Organic LETTERS

Letter

pubs.acs.org/OrgLett

tert-Butyl Nitrite: Organic Redox Cocatalyst for Aerobic Aldehyde-Selective Wacker–Tsuji Oxidation

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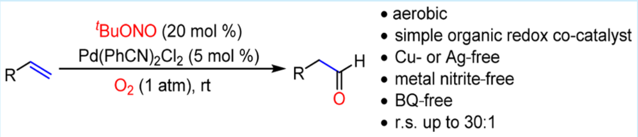
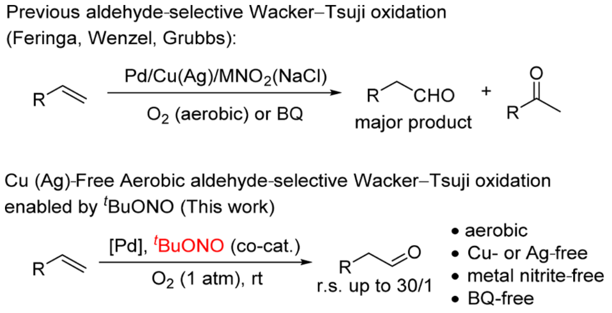
Supporting Information

ABSTRACT: An aldehyde-selective aerobic Wacker–Tsuji oxidation is developed. Using *tert*-butyl nitrite as a simple organic redox cocatalyst instead of copper or silver salts, a variety of aldehydes were achieved as major products in up to 30/1 regioselectivity as well as good to high yields at room temperature.



Wacker–Tsuji oxidation[1] is a palladium–copper cocatalyzed process for converting terminal alkenes to ketones,[2] normally under aerobic conditions and following the Markovnikov rule. Copper salts are usually used as necessary transition metal redox cocatalysts. Despite ketone-selective Wacker–Tsuji oxidation of terminal olefins having been well established, the aldehyde-selective version of this reaction following the *anti*-Markovnikov rule remains a challenge.[3] Remarkable progress has been made recently[4−7] for aerobic[8] and nonaerobic[9] aldehyde-selective Wacker–Tsuji oxidation, especially using benzoquinone (BQ) as the oxidant (Scheme 1). The Pd/Cu/Ag/MNO$_2$ catalytic system gave aldehydes with generally good selectivity.[8]

Scheme 1



The advantage of using clean and green molecular oxygen as the sole oxidant under aerobic conditions is that it supports sustainable chemistry. In fact, inorganic redox cocatalysts such as CuCl and MNO$_2$ (M: Na, K, Ag) are still used under aerobic conditions in most cases. Therefore, an aerobic Wacker–Tsuji oxidation in the absence of metal redox cocatalysts approaches the concept of green chemistry. Herein, an aldehyde-selective aerobic Wacker–Tsuji oxidation enabled by a simple organic redox cocatalyst ^{t}BuONO (TBN) has been developed, where benzoquinone or a copper redox cocatalyst is not involved.

During the ammoxidation of methylarenes,[10a] it was noted that ^{t}BuONO was a convenient organic NO-source which might replace inorganic NO$_2$-salts[10b] in catalysis. Thus, various palladium catalysts were investigated in the aerobic oxidation of **1a** to aldehyde **2a** in ^{t}BuOH at room temperature (Table 1). Nitrile ligands have obvious effects on the regioselectivity as well as the conversion of **2a** (entries 2–8). Pd(PhCN)$_2$Cl$_2$ gives the best regioselectivity (entry 3). When the reaction was carried out in the absence of O$_2$, only 10% conversion was obtained with the oxidation by ^{t}BuONO itself (entry 9). The reaction selectivity has no dependence on the amounts of ^{t}BuONO (entries 10–13). When excess TBN was used, the reaction finished in 30 min. This is consistent with the kinetic study which reveals a zeroth-order dependence of ^{t}BuONO on the initial rate. Despite the fact that an excess amount of ^{t}BuONO has no effect on the conversion of **1a** to **2a**, palladium black could be seen in the reactions with a lower loading of ^{t}BuONO; therefore 20 mol % of TBN was used for further investigation of the substrate scope. The catalyst loading has a slight effect on the reaction yields (entries 3 and 14–16).

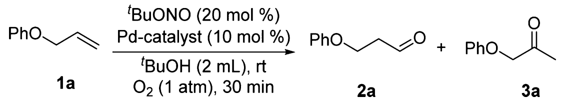
Hypothetically, Pd(CH$_3$CN)$_2$ClNO$_2$ or Pd(CH$_3$CN)$_2$(NO$_2$)$_2$ could be the catalytically active forms which is *in situ* generated from Pd(PhCN)$_2$Cl$_2$ and ^{t}BuONO in the reaction mixture. However, the reaction using either NO$_2$-containing Pd-complex gives only a trace amount of **2a** (entries 17 and 18), suggesting the catalytically active species should not be the NO$_2$-containing Pd-complexes.[11] The stoichiometric Pd-catalyst gives rise to 14% conversion in the absence of ^{t}BuONO and O$_2$, indicating ^{t}BuONO should be a redox cocatalyst for regeneration of Pd(II).

After establishing the optimized reaction conditions (5 mol % of Pd(PhCN)$_2$Cl$_2$, 20 mol % TBN), the scope of aldehyde-selective Wacker–Tsuji oxidation was evaluated (Scheme 2). Various terminal alkenes bearing different functional groups were subjected to the optimized conditions, and aldehyde

Received: April 21, 2016

DOI: 10.1021/acs.orglett.6b01165
Org. Lett. XXXX, XXX, XXX–XXX

Table 1. Reaction Conditions[a]



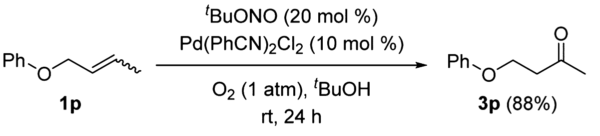
entry	[Pd] (mol %)	^{t}BuONO (mol %)	**2a**/**3a**[b]	**2a** (%)[b]
1	–	20	–	0
2	$Pd(PhCN)_2Cl_2$	none	–	0
3	$Pd(PhCN)_2Cl_2$	20	12/1	71
4	$Pd(p\text{-}MePhCN)_2Cl_2$	20	11/1	76
5	$Pd(p\text{-}CF_3PhCN)_2Cl_2$	20	4.5/1	59
6	$Pd(C_4H_9CN)_2Cl_2$	20	10/1	73
7	$Pd(^tBuCN)_2Cl_2$	20	6/1	75
8	$Pd(MeCN)_2Cl_2$	20	7.5/1	60
9[c]	$Pd(PhCN)_2Cl_2$	20	5/1	10
10	$Pd(PhCN)_2Cl_2$	5	14/1	14
11	$Pd(PhCN)_2Cl_2$	10	10/1	72
12	$Pd(PhCN)_2Cl_2$	30	14/1	72
13	$Pd(PhCN)_2Cl_2$	100	14/1	71
14[d]	$Pd(PhCN)_2Cl_2$ (2.5)	20	10/1	71
15[e]	$Pd(PhCN)_2Cl_2$ (5)	20	13/1	77
16[f]	$Pd(PhCN)_2Cl_2$ (7.5)	20	10/1	82
17	$Pd(CH_3CN)_2Cl(NO_2)$	none	1.5/1	3
18	$Pd(CH_3CN)_2(NO_2)_2$	none	1/1	2
19[g]	$Pd(PhCN)_2Cl_2$	none	2/1	14
20[h]	$Pd(PhCN)_2Cl_2$	20	2/1	40[j]
21[i]	$Pd(PhCN)_2Cl_2$	20	2.3/1	70[j]

[a]Reaction conditions: **1a** (0.5 mmol). [b]By ^{1}H NMR (400 MHz) using 1,4-dioxane as internal standard. [c]Under argon. [d]With 2.5 mol % of [Pd], 180 min. [e]With 5 mol % of [Pd], 90 min. [f]With 7.5 mol % of [Pd], 90 min. [g]With 100 mol % [Pd] in the absence of TBN and O_2. [h]MeOH instead of ^{t}BuOH as solvent. [i]EtOH instead of ^{t}BuOH as solvent. [j]The ratio and yield refer to the total yield of **2a** and acetal.

products were obtained with as high as 30:1 regioselectivity in generally good to high isolated yields. Various functional groups or protecting groups could be tolerated under these reaction conditions. For example, aldehydes **2a** and **2b** bearing PhO- and $PhCO_2$-groups were isolated in 76% and 75% yields with high regioselectivity, providing an easy access to ω-hydroxy aldehydes from corresponding unsaturated alcohol derivatives. The unstable protecting groups such as MOM remained unchanged in the oxidation (**2e–f**, **2n**). Even nitrogen-containing substrates smoothly gave the desired aldehydes in high yields with up to 30:1 selectivity (**2g–j**). The unstable TsO-aldehyde **2o** was also obtained in 77% yield with 24:1 selectivity.

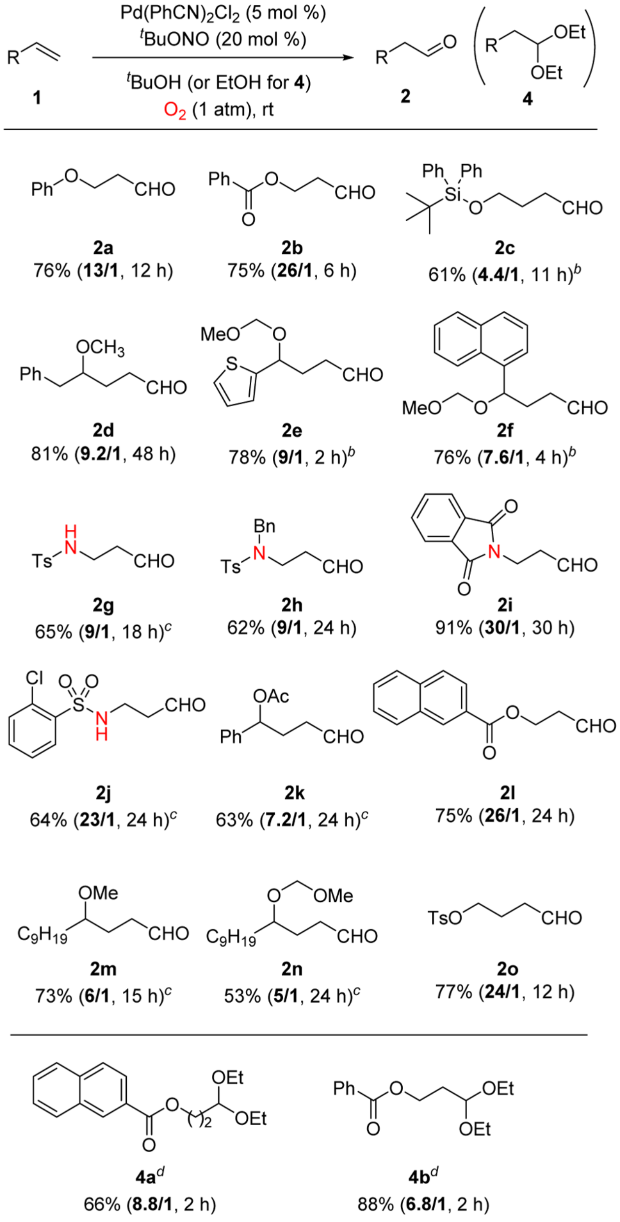
When EtOH was used as solvent instead of ^{t}BuOH, acetal products were achieved in good to high yields with as high as 8.8:1 regioselectivity (**4a–b**).

With respect to the internal alkenes, **1p** has been subjected to the reaction conditions (eq 1) and the normal Wacker product **3p** was obtained in 88% yield, indicating this reaction condition is also suitable for internal alkenes with ketone-selective products.



(1)

Scheme 2. Reaction Scope[a]

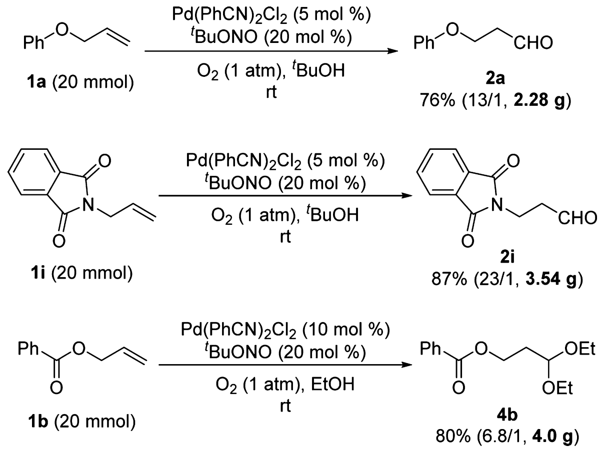


[a]Condition A: **1** (0.5 mmol), $Pd(PhCN)_2Cl_2$ (5 mol %), ^{t}BuONO (20 mol %), ^{t}BuOH, O_2 (1 atm), isolated yields. Ratios refer to aldehyde/ketone. [b]$Pd(PhCN)_2Cl_2$ (10 mol %). [c]$Pd(PhCN)_2Cl_2$ (7.5 mol %). [d]Same as condition A except EtOH instead of ^{t}BuOH and 10 mol % of [Pd] were used. Ratios refer to acetal/ketone.

The aldehyde-selective Wacker–Tsuji oxidation in gram-scale could also result in high regioselectivity and high yields with 5 mol % of the Pd-catalyst (Scheme 3). More than 2 g of aldehydes **2a** and **2i** were obtained with 13:1 and 23:1 selectivity in high yields. With respect to the acetal-selective oxidation, **4b** was obtained with 6.8:1 regioselectivity (acetal/ketone) in 80% yield.

To explore the effects of the palladium catalyst and the role of ^{t}BuONO, the dependence of the initial rate on the concentrations of [Pd], [^{t}BuOH], [**1a**], and [^{t}BuONO] was examined by a kinetic study (Figure 1A–1D). A first-order dependence of the initial rate on the amount of the palladium catalyst was established (Figure 1A). There is no induction phase observed in conversion–time plots, indicating Pd(II) in [$Pd(PhCN)_2Cl_2$] should be the catalytically active form which directly catalyzed this reaction. A first-order dependence of the

Scheme 3. Gram-Scale Reactions



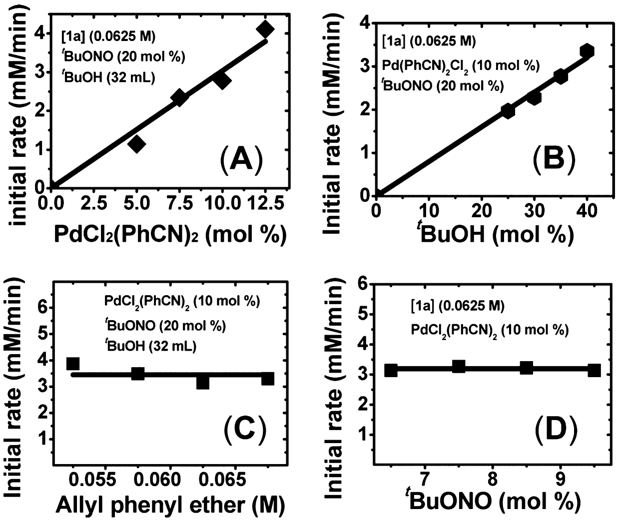
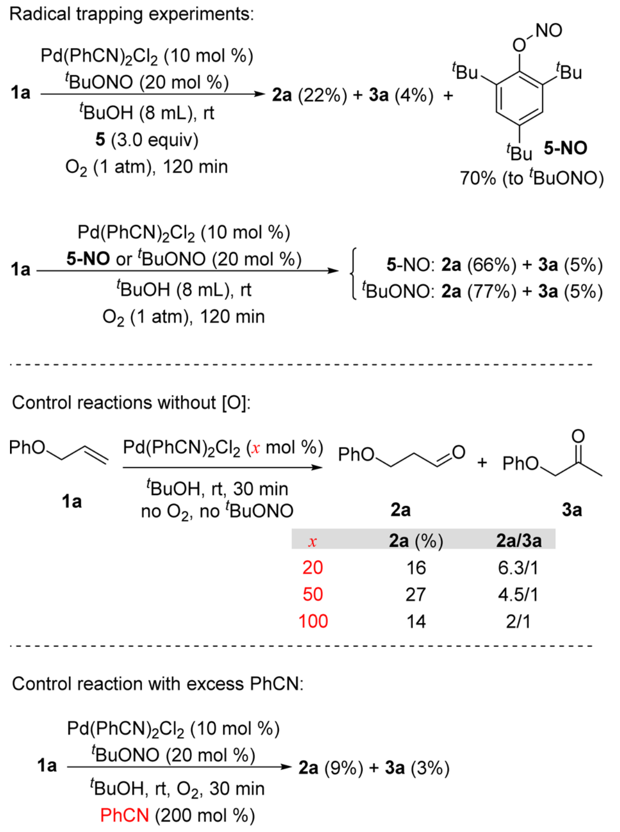


Figure 1. Dependence of the initial rate on (A) [Pd(PhCN)$_2$Cl$_2$] (first-order); (B) [^{t}BuOH] (first-order); (C) [**1a**] (zeroth-order); (D) [^{t}BuONO] (zeroth-order). Conditions: **1a**, Pd(PhCN)$_2$Cl$_2$ (5−12.5 mol %), ^{t}BuONO (20 mol % for A−C, 6.5−9.5 mol % for D), ^{t}BuOH, O$_2$ (1 atm). For details, see Supporting Information.

amount of ^{t}BuOH (solvent) on the initial rate was established (Figure 1B). The zeroth-order dependence of [**1a**] or the amount of ^{t}BuONO on the initial rate was established (Figure 1C−1D), indicating that neither ^{t}BuONO nor **1a** participates in the rate-determining step of this catalysis; therefore, ^{t}BuONO should not directly bond to Pd and stay outside of the catalytic cycle.

^{t}BuONO is a donor of nitric oxide (NO), a stable neutral radical which is easily oxidized to NO$_2$ by O$_2$. Thus, ^{t}BuONO plays the role of redox cocatalyst in this aerobic oxidation reaction. Radical scavenger **5** [2,4,6-tri-*tert*-butylphenol] inhibits this aldehyde-selective Wacker−Tsuji oxidation of **1a** to **2a** (Scheme 4). The **5**-NO adduct was isolated in 70% yield with respect to ^{t}BuONO. Actually, the reaction with **5**-NO instead of ^{t}BuONO afforded **2a** in 66% conversion, explaining the incomplete inhibition of the reaction by radical scavenger **5**. The stoichiometric amount of the Pd-catalyst resulted in 14% conversion of **1a** in the absence of TBN and O$_2$ (Scheme 4, middle). A large amount of palladium black was observed in the reactions in the absence of ^{t}BuONO and O$_2$. The formation of a large amount of palladium black gave rise to the liberation of a

Scheme 4. Control Experiments



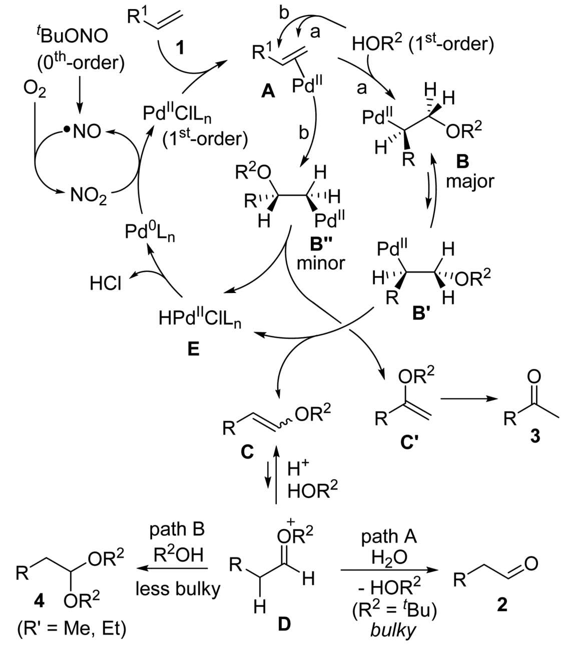
x	**2a** (%)	**2a/3a**
20	16	6.3/1
50	27	4.5/1
100	14	2/1

large amount of PhCN which obviously inhibited the reaction (Scheme 4, bottom). The excess PhCN has another negative effect on the ratios of **2a** and **3a**. In the control reactions, 20 mol % Pd-catalyst without ^{t}BuONO gave 6.3/1 selectivity, whereas the increase in the amount of the Pd-catalyst resulted in an obvious decrease of the aldehyde/ketone ratios. Therefore, Pd(II) should be the catalytically active species for initializing the Wacker−Tsuji oxidation and NO plays the role of redox cocatalyst for the regeneration of Pd(II) from Pd(0).

A plausible mechanism for this aldehyde-selective Wacker−Tsuji oxidation is proposed on the basis of control experiments and kinetic study (Scheme 5). A Pd(II)-catalyzed oxidation is proposed on the basis of kinetic study and previous work. ^{t}BuOH (solvent) attacks **A** to form intermediate **B**, followed by β-elimination to afford **C**. Enol ether **C** is protonated to **2** under equilibrium. A catalytically active Pd(II) species is regenerated by oxidation with NO$_2$. Herein ^{t}BuONO works as a redox cocatalyst, replacing the copper-redox cocatalyst in previous work. The unreactive behavior of Pd(CH$_3$CN)$_2$ClNO$_2$ or Pd(CH$_3$CN)$_2$(NO$_2$)$_2$ suggests that the model of Pd(CH$_3$CN)$_2$Cl(NO$_2$) direct insertion to C=C bonds[11] proposed previously by computation should be ruled out. The zeroth-order dependence of the initial rate on the amount ^{t}BuONO and the first-order dependence of the initial rate on the amount ^{t}BuOH support the Heck-type of formation intermediate **B**, which is further supported by the control experiment with stoichiometric Pd-catalyst in the absence of ^{t}BuONO and O$_2$.

In conclusion, we have developed an aldehyde-selective aerobic Wacker−Tsuji oxidation at room temperature under copper- or silver-free conditions enabled by the catalytic amount of *tert*-butyl nitrite as a simple organic redox cocatalyst.

Scheme 5. Proposed Mechanism



A variety of aldehydes were achieved in generally high regioselectivity as well as good to high yields. The gram-scale synthesis of aldehydes and acetals is also available.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01165.

Experimental details and spectroscopic data for all products (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank the National Natural Science Foundation of China (NSFC 21404096, U1463202), the Fundamental Research Funds for the Central Universities of China (WK2060190026, WK3430000001), and the Anhui Provincial Natural Science Foundation (1608085MB24) for financial support.

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