How do microbes live on the pollutant carbon monoxide? How do microbes split the triple bond of nitrogen gas? When it comes to performing difficult chemistry, microbes often combine a protein scaffold with a highly reactive metallocofactor, employing a hired gun, if you will. Some of these metallocofactors are relatively simple – a single iron atom bound to an enzyme, whereas others are complex, and are best described as multi-metal assemblies or as “great metallocofactors.” In this presentation, audience members will hear about one “great” cluster: the nickel-iron-sulfur cluster of the enzyme carbon monoxide dehydrogenase (CODH), and one “less great” cluster: a mononuclear iron atom coordinated by the enzyme methylphosphonate synthase (MPnS). Whereas the “great” metallocofactor of CODH (aka the C-cluster) enables microbes to live on carbon monoxide, the “less great” mononuclear iron cofactor should not be undersold. Iron-dependent MPnS biosynthesizes methylphosphonate, the compound that is thought to be the source of methane from the upper aerobic ocean. We will consider how “great metallocofactors” are made and how they work. We will also consider how enzymes tune the reactivity of a single iron ion to afford novel reactivity.