

## Accepted Article

**Title:** Sustainable Pd(OAc)<sub>2</sub> Hydroquinone Cocatalyst System for Cis-Selective Dibenzoyloxylation of 1,3-Cyclohexadiene

**Authors:** Alexios G. Stamoulis, Peng Geng, Michael A. Schmidt, Martin D. Eastgate, Alina Borovika, Kenneth J. Fraunhoffer, and Shannon S Stahl

This manuscript has been accepted after peer review and appears as an Accepted Article online prior to editing, proofing, and formal publication of the final Version of Record (VoR). This work is currently citable by using the Digital Object Identifier (DOI) given below. The VoR will be published online in Early View as soon as possible and may be different to this Accepted Article as a result of editing. Readers should obtain the VoR from the journal website shown below when it is published to ensure accuracy of information. The authors are responsible for the content of this Accepted Article.

**To be cited as:** *Angew. Chem. Int. Ed.* 10.1002/anie.202108499

**Link to VoR:** <https://doi.org/10.1002/anie.202108499>

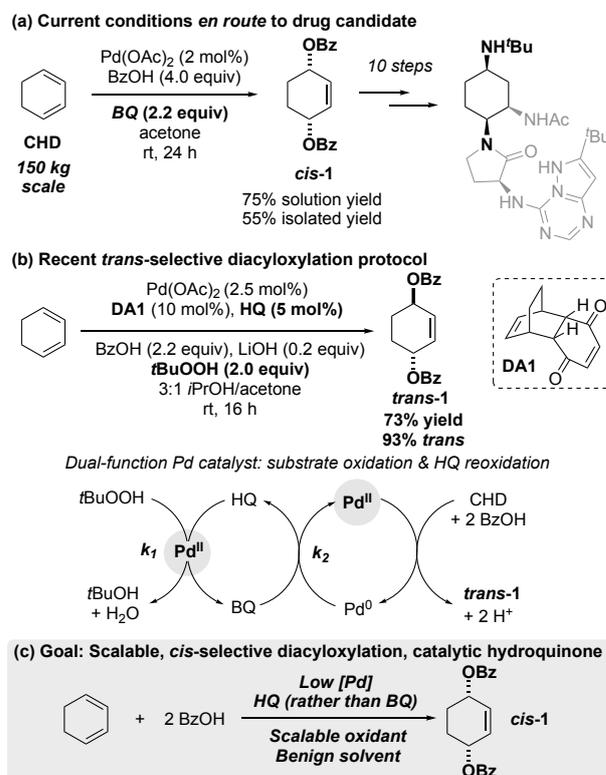
## COMMUNICATION

Sustainable Pd(OAc)<sub>2</sub>/Hydroquinone Cocatalyst System for *Cis*-Selective Dibenzoyloxylation of 1,3-CyclohexadieneAlexios G. Stamoulis,<sup>[a]</sup> Peng Geng,<sup>[b]</sup> Michael A. Schmidt,<sup>[b]</sup> Martin D. Eastgate,<sup>[b]</sup> Alina Borovika,<sup>[b]</sup> Kenneth J. Fraunhoffer,<sup>[b]</sup> and Shannon S. Stahl<sup>[a]\*</sup>

**Abstract:** The 1,4-diacyloxylation of 1,3-cyclohexadiene (CHD) affords valuable stereochemically defined scaffolds for natural product and pharmaceutical synthesis. Existing *cis*-selective diacyloxylation protocols require superstoichiometric quantities of benzoquinone (BQ) or MnO<sub>2</sub>, which limit process sustainability and large-scale application. In this report, reaction development and mechanistic studies are described that overcome these limitations by pairing catalytic BQ with *tert*-butyl hydroperoxide as the stoichiometric oxidant. Catalytic quantities of bromide enable a switch from *trans* to *cis* diastereoselectivity. A catalyst with a 1:2 Pd:Br ratio supports high *cis* selectivity while retaining good rate and product yield. Further studies enable replacement of BQ with hydroquinone (HQ) as a source of cocatalyst, avoiding the handling of volatile and toxic BQ in large scale applications.

Pd-catalyzed oxidations of alkenes and dienes are important industrial processes,<sup>[1]</sup> ranging from the Wacker process for production of acetaldehyde from ethylene,<sup>[2]</sup> to 1,4-diacetyloxylation of 1,3-butadiene, employed in the commercial synthesis of tetrahydrofuran.<sup>[3]</sup> The latter reaction is closely related to 1,4-diacyloxylation of 1,3-cyclohexadiene (CHD) and other cyclic dienes,<sup>[4-7]</sup> which find utility in natural product and pharmaceutical synthesis.<sup>[8-12]</sup> These reactions generate *cis* or *trans* diastereomers, and their utility in synthetic routes (e.g., using Tsuji-Trost allylic substitution<sup>[13-16]</sup> or enzymatic desymmetrization<sup>[17-19]</sup>) depends on selective formation of a single diastereomer. Recently, 1,4-dibenzoyloxylation of CHD was used to access *cis*-1 on 150 kg scale as the first step in the synthesis of an anticancer drug candidate (Scheme 1a).<sup>[11,12]</sup> The reaction, based on a published method by Bäckvall and coworkers,<sup>[20]</sup> employs 2.2 equiv of benzoquinone (BQ), requiring the handling of nearly 500 kg of BQ in this process. BQ is toxic<sup>[21]</sup> and readily sublimes, even at room temperature,<sup>[22]</sup> and the mixture of superstoichiometric BQ and hydroquinone (HQ) byproducts formed in the reaction complicate purification efforts and lower the product yield. These challenges motivated efforts to develop improved reaction conditions. The safety hazards and operational complexities evident in this process highlight the need for a *cis*-selective dibenzoyloxylation method capable of using catalytic quantities of BQ, or ideally hydroquinone (HQ), as a cocatalyst.

BQ reoxidizes Pd<sup>0</sup> to Pd<sup>II</sup> in these reactions,<sup>[23,24]</sup> and seminal work by Bäckvall and coworkers has demonstrated that cocatalysts, such as [Co(salophen)] or [Fe(phthalocyanine)], support *in situ* reoxidation of HQ to BQ using O<sub>2</sub> as the terminal oxidant.<sup>[25-28]</sup> These conditions are only compatible with formation of *trans*-diacyloxylation products, however. Complementary Pd<sup>II</sup>/chloride catalyst systems have been identified for *cis*-diacyloxylation of dienes,<sup>[5]</sup> but the chloride additive inhibits the aerobic cocatalysts, even when used in catalytic quantities.<sup>[29,30]</sup> Stoichiometric MnO<sub>2</sub> is required as a terminal oxidant in order to lower the BQ loading in these reactions.<sup>[6,31]</sup> Recently, Eastgate and coworkers reported a complementary catalytic method, using *tert*-butyl hydroperoxide (*t*BuOOH) as the oxidant.<sup>[7,32]</sup> The Pd catalyst serves a dual role in these reactions (Scheme 1b), promoting both CHD oxidation and reoxidation of HQ by *t*BuOOH (DA1 is a Diels-Alder adduct obtained from reaction of CHD with BQ). These conditions are appealing for large-scale application; however, they similarly access only *trans*-diacyloxylation product (i.e., *trans*-1). The present report outlines development and characterization of a new Pd(OAc)<sub>2</sub>/bromide/BQ cocatalyst system that enables large-scale *cis*-diacyloxylation of CHD with *t*BuOOH as the oxidant (Scheme 1c).



**Scheme 1.** *Cis*- and *trans*-selective diacyloxylation of 1,3-cyclohexadiene (CHD), including a (a) process-scale application leading to a drug candidate,<sup>[12]</sup> (b) *trans*-selective diacyloxylation using *t*BuOOH and catalytic benzoquinone (BQ), with a dual-function Pd catalyst,<sup>[7]</sup> and (c) goals of the present work.

[a] A. G. Stamoulis, and Prof. S. S. Stahl\*  
Department of Chemistry, University of Wisconsin-Madison, Madison, WI 53706 (USA), E-mail: stahl@chem.wisc.edu

[b] P. Geng, Dr. M. A. Schmidt, Dr. M. D. Eastgate, Dr. A. Borovika, Dr. K. J. Fraunhoffer  
Chemical Process Development, Bristol-Myers Squibb, New Brunswick, New Jersey 08903 (USA).

Supporting Information for this article is given via a link at the end of the document.

## COMMUNICATION

Reaction screening efforts were initiated with the previously reported *t*BuOOH/catalytic BQ conditions, evaluating the effect of various additives (base, DA1, etc.; see section 3 of the Supporting Information for screening data). Replacing DA1/HQ (10 mol% each; entry 1, Table 1) with 20 mol% BQ gives almost identical yield and diastereoselectivity, favoring *trans*-1 (entry 2). Addition of chloride to this mixture leads to higher *cis*-1 (entries 3 and 4), accessing 72% *cis* with 10 mol% Bu<sub>4</sub>NCl. Bromide and iodide lead to even higher *cis* selectivity (entries 5–8, also see Tables S3 and S6 in the Supporting Information), and an optimal balance of yield and *cis* selectivity is obtained with 5 mol% Bu<sub>4</sub>NBr (72% yield, 94% *cis*). Efforts to replace BQ with HQ were unsuccessful (entries 9 and 10). These reactions exhibit catalyst decomposition via Pd black formation and low product yields.

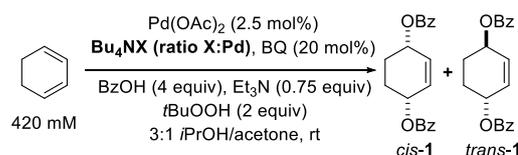
**Table 1.** Reaction screening data and effect of halide additives on yield and diastereoselectivity

Reaction <sup>[a]</sup>	Quinone/Alkene (mol %)	Additive (mol %)	Total product (%) <sup>[b]</sup>	<i>cis</i> selectivity (%) <sup>[b]</sup>
1	DA1 (10 mol%) + HQ (10 mol%)	--	70	8
2	BQ (20 mol%)	--	68	7
3	BQ (20 mol%)	Bu <sub>4</sub> NCl (5 mol%)	28	56
4	BQ (20 mol%)	Bu <sub>4</sub> NCl (10 mol%)	67	72
5	<b>BQ (20 mol%)</b>	<b>Bu<sub>4</sub>NBr (5 mol%)</b>	<b>72</b>	<b>94</b>
6	BQ (20 mol%)	Bu <sub>4</sub> NBr (10 mol%)	48	98
7	BQ (20 mol%)	Bu <sub>4</sub> NI (5 mol%)	14	99
8	BQ (20 mol%)	Bu <sub>4</sub> NI (10 mol%)	6	99
9	HQ (20 mol%)	Bu <sub>4</sub> NBr (5 mol%)	3	95
10	DA1 (10 mol%) + HQ (10 mol%)	Bu <sub>4</sub> NBr (5 mol%)	5	98

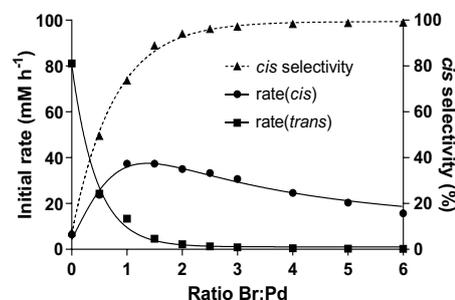
<sup>[a]</sup> [CHD] = 420 mM, [BzOH] = 1680 mM, [Pd(OAc)<sub>2</sub>] = 10.5 mM, [Et<sub>3</sub>N] = 315 mM, [*t*BuOOH] = 840 mM, [biphenyl] = 42 mM (internal standard). <sup>[b]</sup> Yield and selectivity determined by UPLC. See Supporting Information for details.

The effect of halide: Pd ratio on initial rate and *cis* selectivity of the diacyloxylation was investigated more thoroughly (Figure 1). The halide loading was varied between 0–6 equiv relative to Pd and the initial rate and *cis* selectivity were monitored by UPLC. A 1:1 Br: Pd ratio exhibits the highest rate for *cis*-1 formation, but ratios between 2–3:1 Br: Pd show improved selectivity while maintaining good rates (Figure 1a). Chloride does not inhibit *trans*-1 formation as strongly as bromide, and, even at higher Cl: Pd ratios, only moderate diastereoselectivity is observed (Figure 1b). Iodide strongly inhibits formation of *trans*-1, allowing for very high *cis* selectivity (99% *cis*), but it also inhibits the rate of *cis*-1 formation (see Table 1 and Table S7). The relative impact of the different halide ions correlates with the relative binding affinity of the halides for Pd<sup>II</sup> (I > Br > Cl),<sup>[33–36]</sup> and bromide provides the best balance of rate, selectivity, and overall catalyst performance.

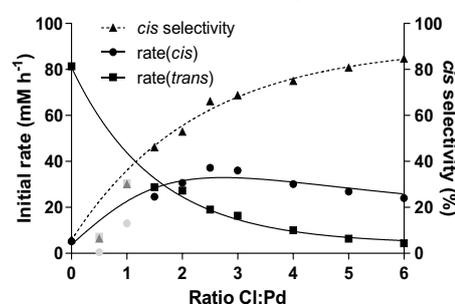
For large-scale applications, it would be ideal to use HQ as the source of cocatalyst to avoid handling of large quantities of BQ;<sup>[37]</sup> however, the data in Table 1 show that poor results are obtained with HQ as the cocatalyst (entries 9–10). In order to



(a) Effect of bromide on rate/selectivity



(b) Effect of chloride on rate/selectivity



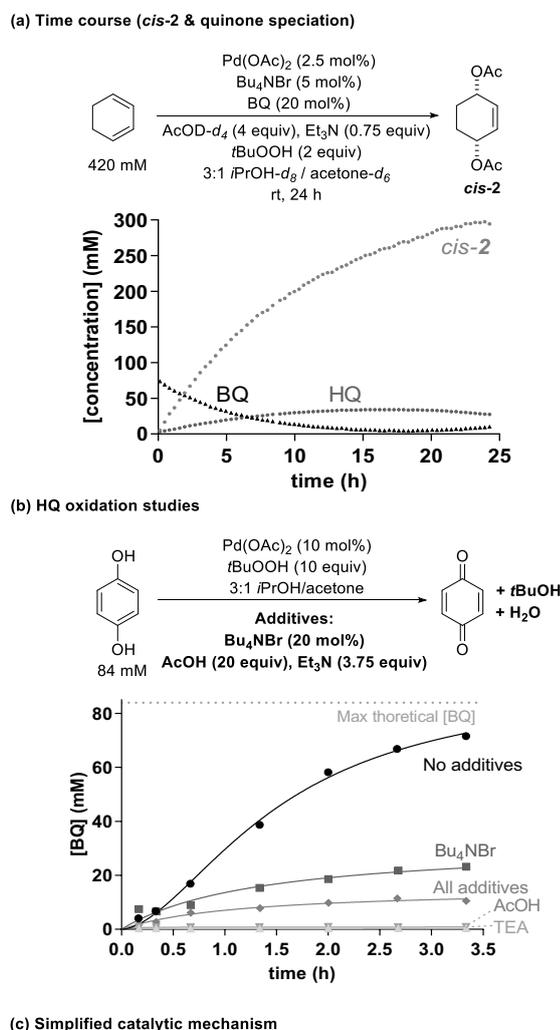
**Figure 1.** Effect of bromide (a) and chloride (b) on the rate and diastereoselectivity of the CHD diacyloxylation reaction. Conditions: [CHD] = 420 mM, [BzOH] = 1680 mM, [Pd(OAc)<sub>2</sub>] = 10.5 mM, [BQ] = 84 mM, [Et<sub>3</sub>N] = 315 mM, [*t*BuOOH] = 840 mM, [biphenyl] = 42 mM (internal standard). Reaction aliquots analyzed by UPLC. The data in gray for chloride plot reflect reactions with significant insoluble solids and they are not included in the empirical curve fits (see Supporting Information for curve fitting equations).

probe the origin of this effect, 1,4-diacetylation of CHD was analyzed by <sup>1</sup>H NMR spectroscopy throughout the reaction time course to track formation of the product *cis*-2 and quinone speciation (Figure 2a and Figure S7). *Cis*-2 forms steadily throughout the reaction, while the quinone speciation never reaches steady state. BQ is slowly consumed during the first 18 h, together with the appearance of HQ and DA1. Formation of DA1 is irreversible and consumes approximately 50% of the original BQ, lowering the amount of BQ/HQ available to support catalytic turnover (Figure S7). At late stages of the reaction, the rate of HQ oxidation is competitive with BQ consumption, and a small increase in [BQ] is evident.

The rate of HQ oxidation evident during catalysis is much slower than expected from the previously reported study of Pd(OAc)<sub>2</sub>-catalyzed oxidation of HQ by *t*BuOOH.<sup>[7]</sup> This behavior was traced to the inhibitory effect of catalytic additives (Bu<sub>4</sub>NBr, AcOH and/or TEA) on HQ oxidation. As shown in Figure 2b, HQ undergoes efficient Pd(OAc)<sub>2</sub>-catalyzed oxidation to BQ in the absence of these additives, as expected,<sup>[7]</sup> while each of the individual additives slow or inhibit the reaction. When all three additives are combined, slow HQ oxidation is observed together with Pd catalyst decomposition (Pd black formation). Pd decomposition under these conditions can arise from the reversible reaction of Pd<sup>II</sup> with HQ to form Pd<sup>0</sup> (see ref. [38] and dashed arrows in Figure 2c), followed by irreversible

## COMMUNICATION

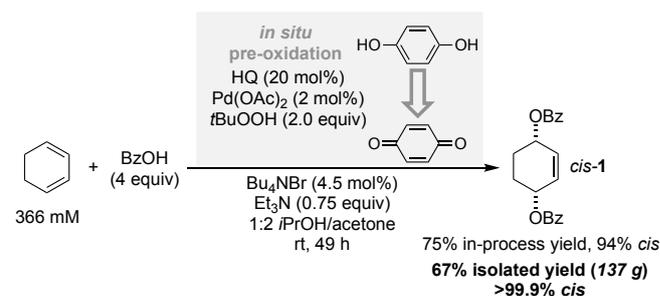
decomposition of Pd<sup>0</sup> into Pd black. Kinetically competent oxidation of HQ is observed, however, if 1 equiv of BQ is included in the reaction mixture, owing to improved Pd<sup>0</sup> stability. Complete conversion of HQ to BQ under these conditions is complete in 16 h, commensurate with the catalytic time course shown in Figure 2a (see section 7b of the Supporting Information for details).



**Figure 2.** (a) Full reaction <sup>1</sup>H NMR time course showing *cis*-2 formation and quinone speciation. Conditions: [CHD] = 420 mM, [AcOH-*d*<sub>4</sub>] = 1680 mM, [Pd(OAc)<sub>2</sub>] = 10.5 mM, [Bu<sub>4</sub>NBr] = 21 mM, [BQ] = 84 mM, [Et<sub>3</sub>N] = 315 mM, [tBuOOH] = 840 mM, [methyl 3,5-dinitrobenzoate] = 21 mM (internal standard). Reaction conducted inside an NMR spectrometer at 24 °C using a 3:1 mixture of *i*PrOD-*d*<sub>8</sub>/acetone-*d*<sub>6</sub> employing AcOD-*d*<sub>4</sub> as the nucleophile to ensure solubility throughout the entire 24-hour time course.<sup>39</sup> (b) HQ oxidation studies under catalytically relevant conditions. Conditions: [HQ] = 84 mM, [AcOH] = 1680 mM, [Pd(OAc)<sub>2</sub>] = 8.4 mM, [Bu<sub>4</sub>NBr] = 16.8 mM, [Et<sub>3</sub>N] = 315 mM, [tBuOOH] = 840 mM, [methyl 3,5-dinitrobenzoate] = 8.4 mM (internal standard). (c) Simplified mechanistic cycle showing trade-off between HQ oxidation and product formation.

The above observations rationalize the ineffectiveness of HQ as a source of cocatalyst (cf. Table 1, entries 9 and 10): because HQ oxidation is relatively slow, the Pd catalyst will decompose

and lead to low product yields unless BQ is included at the start of the reaction. Nonetheless, the results in Figure 2b offer an alternative strategy for use of HQ as the source of cocatalyst. The process is initiated by combining the Pd(OAc)<sub>2</sub> catalyst and *t*BuOOH oxidant with HQ in the absence of other additives. These conditions enable efficient oxidation of HQ to BQ. The other reaction components (NBu<sub>4</sub>Br, NEt<sub>3</sub>, BzOH and CHD) may then be added to this "pre-oxidation mixture" to achieve the desired 1,4-dibenzoyloxylation of CHD. Preliminary optimization of this concept on small scale set the stage for demonstration on larger scale (Figure 3). Minor changes identified as beneficial in this effort include use of a slightly higher Br:Pd ratio (2.25:1) to enhance the *cis* selectivity (deemed more important than rate or total yield of mixed isomers) and use of a higher proportion of acetone in the cosolvent mixture to ensure all components remain soluble throughout the reaction. Implementation of the optimized conditions led to a 75% in-process yield of *cis*-1, with 94% *cis* selectivity, based on HPLC analysis of product mixture. Work-up and crystallization of the reaction stream led to a significant upgrade in the diastereomeric purity (>99.9% *cis*, based on HPLC analysis) and delivered 137 g of the final product (67% yield).



**Figure 3.** Pre-oxidation concept that enables HQ to be used as the cocatalyst (gray box), and demonstration of this sequential process to access 137 g of product, with >99.9% *cis* selectivity, following isolation.

In summary, the results described herein introduce a new catalyst system for *cis*-selective 1,4-diacyloxylation of 1,3-cyclohexadiene, highlighting the efficacy of bromide to alter the stereochemical course of the reaction. The Pd<sup>II</sup> catalyst serves a dual role, catalyzing both 1,4-diacyloxylation of CHD and oxidation of HQ by *t*BuOOH. The ability of this catalyst to operate in the presence of halides contrasts other cocatalyst systems, such as Pd(OAc)<sub>2</sub>/BQ/Co(salophen)/O<sub>2</sub>, that are poisoned by halides. This feature is crucial to achieve the desired *cis* diastereoselectivity with a process-friendly and sustainable oxidant amenable to large-scale application. The insights from these studies have important implications for development of other industrially relevant Pd-catalyzed oxidation methods.

## Acknowledgements

We would like to thank Dr. Antonio Ramirez and Dr. Michaël Fenster for useful discussions. Financial support was provided by Bristol Myers Squibb and by the NSF (CHE-1953926). Spectroscopic instrumentation was supported by the NSF (CHE-1048642), the NIH (R01GM100143 and R01GM127545) and a generous gift from Paul J. and Margaret M. Bender.

## COMMUNICATION

## Conflict of interest:

The authors declare no conflict of interest.

**Keywords:** homogeneous catalysis, palladium, oxidation, difunctionalization, synthetic methods.

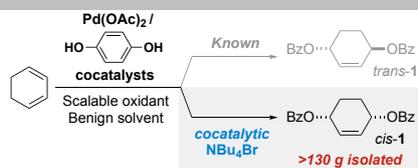
## References.

- [1] D. Wang, J. N. Jaworski, S. S. Stahl, in *Liquid Phase Aerobic Oxidation Catalysis: Industrial Applications and Academic Perspectives* (Eds. S. S. Stahl, P. L. Alsters), Wiley - VCH Verlag GmbH & Co., Weinheim, **2016**, pp. 113–138.
- [2] R. Jira, in *Liquid Phase Aerobic Oxidation Catalysis: Industrial Applications and Academic Perspectives* (Eds. S. S. Stahl, P. L. Alsters), Wiley - VCH Verlag GmbH & Co., Weinheim, **2016**, pp. 139–158.
- [3] Y. Izawa, T. Yokoyama, in *Liquid Phase Aerobic Oxidation Catalysis: Industrial Applications and Academic Perspectives* (Eds. S. S. Stahl, P. L. Alsters), Wiley - VCH Verlag GmbH & Co., Weinheim, **2016**, pp. 159–170.
- [4] R. G. Brown, J. M. Davidson, *J. Chem. Soc. A*, **1971**, 1321–1327.
- [5] J.-E. Bäckvall, R. E. Nordberg, *J. Am. Chem. Soc.* **1981**, *103*, 4959–4960.
- [6] J.-E. Bäckvall, S. E. Bystrom, R. E. Nordberg, *J. Org. Chem.* **1984**, *49*, 4619–4631.
- [7] B. Zheng, M. A. Schmidt, M. D. Eastgate, *J. Org. Chem.* **2016**, *81*, 3112–3118.
- [8] B. M. Trost, S. R. Pulley, *J. Am. Chem. Soc.* **1995**, *117*, 10143–10144.
- [9] B. M. Trost, R. Madsen, S. D. Guile, *Tet. Lett.* **1997**, *38*, 1707–1710.
- [10] Z. Hua, W. Yu, M. Su, Z. Jin, *Org. Lett.* **2005**, *7*, 1939–1942.
- [11] B. M. Trost, G. R. Cook, *Tet. Lett.* **1996**, *37*, 7485–7488.
- [12] a) B. S. Aytar, A. Borovika, C. Chan, J. Deerberg, N. R. Domagalski, M. D. Eastgate, Y. Fan, M. D. B. Fenster, R. V. Forest, F. Gonzalez-Bobes, R. A. Green, M. R. Hickey, N. D. Kopp, T. E. La Cruz, K. Lauser, H. G. Lee, D. K. Leahy, H. Y. Luo, T. M. Razler, S. A. Savage, C. Sfougataki, M. CD. Soumeillant, S. Zaretsky, B. Zheng, Y. Zhu (Bristol-Myers Squibb Company) PCT Int. Appl. WO2019018592 A2, **2019**; b) T. E. La Cruz, F. González-Bobes, M. D. Eastgate, C. Sfougataki, B. Zheng, N. Kopp, Y. Xiao, Y. Fan, K. A. Galindo, C. Pathirana, M. A. Galella, Joerg Deerberg, *J. Org. Chem.* **2021**, DOI: 10.1021/acs.joc.1c01162.
- [13] B. M. Trost, D. L. Van Vranken, *Chem. Rev.* **1996**, *96*, 395–422.
- [14] J. Tsuji, H. Takahashi, M. Morikawa, *Tet. Lett.* **1965**, *49*, 4387–4388.
- [15] B. M. Trost, L. Li, S. D. Guile, *J. Am. Chem. Soc.* **1992**, *114*, 8745–8747.
- [16] B. M. Trost, D. L. Van Vranken, C. Bingel, *J. Am. Chem. Soc.* **1992**, *114*, 9327–9343.
- [17] K. Laumen, M. P. Schneider, *J. Chem. Soc., Chem. Commun.*, **1986**, 1298–1299.
- [18] R. J. Kazlauskas, A. N. E. Weissfloch, A. T. Rappaport, L. A. Cuccia, *J. Org. Chem.* **1991**, *56*, 2656–2665.
- [19] J.-E. Bäckvall, R. Gatti, H. E. Schink, *Synthesis*, **1993**, 343–348.
- [20] J.-E. Bäckvall, K. L. Granberg, R. B. Hopkins, *Acta Chem. Scand.* **1990**, *44*, 492–499.
- [21] *p*-Benzoquinone, MSDS No. B10358: <https://www.sigmaaldrich.com/catalog/AdvancedSearchPage.do> (accessed 05/21/2021).
- [22] C. G. de Kruijff, E. J. Smit, H. A. J. Govers, *J. Chem. Phys.* **1981**, *74*, 5838–5841.
- [23] H. Grennberg, A. Gogoll, J.-E. Bäckvall, *Organometallics* **1993**, *12*, 1790–1793.
- [24] A. Vasseur, J. Muzart, J. Le Bras, *Eur. J. Org. Chem.* **2019**, *19*, 4053–4069.
- [25] J.-E. Bäckvall, R. B. Hopkins, H. Grennberg, M. M. Mader, A. K. Awasthi, *J. Am. Chem. Soc.* **1990**, *112*, 5160–5166.
- [26] J.-E. Bäckvall, A. K. Awasthi, Z. D. Renko, *J. Am. Chem. Soc.* **1987**, *109*, 4750–4752.
- [27] K. Bergstad, H. Grennberg, J.-E. Bäckvall, *Organometallics* **1998**, *17*, 45–50.
- [28] For reviews on the use of catalytic quinones in Pd-catalyzed oxidation reactions, see: (a) J. Piera, J.-E. Bäckvall, *Angew. Chem. Int. Ed.* **2008**, *19*, 3506–3523. (b) J. Liu, A. Guðmundsson, J.-E. Bäckvall, *Angew. Chem. Int. Ed.* **2020**, *29*, 15686–15704.
- [29] Previous work has noted the incompatibility of metal macrocycle cocatalysts with chloride additives: H. Grennberg, J.-E. Bäckvall, *J. Chem. Soc., Chem. Commun.* **1993**, 1331–1332.
- [30] Preliminary results in our lab reproduce the inhibitory effect of chloride noted in ref. 29.
- [31] MnO<sub>2</sub> is problematic and complicated to use as a stoichiometric oxidant on large scale. It generates large quantities of Mn waste, it is not soluble in typical organic solvents, and the different particle sizes and crystal polymorphs of commercially sourced MnO<sub>2</sub> complicate reproducibility.
- [32] M. D. Eastgate, F. G. Buono, *Angew. Chem. Int. Ed.* **2009**, *48*, 5958–5961.
- [33] L. I. Elding, *Inorg. Chim. Acta*, **1972**, *6*, 647–651.
- [34] L. I. Elding, *Inorg. Chim. Acta*, **1972**, *6*, 683–688.
- [35] L. I. Elding, L.-F. Olsson, *Inorg. Chim. Acta*, **1986**, *117*, 9–16.
- [36] S. Ahrland, *Acta Chem. Scand.* **1956**, *10*, 723–726.
- [37] Compared to BQ (cf. ref. 21), HQ has lower toxicity and does not sublime under ambient conditions. *Hydroquinone*, MSDS No. H9003: <https://www.sigmaaldrich.com/catalog/AdvancedSearchPage.do> (accessed 05/21/2021).
- [38] D. L. Bruns, D. G. Musaev, S. S. Stahl, *J. Am. Chem. Soc.* **2020**, *46*, 19678–19688.
- [39] For a direct comparison of screening data with AcOH and BzOH, see Table S2 in the Supporting Information.

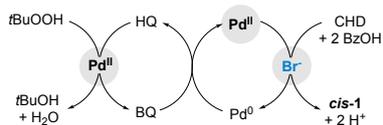
## COMMUNICATION

## COMMUNICATION

We report an efficient and scalable *cis*-selective diacyloxylation protocol that employs catalytic hydroquinone with *t*BuOOH as a benign terminal oxidant. A bromide additive was crucial to obtaining good yields and excellent *cis* selectivity. The study culminates in the implementation of the optimized reaction on large scale.



Dual-function Pd catalyst: substrate oxidation & HQ reoxidation



Alexios G. Stamoulis, Peng Geng, Michael A. Schmidt, Martin D. Eastgate, Alina Borovika, Kenneth J. Fraunhofer, and Shannon S. Stahl\*

Page No. – Page No.

**Sustainable Pd(OAc)<sub>2</sub>/Hydroquinone-Cocatalyst System for *Cis*-Selective Dibenzoyloxylation of 1,3-Cyclohexadiene**

Institute and/or researcher Twitter usernames: @Stahl\_Lab, @UWMadisonChem

Accepted Manuscript