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Catalyst-Controlled Wacker-Type Oxidation: Facile Access to Functionalized Aldehydes

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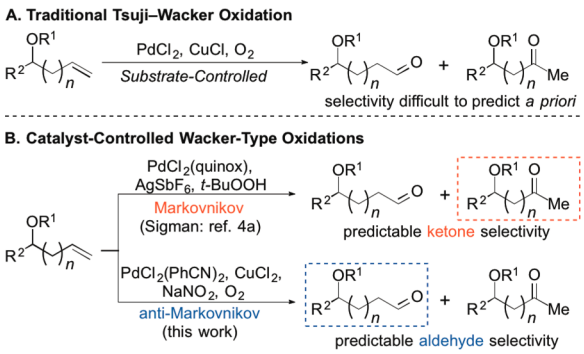
Supporting Information

ABSTRACT: The aldehyde-selective oxidation of alkenes bearing diverse oxygen groups in the allylic and homoallylic position was accomplished with a nitrite-modified Wacker oxidation. Readily available oxygenated alkenes were oxidized in up to 88% aldehyde yield and as high as 97% aldehyde selectivity. The aldehyde-selective oxidation enabled the rapid, enantioselective synthesis of an important pharmaceutical agent, atomoxetine. Finally, the influence of proximal functional groups on this anti-Markovnikov reaction was explored, providing important preliminary mechanistic insight.

The Tsuji–Wacker oxidation is a powerful synthetic tool that provides access to carbonyls from terminal alkenes. The functional group tolerance, versatility, and reliability of this transformation have led to its broad adoption within the synthetic community.[1] The regioselectivity of the Tsuji–Wacker oxidation is substrate-controlled,[2] and methyl ketone products are typically favored in accord with Markovnikov's rule.[1b,c] However, this innate regioselectivity is sensitive to both proximal coordinating groups and the steric environment around the alkene.[3] Thus, the ratio of aldehyde to ketone products formed from oxidation of functionalized substrates can be challenging to predict *a priori* (Scheme 1A).[2,3] Sigman and co-workers recently developed a Wacker-type oxidation system that delivered catalyst-controlled ketone selectivity.[2,4] This system was employed in the oxidation of functionalized alkenes to overcome their poor innate selectivity and provide methyl ketone products in high yield (Scheme 1B).[4a,b] However, while major advances have been made in addressing many other classical limitations of the Wacker process,[5,6] the development of a catalyst-controlled anti-Markovnikov Wacker oxidation has seen only preliminary success.[3,7] Work in this area has focused on aliphatic alkene model systems, and no Wacker-type oxidation has provided reliable aldehyde selectivity across a wide range of allylic and homoallylic functional groups.[3]

Scheme 1. (A) Tsuji–Wacker Conditions Provide a Substrate-Dependent Mixture of Aldehydes and Ketones; (B) Catalyst-Controlled Solutions to Markovnikov and Anti-Markovnikov Regioselectivity in Wacker-Type Oxidations



A general, anti-Markovnikov oxidation of readily accessible oxygen-containing alkenes would enable efficient access to synthetically versatile polyfunctional building blocks. Furthermore, enantioenriched allylic and homoallylic alcohol derivatives can be easily prepared via established synthetic routes.[8] Due to the synthetic versatility of the aldehyde functional group,[9] a reliable aldehyde-selective Wacker would enable diverse catalytic strategies to address the historical challenge[10] of anti-Markovnikov alkene functionalization.[11−13]

Previous efforts to prepare functionalized aldehydes via Wacker oxidations have exploited specifically tailored directing groups to obtain substrate-controlled anti-Markovnikov selectivity.[14,15] Unfortunately, this approach lacks flexibility and requires the synthetic route to be planned around the installation and removal of directing auxiliaries. Furthermore, reliance upon a narrow class of directing groups can result in inherent synthetic incompatibilities. For example, although allylic furfoyl esters provide high substrate-derived aldehyde selectivity, allylic stereocenters are racemized by a reversible palladium-catalyzed rearrangement.[14f] Moreover, functional groups in the homoallylic position are rarely effective at overcoming Markovnikov's rule.[3] Thus, a catalyst-controlled method to oxidize diverse oxygen-containing alkenes to aldehydes remains an elusive but highly desirable tool for organic synthesis.[16]

We recently developed a nitrite-modified Wacker-type catalyst system capable of reversing the innate Markovnikov selectivity exhibited by aliphatic alkenes.[7d] Thus, we set out to evaluate whether Lewis basic oxygen functional groups would interfere with or enhance the aldehyde selectivity of the reaction. In addition to its synthetic value, we anticipated that this line of inquiry would also provide key mechanistic insight into this newly developed nitrite-modified Wacker process.

A series of alkene-containing phenyl ether substrates of varying chain length were subjected to both nitrite-modified

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Wacker conditions and Tsuji–Wacker conditions to evaluate the influence of proximal oxygen-containing functional groups on the regioselectivity (Figure 1). The high anti-Markovnikov

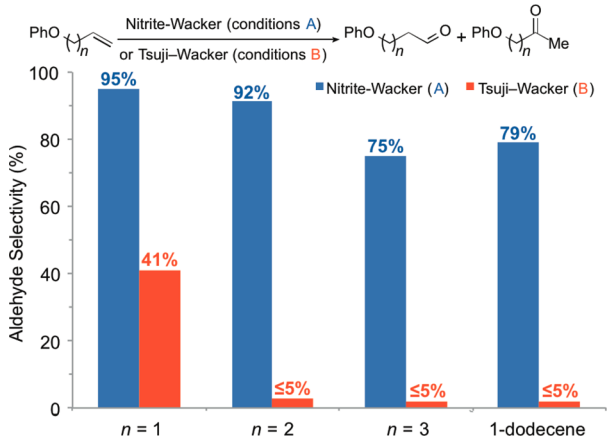
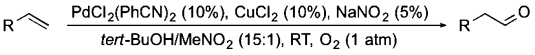


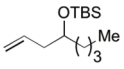
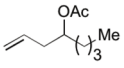
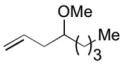
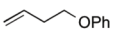
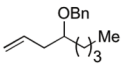
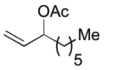
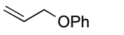
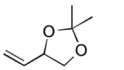
Figure 1. Influence of phenoxy group proximity on regioselectivity in Wacker-type oxidations. (Conditions A) Blue:[7d] $PdCl_2(PhCN)_2$ (12 mol %), $CuCl_2 \cdot H_2O$ (12 mol %), $AgNO_2$ (6 mol %), *t*-BuOH/$MeNO_2$ (15:1), rt, O_2 (1 atm), 6 h. (Conditions B) Red:[1b] $PdCl_2$ (10%), CuCl (1 equiv), DMF/H_2O (7:1), rt, O_2 (1 atm), 24 h.

selectivity exhibited by an unbiased substrate (1-dodecene) under nitrite-modified Wacker conditions was markedly enhanced as the ether moiety approached the alkene (Figure 1). Exceptional aldehyde selectivity (>90%) was observed with both the allylic (n = 1) and homoallylic phenyl ether (n = 2), despite the significant difference in the innate regioselectivity of the two substrates under Tsuji–Wacker conditions. Moreover, substrates bearing a distal ether functional group (n = 3) retained the high regioselectivity observed in the unfunctionalized systems. These encouraging results are consistent with a catalyst-controlled process in which the selectivity is further enhanced by proximal heteroatoms. Following this preliminary success, we sought to optimize the reaction conditions. With oxygenated alkenes, $NaNO_2$ proved to be an effective and inexpensive source of nitrite. This result stands in contrast to our previous work with aliphatic substrates, where it was found that $AgNO_2$ enhanced the rate and selectivity.[7d]

To be a general catalyst-controlled methodology to access functionalized aldehydes, the high anti-Markovnikov selectivity must not be dependent on specific directing groups. With this in mind, we examined a collection of substrates bearing different oxygen-containing functional groups in both the allylic or homoallylic position under the optimized conditions (Table 1). The oxidation of these substrates took place with high aldehyde selectivity (89–96%), allowing the aldehyde product to be isolated in prepartively useful yields (64–88%), irrespective of the nature of the oxygen-containing functional group. In particular, alkyl, aryl and silyl ethers, as well as acetyl esters, were all well tolerated. For comparison, each substrate was additionally subjected to Tsuji–Wacker conditions to determine its innate selectivity. In contrast to the high anti-Markovnikov selectivity observed across the series under nitrite-modified Wacker conditions, the innate selectivity varied greatly as a function of substrate. The excellent aldehyde selectivity provided by the nitrite-modified Wacker oxidation of homoallylic substrates is particularly notable due to their high innate Markovnikov selectivity (≥80% ketone selective). Notably, the selectivity was independent of the innate

Table 1. Influence of Oxygen Functionality on Wacker Oxidations[a]



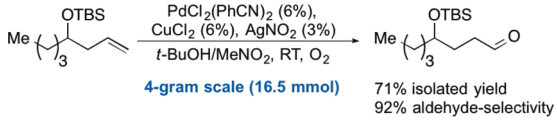
Entry	Substrate	Oxidation Yield (Aldehyde Yield)[b]	Selectivity[c]	Innate Selectivity (Tsuji-Wacker)[d]
1		76%	**90**:10	4:**96**
2		76%	**90**:10	20:**80**
3		71%[e]	**92**:8	9:**91**
4		88%	**91**:9	3:**97**
5		85%	**94**:6	7:**93**
6[f]		75%[e]	**94**:6	**64**:**46**
7		82%	**96**:4	**41**:**59**
8		64%[e]	**92**:8	**86**:14

[a]0.5 mmol of alkene (0.0625 M), 5 h. [b]Yield of isolated aldehyde product. [c]Selectivity (aldehyde/ketone) obtained by ^1H NMR analysis of the unpurified reaction mixture. [d]Reaction conditions:[1b] 0.1 mmol of alkene, $PdCl_2$ (10 mol %), CuCl (1 equiv), DMF/H_2O (7:1, 0.125M), rt (20–25 °C), run to ≥95% conversion. [e]Yield determined by ^1H NMR analysis of the unpurified reaction mixture. [f]$AgNO_2$ used in place of $NaNO_2$.

selectivity, clearly demonstrating catalyst-controlled regioselectivity.

The success of this reaction with challenging, innately ketone-selective homoallylic alcohol derivatives led to the exploration of how the steric properties of this class of substrates influences reactivity and selectivity (Table 2). Having demonstrated that such substrates perform similarly in the reaction irrespective of the substituent on oxygen, a benzyl group was selected as a representative protecting group. Variation at the α-position of the ether provided no significant effect on yield or selectivity (Table 2, entries 1 and 2). Bulkier substrates required an increased reaction time and replacement of $NaNO_2$ with the more active $AgNO_2$ to provide an analogous yield and selectivity (entries 4–9).

In order to assess the applicability of the process on a larger scale, the reaction was attempted on a 4-g scale with a reduced catalyst loading (eq 1). The reaction was 92% aldehyde



(1)

selective, delivering 71% of the aldehyde product. This result suggests that the reaction will be readily amenable to producing significant quantities of the desired aldehyde products.

A catalyst-controlled anti-Markovnikov Wacker oxidation combined with established enantioselective methodologies enables a powerful strategy to access versatile enantioenriched building blocks. To demonstrate the utility of this synthetic approach, we targeted atomoxetine, a norepinephrine reuptake

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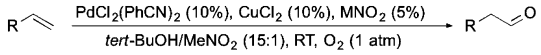
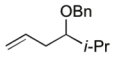
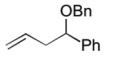
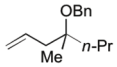
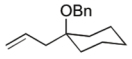
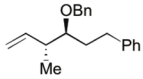
Table 2. Influence of Steric Profile on Aldehyde-Selective Wacker[a]

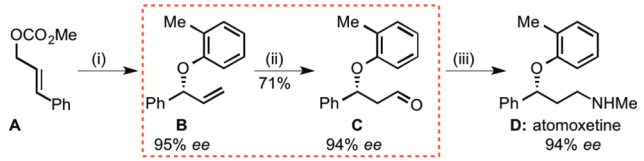


Entry	Substrate	Nitrite Source	Aldehyde Yield[b]	Selectivity[c]	Innate Selectivity (Tsuji–Wacker)[d]
1		$NaNO_2$	80%	93:7	7:93
2		$NaNO_2$	74%	94:6	20:80
3		$NaNO_2$	51%[e]	93:7	9:91
4		$AgNO_2$	77%[f]	90:10	–
5		$NaNO_2$	37%[e]	95:5	8:92
6[g]		$NaNO_2$	75%[e]	88:12	–
7[g]		$AgNO_2$	77%	95:5	–
8		$NaNO_2$	38%[e]	66:34	10:90
9[g]		$AgNO_2$	65%	75:25	–

[a]0.5 mmol of alkene (0.0625 M), 5 h. [b]Yield of isolated aldehyde product. [c]Selectivity (aldehyde/ketone) obtained by ^{1}H NMR analysis of the unpurified reaction mixture. [d]0.1 mmol of alkene, $PdCl_2$ (10 mol %), CuCl (1 equiv), DMF/H_2O (7:1, 0.125 M), rt (20–25 °C), run to ≥95% conversion (24 h). Selectivity determined by ^{1}H NMR analysis. [e]Yield determined by ^{1}H NMR analysis. [f]Isolated as an inseparable mixture of aldehyde and ketone. [g]24 h reaction time

inhibitor approved for the treatment of attention deficit disorder (Scheme 2).[17] At the outset, one potential concern

Scheme 2. Synthesis of Atomoxetine[a]



[a](i) $[Ir(COD)Cl]_2$ (1 mol %), (*R*,*R*,*R*)-(3,5-dioxa-4-phospha-cyclohepta[2,1-a;3,4-a′]dinaphthalen-4-yl)bis(1-phenylethyl)amine (2 mol %), THF, 50 °C, 16 h; (ii) $PdCl_2(PhCN)_2$ (10%), $CuCl_2{\cdot}2H_2O$ (10%), $AgNO_2$ (5%), *t*-BuOH/$MeNO_2$ (15:1), O_2 (1 atm), rt, 5 h; (iii) $NaBH_3CN$ (2 equiv), $MeNH_3Cl$ (excess), rt, 24 h.

with this approach was whether the stereocenter proximal to the alkene would racemize under the nitrite-modified reaction conditions. To test the viability of this route, cinnamyl alcohol derivative **A** was transformed into chiral allylic ether **B** via a highly enantioselective iridium-catalyzed allylic substitution reaction.[18] Upon treatment of **B** with the anti-Markovnikov Wacker conditions, the corresponding aldehyde, **C**, was produced in good yield. Subsequent derivatization via reductive amination demonstrated that the targeted drug, **D**, could be accessed without loss of enantiopurity over the course of the synthetic sequence. The success of this strategy, particularly the retention of stereochemical information at the allylic position, showcases that the nitrite-modified Wacker oxidation is compatible with well-established asymmetric methods and provides access to valuable synthetic products in a modular, catalytic manner.

To provide a foundation for further mechanstic study, we next probed the substrate-derived factors that enhance the catalyst-controlled aldehyde selectivity. To this end, the relative rates of functionalized and unfunctionalized substrates were obtained in a series of one-pot intermolecular competition experiments (Figure 2). Both functionalized substrates

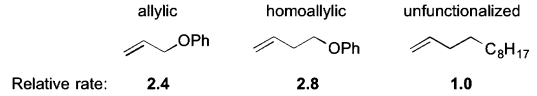


Figure 2. Relative rates of oxidation to aldehyde as a function of substrate under nitrite-modified Wacker conditions (see Table 1 for conditions).

exhibited a substantial increase in the rate of aldehyde formation relative to the unfunctionalized 1-dodecene. We suspect that coordination of the Lewis basic oxygen atom to palladium increases the rate since inductive effects would be mitigated as the oxygen atom is moved further from the alkene.

To further probe the role of the oxygen atom, allylic and homoallylic aryl ethers of varied electronic profiles were prepared and evaluated under the reaction conditions. Inductive effects have recently been demonstrated to play a major role in determining regioselectivity in palladium-catalyzed processes.[5f,19] Interestingly, under the nitrite-modified Wacker conditions, the aldehyde selectivity and rate are only subtly influenced by electronic variation (Figure 3). The

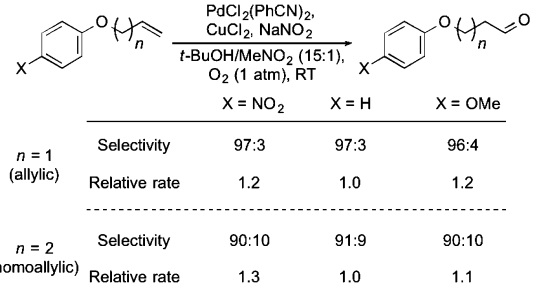


Figure 3. Selectivity and relative rates of oxidation to aldehyde as a function of the substrate's electronic properties under nitrite-modified Wacker conditions (see Table 1 for conditions; 10 min reaction time).

minimal inductive influence is consistent with an apolar, radical-type addition.[20−22] We have previously suggested a radical mechanism to explain the anti-Markovnikov selectivity in light of preliminary mechanistic experiments.[23,24] In addition to illustrating the minimal inductive influence on alkene oxidation, these experiments suggest that electronic modulation does little to enhance or mitigate the coordinating influence of the Lewis basic oxygen functional groups.

In summary, this anti-Markovnikov, nitrite-modified Wacker oxidation provides a facile route for the preparation of functionalized aldehydes from a wide variety of oxygenated alkenes. The reliability and versatility of the methodology bodes well for its immediate application in target-oriented synthesis. The potential of the transformation was illustrated in the rapid, enantioselective synthesis of atomoxetine. Finally, key substrate-derived influences on the regioselectivity were explored, which provided important mechanistic information regarding the interplay between catalyst and substrate control, which will guide ongoing mechanistic evaluation of this important process.

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■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and analytical data. 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.

■ ACKNOWLEDGMENTS

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