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Palladium(II)-Catalyzed Allylic C–H Oxidation of Hindered Substrates Featuring Tunable Selectivity Over Extent of Oxidation

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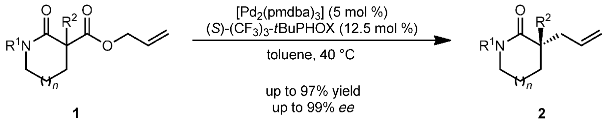
***Abstract:** The use of Oxone and a palladium(II) catalyst enables the efficient allylic C–H oxidation of sterically hindered α-quaternary lactams which are unreactive under known conditions for similar transformations. This simple, safe, and effective system for C–H activation allows for unusual tunable selectivity between a two-electron oxidation to the allylic acetates and a four-electron oxidation to the corresponding enals, with the dominant product depending on the presence or absence of water. The versatile synthetic utility of both the allylic acetate and enal products accessible through this methodology is also demonstrated.*

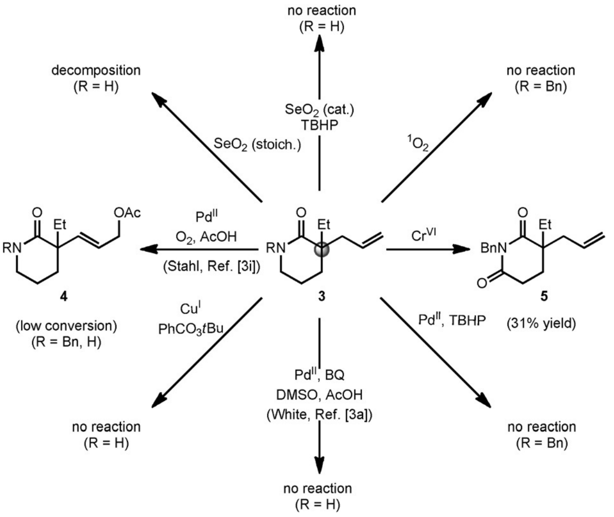
Recent developments in C–H functionalization have made major contributions to organic chemistry and are beginning to change the way chemists approach synthetic transformations.[1] Allylic C–H acetoxylation[2,3] and other functionalizations[4] of terminal olefins have received considerable interest over the past decade as allyl groups are versatile and widespread in synthetic organic chemistry. After the seminal report by White and co-workers of allylic acetoxylation,[3a] numerous research groups have developed alternative conditions for this transformation, mainly differing in the terminal oxidant used.[3]

Complementing reports of the two-electron oxidation of allyl groups to allylic acetates, the four-electron oxidation of allyl groups to enones or enals has also been described. While the oxidation of olefins, particularly cycloalkenes, to enones is well precedented,[5] there exist few examples of the transformation of allyl groups to enals.[6,7] Of these limited cases, most produce the enals in low yield and with poor selectivity over other oxidation products, and/or require activated allylic C–H bonds (i.e., allylbenzenes). None of these methods are reported to be effective on complex or sterically hindered substrates.

Our research group has had a longstanding interest in the asymmetric synthesis of α-quaternary carbonyl compounds by palladium-catalyzed decarboxylative enantioselective allylic alkylation.[8] In 2012 we reported the construction of quaternary α-allyl lactams (**2**), in excellent yield and *ee* using this strategy (Scheme 1).[8c] Given our interest in C–H activation,[9] the utility of allyl groups as functional handles, and the known status of allylic C–H bonds as a privileged motif in the C–H activation literature, we investigated the use of several reported procedures for the C–H functionalization of our lactam products (Scheme 2). Interestingly, the use of either classical[5,10] or modern[3a,i] conditions for allylic oxidations resulted in decomposition, low conversion, or undesired reactivity.



Scheme 1. Enantioselective synthesis of α-quaternary lactams by palladium-catalyzed decarboxylative allylic alkylation. PHOX = phosphinooxazoline, pmdba = 4,4′-methoxydibenzylideneacetone.



Scheme 2. Investigation into the allylic oxidation of lactam **3**. For experimental details see the Supporting Information. BQ = 1,4-benzoquinone, DMSO = dimethylsulfoxide, TBHP = *tert*-butyl hydroperoxide.

We attribute the absence of the desired reactivity to the sterically demanding quaternary center at the homoallylic position. This hypothesis is corroborated by the paucity of sterically encumbered examples of such allylic oxidations in the methods literature. Realizing the amide moiety could act as an internal ligating group, we chose to develop reaction conditions for the substrate-directed palladium-catalyzed allylic C–H acetoxylation of these molecules. We hoped that the use of a directing group, largely unknown in allylic C–

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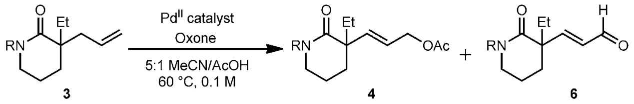
H oxygenation reactions,[11] would enable reactivity even in the most sterically hindered substrates.

We began our studies by screening various palladium(II) catalysts, oxidants, and solvents in the allylic acetoxylation of an *N*-benzoyl lactam (Table 1, entry 1), itself accessed by our allylic alkylation chemistry.[8c] Gratifyingly, exposure of the substrate to palladium(II) acetate and Oxone in a mixture of acetonitrile and acetic acid produced trace amounts of allylic acetate (**4**) and enal (**6**) products. We were pleased to find that Oxone was superior to other oxidants examined, as it is readily available, inexpensive, stable, relatively nontoxic, and environmentally safe.[12] To our knowledge, this is the first report of Oxone as an oxidant for an allylic C–H functionalization reaction.

Table 1: Optimization of the allylic acetoxylation.



Entry	R	Catalyst (mol %)	Oxone (equiv)	*t* [h]	Conv. [%][b]	Yield [%][c]	**4**/**6**[d]
1	Bz	Pd(OAc)$_2$ (5.0)	1.5	96	31	trace	6:1
2	H	Pd(OAc)$_2$ (5.0)	1.5	3	100	41	8:1
3[e]	Bn	Pd(OAc)$_2$ (7.5)	2.5	10	100	62	8:1
4[e]	Bn	Pd(TFA)$_2$ (7.5)	2.5	10	100	62	9:1
5[e]	Bn	[Pd(acac)$_2$] (7.5)	2.5	10	90	55	7:1
6[e]	Bn	[Pd(hfacac)$_2$] (7.5)	2.5	4	100	65	8:1

[a] Reaction conditions: lactam **3** (0.10 mmol), catalyst (0.05 or 0.075 equiv; see table), Oxone (1.5 or 2.5 equiv, see table), MeCN (714 μL), and AcOH (286 μL) at 60 °C for 96 h or until full conversion by TLC. [b] Conversion was determined from the yield of the isolated recovered starting material. [c] Yield is that of isolated combined products **4** and **6**. [d] Ratio determined by ^{1}H NMR analysis of the crude reaction mixture. [e] A solvent mixture of 5:1:1 MeCN/AcOH/Ac$_2$O was used, and 4 Å M.S. (80 mg) were added. acac = acetylacetonate, Bz = benzoyl, hfacac = 1,1,1,5,5,5-hexafluoroacetylacetonate, M.S. = molecular sieves, TFA = trifluoroacetate.

Although the benzoyl-protected lactam gave only low conversion under these conditions, the free N–H lactam performed better, giving moderate conversion to a separable mixture of **4** and **6** (entry 2). Further optimization revealed the *N*-benzyl lactams to be superior to the free lactams, resulting in full conversion within a matter of hours (entries 3–6). Subsequent experiments showed that the addition of acetic anhydride and molecular sieves was necessary to obtain the allylic acetate product in good yield. An examination of other palladium(II) precursors (entries 4–6) led us to select palladium(II) hexafluoroacetylacetonate, as it resulted in the shortest reaction time while maintaining a good ratio of the desired allylic acetate **4** to the undesired enal **6** (entry 6). With all substrates, we found that acetonitrile was necessary as a solvent, as its omission led to a significant decrease in reactivity. In all cases, we observed little or no formation of the methyl ketone or aldehyde products expected from Wacker–Tsuji reactivity.

With the optimized reaction conditions in hand, we investigated the substrate scope of the reaction. We quickly found that the lactam nature of the substrate was critical to achieving good reactivity. Interestingly, cyclic compounds lacking an amide functional group gave only low conversion under our conditions, as did a wide variety of linear amides investigated. The scope of allylic acetoxylation of lactam substrates is shown in Figure 1. Substrates incorporating alkyl groups at the α-position were well tolerated, furnishing the corresponding allylic acetates (**8a**,**b**,**d**,**e**) in good yields and selectivities. Substrates with benzyl (**8c**) or aryl (**8f**) groups at the α-position were also competent.[13] The benzyl group on the lactam nitrogen was not necessary, and could be replaced by other electron-rich groups, such as methyl (**8g**) and *para*-methoxyphenyl (**8j**), or even olefinic groups like methallyl (**8k**), and *trans*-cinnamyl (**8l**).[13] The free N–H lactam was also a successful substrate (**8h**). A quaternary stereocenter was not found to be necessary, with an α-tertiary lactam undergoing acetoxylation in good yield and exclusive selectivity over enal formation (**8i**). Finally, substrates derived

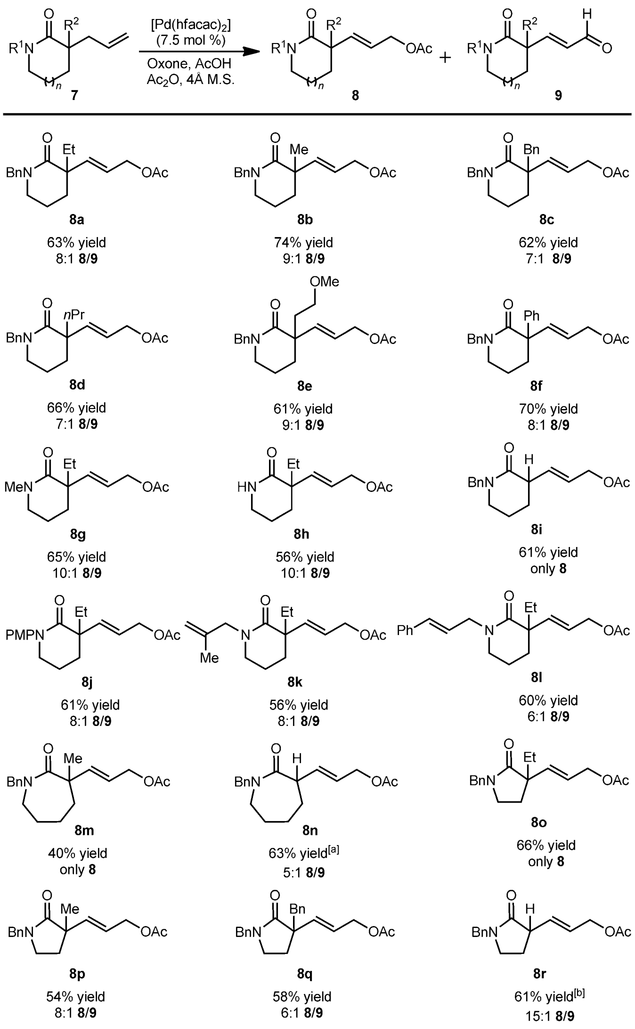


Figure 1. Substrate scope of the allylic acetoxylation. Combined yield of the isolated separable products **8** and **9**. Reaction conditions: lactam **7** (0.2 mmol), [Pd(hfacac)$_2$] (0.075 equiv), Oxone (2.5 equiv), MeCN (1.43 mL), AcOH/Ac$_2$O (1:1, 570 μL) and 4 Å M.S. (160 mg) at 60 °C for 3–6 h. [a] Reaction time = 24 h. [b] Reaction time = 11 h. PMP = *para*-methoxyphenyl.

from caprolactam (**8m**,**n**) and butyrolactam (**8o–r**), readily accessed by our decarboxylative allylic alkylation chemistry, also reacted smoothly.[14]

After exploring the scope of the acetoxylation reaction, we were intrigued about the possibility of optimizing for the enal product seen in small amounts in most acetoxylations. During our early optimization of the allylic acetoxylation reaction, we observed that the omission of molecular sieves or acetic anhydride resulted in a higher degree of enal formation. Using this as a starting point, we identified optimal reaction conditions for enal formation, which are shown in Figure 2. Remarkably, only simple changes to the reaction conditions lead to a significant change in the product ratio, allowing for facile control of the degree of oxidation. Essentially, either the presence or absence of water leads to a switch between a two-electron oxidation of the allyl group into the allylic acetate (i.e. **7**→**8**) and a four-electron oxidation of the allyl group into the enal (i.e. **7**→**9**). While palladium(II) hexafluoroacetylacetonate is an effective catalyst for oxidation to the enal, we opted to use the cheaper and more widely available palladium(II) acetate, as the results were similar. We found the presence of small amounts of water to be necessary to achieve high conversion, and the presence of acetic acid aided in suppressing formation of the methyl ketone (i.e., standard Wacker–Tsuji oxidation).[15]

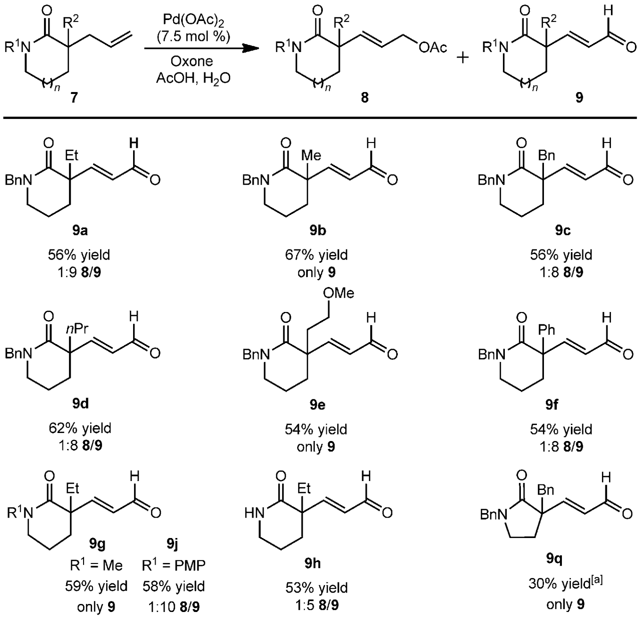
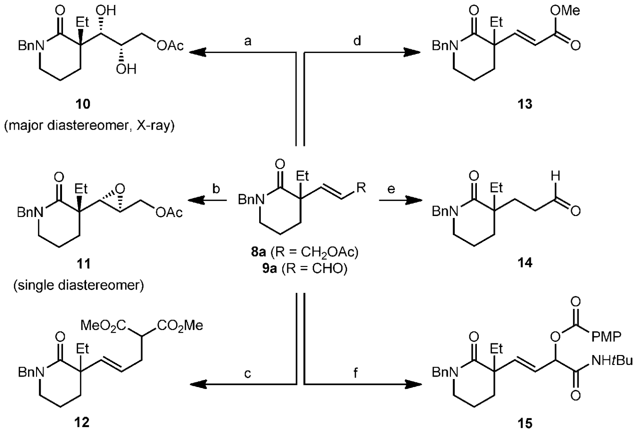


Figure 2. Substrate scope of the enal formation. Combined yield of the isolated separable products **8** and **9**. Reaction conditions: lactam **7** (0.20 mmol), Pd(OAc)$_2$ (0.075 equiv), Oxone (2.5 equiv), AcOH (16.0 equiv), H$_2$O (8.0 equiv), and MeCN (1.82 mL) at 50 °C for 1–2 h. [a] Starting material not fully consumed.

The scope of the enal formation is shown in Figure 2. We found that *N*-benzyl valerolactams with a variety of alkyl groups at the α-position were well tolerated, furnishing the enal products (**9a**,**b**,**d**,**e**) in good yields and selectivities over the allylic acetates. Substrates with α-benzyl and α-phenyl substituents were also successfully oxidized to enals **9c** and **9f**, respectively. As with the allylic acetoxylation reaction, we found that the benzyl-protected nitrogen was not critical, and that the *N*-methyl, *N*-aryl, and N–H substrates were also suitable (**9g**,**j**,**h**).[13] Unfortunately, lactams of other ring sizes showed low conversion (**9q**),[14] and α-tertiary substrates gave predominately the methyl ketone product of a Wacker–Tsuji oxidation (not shown).[15]

The synthetic utility of allylic acetates is well known in the literature, and we were able to transform product **8a** into several functionalized building blocks using a variety of oxidations, reductions, and C–C bond-forming reactions (Scheme 3). Enals are also useful synthetic intermediates, and we were able to derivatize product **9a** by similar methods.



Scheme 3. Synthetic utility of the products. Reaction conditions: a) **8a**, K$_2$OsO$_4$·2H$_2$O, NMO, acetone, H$_2$O, 23 °C, 83 % yield; b) **8a**, *m*CPBA, CH$_2$Cl$_2$, 23 °C, 93 % yield; c) **8a**, [{Ru(*p*-cymene)Cl$_2$}$_2$], Ph$_3$P, LiHMDS, dimethyl malonate, THF, toluene, 60 °C, 82 % yield; d) **9a**, [VO(acac)$_2$], H$_2$O$_2$, H$_2$O, MeOH, 23 °C, 93 % yield; e) **9a**, H$_2$, Pd/C, EtOAc, 23 °C, 97 % yield; f) **9a**, *p*-OMe-C$_6$H$_4$CO$_2$H, *t*BuNC, CH$_2$Cl$_2$, 40 °C, 64 % yield. HMDS = hexamethyldisilazide, *m*CPBA = *m*-chloroperbenzoic acid, NMO = *N*-methyl-morpholine-*N*-oxide, THF = tetrahydrofuran. For additional transformations and full experimental details see the Supporting Information. CCDC 1057691 (**10**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

In summary, we have reported a novel protocol for palladium-catalyzed allylic C–H oxidation using inexpensive, nontoxic, and safe Oxone as the terminal oxidant. This method is far more tolerant of steric bulk than previously known examples, possibly as a result of substrate-directed reactivity. Furthermore, we have discovered that a minor change in reaction conditions allows for access to either the allylic acetate products of a two-electron oxidation or the enal products of a four-electron oxidation. This reactivity switch demonstrates an unusual ability to selectively achieve different increases in oxidation state by a single palladium-catalyzed system. The synthetic utility of the products resulting from these C–H functionalization methods has been demonstrated by conversion of the prototypical products to a range of functionalized heterocycles. Mechanistic studies and investigations of further synthetic applications of the products are currently underway.[16]

Acknowledgements

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Keywords: allylic compounds · C–H functionalization · heterocycles · oxidation · palladium

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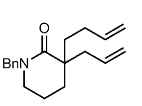
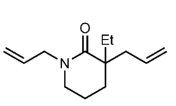
[11] For an example with stoichiometric palladium, see Ref. [3n].

[12] a) Oxone is $KHSO_5 \cdot \frac{1}{2}KHSO_4 \cdot \frac{1}{2}K_2SO_4$. For information on the safety, reactivity profile, and chemical stability of Oxone, see: DuPont Oxone Monopersulfate Compound General Technical Attributes; Technical Report K-20102, October **2008**; b) Sigma Aldrich price, May 5, 2015: $21 kg.

[13] Substrates incorporating terminal olefins (**7s** and **7t**), provided inseparable mixtures of multiple oxidation products upon subjection to either the allylic acetoxylation or enal formation conditions. The mixtures included allylic acetates, enals, methyl ketones, and other compounds.

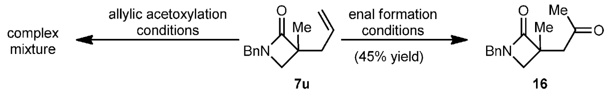


7s



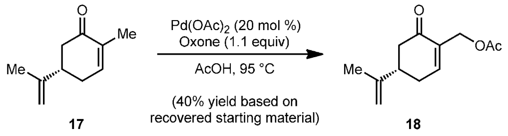
7t

[14] The β-lactam substrate **7u** provided a mixture of the allylic acetate, enal, and methyl ketone products upon treatment with the conditions for allylic acetoxylation. The same substrate furnished only the methyl ketone product **16** in moderate yield upon subjection to the enal conditions.



[15] It is possible that both the allylic acetate and enal products are formed through a palladium(II)-π-allyl intermediate, although other pathways, particularly Wacker-type activation of the olefin, may also be envisioned. The requirement of an electron-rich lactam moiety in the substrate suggests intramolecular direction may play a role in the mechanism. Control experiments show that both the allylic alcohol and the aliphatic aldehyde are smoothly converted to the enal, indicating that either could serve as a mechanistic intermediate. See the Supporting Information for details.

[16] Although it is clear that the allylic oxidation chemistry reported herein has certain scope limitations, the complete applicability of these new conditions for C–H functionalization is not yet fully realized. For example, we recently found that exposure of (*S*)-carvone (**17**) to similar reaction conditions resulted in selective allylic acetoxylation in moderate yield. See the Supporting Information for details.



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