

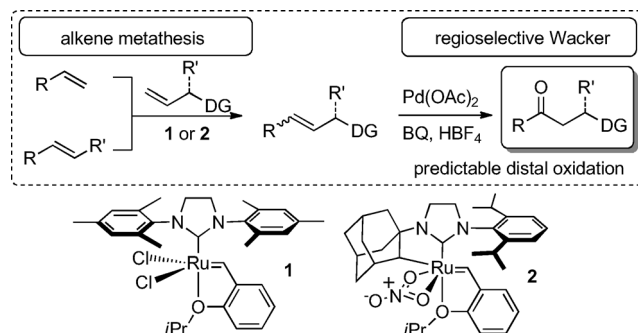
Regioselective Wacker Oxidation of Internal Alkenes: Rapid Access to Functionalized Ketones Facilitated by Cross-Metathesis**

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Dedicated to Professor Erick M. Carreira on the occasion of his 50th birthday

Functionalized ketones are key synthetic intermediates in target-oriented synthesis.^[1] Important carbon–carbon bond-forming processes such as the aldol or Mannich reactions have enabled the preparation of hydroxyketones and aminoketones.^[2] These products are highly sought-after intermediates in the preparation of natural products and drugs, and thus represent key synthetic targets. Novel complementary approaches to their synthesis are therefore in high demand. Although alkene metathesis is a privileged carbon–carbon forming reaction,^[3] it has found only limited use in the preparation of ketones.^[4] This limitation is due to the lack of an efficient methodology to catalyze the oxidation of internal alkenes to carbonyls with regiocontrol. The ubiquitously adopted palladium-catalyzed Tsuji–Wacker reaction would be a logical tool to achieve this transformation.^[5] However, although recent advances in the field have been achieved,^[6,7] the Wacker oxidation still exhibits limited reactivity towards internal alkenes and suffers from poor understanding of the factors determining the regioselectivity. If those challenges could be overcome, the synthetic power of the Tsuji–Wacker oxidation of terminal alkenes could be translated to internal alkenes. Such a desirable catalytic oxidation would enable rapid access to functionalized ketones when coupled to the carbon–carbon forming power of cross-metathesis (CM).

Herein, we report an efficient and regioselective preparation of functionalized ketones by an olefin cross-metathesis/regioselective Wacker oxidation sequence (Scheme 1). A key aspect of this work was the identification of a wide range of directing groups for enabling a regioselective Wacker oxidation of unsymmetrically substituted alkenes, specifically, an oxidation which occurs predictably at the distal position. Importantly, rapid access to the starting materials using *E*- and *Z*-selective cross-metathesis was demonstrated. This combined approach affords a powerful new tool for the synthesis of versatile functionalized ketones and should find applications in target-oriented synthesis.



Scheme 1. Sequential cross-metathesis/regioselective Wacker oxidation for the preparation of functionalized ketones. BQ = benzoquinone.

At the outset of our investigations, we reasoned that the allylic heteroatom placed in close proximity to the alkene could provide an efficient handle to induce the desired regioselectivity.^[8] Previous examples of directed Wacker oxidations of internal alkenes have been limited by low yields, use of peroxide as oxidants, and high oxygen pressure, and were limited in scope.^[6,8] In addition, only recently have efficient catalyst systems for the Wacker oxidation of internal alkenes been developed.^[6] In the classical Tsuji–Wacker oxidation of terminal alkenes, phthalimide and ester directing groups have been shown to direct an anti-Markovnikov attack to form aldehydes from terminal alkenes.^[9] Strikingly, a recent report from Feringa and co-workers demonstrated the inability of neutral palladium(II) complexes to oxidize internal alkenes.^[9b] Instead, internal allylic esters rearranged to the corresponding terminal alkenes prior to oxidation. This inherent limited reactivity of neutral palladium(II) complexes towards internal alkenes prompted us to study our previously reported, highly active dicationic palladium(II) system^[6a] to develop an efficient, regioselective Wacker oxidation of unsymmetrical alkenes.

Initial preliminary experiments using an optimized solvent system (DMA/MeCN/H₂O) led to long reaction times with incomplete conversion. Use of a binary solvent system (MeCN/H₂O) and acid^[10] led to a much more active system and full conversion was obtained. In contrast to the oxidation of unfunctionalized alkenes, DMA is not necessary to prevent isomerization in the presence of coordinating groups.^[6a] Having an efficient protocol in hand, we tested a selection of simple monofunctionalized alkene substrates to efficiently probe the influence of diverse groups on the regioselectivity (Table 1). Allylic alcohol derivatives demonstrated that good regioselectivity could be obtained using common protecting

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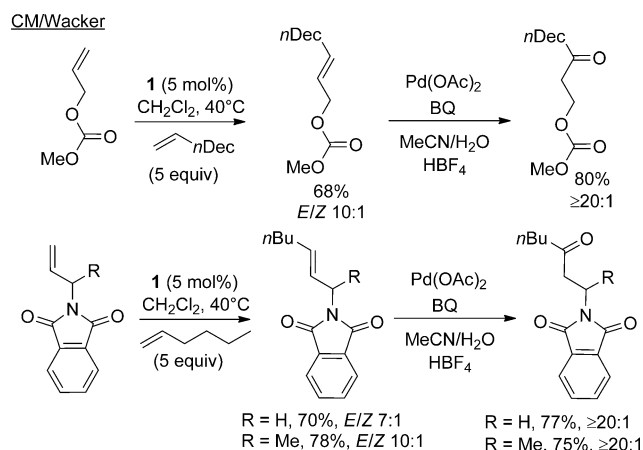
Table 1: Initial scope of directing groups.^[a]

$\text{R}-\text{CH}=\text{CH}-\text{DG} \xrightarrow[\text{MeCN/H}_2\text{O, RT}]{\text{Pd(OAc)}_2 \text{ (5 mol\%)}, \text{BQ (1 equiv)}, \text{HBF}_4 \text{ (0.27 M)}} \text{R}-\text{CH}_2-\text{C}(=\text{O})-\text{DG}$				
Entry	Substrate	Product	Yield [%] ^[b]	Sel. ^[c]
1			71	9:1
2			80	≥ 20:1
3			80	≥ 20:1
4			80	6.5:1
5			83	10:1
6			70	≥ 20:1
7			72	≥ 20:1

[a] 1 mmol alkene, MeCN/H₂O (7:1), 16 h. [b] Yield of isolated product. [c] Sel. = distal oxidation/proximal oxidation. Determined by ¹H NMR analysis. DG = directing group. Bz = benzoyl, Ts = 4-toluenesulfonyl.

groups, such as benzyl (Bn; 9:1). Introduction of a benzoate group increased the regioselectivity to greater than or equal to 20:1. This result is particularly interesting in light of potential known side reactions of allylic esters, such as the well-established palladium-catalyzed allylic substitution and rearrangement.^[11] For example, the recent report from Feringa and co-workers shows a strong preference for allylic rearrangement over oxidation of internal alkenes.^[9b] A branched allylic benzoate afforded a similar excellent result and thus bodes well for the use of more elaborated substrates (entry 3). We then explored the ability of homoallylic functionalities to direct the oxidation reaction, since the corresponding oxidation products are not readily accessible by traditional carbon–carbon forming processes. Synthetically viable regiocontrol for the distal oxidation product was obtained with up to greater than or equal to 20:1 selectivity (entries 4–6). Interestingly, this approach is not limited to protected alcohols, as an β,γ-unsaturated methyl ester afforded the distal oxidation product (entry 6). An allylic NHTs group gave the corresponding aminoketone derivative in high regioselectivity, thus expanding the reaction scope to nitrogen-derived directing groups (entry 7).

With a regioselective Wacker oxidation of internal alkenes in hand, we sought to illustrate the power of a combined cross-metathesis/regioselective Wacker sequence in the preparation of hydroxy- and aminoketones (Scheme 2). Moreover, the coupling with cross-metathesis presented an opportunity to further probe the predictability of the regiocontrol using other directing groups. An allylic carbonate and two allylic phthalimides (a common amine protecting group) were readily accessed using the Grubbs–Hoveyda second-generation catalyst (**1**). The linear substrates afforded high regiocontrol for the distal oxidation product in the subsequent Wacker oxidation. This control is critical, as the

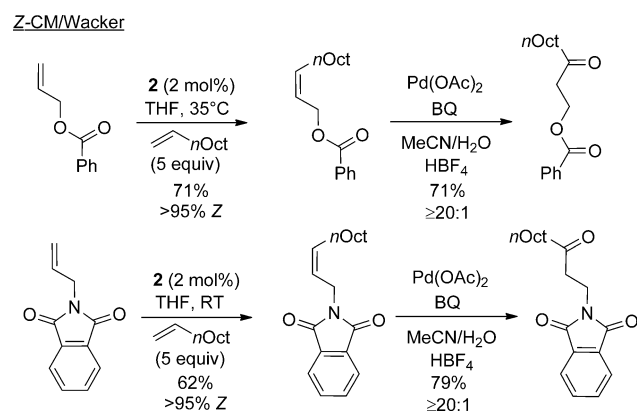


Scheme 2. Preparation and further screening of directing groups enabled by cross-metathesis.

terminal unbranched allyl phthalimide offers dramatically reduced regioselectivity compared to the branched allyl phthalimide in the Tsuji–Wacker oxidation (6:4).^[12] The branched allylic phthalimide similarly afforded the product with high regioselectivity and thus provides access to secondary aminoketones. Overall, both branched and linear protected amine and alcohol substrates enable a regioselective Wacker oxidation to be performed.

Despite recent progress in the oxidation of internal alkenes, Z alkenes have proven either inert or prone to positional isomerization in Wacker-type oxidations.^[13] Since many olefination reactions produce either Z alkenes or a mixture of both Z and E isomers, we sought to probe the effect of alkene geometry upon the oxidation.^[14] To this end, it was critical to access the desired starting materials as stereochemically pure Z isomers to clearly understand the underlying isomeric dependence on the reaction outcome. We thus exploited a new class of chelated ruthenium alkene metathesis catalysts which exhibit exquisite kinetic control to access the corresponding Z substrates (Scheme 3).^[15]

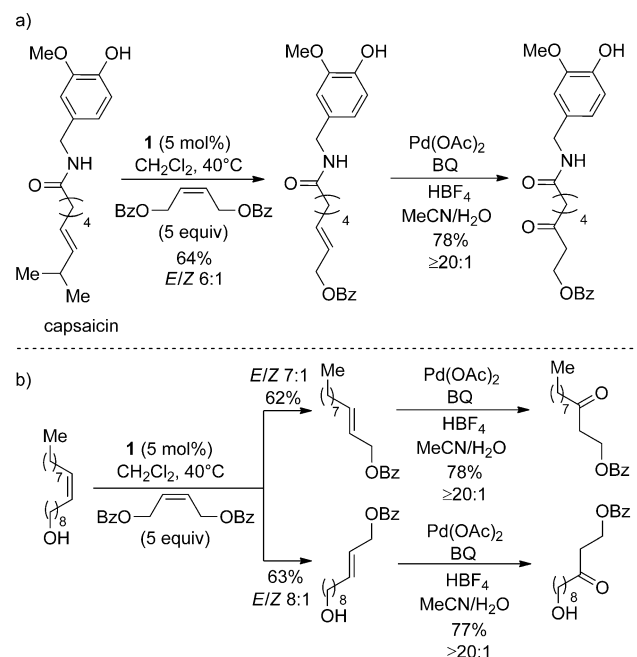
We were pleased to find that the chelated catalyst could cleanly prepare the desired Z substrates from allyl benzoate and allyl phthalimide in good yields and greater than 95%



Scheme 3. Demonstration of an efficient regioselective Wacker oxidation of Z substrates enabled by Z-selective cross-metathesis. THF = tetrahydrofuran.

Z selectivity. These two products were then smoothly transformed into the corresponding ketones in high regioselectivity and yield, comparable to the results obtained for the *E* isomers. These results thus establish that the efficiency of our oxidation protocol towards *E* alkenes also applies to *Z* alkenes.

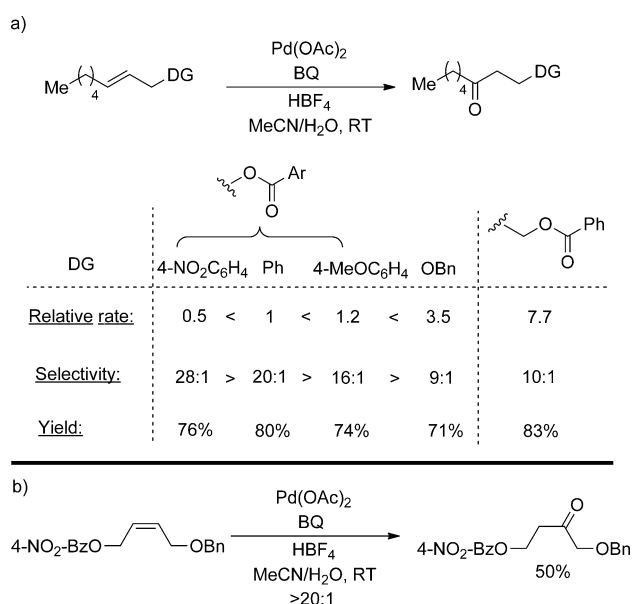
With an interest in further probing the synthetic utility of the metathesis/regioselective Wacker sequence, we explored this strategy in the context of the bioactive, polyfunctionalized alkene starting material capsaicin (Scheme 4a).^[16]



Scheme 4. Applications of the novel synthetic sequence to a polyfunctionalized target as well as in the selective functionalization of a seed oil derivative.

We were delighted to see that both steps worked in good yields, and the regioselectivity of the Wacker step proved to be as high as in the more simple examples. No interference with the directing ability of the benzoate moiety was observed, thus validating the potential of this strategy for complex-molecule functionalization. We envisioned this methodology could also enable rapid generation of functionalized molecules from inexpensive and renewable seed oil derivatives (Scheme 4b).^[17] Oleyl alcohol could be selectively transformed into two substituted allylic benzoate substrates using the catalyst **1**. The two intermediates could further be oxidized in high selectivity to the corresponding ketones under our standard oxidation conditions.

Finally, we explored the origin of regioselectivity of our protocol. We took advantage of the synthetic flexibility offered by the benzoate aromatic moiety to qualitatively study the electronic effects of the substituents on the reaction outcome. Competition experiments were performed between the allylic benzoate derivative and the corresponding 4-NO₂ and 4-MeO derivatives. The relative rates are shown in Scheme 5, with a rate following the order of NO₂ < H < MeO. This long-range electronic effect suggests the significant buildup of a positive charge in the transition state.^[18] Addi-



Scheme 5. Qualitative study of inductive effects on the relative rate and regioselectivity using both a) intermolecular and b) intramolecular competition experiments. Yield is that of the isolated product.

tionally, an allylic OBn was tested to uncover the effect of this group on the relative rate. The benzyl group is more electron-donating than the acyl substituents previously tested. This OBn substrate was oxidized with an increased rate and gave lower selectivity, and is thus consistent with the inductive trend previously observed. To further probe the effect of electron density on the relative oxidation rate, an intramolecular competition experiment using a substrate bearing both an allylic OBn and an allylic 4-NO₂-BzO was performed. The product from the oxidation of the most electron-rich position (distal to the 4-NO₂-BzO group), was oxidized with a remarkable greater than 20:1 regioselectivity. This outcome supplements the results of the intermolecular experiments and demonstrates that protecting-group selection can enable selective oxidation, even when potentially competing directing groups are proximal to the alkene. Benzoyl and benzyl groups are orthogonal protecting groups, and thus, this result will have significant implications in target-oriented synthesis. Overall, although we initially anticipated the regioselectivity might be chelation controlled, the observed rate and selectivity trend indicates that the regioselectivity of the process has a significant inductive component.^[19,20] An inductive model is also consistent with the selectivity obtained with the more electron-withdrawing benzoate as compared to the homoallylic benzyl-protected alcohol and will provide a guide to the selectivity of other Wacker-type oxidations.^[21] For example, Sigman and co-workers recently demonstrated strong directing effects with allylic substituents in the oxidation of internal alkenes by a coordinatively saturated palladium catalyst in combination with peroxide oxidants.^[6d] Further studies will be necessary to fully elucidate the origin of the regioselectivity in Wacker-type processes.

In conclusion, we have described a new synthetic strategy to regioselectively access complex ketone products from simple starting materials. A wide range of functionalized

alkenes were established as efficient substrates for a regioselective Wacker oxidation of internal alkenes, thus producing valuable synthetic intermediates (hydroxyketones, aminoketones, ketoesters). Efficiency of our regioselective Wacker oxidation protocol was demonstrated using both *E* and *Z* isomers prepared by cross-metathesis. Application to the functionalization of a bioactive natural product and seed oil derivatives showcased the potential of this cross-metathesis/regioselective Wacker strategy in target-oriented synthesis. An intriguing long-range inductive dependence was shown by competition experiments and has important implications for future applications. Overall, the high functional-group tolerance of both the cross-metathesis step and the Wacker oxidation, combined with the predictable regioselectivity of the oxidation step, holds great promise in the wide adoption of this strategy in organic synthesis.

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