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Enhanced Catalytic Properties of Copper in O- and N-Arylation and Vinylation Reactions, Using Phosphorus Dendrimers as Ligands

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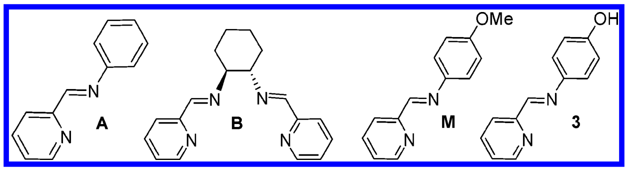
The chemistry of dendrimers is a blossoming area of research with many applications ranging from biology to materials science.[1] The use of these nano-objects in catalysis is also well documented.[2] Metallodendrimers—in which early or late transition metals are incorporated at the focal point, within the cascade structure, or grafted on the surface—have been found to be good catalysts in a number of reactions. However, among several hundred publications presenting catalytic behavior of metallodendrimers, only a few report a strong positive catalytic effect of dendrimers compared to that of monomeric species.[3]

The use of dendrimers as ligands for the copper catalyzed arylation or vinylation of nucleophiles with respectively aryl or vinyl halides has apparently not been reported. These are, however, key reactions for carbon−heteroatom or carbon−carbon bond formation in organic synthesis,[4] leading to a wide range of intermediates and targets for the life science and polymer industries.

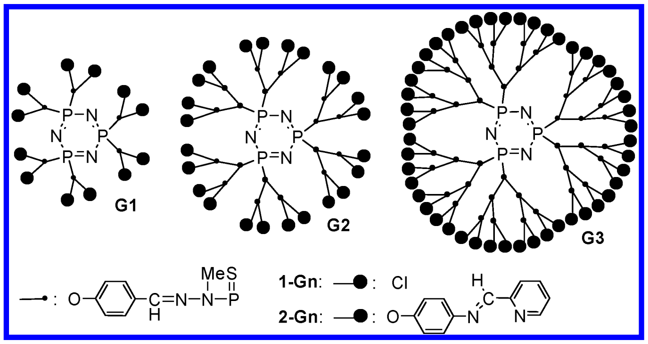
Recently, some of us discovered that multidentate donor ligands (with nitrogen-, oxygen-, or mixed N, O− binding sites), in association with copper precursors, are able to efficiently catalyze C−N, C−O, and C−C bond formation under some of the mildest conditions ever reported.[5]

Among them, the bidentate *N*-[(1*E*)-pyridin-2-ylmethylene]-aniline **A** involving one imino-pyridine chelating ligand, is easily obtained by straightforward condensation of aniline and 2-pyridinecarboxaldehyde. However, this ligand is less versatile than our best polydentate ligands (such as **B**), which require the use of more expensive starting materials.[5] It thus appeared challenging to take advantage of a potential positive catalytic effect of dendrimers in the hope of improving the activity conferred to copper by the bidentate chelator **A**. Hence, phosphorus dendrimers of generation 1 to 3 incorporating the linkage **A** on their outer shell were prepared. Herein we report the outcomes of copper-dendrimer catalyzed arylations and vinylations of oxygen and nitrogen nucleophiles and observe a strong positive dendritic effect for some of these reactions.



New dendrimers **2-Gn** (**n** = **1**, **2**, **3**) were prepared from dendrimers **1-Gn** bearing respectively 6, 12, or 24 P(S)Cl$_2$ end groups[6] and the phenol **3** in the presence of cesium carbonate (see Supporting Information).

The catalytic activity conferred by dendritic ligands to copper was first evaluated in O-arylation reactions and compared to that of the model monomeric ligand **M**, in which the phenolic linker in **3** is capped (Table 1).

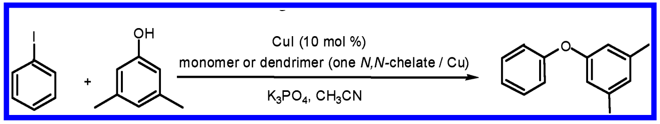


The coupling of PhI with 3,5-dimethylphenol was performed using our standard conditions for this reaction (acetonitrile with K$_3$PO$_4$ as base).[5b] The catalytic system combines CuI (10 mol %) and a monomeric or a dendritic ligand involving imino-pyridine *N*,*N*-chelates. The loading of the latter has been chosen so that the ratio *N*,*N*-chelate-to-copper is equal to 1 in all cases (Table 1).

We observed an optimum catalytic activity when using **2-G3** as the ligand, while monomer **M**, **2-G1**, and **2-G2** were found to promote the reaction with comparable efficiency. The dendritic effect is significant since the yield of diarylether could be improved by about 40% by using third-generation dendrimer (**2-G3**). It must be emphasized that no catalytic activity is observed using copper and dendrimers not decorated with chelating end-groups (**1-Gn** for instance).

We next tried to take advantage of this dendritic effect to perform the reaction at lower temperatures (Table 1, entries 6, 7) Interestingly, diarylether could be obtained in good yield (72%) from

Table 1. Coupling of 3,5-Dimethylphenol with PhI in the Presence of Monomer **M** or Dendritic Ligands **2-G1** to **2-G3**[a]



	monomer or dendrimer					
		% mol	no. of *N*,*N*-chelate	*T* (°C)	*t* (h)	yield (%)[b,c]
1	**M**	10	1	80	20	**61**
2	**2-G1**	0.84	12	80	20	**65**
3	**2-G2**	0.42	24	80	20	**69**
4	**2-G3**	0.21	48	80	20	**85**
5	**2-G3**	0.21	48	80	30	**98**
6	**M**	10	1	55	70	**24**
7	**2-G3**	0.21	48	55	70	**72**[d]

[a] PhI (0.5 mmol), 3,5-dimethylphenol (0.7 mmol), K$_3$PO$_4$ (0.7 mmol), CuI (0.05 mmol), ligand, CH$_3$CN (300 μL), 20 h. [b] GC yields determined with 1,3-dimethoxybenzene as internal standard. [c] Selectivity (yield/conversion of PhI) ≥ 98%; only byproduct is benzene. [d] Under the same conditions, diarylether is formed in only 30% yield with ligand **B**.

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10.1021/ja066505s CCC: $33.50

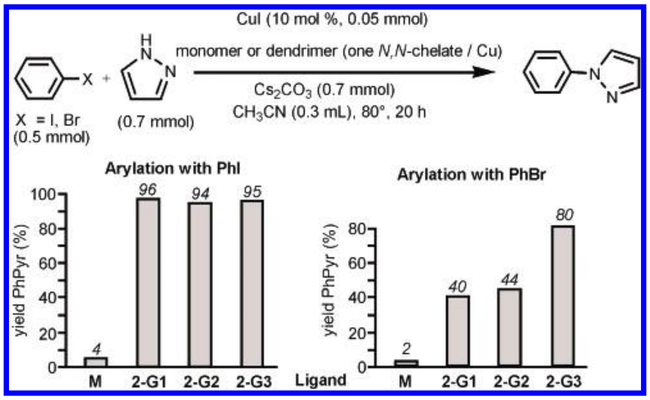
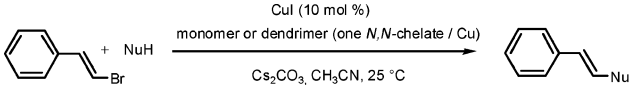


Figure 1. Coupling of pyrazole with PhI and PhBr in the presence of monomer **M** or dendritic ligands **2-G1** to **2-G3**.

Table 2. Coupling of *E*-β-Bromostyrene with *N*- and *O*-Nucleophiles in the Presence of Monomeric and Dendritic Ligands.[a]



	nucleophile	monomer or dendrimer (mol %)	yield (%)[b]
1	pyrazole	**M** (10)	70
2	pyrazole	**2-G3** (0.21)	100
3	3,5-dimethylphenol	**M** (10)	35
4	3,5-dimethylphenol	**2-G3** (0.21)	91

[a] *E*-β-bromostyrene (0.5 mmol), NuH (0.7 mmol), Cs_2CO_3 (0.7 mmol), CuI (0.05 mmol), ligand, CH_3CN (300 μL), 96 h. [b] GC yields determined with internal standard, selectivity: 100%.

iodobenzene at 55 °C using the dendritic ligand **2-G3** (entry 7), whereas the coupling was found to be much less efficient in the presence of the monomeric ligand (entry 6) or with ligand **B** (Table 1, note *d*). To the best of our knowledge, these are among the mildest temperature conditions to date to perform copper-catalyzed arylation of phenols from iodobenzene.[5b]

Hence, these promising preliminary results encouraged us to check if a dendritic enhancement was also observed using other nucleophiles such as nitrogen heterocycles.

First of all, it is worth noting that copper-catalyzed arylation of pyrazole with aryl halides can be efficiently performed by means of different chelates such as oxime derivatives or polydentate Schiff bases.[5e,f] However, in the presence of monomeric ligand **M** (one *N,N*-chelate per copper atom), no coupling reaction occurred, neither from iodobenzene, nor from bromobenzene (Figure 1). Thus this reaction posed a particular challenge for the dendritic ligand. Indeed, upon replacement of **M** by dendrimers **2**, a very strong enhancement of the reaction was observed regardless of the nature of the arylating agent.

In the case of iodobenzene, **2-G1**, **2-G2**, and **2-G3** enabled quantitative conversion of substrate into product within 20 h at 80 °C. When starting from less expensive bromobenzene, the better catalytic activity was once more obtained in the presence of the third generation dendritic ligand **2-G3**, phenylpyrazole being obtained in 80% yield after 20 h at 80 °C. As far we know, such a strong dendritic effect has never been reported in the literature.

To expand the scope of the use of such copper-dendrimer catalysts we also examined (under demanding low-temperature conditions) the vinylation of 3,5-dimethylphenol and pyrazole with *E*-β-bromostyrene.

N-vinylation of pyrazole quantitatively occurred at 25 °C within 4 days with **2-G3** whereas *E*-styrylpyrazole was obtained in only 70% yield under the same conditions with the monomer **M** (Table 2, entries 1,2). The related *E*-styrylarylether could be obtained in 91% yield after 4 days at room temperature when using **2-G3** as the ligand, whereas in the presence of **M**, a poor conversion of only 35% was observed (Table 2, entries 3,4).

Once more, these are the mildest conditions ever reported for performing the coupling between vinyl bromides and nucleophiles (azoles or phenols) using catalytic amounts of copper.[5a]

The general dendritic effect reported here for various coupling reactions is remarkable although it is difficult to explain. For sure, high local concentration of chelating imino-pyridine ligands on the surface of dendrimers is crucial to obtain the best results. Under these conditions, it is reasonable to think that the formation of catalytically active species involving copper(I)/imino-pyridine ligand complexes is favored, thus explaining the observed enhancement of reactivity.

In conclusion we have demonstrated specific advantages for copper(I) catalysis of the very important O- and N-arylation and vinylation of phenol and pyrazole using dendrimer-bound imino-pyridine ligands. The highest yields under the mildest conditions have been obtained for these conversions. Such dendritic enhancement is very rare in the field of organometallic chemistry.

Work is underway to examine the scope of this new catalytic system in arylation and to better understand the phenomena underlying the observed dendritic enhancement.

Supporting Information Available: Synthesis and characterization for dendrimers; procedures for catalysis. This material is available free of charge via the Internet at http://pubs.acs.org.

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JA066505S