## Natural Product Synthesis

Biomimetic Dehydrogenative Diels–Alder Cycloadditions: Total Syntheses of Brosimones A and B**

*Chao Qi, Huan Cong, Katharine J. Cahill, Peter Müller, Richard P. Johnson, and John A. Porco Jr.**

Nature creates an intriguing array of molecular architectures that has attracted extensive investigations on natural product identification, origin, biological activities, and chemical synthesis.[1] In particular, biosynthetic studies have inspired elegant biomimetic total synthesis of natural products.[2] Herein, we report biomimetic syntheses of the natural products brosimones A and B featuring multicatalytic,[3] dehydrogenative Diels–Alder (DHDA) cycloadditions[4] of 2′-hydroxychalcones.

Prenylflavonoid Diels–Alder natural products,[5] mainly isolated from the root bark of mulberry trees (*Morus alba*), are biosynthetically derived from electron-rich 2′-hydroxychalcone dienophiles and flavonoid dienes. Pioneering studies by Nomura and co-workers have determined that the requisite diene subunits arise from prenyl groups in nature. In one key experiment,[6] the natural product artonin I (**1**) was isolated from *Morus alba* cell extract after both prenylated flavone **2** and chalcone **3** were fed to cell culture (Scheme 1).

As part of our continuing interest[7] in the total synthesis of prenylflavonoid Diels–Alder and related natural products,[8] we have recently reported silica-supported silver nanoparticles (AgNPs)[9] as a highly efficient catalyst for [4+2] cycloadditions of 2′-hydroxychalcones. Inspired by the aforementioned biosynthesis studies, further investigation was directed to the development of catalysts that enable biomimetic DHDA cycloadditions employing prenyl groups as diene precursors. In this regard, we envisioned tandem reactions that employ one catalyst system to promote dehydrogenation of prenyl groups to 1,3-substituted
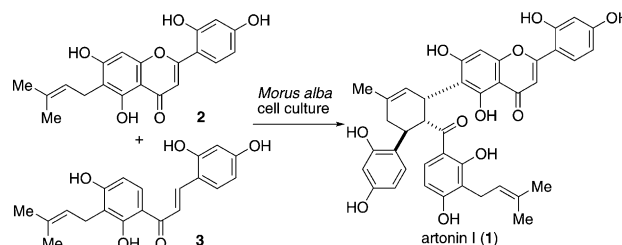
Scheme 1. Proposed biosynthesis of artonin I (**1**).

dienes[10] in combination with silica-supported AgNPs to catalyze Diels–Alder cycloadditions of chalcone dienophiles and in situ-generated dienes.

Brosimones A (**4**)[11] and B (**5**)[12] were both isolated from the plant *Brosimopsis oblongifolia* in Brazil and feature dimeric structures derived from prenyl chalcone **7** (Scheme 2). The intriguing biosynthetic relationship and structures of the brosimones, in particular the [3.3]metacyclophane core[13] of **4**, underscores the compounds as attractive targets for further development of DHDA cycloadditions.

Our initial studies began with model reactions using prenyl chalcone **8**. After screening a number of catalysts and oxidants,[14] we observed that the desired dehydrogenative cycloaddition was catalyzed by a mixture of platinum on activated carbon (Pt/C)[15] and silica-supported AgNPs in an ambient air atmosphere (Table 1, entry 1), which afforded cycloadducts *exo*-**9** and *endo*-**10** in 52% combined yield. We also examined hydrogen scavengers for transfer dehydrogenation, including cyclopentene[16] (entry 3) and norbornene[17] (entry 6). Use of cyclopentene afforded the best yield and mass balance and was chosen as the optimal hydrogen

[*] C. Qi,[+] H. Cong,[+] Prof. Dr. J. A. Porco Jr.
   Department of Chemistry and Center for Chemical Methodology
   and Library Development (CMLD-BU), Boston University
   590 Commonwealth Avenue, Boston, MA 02215 (USA)
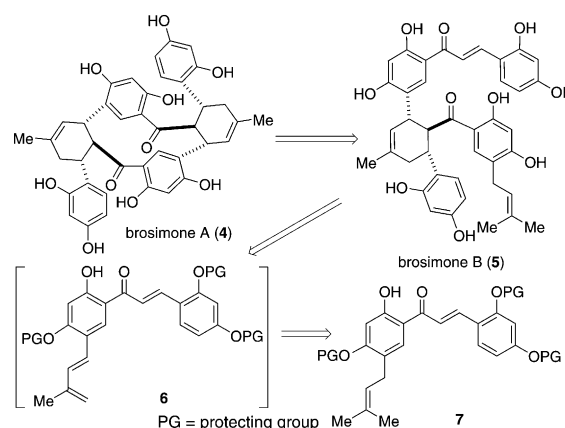   E-mail: porco@bu.edu

   K. J. Cahill, Prof. Dr. R. P. Johnson
   Department of Chemistry, University of New Hampshire
   Durham, NH 03824 (USA)

   P. Müller
   Department of Chemistry, Massachusetts Institute of Technology
   Boston, MA 02139 (USA)
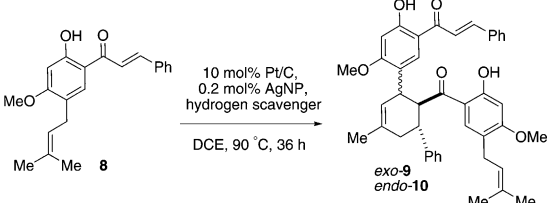
[+] These authors contributed equally to this work.

Scheme 2. Biomimetic synthetic design for brosimones A and B.

Table 1: Development of the initial methodology employing a model prenylchalcone.[a]


Entry	Hydrogen scavenger	Conversion[b]	endo-**10**/exo-**9**[b]
1	air (1 atm)	88% (52%)[c]	52:48
2[d]	O$_2$ (1 atm)	79% (60%)[c]	57:43
3	cyclopentene (9 equiv)	66% (61%)[c]	42:58
4[e]	cyclopentene (9 equiv)	<10%	–
5[f]	cyclopentene (9 equiv)	38% (8%)[c]	72:28
6	norbornene (10 equiv)	76% (44%)[c]	50:50
7	none	40% (18%)[c]	55:45

[a] See the Supporting Information for experimental details. [b] Based on integration of signals in the ^{1}H NMR spectrum. [c] Yield of isolated product shown in parentheses. [d] 5 mol% Pt/C, 0.1 mol% AgNP. [e] In the absence of Pt/C. [f] In the absence of AgNPs.

scavenger. Control experiments showed that reactions with cyclopentene did not proceed without Pt/C (entry 4) and were significantly less efficient in the absence of AgNPs (entry 5). The use of AgNP catalyst also promotes enhanced formation of the desired *exo* diastereomer **9** (entries 3 and 5), which may be explained by conversion of *endo*-**10** to *exo*-**9** under AgNP-catalyzed conditions.[14] Use of Lewis acids such as BF$_3$·Et$_2$O and AgOTf in place of the AgNPs afforded trace amounts of dehydrogenative cycloaddition products.[14]

With a model reaction established, DHDA cycloaddition/dimerization of **11** using the optimized Pt/C-AgNP conditions with cyclopentene as H$_2$ scavenger afforded the cycloadducts *exo*-**12** and *endo*-**13** (1.2:1) in 64% yield.[14] Transfer hydrogenolysis of *exo*-**12** was accomplished employing 1,4-cyclohexadiene as hydrogen donor to afford brosimone B (**5**) with the trisubstituted olefin remaining intact (Scheme 3).[18] Use of ammonium formate[19] as additive was found to further accelerate the hydrogenolysis. Spectral data for synthetic
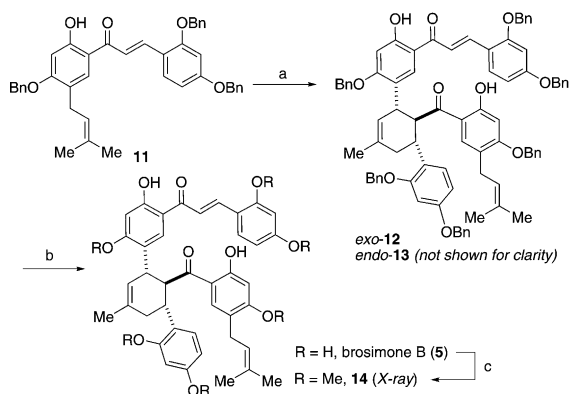
brosimone B were in agreement with those reported by Messana and co-workers for the natural product.[12] Methylation of **5** afforded protected derivative **14**, the structure of which was determined by X-ray crystal-structure analysis.[20]
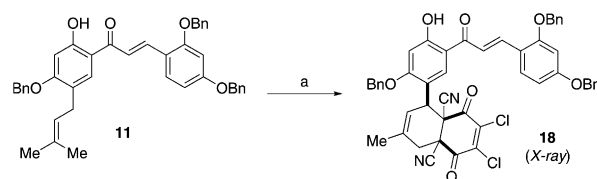
We next studied dehydrogenative cycloaddition of *exo*-**12** to access brosimone A (**4**) (Scheme 4). Treatment of *exo*-**12**
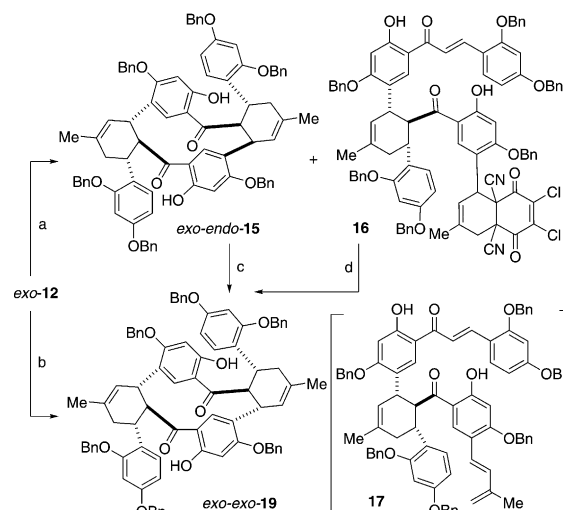
Scheme 4. Dehydrogenative cycloadditions to access cycloadducts *exo-endo*-**15**, **16**, and *exo-exo*-**19**. a) DDQ (1.6 equiv), AgNP (0.3 mol%), PhCl, 90°C, 48 h, *exo-endo*-**15**, 17%, **16**, 34%; b) DDQ (1.5 equiv), AgNP (0.3 mol%), PhCl, 130°C, 72 h, 62%, d.r. >20:1; c) AgNP (0.3 mol%), PhCl, 130°C, 48 h, 95%; d) AgNP (0.4 mol%), PhCl, 130°C, 48 h, 84%.

with catalytic Pt/C and AgNPs in combination with cyclopentene as H$_2$ scavenger did not lead to substantial formation of desired cycloadducts, even at temperatures up to 130°C. After screening a series of reaction parameters, we found that in the presence of excess 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ)[4f,21] and AgNPs as catalyst, *exo*-**12** was converted into the cycloadduct *exo-endo*-**15**[22] in 17% yield using chlorobenzene as solvent at 90°C. Furthermore, the DDQ adduct **16** was isolated in 34% yield, which further supported the intermediacy of diene **17**.[23] In a similar fashion, treatment of prenylchalcone **11** with DDQ in the absence of AgNPs afforded DHDA adduct **18** in 55% yield and 5:1 d.r., with no *exo*-**12** or *endo*-**13** observed (Scheme 5, major *endo* diastereomer shown). The structure and stereochemistry of **18** were confirmed by X-ray crystallography.[20]

Further experiments revealed that increasing the reaction temperature (130°C) for DHDA of *exo*-**12** in the presence of

Scheme 3. Synthesis of brosimone B. a) Pt/C (10 mol%), AgNP (0.2 mol%), cyclopentene, 1,2-dichloroethane (DCE), 110°C, 48 h, 64%, *endo*-**13**:*exo*-**12** = 1:1.2; b) Pd/C (40 mol%), HCO$_2$NH$_4$ (2 equiv), 1,4-cyclohexadiene, acetone, 40°C, 24 h, 85%; c) K$_2$CO$_3$, Me$_2$SO$_4$, acetone, 40°C, 4 h, 15%. Bn = benzyl.


Scheme 5. DDQ-derived cycloadduct formation. a) DDQ (2.1 equiv), DCE, 90°C, 24 h, 55%, d.r. = 5:1.

AgNPs predominantly afforded *exo-exo*-cycloadduct **19** in 62% yield (Scheme 4). Replacement of AgNPs with Lewis acids led to inferior results. Substantial decomposition occurred with BF$_3$·Et$_2$O, Cu(OTf)$_2$,[24] or In(OTf)$_3$[25] as Lewis acids; a 7% yield of **19** was obtained using AgOTf (20 mol%) as catalyst. Cycloadduct **19** was not observed in a control experiment with silica gel at 130°C, demonstrating the utility of AgNPs to access brosimone A derivative **19**.[14] Further studies showed that DDQ adduct **16** could be converted into *exo-exo*-**19** in 84% yield under AgNP-catalyzed conditions, which suggested tandem retro-Diels–Alder/Diels–Alder processes[8a] consistent with temperature-dependent stereoselectivity affording *exo-endo*-**15** (kinetically favored product) and *exo-exo*-**19** (thermodynamically favored product). Moreover, *exo-endo*-**15** was converted exclusively into *exo-exo*-**19** under AgNP-promoted conditions at 130°C. A control experiment without AgNPs also showed trace conversion of **15** to **19**, reinforcing the fact that AgNPs may facilitate tandem retro-Diels–Alder/Diels–Alder processes.

Final hydrogenolysis of *exo-exo*-**19** afforded brosimone A (**4**) in 91% yield (Scheme 6). Methylation of **4** afforded hexamethylether **20**, which allowed unambiguous structure and stereochemical assignments for synthetic brosimone A (**4**) based on X-ray crystallography.[20] The X-ray structure of **20** revealed a C_2-symmetric *syn*-[3,3]metacyclophane[26] structure with slightly distorted aromatic rings[13] (ϕ C$_a$-C$_b$-C$_c$-C$_d$ = 6.4°).

Our previous studies provided strong evidence for an electron-transfer mechanism for AgNP-catalyzed Diels–Alder cycloadditions.[9a] A simplified computational model for AgNP-catalyzed cycloadditions was constructed using the corresponding diene of substrate **14**, which was found to have similar reactivity to hexabenzylether **12** (Scheme 7). Density functional theory was used to predict the energetics of cycloaddition by different mechanisms. The lowest barriers were observed for a process that involved one electron substrate oxidation, deprotonation of the phenol, and complexation of the resultant radical with Ag^I on the surface of
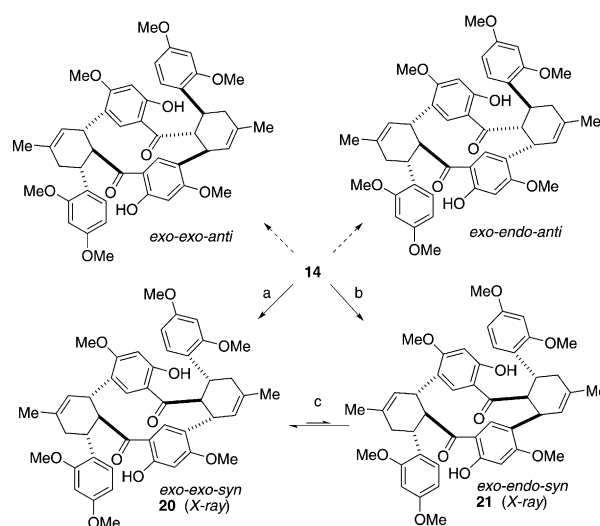
Scheme 7. Model reactions for calculations. a) DDQ (1.5 equiv), AgNP (0.2 mol%), PhCl, 130°C, 72 h, 72%; b) DDQ (1.5 equiv), AgNP (0.2 mol%), PhCl, 90°C, 48 h, 15%; c) AgNP (0.2 mol%), PhCl, 130°C, 48 h, 94%.

the AgNPs.[27] Figure 1 shows the energetics of stepwise intramolecular cycloadditions[28] to yield the observed cycloadducts. Our predicted reaction energetics and calculated transition states[14] support the observation that the *exo-endo-syn* stereoisomer (*exo-endo*-**15**, Scheme 4) is the kinetic product, which may be converted to the more thermodynamically stable *exo-exo-syn* diastereomer (*exo-exo*-**19**, Scheme 4) through cycloreversion. Pathways to *exo-exo-anti* and *exo-endo-anti* products (Scheme 7), which were not observed experimentally, lie at higher energy.[14]

In summary, we have developed biomimetic, dehydrogenative Diels–Alder (DHDA) cycloadditions that have enabled concise syntheses of the natural product brosimone B and the [3.3]metacyclophane natural product brosimone A. The syn-
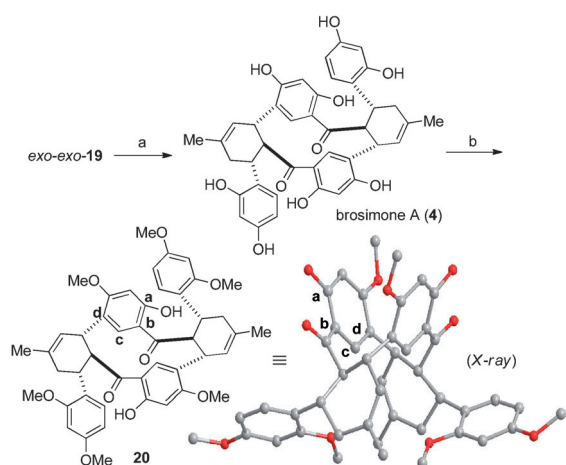
Scheme 6. Synthesis of brosimone A. a) Pd/C (60 mol%), HCO$_2$NH$_4$ (2 equiv), HCO$_2$H, 1,4-cyclohexadiene, acetone, 40°C, 24 h, 91%; b) K$_2$CO$_3$, MeI, acetone, 40°C, 12 h, 13%.
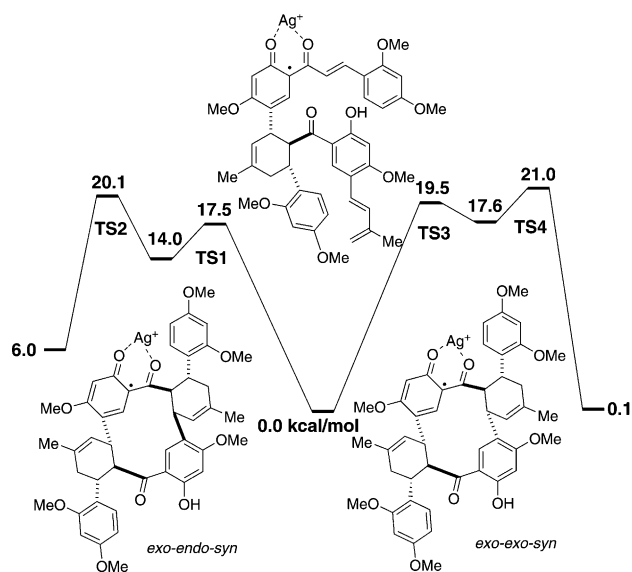
Figure 1. B3LYP/LANL2DZ energetics of AgNP-catalyzed cycloadditions.

theses employ Pt/C-cyclopentene or DDQ to effect dehydrogenation of prenylchalcones in combination with silver nanoparticles to promote subsequent Diels–Alder cycloaddition. Experiments confirmed the formation of a kinetic *exo-endo* diastereomer of a protected form of brosimone A, which could be converted to a thermodynamic *exo-exo* isomer using AgNPs at higher temperature. Density functional theory was used to predict the energetics of AgNP-catalyzed cycloadditions; the lowest barriers were observed for a process involving one electron oxidation, phenol deprotonation, and complexation of the resultant radical with Ag^I on the surface of the AgNP. Further applications of dehydrogenative Diels–Alder cycloadditions and reaction development using silver nanoparticles are ongoing and will be reported in due course.

[1] For reviews, see: a) K. C. Nicolaou, E. J. Sorensen in *Classics in Total Synthesis: Targets, Stratergies, Methods*, Wiley-VCH, Weinheim, **1996**; b) *Biologically Active Natural Products: Pharmaceuticals* (Eds.: S. J. Cutler, H. G. Culter), CRC, Boca Raton, FL, **2000**; c) K. C. Nicolaou, S. A. Snyder in *Classics in Total Synthesis II: More Targets, Strategies, Methods*, Wiley-VCH, Weinheim, **2003**; d) P. M. Dewick in *Medicinal Natrual products: A Biosynthetic Approach*, Wiley-VCH, Weinheim, **2009**; e) K. C. Nicolaou, J. S. Chen in *Classics in Total Synthesis III*, Wiley-VCH, Weinheim, **2011**.

[2] For reviews see: a) E. M. Stocking, R. M. Williams, *Angew. Chem.* **2003**, *115*, 3186–3223; *Angew. Chem. Int. Ed.* **2003**, *42*, 3078–3115; b) M. C. de La Torre, M. A. Sierra, *Angew. Chem.* **2004**, *116*, 162–184; *Angew. Chem. Int. Ed.* **2004**, *43*, 160–181; c) *Biomimetic Organic Synthesis, Vol. 1&2* (Eds: E. Poupon, B. Nay), Wiley-VCH, Weinheim, **2011**.

[3] L. M. Ambrosini, T. H. Lambert, *ChemCatChem* **2010**, *2*, 1373–1380.

[4] For recent examples of dehydrogenative [4+2] cycloadditions, see: a) T. Fukutani, N. Umeda, K. Hirano, T. Satoh, M. Miura, *Chem. Commun.* **2009**, 5141–5143; b) Y. Nakao, E. Morita, H. Idei, T. Hiyama, *J. Am. Chem. Soc.* **2011**, *133*, 3264–3267; c) T. Ozawa, T. Kurahashi, S. Matsubara, *Org. Lett.* **2011**, *13*, 5390–5393; d) E. M. Stang, M. C. White, *J. Am. Chem. Soc.* **2011**, *133*, 14892–14895; e) M. Ohashi, I. Takeda, M. Ikawa, S. Ogoshi, *J. Am. Chem. Soc.* **2011**, *133*, 18018–118021; f) S. Dong, T. Qin, E. Hamel, J. A. Beutler, J. A. Porco, Jr., *J. Am. Chem. Soc.* **2012**, *134*, 19782–19787.

[5] T. Nomura, *Yakugaku Zasshi* **2001**, *121*, 535–556.

[6] Y. Hano, M. Aida, T. Nomura, S. Ueda, *J. Chem. Soc. Chem. Commun.* **1992**, 1177–1178.

[7] H. Cong, D. Ledbetter, G. T. Rowe, J. P. Caradonna, J. A. Porco, Jr., *J. Am. Chem. Soc.* **2008**, *130*, 9214–9215.

[8] a) T. Nomura, T. Fukai, T. Narita, S. Terada, J. Uzawa, Y. Litaka, M. Takasugi, S. Ishikawa, S. Nagao, T. Masamune, *Tetrahedron Lett.* **1981**, *22*, 2195–2198; b) C. Gunawan, M. A. Rizzacasa, *Org. Lett.* **2010**, *12*, 1388–1391; c) E. M. Jung, Y. R. Lee, *Bull. Korean Chem. Soc.* **2008**, *29*, 1199–1204; d) S. Boonsri, C. Gunawan, E. H. Krenske, M. A. Rizzacasa, *Org. Biomol. Chem.* **2012**, *10*, 6010–6021.

[9] For [4+2] cycloadditions with AgNPs, see: a) H. Cong, C. F. Becker, S. J. Elliott, M. W. Grinstaff, J. A. Porco, Jr., *J. Am. Chem. Soc.* **2010**, *132*, 7514–7518; b) C. F. Chee, Y. K. Lee, M. J. C. Buckle, N. A. Rahman, *Tetrahedron Lett.* **2011**, *52*, 1797–1799; c) H. Cong, J. A. Porco, Jr., *ACS Catal.* **2012**, *2*, 65–70; d) H. Cong, J. A. Porco, Jr., *Org. Lett.* **2012**, *14*, 2516–2519.

[10] A. Minami, H. Oikawa in *Biomimetic Organic Synthesis, Vol. 2* (Eds.: E. Poupon, B. Nay), Wiley-VCH, Weinheim, **2011**, pp. 775–782.

[11] I. Messana, F. Ferrari, *Tetrahedron* **1988**, *44*, 6693–6698.

[12] I. Messana, F. Ferrari, J. F. de Mello, M. do Carmo Mesquita de Araujo, *Heterocycles* **1989**, *29*, 683–690.

[13] For a review of strained cyclophane natural products, see: T. Gulder, P. S. Baran, *Nat. Prod. Rep.* **2012**, *29*, 899–934.

[14] For complete experimental details, see the Supporting Information.

[15] For dehydrogenation of alkanes to alkenes using platinum, see: a) S. B. Kogan, M. Herskowitz, *Ind. Eng. Chem. Res.* **2002**, *41*, 5949–5951; b) D. Sebastian, E. G. Bordeje, L. Calvillo, M. J. Lazaro, R. Moliner, *Int. J. Hydrogen Energy* **2008**, *33*, 1329–1334; c) H. Miyamura, K. Maehata, S. Kobayashi, *Chem. Commun.* **2010**, *46*, 8052–8054.

[16] D.-H. Lee, K.-H. Kwon, C. S. Yi, *J. Am. Chem. Soc.* **2012**, *134*, 7325–7328.

[17] K. Wang, M. E. Goldman, T. J. Emge, A. S. Goldman, *J. Organomet. Chem.* **1996**, *518*, 55–68.

[18] M. E. Jung, Y. Usui, C. T. Vu, *Tetrahedron Lett.* **1987**, *28*, 5977–5980.

[19] K. Iikubo, Y. Ishikawa, N. Ando, K. Umezawa, S. Nishiyama, *Tetrahedron Lett.* **2002**, *43*, 291–293.

[20] CCDC 927682 (**14**), 927684 (**18**), 927685 (**20**), and 927683 (**21**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[21] For dehydrogenation of alkenes to dienes using DDQ, see: a) B. Halton, S. G. G. Russell, *Aust. J. Chem.* **1992**, *45*, 1069–1076; b) T. Jigami, K. Takimiya, T. Otsubo, *J. Org. Chem.* **1998**, *63*, 8865–8872; c) R. F. Schumacher, A. R. Rosario, A. C. G. Souza, P. H. Menes, G. Zeni, *Org. Lett.* **2010**, *12*, 1952–1955.

[22] The structure of **15** was assigned by comparison to its hexamethyl ether derivative **21**, which was characterized by X-ray crystal-structure analysis.

[23] DDQ adduct **16** was isolated in 44% yield in the absence of AgNPs in which case cycloadduct **15** was not observed. For experimental details, see the Supporting Information.

[24] C. Guo, J. Song, S. Luo, L. Gong, *Angew. Chem.* **2010**, *122*, 5690–5694; *Angew. Chem. Int. Ed.* **2010**, *49*, 5558–5562.

[25] B. V. Subba Reddy, P. Borkar, J. S. Yadav, P. P. Reddy, A. C. Kunwar, B. Sridhar, R. Gree, *Org. Biomol. Chem.* **2012**, *10*, 1349–1358.

[26] For structural and conformational studies of [3,3]metacyclophane, see: a) M. F. Semmelhack, J. J. Harrison, D. C. Young, A. Gutierrez, S. Rafii, J. Clardy, *J. Am. Chem. Soc.* **1985**, *107*, 7508–7514; b) K. Sako, T. Shinmyozu, H. Takemura, M. Suenaga, T. Inazu, *J. Org. Chem.* **1992**, *57*, 6536–6541; c) M. Shibahara, M. Watanabe, T. Iwanaga, K. Ideta, T. Shinmyozu, *J. Org. Chem.* **2007**, *72*, 2865–2877.

[27] a) A. Henglein, *Chem. Mater.* **1998**, *10*, 444–450; b) J. Liu, R. H. Hurt, *Environ. Sci. Technol.* **2010**, *44*, 2169–2175.

[28] For radical cation-mediated, stepwise cycloadditions, see: a) U. Haberl, O. Wiest, E. Steckhan, *J. Am. Chem. Soc.* **1999**, *121*, 6730–6736; b) N. J. Saettel, O. Wiest, D. A. Singleton, M. P. Meyer, *J. Am. Chem. Soc.* **2002**, *124*, 11552–11559; c) C. S. Sevov, O. Wiest, *J. Org. Chem.* **2008**, *73*, 7909–7915.