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## Regiocontrolled Wacker Oxidation of Cinnamyl Azides

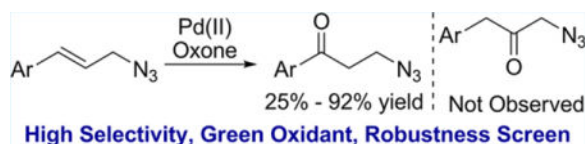
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### Abstract

A highly regioselective Wacker oxidation has been developed for the oxidation of cinnamyl azides. The catalytic oxidation tolerates the azide functionality, and more than 15  $\beta$ -azido ketones were isolated (25–92% yield). High regioselectivity for the aryl ketone is observed in all cases. A robustness screen was conducted to determine functional group tolerance. The products of the oxidation can be readily diversified.

### Graphical abstract



Azides are an attractive functional group due to their versatile reactivity, which provides a distinct handle for further functionalization.<sup>1</sup> Our laboratory has been interested in exploiting the unique rearrangement of allylic azides.<sup>2,3</sup> We are therefore interested in identifying catalyzed protocols that are compatible with an allylic azide. It would be exciting to demonstrate the compatibility of allylic azides with ubiquitous palladium catalysis. The Wacker oxidation, as a classic palladium-catalyzed alkene functionalization, seemed a logical choice for exploration. No Wacker oxidations of allylic azides have been reported. It was not initially clear that an allylic azide would be compatible with oxidative conditions.<sup>4,5</sup> The azide could react with the metal center directly and inhibit the reaction or poison the catalyst. Allylic azides are known to rearrange, which could further complicate the Wacker oxidation.<sup>2,6,7</sup> However, such a reaction could provide efficient catalytic access to  $\beta$ -azido-ketones.

The  $\beta$ -azido-ketone motif has been used as a heterocycle precursor, an intermediate for total syntheses, and a pharmaceutical building block (Scheme 1).<sup>8–13</sup> Additionally, the  $\beta$ -azido-

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#### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b00344. Experimental procedures and characterization data (PDF)

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#### Notes

The authors declare no competing financial interest.

ketone has been used as a triplet nitrene source.<sup>14–16</sup> Typically, this motif is synthesized by conjugate addition of an azide anion or by displacement of sensitive  $\beta$ -halo-ketones.<sup>12,17,18</sup>

The Wacker oxidation has been widely utilized both industrially and academically.<sup>19</sup> Terminal alkenes are excellent substrates, and classically, the ketone product is obtained. However, chemists have struggled to deliver Wacker oxidation methods that provide high selectivity for the oxidation of internal alkenes. This is best illustrated by examining the oxidation of  $\beta$ -methylstyrene (Scheme 2i). While styrene oxidation affords acetophenone with near perfect selectivity,<sup>20–22</sup> the oxidation of  $\beta$ -methylstyrene is only modestly selective for phenylacetone.<sup>23,24</sup> Recent progress has enabled the regioselective oxidation of some internal alkenes. Most notable are contributions from the laboratories of Grubbs and Sigman (Scheme 2ii).<sup>24–28</sup> We hypothesized that an allylic azide could serve as the proximal functionality in a regioselective oxidation. This work describes the Wacker oxidation of cinnamyl azides using oxone as the stoichiometric oxidant. The aryl ketone is obtained in high regioselectivity in all cases (Scheme 2iii).

In these studies, we used a number of precautions when working with azides. Azides are known to be potentially explosive. No incidents were encountered in this work. Safety shields were used for all reactions and operations, including rotary evaporation.<sup>29</sup> No azides were synthesized that contain fewer than nine carbons, which is a common rule of thumb used for determining the stability of an azide.<sup>1,30</sup> If working with more than 1 g of azide, we recommend that a more detailed safety analysis, such as TGA and DSC, be conducted prior to scale-up.

Initial efforts focused on identifying a highly reactive catalyst (Table 1). We were inspired by the observations of Grubbs that “ligand free” cationic palladium complexes could achieve the desired oxidation.<sup>26</sup> Preliminarily, Pd(PhCN)<sub>2</sub>Cl<sub>2</sub> was used as a convenient precatalyst, and a variety of silver salts were added (entries 1–5). Chloride ions exhibit strong coordination, and no Wacker oxidation was observed with the precatalyst alone (entry 1). Oxidation of the azide to the corresponding cinnamaldehyde was observed as a background reaction.<sup>4,5</sup> However, in the presence of silver(I) salts, the desired Wacker oxidation was observed (entries 2–5). Presumably, halogen abstraction generates a more reactive cationic palladium ion *in situ*. The conversion and yield increased with all of the examined noncoordinating counterions. This suggests the formation of solvated Pd<sup>2+</sup>(MeCN)<sub>4</sub> and a presumed leveling effect under the aqueous conditions. The addition of catalytic quantities of benzoquinone was advantageous (entry 5 vs 6). When benzoquinone was used as the stoichiometric oxidant, the yield was diminished (entry 7). Furthermore, control experiments revealed that silver is not necessary (entry 8) and that the nitrate ion is beneficial (entry 8 vs 9). Lastly, the procedure could be further optimized by reducing the amount of water used as a cosolvent and by adding the oxone portionwise to slow the background oxidation (entry 10 vs 11). The final procedure was conducted on the benchtop and uses readily available materials.

To determine the functional group tolerance of this Wacker oxidation, the robustness screen advocated by Glorius was performed (Scheme 3).<sup>31,32</sup> The additive approach provided the ability to rapidly assess the impact of functional groups on the reaction beyond those

represented below (Scheme 4), without the need to synthesize numerous substrates. The full test set, plus a few additional additives, is shown in Scheme 3. Several of the functional groups were well tolerated, including a free alcohol (3a), nitrile (3b), ketone (3c), heterocycle (3d), alkyl halide (3e), and aryl halide (3f). Readily oxidized functional groups, such as aniline (3g), furan (3h), pyrrole (3i), and benzaldehyde (3j), were degraded. Acetal 3l hydrolyzed to benzaldehyde. Terminal alkenes (3m) underwent Wacker oxidation faster than the cinnamyl azide, and alkynes inhibited the reaction (3n and 3o). Additionally, as would be expected for an electrophilic metal center, good ligands inhibited the catalysts (3p–q). In some cases, these limitations could be overcome. For instance, 2,6-lutidine (3r) was not as strong of an inhibitor, and acetanilide (3s) was tolerated even though aniline was not.

A variety of substrates were examined (Scheme 4). The cinnamyl azides are directly available from commercial benzaldehydes.<sup>33</sup> Cinnamyl azide was oxidized in comparable yield to the model substrate (2b). Other electronically neutral or methylated aryl rings provided acceptable yields (2c–f). Double *ortho*-substitution was tolerated, and ketone 2g was isolated in moderate yield. More electron-rich aryl rings were the preferred substrates (2h–n). Even though benzyl acetal 3l was hydrolyzed, the BOM acetal present in 2n was compatible with the reaction. Halogenated arenes showed variable compatibility with the Wacker oxidation (2o–r). A more electron deficient aryl ring provided a diminished yield (2s). We did not observe the  $\alpha$ -azido ketone isomer in any of these reactions.

Conducting a Wacker oxidation on aliphatic azides was complicated by the Winstein rearrangement of allylic azides (Scheme 5).<sup>2,6,7</sup> The equilibrium mixture of azides 4 and 5 was subjected to the reaction conditions. This reaction afforded an acceptable yield of ketone 6, which was contaminated with small quantities of the regioisomer 7. Azide 5 provided aldehyde 8. Aldehyde 8 is not stable under the reaction conditions, and a number of over oxidized products were observed.

This procedure was easily conducted on a gram scale (Scheme 6). The  $\beta$ -azido-ketone was readily diversifiable. The ketone could be selectively reduced to provide alcohol 9. Allylation of the ketone was successful without azide elimination and afforded alcohol 10. A click reaction afforded triazole 11.

In conclusion, we developed a Wacker oxidation for cinnamyl azides that provides the aryl ketone in excellent selectivity. This procedure demonstrates the compatibility of allylic azides with palladium catalysis. The procedure is conducted under air and uses Oxone as the stoichiometric oxidant. A robustness screen was conducted, which defines the limitations of this method. Many substrates provide a high yield of the ketone product, and this procedure can be conducted on a gram scale.

## Supplementary Material

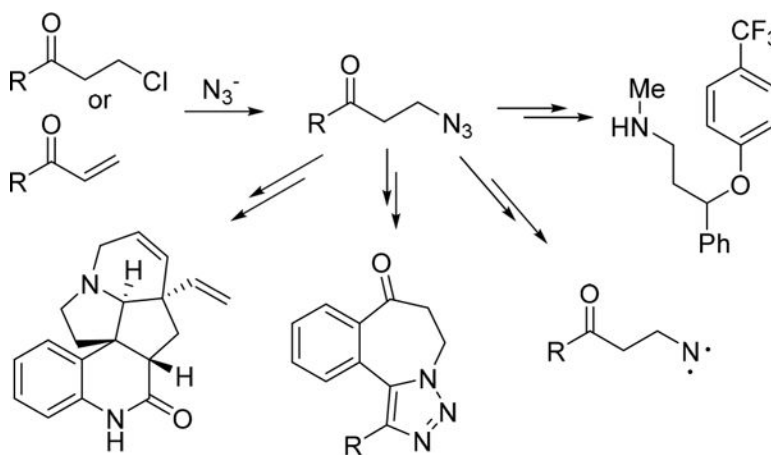
Refer to Web version on PubMed Central for supplementary material.

## Acknowledgments

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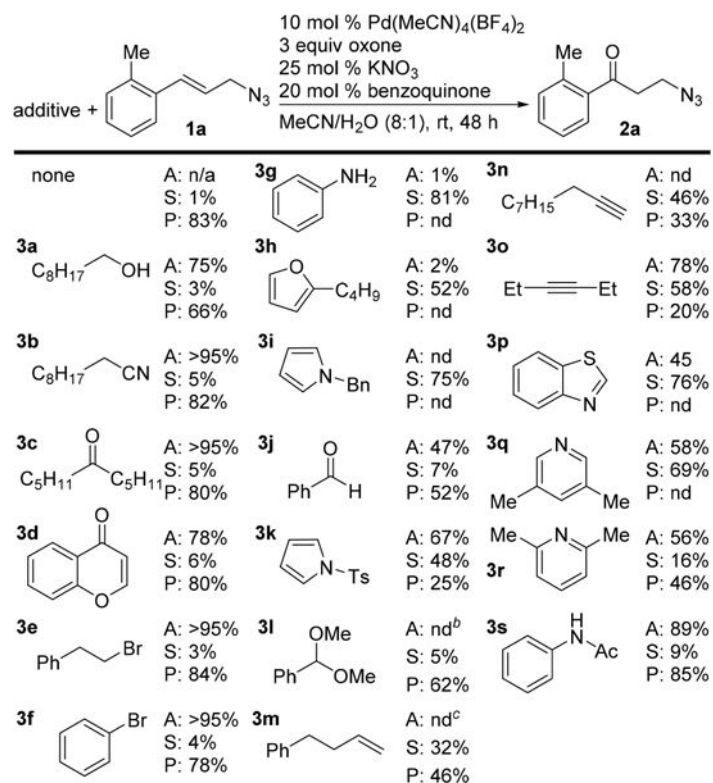
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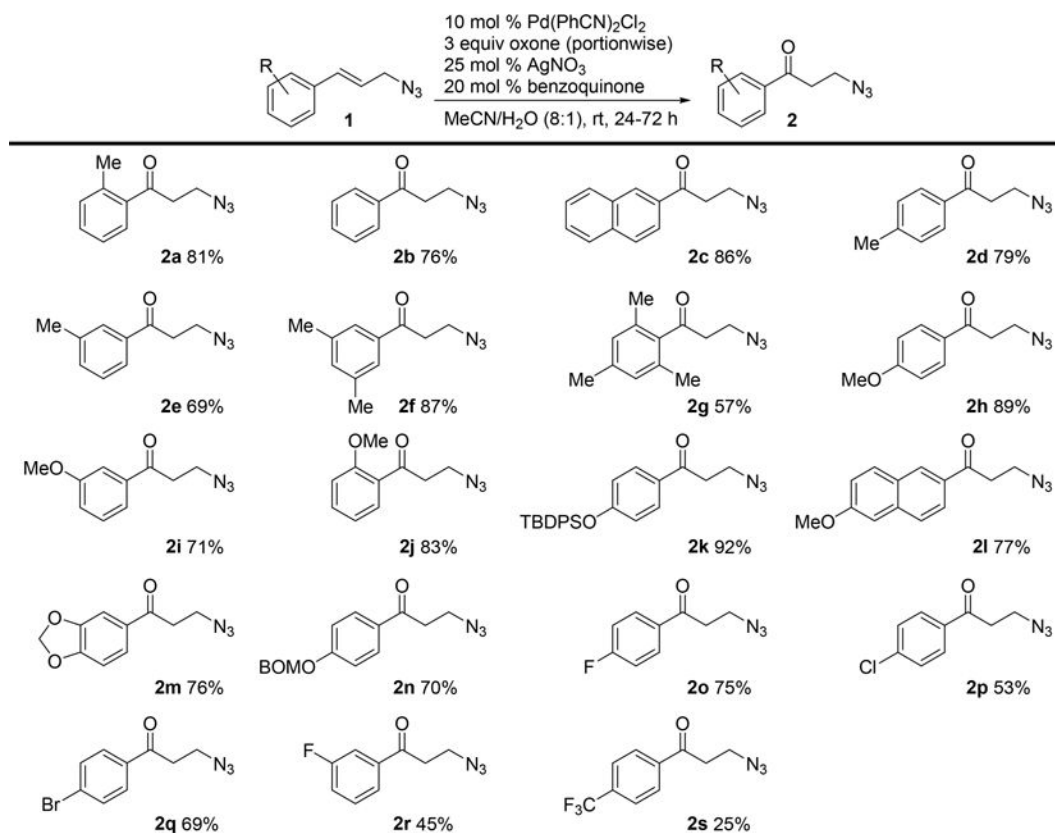


**Scheme 1.**  
 $\beta$ -Azido-Ketone Syntheses and Applications



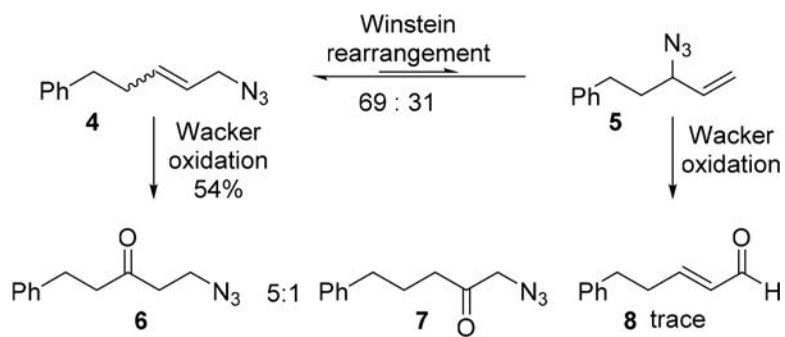
**Scheme 3.**Robustness Screen<sup>a</sup>

<sup>a</sup>A = additive % remaining; S = starting material % remaining; P = product % formed. Reported values determined by GC-FID analysis. A and S were determined based on a single point calibration. P was calibrated by linear regression. Values reported are the average of duplicate trials. <sup>b</sup>Benzaldehyde was observed as the major product. <sup>c</sup>4-Phenyl-2-butanone was observed as the major product.

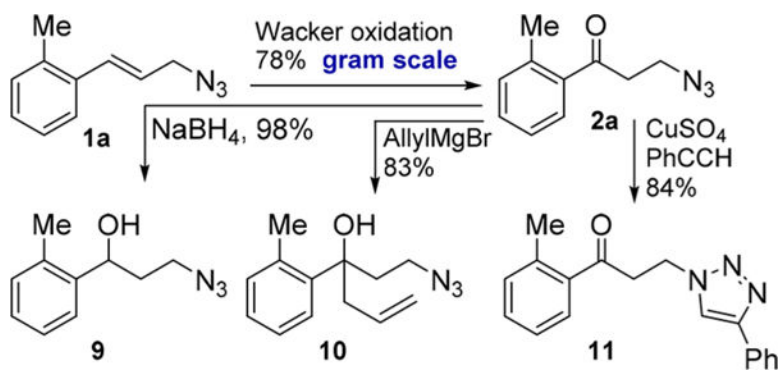
**Scheme 4.**Substrate Scope of Azide-Directed Wacker Oxidation<sup>a</sup>

<sup>a</sup>Yields are of isolated and purified material. Values reported are the average of duplicate trials.



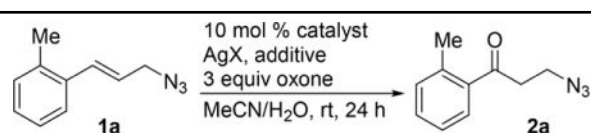


**Scheme 5.**  
Wacker Oxidation on Equilibrating Azide



**Scheme 6.**  
Gram-Scale Reaction and Diversification of Products

Table 1

Optimization of the Wacker Oxidation<sup>a</sup>

entry	[Pd]	AgX	additive(s)	yield <sup>b</sup> (%)
1	Pd(PhCN) <sub>2</sub> Cl <sub>2</sub>			0
2	Pd(PhCN) <sub>2</sub> Cl <sub>2</sub>	AgOTf		33
3	Pd(PhCN) <sub>2</sub> Cl <sub>2</sub>	AgSbF <sub>6</sub>		39
4	Pd(PhCN) <sub>2</sub> Cl <sub>2</sub>	AgBF <sub>4</sub>		18
5	Pd(PhCN) <sub>2</sub> Cl <sub>2</sub>	AgNO <sub>3</sub>		40
6	Pd(PhCN) <sub>2</sub> Cl <sub>2</sub>	AgNO <sub>3</sub>	BQ	73
7 <sup>c</sup>	Pd(MeCN) <sub>4</sub> (BF <sub>4</sub> ) <sub>2</sub>		BQ, KNO <sub>3</sub>	51
8	Pd(MeCN) <sub>4</sub> (BF <sub>4</sub> ) <sub>2</sub>		BQ	59
9	Pd(MeCN) <sub>4</sub> (BF <sub>4</sub> ) <sub>2</sub>		BQ, KNO <sub>3</sub>	71
10 <sup>d</sup>	Pd(PhCN) <sub>2</sub> Cl <sub>2</sub>	AgNO <sub>3</sub>	BQ	67
11 <sup>e</sup>	Pd(PhCN) <sub>2</sub> Cl <sub>2</sub>	AgNO <sub>3</sub>	BQ	80

<sup>a</sup>Reaction conditions: substrate (60 μmol), naphthalene standard (12 μmol), [Pd] (6 μmol, 10 mol %), AgX (15 μmol, 25 mol %), benzoquinone (12 μmol, 20 mol %), Oxone (180 μmol, 3 equiv), water (50 μL), MeCN (400 μL), under air, room temperature.

<sup>b</sup>Conversion and yield were determined by calibrated GC–FID analysis. Reactions were run in duplicate, and the average value is reported.

<sup>c</sup>Reaction was conducted with 1.2 equiv of benzoquinone and no Oxone.

<sup>d</sup>Reaction was run using double the volume of water (100 μL).

<sup>e</sup>Oxone was added portionwise.