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Palladium-Catalyzed Anti-Markovnikov Oxidation of Allylic Amides to Protected β-Amino Aldehydes

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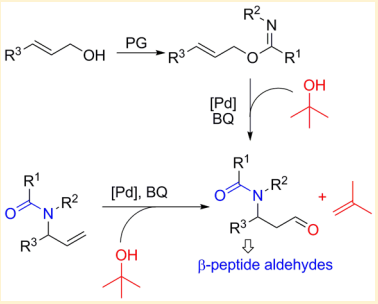
Supporting Information

ABSTRACT: A general method for the preparation of N-protected β-amino aldehydes from allylic amines or linear allylic alcohols is described. Here the Pd(II)-catalyzed oxidation of N-protected allylic amines with benzoquinone is achieved in tBuOH under ambient conditions with excellent selectivity toward the anti-Markovnikov aldehyde products and full retention of configuration at the allylic carbon. The method shows a wide substrate scope and is tolerant of a range of protecting groups. Furthermore, β-amino aldehydes can be obtained directly from protected allylic alcohols via palladium-catalyzed autotandem reactions, and the application of this method to the synthesis of β-peptide aldehydes is described. From a mechanistic perspective, we demonstrate that tBuOH acts as a nucleophile in the reaction and that the initially formed *tert*-butyl ether undergoes spontaneous loss of isobutene to yield the aldehyde product. Furthermore, tBuOH can be used stoichiometrically, thereby broadening the solvent scope of the reaction. Primary and secondary alcohols do not undergo elimination, allowing the isolation of acetals, which subsequently can be hydrolyzed to their corresponding aldehyde products.



INTRODUCTION

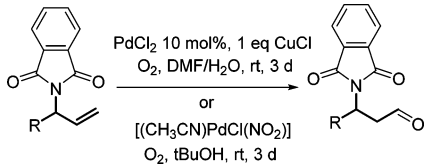
β-Amino acids, in particular unnatural variants, are of increasing importance, not least in the preparation of protease-resistant β-peptides and α/β-peptides.[1,2] Furthermore, β-amino aldehydes, the direct precursors of β-amino acids,[2] are crucial building blocks for the preparation of peptide aldehydes,[3] which enable ligation of unprotected peptides in aqueous solution, show potent bioactivity,[4] and are key intermediates in the synthesis of natural products and pharmaceutical derivatives.[5]

Catalytic approaches for the preparation of β-amino aldehydes rely primarily on the Mannich reaction,[6] Michael additions,[7] hydroformylation,[8] and methodologies such as anti-Markovnikov (AM) hydration of alkynes and the aza-Petasis–Ferrier rearrangement.[9] A highly attractive direct route to protected β-amino aldehydes is through the AM oxidation of N-protected terminal allylic amines under mild and neutral conditions.[10]

Recent progress in the palladium-catalyzed AM oxidation of alkenes made by both our group and Grubbs and co-workers has enabled the realization of selective oxidation of a range of terminal alkenes to aldehydes.[11] Indeed, we recently demonstrated that allylic esters can be oxidized readily to the corresponding aldehydes selectively using a catalyst such as $[(PhCN)_2PdCl_2]$ and the oxidant *p*-benzoquinone in *tert*-butyl alcohol (tBuOH) under ambient conditions.[11c]

The new opportunities arising from Wacker–Tsuji AM oxidations of allylic amines were demonstrated recently by Feringa and co-workers in the AM-selective oxidation of phthalimide-protected allylic amines to their corresponding β^3-amino aldehydes (Scheme 1).[12] However, extension of this method to any other protecting group resulted in loss of AM selectivity, severely limiting its utility (Scheme 1). Hence, despite its obvious synthetic importance, a general method for the synthesis of protected β-amino aldehydes through AM oxidation of the corresponding allylic amines has, until the present report, not been achieved.

Scheme 1. Catalytic Oxidative Synthesis of Phthalimide-Protected β-Amino Aldehydes from Branched Allylic Amines[12]



Herein we show highly selective AM oxidation of branched allylic amines bearing a range of protecting groups to give the corresponding aldehydes under ambient conditions (Scheme 2). The fact that various protecting groups and solvents can be used makes this approach general and flexible in both organic synthesis and peptide chemistry. The key to the success of our method lies in the combination of *p*-benzoquinone (BQ) as the oxidant and tBuOH as the solvent/reagent (in place of the conventional Wacker–Tsuji conditions employing O_2, CuCl, and DMF/H_2O, respectively). Importantly, the method allows for full retention of the stereochemistry of enantioenriched

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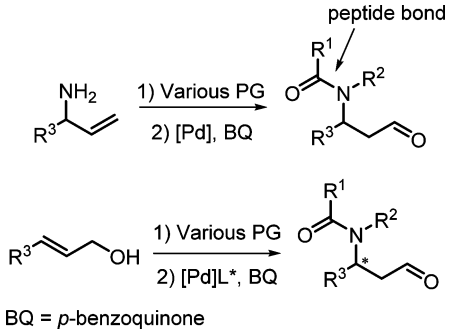
Scheme 2. Catalytic Oxidative Synthesis of Protected β-Amino Aldehydes Described in the Present Report

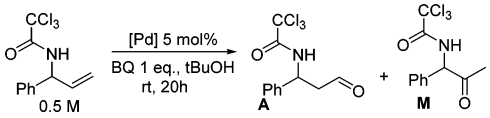


allylic amides, providing a new route for the catalytic asymmetric synthesis of amino aldehydes (Scheme 2). Furthermore, the Pd(II) catalysts used also enable protected β-amino aldehydes to be obtained directly from protected linear allylic alcohols via an autotandem approach. Finally, in earlier studies by both our group and the group of Grubbs, the use of tBuOH as the solvent was perceived to be essential to achieving AM selectivity. Here we demonstrate that the role played by the alcohol, either as a solvent or stoichiometrically, is as a nucleophile and the source of the oxygen atom in the final product. However, although all of the linear and tertiary alcohols employed give full conversion, only tBuOH provides excellent AM selectivity in the oxidation of allylic amides.

RESULTS AND DISCUSSION

The method introduced recently by our group for the oxidation of allylic esters, i.e., with $[(RCN)_2PdCl_2]$ (R = CH_3, Ph) as the catalyst and BQ as the oxidant in tBuOH under ambient conditions,[11c] was applied here in the oxidation of trichloroacetyl-protected phenylallylamine to yield the aldehyde product exclusively (>99:1; Table 1, entry 1). Several related

Table 1. Catalyst Screening



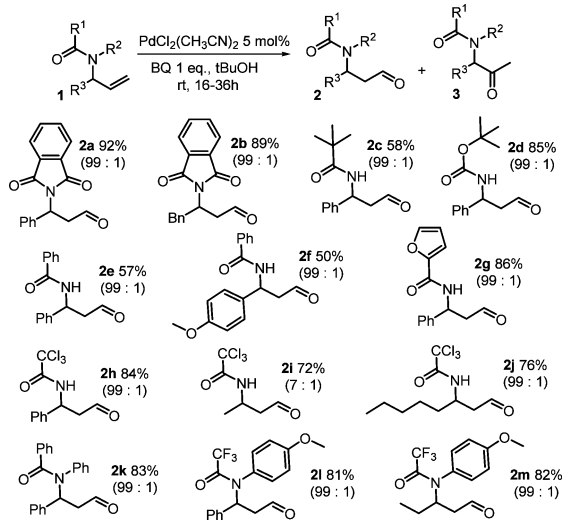
entry	catalyst	conversion[a]	A:M[a]
1	$[(CH_3CN)_2PdCl_2]$	full	99:1
2	$[(i\text{PrCN})_2PdCl_2]$	full	99:1
3	$[(PhCN)_2PdCl_2]$	full	99:1
4	$[PdCl_2]$	30%	99:1
5	$[(MeCN)_2PdCl(NO_2)]$	40%	99:1
6	$[Pd(OAc)_2]$	0%	–

[a]Determined by ^{1}H NMR spectroscopy.

catalysts were tested under the same conditions (Table 1). Complexes of the type $[(RCN)_2PdCl_2]$ (entries 2 and 3) were similarly effective with full conversion and excellent AM selectivity, whereas lower conversion was obtained using $[PdCl_2]$ or $[(MeCN)_2PdCl(NO_2)]$, albeit with full retention of the AM selectivity (entries 4 and 5). Conversion was not observed with $[Pd(OAc)_2]$ (entry 6). The activity observed with $[PdCl_2]$ is less than that when nitrile ligands are present, but the observation that the AM selectivity is retained with all of the catalysts that showed activity suggests that the role of the nitrile ligand is to increase the solubility of the catalyst and to enable ready displacement of a ligand by the substrate (i.e., the alkene).[13]

Substrate Scope and Tolerance of Protecting Groups. The scope of the reaction with regard to protecting groups and substituents was investigated with the readily available catalyst $[(CH_3CN)_2PdCl_2]$ and BQ as the oxidant in tBuOH (Scheme 3). When the catalyst loading was varied from 2.5 to 10 mol %,

Scheme 3. Pd(II)-Catalyzed Oxidation of Allylic Amides[a]



[a]Isolated yields and (in parentheses) aldehyde:ketone ratios are shown.

only the reaction rate was affected (it increased), and no change in AM selectivity was observed (typically >99:1 aldehyde:ketone). Notably, the addition of excess BQ oxidant did not increase the reaction rate. Further studies employed a catalyst loading of 5 mol % and stoichiometric BQ with a substrate concentration at 0.5 M in tBuOH.

Phthalimide-protected allylic amines were oxidized to aldehydes **2a** and **2b** with excellent selectivity (>99:1; Scheme 3) using a reduced reaction time of 16 h compared with those required under Wacker–Tsuji conditions (Scheme 1), where 72 h was required together with 10 mol % catalyst.[12] *N*-Boc-protected 1-phenylallylamine (**1d**) was converted to **2d** in high yield and selectivity, which contrasts with the formation of the corresponding ketone product under Wacker–Tsuji conditions as reported earlier.[12] Mono- or bis-N-protected 1-phenylallylamines with a series of protecting groups were also converted to the corresponding aldehydes selectively, including pivalic (**2c**), benzoyl (**2e**), 2-furoyl (**2g**), and trichloroacetyl (**2h**) monoprotected substrates and benzoyl/phenyl (**2k**) and trifluoroacetyl/*p*-methoxyphenyl (**2l**) bisprotected ones. In addition, 4-methoxyphenyl (**2f**), methyl (**2i**), pentyl (**2j**), and ethyl (**2m**) substituted allylic amines with various protecting groups were converted selectively in good isolated yields (Scheme 3). The relatively lower yields of **2c**, **2e**, and **2f** are mainly due to lower conversion of the substrate and formation of enamine side products.

Synthesis of Protected β-Amino Aldehydes from Linear Allylic Alcohols. It should be noted that the synthesis of allylic amine precursors is often challenging.[15] The wide tolerance to protecting groups shown by the present catalytic system, however, allows for protected β-amino aldehydes to be prepared directly from protected linear allylic alcohols in high

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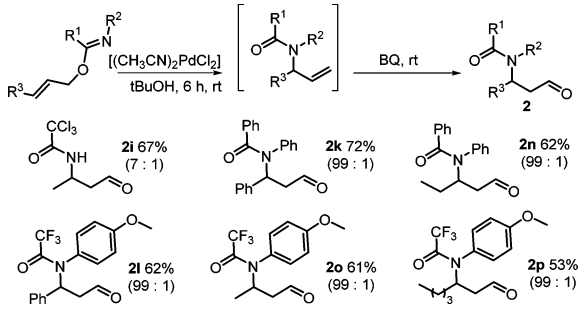
yield and atom economy. Protection of linear allylic alcohols with several imidoyl groups was followed by in situ Pd(II)-catalyzed rearrangement[16] to the protected branched allylic amines and subsequent oxidation to the corresponding aldehydes in good yields (Scheme 4) with the same selectivities

Scheme 4. Synthesis of β-Amino Aldehydes from Allylic Imidates via an Autotandem[14] Reaction[a]

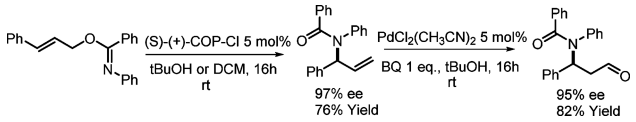


[a]Conditions: total reaction time 36−72 h; 10 mol % catalyst loading added in the first step. Isolated yields and (in parentheses) aldehyde:ketone ratios are shown.

as obtained in the one-step protocol (Scheme 3). Trifluoroacetyl/4-methoxyphenyl-protected but-3-en-2-amine (**2o**) was converted with excellent selectivity (99:1), while trichloroacetyl-protected but-3-en-2-amine (**2i**) provided the same selectivity as in the one-step protocol (7:1 aldehyde:ketone). It should be noted that for product **2p**, the lower yield obtained was due to low conversion in the oxidation of the allylic amide. Furthermore, the slightly lower yields in the tandem reactions (Scheme 4) compared with those for oxidation of isolated allylic amides (Scheme 3) were due to the formation of small amounts of decomposition products, which has been noted earlier as being due to the formation of acetamides and allylic cations.[16a] Notably, the palladium-catalyzed [3,3]-rearrangement of the allylic imidate to the allylic amide was not observed in the case of 3-phenylallyl trichloroacetimidates.[16b]

Importantly, in contrast to the oxidation of allylic esters, where the reversibility of the Pd(II)-catalyzed rearrangement between branched and linear isomers resulted in erosion of the enantiomeric excess in enantioenriched branched allylic esters,[11c] the enantioselectivity is fully retained in the case of allylic amines (Scheme 5). The palladium-catalyzed enantiose-

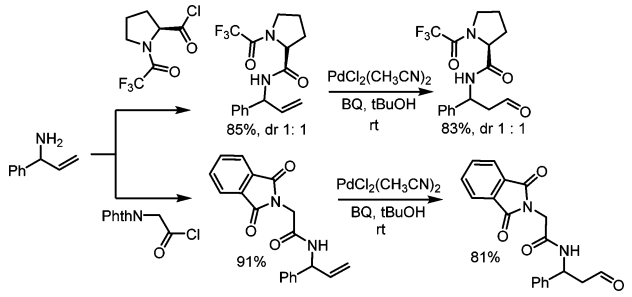
Scheme 5. Asymmetric Overman Rearrangement Followed by Pd(II)-Catalyzed Oxidation to the Aldehyde with Retention of Enantiomeric Excess



lective Overman rearrangement[16] proceeds with excellent enantiomeric excess in tBuOH, and the subsequent Pd(II)-catalyzed oxidation provides the corresponding aldehyde in 95% ee. Hence the synthesis of an optically active β-amino aldehyde can be readily achieved starting from the achiral allylic alcohol.

Synthesis of Protected β-Amino Aldehyde Dipeptides. In view of the substrate scope of the reaction, its application to dipeptide synthesis was examined. 1-Phenylallylamine was protected with *N*-trifluoroacetyl-L-proline and subsequently converted to the corresponding β-amino aldehyde-containing peptide in 83% yield with excellent AM selectivity (Scheme 6). The corresponding dipeptide aldehyde

Scheme 6. Synthesis of β-Peptide Aldehydes via Palladium-Catalyzed Oxidation[a]



[a]Catalyst loading 5 mol %. Isolated yields and diastereomeric ratios determined by ^{1}H NMR spectroscopy are shown.

is obtained with the expected 1:1 ratio of diastereomers. Furthermore, phthalylglycine was coupled to 1-phenylallylamine, and upon oxidation the corresponding aldehyde derivative was obtained in high yield (81%; Scheme 6). The peptide bond here helps the selective oxidation to the β-peptide aldehyde, which circumvents the need for N-deprotection in conventional peptide synthesis.

Role of the Solvent. A key feature of AM oxidations of alkenes with Pd(II) is the requirement that tBuOH be used as solvent.[11] The attack of a nucleophile, i.e., water or alcohol, is viewed as being a key step in the Pd(II)-catalyzed oxidation of alkenes. Indeed, Grubbs and co-workers proposed that tBuOH reacted with an η_2-styrene complex to form an enol ether as an intermediate, followed by hydrolysis with water to release phenylacetaldehyde.[11b,f] The importance of stoichiometric water in the oxidation of styrene was exemplified by the 38% yield of aldehyde achieved when only adventitious water (i.e., from atmospheric moisture) was present.[11b]

In sharp contrast, in both the oxidation of allylic esters reported by our group earlier[11c] and in the oxidation of allylic amines reported here, reduced selectivity was observed with water present, and indeed, water is not needed in order to achieve both full conversion and AM selectivity. The data support a mechanism for the oxidation of these substrates in which water and tBuOH compete as nucleophiles, with the former providing the methyl ketone product and the latter the desired aldehyde product.

In the present study, when methanol or ethanol was used as the solvent, a decrease in AM selectivity (dialkoxy acetal:ketone ca. 2:1) was observed. The formation of dialkoxy acetals is notable and consistent with earlier reports on the oxidation of α-olefins bearing electron-withdrawing substituents in the presence of, in particular, diols.[17] Furthermore, when aldehyde **2h** was added at the start of a reaction, together with an oxidizable allylic amide, it did not form an acetal (Scheme 7). Hence, the formation of the acetal must occur during the catalytic cycle and not subsequent to oxidation of the alkene.

These data confirm the role of the alcohol as a nucleophile. However, the direct formation of the aldehyde product when tBuOH is used as the solvent, even under anhydrous conditions, suggested that an elimination reaction takes place subsequent to the oxidation (Scheme 8). The elimination was

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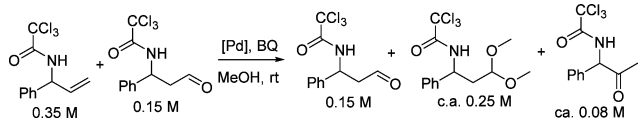
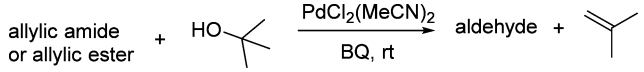
Scheme 7. Oxidation of 1h in the Presence of 2h in Methanol



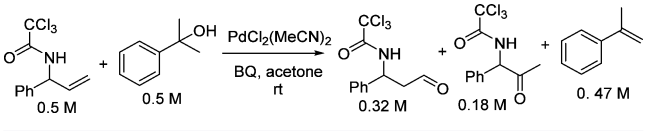
Scheme 8. Oxidation of Allylic Amine or Allylic Ester in the Presence of tBuOH



confirmed by headspace GC analysis with the detection of 2-methylprop-1-ene during the oxidations of both allylic amides and allylic esters. As expected, although other alcohols could be used for the reaction, butene isomers were not detected in the gas phase in those cases. Indeed, neither was 2-methylprop-1-ene observed when the substrate was omitted. Furthermore, when stoichiometric tBuOH was used with acetone as the solvent, full conversion and selectivity were achieved. When tBuOH was omitted from the reaction, conversion was not observed, confirming its role as reagent.

Quantification of the transformation of a tertiary alcohol to its corresponding alkene during the oxidation of allylic amides was obtained using the tertiary alcohol 2-phenyl-2-propanol stoichiometrically in the oxidation of allylic amides in acetone (Scheme 9). 2-Phenyl-1-propene was formed stoichiometrically

Scheme 9. Oxidation of Allylic Amide in the Presence of 2-Phenyl-2-propanol

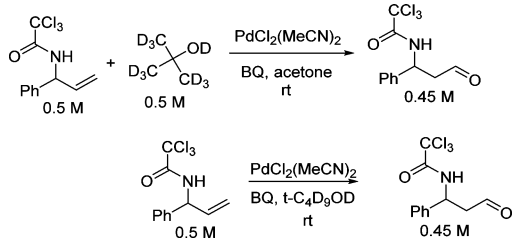


together with full conversion of the allylic amide, albeit notably with a loss in selectivity (aldehyde to ketone ratio of 1.5:1). The decrease in AM selectivity is likely due to water,[18] which competes with sterically hindered tertiary alcohols more effectively than with tBuOH. Indeed, although full AM selectivity was observed when tBuOH was used stoichiometrically in acetone, the addition of 10 equiv of water resulted in a substantial decrease in selectivity to 3:1 (aldehyde:ketone). Similar results were obtained with 3-methylpentan-3-ol and 2,3-dimethylpentan-3-ol (see the Supporting Information for further details).

These data confirm the role of the alcohol in the reaction as a nucleophile and that the direct formation of aldehyde is due to elimination in the case of tertiary alcohols. However, the fact that AM selectivity is achieved only with tBuOH indicates that the selectivity is not solely dependent on either steric factors or the occurrence of the elimination itself.

Mechanistic Considerations. The observation of stoichiometric isobutene formation with tertiary alcohols as well as alkoxy acetals with other alcohols precludes mechanisms in which hydrolysis of an alkyl enol ether intermediate is involved in the catalytic cycle. It is notable that when tBuOH-d_{10} was employed either stoichiometrically with acetone as the solvent and stoichiometric palladium catalyst or as the solvent with Pd(II) (20 mol %), deuterium incorporation into the product was not observed with either **1a** or **1h** (Scheme 10). It should be noted that in both cases full conversion was achieved after 5 h while excellent selectivity was retained (A:M > 99:1).

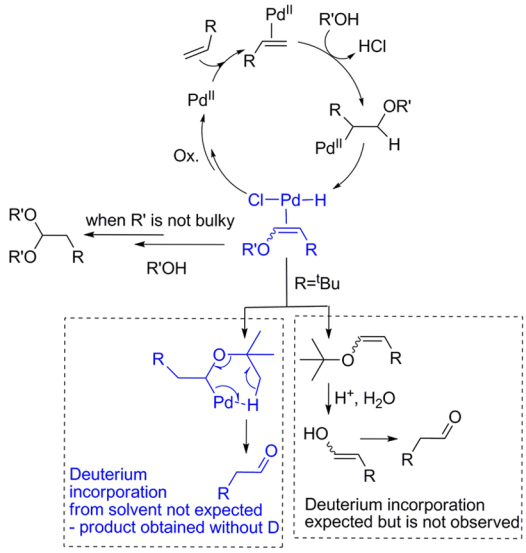
Scheme 10. AM-Selective Oxidations with tBuOH-d_{10}



These data further indicate that hydrolysis of an enol ether, which would involve deuterium incorporation at the β-carbon of the terminal alkene, is unlikely to be involved in the reaction under the conditions employed here. Hence, the mechanism is distinct from that proposed by Grubbs and co-workers in the oxidation of styrene in the presence of stoichiometric water.[11b] Furthermore, the absence of deuterium incorporation when tBuOH-d_{10} was used as the solvent excludes the occurrence of enol tautomerization under the reaction conditions. The absence of deuterium incorporation is consistent with a model in which intramolecular hydrogen transfer from C1 to C2 occurs together with acetal formation.[17b,19]

On the basis of the experimental data, a number of possible nucleophilic pathways can be excluded already (Scheme 11).

Scheme 11. Proposed Mechanism for Aldehyde and Acetal Formation



When primary alcohols are used (i.e., EtOH, MeOH), the corresponding dialkoxy acetals are obtained from allylic amides; however, these acetals are not formed after oxidation from aldehyde products (vide supra, Scheme 7). Hence, although aldehydes are obtained directly when tertiary alcohols are used, in all other cases it is clear that alkoxy acetals are the primary product of the oxidation by palladium. The absence of deuterium incorporation from the solvent excludes enol intermediates in the reaction pathway, and the full retention

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of enantioselectivity excludes the formation of intermediate η_3-allylpalladium complexes.

CONCLUSION

We have demonstrated that protected β-amino aldehydes, from the corresponding protected allylic amines and even from linear allylic alcohols, can be obtained under ambient conditions with a wide range of protecting groups. Furthermore, we demonstrate that tBuOH acts as a nucleophile and provides the aldehyde product directly by means of an elimination to give isobutene. Crucially, the retention of stereochemistry in chiral protected allylic amines and the applicability of this method to peptide synthesis present considerable opportunities in synthesis and chemical biology.

EXPERIMENTAL SECTION

Reagents and Characterization Methods. Reagents were of commercial grade and used as received, unless stated otherwise. Chromatography used Merck silica gel type 9385, 230−400 mesh, and thin-layer chromatography (TLC) used Merck silica gel 60, 0.25 mm, with visualization by UV and potassium permanganate staining. Mass spectra were recorded on an AEI-MS-902 mass spectrometer (EI+) or an LTQ Orbitrap XL (ESI+). ^{1}H and ^{13}C NMR spectra were recorded on a Varian AMX400 spectrometer (400 and 100.59 MHz, respectively) using $CDCl_3$ as the solvent. Chemical shift values are reported in parts per million with the solvent resonance as the internal standard ($CHCl_3$: 7.26 ppm for ^{1}H, 77.0 ppm for ^{13}C). Data are reported as follows: chemical shift (multiplicity, coupling constant(s) in hertz, integration). Multiplicities are abbreviated as follows: s = singlet, d = doublet, t = triplet, q =quartet, br = broad, m = multiplet. ^{13}C spectra were assigned on the basis of APT ^{13}C NMR spectroscopy.

General Procedure for the Oxidation of Allylic Amides. Unless stated otherwise, $[PdCl_2(CH_3CN)_2]$ (0.05 mmol) and *p*-benzoquinone (1 mmol) were dissolved in tBuOH (2 mL). The allylic amide (1 mmol, 0.5 M) was added to the solution, and the mixture was stirred at room temperature until the reaction was complete as determined by TLC analysis. The combined organic layers were washed with water, dried over Na_2SO_4, and concentrated in vacuo. Purification by silica gel flash chromatography yielded the desired aldehyde. For characterization data, see the Supporting Information.

Oxidation of Allylic Imidates to Protected β-Amino Aldehydes. $[PdCl_2(CH_3CN)_2]$ (0.05 mmol) and allylic imidate (0.5 mmol, 0.5 M) were dissolved in tBuOH (1 mL). After 6 h of stirring, *p*-benzoquinone (0.5 mmol) was added to the solution. The reaction mixture was stirred at room temperature until the reaction was complete. The combined organic layers were washed with water, dried over Na_2SO_4, and concentrated in vacuo. Purification by silica gel flash chromatography yielded the desired aldehyde. For characterization data, see the Supporting Information.

ASSOCIATED CONTENT

Supporting Information

Experimental details and spectral characterization of products. 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.

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