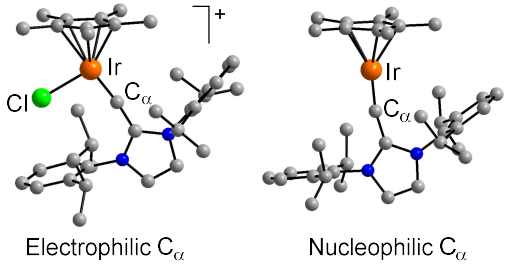
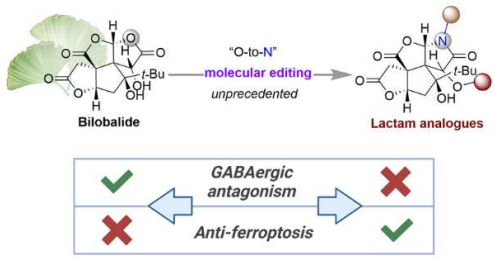
Publications

3. **Ambiphilic Reactivity of Iridium Complexes with *N*-Heterocyclic Vinylidene Ligands**
   T. H. Wong, P. Varava, F. Faraei-Tirani, R. Scopelliti, K. Severin.
   Submitted



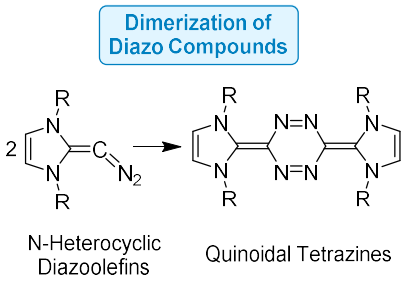
Room-temperature stable diazoolefins provide access to a unique class of carbon-donor ligands: N-heterocyclic vinylidenes. Herein, we describe iridium complexes with terminal N heterocyclic vinylidene ligands. Cationic complexes of type [Cp*IrClL]X (X = SbF6, OTf; L = N-heterocyclic vinylidene) were obtained by reaction of (Cp*IrCl2)2 with an N-heterocyclic diazoolefin, followed by chloride abstraction. Reduction instead of chloride abstraction gave a neutral Cp*IrL complex with a "pogo stick" geometry. Crystallographic analyses of the complexes revealed very short iridium-carbon bonds, suggesting partial carbyne character. The vinylidene ligands display ambiphilic reactivity. The cationic complex forms covalent ad-ducts with halides and pseudohalides, whereas the neutral complex reacts with electrophiles. These transformations generate rare carbon-donor species, including anionic N-heterocyclic olefins with pronounced carbene character or a side-on bound alkylidene ketene.

2. **Lactone-to-Lactam Editing Alters the Pharmacology of Bilobalide**
   X. Jiang†, X. He†, J. Wong†, S. Scheeff, Sam C. -K. Hau, T. H. Wong, Y. Qin, C. H. Fan, B. Ma, N. L. Chung, J. Huang, J. Zhao, Y. Yan, M. Xiao, Tony K. C. Hui, Z. Zuo, William K. -K. Wu, H. Ko, Kim H. -M. Chow, Billy W. -L. Ng.
   JACS Au **2024**, *4*, 3537-3546 [Highlighted in *Synfacts* **2024**, 1091]



Precise transformations of natural products (NPs) can fine-tune their physicochemical properties while preserving inherently complex and evolutionarily optimized parent scaffolds. Here, we report an unprecedented lactone-to-lactam transformation on bilobalide, thus improving its stability and paving the way for biological exploration of previously inaccessible chemical space that is highly representative of the parent structure. This late-stage molecular editing of bilobalide enables facile access to a unique library of lactam analogues with altered pharmacology. Through phenotypic screening, we identify **BB10** as a hit compound with unexpected inhibition of ferroptotic cell death. We further reveal that **BB10** suppresses ferroptosis by restoring the expression of glutathione peroxidase 4 (GPX4) in brain cells. This study highlights that even subtle changes on NP scaffolds can confer new pharmacological properties, inspiring the exploration of simple yet critical transformations on complex NPs.

1. **Head-to-Tail Dimerization of *N*-Heterocylic Diazoolefins**
   P. Varava, T. H. Wong, Z. Dong, A. Gitlina, A. Sienkiewicz, W. Feuerstein, R. Scopelliti, F. Faraei-Tirani, K. Severin.
   Angew. Chem. Int. Ed. **2023**, e202303375



   The head-to-tail dimerization of N-heterocyclic diazoolefins is described. The products of these formal (3+3) cycloaddition reactions are strongly reducing quinoidal tetrazines. Oxidation of the tetrazines occurs in a stepwise fashion, and we were able to isolate a stable radical cation and diamagnetic dications. The latter are also accessible by oxidative dimerization of diazoolefins.

Manuscript in Preparation:

T. H. Wong, D. W. Chen, F. Faraei-Tirani, R. Scopelliti, K. Severin. "Synthesis and Reactivity of a CAAC-Derived N-Heterocyclic Olefin."

T. H. Wong, P. Varava, F. Faraei-Tirani, K. Severin. "Intra/Inter-Ligand C-H Activation in Reactions of *N*-Heterocyclic Diazoolefin with Iridium and Rhodium Complexes."