ORGANIC LETTERS

2008
Vol. 10, No. 15
3275−3278

Highly Efficient Alkene Epoxidation and Aziridination Catalyzed by Iron(II) Salt + 4,4′,4″-Trichloro-2,2′:6′,2″-terpyridine/ 4,4″-Dichloro-4′-*O*-PEG-OCH_3-2,2′:6′,2″-terpyridine

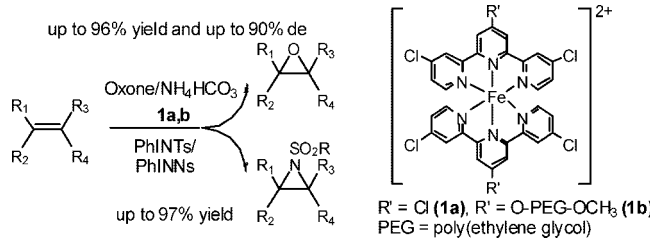
Peng Liu, Ella Lai-Ming Wong, Angella Wing-Hoi Yuen, and Chi-Ming Che*

Department of Chemistry and Open Laboratory of Chemical Biology of the Institute of Molecular Technology for Drug Discovery and Synthesis, The University of Hong Kong, Pokfulam Road, Hong Kong, China

cmche@hku.hk

Received May 21, 2008

ABSTRACT



"Iron(II) salt + 4,4′,4″-trichloro-2,2′:6′,2″-terpyridine" is an effective catalyst for epoxidation and aziridination of alkenes and intramolecular amidation of sulfamate esters. The epoxidation of allylic-substituted cycloalkenes achieved excellent diastereoselectivities up to 90%. ESI−MS results supported the formation of iron−oxo and −imido intermediates. Derivitization of Cl_3terpy to *O*-PEG-OCH_3−Cl_2terpy renders the terpyridine unit to be recyclable, and the "iron(II) salt + 4,4″-dichloro-4′-*O*-PEG-OCH_3-2,2′:6′,2″-terpyridine" protocol can be reused without a significant loss of catalytic activity in the alkene epoxidation.

The search for highly efficient and inexpensive metal catalysts with potential practical applications is a challenge in green chemistry. Compared with many catalysts containing heavy transition metal ions, iron complexes are inexpensive and biocompatible.[1] However, practical applications of iron complexes in organic synthesis are sparse.

Barton and co-workers[2] and subsequently others[3] had reported the important use of pyridine as a ligand in the development of iron-based catalysts for organic oxidations. Notably, iron pyridyl complexes have been shown to be active catalysts for *cis*-dihydroxylation[4] and epoxidation of alkenes,[5] as well as oxidation of alkanes[6] and sulfides.[7] Herein, we report the use of iron complex **1a** or "Fe(II) salt

(1) Bolm, C.; Legros, J.; Le Paih, J.; Zani, L. *Chem. Rev.* **2004**, *104*, 6217.

(2) (a) Barton, D. H. R.; Doller, D. *Acc. Chem. Res.* **1992**, *25*, 504. (b) Barton, D. H. R.; Beviere, S. D.; Chavasiri, W.; Doller, D.; Liu, W. G.; Reibenspies, J. H. *New J. Chem.* **1992**, *16*, 1019. (c) Barton, D. H. R. *Tetrahedron* **1998**, *54*, 5805.

(3) (a) Stavropoulos, P.; Çelenligil-Çetin, R.; Tapper, A. E. *Acc. Chem. Res.* **2001**, *34*, 745. (b) Costas, M.; Mehn, M. P.; Jensen, M. P.; Que, L., Jr. *Chem. Rev.* **2004**, *104*, 939. (c) Groves, J. T. *J. Inorg. Biochem.* **2006**, *100*, 434.

(4) (a) Costas, M.; Tipton, A. K.; Chen, K.; Jo, D.-H.; Que, L., Jr *J. Am. Chem. Soc.* **2001**, *123*, 6722. (b) Chen, K.; Costas, M.; Kim, J.; Tipton, A. K.; Que, L., Jr *J. Am. Chem. Soc.* **2002**, *124*, 3026. (c) Costas, M.; Que, L., Jr *Angew. Chem., Int. Ed.* **2002**, *41*, 2179. (d) Fujita, M.; Costas, M.; Que, L., Jr *J. Am. Chem. Soc.* **2003**, *125*, 9912.

(5) (a) Nam, W.; Ho, R.; Valentine, J. S. *J. Am. Chem. Soc.* **1991**, *113*, 7052. (b) White, M. C.; Doyle, A. G.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2001**, *123*, 7194. (c) Dubois, G.; Murphy, A.; Stack, T. D. P. *Org. Lett.* **2003**, *5*, 2469. (d) Kodera, M.; Itoh, M.; Kano, K.; Funabiki, T.; Reglier, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 7104. (e) Gelalcha, F. G.; Bitterlich, B.; Anilkumar, G.; Tse, M. K.; Beller, M. *Angew. Chem., Int. Ed.* **2007**, *46*, 7293. (f) Anilkumar, G.; Bitterlich, B.; Gelalcha, F. G.; Tse, M. K.; Beller, M. *Chem. Commun.* **2007**, 289.

(6) (a) Kim, C.; Chen, K.; Kim, J.; Que, L., Jr *J. Am. Chem. Soc.* **1997**, *119*, 5964. (b) van den Berg, T. A.; de Boer, J. W.; Browne, W. R.; Roelfes, G.; Feringa, B. L. *Chem. Commun.* **2004**, 2550. (c) Pavan, C.; Legros, J.; Bolm, C. *Adv. Synth. Catal.* **2005**, *347*, 703.

10.1021/ol801157m CCC: $40.75
Published on Web 06/27/2008

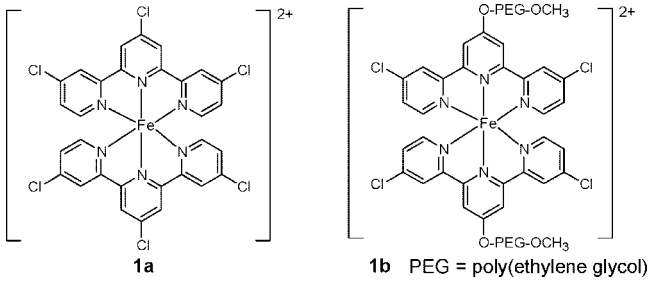


Figure 1. Structure of complex cations of **1a** and **1b**.

+ Cl_3terpy" (Figure 1) as an efficient catalyst for the epoxidation and aziridination of alkenes and intramolecular amidation of saturated C−H bonds of sulfamate esters. Our choice of the Cl_3terpy ligand is due to its robustness under oxidative conditions. Derivitization of Cl_3terpy to *O*-PEG-OCH_3−Cl_2terpy renders the terpy ligand to be recoverable and can be easily separated from the reaction mixture.

Complex **1a** was immediately formed by reacting $Fe(ClO_4)_2{\cdot}6H_2O$ with 4,4′,4″-trichloro-2,2′:6′,2″-terpyridine[8] in MeCN at room temperature. The purple diamagnetic compound formed was characterized by ^{1}H NMR and UV−vis spectroscopies, ESI−MS spectrometry, and X-ray crystallography (see Supporting Information). The average $Fe-N_{pyridine}$ bond distance of **1a** is 1.94 Å, and this complex shows a quasi-reversible Fe(III)/(II) couple at $E_{1/2} = 0.90$ V (vs $Cp_2Fe^{+/0}$) in 0.1 M nBu$_4$NPF$_6$ MeCN solution.

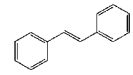
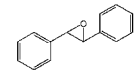
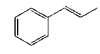
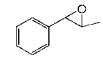
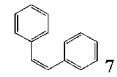
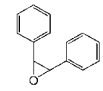
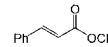
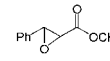
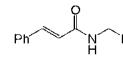
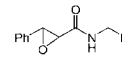
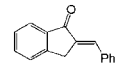
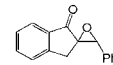
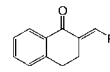
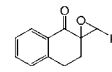
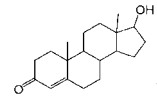
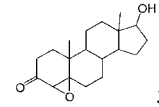
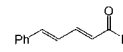
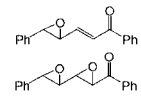
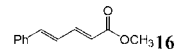
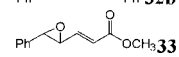
Table 1 depicts the activity of **1a** toward catalytic epoxidation of alkenes, ranging from electron-rich to electron-deficient alkenes by Oxone. Treatment of different alkenes with Oxone and NH_4HCO_3 catalyzed by **1a** (5 mol %) at room temperature for 2 h afforded the corresponding epoxides. Unfunctionalized terminal alkene **2** was readily epoxidized to **19** with 86% yield based on 70% substrate conversion (Table 1, entry 1).

Alkene substrate conversion of only 30% was found when [Fe(terpy)$_2$](ClO$_4$)$_2$ was used as the catalyst, and no epoxide was obtained when Fe(ClO$_4$)$_2{\cdot}6H_2O$ was used under the same reaction conditions (see Supporting Information). Aryl alkenes **3**−**6** were oxidized to corresponding epoxides **20**−**23** with product yields of 90%, 86%, 92%, and 42%, respectively (Table 1, entries 2−5), while no diol product was observed. *Cis*-stilbene **7** was oxidized to **24** in 96% yield with a high stereoselectivity [*cis*:*trans* ratio of 27:1] (Table 1, entry 6). Epoxidation of cyclohexene **8** afforded **25** as the only product in 96% yield with no alcohol or ketone formed (Table 1, entry 7). The electron-deficient alkenes **9**−**13** (Table 1, entries 8−12) were effectively oxidized to their corresponding epoxides with up to 96% yield and 100% substrate conversion in 2 h. Steroid **14** was selectively oxidized to epoxide **31** with an α:β ratio of 3:1 (Table 1, entry 13). The unprotected hydroxyl group of the steroid remained unchanged.

(7) (a) Legros, J.; Bolm, C. *Angew. Chem., Int. Ed.* **2004**, *43*, 4225. (b) Legros, J.; Bolm, C. *Chem.−Eur. J.* **2005**, *11*, 1086.

(8) Wieprecht, T.; Xia, J.; Heinz, U.; Dannacher, J.; Schlingloff, G. *J. Mol. Catal. A-Chem.* **2003**, *203*, 113.

Table 1. Epoxidation of Alkenes by Oxone Catalyzed by **1a**[a]

entry	substrate	product	yield[b] (conversion[c]) (%)
1	 **2**	 **19**	86 (70)
2	 **3**	 **20**	90 (99)
3	 **4**	 **21**	86 (56)
4	 **5**	 **22**	92 (99)
5	 **6**	 **23**	42 (76)
6	 **7**	 **24**	96 (*cis:trans* = 27:1)[c] (99)
7	 **8**	 **25**	96 (99)
8	 **9**	 **26**	96 (100)
9	 **10**	 **27**	95 (92)
10	 **11**	 **28**	92 (75)
11	 **12**	 **29**	83 (99)
12	 **13**	 **30**	86 (99)
13	 **14**	 **31**	84 (α:β = 3:1)[c] (82)
14	 **15**	 **32a** **32b**	71[d]/23[e] (100)
15	 **16**	 **33**	83[d] (100)
16	 **17**	 **34**	83 (*cis:trans* = 1:7)[c] (80)
17	 **18**	 **35**	83[f] (*cis:trans* = 1:10)[c] (76)

[a] Reaction conditions: substrate/**1a**/Oxone/NH_4HCO_3 molar ratio = 1/0.05/1.3/4, rt, 2 h. [b] Product yields based on conversions. [c] Determined by GC analysis or ^{1}H NMR spectroscopy of crude product. [d] Yield of γ,δ-monoepoxide. [e] Yield of α,β:γ,δ-diepoxide. [f] Solvent for reaction: CH_3CN/H_2O = 2/1.

The epoxidation of α,β:γ,δ conjugated alkene **15** catalyzed by **1a** (Table 1, entry 14) afforded the γ,δ-monoepoxide **32a** in 71% yield and α,β:γ,δ-diepoxide **32b** as the minor product (23% yield). γ,δ-Monoepoxide **33** was obtained as the only product in the **1a**-catalyzed epoxidation of **16** (Table 1, entry 15). No α,β-monoepoxide was detected in both cases. The selectivity of **1a**-catalyzed epoxidation of α,β:γ,δ conjugated alkene is different from those previously reported, in which α,β-epoxide was obtained as the major product when [Ru^{IV}(2,6-Cl_2TPP)Cl_2] (2,6-Cl_2TPP = 2,6-dichloropyridine tetraphenyl porphyrin) was used as the catalyst and 2,6-

dichloropyridine *N*-oxide was used as the terminal oxidant.[9] Epoxidation of the allylic alkenes **17** and **18**, catalyzed by **1a**, afforded **34** and **35** in a *cis*:*trans* ratio of 1:7 and 1:10, respectively (Table 1, entries 16 and 17). These values are *higher than that of 1:3 reported for the same reactions when m-CPBA was used as the oxidant in the absence of metal catalyst.*[10]

The catalytic activity of **1a** toward aziridination of alkenes and amidation of sulfamate esters was also evaluated (Table 2). Styrene **3** undergoing intermolecular aziridination with PhINTs or PhINNs (Ts = *p*-toluenesulfonyl; Ns = *p*-nitrobenzenesulfonyl) in the presence of **1a** afforded aziridine **47** in 95% yield and 86% substrate conversion and aziridine **48** in 97% yield and 81% substrate conversion, respectively (Table 2, entries 1 and 2). Cycloalkene **36** and aliphatic terminal alkene **37** were converted to corresponding aziridines **50** and **51** in 68% and 78% yield, respectively (Table 2, entries 4 and 5). Unsaturated sulfonamides **38**−**41** were intramolecularly cyclized to give **52**−**55**, respectively, in up to 92% yield (Table 2, entries 6−9). Unsaturated sulfonamides **42** and **43** possessing allylic C−H bonds, which are likely to undergo intramolecular amidation, underwent intramolecular aziridination to give **56** and **57** as the only products (Table 2, entries 10 and 11). The catalytic intramolecular amidation of sulfamate esters **44**−**46** catalyzed by **1a** (Table 2, entries 12−14) gave rise to **58**−**60** as single products in 86%, 90%, and 84% yield, respectively.

Recently, there has been a surge of interest in nonheme iron−oxo and −imido complexes.[11] Reactive Fe═O and Fe═NTs intermediates were, respectively, detected by ESI−MS when an MeCN solution of **1a** was treated with Oxone or PhI═NTs (in a molar ratio of 1:4). Cluster peaks at *m*/*z* 371.9 and 448.5 with peak separation of 0.5 Da were observed, and the corresponding zoomed scan spectra (see Supporting Information) match the simulated spectra for the $[Fe(Cl_3terpy)_2O]^{2+}$ and $[Fe(Cl_3terpy)_2(NTs)]^{2+}$ ions, respectively. The relative rates of epoxidation and aziridination of *para*-substituted styrenes (*para*-substituent = MeO, Me, H, Cl, Br, CF_3) were examined. An electron-rich substituent accelerates the reaction, whereas an electron-deficient substituent retards the reaction. Plots of log k_Y/k_H vs σ_p^+ reveal *a linear relationship from which the slopes of the plots are −0.55 and −0.72 (see Supporting Information) for epoxidation and aziridination, respectively*. The observed ρ^+ value (−0.55) for epoxidation is 2−3.6-fold smaller in magnitude than those reported for styrene oxidation by peracids (ρ^+ = −1.2),[12] and $(F_{20}TPP)Fe^{IV}$═O (ρ^+ = −1.1 to −2.0; TPP = tetraphenyl porphyrin).[13] This suggests that the reaction of styrenes with the proposed $[Fe(Cl_3terpy)_2O]^{2+}$ intermediate is less sensitive to the *para*-substituent of styrene, and there is less charge developed at the benzylic C_α atom in the reaction. This is consistent with the high stereoselectivity observed in the **1a**-catalyzed epoxidation of *cis*-stilbene to *cis*-stilbene oxide. In contrast, the observed ρ^+ value (−0.72) for aziridination is comparable (1.5-fold smaller in magni-

Table 2. Intermolecular[a] and Intramolecular[b] Aziridination of Alkenes and Sulfonamides and Intramolecular Amidation[c,d] of Sulfamate Esters Catalyzed by **1a**

entry	substrate(s)	product	yield[e] (conversion[f]) (%)
1	**3** + PhINTs (1.5 equiv)	**47**	95 (86)
2	**3** + PhINNs (1.5 equiv)	**48**	97 (81)
3	**4** + PhINTs (1.5 equiv)	**49**	86 (75)
4	**36** + PhINTs (1.5 equiv)	**50**	68 (61)
5	**37** + PhINTs (3.0 equiv)	**51**	78 (63)
6	**38**	**52**	91 (100)
7	**39**	**53**	92 (100)
8	**40**	**54**	90 (100)
9	**41**	**55**	86 (100)
10	**42**	**56**	96 (94)
11	**43**	**57**	92 (98)
12	**44**	**58**	86[c] (70)
13	**45**	**59**	90[d] (62)
14	**46**	**60**	84[d] (68)

[a] Reaction conditions: substrate/**1a** molar ratio = 1/0.05, 40 °C, 12 h. [b] Substrate/**1a**/$PhI(OAc)_2$ molar ratio = 1/0.05/1.5, 40 °C, 12 h. [c] Substrate/**1a**/$PhI(OAc)_2$/MgO molar ratio = 1/0.05/1.4/2.3, 80 °C, 12 h. [d] Substrate/**1a**/$PhI(OAc)_2$/MgO molar ratio = 1/0.05/2.8/4.6, 80 °C, 12 h. [e] Product yields based on conversions. [f] Determined by GC analysis or ^1H NMR spectroscopy of crude product.

(9) (a) Hummelen, J. C.; Wynberg, H. *Tetrahedron Lett.* **1978**, *12*, 1089. (b) Zhang, J.-L.; Che, C.-M. *Chem.−Eur. J.* **2005**, *11*, 3899.

(10) (a) Chan, W.-K.; Liu, P.; Yu, W.-Y.; Wong, M.-K.; Che, C.-M. *Org. Lett.* **2004**, *6*, 1597. (b) Chan, W.-K.; Wong, M.-K.; Che, C.-M. *J. Org. Chem.* **2005**, *70*, 4226.

(11) (a) Chen, K.; Que, L., Jr *Angew. Chem., Int. Ed.* **1999**, *38*, 2227. (b) Rohde, J.-U.; Bukowski, M. R.; Que, L., Jr *Curr. Opin. Chem. Biol.* **2003**, *7*, 674. (c) Rohde, J.-U.; In, J.-H.; Lim, M. H.; Brennessel, W. W.; Bukowski, M. R.; Stubna, A.; Münck, E.; Nam, W.; Que, L., Jr *Science* **2003**, *299*, 1037. (d) He, C.; Mishina, Y. *Curr. Opin. Chem. Biol.* **2004**, *8*, 201. (e) Avenier, F.; Latour, J.-M. *Chem. Commun.* **2004**, 1544. (f) Kryatov, S. V.; Rybak-Akimova, E. V. *Chem. Rev.* **2005**, *105*, 2175. (g) Halfen, J. A. *Curr. Org. Chem.* **2005**, *9*, 657. (h) Klinker, E. J.; Jackson, T. A.; Jensen, M. P.; Stubna, A.; Juhász, G.; Bominaar, E. L.; Münck, E.; Que, L., Jr *Angew. Chem., Int. Ed.* **2006**, *45*, 7394. (i) Wang, Z.; Zhang, Y.; Fu, H.; Jiang, Y.; Zhao, Y. *Org. Lett.* **2008**, *10*, 1863.

(12) Ogata, Y.; Tabushi, I. *J. Am. Chem. Soc.* **1961**, *83*, 3440.

(13) Lee, K. A.; Nam, W. *Bull. Korean Chem. Soc.* **1996**, *17*, 669.

tude) to that of $[Ru^{VI}(TPP)(NTs)_2]$ ($\rho^+ = -1.1$).[14] This reveals that the C−N bond formation catalyzed by **1a** is more sensitive to the electronic effect of the *para*-substituent of styrene.

The catalyst loading for alkene epoxidation can be reduced to 3 mol % without significantly affecting the product yield and substrate conversion. As an example, using chalcone **9** (3 mol %) as substrate, epoxide **26** was obtained in 91% yield and 86% substrate conversion under the same reaction conditions over 2 h. Moreover, the catalysis described in this work can be scaled up to gram level. As an example, epoxide **26** (9.1 g, 40.6 mmol) was obtained in 81% yield based on 91% substrate conversion by a one-pot reaction of chalcone **9** (10.5 g, 50.4 mmol) with Oxone (40.3 g, 65.5 mmol) and NH_4HCO_3 (15.9 g, 201.6 mmol) in the presence of complex **1a** (2.3 g, 2.5 mmol) for 2 h at room temperature. After the one-pot reaction, the Cl_3terpy ligand was recovered in 89% (2.05 g, isolated yield).

The Cl_3terpy ligand is oxidatively robust and can be reused for catalysis simply by addition of a new batch of $Fe(ClO_4)_2{\cdot}6H_2O$ to the reaction mixture. A solution of MeCN:H_2O (3:2) containing **1a** (5 mol %), Oxone:NH_4HCO_3 (1.3:4; 0.2 mmol), and alkene substrate **9** (0.2 mmol) was stirred at room temperature for 2 h. The substrate conversion of **9** was 100% as detected by ^{1}H NMR spectroscopy. The catalysis stopped, and presumably, **1a** underwent demetalation to give the free Cl_3terpy ligand. Without isolation of the Cl_3terpy ligand, a new batch of $Fe(ClO_4)_2{\cdot}6H_2O$ (5 mol %), oxidant (1 equiv), and **9** (0.2 mmol) was added to the reaction mixture, which was allowed to stir for another 2 h at room temperature. The added $Fe(ClO_4)_2{\cdot}6H_2O$ reacted with the Cl_3terpy to regenerate complex **1a** in situ, as evidenced by its absorption λ_{max} at 561 and 321 nm. The in situ generated **1a** subsequently catalyzed the epoxidation of alkene **9** to chalcone α,β-epoxide **26** (92% yield with 93% substrate conversion) in the second run (see Supporting Information).

To simplify the recovery, the Cl_3terpy ligand was derivitized to *O*-PEG-OCH_3−Cl_2terpy, MW = 9010 (details of synthesis and characterization are given in the Supporting Information); $[Fe(O\text{-PEG-}OCH_3{-}Cl_2terpy)_2]^{2+}$ **1b** (characterized by ^{1}H NMR) was formed in situ by reacting $Fe(ClO_4)_2{\cdot}6H_2O$ (10 mmol) with 4,4″-dichloro-4′-*O*-PEG-OCH_3-2,2′:6′,2″-terpyridine (10 mmol) in MeCN (30 mL) at room temperature. The reactivity of **1b** toward catalytic epoxidation and aziridination of alkenes was examined. Complex **1b** catalyzed the epoxidation of **9** to **26** in 96% yield and the aziridination of **38** to **52** in 93% yield. The substrate conversion was 100% in both cases.

The *O*-PEG-OCH_3−Cl_2terpy ligand can be separated from the reaction products by diluting the reaction mixture with H_2O followed by Et_2O extraction. The ligand left in the aqueous layer can be reused to catalyze alkene epoxidation. As an example, an MeCN:H_2O (3:2) solution of **9** (0.2 mmol), catalyst **1b** (5 mol %), and Oxone:NH_4HCO_3 (1.3:4; 0.2 mmol) was stirred at room temperature for 2 h. The epoxide product was obtained in 96% yield by an Et_2O extraction. The *O*-PEG-OCH_3−Cl_2terpy ligand left in the aqueous phase was used to regenerate complex **1b** in situ by adding $Fe(ClO_4)_2{\cdot}6H_2O$, so as to restart the catalysis. This process was repeated 5 times to afford the chalcone α,β-epoxide **26** with 93% yield and 89% substrate conversion after 5 runs (see Supporting Information).

In summary, we have developed an efficient and robust protocol based on recyclable Cl_3terpy or *O*-PEG-OCH_3−Cl_2terpy ligand and Fe(II) salt to perform catalytic oxidation and C−N bond formation reactions. Work is ongoing to further expand the practical uses of these iron complexes in organic synthesis.

Acknowledgment. We are thankful for the financial support of The University of Hong Kong (University Development Fund), Hong Kong Research Grants Council (HKU 7012/05P) and (CityU 2/06C), and the Areas of Excellence Scheme established under the University Grants Committee of the Hong Kong Special Administrative Region, China (AoE/P-10/01).

Supporting Information Available: Experimental procedures and product characterizations. This material is available free of charge via the Internet at http://pubs.acs.org.

OL801157M

(14) Au, S.-M.; Huang, J.-S.; Yu, W.-Y.; Fung, W.-H.; Che, C.-M. *J. Am. Chem. Soc.* **1999**, *121*, 9120.