Advanced Synthesis & Catalysis

DOI: 10.1002/adsc.201400316

Catalytic Electrophilic Halogenations and Haloalkoxylations by Non-Heme Iron Halides

Sujoy Rana,[a] Sukdev Bag,[a] Tuhin Patra,[a] and Debabrata Maiti[a,*]

[a] Department of Chemistry, Indian Institute of Technology, Mumbai – 400076, India
E-mail: dmaiti@chem.iitb.ac.in

Received: March 27, 2014; Published online: August 1, 2014

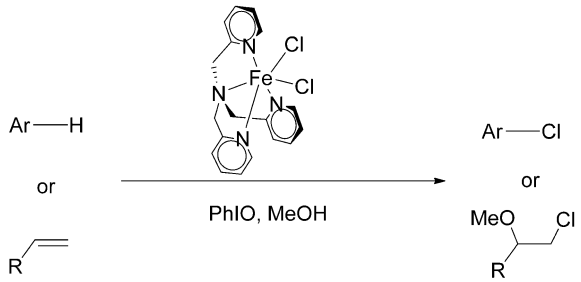
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201400316.

Abstract: Synthetic non-heme iron halides promote sub-stoichiometric aliphatic halogenation reactions *via* a radical mechanism. Complementary to such activity, we have developed an electrophilic halogenation of arenes employing non-heme iron halides. A catalytic version of these reactions has also been developed using potassium halide as the source of halogen atom for arenes at room temperature. Efforts towards understanding the mechanism of these catalytic halogenation reactions led to the discovery of the haloalkoxylation of olefins by a non-heme iron complex. Implications of these findings with respect to natural transformations are also discussed.

Keywords: arenes; catalysis; haloalkoxylation; halogenation; non-heme iron; olefins

Halogenating enzymes such as myeloperoxidase (MPO), chloroperoxidase (CPO), bromoperoxidase (BPO), α-ketoglutarate-dependent halogenase and $FADH_2$-dependent halogenase incorporate halogens in natural products.[1] The majority of these enzymatic halogenation reactions occurs either *via* a radical ($Cl^{\cdot}$) or *via* an electrophilic (hypohalide, e.g., ClO^-) mechanism.[2] Heme peroxidases (MPO, CPO, etc.) catalyze oxidation of Cl^- to ClO^- *via* formation of a transient hypochloritoiron(III)porphyrin intermediate which is responsible for the electrophilic halogenation reactions.[1c,e,3] In the case of non-heme iron enzymes like α-ketoglutarate-dependent halogenase and $FADH_2$-dependent halogenase, a halide radical rebound mechanism has been proposed.[1d]

Halogenations of aliphatic substrates involving the synthetic non-heme iron halide complex, $[(TPA)Fe(III)Cl_2]^+$ were reported by Que and co-workers.[4] Such a halide radical-based reaction was further investigated by Comba and co-workers.[5]



Scheme 1. Electrophilic halogenation by non-heme iron halide.

However, no reports of electrophilic halogenation of arenes are known till date starting with non-heme iron-halide complexes (Scheme 1).

Fujii and co-workers developed an electrophilic chlorination by employing iron(III)isoporphyrin complex *via* formation of iron(III)-*meso*-chloro-isoporphyrin species as active chlorinating source.[7] They have also reported electrophilic chlorination from Fe(III)-heme complex in the presence of TBAOCl *via* formation of a hypochloritoiron(III) porphyrin.[3a] Halogenation of electron-rich arenes was also reported with iron-hydroperoxo species.[8]

Herein we report electrophilic halogenations reactions with non-heme iron halide complexes. Notably, under the present reaction conditions, aliphatic substrates remain unreacted. Initially, we used crystallographically characterized $[(TPA)Fe(II)Cl_2]$ (**1**)[6] and $[(TPA)Fe(II)Br_2]$ (**2**) complexes [TPA = tris(2-pyridylmethyl)amine] for halogenation in ther presence of iodosylbenzene (PhIO) as an oxidant in CH_3CN/MeOH at room temperature using 1,3,5-trimethoxybenzene as a model substrate under anaerobic conditions (Figure 1). A catalytic version of these halogenation reactions was subsequently developed with non-halide complexes $[(TPA)Fe(II)(CH_3CN)_2](ClO_4)_2$ (**3**)[6] using an external halide (e.g., KCl and KBr) in the reaction mixture. Preliminary mechanistic investigations of these halogenation reactions led to the dis-

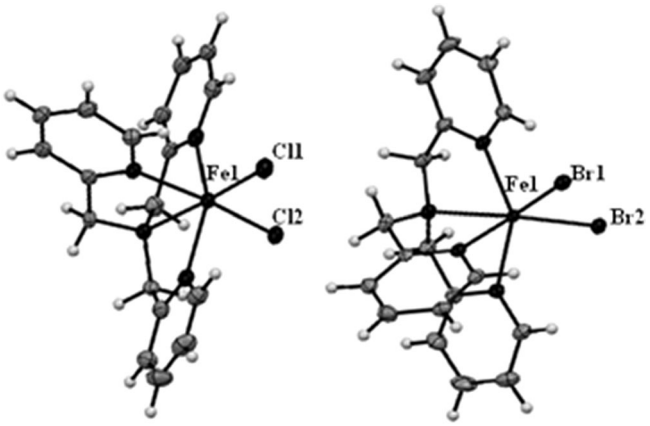
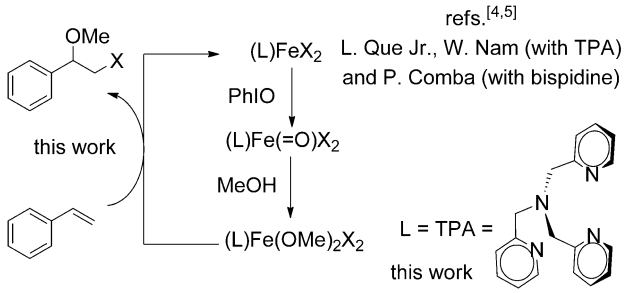
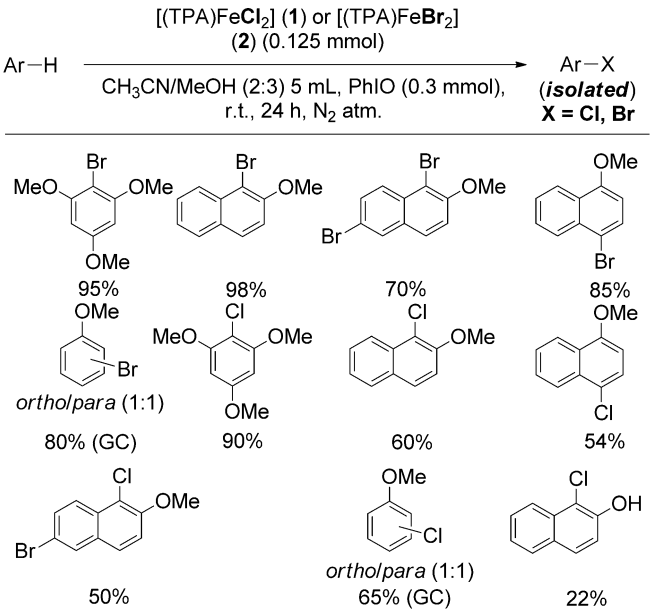


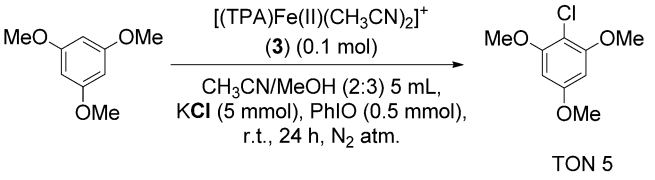
Figure 1. ORTEP diagram of complex [(TPA)Fe(II)Cl_2] (**1**)[6] and [(TPA)Fe(II)Br_2] (**2**). CCDC 964429 (**2**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.



Scheme 2. Haloalkoxylation of olefins by non-heme iron.

Table 1. Substrate scope for chlorination and bromination.





Scheme 3. Catalytic chlorination by non-heme iron species.

covery of the haloalkoxylation of olefins by a non-heme iron complex (Scheme 2).

A 90% yield (isolated) of 2-chloro-1,3,5-trimethoxybenzene was obtained using optimized conditions involving **1** and PhIO. Other oxidants like $PhI(OCOCH_3)_2$, $PhI(OCOCF_3)_2$ and IBX can also be used for this reaction.[9] But H_2O_2 was found to be less efficient for this reaction, whereas TBHP failed to give a halogenated product. Similar to chlorination from **1**, bromination of TMB was achieved in 95% isolated yield with complex **2** (Table 1). Subsequently we tested other arenes using the standard reaction protocol. Naphthalene derivatives provided excellent yields for both chlorination and bromination. Anisole gave *ortho*/*para* regioisomeric halogenated products under the present reaction conditions (Table 1). Encouraged by these findings, we developed the catalytic version (TON 5, Scheme 3) of this halogenation reaction starting with non-halide containing complex [(TPA)Fe(II)$(CH_3CN)_2$]$(ClO_4)_2$ (**3**) in the presence of external halides such as KCl and KBr.

Changes in the UV-vis spectra during halogenation reactions were recorded at −70 °C. Complex **2** gave absorption maxima at 402 nm in CH_2Cl_2. Upon addition of PhIO in methanol, the peak shifted towards the UV region and a shoulder was observed at 352 nm (Figure 2), which is suggestive of the formation of iron(III) species under the reaction conditions.[10]

The choice of solvent was found to be crucial for these halogenation reactions. Chlorination reactions using [(TPA)Fe(II)$(CH_3CN)_2$] $(ClO_4)_2$ (**3**) and KCl in acetonitrile as solvent resulted in only a trace amount (<5%) of 2-chloro-1,3,5-trimethoxybenzene. A combination of CH_3CN/MeOH drastically increased the yield and even the halogenation reaction can be made catalytic using KCl (Scheme 3) in this solvent mixture. Hence the generation of a methanol/methoxy-based iron complex was hypothesized and formation of such a species (Scheme 4) was further verified by experimental observations (*vide infra*).

We have detected the reactive intermediate by ESI-MS at −78 °C. Upon addition of iodosylbenzene to

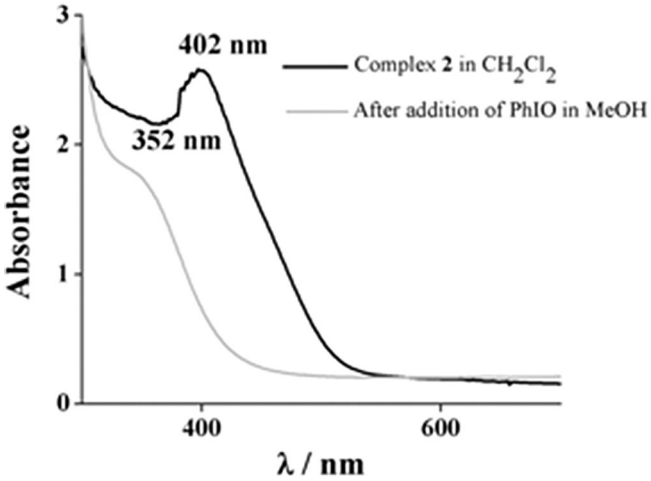


Figure 2. UV-vis spectra changes of **2** upon addition of PhIO.

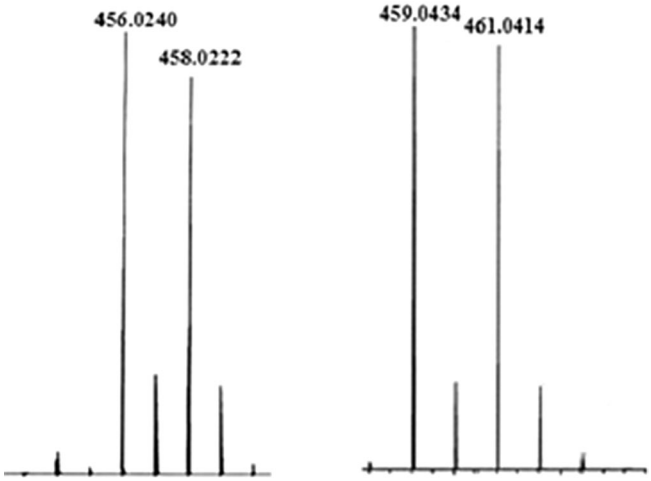
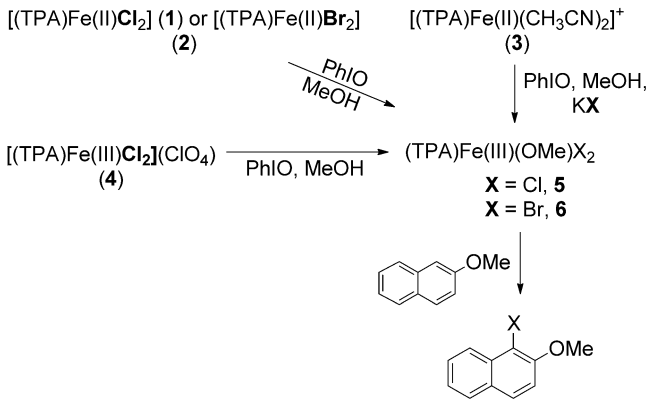


Figure 3. ESI-MS of $[(TPA)Fe(III)^{I}(OCH_3)(Br)]^+$ (**6**), $m/z =$ 456.0240 and $[(TPA)Fe(III)(OCD_3)(Br)]^+$ (**6**-d_3), $m/z =$ 459.0434.

a solution of **1** and 1,3,5-trimethoxybenzene, ESI-MS showed the formation of $[(TPA)Fe(III)(OCH_3)(Cl)]^+$ (**5**). A clear mass pattern for $[(TPA)Fe(III)(OCH_3)(Br)]^+$ (**6**) was also observed by adding PhIO to $[(TPA)Fe(II)Br_2]$ (**2**) in CH_2Cl_2/MeOH (2:3). Labelling experiments using a CH_2Cl_2/CD_3OD mixture produced $[(TPA)Fe(III)(OCD_3)(Br)]^+$ (**6**-d_3) (Figure 3). In the absence of exogenous arene substrates, intermediate **5** or **6** can also be generated at −78 °C. As expected, upon addition of 1,3,5-trimethoxybenzene, these species were consumed with respect to time. We have also observed formation of these intermediates starting with non-halide complexes **3** and iron(III)complex, $[(TPA)Fe(III)Cl_2]ClO_4$ (**4**). Similar to complexes **1**–**3**, **4** produced chloroarene under the standard reaction conditions. The complex **3** produced **5** in the presence of KCl as external halide source. Deuterium labelling experiments with CD_3OD were also carried out successfully using **3** and **4**.



Scheme 4. Halogenation by non-heme iron species.

The complex **2** produced $[(TPA)Fe(IV)(O)Br]^+$ in acetonitrile at −40 °C upon addition of PhIO (ESI-MS, Figure 4).[5] In order to investigate relevance of XO^-/X^+ (X = Cl, Br) for the observed electrophilic halogenation of arenes, we have carried out a phenol red experiment. Oxidation of phenol red *via* electrophilic aromatic halogenation was confirmed by a UV-vis study, which resulted in characteristics peak at 597 nm for bromophenol blue formation.[9,11] Moreover chlorination of anisole with complex **1** (Table 1) gave only monochlorinated product. Such a product formation can also rule out the possibility of a radical

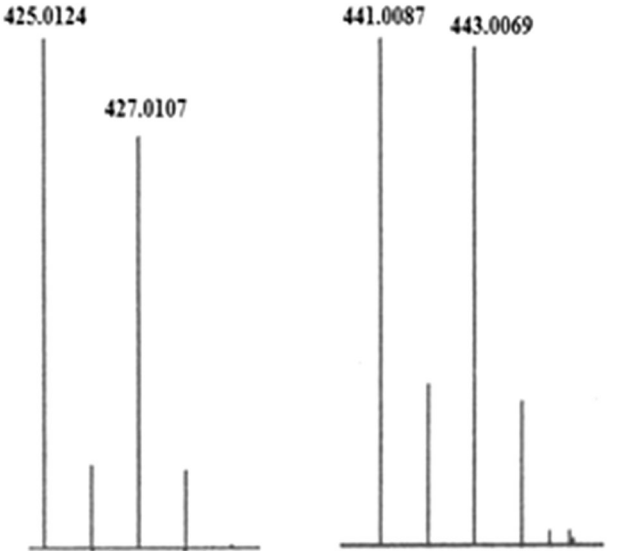


Figure 4. ESI-MS of complex $(TPA)Fe(II)(Br)^+$ (**2**), $m/z =$ 425.0124 and complex $[(TPA)Fe(IV)(O)Br]^+$, $m/z =$ 441.0087.

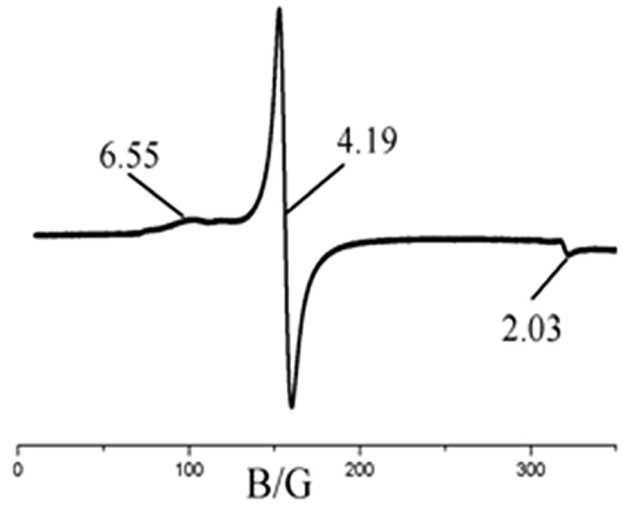
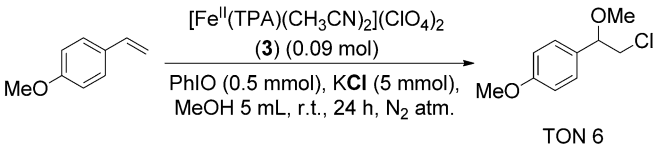


Figure 5. EPR spectrum upon addition of PhIO to **1** (MeOH).

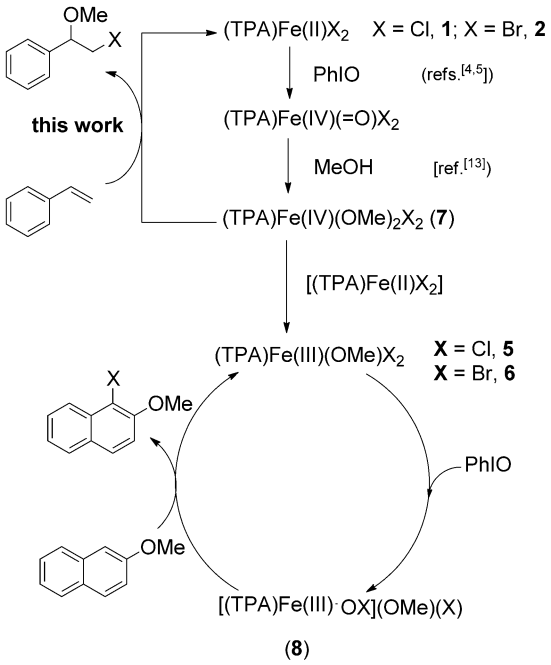


Scheme 5. Catalytic chlorination by non-heme iron species.

halogenation since several isomeric chlorinated products are expected for a radical mechanism.[8b]

The EPR spectrum was recorded (liquid N_2) upon addition of PhIO to [(TPA)Fe(II)Cl_2] (**1**) in CH_3CN/MeOH. We have qualitatively estimated the g tensors which are at the values $g_1=2.03$, $g_2=4.19$, $g_3=6.55$ (Figure 5). This suggests a rhombic geometry with an $S=5/2$ ground state arising from high-spin Fe(III) species.[12] Busch and co-workers have reported very similar EPR spectra for a Fe(III)-high-spin complex ($g_1=2.0$, $g_2=4.3$, $g_3=6.0$) with a tetradentate nitrogen ligand which showed rhombic anisotropy.[12a] Similar EPR spectra of high-spin iron complexes were obtained when PhIO/KCl was added to a solution of **2** and **3**.[9] Combining all the experimental observations (UV-vis, EPR and ESI-MS, including labelling studies), high-spin iron(III)-methoxy-halide complex $[(TPA)Fe(III)(OCH_3)(X)]^+$ (X=Cl, **5** and X=Br, **6**; Scheme 4 and Scheme 6) was proposed under the reaction conditions.

Compounds **5** and **6** can produce **8**, which is the key intermediate for electrophilic halogenation of arenes upon reacting with PhIO. As depicted in Scheme 6, formation of $[(TPA)Fe(IV)(OMe)(X)]^{2+}$ (**7**) can be envisioned from **1** and **2** in PhIO/MeOH.[13] In spite of our best efforts, we failed to detect such an intermediate by spectroscopic techniques. However if such an intermediate is transiently

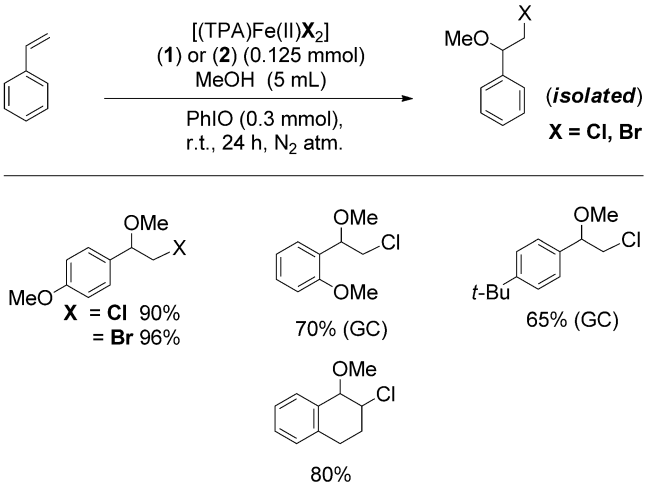


Scheme 6. Proposed mechanism for observed halogenation.

generated during the reaction, halomethoxylation of the olefin may be expected. Interestingly, styrene derivatives produced 2-halo-1-methoxyethylbenzene derivatives under the reaction conditions in excellent yields (Table 2). Without an iron compound, such a haloalkoxylation was not observed. Furthermore, a catalytic version of this reaction was also discovered with TON 6 (Scheme 5).[9]

Unlike non-heme iron halogenase enzymes where halogenation of alkyl substrate occur from (L)Fe(III)(Cl)(OH) *via* radical mechanism,[1d,4,5] in this present study we discovered that the *in situ*

Table 2. Halomethoxylation of olefins by non-heme iron.



formed $[(L)Fe(III)(OCH_3)(X)]^+$ (**5** and **6**) complex can produce electrophilic aromatic halogenation reaction of arenes. Aliphatic substrates remain unreactive. Interestingly, complementary to Nature's selective aliphatic halogenation over hydroxylation from the (L)Fe(III)(Cl)(OH) intermediate,[14] we observed >99% selectivity for aromatic halogenation over methoxylation (Scheme 4).[1d] Note that, only in case of 1,3,5-trimethoxybenzene and 2-methoxynaphthalene as substrate (Table 1), we have detected ~1% arene methoxylation product along with halogenation.

In summary, we have developed unprecedented electrophilic halogenations of arenes starting with non-heme iron halide complexes. A high-spin iron(III)methoxy-halide complex, which generates iron hypohalide upon addition of PhIO, was proposed to be the active halogenating species. Also, haloalkoxylation of olefins by the non-heme iron complex has been discovered based on mechanistic understanding of the halogenation reaction described herein. Both the electrophilic halogenation and haloalkoxylation reactions can be made catalytic using potassium halide. Detailed mechanistic investigation of these reactions is currently undergoing in our laboratory.

Experimental Section

General Procedure for halogenation and halomethoxylation

In a 20-mL screw-cap reaction tube $[Fe(II)(TPA)X_2]$ (X = Cl, Br) (**1**, **2**) or $[Fe(II)(TPA)(CH_3CN)_2](ClO_4)_2$ (**3**) (0.125 mmol or 0.1 mmol) of the prepared non-heme complexes were charged. Subsequently 0.125 mmol (0.25/0.5 mmol of substrates for halomethoxylation) starting material (1 mmol for catalytic reaction) and MeOH/DCM or MeOH/MeCN (3:2) were added to the reaction tube. For halomethoxylation MeOH (5 mL) was used. Then PhIO (0.3 mmol) was added to the reaction mixture. The whole reaction was set inside the glove box. The reaction mixture was stirred for 24 h. After that the reaction tube was removed from the glove box and the reaction mixture was filtered through the celite and washed twice with ethyl acetate. The filtrate was used for GC-MS, GC analysis and isolation.

Acknowledgements

This activity is supported by DST, India. Financial support has been received from CSIR, India (fellowships to S.R. and S.B.), UGC, India (fellowship to T.P.).

References

[1] a) S. J. Klebanoff, *J. Leukoc. Biol.* **2005**, *77*, 598–625; b) E. Malle, P. G. Furtmuller, W. Sattler, C. Obinger, *Br. J. Pharmacol.* **2007**, *152*, 838–854; c) J. H. Dawson, M. Sono, *Chem. Rev.* **1987**, *87*, 1255–1276; d) F. H. Vaillancourt, E. Yeh, D. A. Vosburg, S. Garneau-Tsodikova, C. T. Walsh, *Chem. Rev.* **2006**, *106*, 3364–3378; e) R. Rutter, L. P. Hager, *J. Biol. Chem.* **1982**, *257*, 7958–7961; f) M. Hofrichter, R. Ullrich, *Appl. Microbiol. Biotechnol.* **2006**, *71*, 276–288; g) A. Butler, M. Sandy, *Nature* **2009**, *460*, 848–854; h) J. A. Manthey, L. P. Hager, *Biochemistry* **1989**, *28*, 3052–3057; i) J. A. Manthey, L. P. Hager, *J. Biol. Chem.* **1985**, *260*, 9654–9659; j) M. P. Roach, Y. P. Chen, S. A. Woodin, D. E. Lincoln, C. R. Lovell, J. H. Dawson, *Biochemistry* **1997**, *36*, 2197–2202.

[2] a) K. H. van Pee, C. J. Dong, S. Flecks, J. Naismith, E. P. Patallo, T. Wage, in: *Advances in Applied Microbiology*, Vol 59, Elsevier Academic Press Inc, San Diego, **2006**, pp 127–157; b) J. L. R. Anderson, S. K. Chapman, *Mol. Biosyst.* **2006**, *2*, 350–357; c) D. G. Fujimori, C. T. Walsh, *Curr. Opin. Chem. Biol.* **2007**, *11*, 553–560.

[3] a) Z. Q. Cong, S. Yanagisawa, T. Kurahashi, T. Ogura, S. Nakashima, H. Fujii, *J. Am. Chem. Soc.* **2012**, *134*, 20617–20620; b) L. P. Hager, D. R. Morris, F. S. Brown, H. Eberwein, *J. Biol. Chem.* **1966**, *241*, 1769–1777.

[4] T. Kojima, R. A. Leising, S. P. Yan, L. Que Jr, *J. Am. Chem. Soc.* **1993**, *115*, 11328–11335.

[5] a) P. Comba, S. Wunderlich, *Chem. Eur. J.* **2010**, *16*, 7293–7299; b) J. Bautz, P. Comba, C. L. d. Laorden, M. Menzel, G. Rajaraman, *Angew. Chem.* **2007**, *119*, 8213–8216; *Angew. Chem. Int. Ed.* **2007**, *46*, 8067–8070; c) D. Wang, K. Ray, M. J. Collins, E. R. Farquhar, J. R. Frisch, L. Gomez, T. A. Jackson, M. Kerscher, A. Waleska, P. Comba, M. Costas, L. Que Jr, *Chem. Sci.* **2013**, *4*, 282–291; d) W. N. Oloo, Y. Feng, S. Iyer, S. Parmelee, G. Xue, L. Que Jr, *New J. Chem.* **2013**, *37*, 3411–3415; e) J.-U. Rohde, A. Stubna, E. L. Bominaar, E. Munck, W. Nam, L. Que Jr, *Inorg. Chem.* **2006**, *45*, 6435–6445.

[6] D. Mandon, A. Machkour, S. Goetz, R. Welter, *Inorg. Chem.* **2002**, *41*, 5364–5372.

[7] Z. Q. Cong, T. Kurahashi, H. Fujii, *J. Am. Chem. Soc.* **2012**, *134*, 4469–4472.

[8] a) A. K. Vardhaman, C. V. Sastri, D. Kumar, S. P. de Visser, *Chem. Commun.* **2011**, *47*, 11044–11046; b) A. K. Vardhaman, P. Barman, S. Kumar, C. V. Sastri, D. Kumar, S. P. de Visser, *Chem. Commun.* **2013**, *49*, 10926–10928.

[9] See the Supporting Information for detailed descriptions.

[10] a) F. S. Mei, C. P. Ou, G. L. Wu, L. Cao, F. Han, X. G. Meng, J. Li, D. F. Li, Z. R. Liao, *Dalton Trans.* **2010**, *39*, 4267–4269; b) C. R. Goldsmith, R. T. Jonas, T. D. P. Stack, *J. Am. Chem. Soc.* **2002**, *124*, 83–96.

[11] J. V. Walker, M. Morey, H. Carlsson, A. Davidson, G. D. Stucky, A. Butler, *J. Am. Chem. Soc.* **1997**, *119*, 6921–6922.

[12] a) T. J. Hubin, J. M. McCormick, N. W. Alcock, D. H. Busch, *Inorg. Chem.* **2001**, *40*, 435–444; b) F. Namuswe, T. Hayashi, Y. B. Jiang, G. D. Kasper, A. A. N. Sarjeant, P. Moenne-Loccoz, D. P. Goldberg, *J. Am. Chem. Soc.* **2010**, *132*, 157–167; c) Y. Zang, J. Kim, Y. H. Dong, E. C. Wilkinson, E. H. Appelman, L. Que, *J. Am. Chem. Soc.* **1997**, *119*, 4197–4205; d) N. Y. Oh, M. S.

Seo, M. H. Lim, M. B. Consugar, M. J. Park, J. U. Rohde, J. H. Han, K. M. Kim, J. Kim, L. Que, W. Nam, *Chem. Commun.* **2005**, 5644–5646; e) B. Chakraborty, T. K. Paine, *Angew. Chem.* **2013**, *125*, 954–958; *Angew. Chem. Int. Ed.* **2013**, *52*, 920–924.

[13] J. T. Groves, R. Quinn, T. J. McMurry, M. Nakamura, G. Lang, B. Boso, *J. Am. Chem. Soc.* **1985**, *107*, 354–360.

[14] M. G. Quesne, S. P. de Visser, *J. Biol. Inorg. Chem.* **2005**, *17*, 841–852.

