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Oxidation of Hindered Allylic C–H Bonds with Applications to the Functionalization of Complex Molecules

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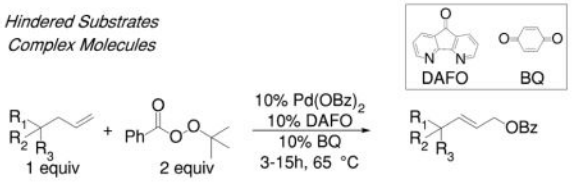
Abstract

We report the palladium-catalyzed oxidation of hindered alkenes to form linear allylic esters. The combination of palladium(II) benzoate, 4,5-diazafluoren-9-one, and benzoquinone catalyzes the mild oxidation of terminal alkenes with *tert*-butyl benzoyl peroxide as an oxidant in the presence of diverse functional groups. Selective oxidation of terminal alkenes in the presence of trisubstituted and disubstituted alkenes has been achieved, and the ability to conduct the reaction on a gram scale has been demonstrated. The mild conditions and high tolerance for auxiliary functionality make this method suitable for the synthesis and derivatization of complex molecules.

Graphical Abstract



Keywords

C–H activation; C–H bond functionalization; allylic oxidation; palladium catalysis; olefin functionalization

C–H bond functionalization reactions could enable concise routes to complex molecules in diverse synthetic contexts, but many C–H bond functionalization reactions conducted on simple substrates do not translate to more-complex analogues.[1] Among C–H bond functionalization reactions, the oxidation of allylic C–H bonds has been investigated by many groups because of the prevalence of olefins and alcohols in natural products and the application of allylic alcohols as synthetic intermediates.[2] Although many catalytic methods

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Notes

The authors declare no competing financial interest.

Supporting Information

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Experimental details for all reactions and analytical details of all relevant materials (PDF)

for allylic oxidation have been reported,[3] current systems do not generally address the challenge of conducting this class of reaction on hindered alkenes, such as those with fully substituted carbon atoms adjacent to the allylic unit. Such allyl units flanked by quaternary carbons are common substructures in natural products. Thus, synthetic methods for the functionalization of such allyl groups would be valuable for both the synthesis and direct functionalization of natural products.[4]

Since the initial reports on the catalytic allylic oxidation of olefins in the 1970s,[5] selective palladium-catalyzed acetoxylations of allylic C–H bonds have been reported (Scheme 1A).[6] Reactions with a variety of ligands, terminal oxidants, and solvents have been investigated.[3] High selectivity for both the linear and branched allylic acetates has been achieved, and acid-sensitive substrates can be functionalized under certain conditions.[6k,7,8] The acetoxylation of substrates containing amides, esters, and acetals has been accomplished in moderate to good yields.[9] Many groups have investigated the mechanisms of these transformations in depth.[6d,g,i,k,l,10] Recently, our group reported a system for the palladium-catalyzed oxidation of α-olefins to linear allylic benzoates with high selectivity for the linear ester under neutral conditions in combination with iridium-catalyzed allylic substitution.[11] This process was used to prepare synthetically valuable enantioenriched products containing new C–O, C–N, and C–C bonds in one pot.

Despite this progress, current methods for the oxidation of allylic C–H bonds have significant limitations. Most relevant to the present investigation, hindered alkenes tend to resist oxidation at the allylic position. Stoltz et al. recently highlighted these constraints (Scheme 1B).[12] The oxidation of substrates containing α-allyl lactams with quaternary centers next to the allyl group occurred to low conversions under both classical and modern catalytic conditions.

Although the authors subsequently devised conditions for the selective oxidation of α-allyl lactams, only trace yields were obtained when other classes of hindered substrates were evaluated.

With these challenges in mind, we assessed whether our conditions for the oxidation of alkenes to terminal allylic esters could be adapted to achieve the oxidation of sterically hindered alkenes with a high tolerance of functional groups and selectivity for linear products (Scheme 1C). Herein, we report the development of conditions for the palladium-catalyzed oxidation of hindered alkenes to form linear allylic benzoates. The ability to oxidize these substrates and the high tolerance of the system for functional groups makes this process particularly valuable for the functionalization of complex natural products containing quaternary carbons at the position α to the allyl unit.

To develop a system capable of functionalizing compounds containing α-quaternary centers, we investigated the oxidation of model substrate **1b** by modifying our previously reported conditions (Table 1). We found that the combination of $Pd(OBz)_2$ and 4,5-diazafluoren-9-one (DAFO)[6l] catalyzes the reaction of **1b** with *tert*-butyl benzoyl peroxide (BzO_2tBu) to form **2b** in 59% yield (Table 1, entry 3). No product was formed when either $Pd(OBz)_2$ or DAFO was omitted from the reaction (Table 1, entries 1 and 2). The high conversion of **1b**

in the absence of DAFO suggests that unligated $Pd(OBz)_2$ catalyzes the decomposition of **1b** in the presence of *tert*-butyl benzoyl peroxide (Table 1, entry 2). The yield of the reaction conducted with 4 equiv of oxidant was similar to that obtained when the reaction was conducted with 2 equiv of oxidant (Table 1, entries 3 and 4). Neither increasing the loading of palladium and ligand to 20 mol % (Table 1, entry 5), nor increasing the loading of ligand to 20 mol % (while maintaining the loading of palladium at 10 mol %) increased the yield of **2b** (Table 1, entry 6). However, the yields of reactions conducted with benzoquinone (BQ) as an additive were higher than those conducted without benzoquinone (Table 1, entries 7–9).

The presence of BQ in the reaction mixture also increased the yields for the oxidation of unprotected homoallylic alcohols. The Sakurai–Hosomi reaction and other reactions of allyl nucleophiles with ketones have been developed for the synthesis of enantioenriched homoallylic alcohols, but the functionalization of tertiary, homoallylic alcohols is challenging because of the electron-withdrawing property of the alcohol and the steric hindrance at the allylic C–H bond.[13–16] In addition, terpenoids containing homoallylic alcohols, such as linalool, have been observed to undergo unproductive side reactions under oxidative conditions resulting in multiple products.[17]

Reactions of model substrate **1m** were conducted in the presence and absence of BQ (Table 2). In the absence of BQ, only low to moderate conversions of **1m** and yields of **2m** were obtained at 1 and 3 h (Table 2, entries 1 and 2). A high conversion of **1m** was observed when the reaction time was extended to 48 h, but a low yield of **2m** was obtained (Table 2, entry 3). In contrast, reactions conducted with added BQ fully converted **1m** within an hour (Table 2, entries 4–6). The yield of **2m** from the reaction with 5 mol % of benzoquinone was the same as that with 10 mol % BQ (Table 2, entries 4 and 5). Reactions containing 10 mol % of other quinones or metal salts gave lower conversions of **1m** at 1 h than did the reaction conducted with 10 mol % BQ (see the Supporting Information).

The origin of the higher rate and higher yield that are observed when the benzoylation reaction is conducted in the presence of BQ than in the absence of BQ is unclear. However, based on numerous precedents, we suggest that BQ could serve as a ligand that promotes the reductive elimination of an allyl palladium intermediate (see the Supporting Information).[6j,k,10c,18] Alternatively, BQ could prevent catalyst decomposition.

Having achieved high yields for the oxidation of two different classes of model substrates, we evaluated our conditions for the oxidation of allylic C–H bonds in a range of compounds (Scheme 2). Many of the products derived from these alkenes could serve as valuable synthetic intermediates (Scheme 2, entries **2a**–**2f**, **2i**–**2m**). In addition, derivatives of natural products were oxidized to provide complex precursors for further diversification (Scheme 2, entries **2g**, **2h**, **2k**, **2l**, **2n**–**2p**). Generally, ^{1}H NMR yields were higher than isolated yields by 10%–20% because of the need to separate the major product from minor byproducts having similar polarity to the major species. A representative ^{1}H NMR spectrum of the crude product derived from the oxidation of **1m** is included in the Supporting Information.

Published attempts to conduct the acetoxylation of C–H bonds of α-allyl ketones resulted in low conversion.[12] We found that reactions of acyclic ketones **1a** and **1b** occurred to full conversion in 10 h, despite the difference in the steric properties of the quaternary centers in these two ketones. Cyclic ketones containing 5-, 6-, and 7-membered rings underwent oxidation in high yields in 15 h (**1c**, **1d**, **1e**). The synthesis of enantioenriched variants of these substrates by asymmetric Tsuji allylic alkylation has been extensively developed because of their value as synthetic intermediates; our functionalization methodology provides products that could be further elaborated.[6l,12,19]

In addition to hindered ketones, hindered α-allyl esters and lactones also reacted to full conversion within <24 h. The model ester, **1f**, was oxidized to **2f** in good yield. Product **2f** is valuable because of its similarity to methyl (*E*)-5-hydroxy-2,2-dimethylpent-3-enoate, which is an intermediate in the synthesis of bryostatin.[20] Furthermore, the selective oxidation of **2f** demonstrates that benzyl esters are compatible with our oxidative reaction conditions.

With these results in hand, we evaluated the allylic oxidation of more complex substrates. We found that a derivative of santonin, which is the five-membered α-allyl lactone **1g**, underwent benzoylation under the conditions we developed in high yield. The cyclohexadiene moiety of **1g**, which is responsible for the biological activity of santonin, did not undergo further oxidation.[21] The six-membered lactone derived from deoxy-artemisnin, **1h**, also underwent oxidation to furnish **2h** in moderate yield.

High product yields were also obtained when linear amide **1i** and lactam **1j** were oxidized under the conditions we developed. Previous attempts to functionalize hindered, linear amides like **1i** resulted in low conversions; lactams were the only class of hindered carbonyl compound that underwent oxidation in synthetically relevant yields.[12] The oxidation of substrate **1k** to **2k** indicates that homoallylic carbamates are also compatible with our reaction conditions.

The benzoylation of homoallylic alcohol **1m** led us to evaluate the oxidation of more complex homoallylic alcohols. Homoallylic alcohols derived from estrone and cholesterone underwent selective allylic oxidation (**1n**, **1p**). These results confirm that alcohols derived from 5- and 6-membered cyclic ketones can be oxidized in moderate to good yields. Products derived from the oxidation of the trisubstituted olefin **1p** did not form in significant quantities, suggesting that this system selectively oxidizes terminal olefins. This observation is corroborated by the selective oxidation of citronellal derivative **1l** and α-ionone derivative **1o**. The selective oxidation of the terminal olefin of **1o** occurs in the presence of trisubstituted and disubstituted alkenes. This selectivity is valuable for the functionalization of terpenoid natural products, which often contain multiple olefins.

The benzoylation of compounds derived from natural products, such as santonin, deoxy-artmesinin, proline, citronellal, estrone, cholesterone, and α-ionone, establishes the utility of our method for the functionalization of complex molecules. To further demonstrate the synthetic value of our benzoylation procedure, **2g** was prepared on a 1 g scale. The selective benzoylation of **1g** is challenging because it contains multiple alkenes. This substrate underwent selective oxidation catalyzed by 5 mol % $Pd(OBz)_2$, 5 mol % DAFO, and 20 mol

% BQ. After 9 h at 65 °C, a 75% yield of **2g** was determined by ^{1}H NMR spectroscopy, and an isolated yield of 70% of **2g** was obtained. These results closely match those obtained when **1g** was benzoylated on a 0.2 mmol scale with a 10 mol % loading of palladium (Scheme 3).

In conclusion, we have demonstrated that the combination of palladium(II) benzoate, 4,5-diazafluoren-9-one, and benzoquinone catalyzes the benzoylation of hindered, terminal olefins in the presence of *tert*-butyl benzoyl peroxide. In many cases, the inclusion of benzoquinone in our reaction conditions led to higher reaction rates and product yields than were obtained in its absence. Under these new conditions, hindered substrates undergo rapid and selective functionalization. The application of this method to natural products provides intermediates for further diversification. Finally, the synthetic relevance of this method has been validated by the gram-scale oxidation of a santonin derivative.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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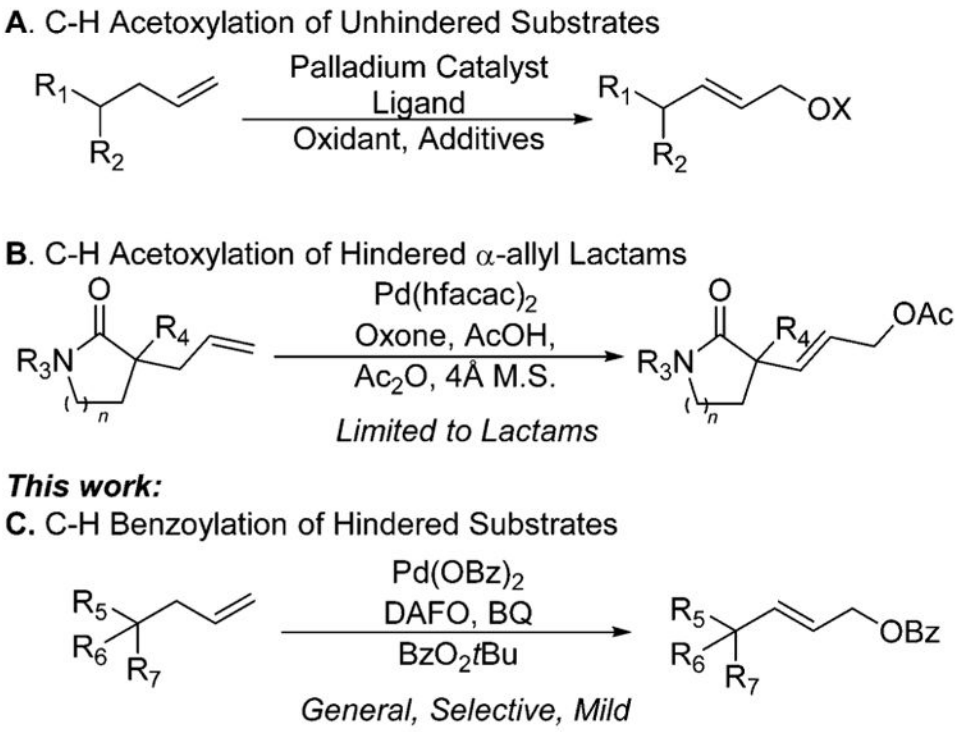
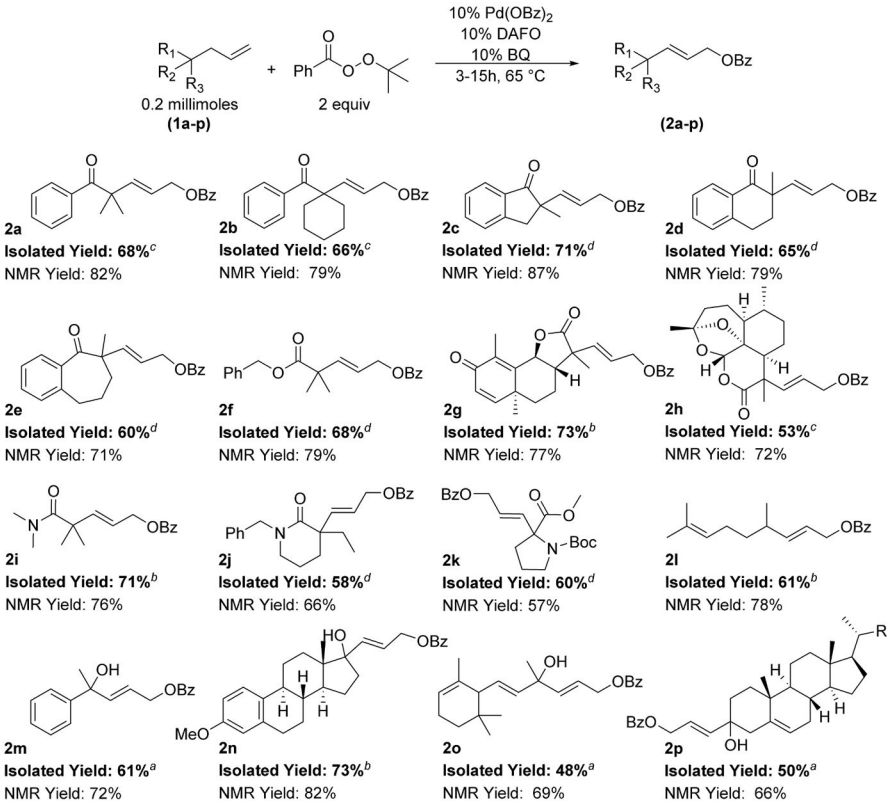
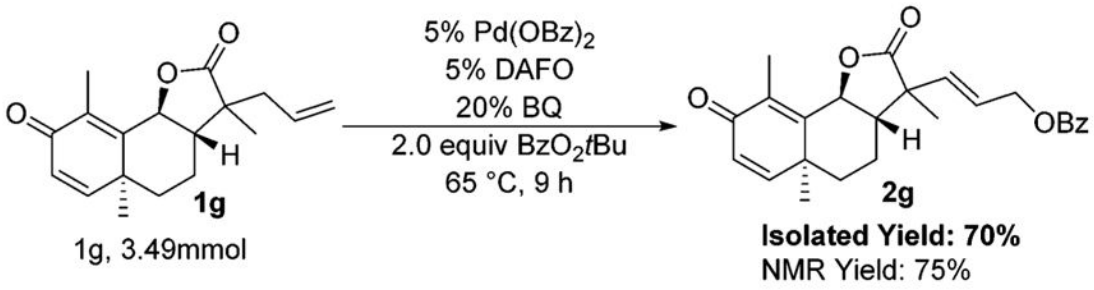


Scheme 1.
C–H Oxidation of α-Olefins



Scheme 2. Scope of C–H Benzoylation of Hindered and Complex Substrates*

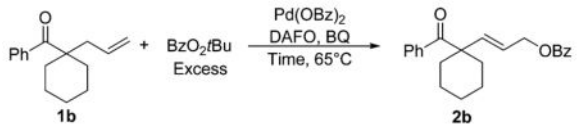
*Conditions: Reactions were conducted with 0.2 mmol (1 equiv) of substrate and 2.0 equiv of BzO_2tBu. Yields were determined by ^1H NMR prior to isolation. [a]Reaction duration was 3 h. [b]Reaction duration was 5 h. [c]Reaction duration was 10 h. [d]Reaction duration was 15 h. R = $(CH_2)_3i$-Pr.



Scheme 3.
Gram-Scale Oxidation of Allyl–Santonin

Table 1

Evaluation of Conditions for the Oxidation of Model Ketone 1b[a]



entry	%Pd(OBz)$_2$	%DAFO	%BQ	yield (%)	unreacted 1b (%)
1	0	10	0	0	quant
2	10	0	0	0	22
3	10	10	0	59	0
4[b]	10	10	0	58	0
5	20	20	0	55	0
6	10	20	0	51	21
7	10	10	10	74	0
8	10	10	50	78	0
9[c]	10	10	10	79	0

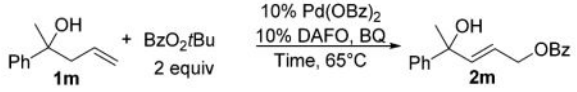
[a] Conditions: Reactions were conducted with 0.1 mmol (1 equiv) of **1b** and 2.0 equiv of BzO$_2$*t*Bu. The ligand, 4,5-diazafluoren-9-one, is abbreviated as DAFO. Benzoquinone is abbreviated as BQ. The reaction duration was 20 h. Yields were determined by ^{1}H NMR.

[b] Reaction was conducted with 4.0 equiv of BzO$_2$*t*Bu.

[c] Average yield of two reactions; reaction duration was 10 h.

Table 2

Evaluation of Conditions for the Oxidation of Homoallylic Alcohol 1m[a]



entry	%BQ	time (h)	yield (%)	unreacted 1m (%)
1	0	1	28	46
2	0	3	28	47
3	0	48	25	0
4	5	1	70	0
5	10	1	70	0
6	50	1	69	0
7	10	3	69	0

[a]Conditions: Reactions were conducted with 0.1 mmol (1 equiv) of **1m** and 2.0 equiv of BzO_2tBu. Yields were determined by ^1H NMR.