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Aldehyde-Selective Wacker-Type Oxidation of Unbiased Alkenes Enabled by a Nitrite Co-Catalyst[**]

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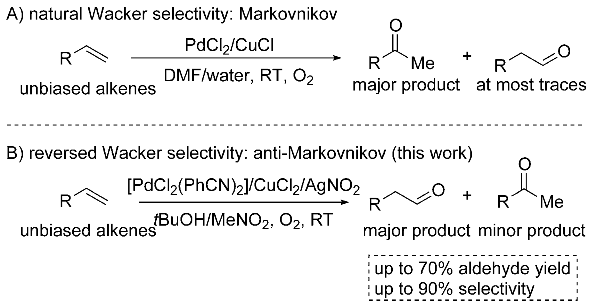
The Wacker oxidation is a premier reaction for the catalytic oxidation of alkenes to carbonyls because of its efficiency and high functional-group tolerance.[1] A recent renaissance of Wacker chemistry has overcome several key limitations of the methodology.[2–4] Despite this progress, the regioselectivity of the Wacker oxidation remains substrate-controlled and thus the majority of terminal alkenes produce predominately methyl ketones, in accord with Markovnikov's rule (Scheme 1 A). Researchers have exploited specific biased alkenes to circumvent Markovnikov's rule and produce aldehydes.[5–8] Unfortunately, the utility of this approach is inherently limited because the vast majority of alkenes are unbiased, and thus mere traces of the anti-Markovnikov aldehyde products are observed.[1d,5,9] A general aldehyde-selective Wacker oxidation would be a key advance in the field of anti-Markovnikov functionalization[10] because aldehydes are not only sought after products but are also versatile synthetic intermediates.[11] For example, anti-Markovnikov hydration and hydroamination products can be accessed from aldehydes through established catalytic processes.[11d,e]



Scheme 1. A) Tsuji–Wacker conditions applied to unbiased alkenes. B) Newly developed aldehyde-selective Wacker oxidation.

Despite many attempts to develop a catalyst-controlled, aldehyde-selective Wacker oxidation, such a variant has remained elusive.[5,12,13] Only moderate aldehyde selectivity can be obtained from unbiased alkenes at low conversions and all methods have universally reverted to the expected ketone selectivity upon reaching synthetically relevant conversions. The inherent challenge of obtaining anti-Markovnikov regioselectivity has thus limited the development of a synthetically viable aldehyde-selective Wacker oxidation without reliance upon substrate control.

1-Dodecene was selected as a model for an unbiased alkene for the development of a catalyst-controlled process, as it contains no chemical handle to reverse the Markovnikov selectivity. For example, although our previously reported conditions oxidize styrene with 97 % aldehyde selectivity in 90 % yield,[8b] 1-dodecene provided only traces of oxidation products with high ketone selectivity and considerable isomerization under these conditions (Figure 1, entry 1). Thus, these conditions are unable to provide aldehyde selectivity without the powerful substrate control offered by the aromatic moiety and a general catalyst-controlled solution remains to be developed.

Prior to our work, Feringa reported that [$PdNO_2Cl(MeCN)_2$], when combined with $CuCl_2$ in *t*BuOH, provided aldehyde in poor yield (< 20 %) but with encouraging selectivity for aldehyde over ketone formation (2.3:1).[12a] Unfortunately, reactions that reach useful yields reverted to Markovnikov selectivity (1:4.5; entry 2). However, it has been suggested that under these conditions, the palladium nitrite generates *tert*-butyl nitrite.[12b]

Based upon this precedent and the possibility that the poor aldehyde yield and selectivity could be due to inefficient generation of a highly aldehyde-selective species from *tert*-

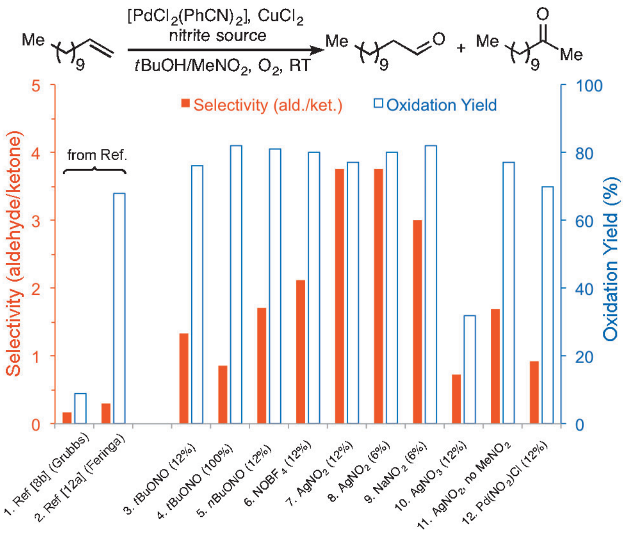


Figure 1. Catalyst optimization. Entries 3–12: 1-dodecene (0.2 mmol), [$PdCl_2(PhCN)_2$] (12 mol %), and $CuCl_2 \cdot 2H_2O$ (12 mol %) were used. Entry 12: [$PdCl_2(PhCN)_2$] was replaced by [$PdNO_2Cl(MeCN)_2$].

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butyl nitrite, we combined catalytic *tert*-butyl nitrite with $PdCl_2$ and $CuCl_2$ co-catalysts and observed significantly increased selectivity, for the first time providing modest aldehyde selectivity above 50% conversion to oxidized products (entry 3). However, an increase of the loading of *tert*-butyl nitrite modestly increased the overall yield but decreased selectivity (entry 4).

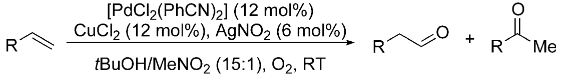
We reasoned that other nitrite sources could enable more efficient access to the selective catalytic species. Of the nitrite sources evaluated, each offered similar oxidation efficiency with varying aldehyde selectivity (entries 3–9). Catalytic $AgNO_2$ provided a significant improvement, leading to good anti-Markovnikov selectivity and synthetically useful yields. Interestingly, no significant difference between 12 and 6 mol% $AgNO_2$ was observed (entries 7 and 8). The comparable selectivity observed with $NaNO_2$ (entry 9) suggests that Ag^I most likely does not play a key co-catalytic role.[14] Furthermore, replacement of the nitrite anion with nitrate dramatically reduced oxidation yield and regioselectivity (entry 10). Attempts to deviate from metal dichloride salts or *t*BuOH[15] universally resulted in significantly decreased yield and selectivity. $MeNO_2$ was found to be the superior cosolvent although its omission from the optimized conditions still provided a somewhat aldehyde-selective process (entry 11).

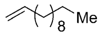
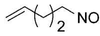
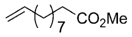
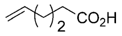
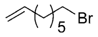
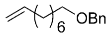
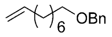
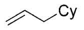
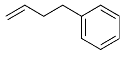
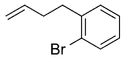
Importantly, when the palladium nitrite catalyst used by Feringa[12a] was applied to the optimized conditions, the process was much less selective (slightly ketone-selective) than with other nitrite sources (entry 12). Thus, we suspect that the nitrite anion does not simply undergo salt metathesis to form $PdNO_2Cl$ in situ and that instead a more complex synergistic interaction between the metals occurs.

With optimized conditions in hand, the functional-group tolerance of the transformation was explored (Table 1). To avoid substrate-derived anti-Markovnikov selectivity, aliphatic substrates bearing only distal functionality were selected.[16] These substrates provided products with yields comparable to those expected under Tsuji–Wacker conditions[1b] but with anti-Markovnikov selectivity. The reaction is compatible with a diverse array of functional groups: alkyl and aryl halides, esters, ethers, and nitro groups were all tolerated. Despite the potential challenge of using unprotected functional groups, carboxylic acids and alcohols still provided synthetically viable yields of the corresponding aldehyde products. The reduced selectivity in these cases could be attributed to an intermolecular Markovnikov attack by these nucleophilic functionalities, thus producing ketones. Although alkene isomerization is a common problem in Wacker-type oxidations, no significant isomerization was observed with any of the substrates. All examples represent the first instances of aldehyde-selective Wacker oxidations on such substrates at synthetically relevant conversion.[5]

Next, the scalability of the process was assessed. Although the palladium loading on a small scale was comparable to Tsuji–Wacker conditions, it was reduced to 7 mol% to accomodate a gram-scale process (Scheme 2). The success of this large-scale reaction demonstrates that the process can maintain high yield and aldehyde selectivity at an increased scale, even with decreased catalyst loading.

Table 1: Aldehyde-selective Wacker-type oxidation of unbiased alkenes.[a]

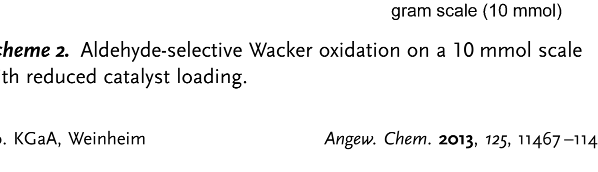


Entry	Substrate	Yield of oxidation (aldehyde)[b] [%]	Sel.[c] [%]
1		80 (63)[d]	79
2		74 (61)	79
3		78 (70)	89
4		72 (59)	79
5		68 (51)[e]	67
6		77 (65)	82
7		70 (59)	81
8		80 (45)	57
9		75 (60)[e]	80
10		77 (69)	89
11		71 (64)[e]	90

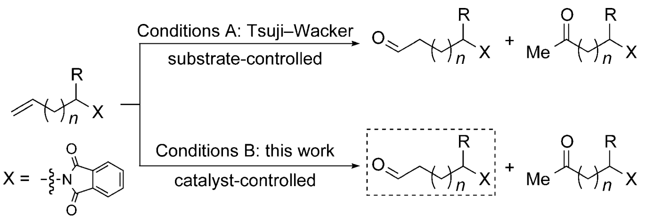
[a] Alkene (0.5 mmol) treated with $[PdCl_2(PhCN)_2]$ (12 mol%), $CuCl_2{\cdot}2\,H_2O$ (12 mol%), and $AgNO_2$ (6 mol%) in *t*BuOH/$MeNO_2$ (15:1, 8 mL) under O_2 atmosphere (1 atm) at 20–25 °C. [b] Yield of isolated aldehyde. Overall yield (of oxidation) calculated using selectivity. [c] Selectivity determined by ^1H NMR analysis. [d] Yield and selectivity both determined by GC analysis. [e] Yield determined by ^1H NMR analysis.

Having demonstrated aldehyde selectivity in unbiased aliphatic alkenes, a set of three phthalimides, which upon minor carbon skeleton changes range from aldehyde- to ketone-selective under traditional substrate-controlled Tsuji–Wacker conditions, were next subjected to the reaction conditions (Scheme 3). For each substrate, products were obtained with high yield and selectivity, regardless of the innate selectivity. Beyond providing preliminary evidence that this process could be a general catalyst-controlled solution to aldehyde selectivity, these results illustrate the efficacy of this process with proximal nitrogen functionality without reliance upon the substrate-controlled regioselectivity.

Previous attempts to develop an aldehyde-selective Wacker oxidation have been plagued by low yields and loss of selectivity over the course of the reaction. Thus, we examined the reaction profile to assess the behavior of the aldehyde selectivity (Figure 2). Upon surpassing 5% conversion, the selectivity stabilized and became relatively independent of both yield and time. This behavior potentially suggests that, once formed, the same catalytic species remains active throughout the remainder of the reaction. The brief induction period in aldehyde selectivity is particularly inter-

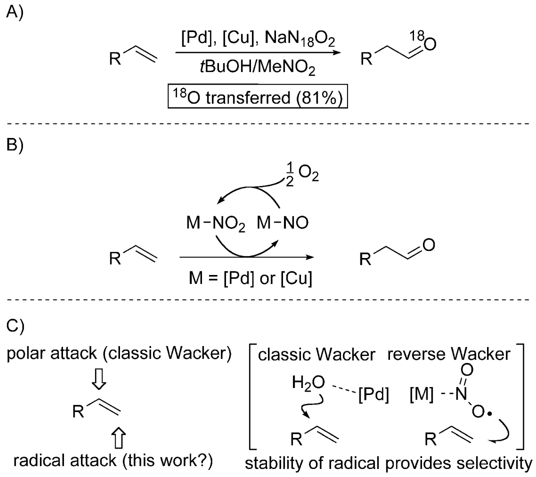


Scheme 2. Aldehyde-selective Wacker oxidation on a 10 mmol scale with reduced catalyst loading.



Substrate	Conditions A selectivity	Conditions B selectivity (yield)
n = 0, R = Me	**99**:1	**99**:1 (79)
n = 0, R = H	**60**:**40**	**98**:2 (75)
n = 1, R = H	15:**85**	**90**:10 (77)

Scheme 3. Comparison of innate selectivity (conditions A) to catalyst-controlled selectivity (conditions B). Conditions A: (Ref. [4b]) $PdCl_2$ (10–30 mol%), CuCl (1 equiv), DMF/H_2O (7:1), RT, O_2 (1 atm). Conditions B: alkene (0.5 mmol), $[PdCl_2(PhCN)_2]$ (12 mol%), $CuCl_2$ (12 mol%), $AgNO_2$ (6 mol%), *t*BuOH/$MeNO_2$ (15:1), RT, O_2 (1 atm). Aldehyde yield determined after purification. Selectivity determined by ^1H NMR analysis prior to purification.



Scheme 4. A) Stoichiometric ^{18}O-labeling experiment. B) Plausible mode of oxygen transfer. C) Radical model to explain anti-Markovnikov selectivity.

esting, as previous systems have commonly demonstrated moderate to high aldehyde selectivity only at very low conversion.

With the aim of providing key preliminary mechanistic insight into this transformation, we sought to elucidate the origin of the aldehydic oxygen atom in our system. To this end, we treated 4-phenyl-1-butene with stoichiometric ^{18}O-labeled $NaNO_2$ ($NaNO_2$ provided comparable selectivity and efficiency to $AgNO_2$, see Figure 1) along with $[PdCl_2(PhCN)_2]$ and $CuCl_2{\cdot}2H_2O$. We were delighted to find compelling evidence that the oxygen atom is derived from the nitrite salt, as the ^{18}O label was effectively (81%) incorporated into the aldehyde (Scheme 4A).[17] Incomplete incorporation is likely due to exchange with adventitious water, however, a competing traditional Wacker-type nucleophilic attack cannot be ruled out. Under our catalytic reaction conditions, NO formed after oxygen transfer could be aerobically oxidized back to NO_2, enabling the catalytic use of the nitrite salt (Scheme 4B).[18] Prior to this work, contradictory reports have suggested that palladium nitrite complexes could oxidize alkenes through attack of either *t*BuOH or the nitrite ligand. Anti-Markovnikov attack by *t*BuOH has been substantiated with specific substrates,[7,8b,12b,19] however it is unlikely to occur under the present conditions, as the aldehydic oxygen atom should not be derived from nitrite after *t*BuOH attack. On the other hand, definitive attack by nitrite salts has been demonstrated only in systems that exhibit high Markovnikov selectivity.[20] The ^{18}O-labeling experiment presented herein thus constitutes the first conclusive experimental illustration that nitrite salts can indeed transfer an oxygen atom to the terminal position of alkenes under palladium catalysis.

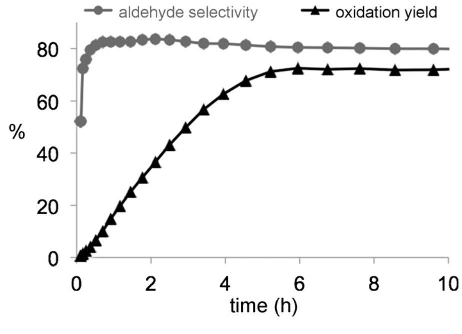


Figure 2. Reaction profile of nitrite-modified Wacker oxidation to assess stability of aldehyde-selective catalytically active species.

The unusual anti-Markovnikov regioselectivity of the oxygen transfer from the nitrite salt combined with the propensity of such salts to generate an NO_2 radical in situ[21,22] leads us to propose that the key mechanistic feature of this reaction is a metal-mediated delivery of an NO_2 radical species across the alkene (Scheme 4C).[23] In traditional Wacker-type oxidations, attack by water upon the coordinated alkene is a polar addition and thus is controlled by Markovnikov's rule.[24] In contrast, radical-type addition to alkenes proceeds selectively at the terminal position because of the increased stability of the secondary radical intermediate.[25–27] Although vinylcyclopropane radical traps appeared to open under the reaction conditions, our attempts to probe radical intermediacy have been stymied by the difficulty to distinguish between one- or two-electron ring-opening pathways.[28] However, we expect that the significant insight provided by the ^{18}O-labeling experiment will continue to provide crucial guidance for further mechanistic study, aimed to determine the ultimate origin of anti-Markovnikov selectivity.

A Wacker-type oxidation of unbiased alkenes affording the anti-Markovnikov aldehyde products has been developed. The success of this system with challenging aliphatic substrates combined with the lack of substrate-derived interference by allylic and homoallylic functionality bodes well for further development of the reaction into an efficient synthetic tool. An informative ^{18}O-labeling experiment suggests an unusual mechanistic manifold, potentially involving the metal-catalyzed attack at the terminal position of the alkene by an NO_2 radical.

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Keywords: alkenes · anti-Markovnikov · oxidation · oxygen · palladium

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[1] a) J. Smidt, W. Hafner, J. Sedlmeier, R. Jira, R. Rüttinger, *Angew. Chem.* **1959**, *71*, 176–182; b) J. Tsuji, *Synthesis* **1984**, 369–384; c) J. M. Takacs, J. Xt, *Curr. Org. Chem.* **2003**, *7*, 369–396; d) J. Tsuji, *Palladium Reagents and Catalysts: New Perspectives for the 21st Century*, 2nd ed. Wiley, Hobken, **2004**; e) R. Jira, *Angew. Chem.* **2009**, *121*, 9196–9199; *Angew. Chem. Int. Ed.* **2009**, *48*, 9034–9037.

[2] Wacker oxidation of internal alkenes: a) T. Mitsudome, K. Mizumoto, T. Mizugaki, K. Jitsukawa, K. Kaneda, *Angew. Chem.* **2010**, *122*, 1260–1262; *Angew. Chem. Int. Ed.* **2010**, *49*, 1238–1240; b) B. Morandi, Z. K. Wickens, R. H. Grubbs, *Angew. Chem.* **2013**, *125*, 3016–3020; *Angew. Chem. Int. Ed.* **2013**, *52*, 2944–2948; c) R. J. DeLuca, J. L. Edwards, L. D. Steffens, B. W. Michel, X. Qiao, C. Zhu, S. P. Cook, M. S. Sigman, *J. Org. Chem.* **2013**, *78*, 1682–1686; d) T. Mitsudome, S. Yoshida, T. Mizugaki, K. Jitsukawa, K. Kaneda, *Angew. Chem.* **2013**, *125*, 6077–6080; *Angew. Chem. Int. Ed.* **2013**, *52*, 5961–5964; e) T. Mitsudome, S. Yoshida, Y. Tsubomoto, T. Mizugaki, K. Jitsukawa, K. Kaneda, *Tetrahedron Lett.* **2013**, *54*, 1596; f) H. R. Darabi, M. Mirzakhani, K. Aghapoor, K. Jadidi, L. Faraji, N. Sakhaee, *J. Organomet. Chem.* **2013**, *740*, 131; g) B. Morandi, Z. K. Wickens, R. H. Grubbs, *Angew. Chem.* **2013**, *125*, 9933–9936; *Angew. Chem. Int. Ed.* **2013**, *52*, 9751–9754.

[3] Dioxygen as the sole oxidant: a) T. Mitsudome, T. Umetani, N. Nosaka, K. Mori, T. Mizugaki, K. Ebitani, K. Kaneda, *Angew. Chem.* **2006**, *118*, 495–499; *Angew. Chem. Int. Ed.* **2006**, *45*, 481–485; b) C. N. Cornell, M. S. Sigman, *Inorg. Chem.* **2007**, *46*, 1903–1909; c) K. M. Gligorich, M. S. Sigman, *Chem. Commun.* **2009**, 3854–3867; d) A. N. Campbell, S. S. Stahl, *Acc. Chem. Res.* **2012**, *45*, 851–863.

[4] Catalyst-controlled Wacker oxidation with Markovnikov selectivity: a) B. W. Michel, A. M. Camelio, C. N. Cornell, M. S. Sigman, *J. Am. Chem. Soc.* **2009**, *131*, 6076–6077; b) B. W. Michel, J. R. McCombs, A. Winkler, M. S. Sigman, *Angew. Chem.* **2010**, *122*, 7470–7473; *Angew. Chem. Int. Ed.* **2010**, *49*, 7312–7315; c) M. S. Sigman, E. W. Werner, *Acc. Chem. Res.* **2012**, *45*, 874–884.

[5] J. Muzart, *Tetrahedron* **2007**, *63*, 7505–7521.

[6] B. Weiner, A. Baeza, T. Jerphagnon, B. L. Feringa, *J. Am. Chem. Soc.* **2009**, *131*, 9473–9474.

[7] J. J. Dong, M. Fañanás-Mastral, P. L. Alsters, W. R. Browne, B. L. Feringa, *Angew. Chem.* **2013**, *125*, 5671–5675; *Angew. Chem. Int. Ed.* **2013**, *52*, 5561–5565.

[8] a) J. A. Wright, M. J. Gaunt, J. B. Spencer, *Chem. Eur. J.* **2006**, *12*, 949–955; b) P. Teo, Z. K. Wickens, G. Dong, R. H. Grubbs, *Org. Lett.* **2012**, *14*, 3237–3239; c) M. Yamamoto, S. Nakaoka, Y. Ura, Y. Kataoka, *Chem. Commun.* **2012**, *48*, 1165–1167.

[9] J. Tsuji, H. Nagashima, H. Nemoto, *Org. Synth.* **1984**, *62*, 9.

[10] Reviews highlighting the need for catalyst-controlled anti-Markovnikov functionalization reactions: a) M. Beller, J. Seayad, A. Tillack, H. Jiao, *Angew. Chem.* **2004**, *116*, 3448–3479; *Angew. Chem. Int. Ed.* **2004**, *43*, 3368–3398; b) L. Hintermann, *Top. Organomet. Chem.* **2010**, *31*, 123–155; c) J. Mahatthananchai, A. M. Dumas, J. W. Bode, *Angew. Chem.* **2012**, *124*, 11114–11152; *Angew. Chem. Int. Ed.* **2012**, *51*, 10954–10990.

[11] a) P. Eilbracht, L. Bärfacker, C. Buss, C. Hollmann, B. E. Kitsos-Rzychon, C. L. Kranemann, T. Rische, R. Roggenbuck, A. Schmidt, *Chem. Rev.* **1999**, *99*, 3329–3366; b) M. B. Smith, J. March, *March's Advanced Organic Chemistry*, 5th ed., Wiley, New York, **2001**; c) E. M. Carreira, L. Kvaerno, *Classics in Stereoselective Synthesis*, 1st ed., Wiley-VCH, Weinheim, **2009**; d) C. Wang, A. Pettman, J. Basca, J. Xiao, *Angew. Chem.* **2010**, *122*, 7710–7714; *Angew. Chem. Int. Ed.* **2010**, *49*, 7548–7552; e) B. L. Conley, M. K. Pennington-Boggio, E. Boz, T. J. Williams, *Chem. Rev.* **2010**, *110*, 2294–2312.

[12] Attempts to obtain aldehyde selectivity in Wacker oxidations of unbiased alkenes: a) B. L. Feringa, *J. Chem. Soc. Chem. Commun.* **1986**, 909; b) T. T. Wenzel, *J. Chem. Soc. Chem. Commun.* **1993**, 862–864; c) T. Ogura, R. Kamimura, A. Shiga, T. Hosokawa, *Bull. Chem. Soc. Jpn.* **2005**, *78*, 1555–1557.

[13] Alternatively, an epoxidation/isomerization tandem process can be used to oxidize alkenes to aldehydes: a) J. Chen, C.-M. Che, *Angew. Chem.* **2004**, *116*, 5058–5062; *Angew. Chem. Int. Ed.* **2004**, *43*, 4950–4954; b) A. D. Chowdhury, R. Ray, G. K. Lahiri, *Chem. Commun.* **2012**, *48*, 5497.

[14] Y. Lu, D.-H. Wang, K. M. Engle, J.-Q. Yu, *J. Am. Chem. Soc.* **2010**, *132*, 5916–5921.

[15] For example, if *t*BuOH is replaced by $MeNO_2$, no conversion is observed.

[16] Styrene was also evaluated and was oxidized in 47 % yield to the aldehyde (≥20:1 selectivity) and cleaved in 12 % yield to the benzaldehyde.

[17] Control experiments and further discussion can be found in the Supporting Information.

[18] Selected examples of aerobic NO_2 turnover in Pd catalysis: a) T. T. Wenzel, *J. Chem. Soc. Chem. Commun.* **1989**, 932–933; b) K. J. Stowers, A. Kubota, M. S. Sanford, *Chem. Sci.* **2012**, *3*, 3192–3195.

[19] G. Dong, P. Teo, Z. K. Wickens, R. H. Grubbs, *Science* **2011**, *333*, 1609–1612.

[20] M. A. Andrews, K. P. Kelly, *J. Am. Chem. Soc.* **1981**, *103*, 2894–2896.

[21] a) "Nitric Acid, Nitrous Acid, and Nitrogen Oxides": M. Thiemann, E. Scheibler, K. W. Wiegand, *Ullmann's Encyclopedia of Industrial Chemistry*, Wiley-VCH, Weinhei, **2012**; b) for a recent examples of nitrite salts serving as precursors to NO_2: S. Maity, S. Manna, S. Rana, T. Naveen, A. Mallick, D. Maiti, *J. Am. Chem. Soc.* **2013**, *135*, 3355–3358.

[22] When the reaction is run in an unsealed vessel (exposed to air), significantly lower yield and selectivity is observed relative to the reaction run in a sealed vessel (under air atmosphere). This is consistent with the formation of NO_2, which is a gas at room temperature.

[23] To probe whether Pd or Cu mediate NO_2 delivery, a reviewer suggested the stoichiometric reaction of $CuCl_2$ and $AgNO_2$ with an alkene. No alkene conversion was observed under these conditions, suggesting that Pd may mediate NO_2 delivery.

[24] J. A. Keith, P. M. Henry, *Angew. Chem.* **2009**, *121*, 9200–9212; *Angew. Chem. Int. Ed.* **2009**, *48*, 9038–9049.

[25] a) S. Z. Zard, *Radical Reactions in Organic Synthesis*, Oxford University Press, New York, **2003**; b) M. S. Kharasch, E. V. Jensen, W. H. Urry, *Science* **1945**, *102*, 128.

[26] For recent examples using a radical strategy to form carbon–nitrogen bonds, see: a) ref. [21b]; b) J. Guin, C. Mück-Lichtenfeld, S. Grimme, A. Studer, *J. Am. Chem. Soc.* **2007**, *129*, 4498–4503.

[27] For a recent example using a radical cation strategy to form carbon–oxygen bonds, see: D. S. Hamilton, D. A. Nicewicz, *J. Am. Chem. Soc.* **2012**, *134*, 18577–18580.

[28] W. Fischetti, R. F. Heck, *J. Organomet. Chem.* **1985**, *293*, 391–405.