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Letter

Regioselective Wacker-Type Oxidation of Internal Olefins in ^tBuOH Using Oxygen as the Sole Oxidant and ^tBuONO as the Organic Redox Cocatalyst

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The industrial oxidation process for converting ethylene to acetaldehyde by means of palladium catalyst is known as the Wacker process.¹ It proceeds under aerobic conditions, and copper salts are usually used as transition metal redox cocatalysts. A wide variety of terminal olefins could be selectively oxidized to the corresponding methyl ketones using Wacker-type oxidation following the Markovnikov rule.² However, Wacker-type aerobic oxidation of internal olefins has been less studied, because it normally proceeds with low activity or with low regioselectivity. Besides, the involvement of a toxic transition metal reagent or hash condition is required.³ For example, Tsuji,^{4a} Keinan,^{4b} et al. have reported the catalytic Wacker-type oxidation of substituted allylic ethers and ester but with relatively low yields (Scheme 1a). Feringa and

Scheme 1. Wacker Oxidation of Internal Olefins Using Oxygen as Terminal Oxidant

a) reported methods



co-workers have developed an aldehyde-selective Wacker– Tsuji oxidation of terminal olefins, in which one example of allylic internal olefin oxidation was included.^{4c} Sigman and coworkers have developed a catalytic system for the Wacker oxidation, in which *tert*-butylhydroperoxide (TBHP) was used as an alternative for the copper salts,⁵ in which two examples using *trans-β*-methylstyrene or *trans*-stilbene were investigated. In both cases, a low yield as a result of oxidative cleavage of the internal olefins and low regioselectivity were observed. Kaneda and co-workers reported a copper-free Wacker-type oxidation of internal olefins using PdCl₂ in the presence of *N,N*dimethylacetamide and high oxygen pressures (3–8 atm).⁶ Grubbs and co-workers reported an oxidation of internal olefins using Pd(OAc)₂ in a mixture of DMA, MeCN, and H₂O, and dilute acid is also necessary in this reaction system.⁷

Considering the facts that the simple internal olefins are easily available from the petrochemical industry and that substituted ketones are the important organic intermediate, the development of a simple, selective, and practical Wacker-type aerobic oxidation of internal alkenes without hazardous cocatalysts or harsh conditions is therefore highly desirable.

We have developed an aldehyde-selective aerobic Wacker– Tsuji oxidation using oxygen as the sole oxidant using *tert*butyl nitrite as a simple organic redox cocatalyst.⁸ No hazardous cocatalysts or harsh conditions are required. We found the solvent is crucial to the regioselectivity. Switching the solvent could realize the regioselectivity (ketone/aldehyde selectivity) control.⁹ During our further investigations, we

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Table 1. Wacker Oxidation of Internal Olefins Using Oxygen as the Terminal Oxidant^a

		D ²	Pd(PhCN) ₂ Cl ₂ (7.5 mol %) ^t BuONO (20 mol %)	2 O			
	F	(1 ~~ K	O_2 (1 atm), ^t BuOH, rt O	R ¹	R^2		
		1	2	3			
entry		1		2	time (h)	yield (%) ^b	2/3°
1	Ph ⁻⁰	1a	Ph ^O	2a	24	97 (91 ^d)	>20:1
2	C C C C C C C C C C C C C C C C C C C	1b		2b	24	83	>20:1
3		1c	o o o	2c	72	83	>20:1
4	H ₃ C	` 1d	H ₃ C	2d	24	53	11:1
5	Ph O	1e	Ph 0	2e	36	79 (70 ^f)	6:1
6	Ph	1f	Ph ⁻⁰	2f	36	81	>20:1
7	BzO	1g	Et O BzO	2g	24	79	5:1
8	MeO	Ph 1h	MeO Ph	2h	48	63 ^e	10:1
9	CI	'h 1i	CI CI	2i	48	84 ^e	10:1
10	Ph O Ph	1j	Ph O Ph	2j	48	75 ^e	15:1
11	O O Ph	1k	O O Ph	2k	36	68	10:1
12	O O O Ph	11		21	48	83	>20:1

^{*a*}Standard conditions: 1 (0.5 mmol), Pd(PhCN)₂Cl₂ (0.0375 mmol, 7.5 mol %), ^{*b*}BuONO (0.1 mmol, 20 mol %), oxygen (1 atm), and ^{*b*}BuOH (2 mL), rt. ^{*b*}Isolated yield. ^{*c*}Ratio of 2/3 is determined by ¹H NMR analysis of crude products. ^{*d*}Reaction was performed in 1 mmol scale. ^{*e*}Isolated yield for a mixture of 2 and 3; for details, see experimental details in Supporting Information. ^{*f*}MeOH was used instead of ^{*b*}BuOH.

found that using the same reaction conditions, the internal olefins could be oxidized with good yields and high regioselectivity without hazardous cocatalysts or harsh reaction conditions (Scheme 1b). Herein we present our recent results in detail.

The optimal reaction conditions were established to evaluate the scope of internal olefins bearing a variety of functional groups by using 7.5 mol % of Pd(PhCN)₂Cl₂, 20 mol % ^tBuONO, and 1 atm of oxygen in the presence of 2 mL of ^tBuOH after screening the reaction conditions (Table 1). Both alkyl and aryl substituted internal olefins 1a–11 could be converted to the corresponding substituted ketones 2a–21 with good yield and high regioselectivity. Aliphatic (*E*)-allylic ethers **1a** and bulky alkyl-substituted (*E*)-allylic ethers **1b** could undergo regioselective Wacker-Tusji oxidation smoothly providing the corresponding ketones **2a-2b** in excellent yields with a regioselectivity of more than 20:1 (entries 1-2). Aliphatic (*E*)-allylic amides **1c-d** could also be converted to the corresponding methyl ketones **2c-d** efficiently with the regioselectivity of more than 10:1 (entries 3-4). When aliphatic (*E*)-homoallylic ester **1e** was subjected to the standard reaction conditions, substituted methyl ketone **2e** was obtained in 79% yield with a regioselectivity of 6:1. Using MeOH instead of 'BuOH did not improve the

regioselectivity and gave a lower yield (entry 5). On the other hand, (Z)-allylic ethers 1f and (Z)-homoallylic ester 1g could also be oxidized using the standard conditions to give the corresponding ketone 2f and 2g in 81% and 79% yields with >20:1 and 5:1 regioselectivities, respectively (entries 6-7). Aromatic (E)-allylic esters with an electron-donating group on the benzoyl group 1h displays a relatively low yield (entry 8), while aromatic (E)-allylic esters with an electron-withdrawing group on the benzoyl group 1i and cinnamyl benzoate 1j reacted smoothly under the standard reaction conditions affording 2i and 2j in 84% and 75% yield, respectively (entries 9-10). Cinnamyl acetate 1k was also subject to the standard conditions, and the corresponding oxidation product 2k could be obtained in 68% yield with 10:1 regioselectivity (entry 11). Aromatic (E)-allylic carbonate 11 was also tolerant of the standard reaction conditions generating 21 in 83% yield with >20:1 regioselectivity (entry 12).

Oxidation of internal olefins without weak coordinating groups has also been investigated, and the results are summarized in Table 2. Cyclohexene 1m and cyclopentene 1n afforded the oxygenation products 2m-n in moderate yields (entries 1-2). Oxidation of linear internal olefins required increased amounts of catalyst loading and prolonged reaction times affording good yields albeit with relatively low regioselectivities. Oxidation of trans-2-octene 10 provided 2octanone (20), 3-octanone (2p), and 4-octanone (2q) in 54%, 28%, and 12% yield, respectively (entry 3). Oxidation of trans-3-octene 1p afforded a mixture of 20, 2p, and 2q in 88% yield with a ratio of nearly 1:1:1 (entry 4). trans- (1q) and cis- (1r) 4-Octene were also subjected to the above-mentioned oxidation conditions, and both produced a mixture of 20, 2p, and 2q in good yields (entries 5-6). Oxidation of 1methylcyclohex-1-ene (1s) was also investigated affording the corresponding oxidation product 2r in 16% yield (entry 7).

To demonstrate the synthetic utility of this aerobic oxidation of internal olefins, cholesterol analogues (1t-1u) as well as a derivative (1v) were prepared and subjected to the standard reaction conditions for 20–24 h. The corresponding oxidation products (2s-2u) were obtained in excellent yields with >20:1 regioselectivities (Table 3). These examples indicate that this protocol could be used as a synthetically practical method for the construction of ketone moieties from internal olefins.

To explore the role of ^tBuONO, control experiments were performed using 2,4,6-tri-*tert*-butylphenol **5** as a radical scavenger. Oxidation of **1a** was inhibited affording **2a** in 4% yield together with the isolation of a **5**-NO adduct in 41% yield calculated according to ^tBuONO (Scheme 2, eq 1). Moreover, the reaction of **1a** under standard conditions for 12 h afforded **2a** in 55% yield. Using **5**-NO instead of ^tBuONO under the same conditions afforded **2a** in 63% yield (eq 2). These results indicate ^tBuONO plays the role of redox cocatalyst that releases nitric oxide (NO), a stable neutral radical that is easily oxidized to NO₂ by O₂.

Oxidation of (*E*)-homoallylic ester **1e** under standard reaction conditions produced **2e** in 79% yield with a regioselectivity of **2e/3e** of 6:1. However, the regioselectivity of **2e/3e** dropped to 5:1 when 20 equiv of water were added (Scheme 3, eq 3). This demonstrates that the solvent (^tBuOH) might be involved in the regioselectivity determining step.

Oxygen in the oxidation product could come from solvent and/or oxygen. To verify the source of oxygen in the product and to gain insight into the mechanism of this oxygenation, a control experiment using $H_2^{18}O$ instead of water ($H_2^{16}O$) was





^aStandard reaction conditions: 1 (0.5 mmol), Pd(PhCN)₂Cl₂ (0.0375 mmol, 7.5 mol %), ^tBuONO (0.1 mmol, 20 mol %), oxygen (1 atm), and ^tBuOH (2 mL), rt. ^bIsolated yield. ^cReaction conditions: 1 (0.5 mmol), Pd(PhCN)₂Cl₂ (0.075 mmol, 15 mol %), ^tBuONO (0.2 mmol, 40 mol %), oxygen (1 atm), and ^tBuOH (2 mL), rt. Yield and regioselectivities of **2** were determined by GC analysis of the crude products.

Table 3. Wacker Oxidation of Internal Olefins Using Oxygen as the Terminal Oxidant a



^{*a*}Reaction conditions: 1 (0.5 mmol), Pd(PhCN)₂Cl₂ (0.0375 mmol, 7.5 mol %), ^{*b*}BuONO (0.1 mmol, 20 mol %), oxygen (1 atm), and ^{*b*}BuOH (1 mL), CH₂Cl₂ (1 mL), rt. ^{*b*}Pd(PhCN)₂Cl₂ (0.075 mmol, 15 mol %) ^{*c*}Isolated yield. ^{*d*}Ratio of 2/3 (distal oxidation/proximal oxidation) is determined by ¹H NMR analysis of crude products.





^aReaction conditions: 1e (0.5 mmol), Pd(PhCN)₂Cl₂ (0.0375 mmol, 7.5 mol %), ^fBuONO (0.1 mmol, 20 mol %), oxygen (1 atm), and ^fBuOH (2 mL), rt.

carried out under the developed conditions (eq 4). A dramatically increased amount of ¹⁸O-labeled compounds

 $[(2e+3e)^{-18}O]$ were detected by HRMS analysis of the final products. This observation is compatible with our previously proposed mechanism^{8,9} in which the oxygen in the product may come from the solvents.

A plausible mechanism for regioselective Wacker–Tsuji oxidation of internal olefins is proposed (Scheme 4). Pd(II) coordinates with internal olefin 1 forming intermediate **A**. Intermediate **A** is then attacked by the ^tBuOH from the site with less steric hindrance to generate intermediate **B**. The β elimination affords enol ether **D** as the main intermediate.

Scheme 4. Proposed Mechanism



Hydrolysis of enol ether with water promoted by HCl affords ketone **2**. The catalytically active Pd(II) species is then regenerated by the oxidation of NO₂ which is in situ generated from the oxidation of NO with molecular oxygen. ^tBuONO is the donor of NO, and NO plays the role of redox cocatalyst.

In conclusion, we have developed a regioselective Wackertype oxidation of internal olefins without the involvement of hazardous cocatalysts or harsh conditions. A catalytic amount of *tert*-butyl nitrite worked as a simple organic redox cocatalyst. A variety of ketones were prepared with generally high regioselectivity in good to high yields.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.9b04503.

Experimental procedures, full analysis data for compounds, and copies of NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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