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

te Grotenhuis, C.; van den Heuvel, N.; van der Vlugt, J.I.; de Bruin, B.

DOI
10.1002/ange.201711028
10.1002/anie.201711028

Publication date
2018

Document Version
Final published version

Published in
Angewandte Chemie

License
CC BY-NC-ND

Citation for published version (APA):
https://doi.org/10.1002/ange.201711028, https://doi.org/10.1002/anie.201711028

General rights
It is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), other than for strictly personal, individual use, unless the work is under an open content license (like Creative Commons).

Disclaimer/Complaints regulations
If you believe that digital publication of certain material infringes any of your rights or (privacy) interests, please let the Library know, stating your reasons. In case of a legitimate complaint, the Library will make the material inaccessible and/or remove it from the website. Please Ask the Library: https://uba.uva.nl/en/contact, or a letter to: Library of the University of Amsterdam, Secretariat, Singel 425, 1012 WP Amsterdam, The Netherlands. You will be contacted as soon as possible.

UvA-DARE is a service provided by the library of the University of Amsterdam (https://dare.uva.nl)
Catalytic Dibenzocyclooctene Synthesis via Cobalt(III)–Carbene Radical and ortho-Quinodimethane Intermediates

Colet te Grotenhuis, Naudin van den Heuvel, Jarl Ivar van der Vlugt, and Bas de Bruin*
Abstract: The metalloradical activation of ortho-benzallylaryl 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\_arylc=C\_aryl 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\^III–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.\(^\text{[1]}\) 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.\(^\text{[2]}\) 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 carbo- and annulation reactions of allenes,\(^\text{[3]}\) rhodium-catalyzed [4+2+2] cycloadditions,\(^\text{[4]}\) palladium-catalyzed cross-couplings,\(^\text{[5]}\) and alkene metathesis processes.\(^\text{[6]}\) Another approach is based on the ring expansion of smaller, more accessible rings.\(^\text{[7]}\) 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 d\(^\text{0}\) cobalt(II) complexes have emerged as radical-type carbene transfer catalysts, proceeding via discrete “carbene radicals”.\(^\text{[8]}\) 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–\(\text{H}\), C=C, and C=C bonds (Figure 2).

Such metalloradical approaches have previously been employed to synthesize cyclopropanes,\(^\text{[9]}\) chromenes,\(^\text{[10]}\) furans,\(^\text{[11]}\) indenes,\(^\text{[12]}\) ketenes,\(^\text{[13]}\) butadienes,\(^\text{[14]}\) and dihydrobenzocyclooctenes in high yields by cobalt-based metal-radical one-electron catalysis.\(^\text{[15]}\) 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 I (ortho-benzallylaryl N-tosyl hydrazones) by [Co(TPP)] (TPP = tetraphenylporphyrin). However, rather than the initially anticipated
production of dihydronaphthalenes 3, we observed the unexpected formation of a range of unique dibenzocyclooctenes 2 by C_{aryl}/C=O 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 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 R_1 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 R_2 substituents attached to the flanking aromatic ring of the benzyl 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 on R_1 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 R_1 substituents only have a minor influence on the product yields.[17]

We continued our investigations of the substrate scope by varying the R_2 substituent, and thereby the electronic properties of the aryl group undergoing the C_{aryl}/C=C coupling (Table 2). Substrates with an electron-donating R_2 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 R_2 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 hindrance in substrate 1n did not hamper ring closure (entry 7).

The disubstituted product 2o was also obtained in excellent yield. Overall, the formation of dibenzocyclooc-
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-

Table 2: Substrate scope varying the R\(^2\) substituent.\(^{[a]}\)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(\text{NNHTs}C\text{OEI}C\text{OEI}C\text{R}^2)</td>
<td>(\text{COEI}C\text{OEI}C\text{R}^2)</td>
<td>83%</td>
</tr>
<tr>
<td>1(h)</td>
<td>(\text{NNHTs}C\text{OEI}C\text{OEI}C\text{OMe})</td>
<td>(\text{COEI}C\text{OEI}C\text{OMe})</td>
<td>61%</td>
</tr>
<tr>
<td>3</td>
<td>(\text{NNHTs}C\text{OEI}C\text{OEI}C\text{CN})</td>
<td>(\text{COEI}C\text{OEI}C\text{CN})</td>
<td>75%</td>
</tr>
<tr>
<td>5</td>
<td>(\text{NNHTs}C\text{OEI}C\text{CN}C\text{CN})</td>
<td>(\text{COEI}C\text{CN}C\text{CN})</td>
<td>71%</td>
</tr>
</tbody>
</table>

Table 2: (Continued)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td>(\text{NNHTs}C\text{OEI}C\text{CN}C\text{CN})</td>
<td>(\text{COEI}C\text{CN}C\text{CN})</td>
<td>85%</td>
</tr>
<tr>
<td>8</td>
<td>(\text{NNHTs}C\text{OEI}C\text{CN}C\text{CN})</td>
<td>(\text{COEI}C\text{CN}C\text{CN})</td>
<td>97%</td>
</tr>
</tbody>
</table>

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

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.
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. 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, which has a surprisingly low barrier (TS3: +6.2 kcal mol⁻¹), producing de aromatized 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 nitro oxide (PBN) as the spin trap. The EPR signal (g = 2.0066, A∥ = 14.5 G, A⊥ = 2.8 G) is characteristic for a PBN-trapped carbene-centered radical, 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 metal-loradical 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 substituents 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**

We thank Ed Zuidinga for MS measurements and Jan Meine Ernsting and Andreas Ehlers for NMR advice. Financial support from the Netherlands Organization for Scientific Research (NWO-CW VICI project 016.122.613) and the University of Amsterdam (Research Priority Area Sustainable Chemistry) is gratefully acknowledged.
Conflict of interest

The authors declare no conflict of interest.

Keywords: carbone radicals · cobalt · dibenzocyclooctenes · metalloradicals · ortho-quinodimethanes

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 gem -ester–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. C. Braga, M. M. Díaz-Requejo, F. Maseras, P. J. Pérez, Organometallics 2017, 36, 172–179.
[20] The allyl-phenyl substrate produced an unknown product. Replacing the ether with a hydrogen atom leads to indene and cyclopropane products. See the Supporting Information for details.

Manuscript received: October 26, 2017
Accepted manuscript online: November 20, 2017
Version of record online: December 6, 2017