

Abstract:**C-H bond halogenation reaction mediated by heterodinuclear Fe M (M= Cu, Ag, Au) complexes****Co-supervisor 1: Prof. Dr. Kallol Ray, HU Berlin****Co-supervisor 2: Prof. Dr. Sebastian Hasenstab-Riedel, FU Berlin**

Carbon–halogen (C–X) bonds are amongst the most fundamental groups in organic synthesis, they are frequently and widely employed in the synthesis of numerous organic products. As a result, methods that allow the selective and efficient formation of the carbon-halogen bond are highly desirable. An evolving approach is the utilization of transition-metals to catalyze the C-X bond forming reactions. This proposal describes possible ways to undergo C-X bond formation reactions by using heterodinuclear Fe M (M=Cu, Ag, Au) complexes. While high-valent iron(IV)oxo centers will be utilized for the generation of alkyl radicals via C-H bond activation reactions, M-X groups will act as the source of atomic halogen (X[•]) atoms to the alkyl radicals.

Extended description version of the project:

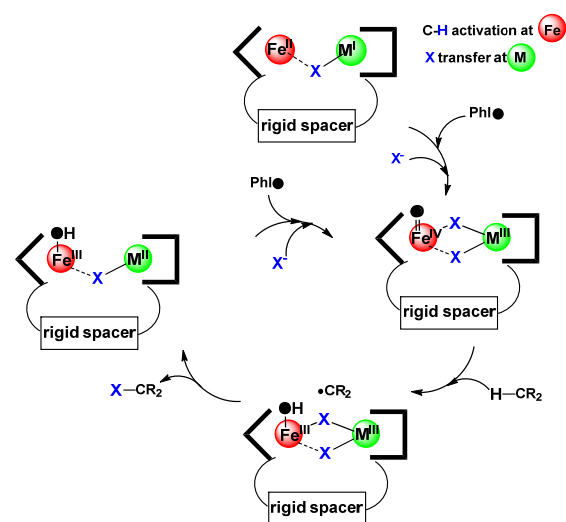
C-H bond halogenation reaction mediated by heterodinuclear Fe M (M= Cu, Ag, Au) complexes

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1. Overall goal of the project

Co-operative effect of an iron center with that of copper, silver and gold halide complexes will be investigated in the catalytic and stoichiometric halogenation of C-H bonds (scheme 1). The iron center will activate dioxygen, nitrous oxide, hydrogen peroxide, or iodosobenzene (PhIO) to generate high-valent iron(IV)oxo cores that are known to perform efficient hydrogen atom transfer (HAT) reactions from C-H bonds to generate carbon based radicals. Cu-, Ag- or Au-X (X=F, Cl, Br) motifs will be employed as suitable source of atomic halogen that would be necessary for the C-X bond formation reactions. The distance between the Fe and M (M=Cu, Ag or Au) sites will be varied (see also



Scheme 1. Catalytic halogenation of C-H bonds at heterodinuclear Fe M (M=Cu, Ag, Au) centers

Fig 1b) to investigate how the Fe M distance controls the rate of formation of the carbon based radical and its subsequent reaction with the M-X unit to form the C-X bond. In this project different ligand systems will be designed with two metal-binding sites: one binding iron(II) center in presence of amine-N or pyridine-N donors and the second binding site based on N-heterocyclic carbene (NHC) ligands that are known to stabilize (NHC)M-X complexes.

2. State of the art

Non-heme iron halogenases are an important subset of the family of α KG-dependent non-heme iron enzymes that utilize O_2 to halogenate substrate C-H bonds in the biosynthesis of some natural products. The active oxidant derived therefrom is proposed to be an $S = 2$ oxoiron(IV)-halide species that abstracts a hydrogen atom to form a hydroxoiron(III)-halide species and a substrate radical (Krebs, C.; Fujimori, D. G.; Walsh, C. T.; Bollinger, J. M., Jr. *Acc. Chem. Res.* **2007**, *40*, 484). In the next step, the incipient radical can undergo rebound with either the hydroxo or halo ligand to afford respective R-OH or R-Cl products. In an elegant study, Matthews et al. (Matthews, M. L.; Neumann, C. S.; Miles, L. A.; Grove, T. L.; Booker, S. J.; Krebs, C.; Walsh, C. T.; Bollinger, J. M., Jr. *Proc. Natl. Acad. Sci. U. S. A.* **2009**, *106*, 17723) showed that substrate positioning controls the chemoselectivity of halogenation over hydroxylation in SyrB2, which was corroborated by HYSCORE studies of SyrB2-substrate-NO complexes. There has been some effort to obtain synthetic models for the oxoiron(IV)-halide intermediates of the halogenases by employing non-heme ligand systems containing pyridine and amine-N based donors. While these complexes serve as suitable spectroscopic models, most oxoiron(IV)-halide complexes have been demonstrated to

perform C-H hydroxylation reactions in contrast to halogenation reactions (Guo, M.; Corona, T.; Ray, K.; Nam, W. *ACS Cent. Sci.* **2019**, *5*, 13) in the enzymatic systems.

A number of NHC based copper, silver, gold complexes have been synthesized over the years (Danopoulos, A. A.; Simler, T.; Braunstein, P. *Chem. Rev.* **2019**, *119*, 3730), and some of them act as good halogen transfer agents. In the present project cooperative effect between high-valent iron(IV)oxo and (NHC)M^I-X or (NHC)M^{III}X₂ cores in the stoichiometric and catalytic C-X bond formation reactions will be targeted.

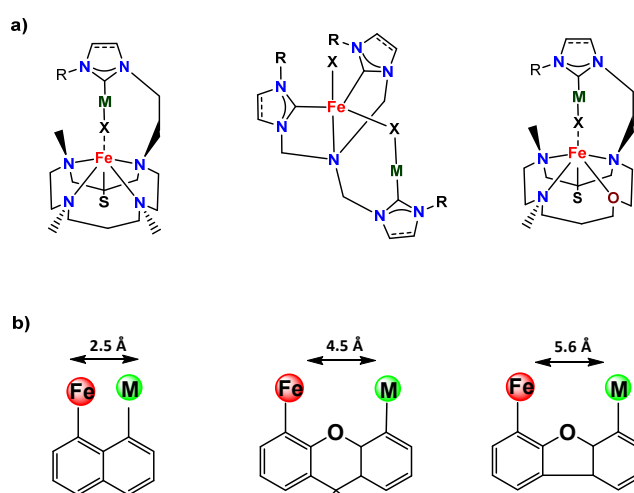


Figure 1: Proposed ligands and complexes

3. Specific aims and how they may be reached

The proposed project can be divided into the following work packages (**WPs**):

In **WP1** synthesis of the ligands and the complexes will be carried out. N4- (Engelmann, X., Malik, D.D., Corona, T., Warm, K., Farquhar, E.R., Swart, M., Nam, W., Ray, K. *Angew. Chem. Int. Ed. Engl.* **2019**, *58*, 4012) or N3O- (Monte Pérez, I.; Engelmann, X.; Lee, Y.-M.; Yoo, M.; Kumaran, E.; Farquhar, E. R.; Bill, E.; England, J.; Nam, W.; Swart, M.; Ray, K. *Angew. Chem., Int. Ed.* **2017**, *56*, 14384) based cyclam ligands act as suitable platforms for the stabilization of high-valent iron(IV)oxo cores. We will now modify these ligands to incorporate a NHC moiety that can bind the M-X motif required for the halogenation reactions (Fig 1a). A tripodal tricarbene ligand will also be tried as a plausible platform for the stabilization of the heterodinuclear Fe-X-M motif. In addition, efforts will be made to systematically vary the distance between iron and M centers (Fig 1b), by changing the rigid spacer in which the iron and M binding motifs will be incorporated.

In **WP2** efforts will be made to access the iron(IV)oxo complexes supported on our proposed ligand frameworks by reacting the starting iron(II) M(I) complexes with suitable oxo transfer reagents (e.g., nitrous oxide, dioxygen, iodosylbenzenes, amine oxides, etc.) at temperatures ranging from +25 °C to -90 °C. The generated intermediates are expected to be metastable and hence will be trapped at low temperatures and characterized by different spectroscopic methods at cryogenic temperatures (Cryo-electrospray mass spectrometry, UV/Vis, High-field Mössbauer, EPR, Resonance Raman, and XAS spectroscopy). Potential avenues for reactivity of these complexes to be pursued are catalytic and stoichiometric C-H bond activation reactions and C-Cl or C-Br formation reactions

WP3 will concentrate on C-F bond formation reactions. The main target will be to explore the potential of our ligand systems to stabilize AuF₃ (Ellwanger, M. A.; Steinhauer, S.; Goltz, P.; Braun, T.; Riedel, S. *Angew. Chem. Int. Ed.* **2018**, *57*, 7210) or Au(CF₃)₂F (Riedel, S. Unpublished Data) and use them as efficient F-transfer reagents. We will try to synthesize the (O)Fe(IV)-F-AuF₂-NHC, or (O)Fe(IV)-F-Au(CF₃)₂-NHC cores where the secondary interaction of the Fe(IV) center may provide additional stability to the AuF₃ or Au(CF₃)₂F moieties.

Facilities: The Ray group is equipped with rapid freeze quench UV/Vis, Mössbauer, X-ray absorption and EPR studies. The Riedel group performs matrix-isolation under cryogenic conditions in combination with IR, UV/VIS, Raman, and EPR spectroscopy for trapping of metal-halogen species.