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COMMUNICATION

# Selective oxygenation of unactivated C-H bonds by dioxygen *via* an autocatalytic formation of oxoiron(V) species

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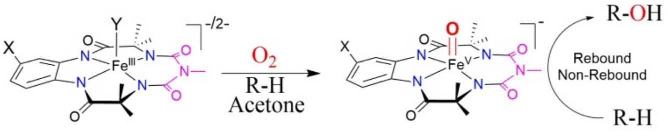
**Selective catalytic oxygenation of unactivated C-H bonds for a series of substrates by dioxygen using iron complexes without the use of co-reductant. Mechanistic studies indicate that the reaction proceeded *via* an autocatalytic formation of oxoiron(V) intermediate which brings in high regioselectivity and stereoretention.**

The development of iron complexes that selectively oxidize industrially useful organic molecules containing unactivated C-H bonds to their corresponding alcohols or ketones using only dioxygen remains a challenge. Synthesis of such complexes would mimic the natural iron-containing oxygenases[1], e.g., cytochrome P450[1b], methane monooxygenase[1c], and naphthalene dioxygenase[1d] among others that activate $O_2$, leading to the formation of high-valent oxoiron intermediates which catalyze the oxidation reaction. Perhalogenated metal porphyrins, such as Fe(TFPPBr$_8$)Cl, are remarkably active and robust catalysts for the oxidation of alkanes under mild conditions.[2] Mechanistic studies indicate that the reaction is not biomimetic, but proceeds *via* the radical chain autoxidation process. The role of the metal complex is limited to the catalytic decomposition of hydroperoxides to produce the oxygenated alcohol and/or ketone. This results in the formation of significant C-C bond scission in several substrates to produce undesired by-products. Subsequently, iron(II) complexes of bispidine ligands have been used for the oxidation of hydrocarbons with $O_2$ *via* an autocatalytic radical chain pathway.[3] The reaction was shown to generate non-heme oxoiron(IV) complex, which displayed very poor selectivity (cis/trans = 4.4:2 plus other side products for cis-dimethylcyclohexane) and TON (~10) for hydrocarbon oxidation. Other non-heme iron(II) complexes such as $[Fe(N_4Py)]^{2+}$ and $[Fe(Bn\text{-}TPEN)]^{2+}$ are not known for C-H bond oxidation[4a] whereas $[Fe(TMC)]^{2+}$ exhibits activity towards C-H bonds having BDE < 80 kcal/mol[4b], although they are known to form oxoiron(IV) species via $O_2$ activation[4c] (see ESI†, Table S1; for comparison of oxygenation reactions by $O_2$ using various iron complexes). Recently, Fukuzumi and coworkers have shown iron(III)-(TAML) catalyzed cyclohexene oxidation by dioxygen *via* an oxoiron(V) autocatalyzed reaction.[5] Although the reaction was selective towards the formation of cyclohexenone, the substrate scope was limited to hydrocarbons having only weak C-H bonds (BDE < 85 kcal/mol). Our group has synthesized biuret modified Fe-TAML complex, $[Et_4N]_2[(bTAML)Fe^{III}\text{-}Cl]$ (**1a**); [bTAML= biuret modified tetramido macrocyclic ligand] which reacts with chemical oxidants (*m*CPBA or NaOCl)[6a,6b] or photochemically generated oxidant, $[\{Ru^{III}(bpy)_3\}Cl_3]$[6c,6d] to form a room temperature stable oxoiron(V) intermediate, which can oxidize 3° C-H bonds with very high selectivity. We have also subsequently demonstrated that axially water-bound complex $[Ph_4P][(bTAML)Fe^{III}\text{-}OH_2]$ (**1b**) in dichloromethane reductively activates $O_2$ to form the corresponding dimeric species $[\{(bTAML)Fe^{IV}\}_2O]^{2-}$ (**2**), which oxidizes alkenes to their corresponding epoxides.[7] The reductive activation of $O_2$ was proposed to form the oxoiron(V) intermediate, which then led to the formation of **2** after comproportionation with **1b**. Since oxoiron(V) intermediates were shown to be formed *via* autocatalytic processes using hydrocarbons with weak C-H bonds like cyclohexene,[5] we were interested in exploring if such methods could be utilized for the selective oxidation of unactivated 3° C-H bonds in hydrocarbons. Herein, we report selective oxygenation of a series of hydrocarbons having unactivated 3° C-H bonds or benzylic C-H bonds by a molecular iron complex, and $O_2$ *via* formation of oxoiron(V) species, $[(bTAML)Fe^V(O)]^-$ (**3**) in aerated acetone solvent. We believe this is the first report on the selective oxygenation of hydrocarbons having unactivated 3° C-H bonds by $O_2$ *via* an autocatalytic formation of oxoiron(V) to date.



R-H = Alkane substrates having C-H bonds
X = -H (**1a**/**1b**), -$NO_2$ (**1c**) and Y = Cl (**1a**/**1c**) or $H_2O$ (**1b**)

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† Footnotes relating to the title and/or authors should appear here.

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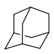
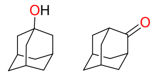
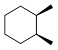
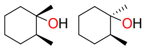
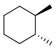
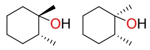
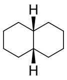
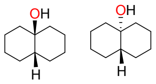
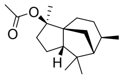
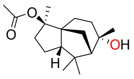
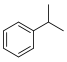
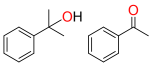
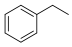
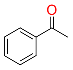
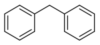
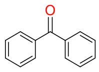
**Scheme 1** Oxygenation of hydrocarbons (RH) by **1a/1b/1c** using dioxygen *via* the formation of [(bTAML)Fe$^{V}$(O)]$^{-}$ in aerated acetone at room temperature.

Our initial studies involved incubation of complex **1b** (0.10 mM) and adamantane (0.10 M) in aerated acetone solvent at room temperature for 20 h. Adamantane was chosen as a model substrate having four $3^o$ C-H (BDE = 96.5 kcal/mole[8]) and twelve $2^o$ C-H bonds (BDE = 98.5 kcal/mole[8]). After 30 min to 1 h of incubation (depending on whether we use bottle grade or rigorously purified substrate and solvent), a slow color change from orange (color of **1b**) to pale green was observed, which with time slowly changed to blue-black. After 20 h, the reaction mixture was filtered through an alumina plug and analyzed by gas chromatography-mass spectroscopy (GC-MS). Product analysis indicated the formation of 10 mM 1-adamantanol and 1 mM of 2-adamantanone (10:1), which corresponds to a $3^o$:$2^o$ regio-selectivity of 25:1 and a TON of 110. The selectivity for 3° C-H bonds, although lower than what is observed for chemically synthesized oxoiron(V)-bTAML,[6] is much higher than classical autooxidation processes (HO· typically affords values near 2, while tBuO· initiated reactions exhibit values around 10).[9a] The selectivities are comparable to other high-valent oxoiron intermediates reported in the literature.[9b] When the same reaction was carried out with **1a**, the selectivity and TON were unchanged, while for **1c**, the TON increased to 120 (Table 1; entry 1). When the reactions were carried out in the absence of $O_2$, no colour change was observed for 12 h. Besides, as expected, no formation of 1-adamantanol or 2-adamantanone was observed. These data strongly indicated that both Fe-bTAML and $O_2$ were involved, and the reaction likely proceeded through a high-valent oxoiron intermediate.

Next, *cis*-1,2-dimethylcyclohexane (*cis*-DMCH, $3^o$ C-H BDE = 93.9 kcal/mole[8]), *trans*-1,2-dimethylcyclohexane (*trans*-DMCH, $3^o$ C-H BDE = 97.4 kcal/mole[8]) and *cis*-decalin ($3^o$ C-H BDE = 93.5 kcal/mole[8]) were explored as substrates. In case of *cis*-1,2-dimethylcyclohexane, $3^o$ hydroxylated products with stereoretention (*cis*/*trans* = 25:1) and $3^o$ to $2^o$ regioselectivity (22:1) was achieved (Table 1; entry 2). On the other hand, *trans*-1,2-dimethylcyclohexane showed much less reactivity under similar reaction condition, although good stereoselectivity is maintained (Table 1; entry 3). For *cis*-decalin, hydroxylation at $3^o$ position (17:1 selectivity over 2°) occurred and a *cis*/*trans* ratio of 8:1 exhibits the stereoretentive nature of the reaction (Table 1; entry 4). Oxidation of cedryl acetate, a natural product derivative of cedrol, having a very rigid structure with five $3^o$ C-H bonds, afforded regioselective hydroxylated product but with lower TON (Table 1; entry 5).

Lastly, substrates having activated C-H bonds (benzylic $3^o$ and $2^o$ C-H bonds) such as ethylbenzene (EB), cumene, and diphenylmethane (DPM) were explored by using the same optimized conditions. For cumene, 2-phenyl-2-propanol and acetophenone were obtained as the major products (ratio 1:1.1) (Table 1; entry 6). The oxidation reactions of ethylbenzene and diphenylmethane by $O_2$ primarily afforded the ketone product with good TON (Table 1; entries 7 and 8). The formation of ketone as the main product was attributed to the over oxidation of the hydroxylated product, which was formed first during the oxygenation reaction (cyclohexanol oxidation by [(bTAML)Fe$^{V}$(O)]$^{-}$ has been reported to be ~350 times faster than cyclohexane oxidation[10]).

**Table 1** Catalytic oxygenation of alkanes by **1a** and **1c** using dioxygen in aerated acetone solvent at room temperature.

| Entry | Substrate | Products | TON | | Yield[a] |
|---|---|---|---|---|---|
| | | | 1a | 1c | |
| 1. |  | <br>$3^o$ : $2^o$ = 25 : 1 | 106 | 120 | 96% |
| 2[b]. |  | <br>*cis* : *trans* = 25 : 1 | 58 | 70 | 91% |
| 3[c]. |  | <br>*trans* : *cis* = 20 : 1 | 18 | 27 | 71% |
| 4[d]. |  | <br>*cis* : *trans* = 8 : 1 | 75 | 116 | 84% |
| 5. |  |  | 22 | 33 | 97% |
| 6. |  | <br>A : K = 1 : 1.1 | 124 | 162 | 90% |
| 7. |  | <br>A : K = 1 : 17 | 120 | 184 | 94% |
| 8. |  | <br>A : K = 1 : 35 | 195 | 252 | 97% |

**Reaction conditions:** Complex **1a/1c** (0.1 mM), substrate (0.1 M) in aerated acetone solvent at room temperature for 20 hours; TON = moles of product/moles of catalyst; TON (within 10% error) values were determined in GC-MS. [a]Yields are based on converted starting material. [b]($3^o$:$2^o$ = 22:1) ; [c]($3^o$:$2^o$ = 3:1) ; [d]($3^o$:$2^o$ = 17:1). A/K denotes alcohol/ketone.

We next proceeded to understand the origin of the selectivity, which typically indicates the formation of high-valent oxoiron intermediates. The colour change observed during the course of the reaction was monitored using UV-Vis spectroscopy. In the initial period (30 - 60 min), a decrease in the peak at 357 nm ($\lambda_{max}$ of **1a**) was observed together with the appearance of peaks at 441 nm and 613 nm, with an isosbestic point at 399 nm. This change in absorption spectra corresponded to the colour change from orange to green observed initially. The UV-Vis spectrum of the green species is identical to the well-characterized Fe$^{V}$(O) species, [(bTAML)Fe$^{V}$(O)]$^{-}$ (**3**, abbreviated as Fe$^{V}$(O)),[6] that was independently synthesized using equimolar amounts of **1a** and *m*CPBA/NaOCl.[6a] The maximum yield of Fe$^{V}$(O) species formed was determined to be > 85% based on the extinction coefficient. Further, ESI-Mass of the green species in acetone revealed a prominent ion peak at the mass to charge ratio, m/z 429.0724 (calculated 429.0730) (ESI†, Fig. S2), which confirmed the formation of $Fe^V(O)$. On similar lines, the formation of $[(NO_2\text{-bTAML})Fe^V(O)]^-$ from **1c**, adamantane, and $O_2$ was also observed in UV-Vis (ESI†, Fig. S3).

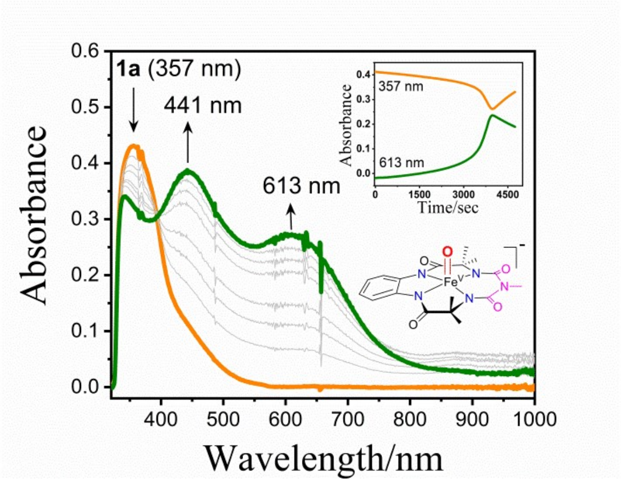
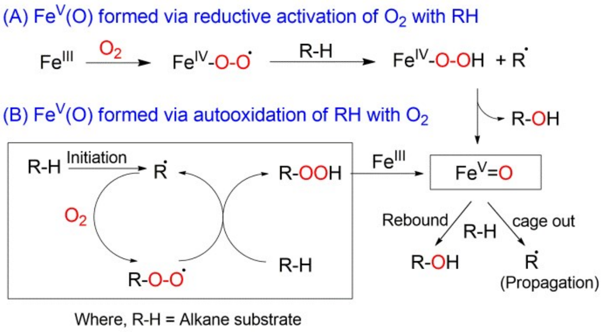


**Fig. 1** UV−Vis absorption spectral changes observed in the oxygenation of **1a** (0.10 mM) with $O_2$ in the presence of adamantane (0.1 M) in aerated acetone solvent at 298 K.

We hypothesized two possible pathways to explain the formation of $Fe^V(O)$: (i) The reductive activation $O_2$ at Fe(III) center of **1a** followed by H atom abstraction from the substrate (RH) by the superoxido species ($Fe^{IV}\text{-OO}\cdot$) and successive homolysis of the hydroperoxido species ($Fe^{IV}\text{-OOH}$) (see scheme 2A). (ii) The operation of an autocatalytic radical chain mechanism leading to alkylhydroperoxide, which would react with **1a** to form $Fe^V(O)$ (see scheme 2B). The kinetic traces for the formation of $Fe^V(O)$ at 613 nm showed sigmoidal curve having a substantial lag phase with all the substrates (Fig. 2a). This sigmoidal nature of the curve is very distinctive of a radical chain mechanism where an induction period is required.[11]



**Scheme 2** Formation of oxoiron(V) species via (A) reductive activation of $O_2$ vs (B) autocatalytic radical chain mechanism.

The induction period for the formation of $Fe^V(O)$ increases with the bond dissociation energies (BDE) of C-H bond for the substrates used. This implies that the initiation step (H atom abstraction) of the radical chain reaction consumes more time for substrates with higher BDE C-H (e.g. *cis*-DMCH) than those with lower BDE (e.g. DPM). Additionally, the length of the induction period was not fully reproducible for the same substrate and depended upon the purity of the substrate and solvent (acetone) used. Similar observations have been reported for the autocatalytic formation of oxoiron(IV) complexes from iron(II) bispidine complexes before.[3] An increment in the induction period was observed with rigorously purified *cis*-DMCH (see ESI†, Fig. S4a). Aged bottle grade hydrocarbons probably contain a small amount of hydroperoxides, which initiate the radical reaction. Acetone, when stored for a long time, shows the formation of the aldol product, diacetone alcohol, which can decrease induction times (ESI†, Fig. S4b). For all kinetic studies, rigorously purified hydrocarbons and acetone were used.

Since the initial results pointed to the operation of radical pathways, $Fe^V(O)$, alkyl hydroperoxide, and a spin trapping agent, DMPO (5,5′-dimethyl-1-pyrroline N-oxide) were added to observe their effects on the induction time. The addition of a catalytic amount of $Fe^V(O)$ to the aerated solution of **1a** (0.10 mM) and substrate (0.1 M) led to a reduction in the induction period (ESI†, Fig. S5). The acceleration of the sigmoidal generation of $Fe^V(O)$ upon the addition of a catalytic amount of $Fe^V(O)$ was also observed. A similar reduction in the induction period was also observed upon increasing the concentration of substrate and addition of a catalytic amount of cumyl hydroperoxide (or $^t$BuOOH) at the start of the reaction (ESI†, Fig. S6 and S7). These results are indicative of the radical chain mechanism.

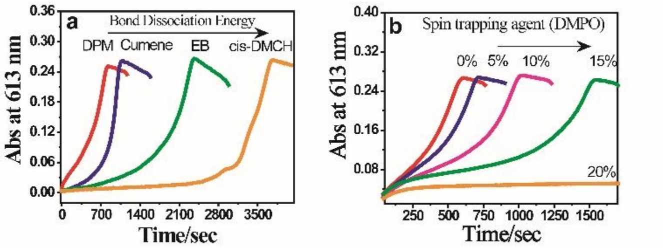


**Fig. 2** UV-Vis time profiles at 613 nm for the reaction of (a) **1a** (0.1 mM) with different substrate (0.1 M) and (b) **1a** (0.1 mM) and DPM (0.1 M) in the presence of DMPO (0 to 20% w.r.t **1a**) in aerated acetone at 298 K.

On the other hand, addition of a catalytic amount of a spin trapping agent, DMPO, to an aerated acetone solution **1a** (0.10 mM) and substrate (O.1 M) resulted in a significant increase in the induction period, which increased with increasing concentration of the DMPO (Fig. 2b). Such effective trapping of the chain carrier radical (alkyl peroxyl radical or alkoxyl radical) by DMPO also supports the involvement of a radical chain pathway during the formation of $Fe^V(O)$.

Based on the above observations, we propose a reaction mechanism involving the catalyst (**1a**/**1b**/**1c**), dioxygen, and substrate (alkanes, RH) (scheme 3). The radical chain reaction initiates with the H-atom abstraction of the substrate to form substrate radical (R·) (initiation step **A**). The initial formation of substrate radical might involve either H-atom abstraction by $Fe^V(O)$ which might be formed via the $Fe^{III}$ catalyzed reductive $O_2$ activation (as shown in scheme 2A) or by the reaction of the substrate molecule with $O_2$ before catalyst addition[12]. Once the radical is formed, it readily reacts with $O_2$ to form the alkylperoxyl radical, ROO· (**B**). The alkylperoxo radical can either (i) abstract the H-atom from another molecule of the substrate to generate the alkylhydroperoxide, ROOH, or (ii)

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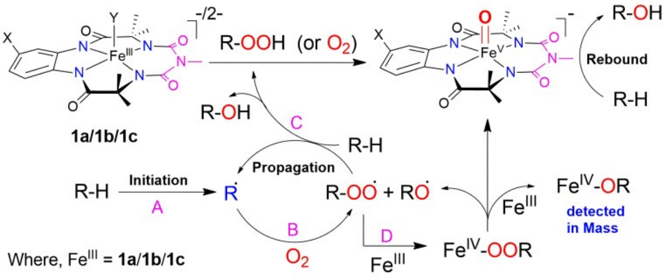
form the alkoxyl radical (RO·) via bimolecular self-reaction (via **C**). Both these alkoxy and peroxy radical are capable of chain propagation. For substrates with strong C-H bonds like adamantane, propagation through the alkoxyl radical is more plausible since it is a much stronger oxidant then the corresponding alkylperoxyl radical ($\Delta H_{BDE}$ of $^tBuO$-H is 105 kcal/mol in comparison to 87 kcal/mol for $^tBuOO$-H).[9b] If ROOH formed, it can convert $Fe^{III}$ to $Fe^{V}(O)$ *via* the "shunt pathway''. In fact, $^tBuOOH$ or cumyl hydroperoxide can cleanly generate $Fe^{V}(O)$ from $Fe^{III}$ (ESI†, Fig. S8). Interestingly, the formation $Fe^{V}(O)$ does not proceed *via* the μ-O-$Fe^{IV}_2$ (**2**) dimer, as has been observed in $CH_3CN$ (ESI†, Fig. S9). The $Fe^{V}(O)$ finally formed can abstract the H-atom to form iron(IV)-hydroxo ($Fe^{IV}$-OH) intermediate and substrate radical (R·), which in turn can either combine to produce the selective oxygenated product (ROH) *via* rebound mechanism. The analysis of the UV-Vis spectra for longer time period shows periodic formation and disappearance of the $Fe^{V}(O)$, which supports this hypothesis (ESI†, Fig. S10). There is another possibility of the formation of $Fe^{V}(O)$ via **D** pathway, which can lead to the formation of $Fe^{IV}$-OR, which was detected by mass spectroscopy (ESI†, Fig. S11). Such monomeric Fe(IV) intermediates are dead ends and are incapable of catalyzing further oxidation reaction. The regioselectivity in adamantane oxidation and the stereoretention in *cis*-DMCH oxidation support the rebound mechanism to some extent. It is essential to mention that formation of these radicals may involve additional pathways, such as the reductive activation of $O_2$ with Fe-bTAML. In fact, reductive activation of $O_2$ with Fe-bTAML leading to the formation of $Fe^{V}(O)$, has been postulated in more hydrophobic solvents like $CH_2Cl_2$.[7]



**Scheme 3** Proposed autocatalytic radical chain mechanism for the oxygenation of alkanes in presecne of **1a/1b/1c** and dioxygen.

In conclusion, the selective catalytic oxidations of 3º C-H bonds for a series of substrates containing unactivated C-H bonds, including the natural product cedryl acetate by dioxygen using the iron complexes **1a** and **1c** have been achieved. The reaction required no usage of any stoichiometric co-reductant. With substrates having activated C-H bonds, TON's up to 250 was observed. Mechanistic studies indicate that the reaction proceeded *via* an autocatalytic radical chain mechanism. The selectivity observed for the hydrocarbon oxidation is uncharacteristic of typically free radical autooxidation of hydrocarbons. With Fe-bTAML complexes **1a** and **1c**, the formation of the $Fe^{V}(O)$ intermediate bring in the high regioselectivity and stereoretention for the oxidation reactions, which has not been observed to date with other iron-based complexes. However, reduction in selectivity in comparison to stoichiometric oxidations by $Fe^{V}(O)$ (25:1 compared to 70:1 for adamantane) indicates that additional free-radical autooxidation pathways are also operational.

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## Conflicts of interest

There are no conflicts to declare.

## Notes and references

1 (a) M. Costas, M. P. Mehn, M. P. Jensen and L. Que, *Chem. Rev.*, 2004, **104**, 939–986. (b) B. Meunier, S. P. de Visser and S. Shaik, *Chem. Rev.*, 2004, **104**, 3947–3980. (c) S. K. Lee, J. C. Nesheim and J. D. Lipscomb, *J. Biol. Chem.*, 1993, **268**, 21569–21577. (d) S. M. Resnick, K. Lee and D. T. Gibson, *J. Ind. Microbiol. Biotechnol.*, 1996, **17**, 438–457.

2 (a) J. E. Lyons, P. E. Ellis and H. K. Myers, *J. Catal.*, 1995, 155, 59–73. (b) M. W. Grinstaff, M. G. Hill, J. A. Labinger and H. B. Gray, *Science*, 1994, **264**, 1311–1314.

3 P. Comba, Y. M. Lee, W. Nam and A. Waleska, *Chem. Commun.*, 2014, **50**, 412–414.

4 (a) S. Hong, Y. M. Lee, W. Shin, S. Fukuzumi and W. Nam, *J. Am. Chem. Soc.*, 2009, **131**, 13910–13911. (b) Y. M. Lee, S. Hong, Y. Morimoto, W. Shin, S. Fukuzumi and W. Nam, *J. Am. Chem. Soc.*, 2010, **132**, 10668–10670. (c) S. Sahu and D. P. Goldberg, *J. Am. Chem. Soc.*, 2016, **138**, 11410–11428.

5 M. Sankaralingam, Y. M. Lee, W. Nam and S. Fukuzumi, *Inorg. Chem.*, 2017, **56**, 5096–5104.

6 (a) M. Ghosh, K. K. Singh, C. Panda, A. Weitz, M. P. Hendrich, T. J. Collins, B. B. Dhar and S. Sen Gupta, *J. Am. Chem. Soc.*, 2014, **136**, 9524–9527. (b) S. Jana, M. Ghosh, M. Ambule and S. Sen Gupta, *Org. Lett.*, 2017, **19**, 746–749. (c) B. Chandra, K. K. Singh and S. Sen Gupta, *Chem. Sci.*, 2017, **8**, 7545–7551. (d) C. Panda, J. Debgupta, D. Díaz Díaz, K. K. Singh, S. Sen Gupta and B. B. Dhar, *J. Am. Chem. Soc.*, 2014, **136**, 12273–12282. (e) S. Pattanayak, A. J. Jasniewski, A. Rana, A. Draksharapu, K. K. Singh, A. Weitz, M. Hendrich, L. Que, A. Dey and S. Sen Gupta, *Inorg. Chem.*, 2017, **56**, 6352–6361.

7 K. K. Singh and S. Sen Gupta, *Chem. Commun.*, 2017, **53**, 5914–5917.

8 Y.-R. Luo, *Handbook of Bond Dissociation Energies in Organic Compounds, CRC Press*, 2004, vol. 126.

9 (a) D. H. R. Barton, A. H. Beck and D. K. Taylor, *Tetrahedron*, 1995, **51**, 5245–5254. (b) M. Costas, K. Chen and L. Que, *Coord. Chem. Rev.*, 2000, **200–202**, 517–544.

10 M. Ghosh, Y. L. K. Nikhil, B. B. Dhar and S. Sen Gupta, *Inorg. Chem.*, 2015, **54**, 11792–11798.

11 A. J. Bissette and S. P. Fletcher, *Angew. Chemie - Int. Ed.*, 2013, **52**, 12800–12826.

12 A. Shamsabadi and V. Chudasama, *Org. Biomol. Chem.*, 2019, **17**, 2865–2872.