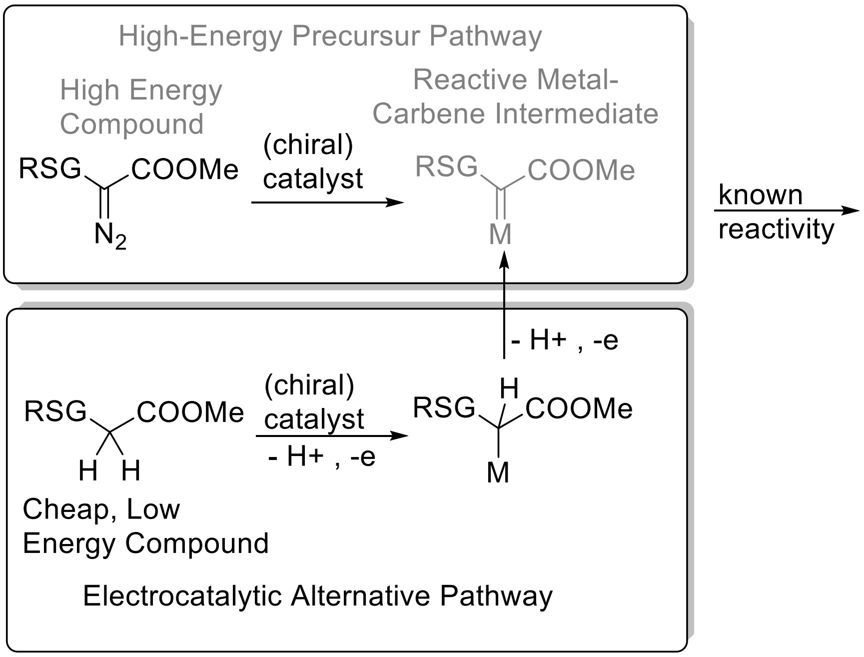
SUMMARY AND OUTLOOK

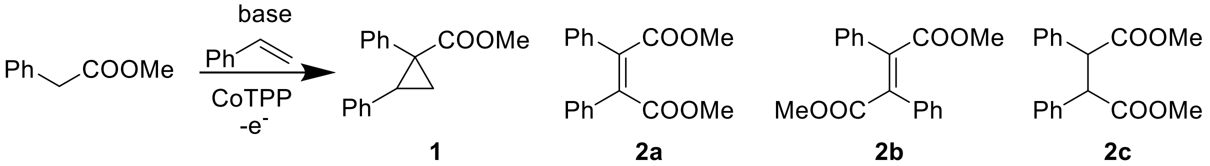
Catalysis has an essential role in our current society, and is key to ensure a sustainable future for a world on which the population and living standards keep on increasing. Many transformations in pharmaceutical-, fine chemical- and commodity chemical industries depend on catalysis. Often second- and third-row transition metals are used as the reactive sites, which undergo two-electron reactivity. First-row transitions metals are represented much less, since they usually perform one-electron reactivity. Single electron reactivity has the consequence that the intermediates formed are radical species (unless specifically designed ligands are used). These are classically considered to be 'too reactive to be selective'. However, we believe that this provides new opportunities by taking advantage of their reactivity and enabling such species for the development of new reactivity. **Chapter 1** describes the strategies used to work with first-row transition metal complexes. Spectator ligands can be used to either change the electronic environment of the metal center or as electron sink which can store and provide electrons. Actor ligands participate in the making and breaking of new chemical bonds. This is either by temporarily storing groups on them (usually a hydrogen atom) or the substrate is the ligand at which the radical transformations take place. In most reported cases, the substrates used are epoxides, azides or diazo compounds. We continued this chapter by providing an overview of carbene reactivity previously studied. Cobalt(II) tetraphenylporphyrin ([Co(TPP)]) has proven to be a suitable catalyst for insertion and addition reactions with/into/to X–H bonds (X = C, O, N, S, Si), C=C and C≡C bonds. Chapter 1 provides an overview of cobalt(II) catalyzed reactions, especially those which involve so-called 'carbene radicals' in ring-closing reactions. Examples involve the synthesis of *2H*-chromenes, indolines, furans and β-lactams.

Metallocarbenes are mostly generated by combining a diazo compound with a metal complex. However, diazo compounds tend to be rather unstable, explosive and toxic. Therefore, in **Chapter 2**, we investigated carbene transfer reactivity from cheap and safe 'low-energy' substrates and [Co(TPP)] (Scheme 1). Double deprotonation and double oxidation should lead to the same intermediates which are obtained when using diazo compounds and should therefore be able to undergo the same follow-up reactivity.
The first part of this chapter describes the development and testing of a new bulk electrolysis set-up. Next, this set-up was used in the attempted electrocatalytic cyclopropanation of methyl phenylacetate and styrene with [Co(TPP)] as the catalyst. However, instead of cyclopropane **1** (Scheme 2), (un)saturated dimers of the acetate were



Scheme 1. Formation of Reactive Metallo-Carbene Intermediates (RSG= Radical Stabilizing Group).

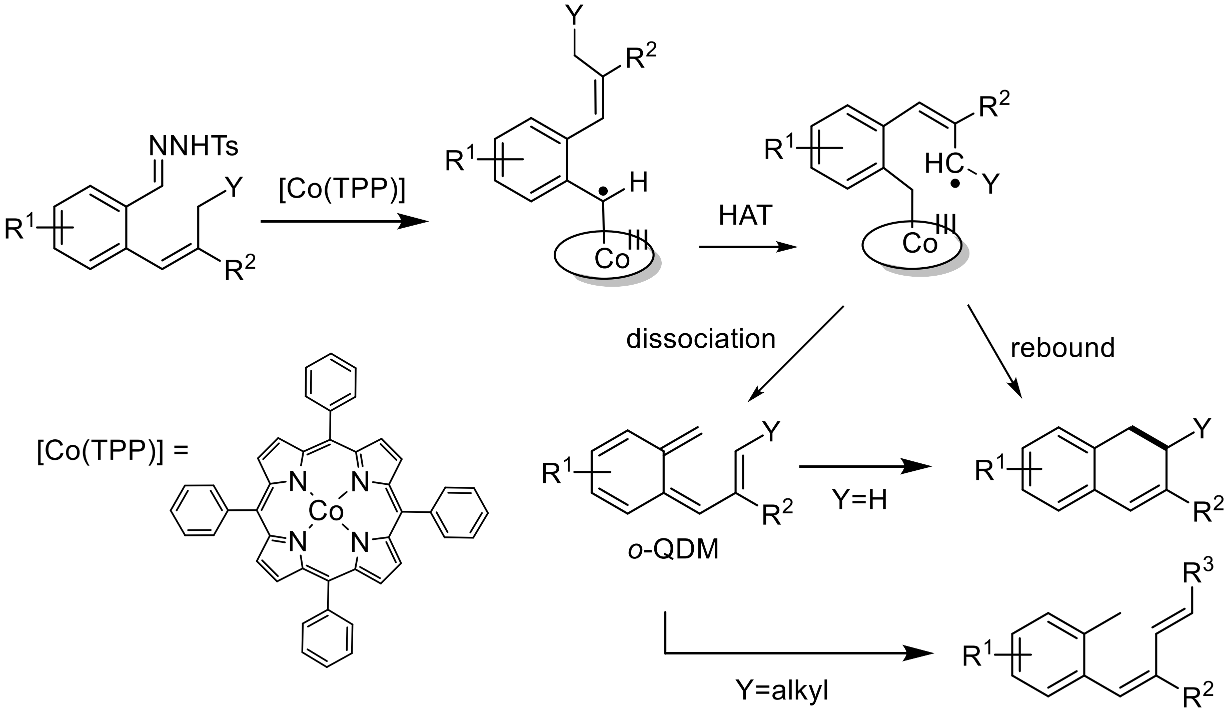
obtained. After optimization of the reaction conditions saturated dimer **2c** was the only observed product, but the (Faraday) yield remained low. Nonetheless, the results described in this chapter are still of interest for the combined research fields of organometallic chemistry and electrosynthesis.



Scheme 2. Bulk electrolysis products.

In the second part of Chapter 2 a chemical oxidation approach was investigated for the formation of carbene intermediates through double oxidation and double deprotonation. The desired cyclopropane was formed in some experiments, but the yields were low. Additionally, these experiments proved to be very sensitive, which made optimization difficult and led to reproducibility issues. Still, the results shown in this part of Chapter 2 demonstrate the proof-of-principle: Carbene-transfer reactivity can occur from cheap, ‘low-energy’ substrates by double deprotonation and double oxidation mediated by [Co(TPP)].

In **Chapter 3** we describe our effort to synthesize dihydronaphthalenes from *o*-styryl *N*-tosyl hydrazones using metalloradical catalysis. In the presence of [Co(TPP)] carbene radical intermediates were formed, which abstract a hydrogen atom from the allyl moiety of the substrate, thus resulting in an allylic radical intermediate. The latter was expected to undergo a radical rebound reaction to give the dihydronaphthalene product (Scheme 3). DFT calculations, however, pointed towards the possibility of an alternative mechanism which proceeds through *ortho*-quinodimethane intermediates, producing the same products. These are formed by homolysis of the weak Co–C bond and continue to form the product by 6π-cyclization (Scheme 3, middle).



SCHEME 3. DIHYDRONAPHTHALENE FORMATION (Y = H) VERSUS E-ARYL DIENE FORMATION (Y = ALKYL) IN [CO(TPP)] CATALYZED REACTIONS; EVIDENCE FOR INVOLVEMENT OF *ORTHO*-QUINODIMETHANE INTERMEDIATES.

Substrate screening revealed that various R^1-substituents are allowed at the aromatic ring for substrates with an R^2 = COOEt substituent at the vinylic position, giving the products in good to excellent yields (~70-90%). However, when the ester moiety of the R^2 group was changed, this had a surprisingly large effect on the (isolated) yields. For the radical rebound pathway, the vinylic substituent should have little influence, but if the reaction proceeds through an *ortho*-quinodimethane intermediate, the R^2-group is expected to have much larger influence, as observed experimentally.

Trapping experiments with TEMPO confirm the involvement of cobalt(III)-carbene radical intermediates. EPR spectroscopic spin-trapping experiments in the presence of *N*-tert-butyl-phenylnitrone (PBN) confirm the radical nature of the catalytic reaction.

To obtain further understanding of the *ortho*-quinodimethane intermediates in Chapter 3, a new range of substrates was synthesized containing an alkyl group at the vinylic position of *o*-styryl *N*-tosyl hydrazones and tested in metalloradical catalysis with [Co(TPP)]. The results are described in **Chapter 4**. Formation of substituted dihydronaphthalene products was initially anticipated, but instead *E*-aryl dienes were isolated in good to excellent yields (Scheme 3, bottom). The mechanism of this transformation, as confirmed by DFT calculations, starts the same as before (see also Chapter 3). The carbene radical abstracts a hydrogen atom from the allylic position of the substrate, leading to an allylic radical species. Subsequent homolysis of the weakened Co–C bond (which is in direct conjugation with the allyl radical) leads to release of an *ortho*-quinodimethane intermediate from the catalyst. The latter reacts further in an ene-type [1,7]-hydride shift to form the observed *E*-aryl dienes. The initially expected 6π-cyclization to form substituted dihydronaphthalenes was not observed at all, even though the substituted dihydronaphthalenes are thermodynamically more stable products than the observed *E*-aryl dienes. DFT calculation are in agreement with the experimental observations, and show that transition state barriers of the pathway leading to *E*-aryl dienes are lower than the ones leading to substituted dihydronaphthalenes, thus explain formation of the kinetic products.

Next, possible applications of the new *E*-aryl dienes were investigated. One of the dienes was combined with several dienophiles, in an attempt to perform a Diels-Alder reaction. Several dienophiles were tested, but in none of the cases the desired conversion was observed. This is probably caused by the substituents around the double bonds. These prevent the diene from rotating to the required s-cis configuration. We further investigated [2+2] cycloaddition reactions of the E-aryl dienes by irradiation with UV/vis light. After one hour of irradiation full isomerization of the double bond was observed, and further irradiation resulted in formation of small amounts of the desired cyclobutene (as detected with ^{1}H-NMR spectroscopy). Unfortunately, however, prolonged irradiation led to conversion of both diene and cyclobutene into a complex mixture of unidentified compounds. Thus, cyclobutenes can be synthesized from the *E*-aryl dienes, but this reaction still requires optimization.

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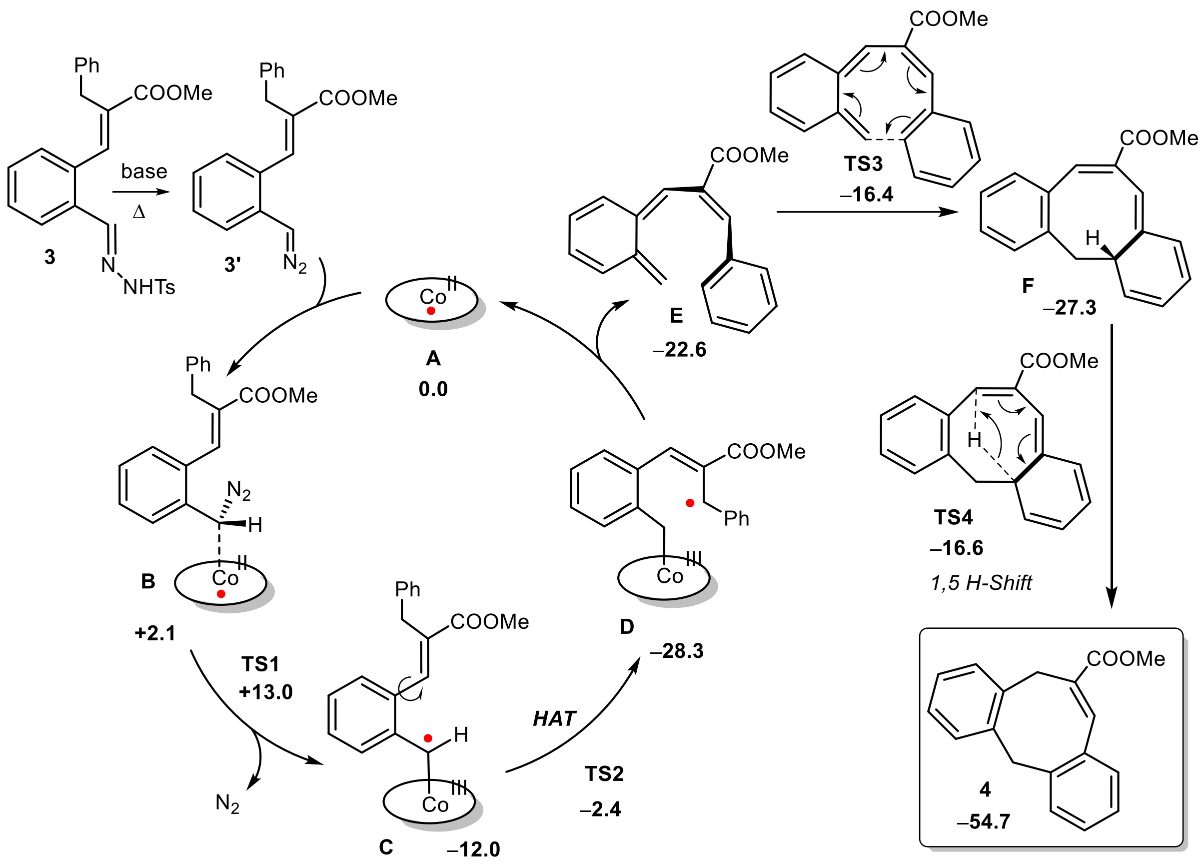

Scheme 4. Proposed catalytic cycle based on DFT calculations.

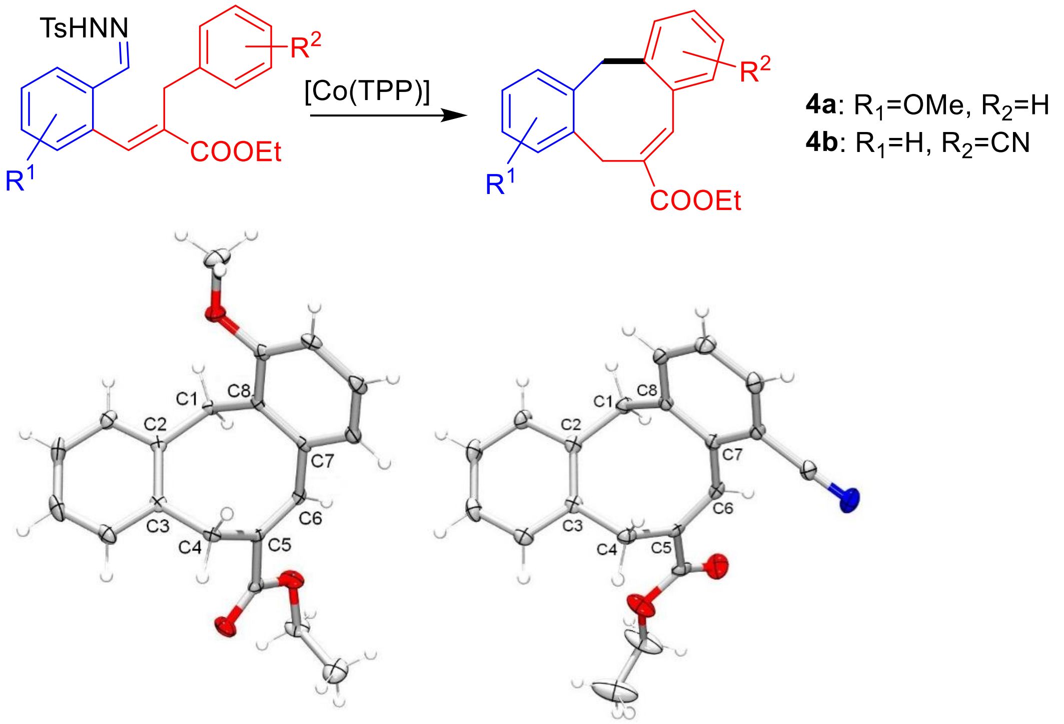

Figure 1. Molecular structure of 4a (left) and 4b (right), as obtained by single crystal X-ray diffraction studies. Selected bond distances [Å]: 2a, 2b C1–C8: 1.513(2), 1.518(3); C4–C5: 1.509(2), 1.511(3); C5–C6: 1.332(2), 1.333(3); C6–C7: 1.476(2), 1.475(3).

In **Chapter 5** we describe the synthesis of dibenzocyclooctenes from *ortho*-benzallylaryl *N*-tosyl hydrazones mediated by [Co(TPP)]. This is a novel route for the synthesis of eight-membered rings, which are typically quite challenging to prepare. Substrate screening revealed that the dibenzocyclooctenes are formed in good to excellent yields when the aromatic rings are substituted with a large variety of different groups. The ester moiety at the allylic position appears to be essential in this transformation, since removal or replacing it leads to the formation of different products.

The proposed reaction mechanism starts with activation of the diazo compound by [Co(TPP)] followed by intramolecular hydrogen atom abstraction (Scheme 4). This is followed by dissociation of an *ortho*-quinodimethane from the catalyst, which undergoes an 8π-cyclization step in which the new C–C bond is formed. Aromaticity in the ring is restored by a [1,5]-hydride shift which also causes the double bond at the allylic position to migrate. This migration was confirmed with 2D-NOESY NMR and X-ray crystallography (Figure 1).

The combined work described in this thesis shows that radical-carbenes can be used in selective reactivity when mediated by [Co(TPP)]. If allyl radical intermediates are generated that are in direct conjugation with the already weak Co–C bond *ortho*-quinodimethanes dissociate from the catalyst. These reactive *ortho*-quinodimethane intermediates react further in a series of unexpected reactions to give stable organic products like dihydronapthalenes, E-aryl dienes and dibenzocyclooctenes. As such, we have developed a novel radical-type methodology for the selective synthesis of these three new classes of compounds. Nearly all of the compounds made by the novel catalytic reactions described in this thesis were never reported before.

OUTLOOK

Based on the work described in this thesis, many follow-up projects can be envisioned. The work in Chapter 2 was promising, but did not result in an applicable process. Nonetheless, the results described provide proof-of-principle and the concept is still a promising pathway to obtain 'high-energy' intermediates from safe and cheap starting materials. For the catalytic bulk electrolysis experiments it will be relevant to find out where the rest of the substrate ends up. Choosing a different electrolyte may be part of the solution, but also different solvents are to be considered.

The other chapters also leave us with many interesting concepts. It would be interesting to investigate whether the aromatic ring in the substrates is essential. In the proposed mechanisms it becomes part of the *ortho*-quinodimethane, but in principle similar intermediates could separate from the catalyst when instead of an aromatic ring, only a double bond is present. Furthermore, it would be interesting to trap the *ortho*-quinodimethane in an intermolecular reaction. This does require proper design of the substrate, since we have seen that the fragment reacts with double bonds (Chapter 3), C–H bonds (Chapter 4) and aromatic rings (Chapter 5).

All reactivity described in this thesis revolves around carbene reactivity. However, it is known that azides react in a similar fashion as diazo compounds. Upon release of dinitrogen they form nitrene radicals instead of carbene radicals. If this trend holds true for the reactivity described in this work, interesting heterocycles may be formed this way. Finally, all reactivity investigated here revolves around the cobalt(II) porphyrin catalyst. Cobalt is a relatively available and non-toxic element, but it would be interesting to investigate other first row transition metals such as iron as well, as this metal is even more abundant and less toxic. However, since it belongs to a different group in the periodic table than cobalt it may take part in different reactivity. It does have a tendency to react in single electron steps, but different oxidation states of the catalyst may be required, as well as different electronic surroundings provided by the (non-innocent) ligands.