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Catalytic Dibenzocyclooctene Synthesis via Cobalt(III)–Carbene Radical and ortho-Quinodimethane Intermediates

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Abstract: The metalloradical activation of ortho-benzaldehyde N-tosyl hydrazones with [Co(TPP)] (TPP = tetraphenylporphyrin) as the catalyst enabled the controlled exploitation of the single-electron reactivity of the redox non-innocent carbene intermediate. This method offers a novel route to prepare eight-membered rings, using base metal catalysis to construct a series of unique dibenzocyclooctenes through selective C=C–C=C cyclization. The desired eight-membered-ring products were obtained in good to excellent yields. A large variety of aromatic substituents are tolerated. The proposed reaction mechanism involves intramolecular hydrogen atom transfer (HAT) to Co(II)–carbene radical intermediates followed by dissociation of an ortho-quinodimethane that undergoes 8π cyclization. The mechanism is supported by DFT calculations, and the presence of radical-type intermediates was confirmed by trapping experiments.

In synthetic chemistry, reactions to synthesize five- and six-membered rings are copious, but access to medium-sized (seven- and eight-membered) rings remains very challenging.[5] Ring closure is often difficult because cyclizations of flexible linear molecules are entropically disfavored and steric interactions within the ring (so-called transannular interactions) make such reactions also enthalpically unfavorable. The combination of these factors often leads to oligomerization or polymerization instead of cyclization. Nonetheless, the synthesis of eight-membered rings is highly desirable as they are present in a variety of natural products with pharmaceutical relevance.[2] Some selected examples of natural products containing eight-membered rings are shown in Figure 1.

One way to address the problems associated with synthesizing these rings is the so-called high-dilution method, in which the substrate concentration is so low that intermolecular reactions become unlikely. However, the large solvent volumes needed typically render this method impractical for large-scale applications. Over the past years, several strategies for the synthesis of eight-membered rings from a single linear precursor have been developed, including carbopalladation reactions of allenes,[3] rhodium-catalyzed [4+2+2] cycloadditions,[4] palladium-catalyzed cross-couplings,[5] and alkene metathesis processes.[6] Another approach is based on the ring expansion of smaller, more accessible rings.[7] However, each of these methods is associated with its own limitations (e.g., poor functional group tolerance or restriction to specific substrate classes) and/or involves the use of scarce transition metals. It is therefore desirable to explore new ways to synthesize such architectures, preferably by base metal catalysis.

Recently, low-spin d⁷ cobalt(II) complexes have emerged as radical-type carbene transfer catalysts, proceeding via discrete “carbene radicals”. Upon formation of a Fischer-type carbene at the low-spin cobalt(II) center of these catalysts, the redox-active Fischer-type carbene undergoes one-electron reduction by the cobalt(II) center, forming a “cobalt(III)–carbene radical” complex. The p orbital of the carbene moiety is dominant in the SOMO of these reactive intermediates, effecting their typical radical-type behavior towards, for example, C–H, C=C, and C=C bonds (Figure 2).

![Figure 1. Natural products containing eight-membered rings.](image1)

![Figure 2. Left: Radical transfer from the cobalt catalyst to a carbene moiety to produce carbon-centered radicals (“carbene radicals”). Right: Open-shell organometallic catalysis involving “one-electron oxidative addition” and “one-electron reductive elimination” elementary steps.](image2)

Such metalloradical approaches have previously been employed to synthesize cyclopropanes,[9] chromenes,[10] furans,[11] indenes,[12] ketenes,[13] butadienes,[14] and dihydronaphthalenes.[15] We now report the synthesis of unique dibenzocyclooctenes in high yields by cobalt-based metal-radical one-electron catalysis.[15] The formation of dibenzocyclooctenes (Scheme 1) is a relevant addition to the known reactivity of carbene radicals because of their potential relevance in total synthesis and the synthetic difficulties associated with the formation of eight-membered rings in general.

As part of our ongoing efforts to explore the catalytic reactivity of cobalt(III)–carbene radicals, we investigated the activation of substituted tosyl hydrazones 1 (ortho-benzaldehyde N-tosyl hydrazones) by [Co(TPP)] (TPP = tetraphenylporphyrin). However, rather than the initially anticipated...
formation of dihydronaphthalenes 3, we observed the unexpected formation of a range of unique dibenzocyclooctenes 2 by Caryl-Caryl cyclization (Scheme 1). The reactions are high-yielding and notably associated with selective C= C double bond isomerization of the allylic moiety. The initially expected formation of six-membered rings by formal carbene insertion into the benzallylic position was not observed at all (Scheme 1). Herein, we report on the scope and mechanism of these metalloradical-catalyzed reactions to prepare well-defined and functionalized dibenzocyclooctenes.

We synthesized a range of substrates with different R1 substituents on the aromatic ring that is present within the core organic skeleton and located adjacent to the carbene precursor fragment (Table 1). Similarly, we also prepared several substrates with different R2 substituents attached to the flanking aromatic ring of the benzylidy moiety of the substrate (Table 2). All substrates were obtained as E/Z mixtures, with 63–91% being the major E isomer. As hydrogen atom transfer (HAT) from the benzylic position to the carbene radical moiety of the cobalt-activated substrate is a key step of the catalytic reaction sequence (Scheme 2), only the E isomer can undergo ring closure in these reactions. The yields in Table 1 and 2 are therefore based on the amount of productive E isomer.

Ring closure of the unsubstituted substrate 1a selectively produced dibenzocyclooctene 2a (isolated in 82% yield; Table 1, entry 1).[16] The presence of an electron-withdrawing group as R1 leads to somewhat higher yields (entries 2–4). Substrates 1e, 1f, and 1g bearing electron-donating groups also produced the corresponding dibenzocyclooctenes in excellent yields (entries 5–7). Thus it appears that R1 substituents only have a minor influence on the product yields.[17]

We continued our investigations of the substrate scope by varying the R2 substituent, and thereby the electronic properties of the aryl group undergoing the Caryl-Caryl coupling (Table 2). Substrates with an electron-donating R2 group at the para position of the substrate produced the corresponding dibenzocyclooctenes in decent yields (entries 1 and 2). Substrates with a donating group at the meta position gave higher yields, but obviously led to isomeric product mixtures with the R2 substituent located either in the ortho (2j) or the para position (2j') with respect to the newly formed C–C bond, with 2j being the major product (entry 3). Similar results were obtained with electron-withdrawing substituents. In entries 4–6, a cyano group was placed at the para, meta, or ortho position of the substrate, respectively. For 2l and 2f, we again found both the ortho- and para-substituted products, with the ortho product being the major one. The yield of 2m is slightly lower (entry 6), which could be due to steric hindrance or a statistical effect as only one of the two ortho positions is available for the ring closure, perhaps triggering the formation of side products. The steric hinderance in substrate 1n did not hamper ring closure (entry 7).

The disubstituted product 2o was also obtained in excellent yield. Overall, the formation of dibenzocyclooctenes was quite uniform, regardless of the R1 substituent: Good yields were regularly obtained with electron-withdrawing groups, while slightly lower yields were generally observed with electron donating groups.

Table 1: Substrate scope varying the R1 substituent.[16]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>Yield [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1a</td>
<td>2a</td>
<td>82</td>
</tr>
<tr>
<td>2</td>
<td>1b</td>
<td>2b</td>
<td>97</td>
</tr>
<tr>
<td>3</td>
<td>1c</td>
<td>2c</td>
<td>87</td>
</tr>
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<td>4</td>
<td>1d</td>
<td>2d</td>
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<tr>
<td>5</td>
<td>1e</td>
<td>2e</td>
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</tr>
<tr>
<td>6</td>
<td>1f</td>
<td>2f</td>
<td>96</td>
</tr>
<tr>
<td>7</td>
<td>1g</td>
<td>2g</td>
<td>78</td>
</tr>
</tbody>
</table>

[a] Reaction conditions: 1a–1g (0.1 mmol, 1.0 equiv), LiO′Bu (0.12 mmol, 1.2 equiv), [Co(TPP)] (5 mol%), benzene (2 mL), 60°C, overnight. [b] Yields of isolated products, corrected for the E/Z ratios of the substrates. Averages of two experiments are given.

Scheme 1. Metalloradical approach for the synthesis of dibenzocyclooctenes 2 from N-tosyl hydrazones 1 by Caryl-Caryl cyclization, as described in this paper, and the initially expected formation of dihydronaphthalenes 3 via formal carbene insertion into the benzallylic C–H bond.
tenes 2 from tosyl hydrazones 1 is very tolerant to the presence of both electron-withdrawing and electron-donating groups on both aromatic rings.

Interestingly, selective double bond migration of the allylic moiety was observed in all cases, with the C=C double bond moving from a position next to the R 1-substituted aryl group in the substrate to a position next to the R 2-substituted aryl group in the product. Disregarding the expected isomers formed in entries 3 and 5 of Table 2, the reactions are highly chemoselective. The position of the C=C double bond, selectively in conjugation with the R 2-substituted aryl moiety, was confirmed by 2D NOESY NMR spectroscopy and X-ray crystallography (see the Supporting Information and Figure 3).

The ester group at the allylic position seems to be essential as substrates lacking this functional group or with a different substituent at this position did not produce dibenzocyclooctenes.

The mechanism of the [Co(por)]-catalyzed formation of dibenzocyclooctene 2a from substrate 1a was investigated with DFT methods (we used a simplified model of TPP without meso Ph substituents for the DFT calculations; i.e., por = porphine). Scheme 2 depicts the proposed catalytic cycle based on our computational studies. The first step is the (uncatalyzed) formation of diazo compound 1a’ from substrate 1a.

Table 2: Substrate scope varying the R 2 substituent.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>Yield [b]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1h</td>
<td>2h</td>
<td>83%</td>
</tr>
<tr>
<td>2</td>
<td>1i</td>
<td>2i</td>
<td>61%</td>
</tr>
<tr>
<td>3</td>
<td>1j</td>
<td>2j/2j’</td>
<td>95% 1.4:1</td>
</tr>
<tr>
<td>4</td>
<td>1k</td>
<td>2k</td>
<td>75%</td>
</tr>
<tr>
<td>5</td>
<td>1l</td>
<td>2l/2l’</td>
<td>71% 1.7:1</td>
</tr>
<tr>
<td>6</td>
<td>1m</td>
<td>2m</td>
<td>66%</td>
</tr>
</tbody>
</table>

[a] Reaction conditions: 1h–1o (0.1 mmol, 1.0 equiv), LiOtfBu (0.12 mmol, 1.2 equiv), [Co(TPP)] (5 mol%), benzene (2 mL), 60 °C, overnight. [b] Yields of isolated products, corrected for the E/Z ratios of the substrates. Averages of two experiments are given.

Table 2: (Continued)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>Yield [b]</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td>1n</td>
<td>2n</td>
<td>85%</td>
</tr>
<tr>
<td>8</td>
<td>1o</td>
<td>2o</td>
<td>97%</td>
</tr>
</tbody>
</table>

The ester group at the allylic position seems to be essential as substrates lacking this functional group or with a different substituent at this position did not produce dibenzocyclooctenes.

The mechanism of the [Co(por)]-catalyzed formation of dibenzocyclooctene 2a from substrate 1a was investigated with DFT methods (we used a simplified model of TPP without meso Ph substituents for the DFT calculations; i.e., por = porphine). Scheme 2 depicts the proposed catalytic cycle based on our computational studies. The first step is the (uncatalyzed) formation of diazo compound 1a’ from substrate 1a. Trapping and activation of the diazo compound by the catalyst leads to (irreversible) dinitrogen loss, producing carbene radical intermediate C in an exergonic reaction sequence with a low barrier. Hydrogen atom transfer (HAT) from the allylic position to the radical-bearing carbene carbon atom then produces allyl radical intermediate D, which is again an exergonic process with a low barrier (+9.6 kcal mol−1). The thus produced delocalized allyl radical moiety of D is in direct conjugation with the already weak Co–C bond of D, thus facilitating homolysis with release of ortho-
quinodimethane (o-QDM) intermediate E from the metal. This behavior is somewhat similar to observations in our previous studies regarding dihydronaphthalene and butadiene formation via related o-QDM intermediates.[14] Metal-catalyzed radical-rebound ring closure from D to form dihydronaphthalene 3a (Scheme 1) is kinetically disfavored compared to the (slightly endergonic) dissociation of o-QDM intermediate E from D (see the Supporting Information, Scheme S1 for details). Intermediate E readily undergoes an 8π cyclization reaction,[22] which has a surprisingly low barrier (TS3: +6.2 kcal mol⁻¹), producing dearomatized intermediate F. The final product 2a is readily produced from intermediate F by a low-barrier [1,5]-hydride shift reaction (TS4: +10.7 kcal mol⁻¹) to regain aromaticity in both rings, which provides a sufficiently large thermodynamic driving force for the entire process. Overall, the formation of dibenzocyclooctene 2a is exergonic by -54.7 kcal mol⁻¹, and the highest global barrier of the catalytic reaction is only +11.8 kcal mol⁻¹. Notably, the [1,5]-hydride shift reaction via TS4 leads to an unavoidable migration of the allylic double bond from one side of the ester moiety to the other, in excellent agreement with the experimental observations shown in Table 1 and 2 as well as Figure 3, which depicts the molecular structures of products 2j and 2m, as determined by single-crystal X-ray diffraction.

We confirmed the radical nature of this reaction by spin trapping experiments with N-tert-butyl nitroxide (PBN) as the spin trap. The EPR signal (g = 2.0066, A_N = 14.5 G, A_H = 2.8 G) is characteristic for a PBN-trapped carbon-centered radical,[12,14] suggestive of the trapping of intermediate C or D. Mass spectrometry confirmed the presence of such PBN-trapped intermediates (see the Supporting Information). The combined data clearly support the mechanism depicted in Scheme 2.

In conclusion, a range of unique dibenzocyclooctenes have been synthesized in good to excellent yields by metalloradical activation of N-tosyl hydrazones 1 using [Co(TPP)] as the catalyst. The resulting novel base metal catalyzed route to eight-membered rings is very different from known synthetic methods, which typically proceed via closed-shell pathways and rely on the use of expensive and scarce transition metals. A large variety of substituents are tolerated, including electron-withdrawing and -donating groups on both aryl rings. The reaction mechanism involves carbene radical formation, which was supported by PBN radical trapping experiments. 2D NOESY NMR spectroscopy and X-ray diffraction studies confirmed C=C double bond migration at the allylic position. This is in agreement with the proposed mechanism, which involves 8π cyclization of ortho-quinodimethane intermediates followed by a [1,5]-hydride shift.

**Acknowledgements**

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Conflict of interest

The authors declare no conflict of interest.

Keywords: carbene radicals · cobalt · dibenzocyclooctenes · metalla radicals · ortho-quinodimethanes

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Angew. Chem. 2018, 130, 146–151

[16] To obtain additional structural information, compound 1a was also hydrogenated to the corresponding dibenzocyclooctane. See the Supporting Information for details.
[17] The observed small variations in product yield upon changing R1 should probably be ascribed to differences in product loss during the purification steps.
[18] NMR analysis showed no indications for allylic C=C double bond isomerization under the applied reaction conditions.
[19] Active participation of a gem-ester moiety in direct carbene insertion reactions into C=C–H bonds has been reported, but is not accessible for carbene radical C and would not explain the double bond migration; see: M. R. Fructos, M. Besora, A. A. C. Braga, M. M. Díaz-Requejo, F. Maseras, P. J. Pérez, Organo- metallocs 2017, 36, 172–179.
[20] The allyl-phenyl substrate produced an unknown product. Replacing the ester with a hydrogen atom leads to indene and cyclopropane products. See the Supporting Information for details.

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