

S ummary

Modern catalysis research tries to address issues such as material scarcity, sustainability or process costs. One solution is to replace expensive and scarce noble metal catalysts based on palladium, platinum, rhodium or iridium with much cheaper and abundant base metal catalysts that use iron, nickel or cobalt. Additionally, and perhaps even more importantly, research in this field can lead to fascinating new reactivities, taking advantage of the preferred one-electron reactivity of first-row transition metals in marked contrast to the common two-electron reactivity of noble metal catalyst.

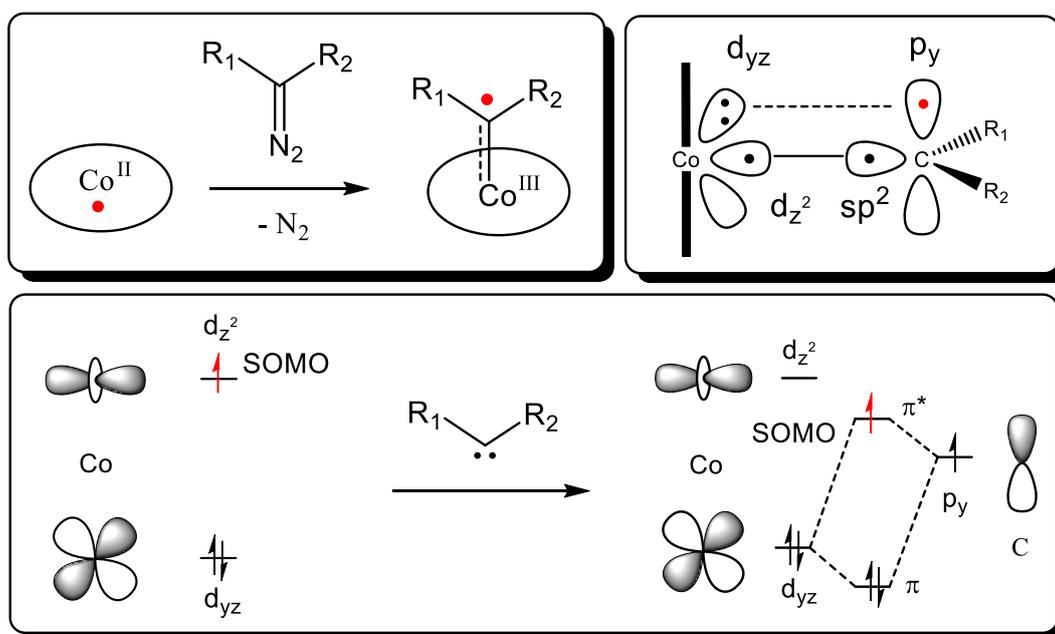


Figure 1. Formation of Co^{III}-carbene radicals upon reacting planar, low-spin cobalt(II) complexes with carbene precursors.

This thesis describes research aimed at understanding and exploiting metallo-radical reactivity and explores reactions mediated by square planar, low-spin cobalt(II) metallo-radical complexes. A primary goal was to uncover novel reactivity of discrete cobalt(III)-bound carbene radicals generated upon reaction of the cobalt(II) catalysts with carbene precursors (Figure 1). Another important goal was to replace cobalt(II)-porphyrin catalysts with cheaper and easier to prepare metallo-radical analogs. Therefore the catalytic activity of planar, low-spin cobalt(II) complexes (Figure 2) based on the dibenzotetraaza[14]annulene (MeTAA) ligand scaffold was investigated. Besides the easier synthetic procedure, these complexes are also more active in catalysis than the corresponding cobalt(II)-porphyrins in a variety of ‘carbene transfer’ reactions, such as cyclopropanation, ketene or indene synthesis.

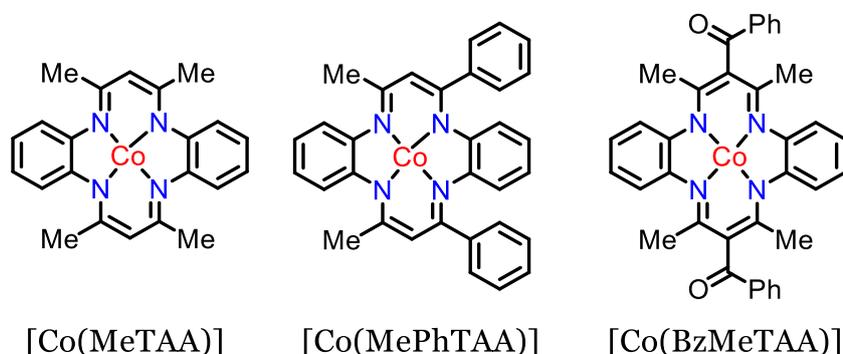


Figure 2. Cobalt(II) dibenzotetraaza[14]annulene developed catalysts.

Chapter 2 describes a new protocol for the catalytic synthesis of cyclopropanes using electron-deficient alkenes using affordable, easy to synthesize and highly active substituted cobalt(II) tetraaza[14]annulenes (Figure 2). These cobalt(II) catalysts are compatible with the use of both diazo compounds and sodium tosylhydrazone salts in one-pot catalytic transformations, affording the desired cyclopropanes in almost quantitative yields. The reaction is practical and fast, and proceeds from readily available starting materials. It does not require slow addition of diazo reagents or tosylhydrazone salts nor heating, and tolerates many solvents including protic ones such as MeOH. This not only makes the synthetic protocol safer, but also substantially expands the substrate scope of carbene transfer reactions in general.

Fast and selective carbene transfer reactions are achieved by taking advantage of the radical mechanism involving discrete cobalt(III)-carbene radical species (Figure 3), with unwanted carbene-carbene dimerization and 1,3-dipolar addition reactions between the electron deficient alkene and the diazo reagent being almost completely suppressed. The catalytic system is robust and can operate with either the alkene or the diazo reagent as limiting reagent, totally inhibiting the dimerization of diazo

compounds. The protocol has been successfully applied to synthesize a variety of substituted cyclopropanes (Figure 4). High yields and selectivities were achieved for various substrates, with an intrinsic preference for *trans*-cyclopropanes.

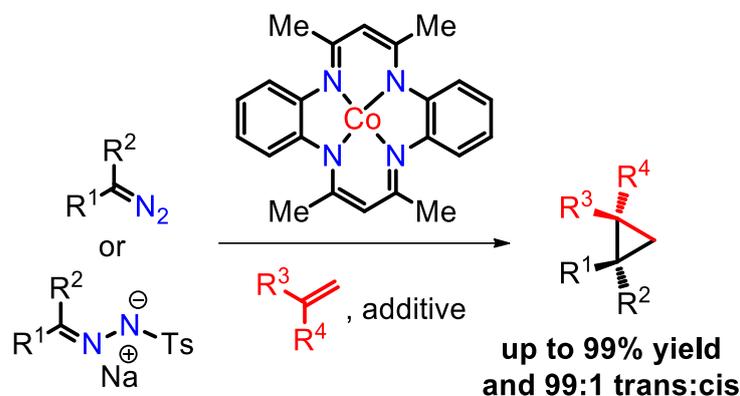


Figure 3. Cyclopropanation of electron deficient alkene with diazo-compounds or tosylhydrazone salts using [Co(MeTAA)] as a catalyst.

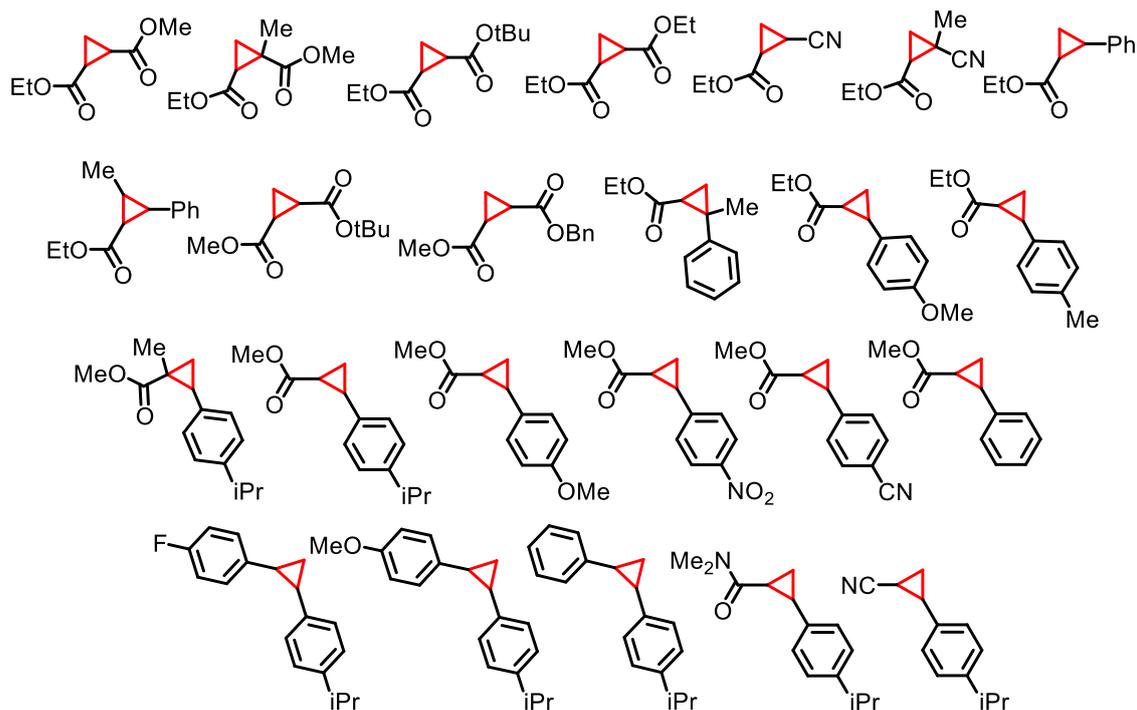


Figure 4. Prepared substituted cyclopropanes presented in this thesis

Chapter 3 describes a detailed kinetic and DFT mechanistic study of these cyclopropanation reactions, aiming at understanding both the superior activity and higher sensitivity of [Co(MeTAA)]-type catalysts compared to cobalt(II)-porphyrins. The intermediacy of cobalt(III)-carbene radicals was demonstrated using a combination of kinetic studies, experimental (EPR) spin-trapping experiments and supporting DFT studies. Reaction progress was monitored in real time, by observing

N_2 formation and measuring its partial pressure under isothermal conditions. Reaction progress kinetic analysis (RPKA) was used to analyse the experimental data to determine the rate law and to identify catalyst deactivation processes by probing the reaction at synthetically relevant conditions, at concentrations similar to the ones used in practice. Therefore, more representative results of reaction behaviour are obtained using this approach when compared to traditional kinetic studies using the initial rate approach. Results showed that the reaction is first order in both [catalyst] and [EDA], and zero order in [methyl acrylate], in agreement with the DFT-calculated mechanism (Figure 5). Moreover, a 1st order catalyst deactivation process was detected, which is much slower than the catalytic reaction steps, but does lead to catalyst decomposition over time during catalysis.

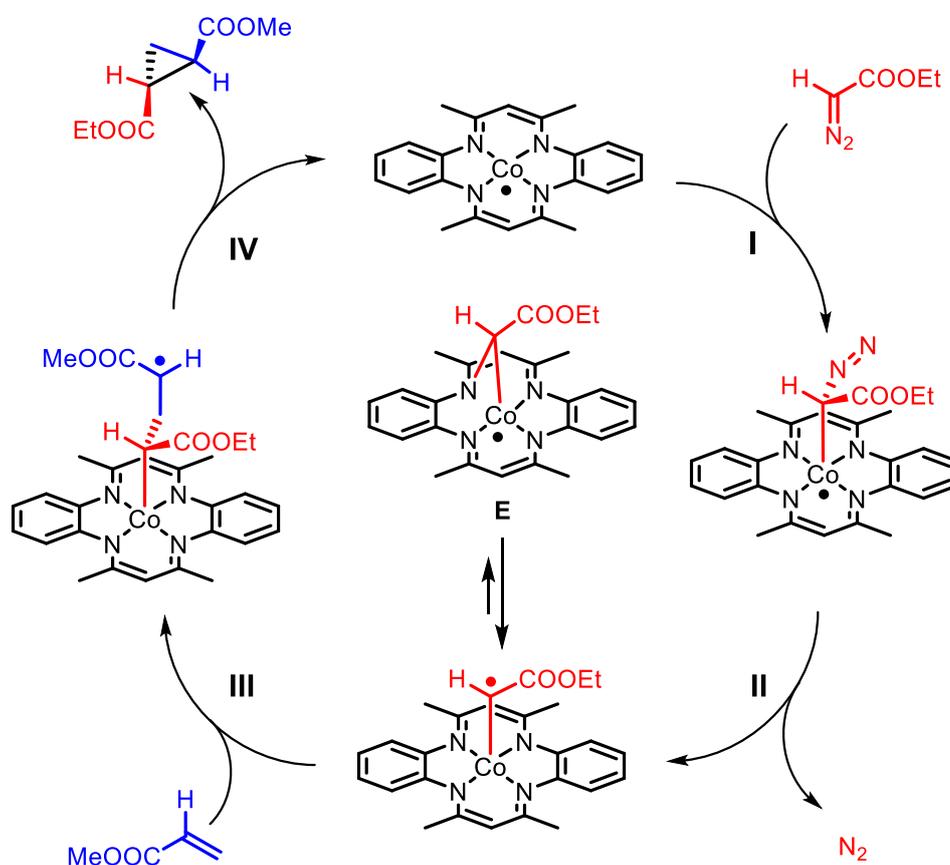


Figure 5. Mechanism of the cyclopropanation of methyl acrylate and ethyl diazoacetate catalysed by [Co(MeTAA)].

The DFT calculated activation parameters corresponding to the rate determining step of the reaction (ΔG^\ddagger , ΔH^\ddagger and ΔS^\ddagger) are in agreement with the experimental values derived from Eyring-analysis of temperature dependent kinetic measurements, thus providing strong support to the proposed metallo-radical mechanism.

Chapter 4 reports an efficient one-pot tandem protocol involving Co^{II} -porphyrin metalloradical catalysed carbonylation of α -diazocarbonyl compounds and a variety of *N*-tosylhydrazones leading to formation of ketenes, which subsequently react with a variety of nucleophiles and imines to form esters, amides and β -lactams (Figure 6). This system has a broad substrate scope and can be applied to various combinations of carbene precursors, nucleophiles and imines. The use of *N*-tosylhydrazones as precursors of diazo compounds in cobalt-porphyrin-based carbene transfer reactions represents an efficient and convenient way to prepare the key carbene radical intermediates responsive for ketene formation. The mechanism of the carbene carbonylation reactions was further investigated by IR spectroscopy and computationally using DFT.

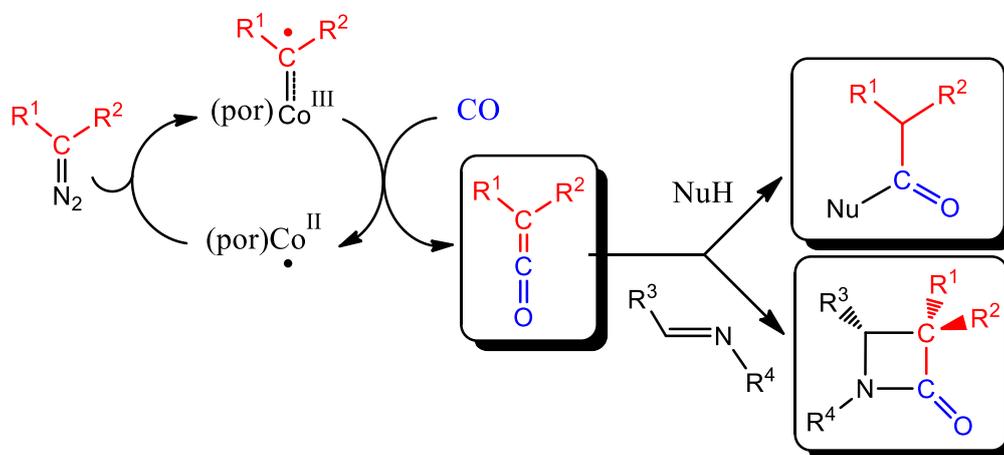


Figure 6. Co^{II} -porphyrin metalloradical catalysed carbonylation of α -diazocarbonyl compounds.

This straightforward methodology has a broad substrate scope and can be applied for various combinations of diazo compounds and nucleophiles or imines. The $[\text{Co}^{\text{II}}(\text{Por})]$ -catalysed carbonylation process offers an efficient way for the homologation of ketones and aldehydes, via tosylhydrazone salts and also provides a diastereoselective method for the transformation of aldehydes to β -lactam derivatives.

Chapter 5 expands the scope of the studies in chapter 4 by taking advantage of the outstanding activity of $[\text{Co}(\text{MeTAA})]$ to activate diazo compounds, thus forming more reactive carbene radical intermediates ready to react with carbon monoxide to afford ketenes (Figure 7).

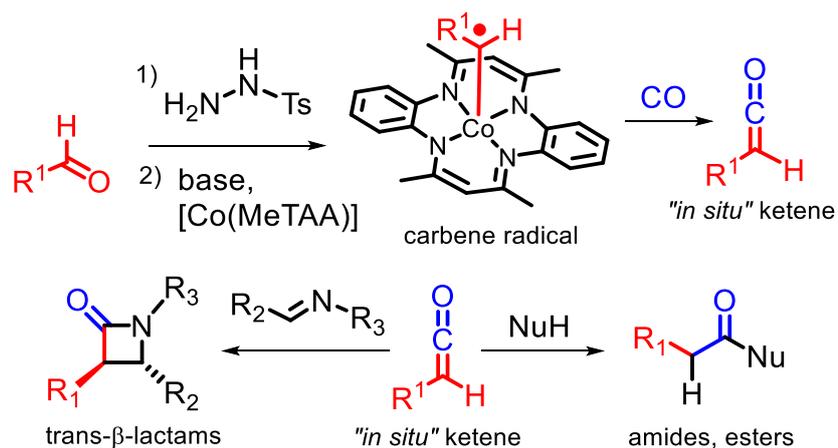


Figure 7. $[\text{Co}(\text{MeTAA})]$ -catalysed homologation of aldehydes.

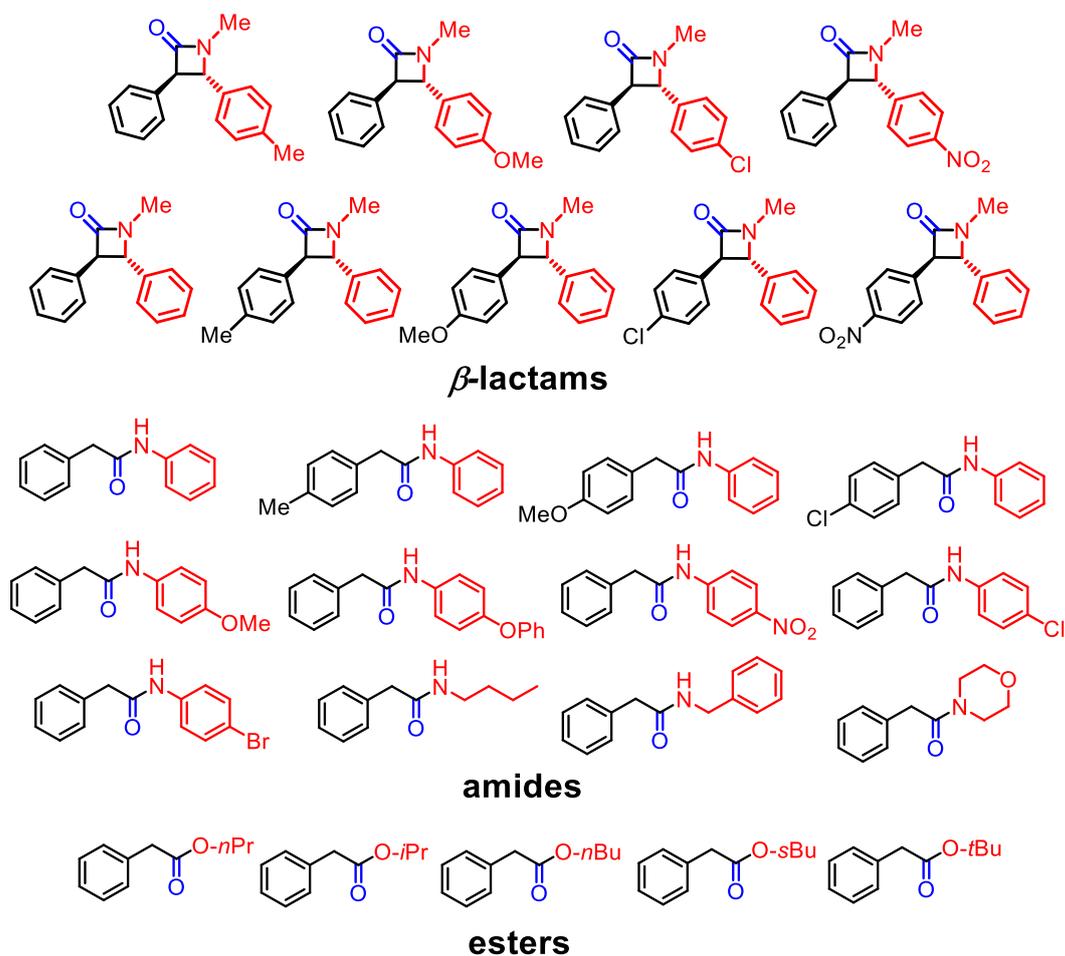


Figure 8. Prepared beta-lactams, amide and esters via the carbonylation of carbene radical intermediates formed using both $[\text{Co}(\text{MeTAA})]$ and $[\text{Co}(\text{TPP})]$.

The cheap and highly active $[\text{Co}(\text{MeTAA})]$ catalyst proved to be compatible with several different reaction conditions, including dual cascade catalysis, tolerating many functional groups, coordinating additives and high reaction temperatures. The protocol presented in this paper provides a reliable method to produce ketenes in a single pot starting from tosylhydrazone salts and carbon monoxide. The reactions proceed via formation of carbene radical intermediates which react with CO to form ketenes. The intrinsic reactivity of ketenes requires *in situ* trapping of these reactive intermediates with amines, alcohols or imines to obtain useful organic building blocks. The substrate scope has been explored, showing that this method can be applied to several different substrates bearing a variety of substituents (Figure 8).

In the final **Chapter 6** we describe the use of cobalt(II)-metalloradical catalysts in ring-closure of *o*-cinnamyl-*N*-tosyl hydrazones to *1H*-indenes. Also these reactions take advantage of the intrinsic reactivity of the unconventional cobalt(III)-carbene radical intermediates. The reaction uses readily available starting materials and is operationally simple, thus representing a practical method for the construction of functionalized *1H*-indene derivatives. As was observed for the cyclopropanation reactions described in Chapter 2, the cheap and easy to prepare low-spin cobalt(II) complex $[\text{Co}^{\text{II}}(\text{MeTAA})]$ (MeTAA = tetramethyltetraaza[14]annulene) proved to be the most active catalyst among those investigated. The metallo-radical catalyzed indene synthesis in this chapter represents a unique example of a net (formal) intramolecular carbene insertion reaction into a vinylic $\text{C}(\text{sp}^2)\text{-H}$ bond, made possible by a controlled radical ring-closure process of the carbene radical intermediate involved (Figure 9).

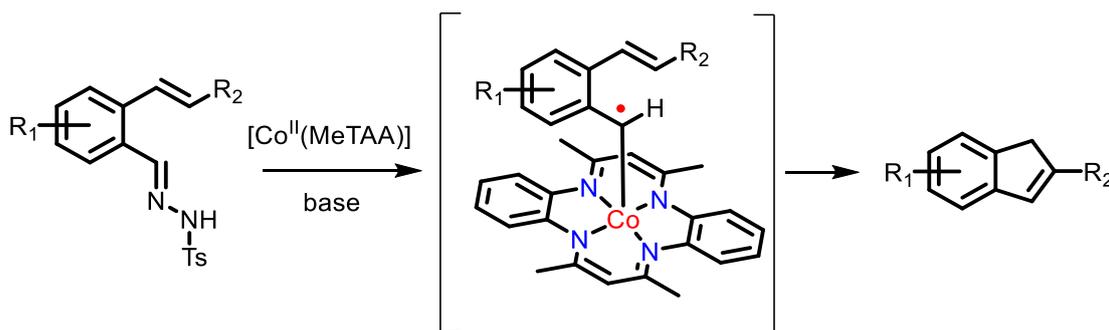


Figure 9. Indene synthesis via $[\text{Co}(\text{MeTAA})]$ coordinated carbene radical intermediates.

The methodology has been successfully applied to a broad range of substrates, producing *1H*-indenes in good to excellent yields (Figure 10). The mechanism was investigated computationally and the results were supported by a series of radical-scavenging experiments. DFT calculations reveal a stepwise process involving activation of the diazo compound leading to formation of a Co^{III} -carbene radical, followed by radical ring-closure to produce an indanyl/benzyl radical intermediate.

Subsequent indene product elimination involving a 1,2-hydrogen transfer step regenerates the catalyst.

Trapping experiments using 2,2,6,6-tetra-methylpiperidine-1-oxyl (TEMPO) radical or dibenzoylperoxide (DBPO) confirm the involvement of cobalt(III) carbene radical intermediates. Deuterium labelling experiments show statistical scrambling of the allylic/benzylic and vinylic protons under the applied reaction conditions. EPR spectroscopic spin-trapping experiments using phenyl *N-tert*-butylnitron (PBN) reveal the radical nature of the reaction.

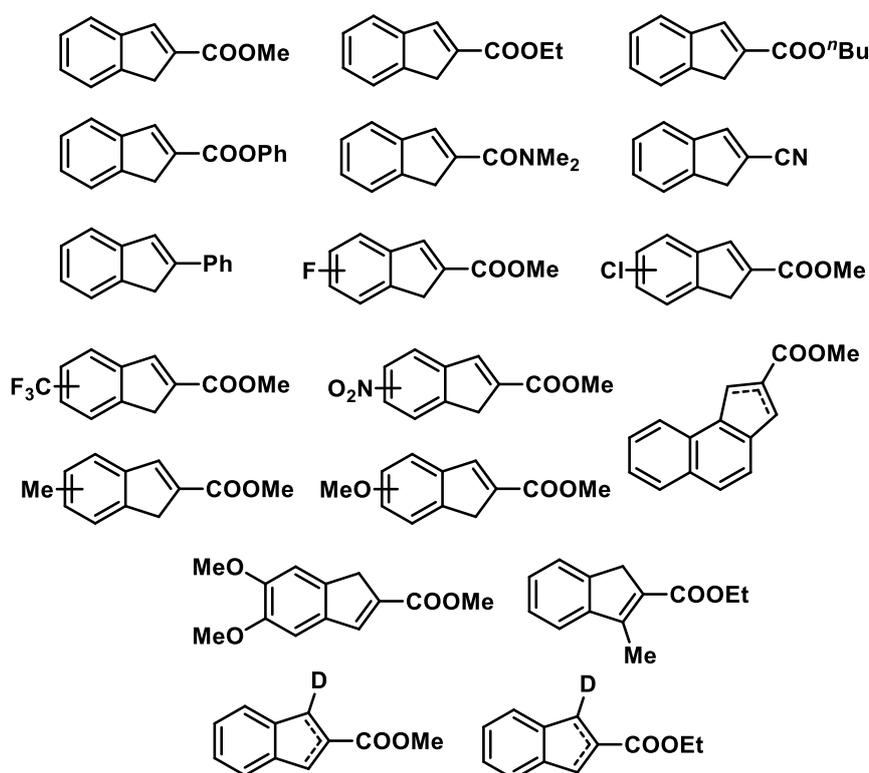


Figure 10. Prepared substituted indenenes from tosylhydrazone salts via a controlled radical ring-closing process

Combined, the work described in this thesis shows that, like in enzymes, controlled metal-catalysed reactions proceeding via radical-type pathways are certainly possible using well-defined metallo-radical complexes of cobalt(II). Generating ‘carbene-radicals’ upon activation of carbene precursors with these catalysis leads to fascinating new reactivities, taking advantage of the preferred one-electron reactivity of cobalt. The intrinsic reactivity of these species can be controlled by changing the ligand, and the reactions lead to interesting products such as cyclopropanes, ketenes and indenenes. Future studies in this direction are expected to uncover many more exciting and novel controlled radical-type pathways, not only of synthetic use but also of academic interest.