



Cite this: *Chem. Commun.*, 2015, 51, 14992

Received 30th July 2015,
Accepted 10th August 2015

DOI: 10.1039/c5cc06402c

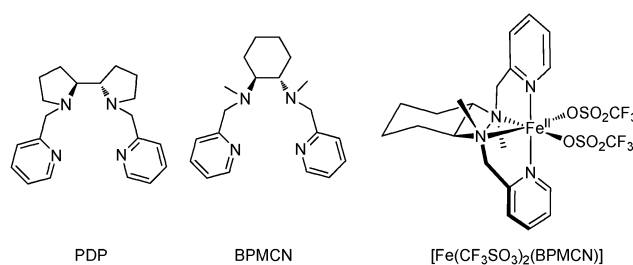
www.rsc.org/chemcomm

H₂ oxidation versus organic substrate oxidation in non-heme iron mediated reactions with H₂O₂[†]

Azin Hassanpour,^a Ferran Acuña-Parés,^b Josep M. Luis,^b Olaf Cusso,^b Silvia Morales de la Rosa,^c José Miguel Campos-Martin,^c Jose L. G. Fierro,^c Miquel Costas,^{*b} Julio Lloret-Fillol^{‡*b} and Rubén Mas-Ballesté^{*a}

Herein we show that species generated upon reaction of α -[Fe(CF₃SO₃)₂(BPMCN)] (BPMCN = *N,N'*-bis(2-pyridylmethyl)-*trans*-1,2-diaminocyclohexane) with H₂O₂ (putatively [Fe^V(O)(OH)(BPMCN)]) is able to efficiently oxidize H₂ to H₂O even in the presence of organic substrates, while species formed in the presence of acetic acid (putatively [Fe^V(O)(OAc)(BPMCN)]) prefer organic substrate oxidation over H₂ activation. Mechanistic implications have been analysed with the aid of computational methods.

Selected iron coordination complexes containing tetradentate aminopyridine ligands have been described over the last decade as biologically inspired oxidation catalysts.^{1–3} These complexes catalyse challenging oxidation reactions including stereospecific hydroxylation of alkanes, *cis*-dihydroxylation of olefins, and oxidation of the water molecule. Desaturation of alkanes has also been described. Mechanistic studies have highlighted the ability of these complexes to form putative high valent and highly electrophilic [(L)Fe^V(O)(OH)]²⁺ species upon reaction with oxidants such as H₂O₂^{4,5} or cerium ammonium nitrate (CAN).⁶ Instead, in the presence of acetic acid, putative [(L)Fe^V(O)(AcO)]²⁺,⁷ (or recently better described as [(L)Fe^{IV}(O)(AcO[•])]²⁺ where L = 1,1'-bis(2-pyridylmethyl)-2,2'-bipyrrolidine = PDP, Scheme 1) species⁸ is formed. The reactivity of [(L)Fe^V(O)(OH)]²⁺ against olefins bears strong resemblance to that of OsO₄.^{9,10} The mechanism proposed takes place through a non-concerted 3+2 reaction between the Fe^V(O)(OH) unit and the olefin to yield the *syn*-diol.^{5,11,12}



Scheme 1 Schematic diagram of tetradentate ligands and the iron complex used in this work.

Likewise, OsO₄ assisted by N-based ligands also reacts with H₂ through a similar 3+2 transition state to yield Os^{VI}O₂(OH)₂ species, breaking the H–H bond.¹³ Other Mn,¹⁴ Ru¹⁴ and Re¹⁵ oxo species activate H₂ through an analogous concerted mechanism. This reaction is remarkable due to the strong and non-polar nature of the H–H bond, and also because no metal–hydrogen interaction occurs during the H–H cleavage. This is in contrast to the most common pathways for H₂ activation, consisting of the oxidative addition of this molecule to a metal (yielding a metal–dihydride complex) or 2+2 heterolysis (generating a metal–hydride fragment and protonation of a nucleophilic site).¹⁶ Thus, 3+2 H₂ oxidation is a much less studied alternative pathway for H–H cleavage. Such a mechanism may be relevant to C–H activation processes,¹⁴ representing a concerted alternative to the stepwise rebound mechanism commonly proposed for alkane hydroxylation.¹⁷ Building on the expected resemblance between the reactivity of the high valent metal–oxide species of group VIII, we hypothesized that [(L)Fe^V(O)(OH)]²⁺, the intermediate responsible for C–H hydroxylation, *cis*-dihydroxylation and water oxidation reactions, may react with the H₂ molecule in a similar manner to OsO₄, while [(L)Fe^V(O)(AcO)]²⁺ (or [(L)Fe^{IV}(O)(AcO[•])]²⁺) would not.

Since non-heme Fe^V(O)(X) species are very elusive we have investigated our hypothesis by analysing reactivity differences in well-known model reactions such as C–H hydroxylation, epoxidation and oxidation of sulfides. The non-heme iron complex [Fe(CF₃SO₃)₂(BPMCN)]¹⁸ (1 mM) was chosen as catalyst and

^a Departamento de Química Inorgánica, Universidad Autónoma de Madrid, 28049 Madrid, Spain. E-mail: ruben.mas@uam.es

^b Departament de Química and Institute of Computational Chemistry and Catalysis (IQCC), Universitat de Girona, Campus Montilivi, 17071 Girona, Catalonia, Spain. E-mail: miquel.costas@udg.edu, julio.lloret@udg.edu; Fax: +34 972-41-81-50

^c Instituto de Catálisis y Petroquímica, CSIC, Marie Curie, 2, Cantoblanco, 28049 Madrid, Spain

[†] Electronic supplementary information (ESI) available: Experimental procedures and computational details. See DOI: 10.1039/c5cc06402c

[‡] Current address: Institute of Chemical Research of Catalonia (ICIQ), Av. Països Catalans 16, 43007 Tarragona, Spain. E-mail: jlloret@icq.es

Table 1 Yields (%) of organic substrate oxidations using H₂O₂ as the oxidant and α -[Fe(CF₃SO₃)₂(BPMCN)] in CH₃CN in the presence (1.5 M) and in the absence of acetic acid in solution

Oxidant		H ₂ O ₂		H ₂ O ₂ + AcOH	
		Ar	H ₂	Ar	H ₂
Atmosphere					
Reagent	Product ^a				
c-Hexane	c-Hexanol ^{b,c} (%)	58	27	55	48
	Standard deviation	(3)	(2)	(1)	(3)
c-Octene	Epoxide ^{b,d} (%)	89	54	89	98
	Standard deviation	(3)	(1)	(5)	(2)
Thioanisole	Sulfoxide ^{b,e,f} (%)	33	22	98	102
	Standard deviation	(2)	(4)	(1)	(1)

^a Experimental conditions: 1 mM [Fe(CF₃SO₃)₂(BPMCN)]; 10 mM H₂O₂ delivered by syringe pump during 30 min at room temperature (25 °C), organic substrate (1 M). Experiments were carried out in an argon atmosphere using regular shlenck techniques or under H₂ atmosphere with an additional constant flow of H₂ (200 cm³ min⁻¹) during the reaction after 3 previous degassing cycles. Values shown are the average of triplicate experiments. ^b Product yields calculated with respect to the oxidant. ^c Trace amounts of cyclohexanone (<5%) were also observed. ^d Trace amounts of *cis*-diol (<5%) were also observed. ^e Trace amounts of sulfone (<5%) were also observed. ^f Overestimation of yield of sulfoxide is within the cumulative experimental error that can be originated from imprecision on H₂O₂ concentration, calibration factors or integration of analytical signals. Otherwise, partial oxidation during the workup cannot be completely discarded.

H₂O₂ (10 eq. delivered *via* a syringe pump for 30 minutes) as an oxidant. Yields of oxidized compounds were compared, in the presence and absence of H₂ as a competitive substrate and the effect of adding AcOH (1.5 M) was studied. The experiments were carried out at 1 atm of H₂ under continuous hydrogen flow to the solution containing the iron catalyst and the organic substrate. The results of these experiments are collected in Table 1.

Inspection of Table 1 reveals that in the absence of acetic acid, the presence of H₂ has an effect on reaction yields. Thus, the yield of oxidized products in cyclohexane and cyclooctene oxidation is reduced by 60% and 40%, respectively. However thioanisole oxidation decreases in a more modest manner (33% vs. 22%). These differences are consistent with a competitive inhibition scenario in which the extent of inhibition is more substantial for the less reactive substrate (cyclohexane). In contrast, sulfide oxidation is modestly affected by the presence of H₂, in accordance with its ease of oxidation reactivity. The effect of H₂ in the oxidation of cyclooctene falls just in the middle of such tendencies. It is worth noting that sulfide oxidation is the easiest process but the yields are quite low in the absence of acetic acid, due to the tendency of the sulfoxide product to coordinate with the iron center, thus, generally deactivating the catalyst (see the ESI†).

The effect of H₂ was further confirmed in a series of experiments under different H₂ pressures. Solutions of H₂O₂ were injected into a reactor containing an acetonitrile solution of the catalyst and the substrate (cyclohexane), under different H₂ pressures. Production of cyclohexanol decreased as the H₂ pressure increased (Fig. 1). In fact, at 10 atm of H₂, absolutely no cyclohexanol was produced. To evaluate the possible effect of just pressure, oxidation of cyclohexane was performed under an atmosphere of 10 atm of argon (see the ESI†). Gas chromatography

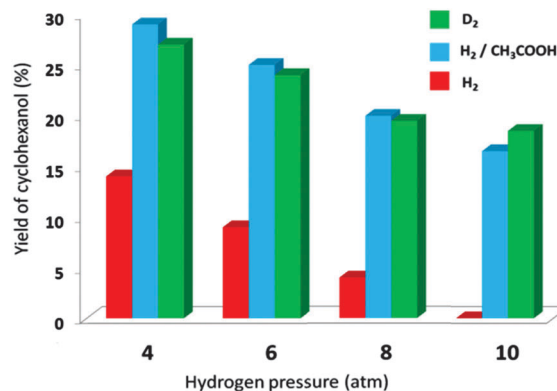


Fig. 1 Yields (%) of cyclohexane oxidation using H₂O₂ as an oxidant and α -[Fe(CF₃SO₃)₂(BPMCN)] in CH₃CN in the presence and in the absence of acetic acid in solution. Experiments were carried at controlled high H₂ pressures (different from experiments shown in Table 1). Results of experiments in the absence of acetic acid at controlled pressures of deuterium gas are also shown. Results shown are the average of duplicate experiments. GC-MS analysis of the cyclohexanol product indicates that deuterium atoms are not incorporated in any case in the alcohol molecule.

analysis of cyclohexanol produced indicates that such pressure of inert gas reduces the alcohol yield by 40%. Thus, although pressure of inert gas has a detrimental effect on catalytic outcome, decreasing the yield of cyclohexanol in the presence of H₂ is far beyond a simple pressure effect. Such dependence of reaction yield on H₂ pressure supports the role of hydrogen as a competitive substrate.

Further evidence in favour of the reaction with H₂ was gained by isotopic labelling analysis of the water product formed from H₂ oxidation by the active high-valent iron species Fe^V(O)(OH). In order to facilitate the distinctive detection of water formed from H₂ oxidation, experiments were conducted using D₂ instead of H₂, so that deuterated water generated by D₂ oxidation can be analyzed by ²D-NMR. Therefore, injection of 10 eq. of H₂O₂ was carried out in a reactor pressurized at 10 atm with D₂ gas containing 3 mL of a 1 mM solution of [Fe(CF₃SO₃)₂(BPMCN)] in CH₃CN. The integration of the signal of HDO was referenced to the natural abundance of the deuterium signal from CH₃CN solvent (experimentally determined to be 9.3 mM). Calibration was made by adding known amounts of D₂O to a standard reaction medium in CH₃CN. A control experiment was also carried out under the same experimental conditions in the absence of the Fe complex. ²D-NMR spectra from the experiment and from the control are shown in Fig. 2. After subtracting the amount of deuterium found in the control (mainly coming from impurities in D₂ gas) we could estimate that *ca.* 0.8 eq. of D₂ (relative to Fe) were converted to HDO by reaction with H₂O₂ in the presence of [Fe(CF₃SO₃)₂(BPMCN)].

Considering that the more active species for H₂ oxidation ([Fe^V(O)(OH)(BPMCN)]²⁺) is generated through a water-assisted mechanism raises the question that whether the addition of extra amount of water would enhance such reactivity. To address this question, we carried out experiments of oxidation of cyclooctene in solutions containing 10% water. Product analysis indicates that the presence of such an excess of water

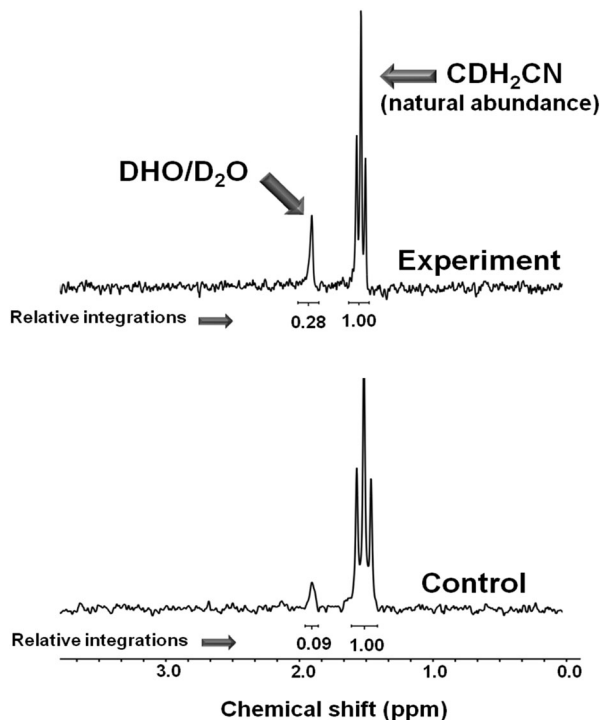


Fig. 2 ^2D -NMR analysis of the reaction mixture resulting from a 1 mM $[\text{Fe}(\text{CF}_3\text{SO}_3)_2(\text{BPMCNCN})]$ solution in CH_3CN pressured to 10 atm of D_2 where 10 mM H_2O_2 was delivered by syringe pump during 30 min. Control experiment without the iron compound is also shown.

results in the significant deactivation of catalytic oxidation (32% yield of epoxide). The presence of H_2 (1 atm) just slightly decreases the epoxide yield (26%). Such a detrimental effect on catalytic activities resulting from high water excesses is possibly due to the role of the water molecule as a competitive ligand that makes more difficult coordination and further activation of hydroperoxide. However, the amount of water originally added together with H_2O_2 (in a concentrated hydrogen peroxide solution (33%), every molecule of H_2O_2 is accompanied by 4 molecules of water approximately) is enough to trigger water assisted pathways,¹⁹ without the negative effect of higher excesses.

Thus, it can be inferred that, once the high-valent iron species is generated, D_2 oxidation can occur. Considering that D–D activation is subjected to a considerable kinetic isotope effect (K.I.E.), this would disfavor D_2 activation, and self-decay pathways would become competitive processes. Consequently, the amount of water generated by D_2 oxidation would be significantly reduced compared to the values expected when H_2 is used (Table 1). Occurrence of K.I.E. was confirmed by performing experiments in the presence of cyclohexane as the organic substrate at different D_2 pressures (Fig. 1). The results observed indicate that D_2 is a rather sluggish substrate compared to H_2 . However, even under these conditions, formation of HDO was confirmed in the presence of cyclohexane at 10 atm of D_2 (0.8 eq.) and at 8 atm of D_2 (0.4 eq.). Overall, albeit modest, the yield of HDO detected represents a significant evidence for H_2 oxidation.

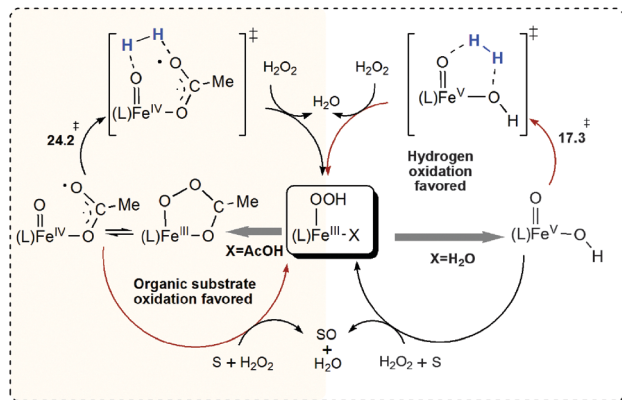
In sharp contrast, the presence of 1 atm H_2 did not affect the catalytic oxidation activity when acetic acid was added to

the reaction medium (Table 1). In fact, as reported before,⁷ acetic acid increased the yields of oxidized products, which is especially significant for sulfide oxidation. The current experiments however show that the oxidant generated in the presence of acetic acid is less prone to react with H_2 despite being very active in the oxidation of different organic substrates. Catalytic cyclohexane oxidation under standard reaction conditions in the presence of acetic acid at different H_2 pressures revealed that generation of cyclohexanol was not completely inhibited even at 10 atm (Fig. 1). Thus, although H_2 oxidation is also possible in the presence of acetic acid, it is clearly less favored than that without acetic acid.

Previous mechanistic studies have shown that in the presence of acetic acid, high valent iron species $\text{Fe}^{\text{V}}(\text{O})(\text{OAc})$ form and they are responsible for C–H hydroxylation and olefin epoxidation.⁷ In light of these precedents, these species appear to be less reactive than $\text{Fe}^{\text{V}}(\text{O})(\text{OH})$ towards H_2 . This result parallels the different reactivity of $\text{Fe}^{\text{V}}(\text{O})(\text{OH})$ and $[\text{Fe}^{\text{V}}(\text{O})(\text{OAc})]$ towards olefins to form *syn*-diols.

The mechanistic implications of H_2 activation by the high valent iron species $[\text{Fe}^{\text{V}}(\text{O})(\text{X})(\text{BPMCNCN})]$ ($\text{X} = \text{OH}^-$ or AcO^-) generated by reaction of the $\text{Fe}(\text{II})$ precursor with excess H_2O_2 in the presence or in the absence of acetic acid have been analyzed by DFT calculations at the B3LYP/6-31G** level, introducing the acetonitrile solvation and dispersion effects in geometry optimizations. Refined values for the final energies were obtained with the cc-pVTZ basis set for all atoms (see the ESI,[†] for full computational details). For $[\text{Fe}^{\text{V}}(\text{O})(\text{OH})(\text{BPMCNCN})]^{2+}$, two possibilities have been examined: (a) the 2+3 homolytic H–H activation and (b) the base assisted heterolytic cleavage in which a CH_3CN molecule acts as an external base. Results obtained indicate that the pathway (a) is the most favorable ($\Delta G^\ddagger = 17.3 \text{ kcal mol}^{-1}$ vs. $\Delta G^{\ddagger\ddagger} = 21.0 \text{ kcal mol}^{-1}$). In good agreement with experimental observations, $[\text{Fe}^{\text{IV}}(\text{O})(\text{AcO}^*)(\text{BPMCNCN})]^{2+}$ oxidizes H_2 via a 2+4 mechanism with a substantially higher energy barrier ($\Delta G^{\ddagger\ddagger} = 24.2 \text{ kcal mol}^{-1}$) than in the case of $[\text{Fe}^{\text{V}}(\text{O})(\text{OH})(\text{BPMCNCN})]^{2+}$ (Fig. S1–S3, ESI[†]). Heterolytic H–H oxidation is expected to be higher in energy than for the $[\text{Fe}^{\text{V}}(\text{O})(\text{OH})(\text{BPMCNCN})]^{2+}$ case since the charge is delocalized in the acetate ligand, leading to a less electrophilic oxo group. Thus, theoretical analysis presents a scenario where intermediates $[\text{Fe}^{\text{V}}(\text{O})(\text{OH})(\text{BPMCNCN})]^{2+}$ and $[\text{Fe}^{\text{IV}}(\text{O})(\text{AcO}^*)(\text{BPMCNCN})]^{2+}$ are active for both the organic substrate oxidation reactions and H–H activation. However, $[\text{Fe}^{\text{V}}(\text{O})(\text{OH})(\text{BPMCNCN})]^{2+}$ active species can engage in a reaction pathway for H_2 oxidation energetically more favorable than the mechanism found for $[\text{Fe}^{\text{IV}}(\text{O})(\text{AcO}^*)(\text{BPMCNCN})]^{2+}$ (Scheme 2). Overall, theoretical modelling offers a rationale for the observed experimental reactivity trend where a distinct balance between H_2 activation and organic substrate oxidation is observed depending on the presence or absence of acetic acid in the reaction media.

Overall, experimental and theoretical data presented in this communication add a new perspective to the mechanistic landscape offered by non-heme iron mediated catalytic oxidation (Scheme 1). High valent species generated by reaction of $[\text{Fe}(\text{CF}_3\text{SO}_3)_2(\text{BPMCNCN})]$ with H_2O_2 in the presence ($[\text{Fe}^{\text{IV}}(\text{O})(\text{AcO}^*)(\text{BPMCNCN})]^{2+}$) or the absence ($[\text{Fe}^{\text{V}}(\text{O})(\text{OH})(\text{BPMCNCN})]^{2+}$) of acetic



Scheme 2 Mechanistic scenario proposed from theoretical calculations relative to the reactivity observed for the balance between H_2 activation and organic substrate oxidation by the mixture of α - $[\text{Fe}(\text{CF}_3\text{SO}_3)_2(\text{BPMCn})]$ and H_2O_2 in CH_3CN in the presence and in the absence of acetic acid.

acid show different reactivity against the H_2 molecule. It has been previously shown that both species are active in oxidation catalysis against substrates such as alkanes, olefins or organic sulfides. Catalysis results are generally improved by adding acetic acid, suggesting that the species generated under these conditions has an enhanced oxidative character and is more versatile.⁷ However, the results shown herein suggest that this is not always the case. In fact, while active species generated in the presence of acetic acid scarcely activate hydrogen, the active intermediate generated in the absence of acetic acid is able to effectively oxidize hydrogen to water. On the basis of this difference, for the species $[\text{Fe}^{\text{V}}(\text{O})(\text{OH})(\text{BPMCn})]^{2+}$ both the oxo and hydroxo sites can cooperatively participate in the hydrogen activation process. In contrast, in the intermediate $([\text{Fe}^{\text{IV}}(\text{O})(\text{AcO}^\bullet)(\text{BPMCn})]^{2+})$ the acetate group is less basic and poorly assists H_2 oxidation.

This work was supported by Spanish Ministerio de Economía y Competitividad (CTQ2012-37420-C02-02 and 01) European Research Council (StG 239910), and Generalitat de Catalunya (2014 SGR 862 and ICREA Academia award to MC). J.L.F. thanks the CELLEX foundation for the starting career program for financial support.

Notes and references

- (a) L. Que, Jr. and W. B. Tolman, *Nature*, 2008, **455**, 8; (b) K. P. Bryliakov and E. P. Talsi, *Coord. Chem. Rev.*, 2014, **276**, 73–96; (c) Z. Codola, J. Lloret-Fillol and M. Costas, *Prog. in Inorg. Chem.*, John Wiley & Sons, Inc., 2014, vol. 59, pp. 447–532.
- (a) J. England, C. R. Davies, M. Banaru, A. J. P. White and G. J. P. Britovsek, *Adv. Synth. Catal.*, 2008, **350**, 883–897; (b) G. J. P. Britovsek, J. England and A. J. P. White, *Inorg. Chem.*, 2005, **44**, 8125–8134; (c) Y. He, J. D. Gordon and C. R. Goldsmith, *Inorg. Chem.*, 2011, **50**, 12651–12660; (d) M. C. White, *Science*, 2012, **335**, 807–809; (e) J. Yoon, S. A. Wilson, Y. K. Jang, M. S. Seo, K. Nehru, B. Hedman, K. O. Hodgson, E. Bill, E. I. Solomon and W. Nam, *Angew. Chem., Int. Ed.*, 2009, **48**, 1257–1260; (f) T. W.-S. Chow, E. L.-M. Wong, Z. Guo, Y. Liu, J.-S. Huang and C.-M. Che, *J. Am. Chem. Soc.*, 2010, **132**, 13229–13239.
- (a) J. M. A. Bigi, S. A. Reed and M. C. White, *Nat. Chem.*, 2011, **3**, 216–222; (b) For an interesting O_2 activation system that performs C–H oxidation with H_2 extrusion see A. Gonzalez-de-Castro, C. M. Robertson and J. Xiao, *J. Am. Chem. Soc.*, 2014, **136**, 8350–8360.
- K. Chen and L. Que, Jr., *J. Am. Chem. Soc.*, 2001, **123**, 6327–6337.
- I. Prat, J. S. Mathieson, M. Güell, X. Ribas, J. M. Luis, L. Cronin and M. Costas, *Nat. Chem.*, 2011, **3**, 788–793.
- I. Garcia-Bosch, Z. Codola, I. Prat, X. Ribas, J. Lloret-Fillol and M. Costas, *Chem. – Eur. J.*, 2012, **18**, 13269–13273.
- R. Mas-Balleste and L. Que, Jr., *J. Am. Chem. Soc.*, 2007, **129**, 15964–15972.
- Y. Wang, D. Janardanan, D. Usharani, K. Han, L. Que, Jr. and S. Shaik, *ACS Catal.*, 2013, **3**, 1334–1341.
- H. C. Kolb, M. S. VanNieuwenhze and K. B. Sharpless, *Chem. Rev.*, 1994, **94**, 2483–2547.
- B. Plietker and M. Niggemann, *Org. Biomol. Chem.*, 2004, **2**, 2403–2407.
- A. Bassan, M. R. A. Blomberg, P. E. M. Siegbahn and L. Que, Jr., *Angew. Chem., Int. Ed.*, 2005, **44**, 2939–2941.
- K. Chen, M. Costas, J. Kim, A. K. Tipton and L. Que, Jr., *J. Am. Chem. Soc.*, 2002, **124**, 3026–3035.
- A. Dehestani, W. H. Lam, D. A. Hrovat, E. R. Davidson, W. T. Borden and J. M. Mayer, *J. Am. Chem. Soc.*, 2005, **127**, 3423–3432.
- J. P. Collman, L. M. Slaughter, T. A. Eberspacher, T. Strassner and J. I. Brauman, *Inorg. Chem.*, 2001, **40**, 6272–6280.
- S. Bi, J. Wang, L. Liu, P. Li and Z. Lin, *Organometallics*, 2012, **31**, 6139–6147.
- Recent Advances in Hydride Chemistry*, ed. M. Peruzzini and R. Poli, Elsevier, Amsterdam, 2001.
- (a) S. P. De Visser, *Coord. Chem. Rev.*, 2009, **253**, 754–768; (b) P. R. Ortiz de Montellano, *Chem. Rev.*, 2010, **110**, 932–948.
- M. Costas and L. Que, Jr., *Angew. Chem., Int. Ed.*, 2002, **12**, 2179–2181.
- (a) D. Quinonero, K. Morokuma, D. G. Musaev, R. Mas-Balleste and L. Que, Jr., *J. Am. Chem. Soc.*, 2005, **127**, 6548–6549; (b) W. N. Oloo, A. J. Fielding and L. Que, Jr., *J. Am. Chem. Soc.*, 2013, **135**, 6438–6441.