Controlling radical-type reactivity with transition metals and supramolecular cages

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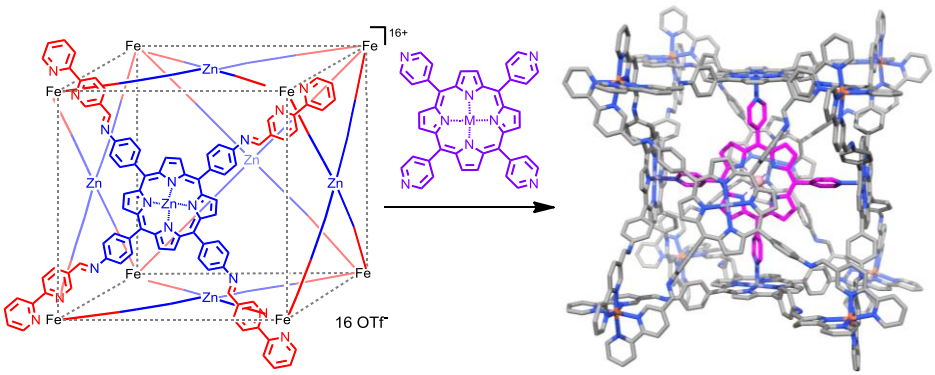
Summary:

Controlling Radical-Type Reactivity with Transition Metals and Supramolecular Cages

In modern society transition metal catalysis plays an important role in a wide variety of chemical transformations. In the context of sustainable chemistry it is desirable to move from precious metals (such as palladium, platinum, iridium, etc.) to base metal catalysts (cobalt, iron, manganese, etc.), which are found in natural metallo-enzymes. These complexes mainly react through one-electron pathways involving (coordinated) radicals. Although it is difficult to tune the reactivity of free radicals, highly selective reactions can be performed in close proximity of a transition metal. Especially cobalt porphyrin complexes have been studied in detail to develop a broad range of radical-type transformations with exceptional selectivity and activity. Controlled formation of 'substrate radicals' in low concentrations is a key feature of these metallo-radical catalysts.

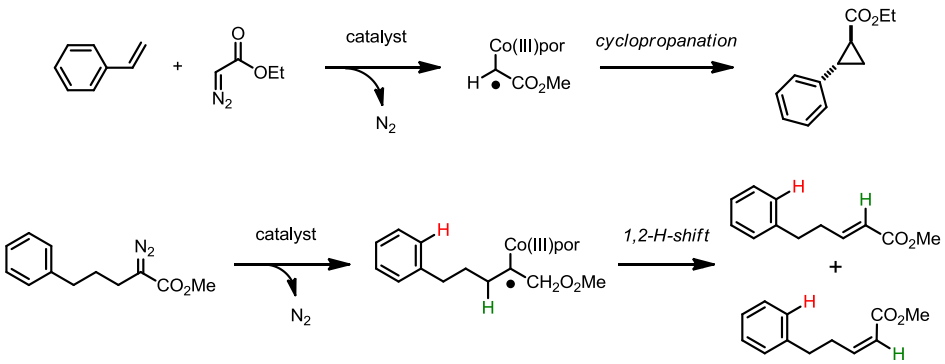
The mechanisms by which these catalysts operate are similar to the one-electron pathways followed by many metallo-enzymes. As such the controlled radical-type reactions discussed in this thesis are 'bio-inspired'. Metallo-enzymes not only exert control of radical-type intermediates by binding the substrates directly to the metal center. Also the second coordination sphere plays a significant role in tuning their reactivity. In order to functionally mimic the (protective) second coordination sphere of metallo-enzymes, several supramolecular cages have been developed. Examples have been reported in which bimolecular decomposition pathways, frequently encountered in metallo-radical catalysis, are effectively suppressed through encapsulation of the catalyst by a supramolecular cage. In a way, these cages thus mimic the protective protein matrix around the active site of a metallo-enzyme. In addition to their protective function, supramolecular cages also enable pre-organization of the substrate and can induce selectivity for specific substrates and products in competitive reactions. In Chapter 1 several illustrative examples are discussed in which these concepts are highlighted.

To improve the activity of cobalt porphyrin catalysts, a new supramolecular cage was developed in **Chapter 2** to efficiently encapsulate a cobalt-porphyrin catalyst. Initially the cubic M_8L_6 cage developed by Nitschke and co-workers was studied for the encapsulation of tetrakis(4-pyridyl)porphyrins. Unfortunately, however, this supramolecular cage proved to be too small to encapsulate the envisioned cobalt porphyrin catalysts. Therefore, a new supramolecular assembly was designed and synthesized by modification of one of the building blocks. The new supramolecular M_8L_6 cage was characterized by NMR spectroscopy, DOSY, Cryo-UHR-ESI-ToF mass spectrometry and molecular modelling techniques. The increased cavity size of this new supramolecular assembly compared to the previously described cubic cage compound allows the selective encapsulation of tetrakis(4-pyridyl)porphyrins ([M(TPyP)], M=H_2, Zn, Co, Scheme 1).



Scheme 1: Encapsulation of tetrakis(4-pyridyl)porphyrins in a new cubic M_8L_6 cage.

The substrate accessibility of this system was demonstrated through radical-trapping experiments and its catalytic activity was studied in *inter*molecular cyclopropanation (Scheme 2, top) and *intra*molecular olefin formation (Scheme 2, bottom). The reactivity of the encapsulated [Co^{II}(TPyP)] complex is significantly increased compared to the free [Co^{II}(TPyP)] catalyst. Additionally, the encapsulated complex has an increased lifetime compared to a benchmark catalyst. The reactions catalyzed by this system are the first examples of cobalt-porphyrin catalyzed radical-type transformations involving diazo compounds that occur inside a supramolecular cage.



Scheme 2: Catalytic reactions examined with the encapsulated catalyst. Cyclopropanation (top) and alkene formation (bottom).

An important disadvantage of the cage described in Chapter 2 is the poor solubility in solvents other than DMF or DMSO, which are not optimal for most of the reactions catalyzed by cobalt porphyrins. Hence, to further exploit the protective environment of the encapsulated catalyst, a related supramolecular cage was synthesized bearing triflimide counter ions instead of triflates. As described in **Chapter 3** this new cage proved soluble in solvents and solvent mixtures which are more convenient to work with, and are also better compatible with the radical-type reactions for which the cage was designed. The new supramolecular cage is still capable of encapsulating porphyrin complexes even in water/acetone mixtures. Furthermore, the assembly proved to be an active and size-selective cyclopropanation catalyst. Employing water/acetone mixtures as the solvent increased the catalytic performance of the encapsulated catalyst in styrene cyclopropanation reactions dramatically. The caged catalyst shows a preference for cyclopropanation of styrenes over other vinylic substrates. While exploring the substrate scope, it became clear that the encapsulated catalyst is a size-selective catalyst, showing preference for cyclopropanation of smaller styrene and diazo substrates. Bulkier substrates react slower than smaller ones, thus allowing size-selective competition reactions (Figure 1).

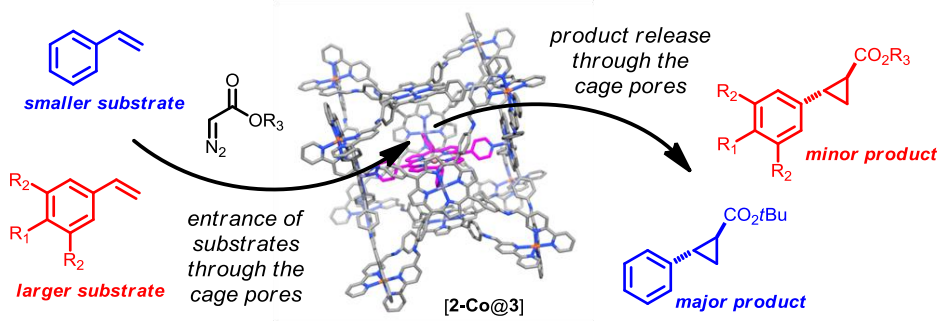


Figure 1: Schematic representation of the proposed pore-size controlled, size-selective transformations catalyzed by the encapsulated catalyst.

In addition to the cobalt(II) porphyrin complexes described above, manganese porphyrin catalyzed epoxidation reactions are also known to suffer from bimetallic deactivation pathways. Therefore in **Chapter 4** we studied the encapsulation of a manganese porphyrin in the cubic M_8L_6 cage. It was shown that it is possible to stabilize the manganese porphyrin catalyst in a cubic self-assembled molecular cage (Figure 2).

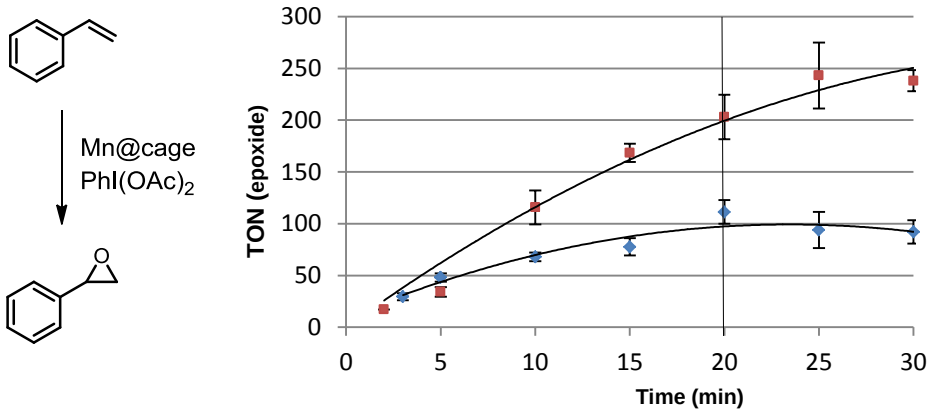


Figure 2: Following the epoxidation of styrene (left) over time with the encapsulated (red squares) and free (blue diamonds) manganese catalysts.

The encapsulated catalyst (red squares) has a longer lifetime, which results in a higher turnover number compared to the free catalyst (bleu diamonds). The obtained catalyst is active in aqueous media for the epoxidation of a variety of alkenes to reach up to 319 turnover numbers towards the desired epoxide product. Furthermore, like in the cobalt catalyzed cyclopranation reactions described in Chapter 3, the encapsulated catalysts could be used as a size-selective epoxidation catalyst for a mixture of bulky and smaller substrates.

The free manganese tetrakis(4-pyridyl)porphyrin catalyst also self-aggregates to form even more size-selective assemblies (Figure 3). However, in these aggregates fewer catalytic centers are accessible to the substrates, leading to a decrease in activity as compared to the cage-encapsulated catalyst.

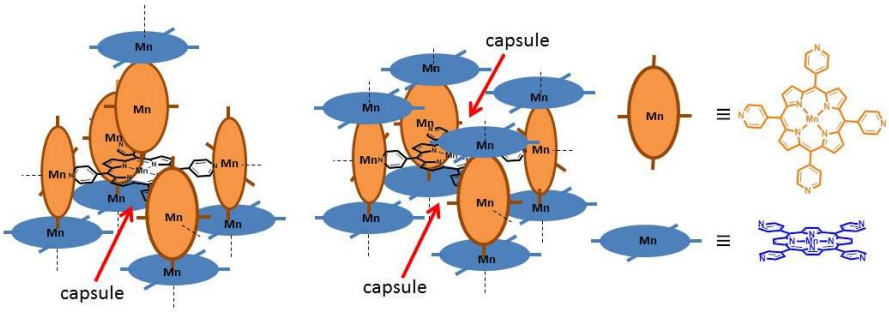


Figure 3: Schematic representations of porphyrin self-aggregation to form protective capsules.

For intramolecular ring-closing reactions bimolecular catalyst deactivation is considered to be less of an issue. To expand the concepts of radical reactivity, in **Chapter 5** a new cobalt porphyrin catalyzed intramolecular ring-closing C–H bond amination reaction was developed, which enables direct synthesis of various N-heterocycles from aliphatic azides. Pyrrolidines, oxazolidines imidazolidines, isoindolines and tetrahydroisoquinoline can be obtained in good to excellent yields in a single reaction step with commercially available catalysts (see Figure 4).

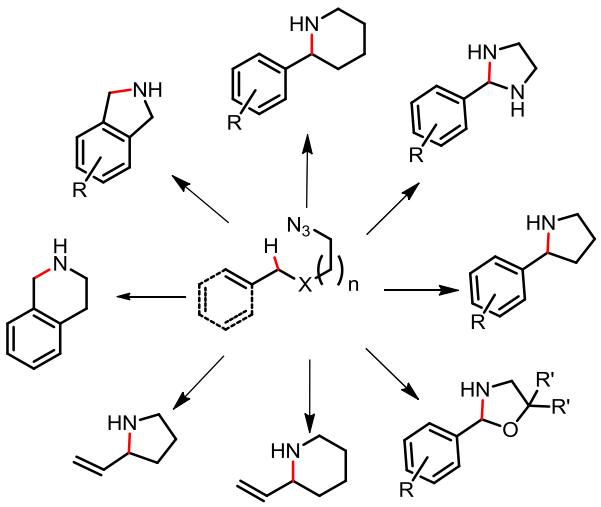
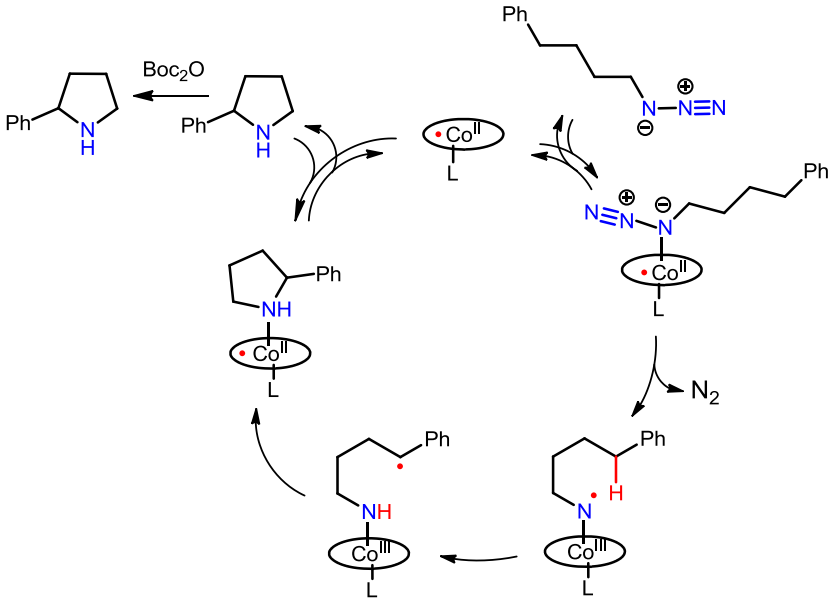


Figure 4: N-heterocylces accessible through the new intramolecular C-H amination protocol.

The use of di-*tert*-butyl dicarbonate (Boc_2O) significantly enhances the reaction rate by preventing competitive binding of the formed amine product through trapping of the heterocycles as their Boc-protected analogues. The highest turnover numbers reported to date for the intramolecular C-H amination of (4-azidobutyl)benzene could be obtained with cobalt(II) tetrakis(mesityl)porphyrin [Co(TMP)] as the catalyst. Furthermore, in marked contrast to all previously reported systems, the catalyst is bench stable and tolerates significant amounts of water during the reaction.

Information about the mechanism of this reaction was collected with the aim to improve the efficiency of the catalytic reaction, and to explore possibilities for enantioselective C–H amination. Kinetic analysis of the reaction in combination with DFT calculations, as described in **Chapter 6**, reveals a metallo-radical-type mechanism involving rate limiting azide activation to form the key cobalt(III)-nitrene radical intermediate (Scheme 3). Subsequent low barrier intramolecular hydrogen atom transfer (HAT) from a benzylic C–H bond to the nitrene-radical intermediate followed by a radical rebound step leads to formation of the desired N-heterocyclic ring products.



Scheme 3: Mechanism for the direct C-H amination from aliphatic azides.

Kinetic isotope competition experiments are in agreement with a radical-type C–H bond activation step (intramolecular KIE = 7), which occurs after the rate limiting azide activation step (intermolecular KIE = 1). The use of di-tert-butyl dicarbonate (Boc_2O) significantly enhances the reaction rate by preventing competitive binding of the formed amine product. Under these conditions, the reaction shows clean first order kinetics in both the [catalyst], and the [azide substrate], and is zero order in [Boc_2O]. Interestingly, modest enantioselectivities (29-46% ee in the temperature range between 100-80 °C) could be achieved in the ring closure of (4-azidobutyl)benzene using a new chiral cobalt porphyrin catalyst equipped with four (1S)-(–)-camphanic-ester groups (Figure 5).

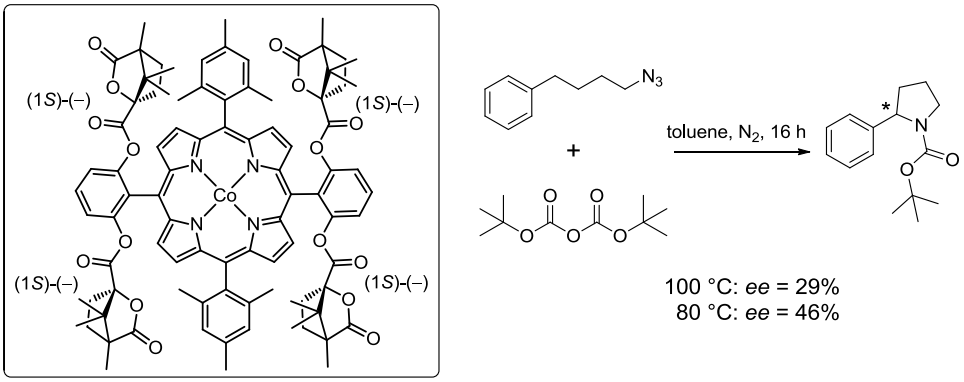


Figure 5: Chiral cobalt porphyrin (left) used in the enantioselective C–H amination reaction (right).

This demonstrates for the first time the feasibility of enantioselective radical-type ring closure reactions from aliphatic azides using metallo-radical catalysis, showing unambiguously that the C–H bond activation and C–N bond formation steps of the overall catalytic ring-closing reaction occur in the coordination sphere of cobalt. No free nitrenes are thus involved in this reaction.

By encapsulation of metallo-porphyrins in supramolecular cages, improved selectivities and turnover numbers were obtained in radical-type catalysis. In addition, new reactivity of cobalt porphyrins was explored in the direct C–H amination of aliphatic azides. The described system showed the highest turnover numbers obtained to date, and the first example of an enantioselective intramolecular C–H amination of aliphatic azides.