

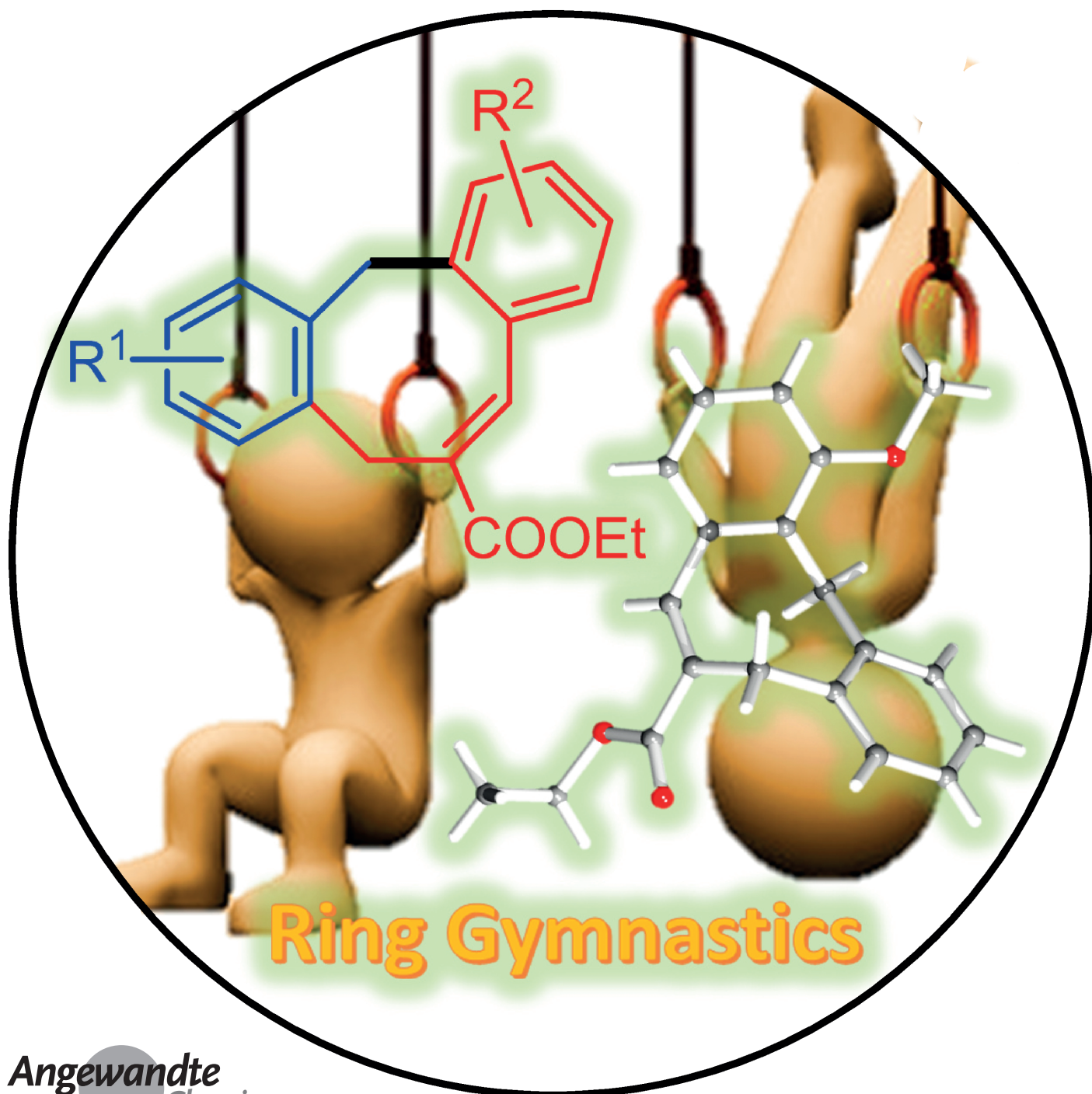
Medium-Ring Compounds

International Edition: DOI: 10.1002/anie.201711028

German Edition: DOI: 10.1002/ange.201711028

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 $C_{\text{carbene}}-C_{\text{aryl}}$ 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.^[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.^[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

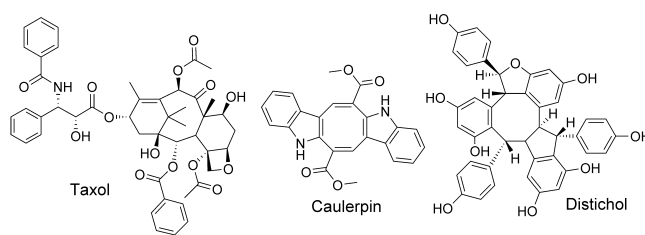


Figure 1. Natural products containing eight-membered rings.

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 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) 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).

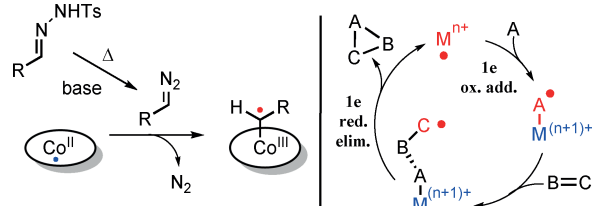


Figure 2. Left: Radical transfer from the cobalt catalyst to a carbene moiety to produce carbon-centered radicals (“carbene radicals”). Right: Open-shell organometallic catalysis involving “one-electron oxidative addition” and “one-electron reductive elimination” elementary steps.

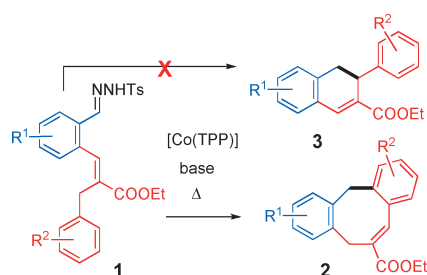
Such metalloradical approaches have previously been employed to synthesize cyclopropanes,^[9] chromenes,^[10] furans,^[11] indenes,^[12] ketenes,^[13] butadienes,^[14] and dihydronaphthalenes.^[14] We now report the synthesis of unique dibenzocyclooctenes in high yields by cobalt-based metalloradical 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*-benzallylaryl *N*-tosyl hydrazones) by [Co(TPP)] (TPP = tetraphenylporphyrin). However, rather than the initially anticipated

[*] C. te Grotenhuis, N. van den Heuvel, Dr. Ir. J. I. van der Vlugt, Prof. Dr. B. de Bruin
Homogeneous, Supramolecular and Bio-Inspired Catalysis (HomKat) group
Van't Hoff Institute for Molecular Sciences (HIMS)
University of Amsterdam
Science Park 904, 1098 XH Amsterdam (The Netherlands)
E-mail: B.deBruin@uva.nl

Supporting information and the ORCID identification number(s) for the author(s) of this article can be found under:
<https://doi.org/10.1002/anie.201711028>.

© 2017 The Authors. Published by Wiley-VCH Verlag GmbH & Co. KGaA. This is an open access article under the terms of the Creative Commons Attribution Non-Commercial NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial, and no modifications or adaptations are made.



Scheme 1. Metalloradical approach for the synthesis of dibenzocyclooctenes **2** from *N*-tosyl hydrazones **1** by $C_{\text{carbene}}-C_{\text{aryl}}$ cyclization, as described in this paper, and the initially expected formation of dihydronaphthalenes **3** via formal carbene insertion into the benzylic C–H bond.

formation of dihydronaphthalenes **3**, we observed the unexpected formation of a range of unique dibenzocyclooctenes **2** by $C_{\text{carbene}}-C_{\text{aryl}}$ 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 benzylic 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 benzylic 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 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 $C_{\text{carbene}}-C_{\text{aryl}}$ 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

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

Entry	Substrate	Product	Yield ^[b]
1			82 %
2			97 %
3			87 %
4			91 %
5			92 %
6			96 %
7			78 %

[a] Reaction conditions: **1a–1g** (0.1 mmol, 1.0 equiv), LiO^tBu (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.

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 **2l'**, 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 dibenzocyclooct-

Table 2: Substrate scope varying the R² substituent.^[a]

Entry	Substrate	Product	Yield ^[b]
1			83 %
2			61 %
3			95 % 1.4:1
4			75 %
5			71 % 1.7:1
6			66 %

Table 2: (Continued)

Entry	Substrate	Product	Yield ^[b]
7			85 %
8			97 %

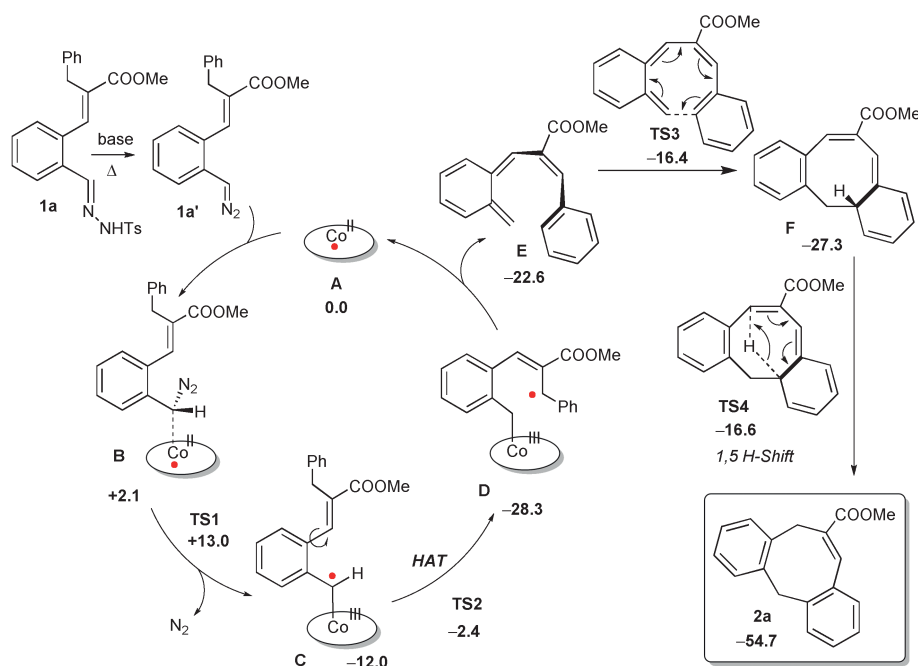
[a] Reaction conditions: **1h–1o** (0.1 mmol, 1.0 equiv), LiO^tBu (0.12 mmol, 1.2 equiv), [Co(TPP)] (5 mol%), benzene (2 mL), 60 °C, overnight. [b] Yields of isolated products, corrected for the *E/Z* ratios of the substrates. Averages of two experiments are given.

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 R¹-substituted aryl group in the substrate to a position next to the R²-substituted aryl group in the product. Disregarding the expected isomers formed in entries 3 and 5 of Table 2, the reactions are highly chemoselective.^[18] The position of the C=C double bond, selectively in conjugation with the R²-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^[19] as substrates lacking this functional group or with a different substituent at this position did not produce dibenzocyclooctenes.^[20]

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**.^[21] 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*-



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

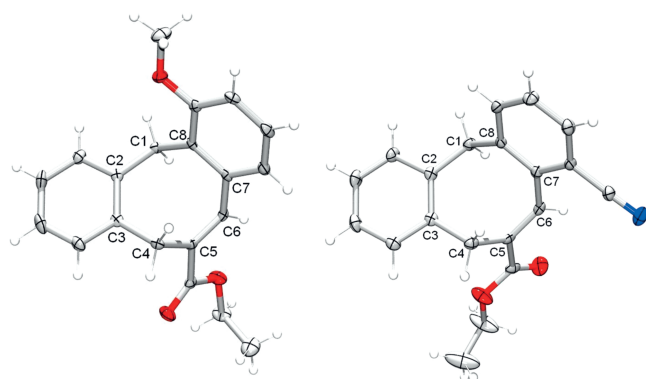


Figure 3. Molecular structures of **2j** (left) and **2m** (right), as obtained by single-crystal X-ray diffraction. Selected bond distances [Å] for **2j** and **2m** (in italics): C1–C8 1.513(2), 1.518(3); C4–C5 1.509(2), 1.511(3); C5–C6 1.332(2), 1.333(3); C6–C7 1.476(2), 1.475(3).

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 8 π 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 nitron (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 metal-radical 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 8 π cyclization of *ortho*-quinodimethane intermediates followed by a [1,5]-hydride shift.

Acknowledgements

We thank Ed Zuinga 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: carbene radicals · cobalt · dibenzocyclooctenes · metalloradicals · *ortho*-quinodimethanes

How to cite: *Angew. Chem. Int. Ed.* **2018**, *57*, 140–151
Angew. Chem. **2018**, *130*, 146–151

- [1] a) G. A. Molander, *Acc. Chem. Res.* **1998**, *31*, 603–609; b) L. Yet, *Chem. Rev.* **2000**, *100*, 2963–3007.
- [2] M. A. Patane, N. A. Petasis, *Tetrahedron* **1992**, *48*, 5757–5821.
- [3] S. M. Ma, E. Negishi, *J. Org. Chem.* **1994**, *59*, 4730–4732.
- [4] S. R. Gilbertson, B. DeBoef, *J. Am. Chem. Soc.* **2002**, *124*, 8784–8785.
- [5] a) K. C. Majumdar, *RSC Adv.* **2011**, *1*, 1152–1170; b) T. J. A. Corrie, L. T. Ball, C. A. Russell, G. C. Lloyd-Jones, *J. Am. Chem. Soc.* **2017**, *139*, 245–254.
- [6] A. Michaut, J. Rodriguez, *Angew. Chem. Int. Ed.* **2006**, *45*, 5740–5750; *Angew. Chem.* **2006**, *118*, 5870–5881.
- [7] a) L. A. Paquette, L. Q. Sun, D. Friedrich, P. B. Savage, *J. Am. Chem. Soc.* **1997**, *119*, 8438–8450; b) L. A. Paquette, D. Friedrich, R. D. Rogers, *J. Org. Chem.* **1991**, *56*, 3841–3849; c) J. J. M. Lamberts, W. H. Laarhoven, *J. Am. Chem. Soc.* **1984**, *106*, 1736–1739.
- [8] a) V. Lyaskovskyy, B. de Bruin, *ACS Catal.* **2012**, *2*, 270–279; b) W. I. Dzik, X. Xu, X. P. Zhang, J. N. H. Reek, B. de Bruin, *J. Am. Chem. Soc.* **2010**, *132*, 10891–10902; c) W. I. Dzik, X. P. Zhang, B. de Bruin, *Inorg. Chem.* **2011**, *50*, 9896–9903.
- [9] a) L. Huang, Y. Chen, G. Y. Gao, X. P. Zhang, *J. Org. Chem.* **2003**, *68*, 8179–8184; b) S. Zhu, J. V. Ruppel, H. Lu, L. Wojtas, X. P. Zhang, *J. Am. Chem. Soc.* **2008**, *130*, 5042–5043; c) D. Inriერი, A. Caselli, E. Gallo, *Eur. J. Inorg. Chem.* **2011**, 5071–5081; d) A. Chirila, B. G. Das, N. D. Paul, B. de Bruin, *ChemCatChem* **2017**, *9*, 1413–1421; e) M. Goswami, B. de Bruin, W. I. Dzik, *Chem. Commun.* **2017**, 53, 4382–4385.
- [10] a) N. D. Paul, S. Mandal, M. Otte, X. Cui, X. P. Zhang, B. de Bruin, *J. Am. Chem. Soc.* **2014**, *136*, 1090–1096; b) N. Majumdar, N. D. Paul, S. Mandal, B. de Bruin, W. D. Wulff, *ACS Catal.* **2015**, *5*, 2329–2366.
- [11] X. Cui, X. Xu, L. Wojtas, M. M. Kim, X. P. Zhang, *J. Am. Chem. Soc.* **2012**, *134*, 19981–19984.
- [12] B. G. Das, A. Chirila, M. Tromp, J. N. H. Reek, B. de Bruin, *J. Am. Chem. Soc.* **2016**, *138*, 8968–8975.
- [13] N. D. Paul, A. Chirila, H. Lu, X. P. Zhang, B. de Bruin, *Chem. Eur. J.* **2013**, *19*, 12953–12958.
- [14] C. Te Grotenhuis, B. G. Das, P. F. Kuijpers, W. Hageman, M. Trouwborst, B. de Bruin, *Chem. Sci.* **2017**, *8*, 8221–8230.
- [15] Related “open-shell organometallic” approaches have been used by the group of Gansäuer to activate epoxides and aziridines with Ti^{III} complexes; see: a) A. Gansäuer, S. Hildebrandt, A. Michelmann, T. Dahmen, D. von Laufenberg, C. Kube, G. D. Fianu, R. A. Flowers II, *Angew. Chem. Int. Ed.* **2015**, *54*, 7003–7006; *Angew. Chem.* **2015**, *127*, 7109–7112; b) A. Gansäuer, S. Hildebrandt, E. Vogelsang, R. A. Flowers II, *Dalton Trans.* **2016**, *45*, 448–452; c) S. Hildebrandt, A. Gansäuer, *Angew. Chem. Int. Ed.* **2016**, *55*, 9719–9722; *Angew. Chem.* **2016**, *128*, 9871–9874.
- [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_{aromatic}-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, *Organometallics* **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.
- [21] a) J. Barluenga, C. Valdés, *Angew. Chem. Int. Ed.* **2011**, *50*, 7486–7500; *Angew. Chem.* **2011**, *123*, 7626–7640; b) Z. Shao, H. Zhang, *Chem. Soc. Rev.* **2012**, *41*, 560–572; c) T. Yao, K. Hirano, T. Satoh, M. Miura, *Angew. Chem. Int. Ed.* **2012**, *51*, 775–779; *Angew. Chem.* **2012**, *124*, 799–803; d) Q. Xiao, Y. Zhang, J. Wang, *Acc. Chem. Res.* **2013**, *46*, 236–247; e) F. Hu, Y. Xia, F. Ye, Z. Liu, C. Ma, Y. Zhang, J. Wang, *Angew. Chem. Int. Ed.* **2014**, *53*, 1364–1367; *Angew. Chem.* **2014**, *126*, 1388–1391.
- [22] J. L. Segura, N. Martin, *Chem. Rev.* **1999**, *99*, 3199–3246; see also Ref. [1].

Manuscript received: October 26, 2017

Accepted manuscript online: November 20, 2017

Version of record online: December 6, 2017