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Dendritic phosphoramidite ligands for Rh-catalyzed [2 + 2 + 2] cycloaddition reactions: unprecedented enhancement of enantiodiscrimination†

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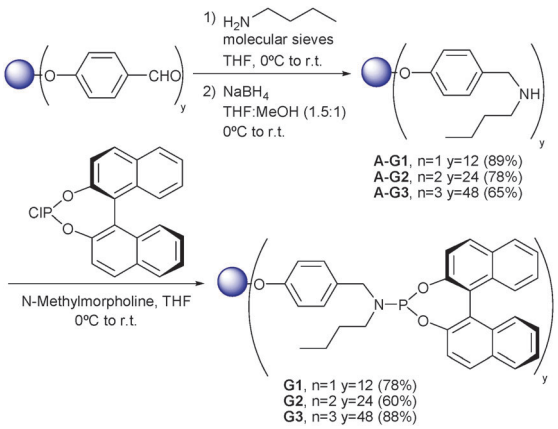
Phosphorus dendrimers containing terminal phosphoramidite ligands have been found to be highly effective and recoverable catalysts for the rhodium(I) catalyzed [2 + 2 + 2] cycloaddition reactions. A strong positive dendritic effect is observed both in the activity and enantiodiscrimination leading to axially chiral biaryl compounds.

The metal-catalyzed [2 + 2 + 2] cycloaddition reaction of three alkynes is a powerful method for the construction of polysubstituted benzenes.[1] A plethora of studies have shown the utility of this method in total synthesis.[2] Among the catalytic systems used, the combination of rhodium with bidentate phosphines has led to excellent results.[3] Rovis *et al.* have successfully applied phosphoramidite ligands in rhodium catalyzed [2 + 2 + 2] cycloadditions of alkynes and alkenylisocyanates achieving moderate regioselectivities but good enantioselectivities.[4] However, to the best of our knowledge, the use of the chiral monodentate phosphoramidites, which have shown excellent properties in combination with rhodium, for instance in hydrogenation reactions,[5] has never been described in the [2 + 2 + 2] cycloaddition of three alkynes.

Dendrimers, nano-objects with astonishing applications in areas ranging from biology to materials science,[6] have also been successfully applied in catalysis.[7] The precise incorporation of ligands in the different domains of the dendrimeric structure has enabled the complexation of metals leading to good catalysts in a number of reactions. Phosphoramidite ligands have been immobilized at the core[8] or used as the focal point of a dendrimer wedge,[9] and their rhodium complexes have been successfully used in asymmetric hydrogenations. However, neither the immobilization of phosphoramidite ligands at the surface of dendrimers nor the use of dendrimers as ligands for the [2 + 2 + 2] cycloaddition reaction of alkynes have apparently been reported, and this has inspired the present study.



Scheme 1 Synthesis of phosphorus dendrimers from generation 1 to 3 containing terminal phosphoramidite ligands.

New phosphorus dendrimers **G1–G3** (Scheme 1 and Fig. 1) were prepared from dendrimers bearing 12, 24 or 48-CHO end groups respectively. Imine formation with *n*-butylamine, followed by $NaBH_4$ reduction afforded the secondary amine to which the chlorophosphite derived from (*S*)-BINOL was added furnishing the desired phosphoramidite capped dendrimers (Scheme 1).

In this way, a new family of phosphorus dendrimers containing terminal phosphoramidite ligands was obtained (Fig. 1). Both monomeric and a branch ligand (**M** and **B** in Fig. 1), which serve as references for the catalytic results, were prepared following the synthetic strategy outlined in Scheme 1 but starting from *p*-anisaldehyde and a branch grown on *p*-anisaldehyde, respectively.

The catalytic activity conferred by dendritic ligands to rhodium was first evaluated in the partial intramolecular cycloaddition between an *N*-tosyl tethered 1,6 diyne **1** and phenylacetylene **2**, and compared to that of the commercially available phosphoramidite (*S*)-MonoPhos and the model monomeric ligand **M** (Table 1). The cycloaddition was performed in refluxing toluene using the dimer $[Rh(C_2H_4)_2Cl]_2$ as the

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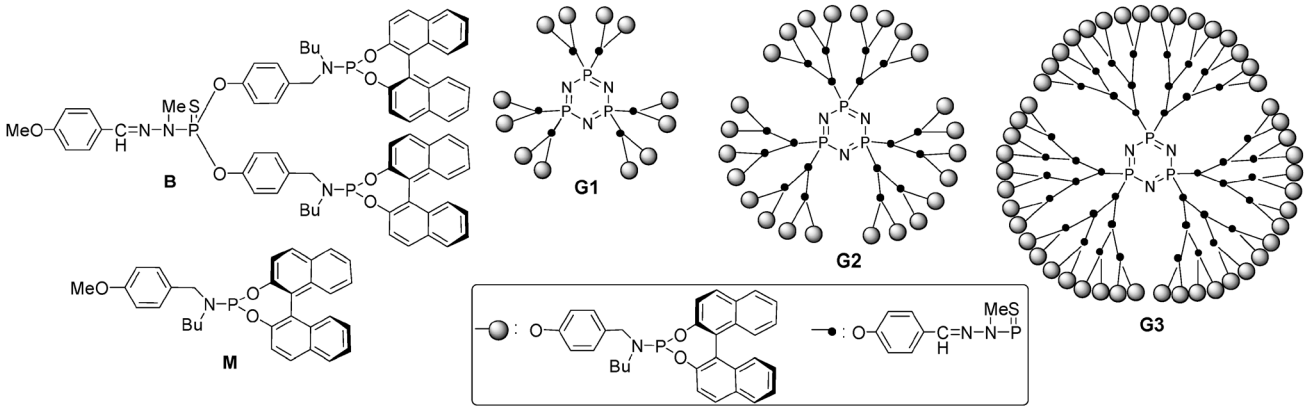
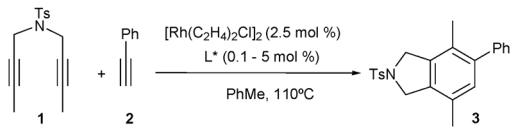


Fig. 1 Dendrimers **G1**, **G2** and **G3**, monomer **M** and branch **B** models synthesized for the present study.

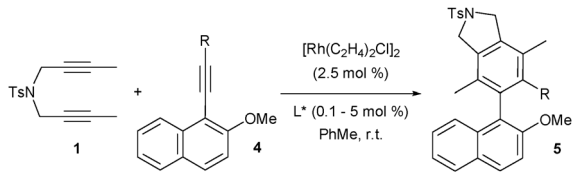
Table 1 [2 + 2 + 2] cycloaddition reaction between *N*-tosyl 1,6-diyne **1** and phenylacetylene **2**[a]



Entry	Run	L* (% mol)/ligand units	Yield[b] (%)
1	1	(*S*)-MonoPhos (5)/1	33
2	1	**M** (5)/1	61
3	1	**G1** (0.4)/12	93
4	1	**G2** (0.2)/24	89
5	1	**G3** (0.1)/48	96
6	2[c]	**G3** (0.1)/48	94
7	3[c]	**G3** (0.1)/48	95

[a] Conditions: **1** (0.15 mmol), **2** (0.75 mmol), $[Rh(C_2H_4)_2Cl]_2$ (2.5 mol%) and L* (0.1–5 mol%) in PhMe at 110 °C for 2 h. [b] Yield of the isolated product. [c] The catalytic system was recovered on hexane precipitation and filtered and reused without further manipulation. Ts = *p*-toluenesulfonyl.

Table 2 [2 + 2 + 2] cycloaddition reaction between *N*-tosyl 1,6-diyne **1** and 2-methoxynaphthalene alkynyl derivatives **4**[a]



Entry	R	L* (% mol)/ligand units	Yield[b] (%)	ee[c] (%)
1	$P(O)(OEt)_2$	(*S*)-MonoPhos (5)/1	46	14
2	$P(O)(OEt)_2$	**M** (5)/1	49	<5
3	$P(O)(OEt)_2$	**B** (2.5)/2	32	3
4	$P(O)(OEt)_2$	**G1** (0.4)/12	99	98
5	$P(O)(OEt)_2$	**G2** (0.2)/24	97	96
6	$P(O)(OEt)_2$	**G3** (0.1)/48	98	97
7	$CO_2{}^iPr$	**M** (5)/1	11	2
8	$CO_2{}^iPr$	**B** (2.5)/2	13	8
9	$CO_2{}^iPr$	**G1** (0.4)/12	70	81
10	$CO_2{}^iPr$	**G2** (0.2)/24	74	88
11	$CO_2{}^iPr$	**G3** (0.1)/48	77	90

[a] Conditions: **4** (0.10 mmol), **1** (0.15 mmol), $[Rh(C_2H_4)_2Cl]_2$ (2.5 mol%) and L* (0.1–5 mol%) in PhMe at room temperature for 48 h. [b] Yield of the isolated product. [c] Enantiomeric excess determined by chiral HPLC.

metal source loaded to give a Rh/phosphoramidite ratio equal to one in all cases.

Considerably enhanced catalytic activity was observed when using dendrimers **G1–G3** as ligands as compared to both the model monomer **M** and (*S*)-MonoPhos. Indeed, almost quantitative yields were achieved by using any of the three dendrimer ligands and, most remarkably, the catalytic system could be recovered by precipitation in hexane followed by filtration and reused up to three times without reduction in the yield.[10] Recyclability and reuse of a catalytic system active in the [2 + 2 + 2] cycloaddition reaction have been only sparingly reported.[11]

These promising preliminary results encouraged us to check the capacity for enantiodiscrimination of the catalytic system. The reaction of choice was the [2 + 2 + 2] cycloaddition towards axially chiral biaryl phosphorus compounds described by Tanaka *et al.* using a Rh(I)–BINAP catalytic system.[12] Diyne **1** was treated with the alkynyl phosphonate derived from 2-methoxynaphthalene under the conditions described above but at room temperature (entries 1–6, Table 2). We were pleased to find that **G1**, **G2** and **G3** enabled almost quantitative conversion of the substrate into the product with excellent enantioselectivity, showing a strong dendritic effect, since both (*S*)-MonoPhos and the monomer model gave only residual enantioselectivity.

In order to explore the possibility that the enhanced enantioselectivity arose from a cooperative effect of two proximal centres, the catalytic activity of the branch model **B** was also evaluated. To our surprise, decreased yield and enantioselectivity were obtained (entry 3, Table 2) ruling out this possibility and pointing to an effect of the packing of the dendrimeric structure or a large number of chiral ligands in close proximity as being possible explanations for the dendritic effect observed. To the best of our knowledge, this is the strongest dendritic effect on the stereoselectivity reported in the literature.[9b,13]

Furthermore, [2 + 2 + 2] cycloaddition of alkynyl phosphonate quantitatively occurred with excellent enantioselectivity in three consecutive runs using the phosphoramidite dendrimeric ligands (Fig. 2).

We tested the generality of enantioselective biaryl synthesis using a 2-methoxynaphthalene derived alkynylester as the cycloaddition partner.[14] Good yields and excellent enantioselectivities were again achieved in a process with a strong dendritic effect (entries 7–11, Table 2).

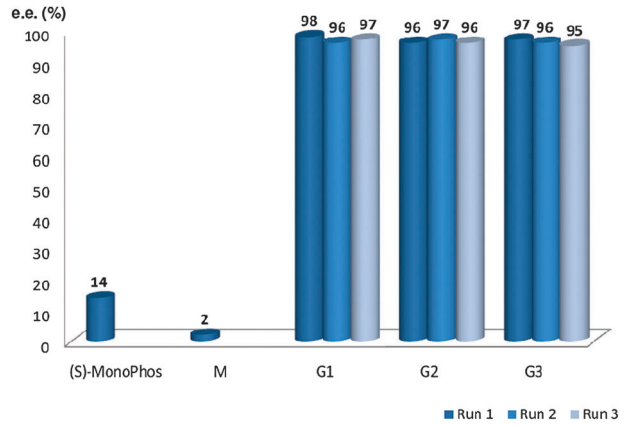


Fig. 2 Enantiomeric excesses achieved in the cycloaddition of **1** and **4** (R = P(O)(OEt)$_2$) using (*S*)-MonoPhos, **M** and dendrimeric ligands **G1–G3** in three successive runs (yields above 97% in all runs).

In conclusion, we have described a new highly active and recyclable catalytic system based on the combination of rhodium(I) and phosphoramidite capped phosphorus dendrimers for the stereoselective [2 + 2 + 2] cycloaddition reaction of alkynes. An unprecedented dendrimer enhancement of the stereoselectivity has been observed showing the importance of the dendrimer scaffold not only in the recovery and recyclability of the catalyst but also most importantly in the activity and enantioinduction of the phosphoramidite-based catalysts.

Further investigation with regard to the scope of this new catalytic system in [2 + 2 + 2] cycloaddition reaction is currently in progress.

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