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Radical-type Reactions Controlled by Cobalt: From Carbene Radical Reactivity to the Catalytic Intermediacy of Reactive *o*-Quinodimethanes

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Dedicated to Professor Michael P. Doyle, in recognition of his excellent contributions to the field of metallo-carbene chemistry.

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Abstract In this account, we summarize our recent efforts in the fields of 'open-shell organometallic chemistry' and 'metalloradical catalysis'. We focus in particular on the use of so-called 'carbene radicals' for the synthesis of a variety of useful synthons for organic chemistry. We further show that unexpected reactivity arises from catalytic synthesis of unusual *o*-quinone methide and *o*-quinodimethane intermediates that undergo subsequent rearrangements to uncommon products.

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- 3 Carbene and Nitrene (Radical) Precursors
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Key words carbene radicals, carbene reactivity, metalloradical catalysis, *o*-quinodimethanes, open-shell organometallic chemistry

1 Introduction

In organometallic chemistry one-electron and radical-type elementary steps remain relatively underexplored in the development of new catalytic reactions. This is perhaps caused by an obstinate and dogmatic belief that radicals would always be 'too reactive to be selective'. While this is perhaps the case for free radicals, selective radical-type reactions are certainly possible in the coordination sphere of transition metals. In fact, nature solves its most difficult

and most interesting biosynthetic problems using the radical-type reactivity of metallo-enzymes. These reactions proceed with ultrahigh precision and selectivity, despite their radical nature. As such metallo-enzymes form an important source of inspiration for the development of new catalytic reactivity on the basis of radical-type elementary steps and one-electron reactivity. Our group takes an interest in developing such reactions, and has been active in this field since 2002.¹ Our initial investigations were focused on stoichiometric open-shell organometallic reactions, and as part of these investigations we discovered that activation of carbene precursors with iridium(II) compounds led to the

Figure 1 Reaction of $[(\text{Me}_3\text{TPA})\text{Ir}^{\text{II}}(\text{ethene})]^{2+}$ with ethyl diazoacetate in acetonitrile leading to ethene–carbene coupling. The reaction proceeds via an Ir^{III} –carbene radical intermediate, which has its spin density mostly located at the 'carbene carbon' atom.

formation of unusual Ir^{III}–carbene radical intermediates. These species turned out to have most of their spin density located at the ‘carbene carbon’ atom (Figure 1).^{1j}

Soon after this discovery, we showed (in collaboration with the group of Zhang) that very similar Co^{III}–carbene and Co^{III}–nitrene radical intermediates play an essential role in the catalytic carbene and nitrene transfer reactivity of planar, low-spin cobalt(II) catalysts.² Since then, the field has developed in various directions, providing several new and useful catalytic protocols for organic synthesis.

This account is focused on our recent contributions to the field of cobalt(II) ‘metalloradical catalysis’.³ Multiple new reactions were developed on the basis of the one-electron radical-type reactivity of cobalt(II) in reactions with carbene and nitrene precursors (Scheme 1), and the mechanisms of these reactions have been studied in detail by using a combination of spectroscopic studies, model reactions, spin trapping, and supporting DFT calculations. These studies clearly revealed the redox noninnocence of nitrenes and carbenes when bound to cobalt(II), which convert into cobalt(III)–nitrene and –carbene radical species (one-electron reduced nitrene or carbene units) by intramolecular single-electron transfer from cobalt(II) to the nitrene or carbene moiety (Scheme 1). As such, discrete nitrogen- or carbon-centered radical species are generated, and it was recognized that such ‘carbene and nitrene radicals’ have the potential to mediate a variety of selective radical-type transformations.⁴

A concrete recent example from our group concerning the involvement of nitrene radical intermediates in catalytic ring-closure reactions of aliphatic azides to generate N-heterocycles is shown in Scheme 2.⁵

Scheme 1 Left: Metalloradical catalysis concepts. Right: Redox noninnocence of nitrenes and carbenes generated at cobalt(II) metallo-radicals

Scheme 2 Catalytic cycle using an aliphatic azide as the nitrene source

The azide substrate interacts with the catalyst, which results in dinitrogen loss of the substrate and the formation of a nitrene radical intermediate. The next step is hydrogen atom abstraction of the benzylic position followed by the radical rebound step in which the heterocycle is formed.

Biographical Sketches

Bas de Bruin (born 1971) completed his PhD at the Radboud University Nijmegen (Prof. A. W. Gal, 1999). After post-doctoral research at the MPI für Bio-Anorganische Chemie in Mülheim a/d Ruhr (Prof. K. Wieghardt), he returned to the Radboud University Nijmegen

as an assistant professor. In 2005, he moved to the University of Amsterdam, where he was promoted to associate professor in 2008 and to full professor in 2013. His research focuses on radical organometallic chemistry, metalloradical catalysis, EPR spectroscopy, olefin oxygen-

ation, polymer synthesis, mechanistic studies, and computational catalysis. He is particularly interested in the development of new (bio-inspired) catalytic transformations.

Colet te Grotenhuis (born 1989) obtained her Master degree cum laude at the Radboud University Nijmegen (2013). Her dissertations were on ‘reactivity catalytic in phosphorus’ (Prof. F. P. J. T. Rutjes, Radboud University Nijmegen)

and ‘hydrogels by polymer crosslinking’ (Prof. O. A. E. Scherman, Cambridge University UK). Next, she completed her PhD at the University of Amsterdam (Prof. B. de Bruin, 2018) on the topic of ‘taming carbon-centered radicals with

cobalt’. The next step in her career will be a postdoctoral fellowship. Her main interests lie in the understanding of catalytic transformations and employing these for the development of new reactivity.

The unprotected product also interacts with the catalyst and therefore Boc protection is required to prevent product inhibition. Follow-up studies performed in our lab have shown that this transformation is about 2.5 times faster when a Co(III) corrole is used as the catalyst instead of [Co(TPP)]. The difference in activity is due to the higher electron density of the corrole complex.⁶

2 General (Fischer-Type) Carbene and Nitrene Reactivity and Their Relation to Carbene and Nitrene Radical Reactivity

The discrete spin density at the carbon and nitrogen atoms of the abovementioned nitrene and carbene radical species leads to typical radical-type reactivity (Scheme 1, Scheme 2), distinct from traditional closed-shell (Fischer-type) nitrenes and carbenes. However, the species reveal also many similarities with the more common Fischer-type species. In order to better illustrate the similarities and differences, we here provide a short overview of general carbene and nitrene reactivity of the closed-shell Fischer-type species first, before we move on to a more detailed description of their one-electron-reduced radical analogs.

Most typically, Fischer-type nitrene and carbene complexes reveal electrophilic reactivity of the reactive nitrene or carbene moiety. The electrophilic nature of these species can be easily understood on the basis of their frontier orbital interactions, as illustrated in Figure 2 (left) for a typical Fischer-type carbene complex.

Figure 2 Left: Typical Fischer-type carbene and associated MO diagram explaining its electrophilic reactivity. Right: Carbene radical and associated MO diagram explaining the observed intramolecular reduction of the carbene moiety leading to its carbon-centered radical reactivity and reduced electrophilicity

The LUMO of the Fischer-type carbene (or nitrene) complex is a π^* antibonding orbital between one of the metal d π -type orbitals and the carbon (or nitrogen) p orbital. The LUMO is polarized to carbon (or nitrogen), resulting in electrophilic reactivity of the carbene carbon (or nitrene nitrogen) atom.

Fischer metal carbene (or metal nitrene) reactions include a variety of carbene (or nitrene) insertion and addition reactions with/into/to X–H bonds (X = C, O, N, S, Si), C=C, and C≡C bonds.⁷ As such, a large body of reactions involving the reactivity of carbenes (and nitrenes) has been developed relying on the electrophilic nature of these hypovalent species, and has shown to be of tremendous value for complex molecule synthesis.⁸

3 Carbene and Nitrene (Radical) Precursors

Several routes to obtain carbene and nitrene complexes have been reported. Early reports on nitrene transfer reactions relied on the use of powerful oxidants such as iminoiodanes⁹ and haloamine-T,¹⁰ but more recently the use of azides as nitrene sources became more popular (see for example Scheme 1 and Scheme 2).^{7b} The use of azides as precursors has the advantage that the only side-product formed in the nitrene transfer step is dinitrogen (Scheme 1). Azides are also easier to synthesize and have a longer storage stability.^{4c,11} Carbene complexes are most commonly generated from diazo compounds, which (as in formation of nitrene complexes from azides) generate the hypovalent carbene moiety upon loss of dinitrogen. However, the direct use of diazo compounds is often problematic, as many of these compounds are unstable, explosive, and toxic.^{7c} Furthermore, reactions proceeding via Fischer-type carbene intermediates typically require slow addition of diazo compounds (or diazo compound precursors) using e.g. syringe-pump techniques to prevent carbene-carbene dimerization; unwanted side-reactions that typically proceed through the attack of the nucleophilic carbon atom of a diazo compound on the electrophilic carbon atom of a typical Fischer-type carbene intermediate. For that reason, several new approaches have been developed to generate metal-carbene complexes, which have recently been reviewed by Jia and Ma.^{7c} One of the most attractive approaches to generate metal-carbene intermediates is shown in Scheme 3. In situ generation of diazo compounds from safe and easy-to-synthesize tosyl hydrazones by base-triggered thermolysis in the presence of a catalyst gives rise to safe and convenient reaction conditions, with low steady state concentrations of the diazo compound. This is possible because the reactive diazo compound gets rapidly consumed in the catalytic follow-up reaction.¹²

The tosyl hydrazone method depicted in Scheme 3 solves most of the abovementioned safety issues, but carbene-carbene dimerization is not (or not fully) prevented for reactions involving Fischer-type carbenes.¹³ Furthermore, energy loss and waste formation (TsH and/or salts thereof) is still an issue.

Scheme 3 Metal-carbene formation involving trapping of in situ formed diazo compounds generated by base-mediated thermolysis of tosyl hydrazones

4 Formation and Intrinsic Radical-Type Reactivity of Carbene and Nitrene radicals

Carbene (nitrene) radical intermediates can be formed in a similar manner as reported for the generation of Fischer-type carbene (nitrene) intermediates, by using the same type of precursors. The difference between a carbene (nitrene) radical intermediate and a traditional Fischer-type carbene (nitrene) arises from the use of a planar, low-spin and open-shell, paramagnetic metalloradical cobalt(II) catalysts instead of a traditional closed-shell, diamagnetic catalyst such as Cu(I), Rh(II)₂, or Ru(II). The radical-type reactivity of carbene and nitrene radical species can be easily understood on the basis of their frontier orbital interactions, as illustrated in Figure 2 (right) for a carbene radical complex. Carbene formation at planar low-spin cobalt(II) species will push up the energy of the half-filled *d*₂₂ orbital, above the carbon-dominated π*-antibonding orbital, thus resulting in intramolecular single-electron transfer from the *d*₂₂ orbital of the metal into this π*-antibonding orbital (Figure 2), effectively producing a 'carbene radical' complex (one-electron reduced Fischer-type carbene).^{4b} Since the electron in the SOMO of the complex mainly resides on the carbon atom, the carbene carbon atom reacts in fact as a carbon radical. At the same time, the presence of an unpaired electron in this orbital reduces the electrophilicity of the carbene carbon atom when compared to a traditional Fischer-type carbene.^{4b,7b,8a} This explains why carbene radical complexes show a much lower tendency to carbene-carbene dimerization from diazo compounds than traditional Fischer-type carbenes generated at Cu(I), Rh(II)₂, or Ru(II).^{4a} The orbital arrangement in 'nitrene radical' species is similar.¹⁴

5 Types of Cobalt Catalysts Used in Reactions Involving Carbene and Nitrene Radicals

Several ligand systems are used for radical carbene or radical nitrene reactivity, but most are based on the salen or porphyrin motif (Figure 3).^{4b,f,15} Recently, also the tetraaza[14]annulene scaffold has been recognized as a highly useful ligand in cobalt-catalyzed metalloradical catalysis, leading to high activities.^{4g,i,16}

Figure 3 Examples of complexes used for carbene and nitrene transfer

The porphyrin motif is inspired by nature and resembles both the heme ring of cytochrome P450 (a porphyrin containing iron) and the corrole ring in co-enzyme B12 in a variety of B12-dependent enzymes.¹⁷ These types of enzymes are known for oxidation and alkylation reactions under mild conditions.¹⁸ The synthesis of porphyrins is sometimes challenging, but in the end the motif has many options for varying both the steric and electronic properties around the active site, making the synthetic efforts worthwhile. The complexes described in Figure 3 have been intensively studied as catalysts for cyclopropanation reactions, using various alkenes and diazo compounds as the carbene transfer agents. A significant advantage of the cobalt-porphyrin ([Co(por)]) systems is that they can perform this reaction using acceptor-acceptor substituted diazo compounds, which are the most difficult types of diazo compounds to activate.^{4f,19} The [Co(por)] catalysts are predominantly used for the cyclopropanation of alkenes and alkynes.^{4f} The first catalytic cyclopropanation with [Co(TPP)] was published in 2003 by the group of Cenini.²⁰ The group of Zhang has developed a variety of different porphyrins with chiral substituents enabling them to perform these reactions with high enantioselectivity (Figure 4).^{19,21} Next to cyclopropanation, cobalt porphyrins have also been used for C-H activation.^{15a} Here the challenge lies in the chemoselectivity, since most organic molecules contain many very similar C-H bonds. These reactions are very desirable, because in principle they allow chemists to perform chemical transformations without any pre-functionalization of the substrate, thus leading to fewer steps and less waste.^{15a} The porphyrin moiety enables such selectivity in C-H activation because of several factors: (1) shape and regioselectivity can be achieved by modification of the backbone with bulky groups or functional groups which can interact with the substrate; (2) low catalyst loading can be

achieved by putting suitable substituents on the ligand; and (3) it is possible to attach chiral groups to the porphyrin ligand.^{15a}

Figure 4 Chiral cobalt-porphyrin complexes published by Zhang

Cobalt-salen complexes (Figure 3) are known for similar reactivity as the porphyrins described above. Salen complexes have been used for carbene transfer reactions to form, amongst others, cyclopropanes.^{15b,22} Because of the chirality that can be installed into the backbone of the ligand, a lot of research has been devoted to achieve enantioselective cyclopropane synthesis.^{22a,c} In Scheme 4 the reaction developed by Katsuki is depicted. With the chiral complex they used they were able to synthesize cyclopropanes in excellent *cis* diastereoselectivity (98:2) and enantioselectivity (98% ee) in very good yields (89%). Furthermore, they showed that applying a catalyst with the opposite chirality in the backbone allows formation of the other enantiomer of the product.^{22c}

Besides [Co(por)] and [Co(salen)] complexes, cobalt(II) tetraaza[14]annulenes (Figure 3) were recently also disclosed to be useful metalloradical catalysts. The general motive is comparable to the porphyrin, with a fully aromatic backbone and four nitrogen atoms which coordinate to the metal. Because of these similarities [Co(MeTAA)] ($R^1 = \text{Me}$, $R^2 = \text{H}$ in Figure 3) has similar reactivity as the cobalt-porphyrin complex, but different properties nonetheless.

For decades researchers only looked into the coordination chemistry of [Co(MeTAA)], but recently our group has shown that these complexes are actually highly active metalloradical catalysts proceeding via carbene radical intermediates.^{4g,1,23}

A large range of cyclopropanation reactions with [Co(MeTAA)] as catalyst have been shown to proceed in nearly quantitative yield. Dimerization of the diazo compound is inhibited and the cyclic products are formed with high diastereoselectivity, resulting in the formation of mainly *trans* cyclopropanes. The mechanism has been extensively investigated both experimentally and by using DFT calculations, which confirm that for [Co(MeTAA)] catalyst the barriers are lower than those observed for the [Co(TPP)] catalyst. EPR results provide strong support for the proposed metalloradical mechanism (Figure 5).^{23b,24}

Figure 5 Isotropic X-band EPR spectrum of the PBN- (left) and DMPO- (right) trapped carbon-centered radicals ($T = 298 \text{ K}$).

A last variant of the available catalysts we would like to discuss is the encapsulated cobalt porphyrin (Scheme 5). In this case the active site is placed inside a cage and the substrates have to enter through the pores of the shell. This has resulted in the development of size-selective cyclopropanation procedures in homogeneous solution (Figure 6). Furthermore, the properties of the cage enable this transformation to proceed in aqueous media.²⁵

Scheme 4 Cyclopropanation with a chiral cobalt-salen complex results in product formation with both high *cis* diastereoselectivity and enantioselectivity.

Scheme 5 Synthesis of cubic cages and subsequent encapsulation of tetrapyrroline-substituted metallo-porphyrins

Figure 6 Schematic representation of the proposed pore-size-controlled, size-selective transformations catalyzed by 'caged catalyst' [2-Co@1]

6 Applications of Cobalt-Catalyzed Ring-Closure Reactions via Carbene Radicals

This account primarily focuses on cobalt-carbene radical reactivity, and in particular on the development of new catalytic reactions based on the intrinsic radical-type behavior of these catalytic intermediates. Cobalt-carbene radicals offer a tremendous opportunity to develop new ring-closing protocols. Several of such protocols have already been disclosed, but there are many still undisclosed prospects. The following section of this account provides an overview of the use of cobalt-carbene radicals in reported catalytic ring-closing reactions.

In 2012, the Zhang group published the regioselective synthesis of trisubstituted furans as depicted in Scheme 6. Radical addition of the Co(III)-carbene radical to an alkyne results in formation of a vinyl radical intermediate (right to bottom in Scheme 6). This linear species undergoes ring-forming radical addition to the carbonyl group followed by release of the furan through radical β -scission.^{4k}

Scheme 6 [Co(porphyrin)]-catalyzed radical ring-closing reaction to form furans

Recently, our group has added a series of intra- and intermolecular coupling reactions to the palette of cobalt porphyrin reactivity, producing ring compounds of various sizes (three-, four-, five-, and six-membered rings). A summary of these reactions is presented below.

A reaction, which at first glance looks related to the above mentioned cyclopropanation, is the difluorocarbene transfer, in which again the product obtained is a cyclopropane. However, now the precursor is not a (protected) diazo compound, but the carbene is formed from the trifluoromethyl anion upon loss of fluoride at the catalyst (first and second step in Scheme 7). This is followed by stepwise radical-type addition to the olefin double bond, forming a Co^{III}-CF₂-alkyl species containing a ligand-centered radical. Subsequent ring closing produces the *gem*-difluorocyclopropane and releases the catalyst.²⁶

Scheme 7 Proposed catalytic cycle for the difluorocyclopropanation of *n*-butyl acrylate catalyzed by a cobalt(II)-porphyrinato complex.

Intermolecular coupling of a diazo compound and carbon monoxide led to the formation of ketenes, which were in situ converted to more stable products such as β -lactams (Scheme 8). Upon activation of a diazo compound, a carbene radical intermediate was formed, which could be carbonylated with carbon monoxide resulting in the formation of ketenes. These were trapped in situ with amines, alcohols, or imines to yield esters, amides or β -lactams, respectively, in one-pot cascade reactions. The reaction sequence leading to β -lactams is shown in Scheme 8 and proceeds well both with [Co(TPP)] and [Co(MeTAA)] for a broad range of substrates.^{4m,23a}

Scheme 8 One-pot catalytic protocol to β -lactams involving carbene (radical) carbonylation and trapping of the ketene intermediates with imines

Another example of our group which we want to highlight is the synthesis of indolines. As depicted in Scheme 9 the catalytic cycle starts by coordination of the diazo substrate to the cobalt porphyrin catalyst. This is followed by loss of dinitrogen and the formation of a carbon-centered radical intermediate. [1,5]-Hydrogen atom transfer leads to a stabilized benzylic radical (DFT calculations show strong delocalization of the spin density over the aromatic ring) which ring-closes through a radical-rebound step. DFT calculations reveal surprisingly low barriers for all steps in the reported cycle, making the formation of the diazo compound from the tosyl hydrazone precursor the rate-limiting step of this conversion. These reactions have a broad substrate scope.

Scheme 9 Indoline synthesis with [Co^{II}(TPP)] via carbene radicals

7 Intermediacy of *o*-Quinone Methides and *o*-Quinodimethanes in Carbene Ring-Closing Reactions

We have found that in many of the investigated reactions *ortho*-quinodimethanes or *ortho*-quinone methides are important intermediates in the catalytic cycle. These are reactive intermediates, which can be formally considered being derived from *o*-cresol or *o*-xylene after double hydrogen atom abstraction (Figure 7). They may have some biradical character, although their reported reactivity is dominated by closed-shell cycloaddition reactions and related pericyclic reactions of synthetic use in organic chemistry.²⁷

Figure 7 *o*-Quinone methides and *o*-quinodimethanes can formally be considered being derived from *o*-cresols or *o*-xylenes after double hydrogen atom abstraction.

Cobalt(II) metalloradical catalysis in fact allows the catalytic synthesis of these interesting and reactive 'dearomatized' compounds from tosyl hydrazones, giving access to several interesting follow-up products. Relevant examples are described in the following section.

We published in 2014 that activation of salicyl *N*-tosyl hydrazones by a cobalt porphyrin catalyst in the presence

Scheme 10 Catalytic cycle for 2*H*-chromene formation from a diazo compound and acetylene by cobalt porphyrins

of alkynes produces 2*H*-chromenes in a regioselective manner (Scheme 10). This is again a one-pot synthetic protocol, starting from cheap and readily available starting materials with abroad substrate scope. In the catalytic cycle the carbene radical adds to the triple bond and produces a vinyl radical species (**D**, Scheme 10). The cycle continues with hydrogen atom abstraction of the phenol, which leads to spontaneous dissociation of *o*-quinone methide **E** from the catalyst. The last step is an endocyclic ring closure to form the 2*H*-chromene product.⁴¹

Recently, the [Co(MeTAA)] catalyst was shown to be a highly effective catalyst for the synthesis of a series of five-membered ring compounds: 1*H*-indenes.⁴¹ Scheme 11 displays the catalytic cycle for the synthesis of 1*H*-indenes from diazo compounds (based on trapping and kinetic isotope experiments and confirmed with DFT calculations). The catalytic cycle starts by coordination of the substrate to the [Co(MeTAA)] catalyst (**A**) to form carbenoid intermediate **B**.

Scheme 11 Catalytic cycle in which [Co(MeTAA)] catalyzes the formation of 1*H*-indenes through carbene radical intermediates

Release of dinitrogen leads to the formation of carbene radical species **C**. As described above, intramolecular reduction takes place resulting in single-electron transfer from the cobalt atom to the p_y orbital on the substrate carbon

atom. This carbene radical then attacks the vinylic double bond to form a five-membered ring (intermediate **D**). The radical is now localized at the benzylic position. From here on, there are two possible pathways to arrive at the 1*H*-indene product **F**. Either a [1,2]-hydrogen atom shift leads to formation of intermediate **E**, which quickly undergoes homolysis of the Co–C bond with release of the product. Alternatively, dearomatized dimethide **F'** could dissociate from the catalyst by cleavage of the Co–C bond, and subsequent re-aromatization forms product **F**.

In a follow-up study, we encountered a series of selective reactions in which completely different products are formed depending only on small variations in the substitution pattern of the substrate (Scheme 12).^{28,29} These reactions involve a series of related *o*-styryl *N*-tosyl hydrazones activated by metalloradical catalysis to produce dihydronaphthalenes, *E*-aryl dienes, and dibenzocyclooctenes, all in high isolated yields. Each of these reactions has a broad substrate scope, and they all proceed via *o*-quinodimethane intermediates.

Scheme 12 Formation of dihydronaphthalenes, *E*-aryl dienes, and dibenzocyclooctenes, depending only on the substitution pattern of the allyl moiety of the substrate

We first investigated the synthesis of dihydronaphthalenes from *o*-styryl *N*-tosyl hydrazones using metalloradical catalysis.²⁸ 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 13). However, DFT calculations revealed a low barrier alternative mechanism, which proceeds through *o*-quinodimethane intermediates to produce the same products. These are formed by homolysis of the weak Co–C bond and continue to form the product by 6 π -cyclization (Scheme 13, middle).

Scheme 13 Dihydronaphthalene formation ($Y = H$) versus E -aryl diene formation ($Y = \text{alkyl}$) in $[\text{Co}(\text{TPP})]$ -catalyzed reactions; evidence for involvement of o -quinodimethane intermediates

Substrate screening revealed that various R^1 substituents are allowed at the aromatic ring for substrates with an $R^2 = \text{COOEt}$ 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 o -quinodimethane intermediate, the R^2 group is expected to have much larger influence, as observed experimentally.

To obtain further understanding of the o -quinodimethane intermediates suggested above, a new range of sub-

strates was synthesized containing an alkyl group at the vinylic position of o -styryl N -tosyl hydrazones and tested in metalloradical catalysis with $[\text{Co}(\text{TPP})]$. Formation of substituted dihydronaphthalene products was initially anticipated, but instead E -aryl dienes were isolated in good to excellent yields (Scheme 12, middle; Scheme 13, bottom).²⁸ The mechanism of this transformation, as confirmed by DFT, starts the same as before. 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 $\text{Co}-\text{C}$ bond (which is in direct conjugation with the allyl radical) leads to release of an o -quinodimethane intermediate from the catalyst (Scheme 13). The latter reacts further in an ene-type [1,7]-hydride shift to form the observed E -aryl dienes (Scheme 14). 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 calculations 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 (Scheme 14).²⁸

Early 2018, we described the synthesis of dibenzocyclooctenes from o -benzallylaryl N -tosyl hydrazones mediated by $[\text{Co}(\text{TPP})]$.²⁹ This is a new route for the synthesis of eight-membered rings, which are typically quite challenging to prepare. These unusual reactions follow related pathways. 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 remov-

Scheme 14 Pathway for butadiene formation from intermediate **B** has the lowest barrier

al 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 15). This is followed by dissociation of an *o*-quinodimethane from the

Scheme 15 Proposed catalytic cycle for dibenzocyclooctene formation based on DFT calculations

Figure 8 Molecular structure of **4a** (left) and **4b** (right), as obtained by single-crystal X-ray diffraction studies. Selected bond distances [Å]: **4a**, **4b** 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)

catalyst, which in this case undergoes an 8π -cyclization step in which a 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 8).²⁹

The abovementioned metalloradical reactions that produce *o*-quinone methide and *o*-quinodimethane intermediates in a catalytic manner are highly interesting, both from a synthetic perspective and from a mechanistic point of view. They give rise to a variety of products that are difficult to prepare otherwise, such as *2H*-chromenes, *1H*-indenes, dihydronaphthalenes, *E*-aryl dienes, and dibenzocyclooctenes. Traditional organic synthesis of these compounds requires multi-step reactions, while they can be prepared in one-step one-pot reactions using cobalt(II) metalloradical catalysis. We are convinced that there are many other reactions to be uncovered proceeding via these intermediates.

However, it is important to realize that the involvement of *o*-quinone methides and *o*-quinodimethane intermediates also puts restrictions on the applicability of chiral catalysts in cobalt(II) metalloradical catalysis. As the enantioselectivity determining ring-closing steps in many of these reactions is in fact uncatalyzed, taking place far from the influence of the (chiral) metal catalyst, this prevents the catalyst of having a direct influence on the stereochemistry of the products. From the data presently available it seems that in all reactions proceeding via carbene radical intermediates that proceed on to produce coordinated substrate-centered radicals in direct conjugation with the already

Scheme 16 Metalloradical pathways generating substrate-centered radicals in direct conjugation with the weak Co–C bond lead to dissociation of *o*-quinone methides or *o*-quinodimethane intermediates: No radical rebound steps and no enantiocontrol by the catalyst.

weak Co–C bond, the latter becomes so weak that spontaneous dissociation of *o*-quinone methide and *o*-quinodimethane intermediates occurs under the applied catalytic conditions before ring closure (Scheme 16). This avoids radical-rebound steps and thus prevents enantioselective catalysis in all cases reported thus far.

On the other hand, in reactions where carbene radical intermediates react on to produce coordinated substrate-centered radicals that are electronically isolated from, but geometrically close to the weak Co–C bond, the reactions proceed via radical-rebound (i.e. one-electron reductive elimination) steps directly influenced by the chirality of the catalyst, thus allowing enantioselective catalysis (Scheme 17).³⁰

8 Conclusion

It should be clear from the above examples that the scope of carbene radicals and metalloradical catalysis goes far beyond cyclopropanation. The scope of these compounds is broad, and likely many new reaction pathways leading to interesting new products are still to be uncovered. A particularly interesting observation in this perspective is the catalytic formation of *o*-quinone methides and *o*-quinodimethanes in cobalt(II) metalloradical catalysis, both from a synthetic perspective and from a mechanistic point of view. They give rise to a variety of products that are difficult to prepare otherwise, such as 2*H*-chromenes,

1*H*-indenes, dihydronaphthalenes, *E*-aryl dienes, and dibenzocyclooctenes. Many other reactions proceeding via these unusual intermediates are likely still to be uncovered. While their involvement puts restrictions on the applicability of chiral catalysts in cobalt(II) metalloradical catalysis, they offer many opportunities to develop new one-step, one-pot protocols for the synthesis of complex molecules which would otherwise require elaborate multi-step synthesis when using more traditional organic chemistry protocols.

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