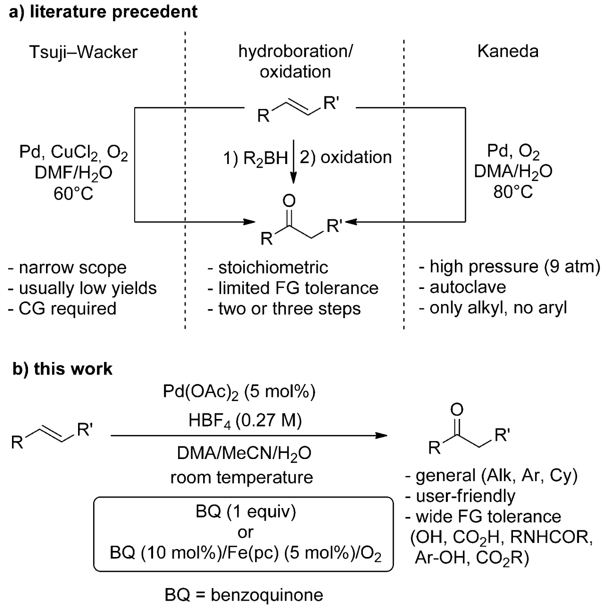
DOI: 10.1002/ange.201209541

Practical and General Palladium-Catalyzed Synthesis of Ketones from Internal Olefins**

*Bill Morandi, Zachary K. Wickens, and Robert H. Grubbs**

Ketones are ubiquitous chemical entities across the molecular sciences.[1] They serve as versatile intermediates in target-oriented synthesis, are present in a wide range of natural products and drugs, are valuable industrial products, and mediate important biochemical pathways. A simple catalytic oxidation of internal alkenes under ambient conditions would therefore represent a powerful synthetic tool to access valuable ketones, since simple internal olefins are easily accessible from petroleum and renewable resources such as seed oils. Additionally, well-established synthetic routes exist to access more functionalized internal alkenes, such as carbonyl olefination[2] and olefin metathesis.[3] Owing to the lack of an efficient catalytic transformation to synthesize ketones from internal olefins, the hydroboration/oxidation sequence is still commonly used, particularly in target-oriented synthesis (Scheme 1).[4] A major drawback of this procedure is the low functional-group (FG) compatibility of highly reactive borane reagents, as well as the inherent stoichiometric and multistep nature of the process. A direct, catalytic methodology to perform this transformation would be highly desirable. A well-studied catalytic transformation to access methyl ketones from terminal olefins is the Tsuji–Wacker reaction.[5] However, in this reaction internal olefins are unreactive unless suitable coordinating groups (CGs) are present to facilitate the process. In the latter case, the success of the transformation is highly substrate-dependent, as shown by the variable reported yields.[6] These aspects considerably limit the scope of the transformation. More recently, Kaneda and co-workers disclosed an elegant oxygen-coupled, copper-free Wacker oxidation of internal olefins.[7] This protocol shows improved substrate scope, but requires the use of high oxygen pressures (9 atm before addition of alkene followed by 3 atm) and special equipment (autoclave). This limits its application in laboratory-scale research.[8] Moreover, it has recently been emphasized that the ease of use of a synthetic methodology is of paramount importance to its broad adoption across the molecular sciences.[9] Therefore, the development of a general and convenient palladium-catalyzed oxidation of internal olefins to access ketones is still an unmet challenge in catalysis.



Scheme 1. Summary of the work. BQ = benzoquinone, CG = coordinating group, DMA = dimethylacetamide, FG = functional group, pc = phthalocyanine.

Herein, we report a simple catalytic method for the preparation of ketones from a broad range of internal olefins. Wide functional-group tolerance (alcohol, acid, aldehyde, ester, phenol, amide, alkyl, aryl, cyclic) should ensure broad applicability across the chemical sciences. The process requires a simple palladium complex, an inexpensive oxidant, dilute acid and proceeds under ambient conditions. Alternatively, the reaction can be scaled-up and coupled to oxygen (1 atm, balloon) as a terminal oxidant using a biomimetic triple catalytic system. Mechanistically intriguing features of this transformation have been revealed, such as an important synergistic solvent effect, a complex acid dependence, and a difference in reactivity between *trans* and *cis* alkenes.

At the outset of our investigations, we intended to devise a protocol including the following features to ensure broad synthetic utility: room temperature, ambient pressure, simple setup, and broad functional-group tolerance. We initially started with the following reaction conditions: MeCN/H_2O as the solvent, *trans*-4-octene as model substrate, palladium acetate as catalyst, and benzoquinone (BQ) as an easy to

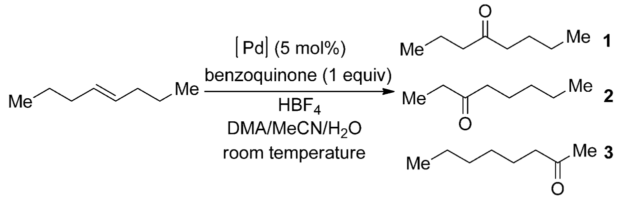
---

[*] Dr. B. Morandi, Z. K. Wickens, Prof. Dr. R. H. Grubbs
Division of Chemistry and Chemical Engineering
California Institute of Technology
Pasadena, CA 91125 (USA)
E-mail: rhg@caltech.edu

[**] We thank Scott Virgil and the Caltech Center for Catalysis for technical assistance. We gratefully acknowledge financial support from King Abdullah University of Science and Technology Center in Development, King Fahd University of Petroleum and Minerals, the NSF, and the Swiss National Science Foundation for a fellowship to B.M.

Supporting information (including detailed procedures) for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201209541.

Table 1: Optimization Studies.[a]



Entry	[Pd]	HBF$_4$	DMA/MeCN/H$_2$O	Yield [%][b]
1	Pd(OAc)$_2$	0	0:7:1	0(0)
2	[Pd(MeCN)$_4$](BF$_4$)$_2$	0	0:7:1	37(41)
3	[Pd(MeCN)$_4$](BF$_4$)$_2$	0	3.5:3.5:1	26(1)
4	[Pd(MeCN)$_4$](BF$_4$)$_2$	0.27 M	3.5:3.5:1	81(3)
5	Pd(OAc)$_2$	0.27 M	3.5:3.5:1	87(2)
6	Pd(OAc)$_2$	0.27 M	7:0:1	32(6)
7	Pd(OAc)$_2$	0.27 M	0:7:1	89(8)
8	Pd(OAc)$_2$	0.13 M	3.5:3.5:1	69(2)
9	Pd(OAc)$_2$	0.4 M	3.5:3.5:1	84(3)

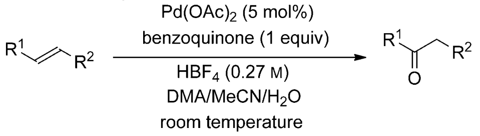
[a] 0.2 mmol substrate, 16 h. [b] Yield of 4-octanone obtained by GC using tridecane as a standard, yields in parentheses represent the combined yield of **2** and **3**.

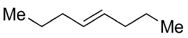
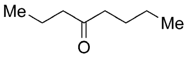
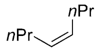
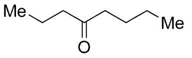
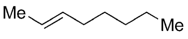
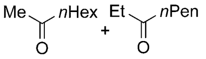
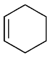
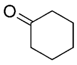
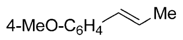
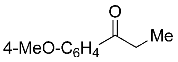
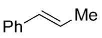
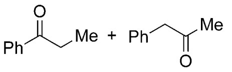
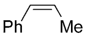
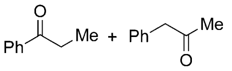
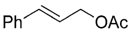
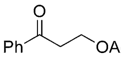
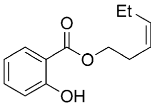
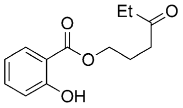
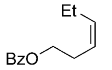
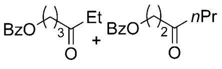
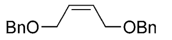
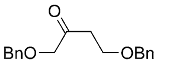
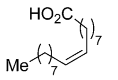
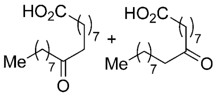
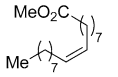
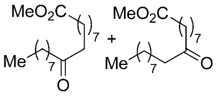
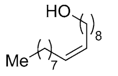
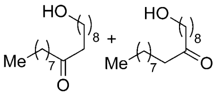
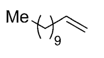
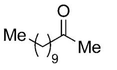
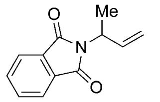
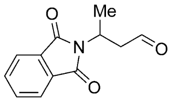
handle, inexpensive oxidant (Table 1, entry 1). Initial experiments afforded no conversion to the desired product, 4-octanone. To increase the electrophilicity of the catalyst towards the less reactive internal double bonds, a dicationic palladium complex was tested. It was found that the use of [Pd(MeCN)$_4$](BF$_4$)$_2$ afforded nearly full conversion of the starting material to a mixture of octanone isomers (Table 1, entry 2).

The low yield of 4-octanone is due to rapid competing isomerization of the double bond under these conditions, resulting in extensive formation of 3- and 2-octanone. The addition of DMA as a cosolvent almost completely suppressed isomerization,[10] but only low conversion of starting material was observed (Table 1, entry 3). To increase the reactivity of this system, a wide range of additives, including noncoordinating acids, were evaluated.[11] Addition of HBF$_4$ afforded full conversion to the desired product, 4-octanone, with only traces of the two other isomers (Table 1, entry 4). The use of Pd(OAc)$_2$ as catalyst resulted in an even improved yield under the same conditions (Table 1, entry 5). It is likely that a similar dicationic complex is generated in situ in the presence of HBF$_4$ through protonation of the acetate ligands. Control reactions showed that the use of a binary DMA/H$_2$O solvent mixture afforded a lower conversion and, surprisingly, increased formation of the isomers (Table 1, entry 6). The MeCN/H$_2$O solvent system resulted in high conversion with increased isomerization (Table 1, entry 7). Deviation from the ideal 1:1 ratio of DMA/MeCN proved ineffective. More DMA did not further improve the selectivity for oxidation over isomerization, whereas more MeCN accelerated the reaction at the cost of selectivity. A synergistic solvent effect thus appears to be a key aspect of this reaction. Lowering the amount of acid had a deleterious effect on conversion, while increasing it did not afford any further improvement (Table 1, entries 8–9). Use of weaker acids such as acetic acid afforded no product formation.

We then studied the scope of the transformation. Simple olefins, both acyclic and cyclic, were oxidized in an efficient manner (Table 2, entries 1–4). Styrene derivatives also afforded the product in high yields. High regioselectivity for the Markovnikov product could be obtained for the methoxy

Table 2: Substrate Scope.[a]



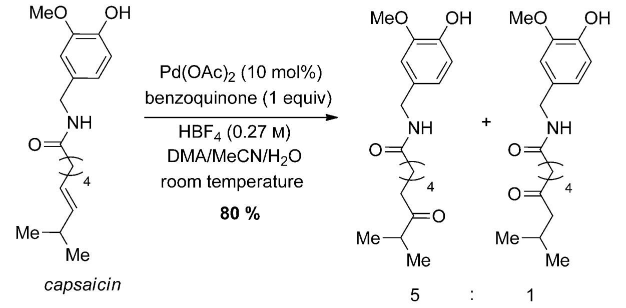
Entry	Substrate	Product	Yield [%][b]
1			78 (87)[c]
2			70[c]
3			87[c] (2.5:1)[d]
4			75[c]
5			84
6[e]			91 (1:1)[f]
7[e]			91 (1.4:1)[f]
8[e,g]			80
9			75[h]
10			91 (4:1)[d]
11[g]			53
12			82 (1:1)[d]
13			84 (1:1)[d]
14			76 (1:1)[d]
15			86
16			87

[a] 1 mmol alkene, DMA/MeCN/H$_2$O (3.5:3.5:1), 16 h. [b] Yields of isolated products. [c] Yield determined by GC using tridecane as a standard. [d] Product ratio. [e] MeCN/H$_2$O (7:1). [f] Product ratio, isomers could be separated by column chromatography. [g] 10 mol% Pd catalyst. [h] 19% of the minor isomer was present in the crude reaction mixture and was not isolated.

derivative (Table 2, entry 5). The electron-neutral aromatic substrate afforded a nearly 1:1 mixture of isomers, with a slight difference in regioselectivity for the *trans* and the *cis* alkene (Table 2, entries 6–7). Cinnamyl acetate, in contrast, afforded full regioselectivity for the Markovnikov product, thus suggesting a strong directing effect of the acetate group (Table 2, entry 8). Importantly, no benzaldehydes were obtained as side-products with styrenes (Table 2, entries 5–8), which is in contrast to the reactions using high pressure of oxygen.[12] O-functionalized homoallylic compounds afforded good regioselectivity (4:1) for oxidation of the more distal position (Table 2, entries 9–10).

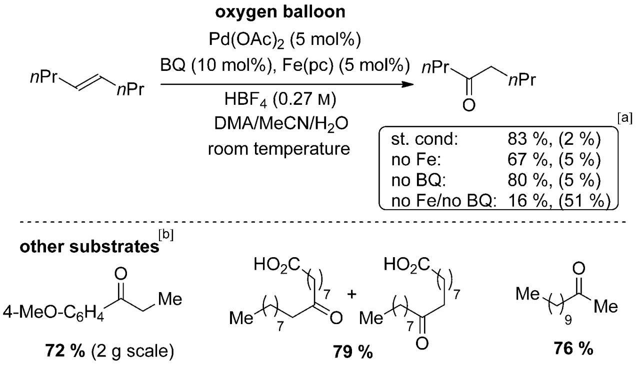
In light of recent growing interest for direct functionalization of compounds derived from seed oil,[13] unprotected oleic acid derivatives (Table 2, entries 12–14) were examined. The method proceeded in high yield with these compounds bearing unprotected acid and alcohol functional groups. Finally, we briefly evaluated the ability of this system to perform the oxidation of terminal olefins. Dodecene, a substrate classically prone to isomerization in Wacker chemistry,[14] afforded the desired product in high yield. Allylic phthalimides were recently shown by Feringa and co-workers to afford regioselective formation of the aldehyde,[15] and this outcome was also obtained using our conditions.

With continuing interest in testing the synthetic potential of this new transformation, we probed its application on a polyfunctionalized natural product. Capsaicin is an important compound with applications in cancer[16] and pain-relief[17] research. The internal alkene group was smoothly oxidized in the presence of the other functional groups, affording high yield of the desired product (Scheme 2). This result bodes well for the application of this methodology to more complex targets. The notable regioselectivity (5:1) was rationalized by steric repulsion in the hydroxypalladation step between the Pd center and the *i*Pr group.



Scheme 2. Oxidation of a bioactive natural product.

Recognizing the inherent limitation of the use of stoichiometric benzoquinone for larger-scale applications, we undertook preliminary investigations to use oxygen as terminal oxidant. Bäckvall and co-workers have extensively studied a biomimetic triple catalytic system to facilitate palladium-catalyzed oxidation reactions under atmospheric pressure of oxygen by using catalytic amounts of benzoquinone.[18] Initial results using only 10 mol% benzoquinone and 5 mol% Fe(pc) (pc = phthalocyanine) mirrored the outcome of the stoichiometric process. Control experiments showed that the reaction using both the iron catalyst and benzoquinone afforded the highest yield and best prevented isomerization. Unexpectedly, catalyst turnover was also observed in the absence of redox catalysts (Scheme 3). Indeed, the reaction went nearly to completion in all three control reactions performed. Under the directly oxygen-coupled system, full conversion to a mixture of octanone isomers (16%, 20%, 31%) was obtained. This unprecedented outcome might be the result of a synergistic solvent effect, as DMA was previously shown to facilitate direct coupling to oxygen in palladium catalysis.[10] The low selectivity for 4-octanone was a result of rapid competing isomerization under these conditions. It is conceivable that the iron catalyst and benzoquinone suppress isomerization through the trapping of a putative palladium hydride species.[19] Alternatively, the redox catalysts could accelerate the rate of oxidation relative to that of isomerization.[20] Despite the mixture of isomers obtained, this result holds great promise for the potential development of a direct oxygen-coupled oxidation of internal olefins under ambient conditions.[21] We then applied the triple catalytic system to the oxidation of selected key substrates from Table 2 in good yields. The results obtained with this system bode well for larger-scale application, a feature further confirmed by the comparable yield obtained for the oxidation of *trans*-anethole on a 2 g scale.



Scheme 3. Catalytic system for aerobic oxidation. [a] Yields determined by GC using tridecane as a standard. Yields in parentheses represent the combined yield of **2** and **3**. [b] Yields of isolated products.

Owing to the scarcity of reports involving oxidation of internal olefins and the corresponding lack of mechanistic information, we became interested in following the progress of the reaction with stoichiometric benzoquinone and both *trans*-4-octene (Figure 1 a) and *cis*-4-octene (Figure 1 b). Oxidation of the *cis* isomer was significantly faster and proceeded with slightly more isomerization than of the *trans* isomer.[22] The data did not fit a simple first-order rate law, and thus seems to indicate a more complex dependence on alkene concentration.[23]

In conclusion, we have developed a general and practical palladium-catalyzed oxidation to access ketones from a wide variety of internal olefins. The novel transformation showed

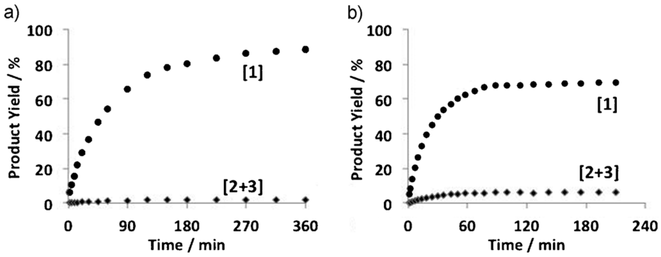


Figure 1. Reaction Progress. a) *trans*-4-Octene as substrate. b) *cis*-4-Octene as substrate. **1** = 4-Octanone, **2** = 3-octanone, **3** = 2-octanone.

a wide substrate scope (alcohol, acid, aldehyde, ester, phenol, amide, alkyl, aryl, cyclic) under experimentally simple reaction conditions. Applications of this procedure to the oxidation of a natural product and unprotected seed-oil derivatives have been reported, as well as mechanistically intriguing features (synergistic solvent effect, acid dependence, and increased reactivity of *cis* alkenes). Importantly, an oxygen-coupled procedure was developed for larger-scale applications. We anticipate that this reaction could find broad use across the chemical sciences owing to its simplicity and generality.

Received: November 28, 2012
Published online: January 16, 2013

Keywords: alkenes · ketones · oxidation · oxygen · palladium

---

[1] H. Siegel, M. Eggersdorfer, *Ullmann's Encyclopedia of Industrial Chemistry, Vol. 18*, 6th ed. (Eds.: M. Bohnet), VCH, Weinheim, **2003**, p. 739.

[2] T. Takeda, *Modern Carbonyl Olefination: Methods and Applications*, Wiley-VCH, Weinheim, **2004**.

[3] R. H. Grubbs, *Handbook of Metathesis*, Wiley-VCH, Weinheim, **2003**.

[4] Selected very recent examples of the use of hydroboration in medicinal chemistry and total synthesis: a) X. Chen, J. Mihalic, P. Fan, L. Liang, M. Lindstrom, S. Wong, Q. Ye, Y. Fu, J. Jaen, J.-L. Chen, K. Dai, L. Li, *Bioorg. Med. Chem. Lett.* **2012**, *22*, 363; b) A. R. Hudson, R. I. Higuchi, S. L. Roach, L. J. Valdez, M. E. Adams, A. Vassar, D. Rungta, P. M. Syka, D. E. Mais, K. B. Marschke, L. Zhi, *Bioorg. Med. Chem. Lett.* **2011**, *21*, 1654; c) H. Sun, J. Lu, L. Liu, H. Yi, S. Qiu, C.-Y. Yang, J. R. Deschamps, S. Wang, *J. Med. Chem.* **2010**, *53*, 6361; d) C.-C. Tseng, H. Ding, A. Li, Y. Guan, D. Y.-K. Chen, *Org. Lett.* **2011**, *13*, 4410; e) A. B. Dounay, P. G. Humphreys, L. E. Overman, A. D. Wrobleski, *J. Am. Chem. Soc.* **2008**, *130*, 5368; f) Y. Harrak, C. M. Barra, A. Delgado, A. R. Castano, A. Llebaria, *J. Am. Chem. Soc.* **2011**, *133*, 12079.

[5] a) J. Tsuji, *Synthesis* **1984**, 369. For a recent example of a copper-free Wacker-type oxidation affording no reaction with *cis*-4-decene, see: b) C. N. Cornell, M. S. Sigman, *Org. Lett.* **2006**, *8*, 4117. Selected examples of successful reactions of internal alkenes with nitrogen nucleophiles: c) C. Martínez, K. Muñiz, *Angew. Chem.* **2012**, *124*, 7138; *Angew. Chem. Int. Ed.* **2012**, *51*, 7031; d) G. Liu, S. S. Stahl, *J. Am. Chem. Soc.* **2006**, *128*, 7179.

[6] Selected examples of successful reactions using coordinating groups: a) B. M. Trost, T. L. Calkins, *Tetrahedron Lett.* **1995**, *36*, 6021; b) Y. Sato, N. Saito, M. Mori, *J. Org. Chem.* **2002**, *67*, 9310; c) S. B. Narute, N. C. Kiran, C. V. Ramana, *Org. Biomol. Chem.* **2011**, *9*, 5469. Unsuccessful reactions using coordinating groups (yield < 50 %): d) L. Raffier, F. Izquierdo, O. Piva, *Synthesis* **2011**, 4037; e) K. Lee, H. Kim, J. Hong, *Org. Lett.* **2009**, *11*, 5202; f) P. Mukherjee, S. J. S. Roy, T. K. Sarkar, *Org. Lett.* **2010**, *12*, 2472.

[7] T. Mitsudome, K. Mizumoto, T. Mizugaki, K. Jitsukawa, K. Kaneda, *Angew. Chem.* **2010**, *122*, 1260; *Angew. Chem. Int. Ed.* **2010**, *49*, 1238.

[8] For a recent reference describing the low applicability of Wacker procedures under high oxygen pressure, see: K. M. Gligorich, M. S. Sigman, *Chem. Commun.* **2009**, 3854.

[9] a) C. N. Cornell, M. S. Sigman, *Inorg. Chem.* **2007**, *46*, 1903; b) J. M. Hoover, S. S. Stahl, *J. Am. Chem. Soc.* **2011**, *133*, 16901; c) Y. Fujiwara, V. Domingo, I. B. Seiple, R. Gianatassio, M. D. Bel, P. S. Baran, *J. Am. Chem. Soc.* **2011**, *133*, 3292; d) F. Y. Kwong, S. L. Buchwald, *Org. Lett.* **2002**, *4*, 3517; e) S. Zhou, K. Junge, D. Addis, S. Das, M. Beller, *Org. Lett.* **2009**, *11*, 2461.

[10] DMA has been shown to minimize isomerization in recent Wacker-oxidations: a) Ref. [7]; b) T. Mitsudome, T. Umetani, N. Nosaka, K. Mori, T. Mizugaki, K. Ebitani, K. Kaneda, *Angew. Chem.* **2006**, *118*, 495; *Angew. Chem. Int. Ed.* **2006**, *45*, 481.

[11] Acid has been suggested to prevent formation of Pd-black and accelerate the oxidation of Pd^0 by benzoquinone in other palladium-catalyzed oxidations, see: a) H. Grennberg, A. Gogoll, J.-E. Bäckvall, *Organometallics* **1993**, *12*, 1790; b) D. G. Miller, D. D. M. Wayner, *J. Org. Chem.* **1990**, *55*, 2924; c) D. G. Miller, D. D. M. Wayner, *Can. J. Chem.* **1992**, *70*, 2485; d) J.-E. Bäckvall, R. B. Hopkins, *Tetrahedron Lett.* **1988**, *29*, 2885.

[12] Aldehyde formation has been observed with styrene derivatives under high O_2-pressure, see: a) A. Wang, H. Jiang, *J. Org. Chem.* **2010**, *75*, 2321; b) J.-Q. Wang, F. Cai, E. Wang, L.-N. He, *Green Chem.* **2007**, *9*, 882.

[13] a) A. Corma, S. Iborra, A. Velty, *Chem. Rev.* **2007**, *107*, 2411; b) For a critical discussion of the application of catalysis to renewable resources, see: M. Beller, *Eur. J. Lipid Sci. Technol.* **2008**, *110*, 789.

[14] B. W. Michel, A. M. Camelio, C. N. Cornell, M. S. Sigman, *J. Am. Chem. Soc.* **2009**, *131*, 6076.

[15] B. Weiner, A. Baeza, T. Jerphagnon, B. L. Feringa, *J. Am. Chem. Soc.* **2009**, *131*, 9473.

[16] a) A. Mori, S. Lehmann, J. O'Kelly, T. Kumagai, J. C. Desmond, M. Pervan, W. H. McBride, M. Kizaki, H. P. Koeffler, *Cancer Res.* **2006**, *66*, 3222; b) K. Ito, T. Nakazato, K. Yamato, Y. Miyakawa, T. Yamada, N. Hozumi, K. Segawa, Y. Ikeda, M. Kizaki, *Cancer Res.* **2004**, *64*, 1071.

[17] a) I. Kissin, *Anesth. Analg.* **2008**, *107*, 271; b) M. J. Caterina, M. A. Schumacher, M. Tominaga, T. A. Rosen, J. D. Levine, D. Julius, *Nature* **1997**, *389*, 816.

[18] For a recent review see: a) J. Piera, J.-E. Bäckvall, *Angew. Chem.* **2008**, *120*, 3558; *Angew. Chem. Int. Ed.* **2008**, *47*, 3506. For seminal reports: b) J.-E. Bäckvall, A. K. Awasthi, Z. D. Renko, *J. Am. Chem. Soc.* **1987**, *109*, 4750; c) J.-E. Bäckvall, R. B. Hopkins, H. Grennberg, M. M. Mader, A. K. Awasthi, *J. Am. Chem. Soc.* **1990**, *112*, 5160.

[19] N. Decharin, S. S. Stahl, *J. Am. Chem. Soc.* **2011**, *133*, 5732.

[20] Interestingly, benzoquinone has been shown to behave as a non-innocent oxidant: a) K. L. Hull, M. S. Sanford, *J. Am. Chem. Soc.* **2009**, *131*, 9651; b) M. S. Chen, N. Prabagaran, N. A. Labenz, M. C. White, *J. Am. Chem. Soc.* **2005**, *127*, 6970; c) J.-E. Bäckvall, S. E. Bystroem, R. E. Nordberg, *J. Org. Chem.* **1984**, *49*, 4619. We recently described two anti-Markovnikov Pd-catalyzed reactions using benzoquinone: d) G. Dong, P. Teo, Z. K. Wickens, R. H. Grubbs, *Science* **2011**, *333*, 1609; e) P. Teo, Z. K. Wickens, G. Dong, R. H. Grubbs, *Org. Lett.* **2012**, *14*, 3237.

[21] For reviews on directly oxygen-coupled palladium chemistry, see: a) S. S. Stahl, *Angew. Chem.* **2004**, *116*, 3480; *Angew. Chem.*

Int. Ed. **2004**, *43*, 3400; b) A. N. Campbell, S. S. Stahl, *Acc. Chem. Res.* **2012**, *45*, 851; c) Ref. [8].

[22] Other *cis*-alkenes studied in this work did not show detectable isomerization by analysis of the crude NMR-spectrum. However, it is possible that the amount of minor isomer(s) was too small for the detection limit of NMR-spectroscopy.

[23] A recent mechanistic study of a copper-free Tsuji-Wacker under oxygen reported saturation kinetics for the alkene: a) B. J. Anderson, J. A. Keith, M. S. Sigman, *J. Am. Chem. Soc.* **2010**, *132*, 11872.