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JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

Communication

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Discovery of a Metalloenzyme-like Cooperative Catalytic System of Metal Nanoclusters and Catechol Derivatives for the Aerobic Oxidation of Amines

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Supporting Information

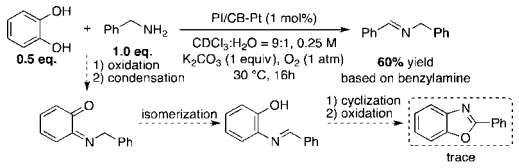
ABSTRACT: We have discovered a new class of cooperative catalytic system, consisting of heterogeneous polymer-immobilized bimetallic Pt/Ir alloyed nanoclusters (NCs) and 4-*tert*-butylcatechol, for the aerobic oxidation of amines to imines under ambient conditions. After optimization, the desired imines were obtained in good to excellent yields with broad substrate scope. The reaction rate was determined to be first-order with respect to the substrate and catechol and zero-order for the alloyed Pt/Ir NC catalyst. Control studies revealed that both the heterogeneous NC catalyst and 4-*tert*-butylcatechol are essential and act cooperatively to facilitate the aerobic oxidation under mild conditions.

Cooperative catalysis is one of the most efficient strategies to realize high reactivity and selectivity in chemical transformations since two or more catalytic centers work in a synergetic manner to reduce the energy of the transition state to a much greater degree than could either catalyst working independently.[1] In Nature, numerous examples of such cooperative catalytic systems are observed in metalloenzymes that utilize both a metal and an organic cofactor to facilitate highly efficient chemical reactions. Chemists have applied a similar approach in developing efficient catalytic systems for homogeneous catalysis,[2] but to our knowledge, the cooperative use of metal nanoclusters (NCs) and organic co-catalysts has not yet been reported, despite the recent emergence of metal NCs in catalytic transformations.

One of the most elegant examples of cooperative catalytic systems in Nature can be found in redox-active metalloenzymes such as amine oxidase.[3] To better understand the mechanistic details of these enzymatic oxidative reactions, chemists have built and examined simplified model systems that mimic the active site of these metalloenzymes.[4] Based on these studies, it is believed that these aerobic oxidations proceed via organic cofactor-assisted electron transfer from the substrate to the molecular oxygen coordinated to the metal ion center. These metalloenzymes have, in turn, inspired numerous biomimetic homogeneous catalytic systems for aerobic oxidations.[5]

In contrast, metal NCs are well established as highly active catalysts for various aerobic oxidation reactions.[6] However, these metal catalysts possess some limitations with respect to the oxidative transformations of amines to imines, in that high reaction temperatures are needed, which limits the scope of the reaction.[7] Herein, we delineate our serendipitous discovery of an unprecedented cooperative catalytic system of a heterogeneous metal NC catalyst and simple organic cofactors such as catechols or *o*-benzoquinones that overcomes the current limitations for metal NC-catalyzed aerobic oxidation of amines to imines.

Scheme 1. Reaction of Catechol and Benzylamine



With our long-standing interest in the development of highly efficient heterogeneous catalysts, we reported an effective protocol for the immobilization of metal catalysts with styrene-based copolymers through a process known as polymer incarceration (PI).[6d,8] We have shown that various gold, platinum, and gold-bimetallic NCs could be stabilized and immobilized by the polymer supports and act as highly active heterogeneous catalysts for various aerobic oxidation reactions under ambient conditions.[9]

Recently, we reported the oxidative preparation of 2-substituted benzoxazoles catalyzed by Pt NCs.[10] Based on our proposed mechanism, we considered the possibility of utilizing catechols and amines as starting materials to synthesize these 5-membered heterocycles. We initially chose pyrocatechol and benzylamine for our model reaction and conducted our experiment under the optimized conditions for the preparation of 2-substituted benzoxazoles (Scheme 1).

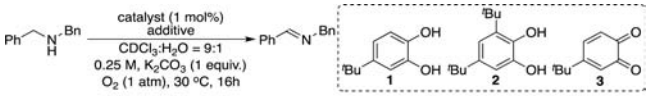
To our surprise, we obtained the unexpected *N*-benzylidene benzylamine as the major product instead of the desired benzoxazole. This was quite remarkable in that the amine oxidation occurred with substoichiometric amounts of the pyrocatechol under very mild conditions. These preliminary results suggested that catalytic amounts of catechol-type derivatives could be utilized to facilitate the aerobic amine oxidation under ambient conditions, and so we began our investigations into the aerobic oxidative imine formation reactions by performing some control studies (Table 1).

We chose dibenzylamine as model substrate and screened various catechol- and benzoquinone-based compounds as additives in the presence of the polymer-incarcerated, carbon-stabilized Pt NC catalyst (PI/CB-Pt). Without any additives,

Received: July 16, 2012
Published: August 1, 2012

   dx.doi.org/10.1021/ja306934b | *J. Am. Chem. Soc.* 2012, 134, 13970−13973

Table 1. Control Studies[a]



entry	catalyst	additive [equiv]	yield [%][b]	entry	catalyst	additive [equiv]	yield [%][b]
1	PI/CB-Pt	-	<5	10	-	**1** [1.0]	nd
2	PI/CB-Pt	pyrocatechol [0.1]	<5	11	-	**3** [1.0]	nd
3	PI/CB-Pt	**1** [0.1]	34	12[d]	PI/CB-Pt	**3** [1.0]	nd
4	PI/CB-Pt	**2** [0.1]	<5	13	Na_2PtCl_6	**1** [0.1]	nd
5	PI/CB-Pt	**3** [0.1]	34	14	Na_2PtCl_6	**3** [0.1]	nd
6	PI/CB-Pt	*o*-chloranil [0.1]	<5	15	$PtCl_2$	**1** [0.1]	nd
7	PI/CB-Pt	DDQ [0.1]	nd[c]	16	$PtCl_2$	**3** [0.1]	nd
8	-	*o*-chloranil [1.0]	nd	17	Pt/C	**1** [0.1]	21
9	-	DDQ [1.0]	nd	18	Pt/C	**3** [0.1]	10

[a]Reaction conditions: dibenzylamine (0.25 mmol) under a balloon pressure of oxygen gas. [b]Determined by GC analysis using anisole as an internal standard. [c]Not detected. [d]Under an atmosphere of argon.

only trace amounts of the desired product were obtained under mild conditions (Table 1, entry 1). Catalytic amounts of the pyrocatechol failed to improve the yield for oxidation of dibenzylamine (entry 2). 4-*tert*-Butylcatechol **1** improved the yield of the desired imine to 34% (entry 3), while the bulkier catechol **2** was not as effective (entry 4). We also considered the oxidized form of 4-*tert*-butylcatechol **3** as an additive and obtained similar results (entry 5). Other quinones such as *o*-chloranil and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) were examined, but the yield could not be improved (entries 6 and 7). The desired product was not formed in the absence of PI/CB-Pt catalyst, even when stoichiometric amounts of **1**, **3**, or strongly oxidizing benzoquinones such as *o*-chloranil and DDQ were used (entries 8−11). Under an atmosphere of argon, the desired oxidative reaction did not proceed, even with stoichiometric amounts of **3** and PI/CB-Pt as a catalyst (entry 12). We also examined other homogeneous and heterogeneous Pt as catalyst with a catalytic amount of **1** or **3** and found that only Pt/C could provide the desired product, albeit with lower yields (entries 13−18).

Having determined the best additive, we began to optimize the reaction conditions (Table 2). Through careful adjustment of the

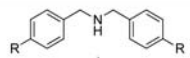
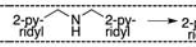
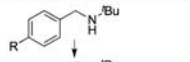
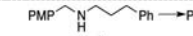
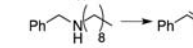
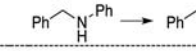
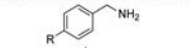
Table 2. Optimization of Reaction Conditions[a]

entry	M	*T* [°C]	*x*	yield [%][b]	entry	M	*T* [°C]	*x*	yield [%][b]
1	Pt	30	10	50	7	Pt/Pd	35	10	69
2	Au	30	10	4	8	Pt/Ru	35	10	66
3	Pd	30	10	38	9	Pt/Ir	35	10	65
4	Ir	30	10	36	10	Pt/Ru	35	20	84
5	Pt	35	10	61	11	Pt/Ir	35	20	90
6	Pt	40	10	50	12	Pt/Ir	35	0	<5

[a]Reaction conditions: dibenzylamine (0.25 mmol), PI/CB-M (0.5 mol %), **1** (*x* mol %), and K_2CO_3 (0.5 equiv) in $CDCl_3$:H_2O (9:1), *c* = 0.5 M, under a balloon pressure of oxygen gas. [b]Determined by GC analysis using anisole as an internal standard.

reaction conditions, we improved the yield to 50% (entry 1). We detected only trace amount of the desired compounds with Au(0) (entry 2). We examined various PI metal NC catalysts and found that Pd and Ir also provided the desired imine, albeit with lower yields (entries 3 and 4). Slightly increasing the temperature to 35 °C improved the yield (entry 5), while at a higher reaction

Table 3. Amine Oxidation Catalyzed by PI/CB-Pt/Ir and 1[a]

entry	substrate (**4a**–**4r**) / product (**5a**–**5r**)		**1** [mol%]	GC yield [%][b]	isolated yield [%]
1		R = H (**5a**)	20	88 (3)	78
2		R = Me (**5b**)	15	87	84
3		R = OMe (**5c**)	15	78	72
4		R = Cl (**5d**)	30	88[c]	82
5		R = CF_3 (**5e**)	50	75	80
6[d]		(**5f**)	15	73[c]	81
7[e]		R = H (**5g**)	35	85	74
8		R = Me (**5h**)	25	88	85
9		R = Cl (**5i**)	40	93	90
10[g]		(**5j**)	20	64[c]	69
11[g]		(**5k**)	20	67[c]	70
12	tetrahydroquinoline → quinoline	(**5l**)	30	81	82
13[f]		(**5m**)	60	60[c]	65
14		R = H (**5n**)	40	77 (8)	74
15		R = Me (**5o**)	40	80	75
16		R = OMe (**5p**)	30	80	73
17		R = Cl (**5q**)	40	60	52
18		R = CF_3 (**5r**)	50	57	55

[a]Reaction conditions: secondary amines (0.25 mmol) or primary amines (0.5 mmol), PI/CB-Pt/Ir (0.5 mol %), and K_2CO_3 (0.5 equiv) in $CHCl_3$:H_2O (9:1), *c* = 0.5 M, under a balloon pressure of oxygen gas for 16 h at 35 °C. [b]Determined by GC analysis using anisole as the internal standard; the selectivity with respect to benzoxazole is shown in parentheses. [c]Determined by ^1H NMR analysis using 1,1,2,2-tetrachloroethane as the internal standard. [d]Using 0.75 equiv of K_2CO_3. [e]No leaching was observed for Pt (detection limit: 0.12%) and Ir (detection limit: 0.03%) by ICP analysis. [f]Using 0.1 equiv of K_2CO_3.

temperature, the yield of the desired product decreased (entry 6). Next, various Pt-based bimetallic NC catalysts were applied to the aerobic amine oxidation reaction (entries 7−9). Only Pt/Ir alloyed NCs[9d,e] were found to give the desired product in 90% yield (entry 11). Scanning transmission electron microscopy analysis revealed the formation of 1.5 nm (±0.28 nm) alloyed NCs with good distribution, and catalytic activity might have been tuned electronically by the formation of alloyed NCs.[11] Without the catechol derivative, even PI/CB-Pt/Ir failed to catalyze this reaction (entry 12).

We examined the substrate scope of the aerobic oxidation of amines to imines under the optimized conditions (Table 3). Dibenzylamines substituted with electron-donating and electron-withdrawing groups underwent oxidation to generate the corresponding imines in high to excellent yields (entries 2−6). Less reactive dibenzylamines with electron-withdrawing groups required higher catechol loadings (entries 4 and 5). Bulkier substrates like *tert*-butyl-substituted benzylamines required higher loadings of the catechol additive than did dibenzylamines, but these substrates provided the desired products with better conversions and higher selectivities (entries 7−9). *N*-Alkyl benzylamines underwent the desired aerobic oxidation to imines with relatively good yields (entries 10 and 11). In the case of 1,2,3,4-tetrahydroquinoneline, a second dehydration reaction occurred to furnish quinoline (entry 12). We also attempted to oxidize a *N*-aryl secondary amine, and the desired imine was obtained with excellent selectivity and moderate conversion (entry 13). Next, we examined primary amines with different substituents and found that imines were generated in good yields,

dx.doi.org/10.1021/ja306934b | J. Am. Chem. Soc. 2012, 134, 13970−13973

except for amines possessing electron-withdrawing substituents (entries 14−18).

To gain mechanistic insight into the aerobic amine oxidation reaction, we first performed kinetic studies to investigate the roles of the catechol derivative and the bimetallic Pt/Ir NCs in this reaction system.[11] A steady-state catalytic cycle was established in which well-behaved first-order kinetics were observed for both the amine substrate **4a** (SI Figure 4) and catechol **1** (SI Figure 5), but zero-order for the bimetallic catalyst (SI Figure 7).[11] The reaction rate (r) can be described as $r = k_{obs}[\mathbf{1}][\mathbf{4a}]$ (eq 1). We also performed kinetic isotope studies and found that the kinetic isotope effect value was 7.53 (SI Figure 8).[11]

Cognizant of the importance of catechols in the aerobic oxidation reaction of amines to imines, we considered several possibilities in which catechol **1** could facilitate such a reaction (Figure 1a). Based on our previous studies, one possible role of **1**

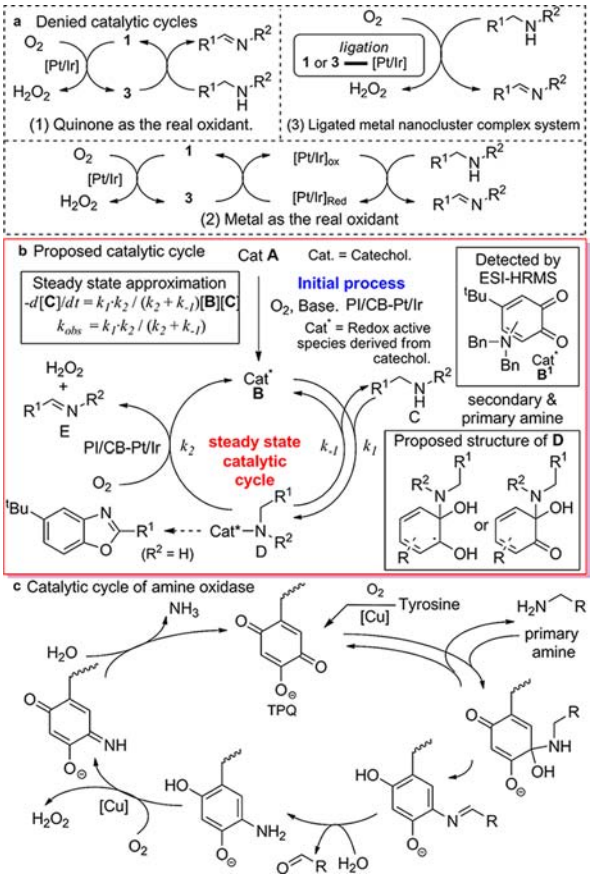


Figure 1. Proposed and denied catalytic cycles.

is to act as a precursor to the real oxidant (quinone **3**) for the imine formation, and the Pt/Ir NCs could regenerate the spent oxidant and restart the catalytic cycle (Figure 1a-(1)).[9h] This possibility was excluded since stoichiometric amounts of quinones do not mediate the amine oxidation (Table 1, entries 8−11). Conversely, Pt/Ir NCs could also act as the oxidizing reagent for the amine oxidation to imines and then be regenerated by **3** (Figure 1a-(2)).[12] Since the oxidation of amines does not occur in the presence of stoichiometric amounts of **3** in the absence of oxygen gas (Table 1, entry 12), we denied the possibility of this catalytic cycle. We also eliminated the possibility that Pt/Ir catalyst was activated by **1** and molecular oxygen to form an activated NC catalyst since the recovered catalyst itself did not catalyze this oxidation without addition of **1** (SI Scheme 3).[11] Another possibility is through some type of ligand-accelerated, metal NC-catalyzed aerobic oxidation reaction in which **1** or its oxidized form acts as a ligand (Figure 1a-(3)).[13] If this scenario were true, then we would anticipate the rate order of the PI/CB-Pt/Ir to not be zero-order, since that of the catechol is first-order.

Based on these mechanistic studies, we propose the mechanism shown in Figure 1b. We believe that, during the initial stages of the catalytic cycle, **1** is oxidized in the presence of PI/CB-Pt/Ir, base, and O_2 to form redox-active species **B**. Interestingly, the amine oxidation appears to occur at a faster rate during this initial period (<30 min, SI Figure 4).[11] We hypothesize that the misbehaved kinetics at the early stages of the reaction could be due to some chemical modification of the catechol by the starting material (SI Figure 3). Through HR-MS analysis of a mixture containing **3** and **4a**, we detected a mass peak of 360 (MH^+) that corresponds to an adduct derived from the 1,4- or 1,6-addition of **4a** to **3** followed by a $2e^-$ oxidation reaction ($\mathbf{B^1}$).[11] The covalent modification of **B** with amine **C** is reasonable since benzoxazoles are obtained as side products (Table 3, entries 1 and 14) and various complexes derived from oxidized catechols and amines have been detected in the mechanistic study of amine oxidases.[14] After this initial process, the reaction system establishes a steady-state catalytic cycle in which the amine reactant **C** is expected to form **D** under equilibrium, and this complex undergoes aerobic oxidation to form our desired imine **E** and regenerate our active catalyst **B**. In addition, eq 1, derived from our kinetic studies, strongly supports this mechanistic insight, and the rate-determining step should be formation of **D** from **B** and **C**.[19]

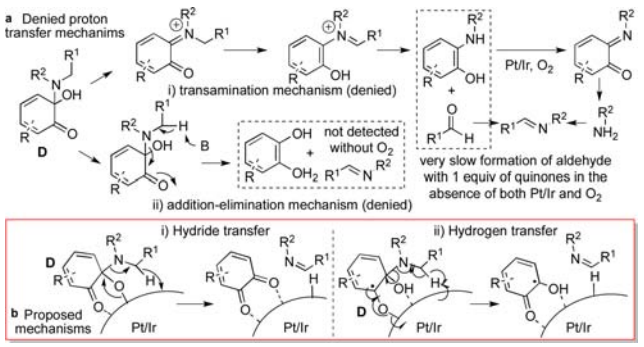
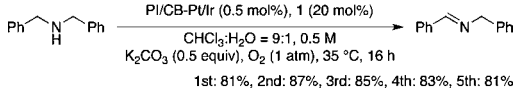


Figure 2. Proposed and denied mechanisms.

Scheme 2. Recovery and Reuse of PI/CB-Pt/Ir



In biological systems, similar catalytic cycles for the amine oxidation reaction, catalyzed by amine oxidase containing copper ion as metal center and 2,4,5-trihydroxy-phenylalanine-quinone (TPQ) cofactors, have been well studied.[3] In these enzymatic systems, TPQ is formed as a redox-active cofactor from tyrosine through a self-processing oxidative reaction catalyzed by the copper ion (Figure 1c).[15] Although these two reaction systems share common characteristics, such as the use of an oxidizing metal catalyst and a quinone-type co-catalyst, there is an important difference in that secondary amines are good

dx.doi.org/10.1021/ja306934b | J. Am. Chem. Soc. 2012, 134, 13970−13973

substrates for our catalytic system, while biological systems generally cannot oxidize or are inhibited strongly by secondary amines.[14b,16] We believe the mechanistic pathway of our catalytic system and that of amine oxidases diverge after the formation of the key hemiaminal intermediate **D** (Figures 1b and 2).[11] In enzymatic systems, dehydration of amines occurs through proton transfer (Figure 2a). Two mechanisms for this proton-transfer process have been postulated, transamination (Figure 2a-(i)) and addition−elimination (Figure 2a-(ii)), and both were confirmed to be operational depending on the type of amine oxidase.[14b,15b,16a,17] However, both mechanisms can be ruled out on the basis of our control experiments.

To explain our experimental results, we propose an alternative mechanism in which the quinone hemiaminal intermediate **D** is complexed to the metal NC surface and undergoes hydride transfer to afford the desired imine (Figure 2b-(i)). The hydride-transfer mechanism is precedented in metal NC literature and forms the basis of our proposed mechanism.[18] It should be noted that the oxidation of amines in our reaction could occur through a single-electron-transfer mechanism (Figure 2b-(ii)), although the use of radical inhibitors 2,2,6,6-tetramethylpiperidinoxyl and 2,6-di-*tert*-butyl-*p*-cresol only slightly diminished the yield of the desired imine (SI Table 13).[11]

Finally, we attempted to recover and reuse PI/CB-Pt/Ir and found that the heterogeneous catalyst could be recovered easily by filtration and reused up to five times without loss of catalytic activity (81−87% yield for first through fifth uses; Scheme 2).[11]

In summary, we have discovered that the combination of heterogeneous bimetallic Pt/Ir alloyed nanoclusters and 4-*tert*-butylcatechol acts as an effective catalytic system for the aerobic oxidation of amines to imines under mild conditions. Mechanistic studies suggest that the Pt/Ir NCs and the catechol derivative work cooperatively to facilitate oxidation of the amines to imines. We believe this is the first example of a metalloenzyme-like cooperative catalytic system of metal NCs and a simple redox-active organic cofactor for an aerobic oxidation reaction. Further mechanistic studies and application of this catalytic system to other redox processes are ongoing and will be reported in due course.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Procedures, kinetic studies, and spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was partially supported by a Grant-in-Aid for Science Research from the Japan Society for the Promotion of Science (JSPS), Global COE Program, The University of Tokyo, MEXT, Japan, and NEDO. We also thank Mr. Noriaki Kuramitsu (The University of Tokyo) for STEM and EDS analysis.

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(19) Alternatively, the rate-determining step could be derived from the oxidation of **D** in which the intermediate is oxidized without the involvement of the Pt/Ir NCs. We thank a reviewer for making this suggestion.