Chapter 3

Palladium - catalysed anti-Markovnikov oxidation of allylic amides to protected β-amino aldehydes

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) catalysed oxidation of N-protected allylic amines with benzoquinone is achieved in t-BuOH 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-catalysed autotandem reactions and the application of this method to the synthesis of β-peptide aldehydes is described. From a mechanistic perspective, we demonstrate that t-BuOH 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 t-BuOH 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 hydrolysed to their corresponding aldehyde products.

This chapter was published in part:
3.1 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,\(^3\) are crucial building blocks for the preparation of peptide aldehydes,\(^1\) 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 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.\(^10\)

Recent progress in the palladium-catalysed AM oxidation of alkenes made by both our group and Grubbs and co-workers, has enabled the realisation of selective oxidation of a range of terminal alkenes to aldehydes.\(^11\) Indeed, we recently demonstrated that allylic esters can be oxidised readily to the corresponding aldehydes selectively using a catalyst such as \([\text{PhCN})_2 \text{PdCl}_2\] and the oxidant \(\text{p-benzoquinone in tert-butyl alcohol (t-BuOH)}\) under ambient conditions.\(^12\)

The new opportunities arising from Wacker-Tsuji AM oxidation of allylic amines was demonstrated recently by Feringa and co-workers in the AM-selective oxidation of phthalimide-protected allylic amines to their corresponding \(\beta^3\)-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 worth, 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.\(^12\)](image)

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 t-BuOH as the solvent / reagent (in place of the conventional Wacker-Tsuji conditions employing \(O_2\), CuCl and DMF/H\(_2\)O, respectively). Importantly, the method allows for full retention of the stereochemistry of enantioenriched 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 t-BuOH as solvent was perceived to be essential to achieving AM selectivity. Here we demonstrate that the role played by the alcohol, either as solvent or stoichiometrically, is as a nucleophile and the source of oxygen atom in the final product. However, although all of the linear and tertiary alcohols employed give full conversion, only t-BuOH provides excellent AM selectivity in the oxidation of allylic amides.

\[ \text{Scheme 2. Catalytic oxidative synthesis of protected } \beta\text{-amino aldehydes described in this chapter.} \]

3.2 Results and discussion

The method introduced recently by our group for the oxidation of allylic esters, \textit{i.e.}, with \([(RCN)_2\text{PdCl}_2] (R = \text{CH}_3, \text{iPr, Ph}) as the catalyst and BQ as the oxidant in t-BuOH under ambient conditions,\(^{[11c]}\) was applied here in the oxidation of trichloroacetyl-protected allylamine to yield the aldehyde product exclusively (>99:1; Table 1, entry 1).

Table 1. Catalyst Screening

<table>
<thead>
<tr>
<th>entry</th>
<th>catalyst</th>
<th>conversion</th>
<th>A : M*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>([(\text{CH}_3\text{CN})_2\text{PdCl}_2])</td>
<td>full</td>
<td>99 : 1</td>
</tr>
<tr>
<td>2</td>
<td>([(\text{iPrCN})_2\text{PdCl}_2])</td>
<td>full</td>
<td>99 : 1</td>
</tr>
<tr>
<td>3</td>
<td>([(\text{PhCN})_2\text{PdCl}_2])</td>
<td>full</td>
<td>99 : 1</td>
</tr>
<tr>
<td>4</td>
<td>[\text{PdCl}_2]</td>
<td>30%</td>
<td>99 : 1</td>
</tr>
<tr>
<td>5</td>
<td>([(\text{MeCN})_2\text{PdCl(NO}_2))]</td>
<td>40%</td>
<td>99 : 1</td>
</tr>
<tr>
<td>6</td>
<td>[\text{Pd(OAc)}_2]</td>
<td>0%</td>
<td>-</td>
</tr>
</tbody>
</table>

*Conversion and ratio is determined by \(^1\text{H NMR spectroscopy.}\)

Several related catalysts were tested under the same conditions (Table 1). Complexes of the type \([(RCN)_2\text{PdCl}_2]\) (entries 2 and 3) were similarly effective with full conversion and AM selectivity, whereas lower conversion was obtained using \[\text{PdCl}_2\] or \([(\text{MeCN})_2\text{PdCl(NO}_2)\)] albeit with full retention of the AM selectivity (entries 4 and 5). Conversion was not observed with \[\text{Pd(OAc)}_2\] (entry 6). The activity observed with
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$[\text{PdCl}_2]$ is less than that where nitrile ligands are present, but the observation that 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.\textsuperscript{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 $[(\text{CH}_3\text{CN})_2\text{PdCl}_2]$ and BQ as the oxidant in t-BuOH (Scheme 3). When the catalyst loading was varied from 2.5 to 10 mol%, 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 t-BuOH.

Phthalimide-protected allylic amines were oxidised to aldehydes 2a and 2b with excellent selectivity (> 99:1; Scheme 3) using a reducing reaction time reduced of 16 h compared with those required under Wacker-Tsuji conditions (Scheme 1), where 72 h was required together with 10 mol% catalyst.\textsuperscript{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.\textsuperscript{12} Mono- or bis-N-protected 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/ methoxyl phenyl (2l) bis-protected ones. In addition, 4-methoxylphenyl (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 yield 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 protected allylic amine precursors is often challenging. The wide tolerance to protecting groups shown by the present catalytic system, however, allows for protected β-amino aldehydes to be prepared directly from linear allylic alcohols in high yield and atom economy. Protection of linear allylic alcohols with several imidoyl groups was followed by *in situ* Pd(II)-catalysed rearrangement to the protected branched allylic amines and subsequent oxidation to the corresponding aldehydes in good yields (Scheme 4) with the same selectivities 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. Notably, the palladium catalysed [3,3]-rearrangement of the allylic imidate to the allylic amide was not observed in the case of 3-phenylallyl trichloroacetimidates.

![Scheme 4](image)

**Scheme 4.** Synthesis of β-amino aldehydes from allyl imidate via an Autotandem reaction.

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

Importantly, in contrast to the oxidation of allylic esters, where the reversibility of the Pd(II) catalysed rearrangement between branched and linear isomers resulted in erosion of enantiomeric excess in enantioenriched branched allylic esters, the enantioselectivity is fully retained in the case of allylic amines (Scheme 5). The palladium-catalysed enantioselective Overman rearrangement proceeds with excellent enantiomeric excess in t-BuOH, and the subsequent Pd(II)-catalysed oxidation provides the corresponding aldehyde in 95% ee. Hence the synthesis of an enantiomeric rich β-amino aldehyde can be achieved readily starting from the achiral allylic alcohol.
Scheme 5. Asymmetric Overman rearrangement followed by Pd(II) catalysed oxidation to aldehyde with retention of enantiomeric excess

**Synthesis of protected β-amino-aldehyde dipeptides** In the view of the substrate scope of the reaction, its application to dipeptide synthesis was examined. 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), to provide the corresponding dipeptide aldehyde with the expected 1:1 ratio of diastereomers. Furthermore, phthalylglycine was coupled to 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 β-peptide aldehyde, which circumvents the need for N-deprotection in conventional peptide synthesis.

![Scheme 6](image)

**Scheme 6.** Synthesis of β-peptide aldehyde via palladium catalysed oxidation

Catalyst loading 5 mol%; Isolated yields and diastereomeric ratios determined by $^1$H NMR spectroscopy are shown.

**Role of the Solvent.** A key feature of AM oxidations of alkenes with Pd(II) is the requirement that $t$-BuOH 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) catalysed oxidation of alkenes. Indeed, Grubbs and co-workers proposed that $t$-BuOH reacted with an $\eta_2$-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 in that report by the 38% yield of aldehyde achieved when only adventitious water (i.e. from atmospheric moisture) was present.

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 $t$-BuOH 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 oxidisable 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.

Scheme 7. Oxidation of 1h in the presence of 2h in methanol.

These data confirm the role of the alcohol as nucleophile. However, the direct formation of the aldehyde product when t-BuOH is used as solvent, even under anhydrous conditions, suggested that an elimination reaction takes place subsequent to the oxidation (Scheme 8). The elimination was confirmed by headspace GC analysis with the detection of 2-methyl-propene during the oxidation 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-methyl-propene observed when the substrate was omitted. Furthermore, when stoichiometric t-BuOH was used with acetone as the solvent, full conversion and selectivity were achieved. When t-BuOH was omitted from the reaction, conversion was not observed, confirming its role as reagent.

Scheme 8. Oxidation of allylic amines or allylic esters in the presence of t-BuOH.

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 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 t-BuOH. Indeed, although full AM selectivity was observed when t-BuOH 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 Experimental section 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 t-BuOH indicates that the selectivity is not solely dependent on either steric factors or on 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 t-BuOH-d10 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 t-BuOH-d10.](image)

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. Furthermore, the absence of deuterium incorporation when t-BuOH-d10 was used as the solvent excludes the occurrence of enol tautomerisation under 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.
Scheme 11. Proposed mechanism for aldehyde and acetal formation.

On the basis of the experimental data, a number of possible nucleophilic pathways can be excluded already (Scheme 11). 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 8). 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 of enantioselectivity excludes the formation of intermediate \( \eta_1 \)-allyl palladium complexes.

3.3 Conclusion

We have demonstrated that protected \( \beta \)-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 t-BuOH 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.

3.4 Experimental section

3.4.1 General procedures and methods

All reagents are of commercial grade and used as received unless stated otherwise. Chromatography: Merck silica gel type 9385 230-400 mesh, TLC: Merck silica gel 60, 0.25 mm, with visualisation by UV and potassium permanganate staining. Mass spectra were recorded on an AEI-MS-902 mass spectrometer (EI+) or a LTQ Orbitrap XL (ESI+). \(^1\)H- and \(^13\)C-NMR spectra were recorded on a Varian AMX400 (400 and 100.59 MHz, respectively)
using CDCl$_3$ as solvent. Chemical shift values are reported in ppm with the solvent resonance as the internal standard (CHCl$_3$: 7.26 for $^1$H, 77.0 for $^{13}$C). Data are reported as follows: chemical shifts, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), coupling constants (Hz), and integration. $^{13}$C NMR spectra were assigned based on APT $^{13}$C-NMR spectroscopy.

**General procedure for the oxidation of allylic amides**

$[\text{PdCl}_2(\text{CH}_3\text{CN})_2]$ (0.05 mmol) and $p$-benzoquinone (1 mmol) were dissolved in t-BuOH (2 ml). The allylic amide (1 mmol, 0.5 M) was added to the solution and stirred at room temperature until the reaction was complete as determined by T.L.C. analysis. The combined organic layers were washed with water, dried over Na$_2$SO$_4$, and concentrated in vacuo. Purification by flash silica-gel chromatography yielded the desired aldehyde. For characterisation see section 3.4.3.

**Oxidation of allylic imidate to protected β-amino-aldehyde**

$[\text{PdCl}_2(\text{CH}_3\text{CN})_2]$ (0.005 mmol to 0.05 mmol) and allylic imidate (0.5 mmol, 0.5 M) were dissolved in the t-BuOH (1 ml). After stirring for 6h, $p$-benzoquinone (0.5 mmol) was added in 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$_2$SO$_4$, and concentrated in vacuo. Purification by silica-gel flash chromatography yielded the desired aldehyde. For characterisation see section 3.4.3.

**3.4.2 Preparation of Substrates**

Preparation and protection of branched allylic esters

Substrate 1a and 1b were prepared using the Mitsunobu reaction as described elsewhere.$^{[12]}$ Substrates 1c, 1d, 1e, 1f and 1g are prepared by protection of the corresponding allylic amine.

![Diagram of the Mitsunobu reaction](image)

General method: The appropriate allylic alcohol (10 mmol) was dissolved in dichloromethane and the solution cooled to -15°C. Aqueous KOH (50 %, 10 mL) and tetrabutyl ammonium hydrogen sulfate (44 mmol, 15 mg) were added at -15°C, followed by dropwise addition of trichloracetonitrile (11.7 mmol, 1180 μl). The resulting mixture was stirred for 30 min at -15°C, followed by 30 min at RT. The solution was diluted with dichloromethane and water was added. The organic phase was separated, and the aqueous phase was extracted twice with dichloromethane. The combined organic phases were dried over Na$_2$SO$_4$, concentrated in vacuo, and filtered over silica gel (2 cm). The silica gel was isolated by evaporation of the solvent in vacuo.$^{[20]}$

$\text{K}_2\text{CO}_3(2 \text{ mg/mL xylene})$ was added to a solution of the allylic imidate (1 equiv) in xylene (6 ml per 1 mmol of trichloroacetimidate) and the mixture heated to 140°C for 24 h. The reaction mixture was cooled to room temperature, concentrated in vacuo, and filtered over a short column of silica gel (eluent toluene) to yield the trichloroacetyl protected allylic amides 1h, 1i, 1j.$^{[21]}$
5 M NaOH (aq) (30 equiv) was added to a solution of the corresponding amide (1 equiv) in absolute ethanol (5 mL per 1 mmol of amide), and the mixture was stirred at room temperature for 24 h. The mixture was concentrated in vacuo to remove ethanol and the aqueous residue was acidified to pH 1 by the addition of 6 M HCl (aq.) and washed three times with CH$_2$Cl$_2$. Na$_2$CO$_3$ was added to the aqueous layer to increase the pH to 8. The mixture was extracted three times with diethyl ether. The combined organic layers were dried over Na$_2$SO$_4$, filtered, and concentrated under reduced pressure to provide the corresponding allylic amine.\[21\]

Preparation of 1c, 1e, 1f and 1g: A solution of benzoyl, pivaloyl or furoyl chloride (1.2 mmol) in dry dichloromethane (2mL) was added slowly to a stirred solution of the appropriate allylic amine (1 mmol) in dry pyridine (2.7 mL), at 0 °C. The reaction mixture was stirred under an inert atmosphere at room temperature for 3 h. The mixture was concentrated in vacuo and the residue dissolved in chloroform, washed with NaHCO$_3$ (aq.) and brine. The organic layer was dried over Na$_2$SO$_4$, filtered and concentrated in vacuo. The crude product was purified by flash column chromatography.\[22\]

Substrate 1d: (Boc)$_2$O (810 mg, 3.71 mmol) was added to a stirred solution of allylic amine (3.71 mmol) in dioxane (8mL) containing 8 mL aqueous solution of NaOH (2.5 M) and the mixture was stirred at room temperature for 30 min. After addition of water (10 mL), the mixture was extracted with diethyl ether. The combined organic phases were washed with brine, dried (Na$_2$SO$_4$), and concentrated in vacuo. The residue was purified by flash column chromatography.\[23\]

Substrates 1k, 1l and 1m were prepared by rearrangement of the corresponding allylic imidates. Sodium hydride (60% in mineral oil, 1.1 equiv) was added to a solution of allylic alcohol in THF (2 ml / mmol) at 0 °C. After stirring at room temperature for 2 h, a solution of 2,2,2-trifluoro-N-(4-methoxy-phenyl)-acetimidoyl chloride or N-phenyl benzimidoyl chloride (1.0 equiv) in THF (0.5 mL / mmol) was added. Stirring was continued for 2 h, then water (10 mL / mmol) and MTBE (10 mL / mmol) were added. The organic and aqueous phases were separated and the aqueous phase was extracted with MTBE (10 mL / mmol). The combined organic phases were dried over Na$_2$SO$_4$ and concentrated in vacuo. The residue was purified by column chromatography (pentane + NEt$_3$) to afford the desired allylic imidate.\[24\]

Alllylic imidate was added at room temperature to a solution of bis(acetonitrile)dichloropalladium(II) (5 mol%) in DCM (2ml /mmol) and the mixture stirred overnight. The mixture was concentrated in vacuo and filtered over silica gel using DCM as eluent. The solvent was removed in vacuo to yield the corresponding allylic amide.
3.4.3 Characterisation of products

**N-(3-oxo-1-phenylpropyl)pivalamide 2c** Isolated by flash column chromatography on silica gel (pentane/ether = 6 : 4). The title compound was obtained as a white solid (58% yield). HRMS (ESI+) calc. for $\text{C}_{14}\text{H}_{20}\text{NO}_2$ (M+H)$^+$ 234.1488, found 234.1489;

$^1\text{H NMR (400 MHz, CDCl}_3\text{)}$ δ 9.69 (s, 1H), 7.32-7.17 (m, 5H), 6.24 (s, 1H), 5.42 (dd, $J$ = 6.4 Hz, 14.2 Hz, 1H), 2.90 (m, 2H), 1.13 (s, 9H); $^{13}\text{C NMR (101 MHz, CDCl}_3\text{)}$ δ 200.4, 177.9, 140.5, 128.9, 127.8, 126.3, 49.0, 48.4, 38.7, 27.4.

**tert-butyl (3-oxo-1-phenylpropyl)carbamate 2d** Isolated by flash column chromatography on silica gel (pentane/ether = 6 : 4). The title compound was obtained as a white solid (85 % yield). HRMS (ESI+) calc. for $\text{C}_{14}\text{H}_{20}\text{NO}_3$ (M+H)$^+$ 272.1257, found 272.1256;

$^1\text{H NMR (400 MHz, CDCl}_3\text{)}$ δ 9.74 (s, 1H), 7.37-7.27 (m, 5H), 5.20-5.13 (m, 2H), 3.02-2.88 (m, 2H), 1.42 (s, 9H); $^{13}\text{C NMR (101 MHz, CDCl}_3\text{)}$ δ 200.1, 155.0, 140.9, 128.8, 127.7, 126.2, 79.9, 50.1, 49.8, 28.3.

**N-(3-oxo-1-phenylpropyl)benzamide 2e** Isolated by flash column chromatography on silica gel (pentane/ether = 5 : 5). The title compound was obtained as a light yellow solid (50 % yield). HRMS (ESI+) calc. for $\text{C}_{16}\text{H}_{16}\text{NO}_2$ (M+H)$^+$ 254.1175, found 254.1171;

$^1\text{H NMR (400 MHz, CDCl}_3\text{)}$ δ 9.81 (s, 1H), 7.78-7.76 (m, 2H), 7.52-7.29 (m, 8H), 6.95 (m, 1H), 5.73-5.68 (dd, $J$ = 6.5 Hz, 14.1 Hz, 1H), 3.24-3.18 (dd, $J$ = 6.5 Hz, 17.0 Hz, 1H), 3.09-3.03 (dd, $J$ = 6.5 Hz, 17.0 Hz, 1H); $^{13}\text{C NMR (101 MHz, CDCl}_3\text{)}$ δ 200.5, 166.7, 140.3, 133.9, 131.7, 128.9, 128.6, 127.9, 126.9, 126.5, 49.1, 48.8.

**N-(1-(4-methoxyphenyl)-3-oxopropyl)benzamide 2f** Isolated by flash column chromatography on silica gel (pentane/ether = 6 : 4). The title compound was obtained as a yellow solid (50 % yield). HRMS (ESI+) calc. for $\text{C}_{17}\text{H}_{18}\text{NO}_3$ (M+H)$^+$ 284.1281, found 284.1279;

$^1\text{H NMR (400 MHz, CDCl}_3\text{)}$ δ 9.81 (s, 1H), 7.76-7.74 (m, 2H), 7.51-7.29 (m, 5H), 6.89-6.83 (m, 3H), 5.68-5.63 (dd, $J$ = 6.5 Hz, 14.1 Hz, 1H), 3.79 (s, 3H), 3.23-3.16 (dd, $J$ = 6.5 Hz, 16.8 Hz, 1H), 3.06-3.00 (dd, $J$ = 6.3 Hz, 16.8 Hz, 1H); $^{13}\text{C NMR (101 MHz, CDCl}_3\text{)}$ δ 200.5, 166.6, 159.2, 134.0, 132.3, 131.7, 128.5, 127.8, 126.9, 114.3, 55.3, 48.8, 48.6.
N-(3-oxo-1-phenylpropyl)furan-2-carboxamide 2g Isolated by flash column chromatography on silica gel (pentane/ether = 5 : 5). The title compound was obtained as a white solid (86 % yield). HRMS (ESI+) calc. for C\textsubscript{14}H\textsubscript{14}NO\textsubscript{3} (M+H)\textsuperscript{+} 244.0968, found 244.0968; 
\begin{align*}
\text{\textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3})} & \delta 9.80 (s, 1H), 7.43 (m, 1H), 7.38-7.27 (m, 5H), 7.13-7.12 (d, J = 3.4 Hz, 1H), 6.95 (m, 1H), 6.50-6.90 (m, 1H), 5.71-5.66 (dd, J = 6.5 Hz, 14.7 Hz, 1H), 3.22-3.16 (dd, J = 6.9 Hz, 16.9 Hz, 1H), 3.08-3.02 (dd, J = 6.1 Hz, 17.0 Hz, 1H); \\
\text{\textsuperscript{13}C NMR (101 MHz, CDCl\textsubscript{3})} & \delta 199.9, 157.6, 154.6, 144.0, 140.0, 128.9, 126.5, 114.7, 112.2, 48.9, 48.2.
\end{align*}

2,2,2-trichloro-N-(3-oxo-1-phenylpropyl)acetamide 2h Isolated by flash column chromatography on silica gel (pentane/ether = 6 : 4). The title compound was obtained as a white solid (84 % yield). HRMS (ESI+) calc. for C\textsubscript{11}H\textsubscript{11}Cl\textsubscript{3}NO\textsubscript{2} (M+H)\textsuperscript{+} 293.9849, found 293.9851; 
\begin{align*}
\text{\textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3})} & \delta 9.78 (s, 1H), 7.60 (bs, 1H), 7.40-7.32 (m, 5H), 5.44-5.39 (m, 1H), 3.29-3.23 (dd, J = 5.6 Hz, 17.7 Hz, 1H), 3.12-3.06 (dd, J = 6.0 Hz, 17.7 Hz, 1H); \\
\text{\textsuperscript{13}C NMR (101 MHz, CDCl\textsubscript{3})} & \delta 199.6, 161.3, 138.7, 129.1, 128.3, 126.3, 104.9, 50.7, 47.8.
\end{align*}

2,2,2-trichloro-N-(4-oxobutan-2-yl)acetamide 2i Isolated by flash column chromatography on silica gel (pentane/ether = 7 : 3). The title compound was obtained as a yellow oil (72 % yield). HRMS (ESI+) calc. for C\textsubscript{11}H\textsubscript{11}Cl\textsubscript{3}NO\textsubscript{2} (M+H)\textsuperscript{+} 231.9693, found 231.9693; 
\begin{align*}
\text{\textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3})} & \delta 9.79 (s, 1H), 7.17 (bs, 1H), 4.40-4.30 (m, 1H), 2.88-2.82 (dd, J = 5.0 Hz, 18.0 Hz, 1H), 2.81-2.75 (dd, J = 5.6 Hz, 18.1 Hz, 1H), 1.38-1.36 (d, J = 6.8 Hz, 3H); \\
\text{\textsuperscript{13}C NMR (101 MHz, CDCl\textsubscript{3})} & \delta 200.2, 161.2, 92.4, 48.2, 43.4, 19.7.
\end{align*}

2,2,2-trichloro-N-(1-oxooctan-3-yl)acetamide 2j Isolated by flash column chromatography on silica gel (pentane/ether = 6 : 4). The title compound was obtained as yellow oil (76 % yield). HRMS (ESI+) calc. for C\textsubscript{10}H\textsubscript{17}Cl\textsubscript{3}NO\textsubscript{2} (M+H)\textsuperscript{+} 288.0319, found 288.0315; 
\begin{align*}
\text{\textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3})} & \delta 9.78 (s, 1H), 7.12 (bs, 1H), 4.26-4.18 (m, 1H), 2.82-2.79 (m, 2H), 1.73-1.58 (m, 2H), 1.42-1.28 (m, 6H), 0.87 (m, 3H); \\
\text{\textsuperscript{13}C NMR (101 MHz, CDCl\textsubscript{3})} & \delta 200.4, 161.5, 92.5, 47.6, 47.0, 33.8, 31.2, 25.7, 22.4, 13.8.
\end{align*}

N-(3-oxo-1-phenylpropyl)-N-phenylbenzamide 2k Isolated by flash column chromatography on silica gel (pentane/ether = 7 : 3). The title compound was obtained
as a yellow oil (83 % yield). HRMS (ESI+) calc. for C_{22}H_{20}NO_{2} (M+H)^+ 330.1488, found 380.1484;

\^H NMR (400 MHz, CDCl\textsubscript{3}) \( \delta \) 9.88 (s, 1H), 7.28-6.99 (m, 13H), 6.69-6.60 (m, 3H), 3.25-3.17 (dd, \( J = 9.6 \) Hz, 16.2 Hz, 1H), 3.01-2.96 (dd, \( J = 5.9 \) Hz, 16.3 Hz, 1H); \^{13}C NMR (101 MHz, CDCl\textsubscript{3}) \( \delta \) 200.0, 171.1, 139.6, 138.6, 136.2, 130.3, 129.3, 128.6, 128.5, 128.3, 128.2, 128.1, 127.6, 127.5, 54.4, 45.5.

2,2,2-trifluoro-N-(4-methoxyphenyl)-N-(3-oxo-1-phenylpropyl)acetamide 2l
Isolated by flash column chromatography on silica gel (pentane/ether = 7 : 3). The title compound was obtained as a white solid (81 % yield). HRMS (ESI+) calc. for C_{18}H_{17}F_{3}NO_{3} (M+H)^+ 352.1155, found 352.1157;

\^H NMR (400 MHz, CDCl\textsubscript{3}) \( \delta \) 9.82 (s, 1H), 7.32-7.27 (m, 3H), 7.13-7.05 (m, 3H), 6.89-6.86 (m, 1H), 6.63-6.60 (m, 1H), 6.69-6.45 (m, 1H), 6.26-6.24 (m, 1H), 3.79 (s, 3H), 3.16-3.09 (dd, \( J = 9.3 \) Hz, 16.7 Hz, 1H), 2.98-2.92 (dd, \( J = 6.1 \) Hz, 16.6 Hz, 1H); \^{13}C NMR (101 MHz, CDCl\textsubscript{3}) \( \delta \) 198.7, 160.0, 156.8 (q, \( J_{CF} = 35.5 \)), 136.7, 131.9, 131.4, 128.8, 128.6, 128.5, 126.7, 113.8, 113.5, 112.0 (q, \( J_{CF} = 288.6 \) Hz), 55.3, 55.3, 44.8; \(^{19}F\text{-NMR} (376 MHz, CDCl\textsubscript{3}) \delta = -67.0.

2,2,2-trifluoro-N-(4-methoxyphenyl)-N-(1-oxopentan-3-yl)acetamide 2m
Isolated by flash column chromatography on silica gel (pentane/ether = 7 : 3). The title compound was obtained as a dark yellow oil (82 % yield). HRMS (ESI+) calc. for C_{14}H_{17}F_{3}NO_{3} (M+H)^+ 304.1155, found 304.1156;

\^H NMR (400 MHz, CDCl\textsubscript{3}) \( \delta \) 9.75 (s, 1H), 7.12-6.89 (m, 2H), 6.91-6.89 (m, 2H), 5.08-5.04 (m, 1H), 3.83 (s, 3H), 2.60-2.54 (m, 3H), 1.69-1.59 (m, 2H), 1.02 (m, 3H); \^{13}C NMR (101 MHz, CDCl\textsubscript{3}) \( \delta \) 199.7, 160.3, 157.3 (q, \( J_{CF} = 35.0 \)), 131.6, 131.2, 115.0, 114.5, 114.3, 112.1 (q, \( J_{CF} = 288.6 \) Hz), 55.6, 55.0, 46.5, 25.8, 11.2; \(^{19}F\text{-NMR} (376 MHz, CDCl\textsubscript{3}) \delta = -67.2.

N-(1-oxopentan-3-yl)-N-phenylbenzamide 2n
Isolated by flash column chromatography on silica gel (pentane/ether = 6 : 4). The title compound was obtained as a dark yellow oil (62 % yield). HRMS (ESI+) calc. for C_{18}H_{20}NO_{2} (M+H)^+ 282.1488, found 282.1485;

\^H NMR (400 MHz, CDCl\textsubscript{3}) \( \delta \) 9.86 (s, 1H), 7.22-7.03 (m, 10H), 5.15 (m, 1H), 2.87-2.80 (dd, \( J = 8.9 \) Hz, 16.4 Hz, 1H), 2.76-2.71 (dd, \( J = 4.3 \) Hz, 16.5 Hz, 1H), 1.89-1.57 (m, 2H), 1.09 (t, \( J = 7.3 \) Hz, 3H); \^{13}C NMR (101 MHz, CDCl\textsubscript{3}) \( \delta \) 200.8, 171.4, 136.6, 129.7, 129.2, 128.9, 128.2, 127.6, 127.3, 54.9, 47.2, 26.2, 11.4.

2,2,2-trifluoro-N-(4-methoxyphenyl)-N-(4-oxobutan-2-yl)acetamide 2o
Isolated by flash column chromatography on silica gel (pentane/ether = 6 : 4). The title
AM oxidation of allylic amides

Compound was obtained as a yellow oil (61 % yield). HRMS (ESI+) calc. for C_{13}H_{15}F_{3}NO_{3} (M+H)^+ 290.0998, found 290.1000;

\( ^1H \) NMR (400 MHz, CDCl₃) \( \delta \) 9.75 (s, 1H), 7.11-7.06 (m, 2H), 6.92-6.90 (m, 2H), 5.24-5.15 (m, 1H), 3.83 (s, 3H), 2.77-2.68 (dd, \( J = 7.9 \) Hz, 16.7 Hz, 1H), 2.55-2.49 (dd, \( J = 6.2 \) Hz, 16.7 Hz, 1H), 1.21 (d, \( J = 6.8 \) Hz, 3H); \( ^{13}C \) NMR (101 MHz, CDCl₃) \( \delta \) 199.1, 160.1, 156.5 (q, \( J_{CF} = 35.1 \) Hz), 131.4, 131.1, 127.1, 114.2, 114.0, 111.9 (q, \( J_{CF} = 288.5 \) Hz), 55.4, 49.1, 48.1, 18.5; \( ^{19}F \)-NMR (376 MHz, CDCl₃): \( \delta = -67.5 \).

2,2,2-trifluoro-N-(4-methoxyphenyl)-N-(1-oxooctan-3-yl)acetamide

Isolated by flash column chromatography on silica gel (pentane/ether = 6 : 4). The title compound was obtained as a yellow oil (53 % yield). HRMS (ESI+) calc. for C_{17}H_{22}F_{3}NO_{3} (M+H)^+ 346.1624, found 346.1626;

\( ^1H \) NMR (400 MHz, CDCl₃) \( \delta \) 9.74 (s, 1H), 7.10-7.04 (m, 2H), 6.92-6.89 (m, 2H), 5.15-5.12 (m, 1H), 3.83 (s, 3H), 2.62-2.51 (m, 2H), 1.58-1.30 (m, 8H), 0.89 (m, 3H); \( ^{13}C \) NMR (101 MHz, CDCl₃) \( \delta \) 199.5, 160.1, 157.0 (q, \( J_{CF} = 34.0 \) Hz), 131.4, 131.0, 127.0, 114.2, 114.0, 111.9 (q, \( J_{CF} = 288.7 \) Hz), 55.4, 53.2, 46.6, 32.4, 31.4, 26.0, 22.4, 13.9; \( ^{19}F \)-NMR (376 MHz, CDCl₃): \( \delta = -67.2 \).

3.4.4 Enantioselective synthesis of protected β-amino aldehydes by rearrangement / oxidation

[(S)-(+)-COP-Cl, as catalyst, (7.32 mg, 0.005 mmol) and AgOOCF₃ (1.1 mg, 0.005 mmol) were dissolved with stirring in t-BuOH (0.2 mL) and protected from light. After 3 h, a solution of 3-phenylallyl (N-phenyl)benzimidate (31.5 mg, 0.1 mmol) and iPr₂NEt was added and was stirred at room temperature for 3 d. The solution was concentrated and the residue was purified by column chromatography on silica gel. 76% yield of allylic amide with 97% ee was obtained.\[15a\]

\[ [\text{PdCl}_2(\text{CH}_3\text{CN})_2] \ (0.005 \text{ mmol, 1.2 mg}) \text{ and enantiomerically pure allylic imidate (0.05 mmol, 16 mg) were dissolved in the t-BuOH (0.1 mL), p-Benzooquinone (0.05 mmol, 5.4 mg) was added in the solution. The reaction mixture stirred at room temperature for 20h. The combined organic layers were washed with water, dried over Na₂SO₄, and concentrated in vacuo. Purification by silica-gel flash chromatography yielded the desired aldehyde (82 % yield).] \]
amino aldehyde (14 mg, 0.04 mmol) in 1 mL of MeOH. After stirring at room temperature for 1 h, the reaction mixture was quenched with saturated aqueous NH₄Cl (10 mL) and extracted 3 times with ethyl acetate (30 mL). The combined organic layers were washed with brine and dried over Na₂SO₄, the solvents were removed in vacuo. The crude product was purified by silica-gel column chromatography (Pentane/EtOAc) to yield the desired product (93 % yield, 13 mg). Enantiomeric excess was determined by HPLC.

3.4.5 Synthesis of β-peptide-aldehydes

Preparation of substrates: To a stirred solution of 1-phenyl allylamine (1 mmol) in triethylamine (1.1 equiv) in DCM (1 ml), a solution of (S)-N-(trifluoroacetyl)pyrrolidine-2-carbonyl chloride or Phthalylglycyl chloride (1 mmol) in dry dichloromethane (4 ml) was added slowly at 0 °C. The reaction was stirred under an inert atmosphere at room temperature for 16 h. The mixture was washed with water and dried over Na₂SO₄, filtered and concentrated. The product was purified by flash column chromatography.

Procedure for Oxidations: [PdCl₂(CH₂CN)₂] (0.005 mmol to 0.025 mmol) and p-benzoquinone (1 mmol) were dissolved in t-BuOH (2 ml). Allylic amide (1 mmol, 0.2 M) was added to the mixture and stirred at room temperature until the reaction was complete as determined by T.L.C. analysis. The combined organic layers were washed with water, dried over Na₂SO₄, and concentrated in vacuo. Purification by flash silica-gel chromatography yielded the desired aldehyde. Due to the low solubility of phthalylglycyl protected allylic amine in t-butanol, acetone was added as co-solvent for the reaction (acetone : t-butanol, 1 : 1 v/v)

![2-(1,3-dioxoisindolin-2-yl)-N-(3-oxo-1-phenylpropyl)acetamide](image)

Isolated by flash column chromatography on silica gel (pentane/acetone = 3 : 1). The title compound was obtained as a white solid (81 % yield).
AM oxidation of allylic amides

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 9.70 (s, 1H), 7.87-7.85 (dd, $J$ = 3.0 Hz, 5.4 Hz, 2H), , 7.74-7.72 (dd, $J$ = 3.0 Hz, 5.4 Hz, 2H), 7.35-7.26(m, 5H), 6.72-6.70 (d, $J$ = 7.8 Hz, 1H), 5.54-5.50 (dd, $J$ = 6.3 Hz, 14.0 Hz, 1H), 4.33 (s, 2H), 3.13-3.08 (dd, $J$ = 6.3 Hz, 17.2 Hz, 1H), 2.99-2.93 (dd, $J$ = 6.3 Hz, 17.2 Hz, 1H); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 200.2, 167.7, 165.6, 139.7, 134.2, 131.9, 128.9, 127.9, 126.4, 123.6, 49.1, 48.5, 40.8.

(2S)-N-(3-oxo-1-phenylpropyl)-1-(2,2,2-trifluoroacetyl)pyrrolidine-2-carboxamide

Isolated by flash column chromatography on silica gel (pentane/ether = 1 : 3). The title compound was obtained as a yellow oil (83 % yield).

1H NMR (400 MHz, CDCl3) $\delta$ 9.73-9.69 (s, 1H), 7.37-7.25(m, 5H), 7.10 (bs, 1H), 5.48-5.40 (m, 1H), 4.55-4.49(m, 1H), 3.78-3.67(m, 2H), 3.03-2.90 (m, 2H), 2.03-1.94 (m, 1H); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 199.8, 199.7, 169.0, 168.9, 157.37 (q, $J_{CF}$ = 286.7 Hz), 140.0, 139.9, 128.9, 128.9, 127.8, 126.4, 126.2, 120.4 (q, $J_{CF}$ = 37.6 Hz), 61.4, 61.3, 49.3, 49.2, 48.8, 48.7, 47.4, 27.4, 27.2, 25.1; $^{19}$F-NMR (376 MHz, CDCl$_3$): $\delta$ =−72.4. HRMS (ESI+) calc. for C$_{17}$H$_{17}$F$_3$N$_2$O$_3$ (M+H)$^+$ 343.1264, found 343.1270

3.4.6 Role of alcohol as nucleophile

Procedure: 0.1 mmol allylic amide (28 mg) was added in the solution of 0.01 mmol PdCl$_2$(MeCN)$_2$ (2.6 mg), 0.1 mmol BQ (10.8 mg), 0.1 mmol 2-Phenyl-2-propanol (13.6 mg), 0.2 ml acetone. The mixture was stirred at room temperature for 18h.

Phenyl-1-propene: $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.40-7.20 (m, 5H), 5.27 (s, 1H), 4.98 (s, 1H), 1.91 (s, 3H).

2,2,2-trichloro-N-(2-oxo-1-phenylpropyl)acetamide: $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.16 (s, 1H), 7.46-7.31 (m, 5H), 5.44 (d, $J$ = 5.8 Hz, 1H), 2.16 (s, 3H)
Figure 2. $^1$H NMR spectrum in CDCl$_3$ of the reaction mixture obtained upon oxidation of allylic amide with 2-Phenyl-2-propanol.

Figure 3. $^1$H NMR spectrum in CDCl$_3$ of 2,2,2-trichloro-N-(2-oxo-1-phenylpropyl)acetamide.
Oxidation of 1h in acetone with 1 equiv. of tert-butanol and 10 equiv. of D$_2$O

0.1 mmol allylic amide (28 mg) was added in the solution of 0.01 mmol PdCl$_2$ (MeCN)$_2$ (2.6 mg), 0.1 mmol BQ (10.8 mg), 0.1 mmol t-butanol (9.6 μL), 1 mmol D$_2$O (18 μL), 0.2 ml (CD$_3$)$_2$CO. The mixture was stirred at room temperature for 18 h. The $^1$H NMR spectrum of the reaction mixture, diluted by adding (CD$_3$)$_2$CO, was recorded directly. Subsequently, the reaction mixture was diluted in CH$_2$Cl$_2$, washed with water, dried over MgSO$_4$ and concentrated in vacuo. The $^1$H NMR spectrum of the product mixture was obtained in both CDCl$_3$ and (CD$_3$)$_2$CO.

2,2,2-trichloro-N-(3-oxo-1-phenylpropyl)acetamide:

$^1$H NMR [400 MHz, (CD$_3$)$_2$CO] δ 9.78 (s, 1H), 7.66 (s, 1H), 7.49-7.28 (m, 5H), 5.57 (m, 1H), 3.27 (dd, 1H), 3.13 (dd, 1H).

$^1$H NMR (400 MHz, CDCl$_3$) δ 9.79 (s, 1H), 7.62 (bs, 1H), 7.40-7.32 (m, 5H), 5.43 (m, 1H), 3.27 (dd, 1H), 3.10 (dd, 1H).

2,2,2-trichloro-N-(2-oxo-1-phenylpropyl)acetamide:

$^1$H NMR [400 MHz, (CD$_3$)$_2$CO] δ 8.66 (s, 1H), 7.49-7.28 (m, 5H), 5.66 (d, 1H), 2.16 (s, 3H).

$^1$H NMR (400 MHz, CDCl$_3$) δ 7.40-7.20 (m, 5H), 5.44 (s, 1H), 2.16 (s, 3H).

Figure 4. $^1$H NMR spectrum in (CD$_3$)$_2$CO of the reaction mixture.
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Figure 5. $^1$H NMR spectrum of the product mixture, recorded in (CD$_3$)$_2$CO (top) and in CDCl$_3$ (bottom); Note that in CDCl$_3$, the signals from the ketone product overlap with those of the aldehyde product.

**Oxidation of $^1$h in acetone with 1 eq of 2-phenyl-2-propanol and 10 eq. of D$_2$O**

0.1 mmol allylic amide (28 mg) was added to a solution of 0.01 mmol of PdCl$_2$(MeCN)$_2$ (2.6 mg), 0.1 mmol of BQ (10.8 mg), 0.1 mmol of 2-phenyl-2-propanol (13.6 mg), 1 mmol of D$_2$O (18 μL) and 0.2 ml of (CD$_3$)$_2$CO. The mixture was stirred at room temperature for 18h. The $^1$H NMR spectrum of the reaction mixture was recorded after dilution in (CD$_3$)$_2$CO directly. Subsequently the reaction mixture was diluted in CH$_2$Cl$_2$, washed with water, dried over MgSO$_4$ and concentrated in vacuo. The $^1$H NMR spectra of the product mixture were obtained in CDCl$_3$ and (CD$_3$)$_2$CO.

**2,2,2-trichloro-N-(3-oxo-1-phenylpropyl)acetamide:**

$^1$H NMR [400 MHz, (CD$_3$)$_2$CO] $\delta$ 9.78 (s, 1H), 7.66 (s, 1H), 7.49-7.28 (m, 5H), 5.57 (m, 1H), 3.27 (dd, 1H), 3.13 (dd, 1H).

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 9.79 (s, 1H), 7.40-7.32 (m, 5H), 5.43 (m, 1H), 3.27 (dd, 1H), 3.10 (dd, 1H).

**2,2,2-trichloro-N-(2-oxo-1-phenylpropyl)acetamide:**

$^1$H NMR [400 MHz, (CD$_3$)$_2$CO] $\delta$ 8.66 (s, 1H), 7.49-7.28 (m, 5H), 5.66 (d, 1H), 2.16 (s, 3H).

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.40-7.20 (m, 5H), 5.44 (m, 1H), 2.16 (s, 3H).

**2-phenyl-2-propanol:**

$^1$H NMR [400 MHz, (CD$_3$)$_2$CO] $\delta$ 7.53-7.18 (m, 5H), 3.99 (s, 1H), 1.51 (s, 6H).

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.49-7.26 (m, 5H), 1.59 (s, 6H).
AM oxidation of allylic amides

Figure 6. $^1$H NMR spectrum of reaction mixture in (CD$_3$)$_2$CO.

Figure 7. $^1$H NMR spectrum of product mixture in (CD$_3$)$_2$CO (top) and CDCl$_3$ (bottom). Note that in CDCl$_3$, the signals from the ketone product overlap with those of the aldehyde product.
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3.4.7 Stability of tertiary alcohols toward dehydration under reaction conditions

2-phenyl-2-propanol

0.25 mmol of 2-phenyl-2-propanol (34 mg) was added to a solution of 0.025 mmol of \( \text{PdCl}_2(\text{MeCN})_2 \) (6.5 mg), 0.25 mmol of BQ (27 mg) and 0.5 ml of \((\text{CD}_3)_2\text{CO}\). The reaction mixture was stirred at room temperature for 72 h. The \(^1\text{H} \) NMR spectrum of the reaction mixture was recorded following dilution in \((\text{CD}_3)_2\text{CO}\) directly.

2-phenyl-2-propanol: \(^1\text{H} \) NMR [400 MHz, \((\text{CD}_3)_2\text{CO}\)] \( \delta \) 7.53-7.16 (m, 5H), 1.51 (s, 6H).

Phenyl-1-propene: \(^1\text{H} \) NMR [400 MHz, \((\text{CD}_3)_2\text{CO}\)] \( \delta \) 7.53-7.16 (m, 5H), 5.39 (s, 1H), 5.08 (s, 1H), 2.13 (s, 3H).

![Figure 8. \(^1\text{H} \) NMR spectrum of the reaction mixture in \((\text{CD}_3)_2\text{CO}\).](image)

3-methyl-3-pentanol

0.25 mmol 3-methyl-3-pentanol (31 μL) was added to a solution of 0.025 mmol of \( \text{PdCl}_2(\text{MeCN})_2 \) (6.5 mg), 0.25 mmol of BQ (27 mg) and 0.5 ml of \((\text{CD}_3)_2\text{CO}\). The reaction mixture was stirred at room temperature for 18 h. The \(^1\text{H} \) NMR spectrum of the reaction mixture was recorded following dilution in \((\text{CD}_3)_2\text{CO}\) directly.

3-methyl-3-pentanol: \(^1\text{H} \) NMR [400 MHz, \((\text{CD}_3)_2\text{CO}\)] \( \delta \) 1.43 (q, 4H), 1.05 (s, 3H), 0.85 (t, 6H)

3-methyl-pent-2-ene: \(^1\text{H} \) NMR [400 MHz, \((\text{CD}_3)_2\text{CO}\)] \( \delta \) 5.15 (m, 1H), 1.95 (q, 2H), 1.56 (s, 3H), 1.53 (d, 3H), 0.94 (t, 3H).
0.25 mmol of 2,3-dimethyl-3-pentanol (35 μl) was added to a solution of 0.025 mmol of PdCl₂(MeCN)₂ (6.5 mg), 0.25 mmol of BQ (27 mg) and 0.5 ml of (CD₃)₂CO. The reaction mixture was stirred at room temperature for 72 h. The 1H NMR spectrum of the reaction mixture was recorded following dilution in (CD₃)₂CO directly.

2,3-dimethyl-3-pentanol

0.25 mmol of 2,3-dimethyl-3-pentanol (35 μl) was added to a solution of 0.025 mmol of PdCl₂(MeCN)₂ (6.5 mg), 0.25 mmol of BQ (27 mg) and 0.5 ml of (CD₃)₂CO. The reaction mixture was stirred at room temperature for 72 h. The 1H NMR spectrum of the reaction mixture was recorded following dilution in (CD₃)₂CO directly.

2,3-dimethyl-3-pentanol: ¹H NMR [400 MHz, (CD₃)₂CO] δ 1.68 (m, 1H), 1.44 (q, 2H), 1.00 (s, 3H), 0.87 (m, 9H).

3,4-dimethyl-pent-2-ene: ¹H NMR [400 MHz, (CD₃)₂CO] δ 2.01 (m, 2H), 1.60 (m, 9H), 0.94 (m, 3H).

2,3-dimethyl-pent-2-ene: ¹H NMR [400 MHz, (CD₃)₂CO] δ 5.19 (m, 1H), 2.21 (m, 1H), 1.54 (m, 6H), 1.08 (d, 6H).
Figure 10. $^1$H NMR spectrum in (CD$_3$)$_2$CO of the reaction mixture.

3.4.8 Reactions carried out with and in deuteriated t-BuOH

Scheme 12

Procedure: 0.05 mmol allylic amide (14 mg) was added in the solution of 0.05 mmol PdCl$_2$(MeCN)$_2$ (13 mg), 0.05 mmol BQ (5.4 mg), 0.05 mmol t-C$_6$D$_9$OD (15 µl), 85 µl acetone. The mixture was stirred at room temperature for 5h. The reaction solution was measured by 1H NMR by adding CDCl$_3$ directly without workup.
AM oxidation of allylic amides

Figure 11. $^1$H NMR spectrum in CDCl$_3$ of the reaction mixture of Scheme 12 using stoichiometric C$_4$D$_9$OD

Scheme 13

Procedure: 0.125 mmol allylic amide (36mg) was added in the solution of 0.025 mmol PdCl$_2$(MeCN)$_2$ (6.5 mg), 0.125 mmol BQ (13.5 mg), 250 µl t-C$_4$D$_9$OD. The mixture was stirred at room temperature for 5h. The reaction solution was measured by $^1$H NMR by adding CDCl$_3$ directly without workup.

Figure 12. $^1$H NMR spectrum in CDCl$_3$ of the reaction mixture of Scheme 13 using C$_4$D$_9$OD as solvent
Procedure. 0.125 mmol allylic amide (33 mg) was added in the solution of 0.025 mmol PdCl₂(MeCN)₂ (6.5 mg), 0.125 mmol BQ (13.5 mg), 250 μl t-C₄D₉OD. The mixture was stirred at room temperature for 72 h. The 1H NMR spectrum of the reaction mixture was recorded after dilution in CDCl₃ and shows no incorporation of deuterium from the solvent.

3-(1,3-dioxoisoindolin-2-yl)-3-phenylpropanal: ¹H NMR (400 MHz, CDCl₃) δ 9.74 (s, 1H), 7.75 (m, 2H), 7.63 (m, 2H), 7.45 (m, 2H), 7.28-7.22 (m, 3H), 5.85 (dd, 1H), 3.90 (dd, 1H), 3.35 (dd, 1H).

Figure 13. ¹H NMR spectrum of reaction mixture (scheme 14) in CDCl₃.

3.5 Bibliography

AM oxidation of allylic amides


It should be noted that in the absence of substrate under otherwise catalytic conditions, spontaneous partial dehydration (20-50%) of tertiary alcohols other than t-BuOH was observed over a 72 h period by $^1$H NMR spectroscopy. The dehydration, in addition to releasing water into the reaction mixture that can potentially increase the amount of ketone formed, reduces the amount of alcohol available for AM oxidation.


