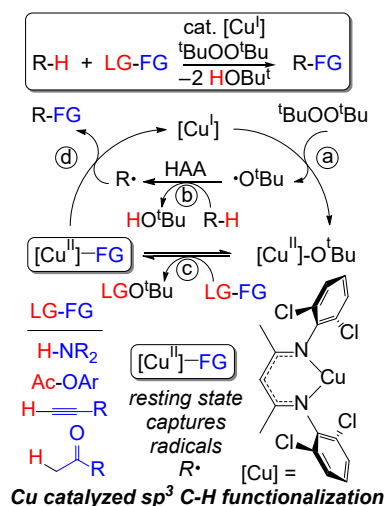


We develop environmentally friendly new methods for organic synthesis through ubiquitous C-H bonds, explore the interconversion of nitrogen and ammonia as carbon-free fuels, and decode ways that biology communicates using nitric oxide as a molecular messenger. Our laboratory studies how chemical reactions work that are catalyzed by metal ions such as iron, copper, and zinc to better enable new insights into the development of useful catalysts for synthesis and energy applications as well as to lay the groundwork for therapeutic interventions connected with nitric oxide misregulation.

Guided and enabled by synthetic inorganic chemistry, we seek to understand key intermediates that control C-H functionalization, ammonia/nitrogen interconversion, and bioinorganic nitric oxide processing. We employ a diverse range of synthesis and characterization techniques to reveal insights into chemical structure and reactivity. Beyond more traditional inorganic and organic synthesis techniques, students regularly perform X-ray crystallography, EPR spectroscopy, low temperature UV-vis spectroscopy, and DFT calculations. We also collaborate extensively with scientists from other institutions to study new molecules we make by resonance Raman spectroscopy as well as X-ray absorption and emission spectroscopy.

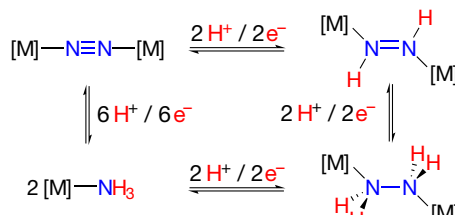
### C-H Functionalization

Through mechanistic understanding of reactive copper intermediates, we develop new reactions to directly convert  $sp^3$  C-H to C-C, C-N, C-O, and C-S bonds. These methods offer unique synthetic opportunities for the late stage functionalization of organic molecules. A key aspect of our approach involves the rational design of low coordinate copper(II) complexes [Cu(II)]-FG such as amides, phenoxides, aryls, and acetylides that efficiently capture carbon based radicals  $R^\bullet$  to provide functionalized products R-FG.



### Ammonia - A Carbon-Free Fuel

Ammonia is a carbon-free fuel produced on a scale of over 150 M tons / year. We examine the fundamental chemistry of N-H and N-N bond cleavage and formation to enable the development molecular electrocatalysts based on iron and copper to cleanly generate energy from  $NH_3$  and ultimately, to sustainably produce  $NH_3$  from  $N_2$ . Using specially designed molecular scaffolds, we examine H-bonding to metal bound diazene ( $N_2H_2$ ) ligands in metal complexes  $[M]-N_2H_2-[M]$  to uncover low barrier pathways for N-H bond formation and cleavage. Mechanistically considering pathways for N-H cleavage and N-N bond formation, we have also developed families of iron and copper based molecular electrocatalysts for ammonia oxidation.



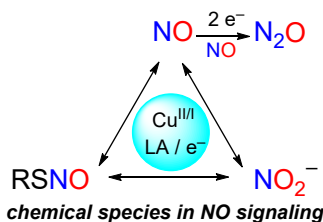
interconversion of  $N_2$  and  $NH_3$  via  $2H^+/2e^-$  steps



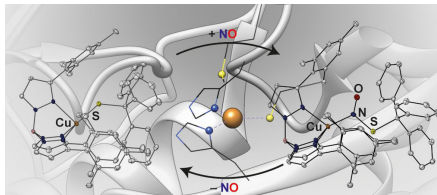
electrochemical oxidation of ammonia

### Modeling NO Signaling Chemistry

Nitric oxide (NO) is a powerful signaling molecule with far reaching effects. Inspired by Cu and Zn environments in biology, we employ synthetic models that outline pathways to interconvert molecules in NO signaling such as nitrate, nitrite, and S-nitrosothiols (RSNO).



For instance, a copper(II) thiolate [Cu(II)]-SR that serves as a model for a type 1 copper electron transfer site reversibly binds NO by insertion into the Cu-S bond to give the corresponding copper(I) S-nitrosothiol adduct [Cu(I)](RSNO). Not only does this pathway interconnect NO and S-nitrosothiol signals, but the inability of the copper(I) S-nitrosothiol adduct to undergo reduction reveals that NO binding to the copper(II) thiolate serves as a reversible switch that controls electron-transfer.



## Timothy H. Warren

### Synthetic Inorganic Chemistry for Catalysis and Biology

ROSENBERG PROFESSOR  
AND CHAIRPERSON

(b. 1970)

B.S., 1992,

Univ. of Illinois at Urbana-Champaign;

Ph.D., 1997,

Massachusetts Inst. of Technology;

Postdoctoral Fellow, 1997-1999,

Univ. of Münster

Professor, 1999 – 2021,

Georgetown Univ.



517-353-xxxx

#### SELECTED PUBLICATIONS

*A Three Coordinate Copper(II) Alkynyl Complex in C-C Bond Formation: The Sesquicentennial of the Glaser Coupling*, Bakhoda, A.; Okoromoba, O.; Greene, C.; Boroujeni, M. R.; Bertke, J. A.; Warren, T. H., *J. Am. Chem. Soc.* **2020**, *142*, 18483-18490.

*Lewis Acid Coordination Redirects S-Nitrosothiol Signaling Output*, Hosseininasab, V.; McQuilken, A. C.; Bakhoda, A.; Bertke, J. A.; Timerghazin, Q. K.; Warren, T. H., *Angew. Chem. Int. Ed.* **2020**, *59*, 10854-10858. Noted as a Very Important Paper.

*Tris(pyrazolyl)borate Copper Hydroxide Complexes Featuring Tunable Intramolecular H-bonding*, Gardner, E. J.; Cobb, C. R.; Bertke, J. A.; Warren, T. H., *Inorg. Chem.* **2019**, *58*, 11248-11255.

*Copper-Catalyzed C(sp<sup>3</sup>)-H Amidation: Sterically Driven Primary and Secondary C-H Site-Selectivity*, Bakhoda, A.; Jiang, Q.; Bertke, J. A.; Cundari, T. R.; Warren, T. H., *Angew. Chem. Int. Ed.* **2019**, *58*, 3421-3425.

*Nitrosyl Linkage Isomers: NO Coupling to N<sub>2</sub>O at a Mononuclear Site*, Kundu, S.; Phu, P. N.; Ghosh, P.; Kozimor, S. A.; Bertke, J. A.; Stieber, S. C. E.; Warren, T. H., *J. Am. Chem. Soc.* **2019**, *141*, 1415-1419.

*Copper(II) Activation of Nitrite: Nitrosation of Nucleophiles and Generation of NO by Thiols*, Kundu, S.; Kim, W. Y.; Bertke, J. A.; Warren, T. H., *J. Am. Chem. Soc.* **2017**, *139*, 1045-1048. Highlighted as a JACS Spotlight: "Nitric Oxide on a New Route"

*Copper Catalyzed sp<sup>3</sup> C-H Etherification with Acyl Protected Phenols*, Salvador, T. K.; Arnett, C. H.; Kundu, S.; Sapiezynski, N. G.; Bertke, J. A.; Boroujeni, M. R.; Warren, T. H., *J. Am. Chem. Soc.* **2016**, *138*, 16580-16583.

*A Motif for Reversible Nitric Oxide Interactions in Metalloenzymes*, Zhang, S.; Melzer, M. M.; Nermin Sen, S.; Çelebi-Ölçüm, N.; Warren, T. H., *Nature Chem.* **2016**, *8*, 663-669.