

Experimental Evidence for Cobalt(III)-Carbene Radicals: Key Intermediates in Cobalt(II)-Based Metalloradical Cyclopropanation

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S Supporting Information

ABSTRACT: New and conclusive evidence has been obtained for the existence of cobalt(III)-carbene radicals that have been previously proposed as the key intermediates in the underlying mechanism of metalloradical cyclopropanation by cobalt(II) complexes of porphyrins. In the absence of olefin substrates, reaction of [Co(TPP)] with ethyl styryldiazoacetate was found to generate the corresponding cobalt(III)-vinylcarbene radical that subsequently dimerizes via its γ -radical allylic resonance form to afford a dinuclear cobalt(III) porphyrin complex. X-ray structural analysis reveals a highly compact dimeric structure wherein the two metalporphyrin units are arranged in a face-to-face fashion through a tetrasubstituted 1,5-hexadiene C₆-bridge between the two Co(III) centers. The γ -radical allylic resonance form of the cobalt(III)-vinylcarbene radical intermediate could be effectively trapped by TEMPO via C–O bond formation to give a mononuclear cobalt(III) complex instead of the dimeric product. The allylic radical nature and related reactivity profile of the cobalt(III)-carbene radical, including its inability to abstract hydrogen atoms from toluene solvent, were established by DFT calculations.

Cyclopropanation of alkenes via carbene transfer from diazo reagents represents an important class of organic transformations. The resulting three-membered cyclopropanes, especially in their optically active forms, have found a wide range of fundamental and practical applications.¹ To enhance reactivity and control stereoselectivities, complexes of different transition metals supported by various chiral ligands have been developed to catalyze the stereoselective construction of the smallest carbocyclic structures.² Represented by the most recognized dirhodium(II) complexes of chiral carboxamidates and carboxylates, several classes of chiral metal catalysts have been demonstrated to enable successful asymmetric cyclopropanation reactions for certain combinations of alkenes and diazo reagents, affording the corresponding cyclopropane derivatives in high yields with excellent diastereoselectivity and enantioselectivity.^{2,3} Mechanistically, it has been shown that most existing catalytic systems share a general cyclopropanation mechanism that involves electrophilic (Fischer-type) metalcarbenes as the key intermediates.^{2–4} Because of the electrophilic nature of the metalcarbene intermediates, highly enhanced reactivity has been achieved for cyclopropanation of aromatic and other electron-rich olefins. For the same reason, cyclopropanation of

electron-deficient olefins has proven to be challenging. The electrophilic nature of the metalcarbene intermediates is also responsible for the notorious side reaction of carbene dimerization, a problem in cyclopropanation that often has to be addressed through the slow addition of diazo reagents and/or by the use of excess olefins.

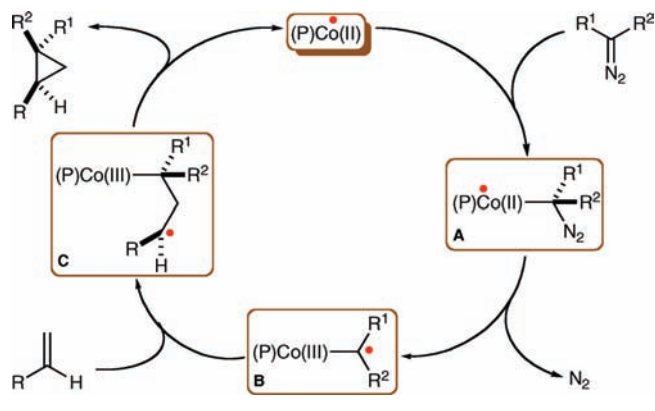
Different from the Rh(II)₂-based and other closed-shell metal catalysts, cobalt(II) complexes of porphyrins, [Co(Por)], which exist as stable metalloradicals with a well-defined low-spin (d_{xy})²(d_{xz,yz})⁴(d_{z²})¹ electronic configuration, have recently been developed into a unique class of open-shell catalysts for cyclopropanation.⁵ Supported by a toolbox of D₂-symmetric chiral porphyrins with tunable electronic, steric, and chiral environments,^{5a,6} we have demonstrated that Co(II)-based chiral metalloradical catalysts [Co(D₂-Por*)] are highly effective for asymmetric cyclopropanation of a broad scope of olefin substrates in excellent diastereoselectivity and enantioselectivity.^{5–9} Particularly, the Co(II)-based metalloradical system permits for the first time efficient asymmetric cyclopropanation of electron-deficient olefins.^{7b–d,f,g} Furthermore, as a practical attribute that is atypical for other metal-based catalytic systems, Co(II)-catalyzed cyclopropanation reactions can be operated in a one-time protocol without the need of slow addition of diazo reagents and with the alkene as the limiting reagent owing to the absence of the competitive carbene dimerization side reaction. It is evident that the cyclopropanation reactivity profile of the Co(II)-based open-shell metalloradical system is distinctly different from those of the widely studied Rh₂ and other closed-shell systems, suggesting the involvement of catalytic intermediates that are nonelectrophilic.^{5b,7a,10}

Our recent EPR spectroscopic investigations and systematic DFT calculations have led to the disclosure of an unprecedented reaction mechanism of the Co(II)-catalyzed cyclopropanation (Scheme 1) that involves an unusual Co(III)-carbene radical (**B**) as the key intermediate undergoing a stepwise radical addition–substitution pathway.¹¹ Different from the common electrophilic Fischer-type carbene intermediates, the new radical carbene intermediate **B** is effectively an [Co(Por)]-supported carbon-based radical,¹² which is capable of undergoing common radical reactions (such as radical addition and radical substitution)¹³ but is not “free”, as its reactivity is well controlled by the electronic, steric, and chiral environments of the covalently attached [Co(Por)] element. While the proposed Co(III)-carbene radical intermediate

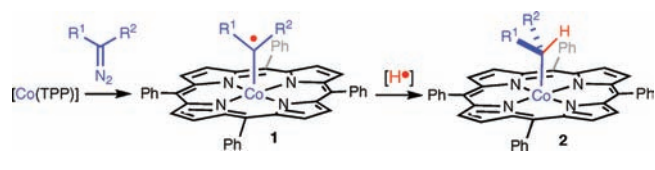
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Scheme 1. Mechanism of Metalloradical Cyclopropanation



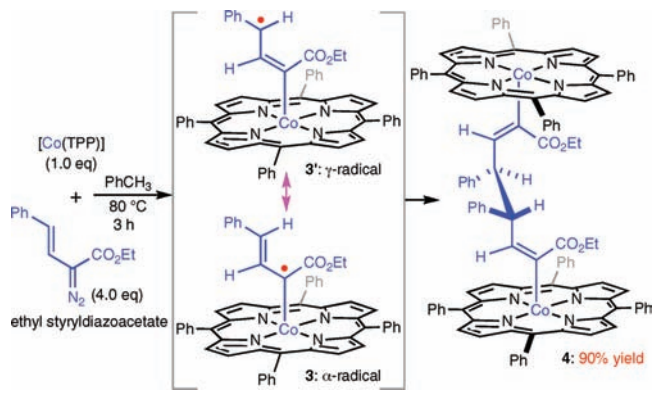
Scheme 2. Stoichiometric Reactions of [Co(TPP)] with Diazo Reagents and Subsequent H-Atom Abstraction Process



B was experimentally detected from a reaction mixture by EPR spectroscopy and ESI mass spectrometry,^{11,14} our early efforts toward direct characterizations of the intermediates in isolated forms have been met with formidable challenges due to their high reactivity, resulting in multiple decomposition products. With the use of ethyl styryldiazoacetate as a unique carbene source, herein we wish to report our recent success in obtaining conclusive chemical evidence to support the existence of the Co(III)-carbene radicals. Taking advantage of allylic radical resonance, we show that the resulting cobalt(III)-vinylcarbene radical, generated in a stoichiometric reaction of ethyl styryldiazoacetate with [Co(TPP)] in the absence of olefin substrates, cleanly dimerizes and can be effectively trapped by TEMPO in its allylic γ -radical resonance form to afford the respective C–C or C–O radical coupling products in high yields. Based on DFT calculations, we give an account on the spin density distribution of the cobalt(III)-vinylcarbene radical and provide both kinetic and thermodynamic grounds for its stability toward H-atom abstraction reactions.

To characterize the Co(III)-carbene radicals, a series of diazo reagents with different types of α substituents, including diazoacetates, aryldiazoacetates, and diazomalones, were employed as carbene sources to react with [Co(TPP)] in the absence of olefin substrates (Scheme 2). Our attempts from these experiments failed to provide concrete evidence for the formation of carbene radicals **1**, as these stoichiometric reactions typically gave a complex mixture of products. Among several organic and organometallic species in the reaction mixtures, the corresponding Co(III)-alkyl complex **2** (Scheme 2, $R^1 = \text{H}$, $R^2 = \text{CO}_2\text{Et}$) could be positively identified by NMR spectroscopy from the reaction with ethyl diazoacetate. The single-crystal X-ray structure of this compound was previously reported by Cenini and co-workers.^{5c} Chan and co-workers recently reported an analogous reaction with [Rh(II)(Por)].¹⁵ While it seems reasonable to assume that **2** would be formed directly from the Co(III) carbon-based radical intermediate **1** (Scheme 2, $R^1 = \text{H}$, $R^2 = \text{CO}_2\text{Et}$) by a hydrogen

Scheme 3. Generation of Cobalt(III)-Vinylcarbene Radical from Reaction of [Co(TPP)] with Ethyl Styryldiazoacetate and Subsequent Homodimerization via C–C Bond Formation



atom abstraction process (from solvents or some other sources in the system), Cenini and co-workers proposed a different Co(II) intermediate for its formation.^{5c} In light of this ambiguity,^{5c} it is clear that observation of **2** could not be taken as convincing evidence for the existence of the Co(III)-carbene radicals.

In a search for more definite experimental evidence for the key Co(III)-carbene radical intermediate, we then turned our attention to the use of ethyl styryldiazoacetate as the carbene source for the stoichiometric reaction with [Co(TPP)] (Scheme 3). It was envisioned that the corresponding carbene α -radical **3** would be stabilized by its γ -radical resonance form **3'** due to its allylic nature (Scheme 3). Different from our previous experiments with other diazo reagents, the reaction of [Co(TPP)] with 4 equiv of ethyl styryldiazoacetate in toluene at 80 °C was found to be pleasingly clean and generated only one major product (**4**), which could be isolated in 90% yield after 3 h of reaction. The data obtained from NMR and HRMS measurements (see Supporting Information) show **4** to be a dimeric cobalt(III) porphyrin complex. Particularly, proton resonances with unusual negative chemical shifts appeared in the high-field region of its ¹H NMR spectrum, which is indicative of the presence of hydrogen-containing ligands in the axial position of **4**. The detailed structure of **4** (Scheme 3) was finally unveiled by single-crystal X-ray diffraction, which is consistent with all the spectroscopic data. As shown in Figure 1, the two cobalt porphyrins in **4** are arranged in a face-to-face fashion through a tetrasubstituted 1,5-hexadiene C₆-bridge between the two Co(III) centers; the distance between the two cobalt ions is 9.02 Å. It is instantly recognizable that the dinuclear complex **4** was formed from the radical dimerization of the initially generated Co(III)-carbene α -radical **3** via its γ -radical allylic resonance form **3'** (Scheme 3).¹³

In an effort to probe the electronic structure of the cobalt(III)-vinylcarbene radical, DFT calculations were performed on (Por)Co-C(CO₂Me)(CHCHPh) (**5**, Figure 2), which serves as a model complex for **3** (Scheme 3). As illustrated by Figure 2, the calculated spin density is mainly distributed over the “carbene” moiety with little spin density left at the metal center, indicating effective spin transfer from the Co(II) ion of [Co(TPP)] to the “carbene” moiety of the product after the reaction. Moreover, the spin density in the “carbene” moiety is found to be concentrated mostly on the α and γ atoms with similar values (α -C, 46.8; γ -C, 49.9), which supports a strong

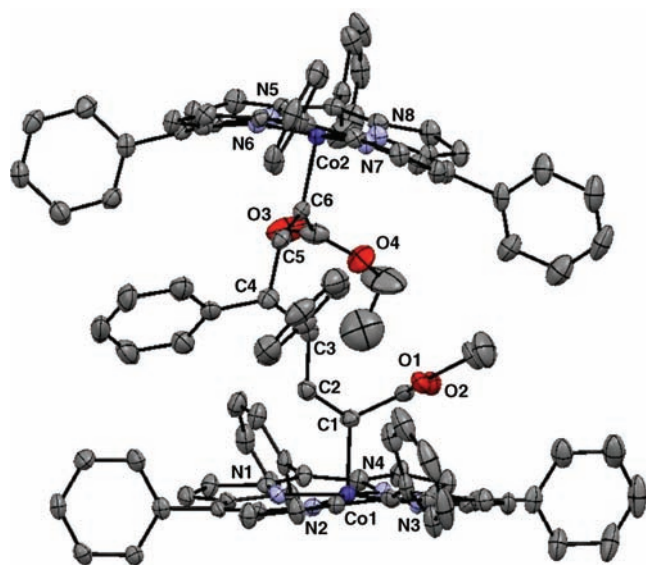


Figure 1. Single-crystal X-ray structure of **4** with thermal ellipsoids drawn at 30% probability. Hydrogen atoms and chloroform solvent molecule are omitted for clarity. Selected bond distances (Å): Co1–C1, 1.917(4); C1–C2, 1.325(5); C2–C3, 1.508(6); C3–C4, 1.574(6); C4–C5, 1.521(6); C5–C6, 1.305(5); C6–Co2, 1.931(4); Co1–Co2, 9.0170(9).

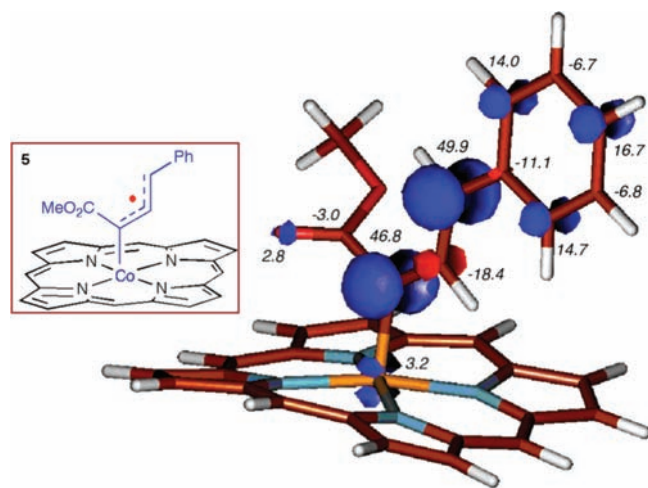
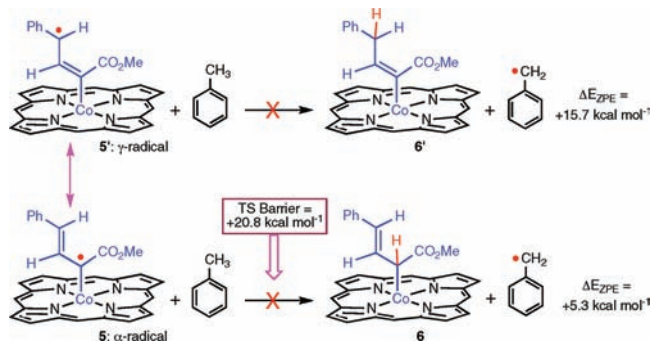


Figure 2. Plot of the calculated spin density distribution for (Por)Co–C(CO₂Me)(CHCHPh) model complex **5**, showing substantial delocalization of the unpaired electron over the α and γ carbon atoms. The numbers represent the calculated spin densities on the respective atoms.

contribution of the allylic radical resonance structures **3** (carbene α -radical) and **3'** (carbene γ -radical) to the electronic structure of **3** (Scheme 3). Further DFT calculations using the broken-symmetry methodology (see Supporting Information) indicate that the dimerization of carbene γ -radical **3'** via radical C–C coupling is a low-barrier process, explaining the facile formation of **4** (Scheme 3). The absence of the alternative dimerization process through the α -radical resonance form **3** is probably steric in origin.

The radical dimerization (Scheme 3) proceeded very cleanly and was found to be free of products from hydrogen atom abstraction, even though the reaction was performed with toluene as the solvent. As previously mentioned, products from

Scheme 4. DFT-Calculated Kinetic and Thermodynamic Parameters for Hydrogen Atom Transfer from Toluene to Cobalt(III)-Vinylcarbene Radical and Its Allylic Resonance Form

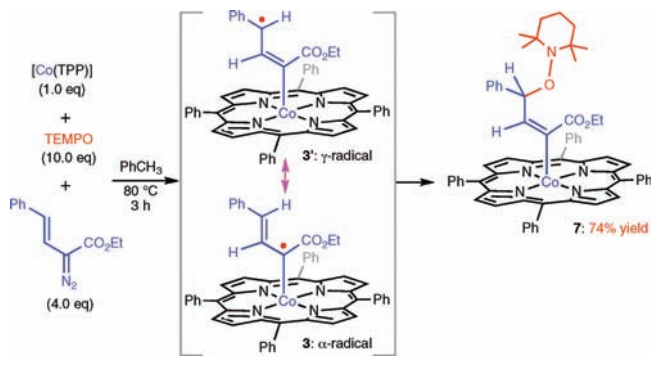


the hydrogen atom abstraction process were often observed in the reactions with ethyl diazoacetate and other diazo reagents (Scheme 2). To understand this unique reactivity profile of ethyl styryldiazoacetate as the carbene source, the hypothetical hydrogen atom abstraction reaction of cobalt(III)-vinylcarbene α -radical **5** and its allylic resonance form γ -radical **5'** from toluene was investigated by DFT calculations (Scheme 4). According to DFT, the hydrogen atom transfer (HAT) from toluene to the α -carbon position (reaction via the α -radical resonance form **5**) and the γ -carbon position (reaction via the γ -radical resonance form **5'**) is uphill by +5 and +16 kcal mol^{−1}, respectively (see Supporting Information). The high value of the energy associated with HAT from toluene to γ -radical **5'** explains well the absence of the corresponding hydrogen atom abstraction product **6'** (Scheme 4). Since the value of +5 kcal mol^{−1} associated with the HAT process to α -radical **5** is not high enough to explain the absence of the corresponding hydrogen atom abstraction product **6**, the activation barrier for the process was calculated. Hydrogen atom transfer from toluene to α -radical **5** at the sterically least hindered side (i.e., the toluene facing the side of the carbonyl group; see Supporting Information) has a calculated transition state barrier of +20.8 kcal mol^{−1} (relative to the isolated vinyl carbene radical and toluene). This barrier is high enough to hamper any HAT, since the competing C–C coupling of γ -radical **5** is essentially barrierless. Hence, we conclude that the absence of **6** is kinetic in origin, while the formation of **6'** is thermodynamically unfavorable.

Although the homocoupling of γ -radical **3'** is a very facile process (Scheme 3), it was shown that the radical could be effectively captured by radical traps. For example, when the reaction of [Co(TPP)] with 4 equiv of ethyl styryldiazoacetate was performed in toluene at 80 °C in the presence of an excess of the stable radical 2,2,6,6-tetramethylpiperidine *N*-oxide (TEMPO) (10 equiv), heterocoupling between γ -radical **3'** and TEMPO was found to be the dominant process, affording the heterodimer **7** via C–O bond formation in 74% isolated yield, with almost no formation of the homocoupling product **4** (Scheme 5).^{16,17} The isolation and characterization of **7** provide further convincing evidence for the existence of cobalt(III)-vinylcarbene α -radical **3** and its allylic resonance form γ -radical **3'**.

In summary, our combined experimental and theoretical studies have shown that the metalloradical [Co(TPP)] is capable of activating ethyl styryldiazoacetate to generate the corresponding

Scheme 5. Generation of Cobalt(III)-Vinylcarbene Radical from Reaction of [Co(TPP)] with Ethyl Styryldiazoacetate and Subsequent Trapping by TEMPO via C–O Bond Formation



Co(III)-vinylcarbene radical that exists in α -carbon-based and γ -carbon-based allylic radical resonance forms. The Co(III)-supported carbene radical, which is incompetent for H-atom abstraction, can cleanly self-dimerize via radical C–C coupling or can be effectively trapped by TEMPO via radical C–O coupling. We take these results as new experimental evidence for the existence of Co(III)-carbene radicals that are key intermediates in the radical-type mechanism of Co(II)-based metallo-radical catalysis for cyclopropanation.

ASSOCIATED CONTENT

S Supporting Information. Experimental details and analytical data for all new compounds, details of the DFT computational study; and all optimized geometries (pdb files). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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- (16) When preformed **4** (via Scheme 3) was reacted with TEMPO (10 equiv) in toluene at 80 °C for 3 h, no formation of **7** was observed.

- (17) When ethyl styryldiazoacetate (**4** equiv) was reacted with TEMPO (10 equiv) first in toluene for 3 h at 80 °C, followed by addition of [Co(TPP)], no formation of **7** or **4** was observed, even after further reaction for an additional 3 h at 80 °C.