Letter

Dehydrogenative Synthesis of Linear #,#-Unsaturated Aldehydes with Oxygen at Room Temperature Enabled by tBuONO

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Dehydrogenative Synthesis of Linear α,β-Unsaturated Aldehydes with Oxygen at Room Temperature Enabled by ^{t}BuONO

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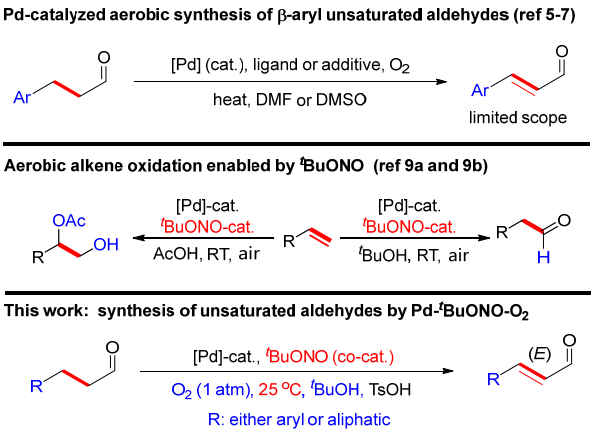
ABSTRACT: Synthesis of linear α,β-unsaturated aldehydes via a room-temperature oxidative dehydrogenation has been realized by the cocatalysis of an organic nitrite and palladium with molecular oxygen as the sole clean oxidant. Linear α,β-unsaturated aldehydes could be efficiently prepared under aerobic catalytic conditions directly from corresponding saturated linear aldehydes. Besides linear products, the aromatic analogy could also be smoothly achieved by the same standard method. The organic nitrite redox cocatalyst and alcohol solvent play key role for realizing this method.

KEYWORDS: *dehydrogenation, α,β-unsaturated aldehydes, palladium, organic nitrite, co-catalysis*

Linear α,β-unsaturated aldehydes are highly useful synthetic blocks in organic synthesis. The strategy of direct preparation of linear α,β-unsaturated aldehydes by corresponding α,β-dehydrogenative oxidation exhibits an efficient straightforward pathway.[1-7] Compared to aromatic α,β-unsaturated aldehydes, the synthetic methods to linear α,β-unsaturated aldehydes have been less reported. The approaches with hazardous stoichiometric oxidants such as PhSeCl, IBX, and Pd(II)-Ag(I) have been reported decades ago (Scheme 1).[1-4] The indirect route with stoichiometric palladium-mediated dehydrogenation, namely Saegusa reaction, transforms enol silyl ethers to linear α,β-unsaturated aldehydes.[2a] As a more general synthetic method, the α,β-dehydrogenative oxidant of aldehydes with excess IBX (2-iodoxybenzoic acid) has been found to be efficient at elevated temperatures in DMSO and PhF.[4] However, this method is flawed by the limited solubility of IBX in many common organic solvents as well as the limited scope of aldehyde. With respect to the transition metal-catalyzed dehydrogenation of aldehydes, despite remarkable progress has been accomplished by Wang, Stahl, and Huang *et al*, the scope of aldehyde has still been limited to few aromatic aldehydes.[5-8] So far, the synthesis of linear α,β-unsaturated aldehydes via catalytic oxidative α,β-dehydrogenation has still remained unrevealed.

In another hand, molecular oxygen is a clean and cheap oxidant which has been widely used in industrial oxidations as well as organic synthesis. Despite O_2 has many advantages, the activation of O_2 to form reactive [O] in transition metal catalysis normally involves the redox cocatalyst such as copper or the acceleration with a special ligand such as diazafluoren (DAF).[5-6] Recently, we have reported organic nitrite-Pd-cocatalyzed *anti*-Markovnikov Wacker oxidation and aerobic acetoxyhydroxylation of alkenes enabled by the activation of O_2 with ^{t}BuONO.[9-10] Herein, we have developed a highly efficient catalytic system for a ligand-free aerobic dehydrogenation of saturated aldehydes to linear α,β-unsaturated aldehydes, in which both aliphatic and aromatic aldehydes are generally suitable, in which bases or primary amine-cocatalysts were not involved.

Scheme 1. Dehydrogenation to α,β-Unsaturated Aldehydes

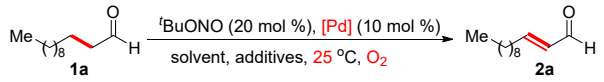


Initially, for comparison, the literature methods were tested in the oxidative dehydrogenation of aliphatic aldehyde **1a** to the corresponding α,β-unsaturated aldehyde **2a**. All these Pd-catalyses were found ineffective (Table 1, entries 2-4). The elevated reaction temperature, basic reaction medium or amine-cocatalysts made the unstable aliphatic aldehyde **1a** consumed via aldol condensation and other side-reaction. The IBX-oxidative dehydrogenation gave no **2a** either (entry 1). Thus all literature methods tested here failed for the efficient conversion of **1a** to **2a**.

When $Pd(PhCN)_2Cl_2$ used instead of $Pd(OAc)_2$, only the reaction in ^{t}BuOH gave a moderate yield of **2a** (entries 5-7), in which the conditions have been used in the aldehydes-selective Wacker oxidation in previous report.[9a] The reaction in the presence of K_2CO_3 afforded no **2a** (entry 6), indicating bases destroy either aldehyde substrates or α,β-unsaturated aldehydes. The coordinative aprotonic co-solvent such as PhCN and DMSO inhibited the reaction (entries 7-8). Surprisingly, the addition of toluene increased the yield to 61% (entry 9). The reaction under weakly acidic conditions gave rise to the elevation of the yield to 70% (entry 10). When mesitylene ($C_6H_3Me_3$) was used instead of toluene, the yield was further increased to 88% (entry 11). The role of ^{t}BuOH and mesitylene is not clear. Neither reaction under argon nor in the absence of redox cocatalyst ^{t}BuONO succeeded (entries 12-13). The reaction with inorganic redox co-catalyst $NaNO_2$ instead of ^{t}BuONO gave diminished yield of **2a** (entry 14). The reaction with 7.5 mol % of $Pd(PhCN)_2Cl_2$ afforded comparable yield of **2a**, thus the

condition demonstrated in entry 16 was chosen as the standard reaction condition for further investigation of the scope of this method.

Table 1. Reaction Conditions[a]



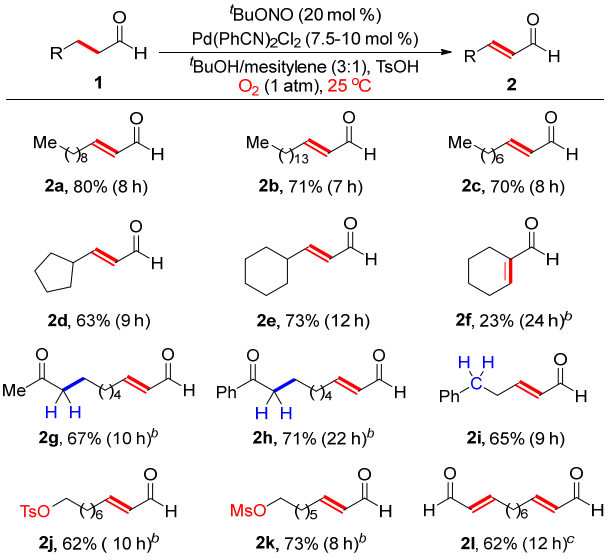
entry	[Pd]	solvent	additive	**2a**(%)[b]
1[c]	– (with IBX)	DMSO	PhF	trace
2[d]	$Pd(TFA)_2$	DMSO	ligand	9
3[e]	$Pd(OAc)_2$	DMF	K_2CO_3, ligand	23
4[f]	$Pd(OAc)_2$	DMSO	*o*-anisidine	0
5	$Ph(PhCN)_2Cl_2$	^{t}BuOH	none	46
6	$Pd(PhCN)_2Cl_2$	^{t}BuOH	K_2CO_3	0
7	$Pd(PhCN)_2Cl_2$	^{t}BuOH	PhCN	0
8	$Pd(PhCN)_2Cl_2$	^{t}BuOH	DMSO	0
9	$Pd(PhCN)_2Cl_2$	^{t}BuOH	PhMe	61
10	$Pd(PhCN)_2Cl_2$	^{t}BuOH	PhMe, TsOH	70
11	$Pd(PhCN)_2Cl_2$	^{t}BuOH	$C_6H_3Me_3$, TsOH	88
12[g]	$Ph(PhCN)_2Cl_2$	^{t}BuOH	$C_6H_3Me_3$, TsOH	trace
13[h]	$Pd(PhCN)_2Cl_2$	^{t}BuOH	$C_6H_3Me_3$, TsOH	trace
14[i]	$Pd(PhCN)_2Cl_2$	^{t}BuOH	$C_6H_3Me_3$, TsOH	68
15	none	^{t}BuOH	$C_6H_3Me_3$, TsOH	0
16[j]	$Pd(PhCN)_2Cl_2$	^{t}BuOH	$C_6H_3Me_3$, TsOH	88(80)[k]

[a] Conditions: **1a** (0.5 mmol), [Pd] (10 mol %), ^{t}BuONO (20 mol %), ^{t}BuOH (2 mL), co-solvent (PhCN, DMSO, PhMe, or $C_6H_3Me_3$, 0.5 mL), acid or base (1 equiv), 8 h. [b] Determined by ^{1}H NMR with internal standards. [c] Ref. 4: IBX in DMSO-PhF, 80 °C. [d] Ref. 5a: $Pd(TFA)_2$/diazafluoren, 80 °C, 1 day. [e] Ref. 6: $Pd(OAc)_2$/diazafluoren with K_2CO_3, 30 °C, 2 days. [f] Ref. 7: $Pd(OAc)_2$ (10 mol %), *o*-anisidine (20 mol %), DMSO, O_2, 60 °C, 1 day. [g] Argon instead of O_2. [h] No ^{t}BuONO. [i] $NaNO_2$ instead of ^{t}BuONO. [j] Using 7.5 mol % of $Pd(PhCN)_2Cl_2$. [k] Isolated yield was shown in parentheses.

With the standard reaction conditions in hand (Table 1, entry 16), the scope of this oxidative dehydrogenation of aldehyde has been evaluated (Scheme 2). This standard reaction condition is mild enough to let various aliphatic aldehydes to survive (**2a-2l**). For example, the α,β-unsaturated aldehydes (**2a-2e**) bearing aliphatic chain and ring at γ-position could be achieved in 63-80% of yields. The benzyl position kept unchanged in the dehydrogenation (**2i**). This catalytic system could realize the selective α,β-dehydrogenation of aldehydes, keeping the ketone moiety unchanged (**2g-2h**). Protected hydroxyl groups such as TsO- and MsO-groups have all survived in the reaction (**2j-2k**). Both sides of the dialdehyde **1l** could be dehydrogenated to give **2l** in 62% of yield.

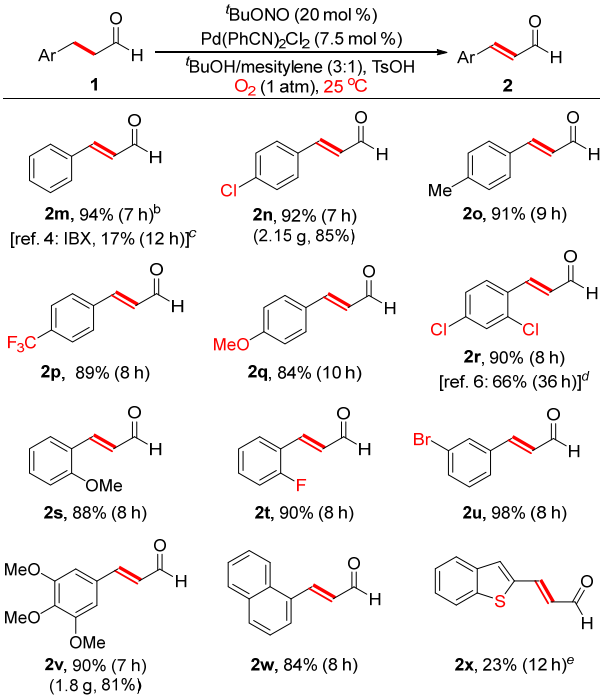
Besides the synthesis of linear α,β-unsaturated aldehydes, the method is also efficient for the synthesis of β-aryl analogy, exhibiting even more efficiency (Scheme 3). All α,β-unsaturated aldehydes bearing substituted phenyl groups were isolated in high yields, from 84% to 98% (**2m-2v**). Aldehyde **2r** was previously obtained in 66% yield under basic conditions in previous report,[6a] whereas it was isolated in 90% of yield by current method. The bromo-substituent could survive in this palladium-catalyzed reaction (**2u**). Cinnamaldehyde **2m** was obtained in only 17% of yield by the IBX oxidation system, whereas it performed well in current Pd-^{t}BuONO cocatalytic system to afford in 94% of yield. The γ-naphthyl substituted product **2w** was obtained in 84% of yield. Benzothienyl moiety is highly unstable under oxidative conditions and the corresponding product was isolated in a low yield (**2x**).

Scheme 2. Aliphatic Aldehydes[a]



[a] Standard condition: **1** (0.5 mmol), $Pd(PhCN)_2Cl_2$ (7.5 mol %), ^{t}BuONO (20 mol %), ^{t}BuOH, mesitylene, O_2 (1 atm), isolated yields. [b] [Pd] (10 mol %). [c] Two cycles of the standard condition.

Scheme 3. β-Aryl Aldehydes[a]

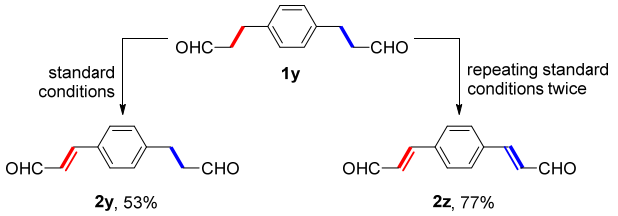


[a] Standard condition: **1** (0.5 mmol), $Pd(PhCN)_2Cl_2$ (7.5 mol %), ^{t}BuONO (20 mol %), ^{t}BuOH, mesitylene, O_2 (1 atm), isolated yields. [b] $Pd(PhCN)_2Cl_2$ (5 mol %). [c] Conditions in ref. 4 with IBX. [d] From ref. 6. [e] $Pd(PhCN)_2Cl_2$ (10 mol %).

This method has been applied in the gram-scale synthesis. With 5 mol % of [Pd]-catalyst, either **1n** and **1v** were converted to desired α,β-unsaturated aldehydes **2n** (2.15 g) and **2v** (1.8 g) in 85% and 81% of yields, respectively.

The control of the selectivity is important for the substrates bearing more than one carbonyl groups. To test the ability of selective dehydrogenation of dialdehydes, dialdehyde **1y** was subjected to the standard conditions, affording the corresponding product **2y** bearing a single α,β-unsaturated carbonyl in moderated yield, with recovery of the starting materials (Scheme 4). Repeating the standard conditions twice afforded the dual α,β-unsaturated product **2z** in 77% of yield.

Scheme 4.



In the kinetic study, the initial rate is first-order dependent on the amount of $Pd(PhCN)_2Cl_2$, proving that Pd(II) is catalytic active species in this dehydrogenation reaction, which involves the rate-determining step (Fig. 1A). The zeroth-dependence of [^{t}BuONO] or substrate **1a** on the initial rate indicates that neither nitric oxide nor **1a** has been involved in the rate-determining step ((Fig. 1B and 1C)). Thus the β-H elimination should not be the rate-determining step and ^{t}BuONO should act as a redox co-catalyst other than a ligand which enables the oxidative regeneration of Pd(II) from Pd(0). Since only the amount of [Pd] exhibits a first order dependence on initial rate, the regeneration of catalytically active species Pd(II) should be the rate determining step.

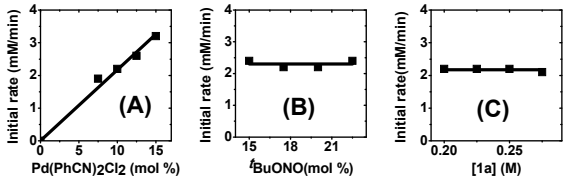
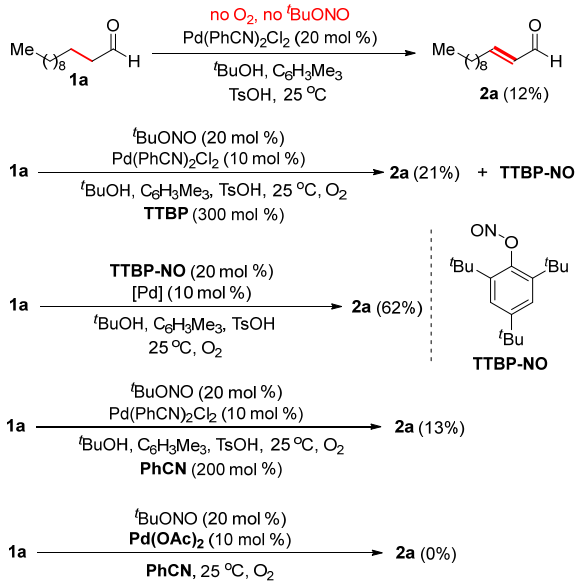


Figure 1. The dependence of the initial rate on: (A) [$Pd(PhCN)_2Cl_2$] (1st-order), (B) [^{t}BuONO] (0th-order), and (C) [**1a**]: (0th-order). For details, see SI.

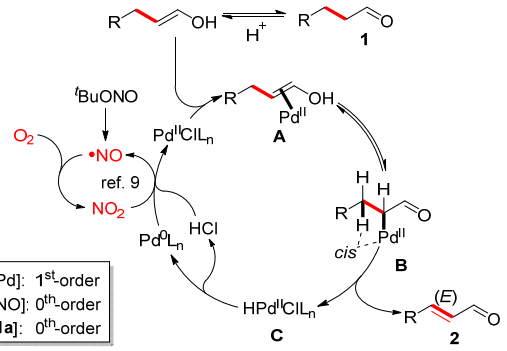
In the control reaction, 20 mol % of Pd(II) afforded 12% of **2a** in the absence of oxidant (Scheme 5). The radical trapping experiment shows that the radical scavenger TTBP inhibited the dehydrogenation of **1a**. The radical scavenger could not totally shut down the reaction because the trapping product TTBP-NO was still reactive (Scheme 5, bottom). These results were consistent with previous report.

A possible mechanism has been proposed in Scheme 6. In previous work, the redox cocatalytic role of ^{t}BuONO has been assigned by the kinetic study as well as control experiments.[9] Herein the enol-Pd complex **A** transforms to **B**, followed by the β-hydrogen elimination to afford the α,β-unsaturated aldehyde **2**. Pd(0) was regenerated by the oxidation of NO_2. The detailed mechanism is still unclear and under exploration.

Scheme 5. Control Experiments



Scheme 6. Proposed Mechanism



In conclusion, we have developed an efficient synthesis of linear α,β-unsaturated aldehydes via room-temperature oxidative dehydrogenation cocatalyed by an organic nitrite and palladium with molecular oxygen as the sole clean oxidant. Besides linear products, β-aryl unsaturated aldehydes could also be highly efficiently achieved by the same standard method. The organic nitrite redox co-catalyst and alcohol solvent play key role for realizing this method. The kinetic study as well as control experiments revealed the role of ^{t}BuONO as a redox cocatalyst which enabled the aerobic oxidative dehydrogention of aldehydes.

ASSOCIATED CONTENT

Supporting Information

Experimental details and spectroscopic data for all products. This material is available free of charge *via* the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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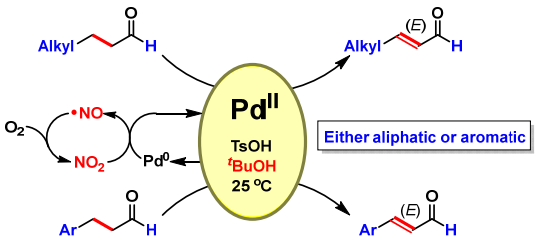
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