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Highly selective Wacker reaction of styrene derivatives: a green and efficient aerobic oxidative process promoted by benzoquinone/NaNO₂/HClO₄ under mild conditions

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A highly efficient system for aerobic Wacker oxidation has been developed, which was selective to the oxidation of styrene derivatives.
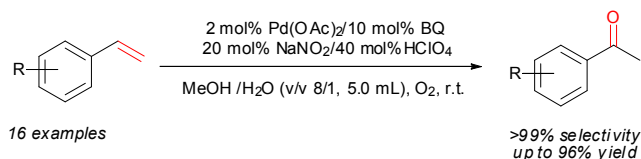
COMMUNICATION

Highly selective Wacker reaction of styrene derivatives: a green and efficient aerobic oxidative process promoted by benzoquinone/NaNO₂/HClO₄ under mild conditions

Guofu Zhang, Xiaoqiang Xie, Yong Wang, Xin Wen, Yun Zhao and Chengrong Ding*

A green and efficient catalytic redox system for the aerobic oxidative Wacker oxidation of styrene derivatives at room ₁₀ temperature using molecular oxygen as the terminal oxidant without copper chloride has been developed. The newly developed system exhibited excellent catalytic activity for the smooth transformation of terminal styrene derivatives to the desired methyl ketones with up to 96% yield and >99% ₁₅ selectivity.

The Wacker oxidative reaction of terminal olefins, one of the most efficient protocols for the construction of aldehydes or methyl ketones, has attracted great attention during the past five decades.[1] Initially, the reaction was carried out in the presence of ₂₀ copper chloride, yet the formation of chlorinated by-products was generally unavoidable and the reactor was easily corroded.[2] In order to overcome these drawbacks, chemical researchers have put immense amount of focus on developing chloride-free Wacker-oxidation systems by introducing various kinds of ₂₅ oxidants instead of CuCl₂ to promote the reoxidation of Pd(0) into highly active Pd(II) and thus complete the whole catalytic cycle.[3] In 1964, Selwitz and co-workers reported that palladium-catalyzed Wacker oxidation could be carried out with benzoquinone (BQ) as the oxidant.[3a] Later on, Matveev and co-₃₀ workers utilized heteropoly acid (HPA) as the oxidant to achieve Wacker oxidation.[3b] Although these methods provided valuable directions for lab researches, a stoichiometric amount of BQ or HPA was demanded, which induced serious consequent problems in later product isolation and thus limited their practical ₃₅ applications.
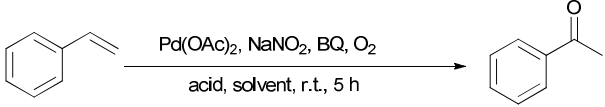
Recently, Wacker oxidation using oxygen as the terminal oxidant has gained high popularity as oxygen is freely available

and its reductive product is environmentally friendly water.[4] Backvall and co-workers have announced a mild catalytic ₄₀ oxidative system Pd(OAc)₂/iron phthalocyanine (FePc)/HQ/O₂ for aerobic Wacker oxidation of a series of alkenes.[5] Their work also demonstrated that FePc could act as an efficient electron transfer agent in oxidizing hydroquinone (reduced state of BQ), so only a catalytic amount of BQ was needed. Recently, Liang, ₄₅ Hu and other workers have proved that NOₓ gas generated in-situ by sodium nitrite/acid was an active electron transfer species in aerobic oxidations, oxidative degradations of environmental pollutants and C_{sp3}-H bonds functionalization.[6] Our group also explored some aerobic oxidative reactions like oxybromination ₅₀ and deoximation reactions using similar oxidative systems as well.[7] Inspired by these encouraging works, we are triggered to explore the possibility that NOₓ could also be introduced into the Wacker oxidation as sodium nitrite is more commercially available and easier to be removed in subsequent product ₅₅ isolation compared with other co-oxidants like FePc. If the assumption is feasible, the developed system may provide a practical protocol. Thus we wish to report a novel, mild and efficient system for aerobic Wacker oxidation, which uses Pd(OAc)₂ as the catalyst, molecular oxygen as the terminal ₆₀ oxidant and NaNO₂/HClO₄/BQ as the redox assistant reagents. Additionally, we aim to extend the substrate scope to substituted styrenes because their transformation to the corresponding methyl ketones with excellent selectivities and yields is still challenging.[8]

To optimize experimental conditions, styrene was selected as ₆₅ the model substrate and the detailed results were summarized in Table 1. The probed reaction was carried out with Pd(OAc)₂ as the catalyst, BQ/NaNO₂ as the oxygen-activating agents, HClO₄ as the initiator of sodium nitrite at room temperature. Initially with CH₃CN as the solvent, 27% yield of the desired

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acetophenone was observed (Table 1, entry 1). To our delight, switching the solvent to aqueous methanol improved the yield to 91% (Table 1, entry 2). Then we studied the effect of solvent to this Wacker transformation, however, other aqueous solvents like DMSO/H$_2$O, DMF/H$_2$O, CH$_2$Cl$_2$/H$_2$O, and EtOH/H$_2$O etc. could only afford the desired product in low to moderate yields (Table 1, entries 3-10). Considering the contribution of acid to the solubility and stabilization of the highly active palladium species, we next examined the influence of acid to the reaction (Table 1, entries 2, 11-15). The use of nitric acid, aimed to avoid the use of NaNO$_2$ as the additional oxidant, only yields the product in trace amount. While replacing HClO$_4$ with other acids such as H$_2$SO$_4$, HCl, HOAc or CF$_3$COOH led to much lower yields, which implied that HClO$_4$ not only acted as an initiator of sodium nitrite, but might also provide an acidic environment to prevent the agglomeration of Pd(0). We then turned our attention to the amount of NaNO$_2$ and BQ, and the results indicated that the combination of 20 mol% NaNO$_2$ and 10 mol% BQ were essential for the promising olefin transformation (Table 1, entries 16-17, 20-22). When the reaction was carried out under air or N$_2$, the oxidation transformation was not promising (Table 1, entries 18-19). Hence, the optimal reaction conditions were: 2 mol% palladium acetate, 10 mol% BQ, 20 mol% NaNO$_2$, 40 mol% HClO$_4$, MeOH/H$_2$O (v/v 8:1), oxygen, at room temperature.
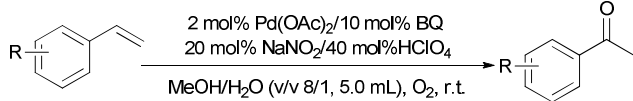
Table 1 Optimization of reaction conditions[a]

Entry	Solvent	Acid	NaNO$_2$ (mol%)	BQ (mol%)	Yield[b] (%)
1	CH$_3$CN/H$_2$O	HClO$_4$	20	10	27
2	**MeOH/H$_2$O**	**HClO$_4$**	**20**	**10**	**91**
3	DMSO/H$_2$O	HClO$_4$	20	10	23
4	DMF/H$_2$O	HClO$_4$	20	10	trace
5	AcOEt/H$_2$O	HClO$_4$	20	10	44
6	EtOH/H$_2$O	HClO$_4$	20	10	61
7	CH$_2$Cl$_2$/H$_2$O	HClO$_4$	20	10	NR
8	CHCl$_3$/H$_2$O	HClO$_4$	20	10	trace
9	AcOH/H$_2$O	HClO$_4$	20	10	NR
10	Dioxane/H$_2$O	HClO$_4$	20	10	NR
11	MeOH/H$_2$O	H$_2$SO$_4$	20	10	47
12	MeOH/H$_2$O	HCl	20	10	trace
13	MeOH/H$_2$O	HOAc	20	10	NR
14	MeOH/H$_2$O	CF$_3$COOH	20	10	43
15	MeOH/H$_2$O	HNO$_3$	-	10	trace
16	MeOH/H$_2$O	HClO$_4$	20	5	73
17	MeOH/H$_2$O	HClO$_4$	20	-	trace[c]
18	MeOH/H$_2$O	HClO$_4$	20	10	37[d]
19	MeOH/H$_2$O	HClO$_4$	20	10	trace[e]
20	MeOH/H$_2$O	HClO$_4$	30	10	91
21	MeOH/H$_2$O	HClO$_4$	10	10	43
22	MeOH/H$_2$O	HClO$_4$	-	10	trace

[a]Reaction conditions: styrene (1.0 mmol), Pd(OAc)$_2$ (2 mol%), BQ, NaNO$_2$, acid (40 mol%), solvent/water (v/v 8/1, 5.0 mL), r.t., 5 h. [b]Isolated yields. [c]24 h. [d]air condition. [e]N$_2$ atmosphere.
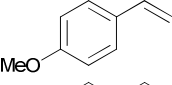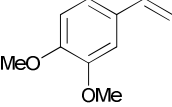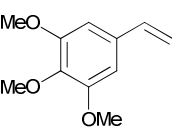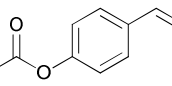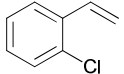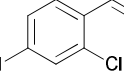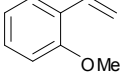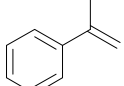
Having developed the new procedure for the palladium-catalyzed Wacker oxidative reaction, we further investigated the substrate scope of this methodology and the results were

summarized in Table 2. We were glad to see that almost all the terminal styrenes tested could smoothly transform to the desired products with excellent yields and selectivities, which was competent to other relative researches.[3g, 8a, 8b, 9] From the table, we could see that various kinds of styrenes, containing electron-donating or electron-withdrawing groups on the phenyl rings (Table 2, entries 2-16), underwent the oxidative transformation smoothly by providing good to excellent yields of methyl aryl ketones. Meanwhile, no aldehyde products were detected during the reaction and the selectivities were >99%. Moreover, substrates with substituents at *ortho*-position could also easily transform into the corresponding products, which implied that steric interactions did not significantly affect the reactivity (Table 2, entries 14-16). Notably, this method was exclusive for the formation of methyl ketones. When α-methylstyrene was tested under the optimal conditions, no product was observed (Table 2, entry 17).

Table 2 Scope of substrate for the aerobic oxidative Wacker reactions[a]

Entry	Reactant	Time (h)	Yield[b] (%)	Selec. (%)
1		5	91	>99
2		5	92[c]	>99
3		5	83	>99
4		5	85	>99
5		5	82	>99
6		5	83	>99
7		5	82	>99
8		5	85	>99
9		5	82	>99

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Entry	Substrate	Time	Yield	Sel.
10	MeO–C₆H₄–CH=CH₂	5	92	>99
11	(MeO)(OMe)C₆H₃–CH=CH₂	24	95	>99
12	(MeO)₂(OMe)C₆H₂–CH=CH₂	24	96	>99
13	AcO–C₆H₄–CH=CH₂	5	95	>99
14	2-Cl-C₆H₄–CH=CH₂	5	84	>99
15	2,4-Cl₂-C₆H₃–CH=CH₂	24	94	>99
16	2-OMe-C₆H₄–CH=CH₂	5	87	>99
17	Ph–C(=CH₂)–	24	NR	-

[a]Reaction conditions: olefins (1.0 mmol), Pd(OAc)₂ (2 mol%), BQ (10 mol%), NaNO₂ (20 mol%), HClO₄ (40 mol%), MeOH/H₂O (v/v 8/1, 5.0 mL), r.t. [b]Isolated yields. [c]Pd(OAc)₂ 5 mol%.

Since the methyl ketone compounds are of great importance in drug synthesis,[4a, 10] we further studied the gram-scale application of this methodology and styrene was taken as a representative substrate. When the amount of the substrate was increased from 1.0 mmol to 50.0 mmol, to our delight, the desired products were isolated in 91%~92% yields (Table 3). The promising results suggested that this aerobic Wacker oxidation system could provide a valuable and convenient protocol for the practical application.

Table 3 Gram-scale test for oxidation of styrene[a]

| Entry	Substrate (mmol)	Time (h)	Yield[b] (%)
1	1.0	5	91
2	10.0	8	91
3	50.0	24	92

[a]Reaction conditions: styrene, Pd(OAc)₂ (2 mol%), BQ (10 mol%), NaNO₂ (20 mol%), HClO₄ (40 mol%), MeOH/water (v/v 8/1) at room temperature. [b]Isolated yields.

Taking into consideration the possible role of NaNO₂ and BQ in the whole catalytic redox cycle and consulting other literatures,[11] we proposed a plausible mechanism for the newly developed oxidative Wacker oxidation system. As illustrated in Scheme 1, the Pd(II) species could promote the formation of

methyl phenyl ketone from the styrene in the presence of water, and its reductive species Pd(0) can be reoxidized by BQ. HNO₂ could be generated from NaNO₂ and HClO₄, which would soon release NO and NO₂. The NO was easily oxidized by atmospheric oxygen to highly active NO₂. And NO₂ acted as the efficient electron transfer agent to oxidize the reductive species of BQ, and thus complete the whole catalytic redox cycle.

In summary, we have demonstrated a green and efficient catalytic redox system using molecular oxygen as the oxidant for the aerobic oxidative Wacker oxidation. The newly developed system exhibited excellent activity for the smooth transformation of terminal styrene derivatives to the desired methyl ketones with high yields and selectivities, which may render a practical protocol for lab and industrial applications.
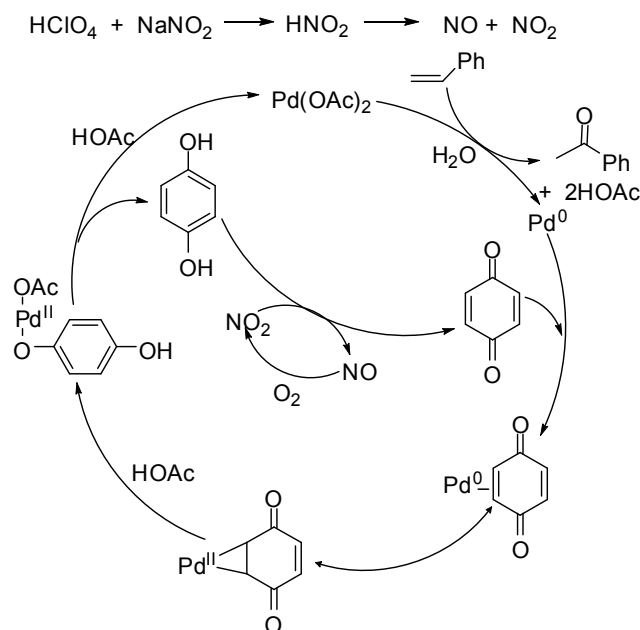
Scheme 1 Plausible mechanism for aerobic oxidative Wacker reactions of terminal styrenes.

Notes and references

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