** with Pd(OAc)₂ (Scheme 1), and fully characterized by ¹H, ¹³C, ³¹P NMR and elemental analysis.† The ³¹P NMR spectrum of **2** did not show any signal for the residual free phosphine at δ =

–17.5 ppm (**1a–c**) and δ = 12.9 ppm (**1a–f**) but only one singlet at δ = 26.5 ppm (**2a–c**) and δ = 35.9 ppm (**2d–f**).

Coupling between phenylacetylene and iodobenzene or bromobenzene in a copper-free Sonogashira procedure was investigated using these dendrimers. Et₃N was used as solvent, the catalyst amount was 1 mol% per catalytic group (*i.e.* 1/4, 1/8 and 1/16 mol% depending on the dendrimer generation, respectively; generation 1, 2 and 3), and the temperature range was 25–120 °C (Table 1). Good conversions were obtained with the 1st and 2nd generation dendrimers **2a,b** at 80 °C in the case of iodo coupling (entries 1 and 2). A negative dendritic effect (Fig. 1) is clearly observed for the metallo-dendrimer of 3rd generation **2c**, however, for which a substantially lower reactivity was obtained (entry 3). This effect is best taken into account by the increased steric effect as the generation number increases. Raising the reaction temperature upon replacing Et₃N by amines with higher boiling points (Bu₂NH, Bu₃N) did not improve the conversion rates, presumably due to the cleavage of



Scheme 1

the P–C bonds of the catalyst at such high temperatures.¹¹ The same effect is observed with dendrimers **2d–f** containing the di-*tert*-butylphosphine ligand which were considerably more reactive than **2a–c**. Indeed, **2d** provided a quantitative conversion at RT within a few hours (entries 4 and 11) whereas complete conversion required 2 days with the dendrimers of 2nd and 3rd generation **2e,f** (entries 5, 6, 12 and 13).

The dendritic catalysts **2a–f** showed very weak reactivity with the aryl chloride substrates, only traces of expected product being observed (conversion below 5%), although monomeric parent compounds were responsible for higher reactivity in particular with aryl chloride substrates.¹⁰

A major purpose of this work was to investigate the possibilities of recovering the metallodendritic catalysts, which was indeed achieved by precipitation of **2b** and **2c** after the reaction using pentane. However, the catalysts **2d–f** are too soluble in pentane and other common solvents for recovery, because of the presence of the *t*-Bu substituents. In a typical procedure, the reaction was carried out under nitrogen at 80 °C with **2b** or **2c** (2 mol%). After decantation in pentane, **2b** was

Table 1 Sonogashira coupling of aryl halide substrates with phenylacetylene^a

Entry	Aryl halide	Solvent	Catalyst (1 mol%)	Temp-erature/°C	React. time/h ^b	Con- version (%) ^c
1	Iodobenzene	Et ₃ N	2a	80	24	79
2	Iodobenzene	Et ₃ N	2b	80	24	72
3	Iodobenzene	Et ₃ N	2c	80	24	46
4	Iodobenzene	Et ₃ N	2d	25	15	97
5	Iodobenzene	Et ₃ N	2e	25	40	100
6	Iodobenzene	Et ₃ N	2f	25	48	100
7	Bromobenzene	Et ₃ N	2a	80	48	17
8	Bromobenzene	Et ₃ N	2b	80	48	15
9	Bromobenzene	Bu ₂ NH	2b	120	20	20
10	Bromobenzene	Et ₃ N	2c	80	48	6
11	Bromobenzene	Et ₃ N	2d	25	17	100
12	Bromobenzene	Et ₃ N	2e	25	48	93
13	Bromobenzene	Et ₃ N	2f	25	48	96

^a Reaction conditions: aryl halide (2 mmol), phenylacetylene (3 mmol), solvent (6 mL), catalyst (1 mol %), N₂. ^b The reaction was monitored by TLC. ^c The product was isolated by column chromatography after the reaction was completed.

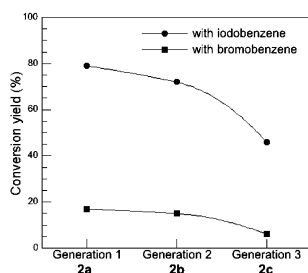


Fig. 1 Conversion of aryl halides with phenylacetylene catalyzed by **2a–c** at 80 °C.

recovered at least six times with an average of 46% conversion and **2c** was recovered at least seven times with an average of 35% conversion, both without loss of activity along these cycles. The recovery of the dendritic catalyst was confirmed by ³¹P NMR, the signal of **2c** or **2d**, initially at 27 ppm, remaining unchanged after each cycle. Nevertheless, a slight shift to 24 ppm of the ³¹P NMR phosphine signal was observed during the catalytic reaction, which shows the intermediacy of a catalytically active species.

In summary, the synthesis and efficacy of three generations of new recoverable dendritic copper-free catalysts for the Sonogashira reaction has been shown for the first time. These studies have also demonstrated the dendritic effect and the strong influence of the nature of the diphosphine substituents on the reactivity and recoverability of the catalysts.

Notes and references

† Selected data for **2a**: ¹H NMR (CDCl₃, 300 MHz) δ 1.16 (br, 68H, CH₂, CH₂Cy), 1.30 (br, 8H, CH₂), 1.59 (br, 32H, CH₂Cy), 1.71 (br, 64H, CH₂Cy), 1.89 (s, 24H, CH₃), 2.34 (s, 20H, CH₂N), 2.55 (s, 32H, NCH₂P, CHP_{Cy}); ¹³C NMR (CDCl₃, 62.9 MHz) δ 23.5 (CH₂), 26.3 (CH₂Cy), 27.4 (CH₂Cy), 29.1 (CH₂Cy), 30.5 (CH₃), 33.4 (CH₂Cy), 48.9 (CH₂N), 52.0 (CH₂N), 61.0 (CHP), 175.9 (CO); ³¹P NMR (CDCl₃, 121.5 MHz) δ 26.5; elemental anal. (calc.) C 56.39%, H 8.63%; (found) C 55.65%, H 8.71%.

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