

## **Towards the Development of Therapeutics: Bergman Cyclization via $\sigma$ -Coordinated Metalloenediynes**

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Enediyne-containing natural products show activity in tumor cells due to thermally-induced Bergman cyclization. In the presence of DNA, the diradical intermediate performs H-atom abstraction from the phosphodiester backbone, cleaving the DNA and inducing apoptosis. It is well known that  $\sigma$ -coordination of enediynes influences reactivity by decreasing the interalkynyl distance which lowers the barrier to cyclization. The challenge is to construct molecules that are thermally stable to handle, yet react at physiological temperatures. Two approaches to achieving this goal are decreasing the interalkynyl distance by controlling geometry using Pt(II) and employing an electron-deficient metal center such as Ti(IV) to withdraw electron density from the alkyne in-plane  $\pi$ -system. Two enediyne-containing ligand frameworks have been prepared which bind to the metal center through either  $\sigma$ -(NH<sub>2</sub>)<sub>2</sub> (**1**) or  $\sigma$ -N<sub>4</sub> (**2**) coordination and complexes using Ti(IV) and Pt(II) are currently being investigated. Additionally, approaches to expand biological substrates using Cu(II) macrocyclic complexes will be discussed.