Summary

Metalloradical Synthesis of Medium-Sized Ring Systems, and Their Applications as Molecular Photoswitches and Synthetic Platforms

The importance of medium-sized rings, especially 8-membered rings, is exemplified by their prevalence in a broad variety of bio-active natural products, fuels, fragrances, and catalysts. These cyclic molecules occupy an unfavorable synthetic space, where the kinetic and thermodynamic barriers associated with their synthesis are typically higher than that for other rings sizes. As a result, efficient approaches for synthesizing these medium-sized molecules are rather scarce, which hampers further research on their applications.

Chemists have been seeking for efficient strategies to synthesize medium-sized ring systems for many years. Amongst all the methodologies developed in this area, homogeneous catalysis has been proven to be the most widely used approach to construct these cyclic molecules. Currently, most homogeneous catalysts build on the reactivity of scare transition metals, and examples of catalysts for synthesis of medium-sized ring structures based on abundant first row transition metals (base metals) are rare. Known investigations on base metal catalysts revealed that the *d*-orbital splitting of these metal catalysts is often smaller than that of their heavier congeners, resulting in open-shell electronic structures and single-electron-transfer reactivity. Due to the limitation of techniques to characterize these metal complexes, predicting the reactivity of open-shell organometallic compounds remains difficult in most cases. The presence of redox-active ligands/substrates complicates matters further. Therefore, our present understanding of catalytic systems based on first row transition metals is still inadequate, which significantly hampers synthetic applications.

In recent years, many metalloenzymes containing base metals were found in nature and were proven to be efficient catalysts in controlling radical-type transformation in biological systems, giving inspiration for the development of new types of homogeneous catalysts containing base metals. **Chapter 1** gives an overview of currently known synthetic approaches for constructing

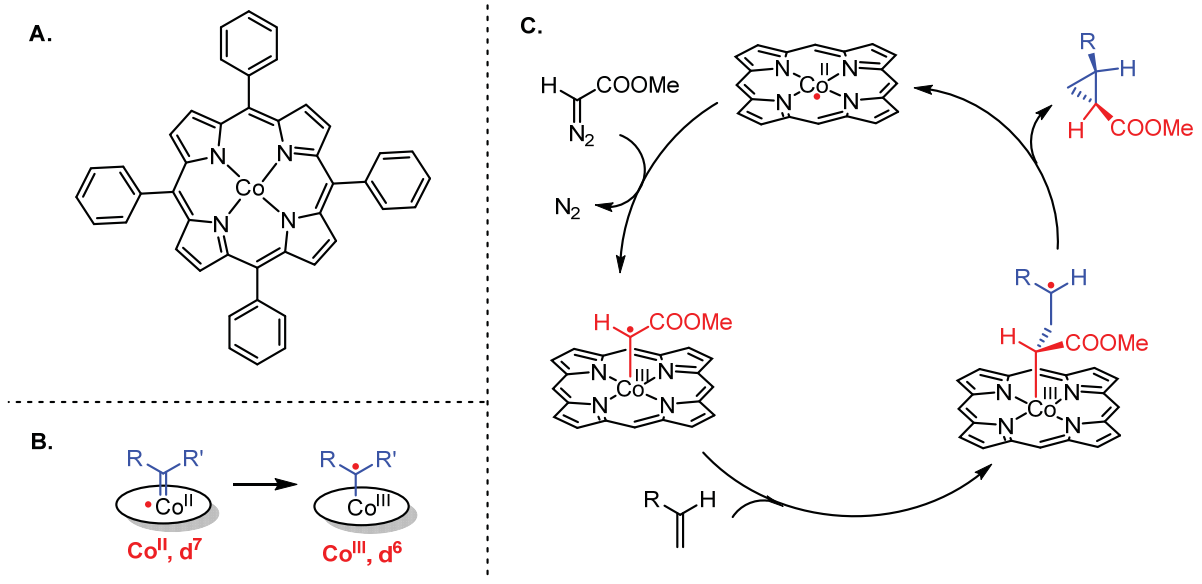
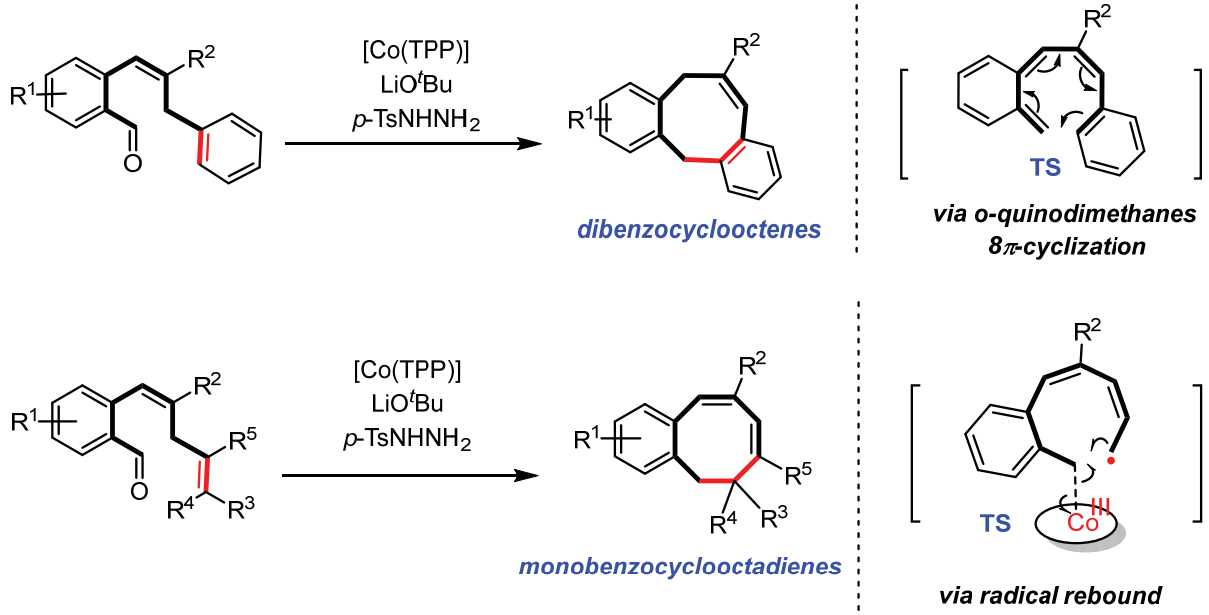


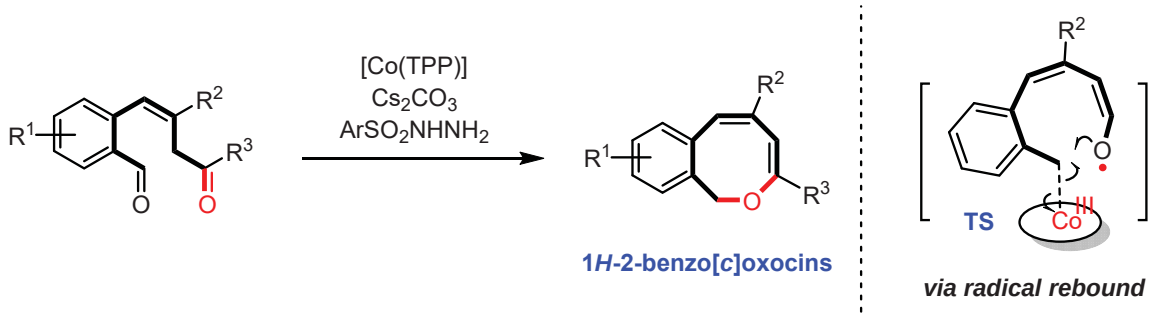
Figure 1. Cobalt(II)-based metalloradical strategy. (A) Chemical structure of [Co^{II}(TPP)] (TPP = tetraphenylporphyrin). (B) Formation of cobalt(III)-carbene radicals. (C) [Co^{II}(por)] catalyzed radical-type transformations (cyclopropanation of olefins) (Chapter 1).

medium-sized ring compounds, and discusses homogeneously catalyzed processes for this purpose, with special attention to the synthetic applications of cobalt-based metalloradical catalysis in cyclization reactions (Figure 1). Since medium-sized ring compounds contain unique cyclic structures with high ring strain, exploring new utilizations of these molecules is of importance as well. In addition to the widely reported applications of medium-sized ring compounds in pharmaceuticals, a brief introduction of incorporating medium-sized cyclic structures in molecular photoswitches is provided. This dissertation aims to explore new synthetic protocols to medium-sized rings with the benefit of metalloradical strategies, and investigate potential applications of these novel cyclic products. As this dissertation will cover both the synthesis and applications of 8-membered rings, the following chapters will be elaborated in two parts.

In the first part of this dissertation (**Chapter 2** and **3**), the synthesis of several types of new medium-sized ring systems is described, using cobalt-based metalloradical strategies. In **Chapter 2**, we described the synthesis of two types of novel 8-membered carbocycles with the assistance of the intrinsic radical-type reactivity of cobalt(III)-carbene radical intermediates: dibenzocyclooctenes and monobenzocyclooctadienes (Scheme 1). Density functional theory (DFT) calculations and experimental results suggest that the reactions proceed via hydrogen atom transfer from the bis-allylic/benzallylic C–H bond to the carbene radical, followed by two divergent processes for ring-closure to the two different types of 8-membered ring products. While the dibenzocyclooctenes are most likely formed by dissociation of *o*-quinodimethanes (*o*-QDMs) which undergo a non-catalyzed 8π-cyclization, DFT calculations suggest that ring-closure to the monobenzocyclooctadienes involves a radical-rebound step in the coordination sphere of cobalt. The latter mechanism implies that unprecedented enantioselective ring-closure reactions will lead to chiral monobenzocyclooctadienes, which was confirmed for reactions mediated by a chiral cobalt-porphyrin catalyst.



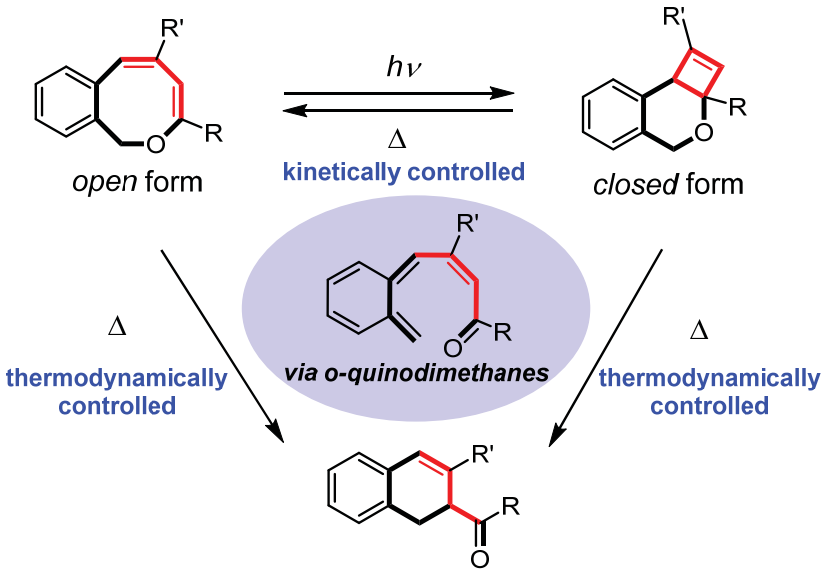
Scheme 1. Metalloradical strategy for the synthesis of dibenzocyclooctenes and monobenzocyclooctadienes (Chapter 2).



Scheme 2. Metalloradical strategy for the synthesis of 1*H*-2-benzo[*c*]oxocins (Chapter 3).

Building on prior results and in view of our continued interest in cobalt-based metalloradical catalysis. We envisioned that related open-shell catalysis could disclose new possibilities for the synthesis of other medium-sized cyclic compounds. In **Chapter 3**, we developed a highly effective metalloradical protocol for the synthesis of a series of new 8-membered *O*-heterocyclic rings: 1*H*-2-benzo[*c*]oxocins (Scheme 2). The adaptable functionalization of the products showcases the potential for a concise strategy to synthesize a broad range of potentially bioactive structures, containing novel medium-sized heterocycles. Thus formed 1*H*-2-benzo[*c*]oxocins also proved to be useful and versatile platforms to prepare a variety of other potentially bioactive substructures. DFT calculations and spin trapping experiments revealed that cobalt(III)-carbene radicals are produced, which are involved in a subsequent intramolecular hydrogen atom transfer step followed by product formation via a radical rebound step. The reactions described in **Chapter 2** and **3** have demonstrated that cobalt-based metalloradical catalysis is a powerful strategy for the synthesis of medium-sized carbo- and heterocycles, affording a variety of novel 8-membered ring compounds under mild reaction conditions, with a broad substrate scope and an excellent functional group tolerance.

With several new types of 8-membered ring compounds in hand, we had investigated their applications. In the second part of this dissertation (**Chapter 4**–**7**), we focused on transformations based on these new 8-membered cyclic molecules, especially 1*H*-2-benzo[*c*]oxocins. In **Chapter 3**, We noticed that these 8-membered heterocycles are highly reactive and easily convert to many interesting structures. For instance, 1*H*-2-benzo[*c*]oxocins can slowly convert to dihydro-4*H*-cyclobuta[*c*]isochromenes under irradiation of sunlight. With the aspiration to understand and employ the photo-responsive properties of 1*H*-2-benzo[*c*]oxocins, we studied the light-triggered ring-contraction of these 8-membered rings, and further investigations based on this unique transformation are described in **Chapter 4**: 1*H*-2-benzo[*c*]oxocins convert to *4,6*-fuesed *O*-heterocyclic dihydro-4*H*-cyclobuta[*c*]isochromenes under irradiation, while dihydro-4*H*-cyclobuta[*c*]isochromenes can reverse back to 1*H*-2-benzo[*c*]oxocins through heating (Scheme 3). Both processes are unidirectional and proceed with good efficiency. Based on the unique conversions between 1*H*-2-benzo[*c*]oxocins and dihydro-4*H*-cyclobuta[*c*]isochromenes, a novel and powerful T-type photoswitch was developed. Spectroscopic and photophysical studies demonstrated that this new photoswitch exhibits outstanding conformational flexibility and high thermal stability in both isomeric states, coupled with sizable quantum yields for the photoreactions. The photoswitching behaviour is independent of the solvent polarity and easy to

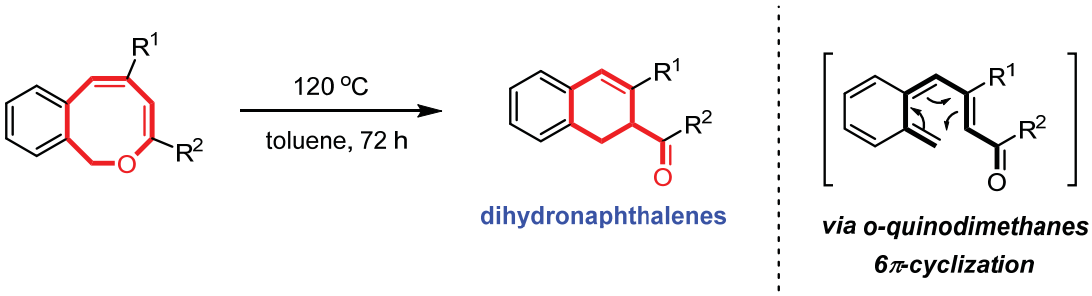


Scheme 3. 1*H*-2-benzo[*c*]oxocins/dihydro-4*H*-cyclobuta[*c*]isochromenes photoswitches, and fatigue to dihydronaphthalenes (Chapter 4 and 5).

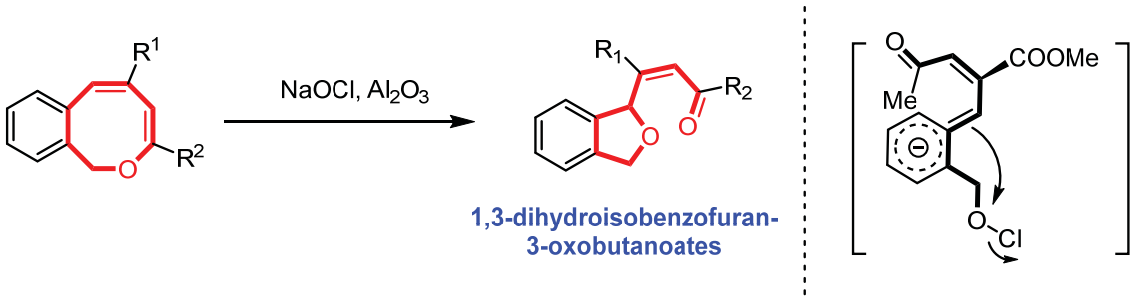
adjust by variation of structural substituents. Promising features including visible-light photoactivation and facile functionalization enable a broad range of applications of these new photoswitches, ranging from energy storage to smart materials. In addition to the switching behaviour, these transformations also provide an efficient strategy to construct cyclobutaisochromenes (substructures of dihydro-4*H*-cyclobuta[*c*]isochromenes), which are important motifs found in natural pharmaceuticals but are difficult to access.

The switching between 1*H*-2-benzo[*c*]oxocins and dihydro-4*H*-cyclobuta[*c*]isochromenes disclosed in **Chapter 4** proceeds via a unique mechanism, in particular concerning the thermal ring-opening pathway: While the light-induced ring-closure adheres to the Woodward–Hoffmann rules, the ring-opening reversion unexpectedly produces thermally forbidden products violating the Woodward–Hoffmann rules. In **Chapter 5** we describe the switching mechanisms of this new T-type photoswitch, as well as the mechanism leading to dihydronaphthalene formation explaining some fatigue associated with the switching process (Scheme 3). Computational studies revealed that ring-closure results from a 4π-cyclization upon irradiation, while the thermal ring-opening process can be explained by ring-opening to an *o*-QDM intermediate that preferentially ring-closes to the desired 1*H*-2-benzo[*c*]oxocin for kinetic reasons. Heating the 1*H*-2-benzo[*c*]oxocins at elevated temperatures with a longer reaction time results in formation of dihydronaphthalenes from the same *o*-QDM intermediate, which is the predominant reason of fatigue of the new photoswitching system described in **Chapter 4**. The DFT calculated pathways of switching, and the generation of dihydronaphthalenes were confirmed with experimental observations.

The thermal ring-contraction of 1*H*-2-benzo[*c*]oxocins provides an efficient and powerful methodology for the synthesis of dihydronaphthalenes, which is the first example of constructing dihydronaphthalenes via the approach of ring-contraction. Further exploration on this methodology was demonstrated in **Chapter 6** (Scheme 4). Various substituted



Scheme 4. Synthesis of dihydronaphthalenes via ring contraction of 1*H*-2-benzo[*c*]oxocins (Chapter 6).



Scheme 5. Synthesis of 1,3-dihydroisobenzofuran-3-oxobutanoates via ring contraction of 1*H*-2-benzo[*c*]oxocins (Chapter 7).

dihydronaphthalenes could be easily obtained via thermal ring-contraction of 1*H*-2-benzo[*c*]oxocins. The reaction exhibits good functional group tolerance, giving the desired ketone-functionalized dihydronaphthalenes in high yields. The proposed mechanism proceeds via *o*-QDM intermediates: 1*H*-2-benzo[*c*]oxocins proceed ring-opening to an *o*-QDM intermediate at high temperature, which subsequently undergoes ring-closure via 6π-cyclization, producing dihydronaphthalenes as products. These reactions proceed with good chemoselectivities, thus providing new synthetic protocols for the synthesis of bioactive derivatives that are difficult to prepare otherwise.

In view of our continued interest in highly strained ring compounds and exploring their synthetic applications, we investigated another unprecedented transformation of 1*H*-2-benzo[*c*]oxocins and the results are described in **Chapter 7**: treatment of 1*H*-2-benzo[*c*]oxocins with sodium hypochlorite in the presence of neutral alumina affords 1,3-dihydroisobenzofuran-3-oxobutanoates (Scheme 5). Unlike traditional pathway of epoxidation, the conjugated acrylate moiety and special enol ring motif within the 1*H*-2-benzo[*c*]oxocins resulted in oxidative ring-contraction, and a series of 5-membered heterocyclic molecules were generated as products. This reaction has proven to be an efficient strategy to construct these unique 5-membered rings in high yield, with good functional group tolerance and high chemoselectivity, of potential interest for future pharmaceutical applications.

This dissertation is centered around new synthetic applications of metalloradical-carbene-transfer strategies in the synthesis of medium-sized rings, and the utilization of these new cyclic products. In the first part of this dissertation, cobalt-based metalloradical strategies were successfully

exploited in the synthesis of medium-sized ring compounds, and three types of novel 8-membered cyclic structures were developed: dibenzocyclooctenes, monobenzocyclooctadienes, and 1*H*-2-benzo[*c*]oxocins. Mechanistic investigations indicated that all these transformations proceed via cobalt(III)-carbene radicals as intermediates, which have been supported by experimental observations, computational studies, and spin trapping experiments. The second part of the thesis exhibits our findings on the employment of these 8-membered cyclic molecules. A novel T-type molecular photoswitch based on the reversible cyclization of 1*H*-2-benzo[*c*]oxocins to dihydro-4*H*-cyclobuta[*c*]isochromenes has been developed, and their switching behavior was investigated with spectroscopic studies and photophysical investigations. Alongside the photo-responsive behavior of 1*H*-2-benzo[*c*]oxocins, these 8-membered heterocycles can easily convert to other bioactive structures, including dihydronaphthalenes and 1,3-dihydroisobenzofuran-3-oxobutanoates, which are important substructures found in several bioactive molecules/enzymes that are difficult to access otherwise.

The results in this dissertation uncover new avenues of metalloradical catalysis, and has led to the development of new synthetic protocols for the synthesis of new medium-sized ring systems showing interesting synthetic and photophysical applications. We hope this research will contribute to a better understanding of metalloradical catalysis, and inspire others for exploring more radical-type transformations with open-shell organometallic system. Moreover, the medium-sized cyclic molecules proved to be useful for the development of new molecular photoswitching systems, and are useful synthetic platforms to prepare other bioactive structures. We foresee that further research on the studied 8-membered ring compounds will disclose other interesting applications of these intriguing molecules.