CHEMISTRY
AN ASIAN JOURNAL
ACES
COMMUNICATION

DOI: 10.1002/asia.201300003

Redox Inactive Metal Ion Promoted C−H Activation of Benzene to Phenol with Pd^{II}(bpym): Demonstrating New Strategies in Catalyst Designs

Huajun Guo, Zhuqi Chen, Fuming Mei, Dajian Zhu, Hui Xiong, and Guochuan Yin*[a]

Activation and functionalization of the C−H bonds in alkanes and aromatic compounds has been a long challenge in the academic community, and selective transformations of methane to methanol and benzene to phenol are most attractive.[1,2] Among the versatile redox metal ions, palladium(II) is the one most investigated.[3] Up to now, at least two long standing challenges in Pd^{II}-catalyzed benzene hydroxylation exist: 1) efficient regeneration of the active Pd^{II} species from the reduced Pd^0 form when oxygen is used as an oxidant, and 2) avoidance of the formation of biphenyl through coupling, which is very common in Pd-catalyzed C−H activation.[4] To accelerate the regeneration of the active Pd^{II} ion, the general protocols include the use of a redox cocatalyst to assist the oxidation of Pd^0 and/or the use of a specific ligand to stabilize the Pd^0 atom to impede its aggregation.[4–6] The presence of the ligand may simultaneously increase the steric hindrance surrounding the Pd^{II} ion, thus preventing the activation of the second benzene by the Pd^{II}-Ph intermediate, which would lead to biphenyl formation through reductive elimination. The drawback of using a ligand is that it apparently reduces the C−H bond activation capability of the Pd^{II} ion, thus causing a loss in its activity towards benzene hydroxylation. For example, even when 1,10-phenanthroline (phen) was used as the ligand of the Pd^{II} ion, phenol was reported as the sole product.[7] However, owing to the reduced oxidizing capability, the reaction had to be carried out at the high temperature of 180 °C. Apparently, novel catalysts still need to be designed for efficient hydroxylation of benzene to phenol.

Recently, it was found that Lewis acids like Sc^{3+}, Y^{3+}, Zn^{2+}, Ca^{2+}, and even BF_3 could promote triphenylphosphine oxygenation by Mn^V(TAML)(O) analogues, sulfoxidation by Fe^{IV}(N4Py)(O), electron transfer and hydrogen abstraction by $(TPB_8Cz)Mn^V(O)$, C−H activation by MnO_4^- or FeO_4^-, and catalytic oxidation of alkane by $[Os^{VI}(N)Cl_4]^-/FeCl_3$.[8] In clarifying the relationships of the reactivity of active metal intermediates with their physicochemical properties in oxidations, we also found that increasing the net charge of a redox metal ion accelerates its rate of electron transfer with increased redox potential.[9] In fact, redox inactive metal ions are extensively applied to modify the reactivity of a redox metal oxide in heterogeneous oxidations, and they also play significant roles in enzymatic oxidations.[10,11] Inspired by these works, herein, we report an early example of benzene hydroxylation to phenol with an in situ-generated Pd^{II}(bpym) catalyst (bpym: 2,2′-bipyrimidine) promoted by a redox inactive metal ion. Through ligation with bpym, the redox inactive Al^{III} ion can greatly promote the C−H activation capability of the Pd^{II} ion in Pd^{II}(bpym), which is originally inactive in benzene functionalization.

Here, catalytic oxidations were performed in trifluoroacetic acid (TFA)/trifluoroacetic anhydride (TFAA) media (95:5, v/v). Reactions were carried out in an oil bath at 100 °C under stirring, and pressured oxygen was used as the oxidant (Table 1). In the presence of four equivalents of trifluoromethanesulfonic acid, simple $Pd(OAc)_2$ as catalyst provides dominantly biphenyl as product with a small quantity of phenol (0.20 mmol vs. 0.027 mmol, entry 1). Similar product distributions were observed in most free Pd^{II} ion-catalyzed benzene functionalizations.[4] For example, Ishii et al. reported that the reaction with $Pd(OAc)_2/PV_xMo_{12-x}O_{40}$ as catalyst affords biphenyl in 10.9 % yield together with 0.3 % of phenol.[4a] Here, the addition of either 2,2′-bipyridine (bpy) or bpym as a ligand to the $Pd(OAc)_2$

Table 1. Lewis acid-promoted benzene hydroxylation by the catalyst Pd^{II}(bpym) in the absence or presence of additives.

Entry	Catalyst	Additive	Yield [mmol] phenol	biphenyl
1	Pd^{II}	–	0.027	0.20
2	Pd^{II} + bpy		–	–
3	Pd^{II} + bpym	–	0.009	0.022
4	Pd^{II} + bpym	$Al(OTf)_3$	0.212	0.054
5	Pd^{II} + bpym	$Bi(OTf)_3$	0.100	0.032
6	Pd^{II} + bpym	$Y(OTf)_3$	0.053	0.047
7	Pd^{II} + bpym	$Yb(OTf)_3$	0.013	0.027
8	Pd^{II} + bpym	$Zn(OAc)_2$	0.006	0.022
9	Pd^{II} + bpym	$Mg(OAc)_2$	0.015	0.022
10	Pd^{II} + bpym	NaOTf	0.056	0.110
11	Pd^{II} + bpym	$Sc(OTf)_3$	–	–
12	Pd^{II} + bpy	$Al(OTf)_3$	0.001	0.010

Reaction conditions: $Pd(OAc)_2$, 0.02 mmol; additive, 0.04 mmol; CF_3SO_3H, 0.04 mmol; TFA, 4 mL; TFAA, 0.2 mL; benzene, 5.6 mmol; O_2, 20 atm; oil bath, 100 °C; 16 h.

---

[a] H. Guo, Z. Chen, F. Mei, D. Zhu, H. Xiong, Prof. G. Yin
School of Chemistry and Chemical Engineering
Huazhong University of Science and Technology
Wuhan 430074 (P. R. China)
Fax: (+86) 27-87543632
E-mail: gyin@mail.hust.edu.cn

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/asia.201300003.

catalyst leads to the complete loss of catalytic activity; however, the addition of 2 equivalents of $Al(OTf)_3$ to the in situ-generated Pd^{II}(bpym) catalyst recovers its catalytic activity to that observed with $Pd(OAc)_2$ alone. However, in sharp contrast to the simple $Pd(OAc)_2$ catalyst, it provides phenol as main product (0.212 mmol) and biphenyl as minor product (0.054 mmol, see entry 4). The time course of the Pd^{II}(bpym)/$Al(OTf)_3$-catalyzed benzene hydroxylation revealed that formation of biphenyl product occurs in the initial 4 hours (Figure 1). After that, no biphenyl product was produced, whereas phenol was generated steadily over the course of 16 hours. Clearly, the formation of biphenyl and phenol is not competitively catalyzed by Pd^{II}(bpym)/$Al(OTf)_3$, and the formation of biphenyl can be attributed to the presence of trace free Pd^{II} ions in the solution. The addition of $Bi(OTf)_3$ also provides phenol as the main product with biphenyl as minor product (0.1 mmol vs. 0.032 mmol, Table 1, entry 5). Other metal ions including Y^{3+}, Sc^{3+}, Yb^{3+}, Zn^{2+}, Ca^{2+}, and Mg^{2+} did not offer efficient hydroxylation. The low efficiencies of Y^{3+}, Sc^{3+}, and Yb^{3+} are possibly related to their poor solubility in TFA media. In fact, at room temperature, the addition of $Al(OTf)_3$ to the TFA solution containing Pd^{II}(bpym) also leads to the formation of a pale yellow precipitate; however, it dissolved at elevated temperature. Significantly, the isolated precipitate demonstrates a similar catalytic activity to that of the Pd^{II}(bpym)/$Al(OTf)_3$ catalyst. Unexpectedly, the oxidation of phenol to benzoquinone was not observed here. Control experiments in which phenol was used as a substrate confirmed that no benzoquinone is formed in this reaction. This result may be rationalized by the fact that phenol oxidation generally proceeds through a $PhO^{\bullet}$ intermediate, whereas in the presence of a strong acid like TFA, protonation of phenol would prevent the $PhO^{\bullet}$ radical formation, thus blocking phenol oxidation.[12]

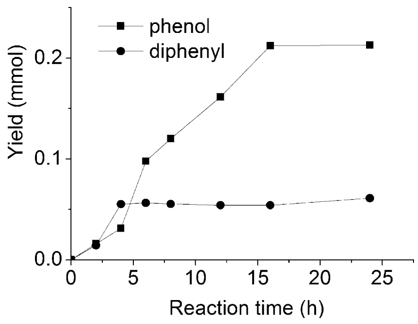


Figure 1. Catalytic kinetics of benzene hydroxylation with Pd^{II}(bpym)/$Al(OTf)_3$ catalyst.

Similar to bpym, bpy may also provide two nitrogen sites for Pd^{II} coordination, but it lacks the extra distal nitrogen for Al^{III} participation. As a result, Pd^{II}(bpy)/$Al(OTf)_3$ is inactive with regard to benzene activation. Further evidence for the ligation of the Al^{III} ion with Pd^{II}(bpym) was provided at analyzing UV/Vis spectra (Figure 2). In acetonitrile, free bpym has an absorption band with a maximum at 229 nm, which is attributed to its $\pi \rightarrow \pi^*$ transition. Upon addition of one equivalent of $Pd(OAc)_2$ to the bpym solution, the peak became red-shifted to a λ_{max} of 252 nm. Owing to a red-shift of a band that originally was below 200 nm, another absorbance with a maximum at 219 nm is observed. The addition of $Al(OTf)_3$ to the bpym solution resulted in similar red-shifts with maxima at 236 and 273 nm. Either adding $Al(OTf)_3$ to the Pd^{II}(bpym) solution or adding $Pd(OAc)_2$ to the Al^{III}(bpym) solution causes bandshifts to λ_{max} values at 228 and 284 nm, thus supporting the notion that both Pd^{II} and Al^{III} are ligated with the bpym ligand. Similar red-shifts were observed when other metal ions were added to the Pd^{II}(bpym) solution (see Figure S1 in the Supporting Information). Taken together, although our attempts to obtain an X-ray structure of a Pd^{II}/Al^{III} bimetallic complex failed, the data suggest that the Al^{III} ion interacts with the Pd^{II}(bpym) through the two distal nitrogen sites in bpym (Figure 3). Periana and co-workers previously used Pt(bpym) for methane activation in concentrated H_2SO_4, and later Goddard et al. proposed that the bpym protonated from the distal nitrogen enhances the C–H activation capability of the Pt^{II} ion.[13] Bercaw and co-workers proposed a similar Lewis acid effect for allylic C–H activation involving $Pd(OAc)_2$ and bpym.[14] In this case, they found that a 2:1 Pd^{II}:bpym ratio was ideal and proposed that the second Pd^{II} coordinates to the backside of the Pd^{II}(bpym) complex and adjusts the electronics of the catalyst to enable C–H activation.

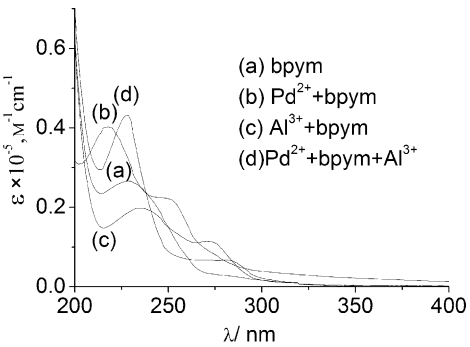


Figure 2. The UV/Vis spectra of Al^{III} and Pd^{II} ligated bpym (0.01 mM) in acetonitrile.

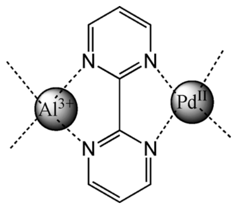


Figure 3. The proposed structure of Pd^{II}(bpym)/$Al(OTf)_3$ catalyst for benzene hydroxylation.

Next, intermolecular competitive hydroxylation of deuterated and undeuterated benzene (1:1 ratio) in normal TFA media with Pd^{II}(bpym)/$Al(OTf)_3$ catalyst revealed that extensive hydrogen/deuterium exchange occurs in both the substrate and the phenol product (Figure 4). After the reaction, only 5.0 % C_6H_6 and 1.8 % C_6D_6 remained, and the dominant substrate is $C_6H_3D_3$, representing 28.3 % of the re-

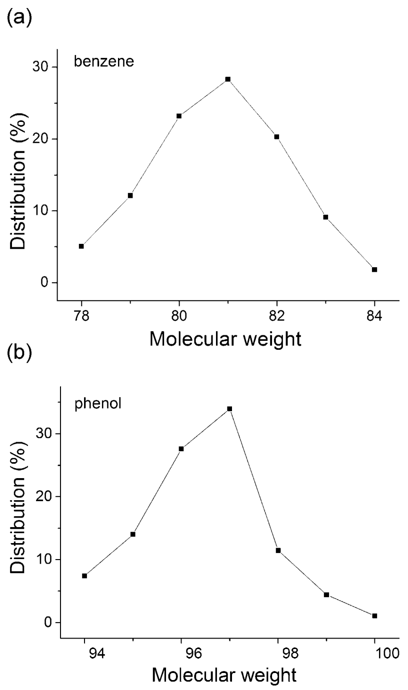
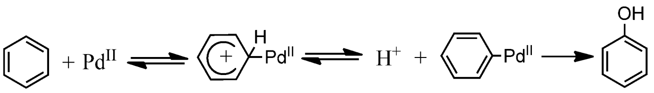


Figure 4. Isotope exchange between undeuterated and deuterated benzene in the Pd^{II}(bpym)/$Al(OTf)_3$-catalyzed benzene hydroxylation.

maining benzene; while the percentages of $C_6H_4D_2$ and $C_6H_2D_4$ are 23.2% and 20.3%, respectively. In the product, perprotio phenol (C_6H_7O) and perdeuterio phenol (C_6D_7O) are only 7.4% and 1.0%, respectively, and partially exchanged phenol dominates in the products, with 27.6% $C_6H_3D_4O$ and 34.0% $C_6H_4D_3O$. Similar isotope distributions were observed when undeuterated benzene was used in deuterated TFA (see Figure S2 in the Supporting Information). Clearly, in the Pd^{II}(bpym)/$Al(OTf)_3$-catalyzed benzene hydroxylation, equilibrium steps for C–H activation before the formation of phenol exist. As shown in Scheme 1, the reaction of the Pd^{II} ion with benzene may first form a σ-complex intermediate, which would generates a Pd^{II}-Ph intermediate upon deprotonation. These two steps are reversible, allowing for extensive hydrogen/deuterium exchange, while the formation of phenol from the Pd^{II}-Ph intermediate is irreversible.



Scheme 1. The C–H activation and phenol formation in Pd^{II}(bpym)/$Al(OTf)_3$-catalyzed benzene hydroxylation.

However, in the absence of $Al(OTf)_3$, only limited isotope exchange was observed in the substrate for the Pd^{II}(bpym)-catalyzed competitive hydroxylation in normal TFA media (Figure 5). After the reaction, C_6H_6 (39.7%) and C_6D_6 (33.5%) are still dominant in the remaining substrate, while the fractions of C_6HD_5 and C_6H_5D are 12.5% and 3.2%, respectively. Unlike in the above-mentioned experiment in which a significant amount of $C_6H_3D_3$ (28.3%) was present, here, the fraction of $C_6H_3D_3$ is only 1.9%. The enhanced oxidizing capability of Pd^{II}(bpym) in the presence of Al^{III} ion has also been evidenced by its positively shifted cathodic peak in the cyclic voltammograms (Figure S3 in the Supporting Information). Taken together, these experiments clearly show that $Al(OTf)_3$ addition greatly promotes the C–H activation capability of the Pd^{II} ion in the Pd^{II}(bpym) catalyst, which leads to a rapid hydrogen/deuterium exchange and subsequent phenol formation, whereas Pd^{II}(bpym) alone is very sluggish concerning the C–H activation of benzene.

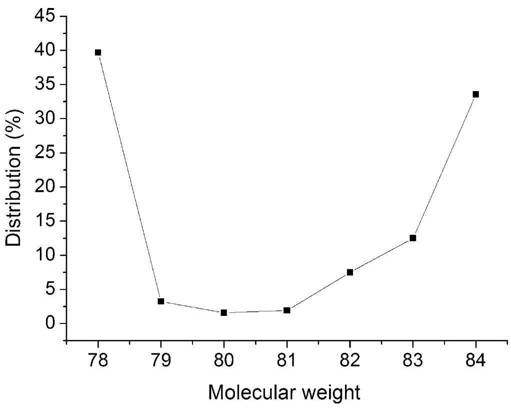


Figure 5. Isotope exchange between undeuterated and deuterated benzene in the Pd^{II}(bpym)-catalyzed benzene hydroxylation.

In summary, this work reveals that the presence of the redox inactive metal ions like Al^{III} may greatly promote the oxidizing capability of Pd^{II}(bpym) with regard to benzene activation, and tune the reactivity of the Pd^{II} ion from benzene coupling to hydroxylation. Hence, our study provides a new strategy for the design of oxidation catalysts, especially for robust substrates.

Experimental Section

General procedure for benzene hydroxylation. In a glass tube, trifluoroacetic acid (4 mL), trifluoroacetic anhydride (0.2 mL), trifluoromethanesulfonic acid (0.04 mmol), palladium(II) acetate (0.02 mmol), aluminum(III) trifluoromethanesulfonate (0.04 mmol), bipyrimidine (0.02 mmol), and benzene (5.6 mmol) were added. The glass tube was equipped with a glass lid with several holes for gas diffusion. Subsequently, the tube was put into a 50 mL stainless autoclave, and the autoclave was charged with 20 atm of oxygen. The charged autoclave was stirred at 100 °C in an oil bath for 16 h. After the reaction, toluene was added to the reaction mixture as an internal standard, and 0.04 mL of the resulting mixture was diluted with 10 mL of acetonitrile/water (6:4, v/v) which had been adjusted to pH 3.5 by trifluoroacetic acid. The above prepared sample was then quantitatively analyzed by HPLC. For the HPLC analysis, a C-18 column (250 mm × 4.6 mm) and an UV detector (210 nm) were used. A mixture of acetonitrile/water (6:4, v/v) was used as the mobile phase at a flow rate of 1 mL min^{-1}.

Acknowledgements

This work was supported by the National Natural Science Foundation of China (Grant 21073228). GC-MS analysis was performed at the Analytical and Testing Center, Huazhong University of Science and Technology.

Keywords: benzene hydroxylation · C–H activation · Lewis acid · oxygen · palladium

[1] a) *Activation and Functionalization of C–H Bonds*, ACS Symposium Series 885 (Eds.: K. I. Goldberg, S. A. Goldman), American Chemical Society, Washington, DC, **2004**; b) L. Boisvert, K. I. Goldberg, *Acc. Chem. Res.* **2012**, *45*, 899–910; c) M. Lersch, M. Tilset, *Chem. Rev.* **2005**, *105*, 2471–2526; d) S. S. Stahl, J. A. Labinger, J. E. Bercaw, *Angew. Chem.* **1998**, *110*, 2298–2311; *Angew. Chem. Int. Ed.* **1998**, *37*, 2180–2192; e) W. D. Jones, *Acc. Chem. Res.* **2003**, *36*, 140–146.

[2] a) B. G. Hashiguchi, S. M. Bischof, M. M. Konnick, R. A. Periana, *Acc. Chem. Res.* **2012**, *45*, 885–898; b) M. Tani, T. Sakamoto, S. Mita, S. Sakaguchi, Y. Ishii, *Angew. Chem.* **2005**, *117*, 2642–2644; *Angew. Chem. Int. Ed.* **2005**, *44*, 2586–2588; c) Y. Zhang, J. Yu, *J. Am. Chem. Soc.* **2009**, *131*, 14654–14655; d) S. M. Kloek, D. M. Heinekey, K. I. Goldberg, *Angew. Chem.* **2007**, *119*, 4820–4822; *Angew. Chem. Int. Ed.* **2007**, *46*, 4736–4738; e) B. Lee, H. Naito, T. Hibino, *Angew. Chem.* **2012**, *124*, 455–459; *Angew. Chem. Int. Ed.* **2012**, *51*, 440–444; f) K. Ohkubo, T. Kobayashi, S. Fukuzumi, *Angew. Chem.* **2011**, *123*, 8811–8814; *Angew. Chem. Int. Ed.* **2011**, *50*, 8652–8655; g) L. Balducci, D. Bianchi, R. Bortolo, R. D'Aloisio, M. Ricci, R. Tassinari, R. Ungarelli, *Angew. Chem.* **2003**, *115*, 5087–5090; *Angew. Chem. Int. Ed.* **2003**, *42*, 4937–4940; h) R. Bal, M. Tada, T. Sasaki, Y. Iwasawa, *Angew. Chem.* **2006**, *118*, 462–466; *Angew. Chem. Int. Ed.* **2006**, *45*, 448–452.

[3] a) K. M. Engle, T. Mei, M. Wasa, J. Yu, *Acc. Chem. Res.* **2012**, *45*, 788–802; b) D. A. Colby, R. G. Bergman, J. A. Ellman, *Chem. Rev.* **2010**, *110*, 624–655; c) S. Gaillard, C. S. J. Cazin, S. P. Nolan, *Acc. Chem. Res.* **2012**, *45*, 778–787; d) L. McMurray, F. O'Hara, M. J. Gaunt, *Chem. Soc. Rev.* **2011**, *40*, 1885–1898; e) S. Enthaler, A. Company, *Chem. Soc. Rev.* **2011**, *40*, 4912–4924; f) J. E. Lyons, *Catal. Today* **1988**, *3*, 245–258; g) S. R. Neufeldt, M. S. Sanford, *Acc. Chem. Res.* **2012**, *45*, 936–946; h) M. S. Sigman, E. W. Werner, *Acc. Chem. Res.* **2012**, *45*, 874–884.

[4] a) T. Yokota, S. Sakaguchi, Y. Ishii, *Adv. Synth. Catal.* **2002**, *344*, 849–854; b) L. C. Passoni, A. T. Cruz, R. Buffon, U. Schuchardt, *J. Mol. Catal. A* **1997**, *120*, 117–123; c) X. Li, Y. Ding, G. Jiao, Z. Pan, D. Jiang, L. Lin, *Chin. J. Catal.* **2005**, *26*, 265–267; d) H. A. Burton, I. V. Kozhevnikov, *J. Mol. Catal. A* **2002**, *185*, 285–290; e) P. Liang, H. Xiong, H. Guo, G. Yin, *Catal. Commun.* **2010**, *11*, 560–562; f) Q. Wu, H. Yang, H. Cheng, Z. Liu, W. You, S. Gao, *J. Mol. Struct.* **2012**, *1030*, 83–88.

[5] a) Y. Obora, Y. Ishii, *Molecules* **2010**, *15*, 1487–1500; b) J. A. Gonçalves, E. V. Gusevskaya, *Appl. Catal. A* **2004**, *258*, 93–98; c) A. Vavasori, L. Toniolo, *J. Mol. Catal. A* **1999**, *139*, 109–119; d) Z. An, X. Pan, X. Liu, X. Han, X. Bao, *J. Am. Chem. Soc.* **2006**, *128*, 16028–16029; e) I. Hatanaka, N. Mitsuyasu, G. Yin, Y. Fujiwara, T. Kitamura, K. Kusakabe, T. Yamaji, *J. Organomet. Chem.* **2003**, *674*, 96–100; f) G. Yin, C. Jia, T. Kitamura, T. Yamaji, Y. Fujiwara, *J. Organomet. Chem.* **2001**, *630*, 11–16; g) G. Yin, C. Jia, T. Kitamura, T. Yamaji, Y. Fujiwara, *Catal. Lett.* **2000**, *69*, 89–91.

[6] a) M. H. Emmert, A. K. Cook, Y. J. Xie, M. S. Sanford, *Angew. Chem.* **2011**, *123*, 9581–9584; *Angew. Chem. Int. Ed.* **2011**, *50*, 9409–9412; b) T. Yoneyama, R. H. Crabtree, *J. Mol. Catal. A* **1996**, *108*, 35; c) J. E. Bercaw, N. Hazari, J. A. Labinger, *J. Org. Chem.* **2008**, *73*, 8654.

[7] T. Jintoku, K. Takaki, Y. Fujiwara, *Chem. Lett.* **1987**, 1865–1868.

[8] a) H. Du, P. Lo, Z. Hu, H. Liang, K. Lau, Y. Wang, W. W. Y. Lam, T. Lau, *Chem. Commun.* **2011**, *47*, 7143–7145; b) S. Yiu, W. Man, T. Lau, *J. Am. Chem. Soc.* **2008**, *130*, 10821–10827; c) W. W. Y. Lam, S. Yiu, J. M. N. Lee, S. K. Y. Yau, H. Kwong, T. Lau, D. Liu, Z. Lin, *J. Am. Chem. Soc.* **2006**, *128*, 2851–2858; d) C. G. Miller, S. W. Gordon-Wylie, C. P. Horwitz, S. A. Strazisar, D. K. Peraino, G. R. Clark, S. T. Weintraub, T. J. Collins, *J. Am. Chem. Soc.* **1998**, *120*, 11540–11541; e) Y. Morimoto, H. Kotani, J. Park, Y. Lee, W. Nam, S. Fukuzumi, *J. Am. Chem. Soc.* **2011**, *133*, 403–405; f) P. Leeladee, R. A. Baglia, K. A. Prokop, R. Latifi, S. P. de Visser, D. P. Goldberg, *J. Am. Chem. Soc.* **2012**, *134*, 10397–10400.

[9] a) Y. Wang, J. Sheng, S. Shi, D. Zhu, G. Yin, *J. Phys. Chem. C* **2012**, *116*, 13231–13239; b) G. Yin, *Acc. Chem. Res.*, **2012**, DOI: 10.1021/ar300208z.

[10] a) R. K. Grasselli, *Top. Catal.* **2002**, *21*, 79–88; b) I. E. Wachs, G. Deo, J. M. Jehng, D. S. Kim, H. Hu, *ACS Symp. Ser.* **1996**, *638*, 292.

[11] a) I. Rivalta, G. W. Brudvig, V. S. Batista, *Curr. Opin. Chem. Biol.* **2012**, *16*, 11–18; b) T. Noguchi, *Photosynth. Res.* **2007**, *91*, 59–69.

[12] a) A. Al-Ajlouni, A. Bakac, J. H. Espenson, *Inorg. Chem.* **1993**, *32*, 5792–5796; b) D. T. Y. Yiu, M. F. W. Lee, W. W. Y. Lam, L. C. Lau, *Inorg. Chem.* **2003**, *42*, 1225–1232.

[13] a) R. A. Periana, D. J. Taube, S. Gamble, H. Taube, T. Satoh, H. Fujii, *Science* **1998**, *280*, 560–564; b) M. Ahlquist, R. A. Periana, W. A. Goddard, III, *Chem. Commun.* **2009**, 2373–2375.

[14] B. Lin, J. A. Labinger, J. E. Bercaw, *Can. J. Chem.* **2009**, *87*, 264–271.

Received: January 2, 2013