A Journal of the Gesellschaft Deutscher Chemiker
Angewandte Chemie
GDCh
International Edition
www.angewandte.org

Accepted Article

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To be cited as: *Angew. Chem. Int. Ed.* 10.1002/anie.201711028
Angew. Chem. 10.1002/ange.201711028

Link to VoR: http://dx.doi.org/10.1002/anie.201711028
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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: Metalloradical activation of *N*-tosyl hydrazones **1** (*o*-benzallyl-aryl-tosylhydrazones), using [Co(TPP)] as a catalyst (TPP = tetraphenylporphyrin), allows controlled exploitation of single-electron reactivity of the redox non-innocent carbene intermediate. This method offers a novel route to prepare 8-membered rings, using base metal catalysis to construct a series of unique dibenzocyclooctenes via selective $C_{carbene}$–C_{aryl} cyclization, producing the desired 8-membered ring products in good to excellent yields. A large variety of aromatic substituents is tolerated. The proposed reaction mechanism involves intramolecular HAT to Co^{III}-carbene radical intermediates, followed by dissociation of *o*-quinodimethides undergoing 8π-cyclisation. 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.[1] Cyclization is often difficult because cyclization of flexible linear molecules is entropically disfavoured and steric interactions within the ring (so-called transannular interactions) make such reactions also enthalpically unfavourable. 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 8-membered rings are shown in Figure 1.

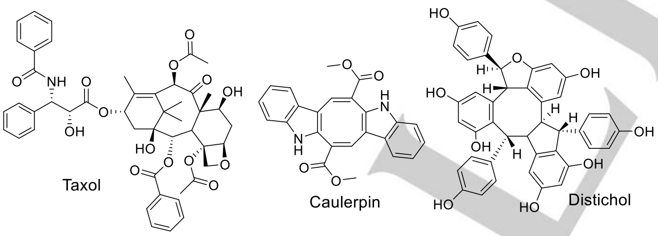


Figure 1. Natural compounds containing 8-membered rings.

One way to address the problems in 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 reactions. Over the past years, several strategies for the synthesis of 8-membered rings from a single linear precursor have been developed, including carbopalladation of allenes,[3] rhodium-catalysed [4+2+2] cycloaddition,[4] palladium-catalysed cross-coupling[5] and alkene metathesis.[6] Another approach is to use ring expansion of smaller, more accessible rings.[7] However, each of these methods is associated with their own limitations (e.g. poor functional group tolerance or restriction to specific substrate classes), and/or involve the use of scarce transition metals. It is therefore desirable to explore new ways to synthesize these architectures, preferably using base metal catalysis.

Recently, low-spin d^7 cobalt(II) complexes have emerged as radical-type carbene transfer catalysts, proceeding via discrete 'carbene radicals'.[8] Upon formation of a Fischer-type carbene at the low-spin cobalt(II) centre of these catalysts, the redox active Fischer-type carbene undergoes one-electron reduction by the cobalt(II) centre, forming a 'cobalt(III)-carbene radical' complex. The *p*-orbital of the carbene moiety is dominant in the SOMO of these reactive intermediates (Figure 2), effecting their typical radical-type behaviour towards e.g. C–H, C=C and C≡C bonds. Such metalloradical approaches were previously employed to synthesise cyclopropanes,[9] chromenes,[10] furans,[11] indenes,[12] ketenes,[13] butadienes[14] and dihydronaphthalenes.[14] We now report the synthesis of unique dibenzocyclooctenes in high yields by employing Co-based metalloradical one-electron catalysis.[15] 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 synthetic difficulties associated with formation of 8-membered rings in general.

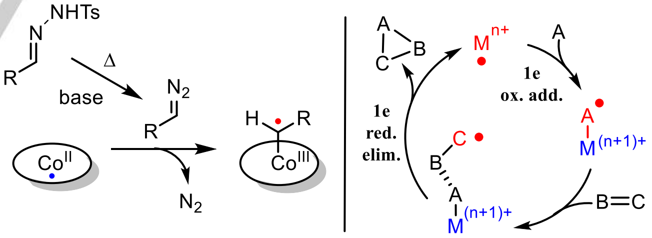
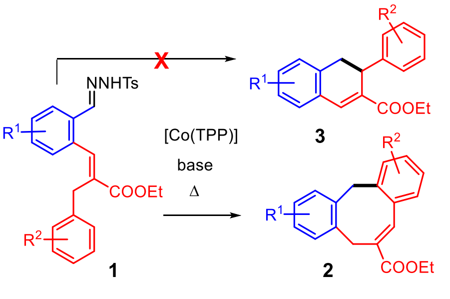


Figure 2. Left: Radical transfer from the cobalt catalyst to a carbene moiety to produce carbon-centred radicals ('carbene radicals'). Right: Open-shell organometallic catalysis involving 'one-electron oxidative addition' and 'one-electron reductive elimination' elementary steps.



Scheme 1. Metalloradical approach to synthesize dibenzocyclooctenes **2** from tosylhydrazones **1** by $C_{carbene}$–C_{aryl} cyclization, as described in this paper, and the initially expected formation of dihydronaphthalenes **3** via formal carbene insertion into the benzallylic C–H bond.

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As part of our ongoing efforts to explore the catalytic reactivity of cobalt(III)-carbene radicals, we explored the activation of substituted tosylhydrazones **1** (*o*-benzallyl-aryl-tosylhydrazones) by [Co(TPP)]. However, rather than the initially anticipated formation of dihydronaphthalenes **3**, we observed the unexpected formation of a range of unique dibenzocyclooctenes **2** by $C_{carbene}$–C_{aryl} cyclization (Scheme 1). The reactions are high yielding, and notably associated with selective C=C double bond isomerisation of the allylic moiety. The initially expected formation of 6-membered rings by formal carbene insertion into the benzallylic position is not observed at all (Scheme 1). Here we report on the scope and mechanism of these metalloradical-catalysed reactions to prepare well-defined and functionalized dibenzocyclooctenes.

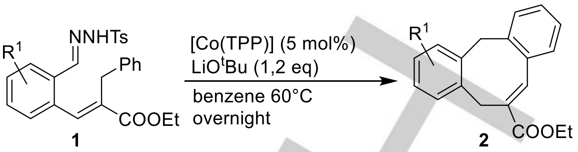
We synthesized a range of substrates with varying R^1-substituents on the aromatic ring that is present within the core organic skeleton and located adjacent to the carbene-precursor fragment (Table 1). Similarly, we also prepared several substrates with different R^2-substituents attached to the flanking aromatic ring of the benzylic moiety of the substrate (Table 2). All substrates were obtained as *E/Z* mixtures, containing 63-91% of the major *E*-isomer. Because 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 productive *E*-isomer.

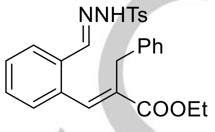
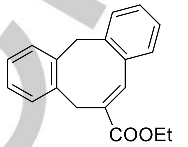
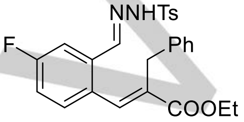
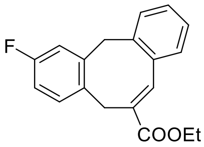
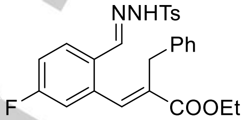
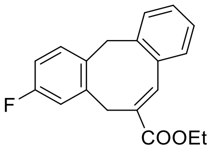
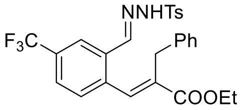
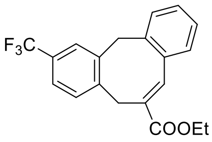
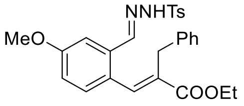
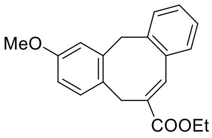
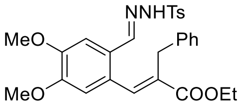
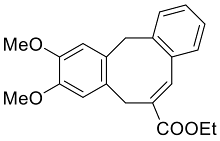
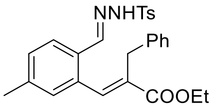
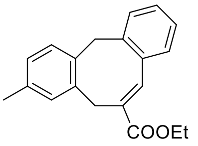
Ring-closure of the unsubstituted substrate **1a** selectively produces dibenzocyclooctene **2a** (82% isolated yield; entry 1, Table 1).[16] Entries 2-4 in Table 1 show that the presence of an electron-withdrawing group for R^1 leads to somewhat higher isolated yields. Substrates **1e**, **1f** and **1g** bearing electron-donating groups also produce the corresponding dibenzocyclooctenes in excellent yields (entries 5-7). Thus, it appears that R^1-substituents only have a minor influence on the isolated 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 $C_{carbene}$–C_{aryl} coupling (Table 2). Substrates with an electron-donating R^2-group at the *para*-position of the substrate produce dibenzocyclooctenes in decent isolated yields (entries 1-2). Substrates with a donating group at the *meta*-position give higher yields, but obviously lead to isomeric product mixtures with the R^2-substituent located either in the *ortho*- (**2j**) or *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 is placed at the *para*-, *meta*- and *ortho*-position of the substrates, respectively. For **2l** and **2l’** we again find both *ortho*- and *para*-substituted products, with the *ortho*-product being the major one. In entry 6 the yield of **2m** is slightly lowered, which could be due to steric hindrance or a statistical effect, as only one of the two *ortho*-positions is available for the ring-closing reaction, perhaps triggering formation of byproducts. Steric hindrance in substrate **1n** did not hamper ring-closure (entry 7).

Also, bis-substituted product **2o** was obtained in excellent yield. Overall, formation of dibenzocyclooctenes **2** from tosyl hydrazones **1** is very tolerant to the presence of both electron-withdrawing and electron-donating groups on both aromatic rings.

Table 1. Substrate scope varying the R^1-substituent[a]



Entry	Substrate	Product	Yield[b]
1	 **1a**	 **2a**	82%
2	 **1b**	 **2b**	97%
3	 **1c**	 **2c**	87%
4	 **1d**	 **2d**	91%
5	 **1e**	 **2e**	92%
6	 **1f**	 **2f**	96%
7	 **1g**	 **2g**	78%

[a] Reaction conditions: *N*-tosylhydrazone (**1a–g**) (0.1 mmol, 1.0 equiv), LiO^{t}Bu (0.12 mmol, 1.2 equiv), [Co(TPP)] (5 mol%), benzene (2 mL), 60 °C, overnight. [b] Isolated yields, average of 2 exp. Corrected for *E/Z* ratio of the substrate.

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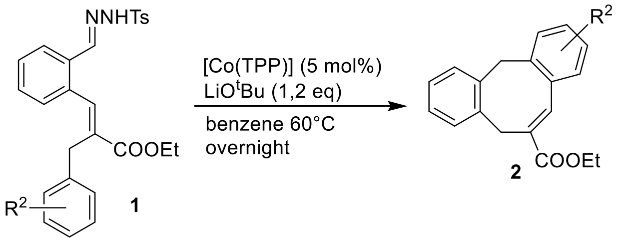
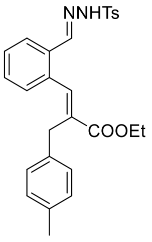
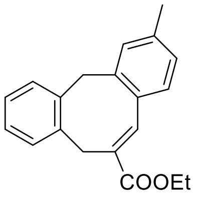
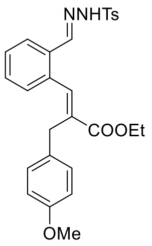
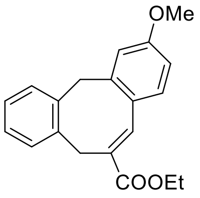
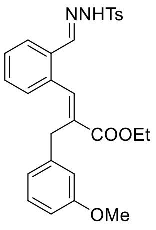
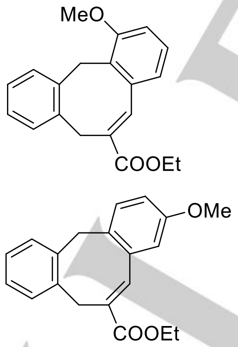
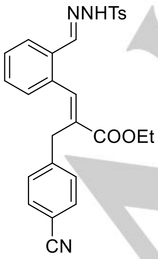
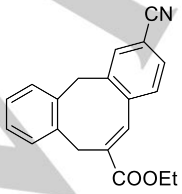
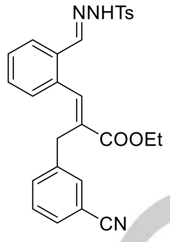
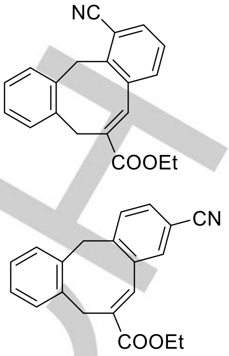
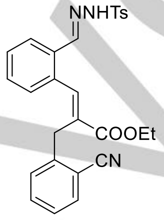
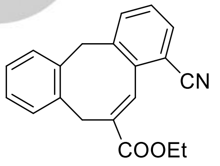
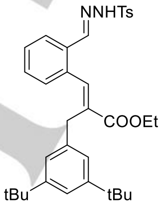
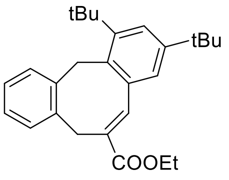
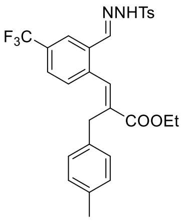
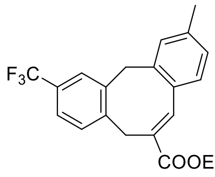
Table 2. Substrate scope varying the R^2-substituent.[a]



Entry	Substrate	Product	Yield[b]
1	 **1h**	 **2h**	83%
2	 **1i**	 **2i**	61%
3	 **1j**	 **2j:2j'**	95% 1.4:1
4	 **1k**	 **2k**	75%
5	 **1l**	 **2l:2l'**	71% 1.7:1
6	 **1m**	 **2m**	66%
7	 **1n**	 **2n**	85%
8	 **1o**	 **2o**	97%

[a] Reaction conditions: *N*-tosylhydrazone (**1h–o**) (0.1 mmol, 1.0 equiv), LiO^{t}Bu (0.12 mmol, 1.2 equiv), [Co(TPP)] (5 mol%), benzene (2 mL), 60 ºC, overnight. [b] Isolated yields, average of 2 exp. Corrected for *E/Z* ratio of the substrate.

Interestingly, selective double bond migration of the allylic moiety is observed in all cases, with the C=C double bond being moved 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, the reactions are highly chemoselective.[18] The position of the C=C double bond, selectively in conjugation with the R^2-substituted aryl moiety, was confirmed with 2D-NOESY-NMR spectroscopy and X-ray crystallography (see ESI and Figure 3).
The ester group at the allylic position seems to be essential, [19] as substrates lacking this functionality or with a different substituent at this position do not produce dibenzocyclooctenes.[20]

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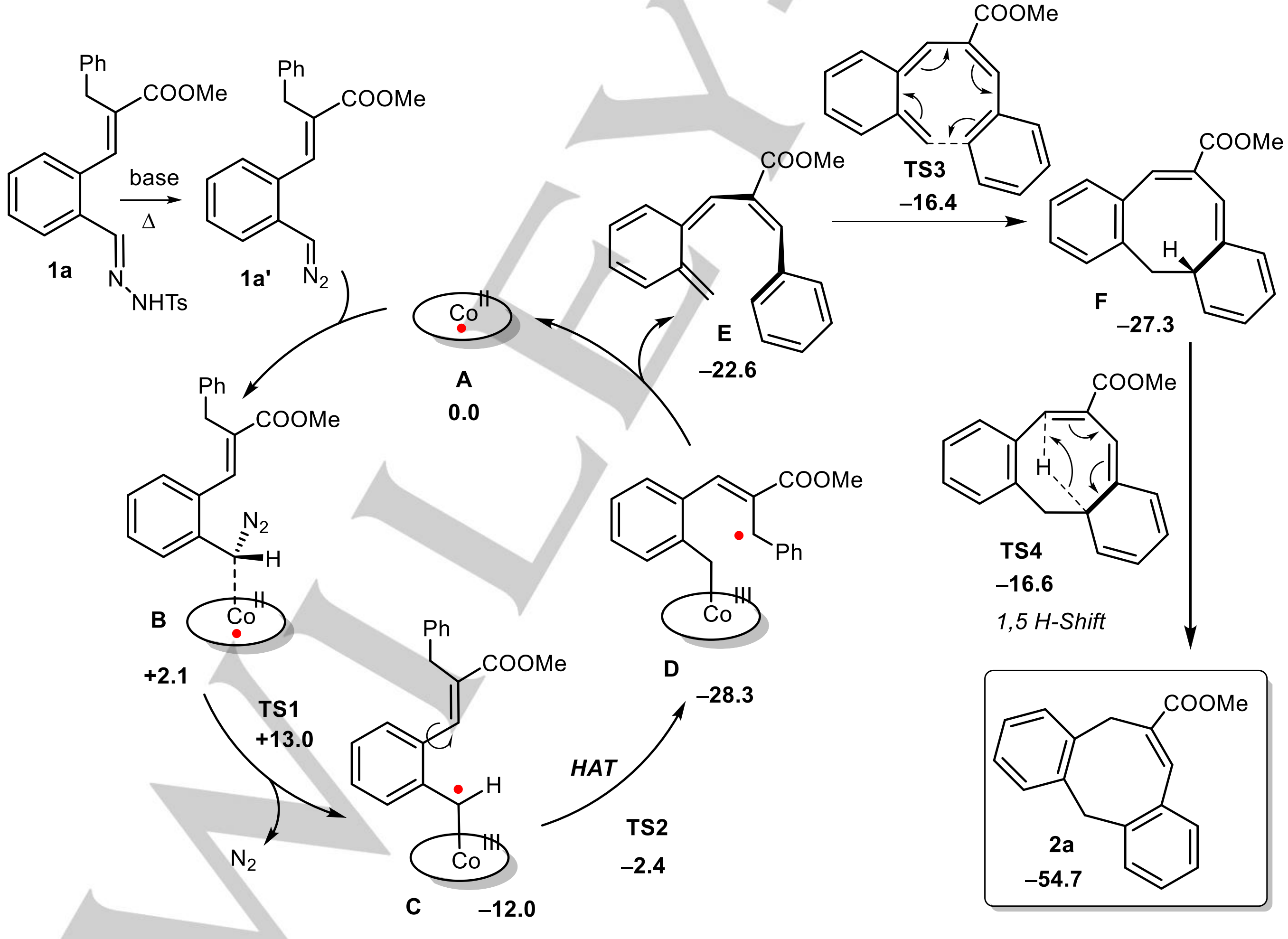
The mechanism of the [Co(por)]-catalysed formation of dibenzocyclooctene **2a** from substrate **1a** was investigated with DFT methods. Scheme 2 depicts the proposed catalytic cycle based on our computational studies. The first step is the (uncatalysed) formation of diazo-compound **1a'** from substrate **1a**.[21] Trapping and activation of the diazo compound by the catalyst leads to dinitrogen loss, producing carbene radical intermediate **C** in a low barrier and exergonic reaction sequence. 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 behaviour is somewhat similar to observations reported in our previous studies regarding dihydronaphthalene and butadiene formation via related o-QDM intermediates.[14] Metal-catalysed radical rebound ring-closure from **D** to form dihydronaphthalene **3a** (Scheme 1), is kinetically disfavoured when compared to the only slightly endergonic dissociation of o-QDM intermediate **E** from **D** (see Scheme S1, ESI for details). Intermediate **E** readily undergoes an 8π-cyclisation 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** via a low barrier [1,5]-hydride shift reaction (**TS4**: +10.7 kcal mol^{-1}) to regain aromaticity in both rings, thus providing sufficient thermodynamic driving force for the entire process. Overall, 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 structure for products **2j** and **2m**, as determined by single crystal X-ray diffraction.

We confirmed the radical nature of this reaction by spin trapping experiments using N-*tert*-butyl nitrone (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-centred radical,[12, 14] suggestive of trapping intermediate **C** or **D**. Mass spectrometry revealed *m/z* values confirming the presence of such PBN-trapped intermediates (see ESI). The combined data clearly support the mechanism depicted in Scheme 2.



Scheme 2. Proposed catalytic cycle based on DFT calculations (BP86, def2-TZVP, m4 grid, disp3 dispersion corrections).

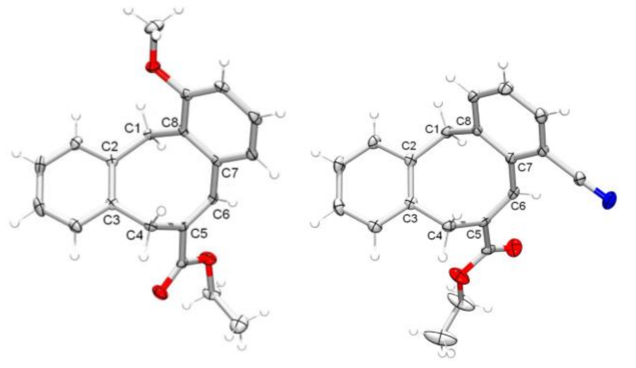


Figure **3**. Molecular structure of **2j** (left) and **2m** (right), as obtained by single crystal X-ray diffraction studies. Selected bond distances [Å]: **2j**, ***2m*** C1−C8: 1.513(2), *1.518(3)*; C4−C5: 1.509(2), *1.511(3)*; C5−C6: 1.332(2), *1.333(3)*; C6−C7: 1.476(2), *1.475(3)*.

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

Keywords: metalloradical • carbene radical • dibenzocyclooctenes • ortho-quinodimethanes • 8-membered ring formation

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[16] To obtain additional structural information, compound **1a** has also been hydrogenated to the corresponding dibenzocyclooctane. See ESI.
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[18] NMR shows no indications for allylic C=C double bond isomerisation under the applied reactions conditions.
[19] Active participation of a *gem*-ester moiety in direct carbene insertion reactions into C$_{\text{aromatic}}$−H bonds has been reported, but is not accessible for carbene radical **C** and would not explain the double bond migration: M. R. Fructos, M. Besora, A .A. C. Braga, M. M. Díaz-Requejo, F. Maseras and P. J. Pérez, *Organometallics*, **2017**, *36*, 172-179.
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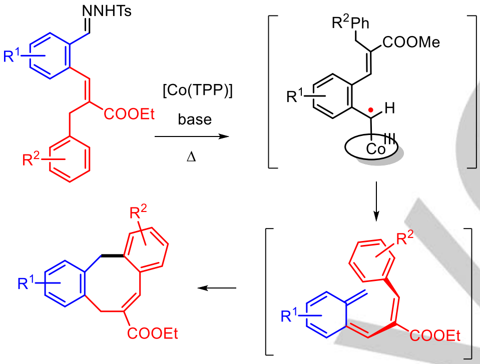
Entry for the Table of Contents

COMMUNICATION

Metalloradical activation of benzallyl-aryl-tosylhydrazones by the [Co(TPP)] catalyst provides an effective method to construct a series of unique dibenzocyclooctenes via selective $C_{carbene}$–C_{aryl} cyclization, producing the desired 8-membered ring products in good to excellent yields. The proposed reaction mechanism involves intramolecular HAT to the key Co^{III}-carbene radicals, followed by dissociation of o-quinodimethides undergoing 8π-cyclisation.



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Catalytic dibenzocyclooctene synthesis via cobalt(III)-carbene radical and *ortho*-quinodimethane intermediates