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Regioselective oxidative coupling of 2,6-dimethylphenol to tetramethyldiphenoquinone using polyamine dendrimer-encapsulated Cu catalysts†

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The polyamine dendrimer-encapsulated Cu complexes are capable of regioselectively catalyzing the oxidative coupling reaction of 2,6-dimethylphenol to tetramethyldiphenoquinone in high yield. The polyamine dendrimer nanovoids encapsulate Cu ions in such a manner that adjacent Cu centers are able to serve as active species for the reaction.

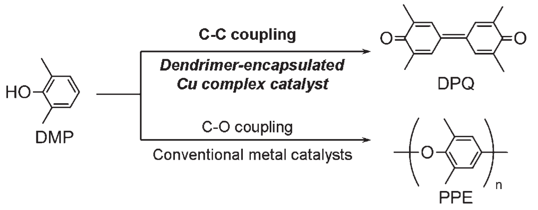
The oxidative coupling reactions of 2,6-dimethylphenol (DMP) have attracted significant attention as techniques for the synthesis of poly(2,6-dimethylphenylene ether) (PPE, the C–O coupling product)[1] and 3,3′,5,5′-tetramethyl-diphenoquinone (DPQ, the C–C coupling product)[2] (Scheme 1). Although various metal catalysts for the C–O coupling to PPE have been reported,[1] catalytic systems for the selective C–C coupling to DPQ have rarely been studied,[2a–c] even though DPQ is highly useful for organic charge transport[3] or as a synthetic intermediate.[4] To date, only three catalysts for the selective C–C coupling of DMP to DPQ have been reported. Bhalerao *et al.* reported that mushroom tyrosinase containing a dicopper center promoted the coupling reaction in a phosphate buffer solution.[2a] Mukherjee *et al.*[2b] and Liu *et al.*[2c] both studied dinuclear Cu complexes with multi-pyridine ligands. Each of these catalytic systems, however, still has significant deficits, including low activity, the requirement to operate at high temperature or low reusability.

A dendrimer is a spherical macromolecule having the regularly branched structure from core to peripheries.[5] By precise design of a dendrimer's constituent units, the branches may be arranged so as to define nanovoids within the molecule. In the catalytic applications of dendrimers, the internal nanovoids not only encapsulate various active metals, but also create suitable reaction environments in the vicinity of the active centers, thus acting as nanoreactors.[6] Based on this principle, we have developed several dendritic nanoreactors using poly(propylene imine) (PPI) dendrimers encapsulating metal complexes,[7] metal nanoparticles,[8] and subnano metal clusters.[9] Recently, the internal nanovoids of the PPI dendrimer were also found to exhibit unique catalysis due to the steric effect of regularly arranged tertiary amino groups, promoting the intramolecular cyclizations.[7c,10]

In this work, we synthesized PPI dendrimer-encapsulated Cu complexes and investigated their catalysis for the oxidative coupling of DMP using molecular oxygen as a green oxidant. The PPI dendrimer allows the Cu species within the dendrimer nanovoids to be present in close proximity to one another, and demonstrate significant catalytic activity and selectivity for the C–C coupling of DMP. Moreover, this dendrimer-encapsulated Cu catalyst could be reused without significant loss of its activity or selectivity.

As the initial step in the preparation of PPI dendrimer-encapsulated Cu complexes, third to fifth generation PPI dendrimers modified with triethoxybenzamide (TEBA) groups on their peripheries (G_x-TEBA, where x denotes the generation number of the dendrimer, Fig. S1, ESI†) were synthesized according to the method presented in previous papers.[8,11] Subsequently, mixtures of $CuCl_2$ and G_x-TEBA in $CH_3CN/CHCl_3$ (1 : 2 v/v) were stirred for 2 h under an Ar atmosphere and the resulting solutions evaporated to afford G_x-$Cu^{2+}{}_n$ (where n denotes the number of Cu^{2+} ions in one dendrimer) as brown, waxy solids.

The encapsulation of Cu^{2+} ions within the G_x-TEBA dendrimers was confirmed by UV-vis absorption spectroscopy. The UV-vis spectra of the G_4-$Cu^{2+}{}_n$ each exhibited a d–d transition band at 819



Scheme 1 Oxidative coupling of 2,6-dimethylphenol (DMP).

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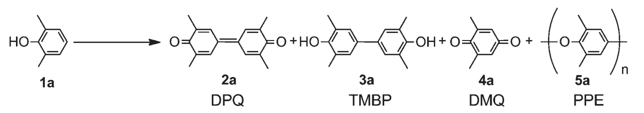
† Electronic supplementary information (ESI) available: Experimental details, XAFS analysis, UV-vis and FT-IR spectra. See DOI: 10.1039/c3ra41817k

Table 1 Oxidative coupling of DMP using various Cu-amine catalysts[a]



Entry	Cu-amine catalyst	Conv. (%)[b]	Yield (%)[b] 2a	3a	4a	5a	Sel. to C–C (%)[c]
1	G_4-$Cu^{2+}{}_2$	9	4	0	1	4	44
2	G_4-$Cu^{2+}{}_8$	25	8	9	1	7	68
3	G_4-$Cu^{2+}{}_{12}$	67	55	10	0	2	97
4	G_4-$Cu^{2+}{}_{16}$	34	15	15	0	4	88
5	G_4-$Cu^{2+}{}_{24}$	16	7	7	0	2	87
6	G_3-$Cu^{2+}{}_2$	30	11	10	1	7	70
7	G_3-$Cu^{2+}{}_6$	54	50	2	0	2	93
8	G_3-$Cu^{2+}{}_{10}$	39	33	3	0	3	92
9	G_5-$Cu^{2+}{}_2$	16	1	7	2	6	50
10	G_5-$Cu^{2+}{}_8$	28	14	7	1	6	75
11	G_5-$Cu^{2+}{}_{16}$	32	19	7	1	5	81
12	G_5-$Cu^{2+}{}_{24}$	38	29	7	0	2	95
13	G_5-$Cu^{2+}{}_{32}$	36	29	4	0	3	92
14	G_5-$Cu^{2+}{}_{48}$	25	11	10	1	3	84
15[d]	G_4-$Cu^{2+}{}_{12}$	>99	97	Trace	0	2	97
16	$CuCl_2$-TEA	9	1	3	0	5	44
17	$CuCl_2$-TMPDA	98	41	4	1	52	46
18	PEI-Cu^{2+}	11	3	4	1	1	63
19[e]	$CuCl_2$	<1	Trace	0	0	0	—
20[f]	G_4-TEBA	N. R.	0	0	0	0	—

[a] Reaction conditions: Cu-amine catalyst (Cu 5 μmol), **1a** (0.5 mmol), $CHCl_3$ (4 mL), 50 °C, O_2 (1 atm). [b] Determined by ^1H NMR internal standard technique. [c] Calculated from the ratio of yield of (**2a** + **3a**) to conv. of **1a**. [d] 18 h. [e] $CuCl_2$ (5 μmol). [f] G_4-TEBA (0.42 mmol).

nm, whereas Cu^{2+} ions in the absence of the dendrimer showed a broad absorption peak centered at 860 nm.[12] A peak was also present at approximately 300 nm, attributed to the LMCT of N– and Cl–Cu.[12,13] The extended X-ray absorption fine structure (EXAFS) spectrum of G_4-$Cu^{2+}{}_{12}$ showed a peak at 1.7 Å corresponding to the Cu–N and Cu–Cl shells and curve-fitting analysis revealed that the Cu species are surrounded by two N and two Cl atoms.[14] Based on these results, each $CuCl_2$ species is coordinated to two nitrogen atoms of the branch units of the dendrimer.

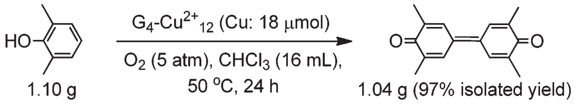
The oxidative coupling reaction of DMP (**1a**) was investigated using several G_x-$Cu^{2+}{}_n$ (x = 3–5) dendrimers at 50 °C under 1 atm of O_2 for 6 h, with the results summarized in Table 1. These data show that n, the ratio of Cu^{2+} to G_x-TEBA, strongly affects both the catalytic activity and the selectivity of G_x-$Cu^{2+}{}_n$. Of the initial series of dendrimers, G_4-$Cu^{2+}{}_{12}$ exhibited the highest activity for the C–C coupling, affording the desired product DPQ (**2a**) along with 3,3′,5,5′-tetramethylbiphenol (TMBP, **3a**), which is known as the reaction intermediate for **2a**,[2c] with 97% selectivity and 67% conversion of **1a** (entry 3). As n is decreased from 12 to 2, both the selectivity for the C–C coupling and the conversion of **1a** decreased drastically to 34% and 9%, respectively (entries 1–3). Conversely, although increasing n from 12 to 24 resulted in decreased conversion of **1a** to 16% with retention of high selectivity for the C–C coupling (entries 3–5). Similar correlations between the catalysis of G_x-$Cu^{2+}{}_n$ and n are also observed for the G_3- and G_5-dendrimers (entries 6–8 and 9–14 for G_3 and G_5), which show maximum efficiency at n = 6 and 24, respectively (entries 7 and 12). Comparing entry 3 to entries 7 and 12, it can be seen that, among the entire series of catalysts, the G_4-$Cu^{2+}{}_{12}$ dendrimer was the most efficient catalyst. In addition, when the reaction time was extended to 18 h, G_4-$Cu^{2+}{}_{12}$ exhibited complete conversion of **1a**, and **2a** was obtained in 97% yield (entry 15).

In order to further examine the high efficiency of G_4-$Cu^{2+}{}_{12}$, several tertiary amine compounds were used instead of the dendrimers.[15] Triethylamine (TEA) and *N*,*N*,*N*′,*N*′-tetramethyl-1,3-propanediamine (TMPDA), both low molecular weight amines, were found to promote non-selective coupling reactions (entries 16 and 17). The use of an irregularly-branched polyethyleneimine modified with TEBA groups (PEI-TEBA)[7b] gave a poor yield of **2a** with lower selectivity for the C–C coupling (entry 18). In addition, the use of solely $CuCl_2$ or G_4-TEBA in place of G_4-$Cu^{2+}{}_{12}$ did not promote the reaction at all (entries 19 and 20). The above results show that the encapsulation of the appropriate quantity of Cu species within nanovoids consisting of the regularly branched tertiary amino groups of G_4-TEBA is the key to obtaining high catalytic efficiency for the C–C coupling reaction of **1a** to **2a**.[16]

G_4-$Cu^{2+}{}_{12}$ could also be applied to gram-scale synthesis in which 1.10 g of **1a** was converted to 1.04 g (97% isolated yield) of **2a** (Scheme 2). In this reaction, the catalyst exhibited very good turnover number (TON) and turnover frequency (TOF) values as high as 485 and 20.2 h^{-1}, respectively, both of which are superior to those reported for other catalyst systems, including mushroom tyrosinase (TON and TOF, 48 and 5.33 h^{-1}),[2a] [(α,α′-bis[(*N*-methyl-2-pyridyl)ethylamino]-2-fluoro-*m*-xylene)$Cu_2(MeCN)_2$][ClO_4]$_2$ (8.6, 1.43 h^{-1})[2b] and [Cu_2(bpnp)(μ-OH)(TFA)$_3$] (100, 4.16 h^{-1}).[2c]

When the oxidative coupling reaction of **1a** was carried out using G_4-$Cu^{2+}{}_{12}$ in α,α,α-trifluorotoluene (TFT), a 96% yield of **2a** was obtained after 18 h, as determined by ^1H NMR analysis. Following the reaction, **2a** was present as a solid and could be easily separated from the reaction mixture by filtration. The filtered TFT solution, still containing the original G_4-$Cu^{2+}{}_{12}$, was successfully reused with no loss of its efficiency, giving a 93% yield of **2a**.[17]

It has been reported that terminal and bridged Cu azide complexes was synthesized by reactions of mono- and bi-nuclear Cu complexes with NaN_3, respectively.[18] Treatment of G_4-$Cu^{2+}{}_n$ with NaN_3 produced a series of dendrimer-encapsulated Cu azide complexes (G_4-$Cu^{2+}{}_n(N_3)$).[19] The Fourier transformed infrared (FTIR) spectra of G_4-$Cu^{2+}{}_{12}(N_3)$ exhibited two peaks, at 2051 and 2079 cm^{-1} (Fig. S9, ESI†),[19] both attributed to the N_3 asymmetric stretch ($\nu_{as}(N_3)$). This spectrum is similar to that of the μ-1,1-binuclear Cu azide complex,[18a,b,d] indicating the presence of adjacent Cu species within the G_4-TEBA nanovoids. Absorption centered around 2048 cm^{-1} was observed in the spectra of both G_4-$Cu^{2+}{}_2(N_3)$ and G_4-$Cu^{2+}{}_8(N_3)$, and was assigned to the terminal



Scheme 2 The gram-scale synthesis of **2a** using G_4-$Cu^{2+}{}_{12}$.

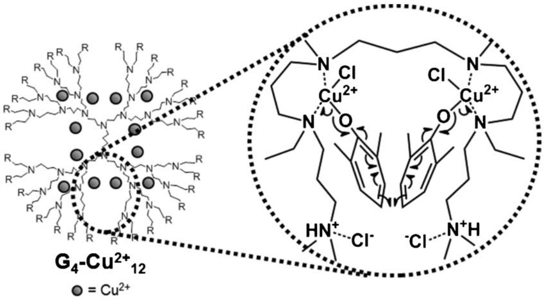


Fig. 1 Proposed reaction intermediate within G_4-Cu^{2+}_{12}.

mononuclear Cu azide complex.[18b,c] The spectra of the G_4-$Cu^{2+}_n(N_3)$ series of dendrimer-Cu species exhibited a clear correlation with the selectivity of the corresponding G_4-Cu^{2+}_n catalysts (Table 1, entries 1–5). G_4-Cu^{2+}_n ($n \geqslant 12$) indicating the formation of binuclear Cu azide complexes showed high selectivities for the C–C coupling (Table 1, entries 3–5), while G_4-Cu^{2+}_n (n = 2 and 8) having the mononuclear Cu azide complexes gave poor selectivities for the C–C coupling (Table 1, entries 1 and 2). These results demonstrate that the formation of adjacent Cu^{2+} species within the G_4-TEBA nanovoids is essential for high selectivity for the C–C selective coupling of **1a**.[1b,1c,2]

We hypothesize the reaction path for the C–C coupling of **1a** to **2a** involving the adjacent Cu^{2+} species within G_4-Cu^{2+}_{12} as follows; a ligand exchange reaction of a Cu^{2+}-Cl species with **1a** occurs to form a Cu^{2+}-phenolate with concurrent generation of HCl which is trapped by a tertiary amino group on the dendrimer.[1d] Within the G_4-Cu^{2+}_{12}, the two Cu^{2+}-phenolates are suitably oriented for the C–C selective coupling reaction *via* one-electron oxidation of the phenolates (Fig. 1), giving **3a**,[2c] and successive oxidation of **3a** yields the final product **2a**.[20] The regularly arranged tertiary amino groups which compose the boundaries of the nanovoid thus work to (1) coordinate Cu ions to generate adjacent active Cu species, (2) promote the facile ligand exchange of Cu–Cl with **1a** through the trapping of HCl at basic sites[21] and (3) accumulate both adjacent Cu species and basic sites within the confines of the nanovoids.

In conclusion, we found that the PPI dendrimer-encapsulated Cu^{2+} complex G_4-Cu^{2+}_{12} is capable of catalyzing the regioselective oxidative coupling of 2,6-dimethylphenol to tetramethyldiphenoquinone. G_4-Cu^{2+}_{12} was also applicable to gram-scale synthesis and exhibited much higher catalytic activity than previously reported catalysts. Moreover, this catalyst could be successfully reused without significant loss of its activity or selectivity. The extremely high efficiency of this catalyst may be attributed to the presence of both adjacent Cu species and basic sites within the nanovoids of the PPI dendrimer following the encapsulation of the appropriate quantity of Cu^{2+} ions.

Acknowledgements

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15 In each of these catalytic systems, the ratio of tertiary amino groups to Cu^{2+} was adjusted equal to that of G_4-$Cu^{2+}{}_{12}$.

16 The substrate scope of G_4-$Cu^{2+}{}_{12}$ was described in the ESI†.

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19 Details of the preparation of G_4-$Cu^{2+}{}_n(N_3)$ as well as FTIR spectra are provided in the ESI†.

20 The oxidation of **3a** with G_4-$Cu^{2+}{}_{12}$ was carried out; G_4-$Cu^{2+}{}_{12}$ quantitatively yielded the final product **2a**. See Scheme S1 in the ESI†.

21 Although the encapsulation of larger quantity of Cu^{2+} ions to G_4-TEBA (n = 16 and 24) induces the formation of adjacent Cu species within the nanovoids, the number of free amino groups to serve as basic sites might decrease compared to that of G_4-$Cu^{2+}{}_{12}$, which caused their low activities and high selectivities to the C–C coupling (Table 1, entry 3 *vs.* entries 4 and 5).