New Methods towards the synthesis of beta-amino acids
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Chapter 4

**Anti-Markovnikov selective Wacker oxidations of phthalimide protected allylic amines: a new catalytic route to $\beta^3$-amino acids**

A new method for the synthesis of $\beta^3$-amino acids is presented. Phthalimide-protected allylic amines are oxidized under Wacker conditions selectively to aldehydes using $\text{PdCl}_2$ and $\text{CuCl}$ or $\text{Pd(MeCN)}_2\text{Cl(NO}_2\text{)}$ and $\text{CuCl}_2$ as complementary catalyst systems. The aldehydes are produced in excellent yields, and the new oxidation method exhibits a large substrate scope. $\beta$-Amino acids and alcohols are synthesized by oxidation or reduction, respectively, and subsequent deprotection.

4.1 Introduction

The Wacker oxidation is an important industrial and synthetic catalytic process for the conversion of olefins. The industrial Wacker-Hoechst process transforms ethylene to acetaldehyde using a homogeneous PdCl₂/CuCl₂ catalyst in an aqueous medium. This reaction has been widely used in natural product synthesis. A simplified mechanism is depicted in scheme 4.01. Pd II coordinates to the double bond of the alkene to form a 2-complex 4.02. Water reacts with 4.02 to form α-hydroxy alkyl palladium species (oxypalladation). Subsequent β-hydride elimination gives a 2-complex 4.04, then H-Pd-Cl reinserts with opposite regioselectivity to form 4.05, which eliminates via transition state TS 1, a H-Pd-Cl species 4.06 and ketone 4.07. Loss of HCl results in a Pd 0-species which is reoxidized to Pd II using CuCl₂ and molecular oxygen.

Usually, the oxidation of terminal alkenes via the Wacker process yields selectively methylketones, but there are few examples showing a preference for aldehyde formation. Until today, the palladium-catalyzed anti-Markovnikov Wacker oxidation of olefins remains a major challenge. In some cases the formation of aldehydes is observed.
in the presence of directing functional groups or by using a palladium-nitro-nitroso redox couple.\textsuperscript{3} The first successful application of a palladium-nitro-nitroso redox couple in oxidations of terminal alkenes to aldehydes was reported by Feringa in 1986.\textsuperscript{4} The oxidation catalyst used is Pd(MeCN)\textsubscript{2}Cl(NO\textsubscript{2}) in combination with CuCl\textsubscript{2} in a molar ratio of 1:4. When tert-butanol is used as a solvent linear alkenes are oxidized to an excess of aldehydes with selectivity up to 70\% for 1-decene \textit{4.08} with 10\% conversion (table 4.1, entry 1).\textsuperscript{4a} A change of solvent to EtOH leads to complete reversal of selectivity towards the ketone (table 4.1, entry 2). Branched olefin \textit{4.09} shows a higher preference for ketone formation (table 4.1, entry 3). Styrene \textit{4.10} is oxidized exclusively to phenylacetaldehyde at 10\% conversion (table 4.1, entry 4).\textsuperscript{4a}

\begin{table}[h]
\centering
\caption{Oxidation with Pd(MeCN)\textsubscript{2}Cl(NO\textsubscript{2})/CuCl\textsubscript{2}.}
\begin{tabular}{|c|c|c|c|c|c|}
\hline
entry & R & solvent & reaction time [h] & conversion [\%] & ratio aldehyde:ketone \\
\hline
1 & C\textsubscript{8}H\textsubscript{17} (\textit{4.08}) & t-BuOH & 1.1 & 10 & 60:40 \\
2 & C\textsubscript{8}H\textsubscript{17} (\textit{4.08}) & EtOH & 20 & 75 & 0:100 \\
3 & CHMe(C\textsubscript{6}H\textsubscript{13}) (\textit{4.09}) & t-BuOH & 3.2 & 18 & 18:82 \\
4 & Ph (\textit{4.10}) & t-BuOH & 2.0 & 10 & 100:0 \\
\hline
\end{tabular}
\end{table}

The mechanism of this reaction is supposed to involve a 1,3-dipolar cycloaddition to form a heterometallocyclopentane \textit{4.12} (scheme 4.02). Usually, palladium-dimers are formed; for simplification of the drawings in schemes 4.02-4.04 these are not shown. \textsuperscript{18}O-labeling data, spectroscopic data and a crystal structure of the palladium-metallacycle\textsuperscript{5} confirm the formation of this intermediate.\textsuperscript{6} \textsuperscript{18}O-enriched Pd(MeCN)\textsubscript{2}Cl(N\textsuperscript{18}O\textsubscript{2}) reacts with 1-decene in toluene under nitrogen atmosphere to give \textsuperscript{18}O labeled 2-decanone.\textsuperscript{6a} Therefore, the oxygen transfer proceeds from the nitro group compared to the mechanism of the regular Wacker oxidation where oxygen comes from water in the reaction mixture (scheme 4.01). Evidence for this pathway also comes from the high stereospecificity observed in the oxidation. It can also be regarded mechanistically as a formal [3+2] cycloaddition (scheme 4.02).\textsuperscript{4,6d}

\begin{scheme}[h]
\centering
\includegraphics[width=0.5\textwidth]{Scheme402.png}
\caption{Formation of the heterometallocyclopentane.}
\end{scheme}
Andrews et al. propose a mechanism for the formation of the ketone from metallacyclopentane 4.12 over a hydrolytic ring opening to 4.13, where \( \beta \)-hydride elimination should be favoured due to conformational flexibility to generate a Pd-C-C-H angle of 0°C; an appropriate orientation necessary for \( \text{syn} \)-elimination.\(^{4d}\) The proposed conversion of the vinyl nitrite complex 4.14 to metallacyclobutane 4.15 might occur via reverse insertion of the H-Pd-X into the olefinic double bond and retro [2+2] cycloaddition (scheme 4.03).

![Scheme 4.03. Formation of the ketone from the heterometallocyclopentane.](image)

The simplified catalytic cycle proposed for the generation of aldehydes from olefins using the palladium-nitro-nitroso redox couple 4.17 in tert-butanol is shown in scheme 4.04.\(^4\) Cycloaddition of olefin and catalyst lead to metallacycle 4.18, followed by \( \beta \)-hydrogen elimination and reoxidation of the palladium-nitroso species 4.20. The oxidation state of palladium is not changing during the reaction, therefore, the role of the CuII-salt might be different from that shown in scheme 4.01; perhaps CuII-ions are incorporated into a heterobimetallic (Cu-Pd) species or being involved in the oxidation of the nitroso to the nitro functionality.\(^4\)
Another mechanism for the oxidation with the palladium nitro-nitroso redox couple has been suggested which includes the role of tert-butanol as a nucleophile (scheme 4.05). With allylacetate as substrate, the solvent tert-butanol acts as a nucleophile and attacks the less hindered terminal position of the olefin. The intermediate alkyl-palladium species $4.21$ has to undergo $\beta$-hydrogen elimination followed by cleavage of the tert-butyl vinyl ether. These assumptions are based on five observations: 1) the reaction is first order in tert-butanol in DMF as solvent, 2) the use of $n$- or sec-butanol lead to formation of acetal and ketal products, 3) the selectivity for aldehyde formation increases in the order $n$-butanol < sec-butanol < tert-butanol, 4) aldehyde selectivity is decreased by adding small amounts of water, but the rate is increased, 5) non-protic solvents give lower aldehyde selectivities and rates.

Very few examples of oxidations of allylic amines to amino aldehydes are known. Cyclic $N$-allyl lactam $4.23$ has been oxidized under Wacker conditions (table 4.2). In the presence of CuCl$_2$ ketone $4.24$ is the major product (table 4.2, entry 1). However, when CuCl is used, more of aldehyde $4.25$ is formed along with olefin isomerization product $4.26$ (table 4.2, entry 2).
Chapter 4

Table 4.2. Oxidation of N-allyl lactams.

<table>
<thead>
<tr>
<th>entry</th>
<th>CuX</th>
<th>4.24 [%]</th>
<th>4.25 [%]</th>
<th>4.26 [%]</th>
<th>4.27 [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CuCl₂</td>
<td>55</td>
<td>13</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>2</td>
<td>CuCl</td>
<td>24</td>
<td>55</td>
<td>17</td>
<td>-</td>
</tr>
</tbody>
</table>

The oxidation of allylic amides 4.28 and 4.29 has to be performed under water-free conditions to obtain good aldehyde selectivities (scheme 4.06). By adding water, the product outcome is reversed, e.g. mostly ketone is formed. Only β-unsubstituted allylic amines were used, employing Pd(MeCN)₂Cl₂, CuCl, and excess of HMPA as catalyst system. Although an aldehyde/ketone ratio of 90/10 is achieved, the isolated yield of the aldehyde does not exceed 68%. The authors attribute the formation of the aldehyde to a coordination of the palladium species with the carbonyl oxygen of the amide.

\[
\text{Scheme 4.06. Oxidation of allylic amines under H₂O-free conditions.}
\]

Acetals are formed as major products of β-unsubstituted allylic amines when Li₂CO₃ is added as additive and Li₂PdCl₄ with excess CuCl₂ are used as oxidants (scheme 4.07).

\[
\text{Scheme 4.07. Oxidation of allylic amines to acetals.}
\]

The oxidation of allylic amine 4.32 is very sensitive to the copper source. Replacing Cu(OAc)₂ with CuCl₂ increases the formation of aldehyde 4.33, while better results are obtained using CuCl (table 4.3, entry 1-3). Optimal selectivities are achieved with addition of HMPA (table 4.3, entry 4), but aldehyde 4.33 was only isolated with a maximum yield of 64%.
Chapter 4: Aldehyde selective Wacker oxidations of allylic amines

Table 4.3. Oxidation of TFA-protected allylic amine.

<table>
<thead>
<tr>
<th>entry</th>
<th>CuX ratio</th>
<th>CuX</th>
<th>ratio 4.33 : 4.34</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Cu(OAc)$_2$</td>
<td>54:46</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>CuCl$_2$</td>
<td>65:35</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>CuCl</td>
<td>75:25</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>CuCl, HMPA</td>
<td>82:12</td>
<td></td>
</tr>
</tbody>
</table>

During the natural product synthesis of tetraponerines, Blechert et al. employed the Wacker oxidation to yield amino aldehyde 4.36 in 76% yield (scheme 4.08). When the o-nitrobenzenesulfonyl (Ns) protecting group was used instead of the carboxybenzyl (Cbz) protecting group only decomposition of the substrate was observed.

The goal of the research described in this chapter was to find a methodology that allows the exclusive formation of aldehydes 4.38 from the oxidation of terminal allylic amines 4.37 (scheme 4.09). A suitable protecting group has to be found that can direct the attack of the nucleophile (water) towards the terminal carbon of the double bond. So far, no method has been developed that gives aldehydes in yields exceeding 80%. Also the substrate scope has been limited to either β-unsubstituted allylic amines (table 4.2, and scheme 4.06 and 4.07) or special building blocks for natural products (table 4.3 and scheme 4.08).

The new methodology presented in this chapter involves the selective anti-Markovnikov oxidation of various phthalimide protected allylic amines to amino aldehydes in excellent yields. No formation of side products, no olefin isomerization or allylic
substitution is observed. This method can be combined with asymmetric allylic amination or asymmetric imine vinylation to be applied in the synthesis of optically active β'-amino acids.

### 4.2 Synthesis of allylic amines

Different methods were used for the synthesis of the starting materials depending on the protecting group for the amino function. Literature procedures or variations thereof were used for these reactions.

The \( p \)-methoxy phenyl (PMP) protected allylic amine 4.40 was synthesized at low temperatures by an addition of vinyllithium to the corresponding \( p \)-methoxyphenyl imine 4.41, which was prepared from benzaldehyde and \( p \)-anisidine in 85% yield (scheme 4.10).\(^{13}\) Vinyllithium freshly prepared from tetravinyltin and \( n \)-BuLi had to be used to achieve high yields.\(^{14}\) When vinylMgBr in Et\(_2\)O was used, no reaction was observed.

\[
\text{PhNHMeO} \quad \text{MeO} \quad \text{PhNH} \\
\text{vinylLi, TMEDA} \quad \text{THF, –75°C, 24h} \quad \text{MeO} \quad \text{PhNH} \\
\text{92%} \\
\]

Scheme 4.10. Synthesis of PMP-protected allylic amine.

Carboxybenzyl (Cbz) protected amine 4.42 and \( p \)-toluenesulfonyl chloride (Ts) protected allylic amine 4.44 were synthesized from allylic amine 4.43 (scheme 4.11). Benzylchloroformate and aqueous saturated NaHCO\(_3\) were added to 4.43 to form 4.42 in good yield.\(^{15}\) Compound 4.44 was synthesized in moderate yield by adding \( p \)-toluenesulfonyl chloride under basic conditions to amine 4.43.\(^{16}\)

\[
\text{PhO} \quad \text{ONH} \quad \text{Ph} \\
\text{aq. NaHCO\(_3\)}, \text{EtOAc, 16h} \quad \text{NH}_2 \quad \text{p-TsCl} \quad \text{Ph} \\
\text{94%} \quad \text{NE\(_3\)}, \text{CH\(_2\)Cl\(_2\)}, \text{16h} \quad \text{4.44} \\
\]


For the synthesis of \textit{tert}-butoxycarbonyl (Boc) protected amine 4.46, a sequence of Swern oxidation and \textit{in situ} Wittig olefination was employed (scheme 4.12).\(^{17}\) \( N \)-Boc-protected amino alcohol 4.45, prepared from \( N \)-Boc-phenylalanine, was oxidized under mild conditions to the corresponding aldehyde. This aldehyde was reacted with prior deprotonated methyl triphenylphosphonium bromide providing the final product 4.46 in low yields. This disappointing result could have originated from insufficient aldehyde
formation during the Swern reaction, which also produced a large amount of salts that could influence the Wittig reaction, or incomplete deprotonation of the Wittig reagent.\textsuperscript{17}

![Scheme 4.12. Synthesis of Boc-protected allylic amine 4.46.](image)

The allylic substitution of alcohol 4.47 with sulfamic acid, catalyzed by an iridium/phosphoramidite catalyst developed by Carreira \textit{et al}, was used to synthesize allylic amine 4.48.\textsuperscript{18,19} Amine 4.48 was in situ protected using benzoyl chloride under basic conditions to give benzoyl (Bz) protected allylic amine 4.49 in good yield over two steps (scheme 4.13).

![Scheme 4.13. Synthesis of Bz-protected allylic amine.](image)

The Mitsunobu reaction can be used for the synthesis of amines from alcohols when acidic amines are employed as nucleophiles.\textsuperscript{20} Starting from allylic alcohol 4.47, triphenylphosphine, diethyl azodicarboxylate solution (DEAD) and \textit{N-o-nitrobenzenesulfonyl-N-tert-butoxycarbonyl amine} were added, and protected alkyl-amine 4.51 was isolated in very good yield (scheme 4.14).\textsuperscript{21} In principal, both the \textit{o-nitrobenzenesulfonyl (o-Ns)} and the Boc group can be selectively deprotected without affecting the other functional group. The Boc-protecting group is removed with trifluoroacetic acid (TFA), whereas deprotection of the \textit{o-Ns} group can be achieved with mercaptoacetic acid and LiOH in DMF.\textsuperscript{21}

![Scheme 4.14. Synthesis of o-Ns-Boc-protected allylic amine.](image)
Also a series of phthalimide-protected amines was synthesized from the corresponding allylic alcohols using the Mitsunobu reaction (table 4.4). In all substrates $S_N2$ and $S_N2'$ reactions of the nucleophile are possible, the latter leading to the usually more stable undesired internal olefin. Substrates with short or long alkyl chains give the branched allylic amines in good yields (table 4.4, entry 1-2). This is also the case for substrates with benzyl- and benzyloxy-groups (table 4.4, entry 5-6) and substrate 4.61 containing a disubstituted alkene (table 4.4, entry 9). Branched product 4.54 (table 4.4, entry 3) and thienyl product 4.59 (table 4.4, entry 8) were formed in moderate yield. The yield and conversion of quartenary amine 4.55 is low because this substrate is sterically demanding and thus reacts very slow in the Mitsunobu reaction (table 4.4, entry 3). Phenyl-substituted allyl alcohol 4.58 gives the terminal olefin in low yields because the $S_N2'$ reaction is favoured to give the more stable and conjugated internal alkene (table 4.4, entry 7).

Table 4.4. Synthesis of phthalimide protected allylic amines.

<table>
<thead>
<tr>
<th>entry</th>
<th>substrate</th>
<th>Yield [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>R = CH$_3$ 4.52</td>
<td>75</td>
</tr>
<tr>
<td>2</td>
<td>R = C$<em>5$H$</em>{11}$ 4.53</td>
<td>76</td>
</tr>
<tr>
<td>3</td>
<td>4.54</td>
<td>52</td>
</tr>
<tr>
<td>4</td>
<td>4.55</td>
<td>12</td>
</tr>
<tr>
<td>5</td>
<td>R = Bn 4.56</td>
<td>62</td>
</tr>
<tr>
<td>6</td>
<td>R = BnOCH$_3$ 4.57</td>
<td>88</td>
</tr>
<tr>
<td>7</td>
<td>R = Ph 4.58</td>
<td>16</td>
</tr>
<tr>
<td>8</td>
<td>4.59</td>
<td>45</td>
</tr>
<tr>
<td>9</td>
<td>4.60</td>
<td>49</td>
</tr>
<tr>
<td>10</td>
<td>4.61</td>
<td>64</td>
</tr>
</tbody>
</table>
4.3 Screening for directing groups

Three catalytic systems were employed in the initial screening for suitable protecting groups for the allylic amine. Method A is based on the palladium-nitro-nitroso redox couple and copper(II) chloride. Pd(MeCN)$_2$Cl(NO$_2$)$_2$ was synthesized from Pd(MeCN)$_2$Cl$_2$ and AgNO$_2$ in MeCN (scheme 4.15). The formation of this catalyst was proven by IR-spectroscopy via the absorption of the NO$_2$-group and by NMR-spectroscopy by a shift of the aromatic protons.

\[
Pd(\text{MeCN})_2\text{Cl}(\text{NO}_2) \quad \text{MeCN} \quad 16h \quad Pd(\text{MeCN})_2\text{Cl}(\text{NO}_2)
\]

Scheme 4.15. Synthesis of catalyst A.

For Wacker oxidations catalyst A was activated under O$_2$ for 2 h at 55°C. The oxidation was performed at 30°C in tert-butanol which is the best solvent for aldehyde selectivity as previously shown in the Feringa group (see paragraph 4.1). Method B and related method C were employing the standard Wacker catalysts palladium(II) chloride, and either copper(I) or copper(II) chloride and O$_2$ as oxidant (table 4.5).

Allylic amine 4.40 with the electron donating p-methoxyphenyl (PMP) protecting group did not show conversion with all catalytic systems (Table 4.5, entry 1-2). Substrate 4.42 with the carboxybenzyl (Cbz) protection gave full conversion in case of method A and B$^{23}$, with a slightly better selectivity of 66:33 for the aldehyde using method B (Table 4.5, entry 4). The tosyl (Ts) protected amine 4.44 gave full conversion, and an aldehyde:ketone ratio of 43:57 with catalyst A, and high selectivity for the ketone using method B (Table 4.5, entry 5-6). The tert-butoxycarbonyl (Boc) protected amine 4.46 gave only low conversion after longer reaction times of two days with method A and an undesired aldehyde:ketone ratio of 35:65 (Table 4.5, entry 7), whereas no conversion was seen with method B (Table 4.5, entry 8). The oxidation of benzoyl (Bz) protected allylamine 4.49 gave full conversion with an aldehyde-ketone ratio of 3:1 in case of method A, and 4:1 for method B (Table 4.5, entry 9-10). Substrate 4.51 with a Boc- and o-Ns protected amine did not react (Table 4.5, entry 11).
Table 4.5. Screening for directing groups using method A, B and C.

<table>
<thead>
<tr>
<th>entry</th>
<th>substrate</th>
<th>cat</th>
<th>time [h]</th>
<th>conversion [%]</th>
<th>A : K&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>R&lt;sup&gt;1&lt;/sup&gt;=Ph, R&lt;sup&gt;2&lt;/sup&gt;=PMP, R&lt;sup&gt;3&lt;/sup&gt;=H (4.40)</td>
<td>A&lt;sup&gt;a&lt;/sup&gt;</td>
<td>72</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>4.40</td>
<td>B</td>
<td>72</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>R&lt;sup&gt;1&lt;/sup&gt;=Ph, R&lt;sup&gt;2&lt;/sup&gt;=Cbz, R&lt;sup&gt;3&lt;/sup&gt;=H (4.42)</td>
<td>A&lt;sup&gt;a&lt;/sup&gt;</td>
<td>16</td>
<td>100</td>
<td>61:39</td>
</tr>
<tr>
<td>4</td>
<td>4.42</td>
<td>B</td>
<td>72</td>
<td>100</td>
<td>70:30</td>
</tr>
<tr>
<td>5</td>
<td>R&lt;sup&gt;1&lt;/sup&gt;=Ph, R&lt;sup&gt;2&lt;/sup&gt;=Ts, R&lt;sup&gt;3&lt;/sup&gt;=H (4.44)</td>
<td>A&lt;sup&gt;a&lt;/sup&gt;</td>
<td>16</td>
<td>100</td>
<td>45:55</td>
</tr>
<tr>
<td>6</td>
<td>4.44</td>
<td>B</td>
<td>72</td>
<td>100</td>
<td>3:97</td>
</tr>
<tr>
<td>7</td>
<td>R&lt;sup&gt;1&lt;/sup&gt;=Ph, R&lt;sup&gt;2&lt;/sup&gt;=Boc, R&lt;sup&gt;3&lt;/sup&gt;=H (4.46)</td>
<td>A&lt;sup&gt;a&lt;/sup&gt;</td>
<td>16</td>
<td>10</td>
<td>35:65</td>
</tr>
<tr>
<td>8</td>
<td>4.46</td>
<td>C</td>
<td>72</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>9</td>
<td>R&lt;sup&gt;1&lt;/sup&gt;=Me, R&lt;sup&gt;2&lt;/sup&gt;=Bz, R&lt;sup&gt;3&lt;/sup&gt;=H (4.49)</td>
<td>A&lt;sup&gt;a&lt;/sup&gt;</td>
<td>72</td>
<td>12</td>
<td>77:23</td>
</tr>
<tr>
<td>10</td>
<td>4.49</td>
<td>B</td>
<td>72</td>
<td>100</td>
<td>80:20</td>
</tr>
<tr>
<td>11</td>
<td>R&lt;sup&gt;1&lt;/sup&gt;=Me, R&lt;sup&gt;2&lt;/sup&gt;=o-Ns, R&lt;sup&gt;3&lt;/sup&gt;=Boc (4.51)</td>
<td>C</td>
<td>72</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>12</td>
<td></td>
<td>A&lt;sup&gt;c&lt;/sup&gt;</td>
<td>16</td>
<td>100</td>
<td>96:4</td>
</tr>
<tr>
<td>13</td>
<td>4.52</td>
<td>B</td>
<td>48</td>
<td>100</td>
<td>&gt;99:1</td>
</tr>
<tr>
<td>14</td>
<td>4.52</td>
<td>C</td>
<td>72</td>
<td>80</td>
<td>94:6</td>
</tr>
</tbody>
</table>

<sup>a</sup>5 mol% Pd-cat, 20 mol% CuCl<sub>2</sub>.  <sup>b</sup>Determined by <sup>1</sup>H-NMR.  <sup>c</sup>1 mol% Pd-cat, 5 mol% CuCl<sub>2</sub>.

Phthalimide proved to be the optimal protecting group resulting in full conversion in case of method A and B (table 4.5, entry 12-13). The highest aldehyde selectivities (>99:1) were achieved using catalyst B, but the reaction took up to three days to completion. Catalyst A is more reactive, a lower catalyst loading can be used (1% of palladium, table 4.5, entry 12), and the oxidation is faster (16h), while aldehyde selectivities are only slightly lower (96:4). Lower conversion and slightly lower aldehyde selectivity are observed when using catalyst C (table 4.5, entry 14). This lower selectivity is attributed in this case to the higher chloride concentration, which could hamper coordination of palladium to the carbonyl oxygen of the substrate. 3,8
4.4 Scope and limitations

Next, the substrate scope was investigated in the oxidation of phthalimide-protected allylic amines (table 4.4). Reactions were usually performed on 1 mmol scale. Methyl substituted allylic amine 4.52 gave the aldehyde in 94% yield. Substrate 4.53 with a long alkyl chain was oxidized with excellent yield (91%) and selectivity (>99:1) (table 4.6, entry 2). Catalyst A was used to oxidize branched amine 4.54 in high yield and selectivity (table 4.6 entry 3). Quartenary amine 4.55 required a higher catalyst loading of A, and the aldehyde was isolated in good yield and a selectivity of 94:6 was found (table 4.6, entry 4). With a benzyl group in the side chain excellent yield and selectivity were achieved (table 4.6, entry 5). The benzyl-protected amino alcohol 4.57 was oxidized in 93% yield (table 4.6, entry 6). The aromatic substrate 4.58 as well as the heteroaromatic thienyl amine 4.59 gave excellent yields and selectivities (table 4.6, entry 7-8). The internal olefin 4.60 could be converted selectively to the β-ketone by using catalyst A (table 4.6, entry 9). However, 2-methyl-substituted olefin 4.61 could not be oxidized with any of the catalysts (table 4.6, entry 10).
Table 4.6. Substrate scope of oxidation of phthalimide protected allylic amines.

<table>
<thead>
<tr>
<th>entry</th>
<th>substrate</th>
<th>cat</th>
<th>time [h]</th>
<th>A : K</th>
<th>isolated yield %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>R = CH₃ (4.52)</td>
<td>B</td>
<td>48</td>
<td>&gt;99:1</td>
<td>94</td>
</tr>
<tr>
<td>2</td>
<td>R = C₅H₁₁ (4.53)</td>
<td>B</td>
<td>72</td>
<td>&gt;99:1</td>
<td>91</td>
</tr>
<tr>
<td>3</td>
<td>(4.54)</td>
<td>A</td>
<td>16</td>
<td>&gt;99:1</td>
<td>93</td>
</tr>
<tr>
<td>4</td>
<td>(4.55)</td>
<td>A</td>
<td>48</td>
<td>94:6</td>
<td>74b</td>
</tr>
<tr>
<td>5</td>
<td>R = Bn (4.56)</td>
<td>B</td>
<td>72</td>
<td>&gt;99:1</td>
<td>94</td>
</tr>
<tr>
<td>6</td>
<td>R = BnOCH₂ (4.57)</td>
<td>B</td>
<td>72</td>
<td>&gt;99:1</td>
<td>93</td>
</tr>
<tr>
<td>7</td>
<td>R = Ph (4.58)</td>
<td>B</td>
<td>72</td>
<td>&gt;99:1</td>
<td>95</td>
</tr>
<tr>
<td>8</td>
<td>(4.59)</td>
<td>B</td>
<td>72</td>
<td>&gt;99:1</td>
<td>77</td>
</tr>
<tr>
<td>9</td>
<td>(4.60)</td>
<td>A</td>
<td>48</td>
<td>&gt;99:1</td>
<td>89</td>
</tr>
<tr>
<td>10</td>
<td>(4.61)</td>
<td>A</td>
<td>72</td>
<td>-</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>B</td>
<td>-</td>
<td>-</td>
<td>0</td>
</tr>
</tbody>
</table>

* By ¹H-NMR, **Pd(MeCN)₂Cl(NO₂) (15 mol%), CuCl₂ (60 mol%).

The Wacker oxidation presented here has a broad substrate scope of aliphatic and aromatic allylic amines. Furthermore, sterically more demanding substrates are oxidized, but reaction times have to be prolonged. Also internal unsubstituted olefins are oxidized to the corresponding β-amino ketones and all products were isolate in high yields.

It is assumed that the high selectivity for the anti-Markovnikov oxidation to the aldehyde with these catalysts results from coordination of the protecting group with the palladium catalyst. The mechanism for the oxidation with catalyst A has been described in paragraph 4.1.6. With this catalyst, the carbonyl oxygen of the phthalimide can stabilize the palladium intermediate. In this hypothesis, the palladium species can coordinate to the olefinic double bond and to the carbonyl oxygen to form intermediate 4.62.24,25 The
nucleophilic attack of water is then directed to the terminal carbon of the alkene to form the six membered complex 4.63 which could be a reason for the observed selectivities (scheme 4.16).

Scheme 4.16. Proposed coordination of the palladium species with the allylic phthalimide protected amine.

4.4.1 Catalytic asymmetric synthesis of an allylic amine and the transformation of β-amino aldehydes

It is envisioned that the new aldehyde-selective oxidation allows the asymmetric synthesis of β-amino acids from allylic compounds using three consecutive catalytic transformations: 1) asymmetric allylic amination, 2) Wacker oxidation, and 3) oxidation of the aldehyde to the carboxylic acid. In the asymmetric allylic amination, allylic carbonate 4.64 reacted with phthalimide to 4.58 with 96% ee catalyzed by an iridium/phosphoramidite complex as described by Helmchen et al. (scheme 4.17).26,27 The yield of this reaction was not as high as reported (65%).28 The product 4.58 can be readily transformed into the primary amine which allows further functionalization, and which is a valuable building block for medicinal chemistry and alkaloid synthesis.26

Scheme 4.17. Asymmetric synthesis of β-amino aldehyde by allylic substitution and Wacker oxidation.

Next, enantioenriched olefin 4.58 was oxidized using catalyst B to aldehyde 4.66 (scheme 4.17). For determination of the enantiomeric excess of the oxidation product 4.66, it had to be transformed into the diacetal 4.67 which was obtained with 96% ee (scheme 4.18).29
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The obtained β-amino aldehydes (table 4.6) can be transformed into β-amino acids and β-amino alcohols which represent valuable building blocks for natural products and pharmaceuticals. Catalytic oxidation of 4.68 with Mn-tmtacn\(^{30}\) and subsequent deprotection with hydrazine\(^{31}\) gave the β-amino acid 4.69 in 87% yield in two steps (scheme 4.19). Mn-tmtacn, which has been previously used for the synthesis of epoxides and diols from alkenes, proves also to be a good catalyst for the oxidation of aldehydes to carboxylic acids. A low catalyst loading can be used in short reaction times, using environmentally benign \(\text{H}_2\text{O}_2\) as oxidant under aqueous conditions. Reduction with 1.0 eq. of \(\text{NaBH}_4\) in MeOH at 0°C for 1h gave selective conversion to the corresponding alcohol 4.70 in 95% yield. Subsequent deprotection with hydrazine gave the β-amino alcohol 4.70 in 90% yield (scheme 4.19).\(^{32}\)

\[
\text{NH}_2\text{CO}_2\text{H} \rightarrow 1) 0.5\% \text{Mn-tmtacn, } \text{Cl}_3\text{CCO}_2\text{H, } \text{H}_2\text{O}_2, \text{H}_2\text{O, MeCN; 87%;}
\]
\[
\text{NH}_2 \text{CHO} \rightarrow 1) \text{NaBH}_4, \text{MeOH, 0°C, 1h; 95%;}
\]
\[
\text{NH}_2\text{OH} \rightarrow 2) \text{H}_2\text{NNH}_2, \text{EtOH, } \Delta, 2.5h; 100\%\]

\[
\text{Mn-tmtacn: } \left[ \begin{array}{c} \text{N} \\ \text{N} \\ \text{N} \\ \text{N} \end{array} \right] \text{(PF}_6\text{)}_2
\]


4.5 Conclusion

In summary, it was demonstrated that aldehydes can be synthesized selectively from phthalimide-protected allylic amines using a catalytic Wacker-type oxidation. After an initial screening of protecting moieties for the amino group, phthalimide showed selective aldehyde formation. This unique effect is attributed to a stabilization of the palladium intermediate through coordination with the carbonyl oxygen of the protecting group. Two catalytic methods were used. Method A based on a palladium-nitro-nitroso redox couple needs shorter reaction times and lower catalyst loadings, however, selectivities for the aldehyde are slightly lower. For less reactive substrates, such as quaternary amine 4.55, branched amine 4.54 and internal olefin 4.60, catalyst A was employed. Method B, using \(\text{PdCl}_2\) and \(\text{CuCl}\), gave excellent selectivity, but requires longer reaction times up to three days. This new methodology is used as a key step in a
new procedure for the asymmetric synthesis of a β-amino acid involving three consecutive catalytic steps. It was shown that enantioenriched β-amino aldehydes can be synthesized via asymmetric allylic amination and oxidation. Furthermore, these aldehydes were transformed into β-amino acids and alcohols. Mn-tmtacn was used to oxidize the aldehyde to the corresponding carboxylic acid. The scope of this new catalytic oxidation method will be explored in the future.

4.6 Experimental

This project was performed in collaboration with Alejandro Baeza Garcia and Thomas Jerphagnon.

General methods. see chapter 2.

General procedure for oxidation reactions with Pd(MeCN)₂Cl(NO₂)/CuCl₂ (method A): Pd(MeCN)₂Cl(NO₂) (0.05 eq) and CuCl₂ (0.2 eq) were activated for 2h in tert-BuOH (0.4 M) at 55°C with an oxygen-filled balloon placed on top of the flask. The catalyst solution was cooled to 30°C and the substrate (1.0 eq) added. The reaction mixture was stirred at 30°C under oxygen and the progress of the oxidation monitored by GC-MS. Full conversion was observed in most cases after 16h. EtOAc (10 mL) and H₂O (10 mL) were added. The aqueous layer was extracted with EtOAc (3 x 10 mL), the combined organic layers washed with saturated aq. NaHCO₃ solution and H₂O, and dried over MgSO₄. The solvent was evaporated in vacuum.

General procedure for oxidation reactions with PdCl₂/CuCl for screening (method B): PdCl₂ (0.1 eq) and CuCl (1.0 eq) were placed in a Schlenk flask, and DMF and H₂O (7:1, 0.05 M), and the protected allylic amine (1.0 eq) were added. An oxygen-filled balloon was placed on top of the flask, and the mixture was stirred vigorously. The progress of the reaction was monitored by GC-MS. After completion, CH₂Cl₂ (10 mL) and H₂O (10 mL) were added. The aqueous layer was extracted with CH₂Cl₂ (3 x 10 mL), the combined organic layers washed with saturated NaHCO₃ solution and H₂O, and dried over MgSO₄. The solvent was evaporated in vacuum.

General procedure for oxidation reactions with PdCl₂/CuCl₂ (method C): PdCl₂ (0.1 eq) and CuCl₂ (0.5 eq) were placed in a Schlenk flask, DMF and H₂O (4:1, 0.05 M), and the protected allylic amine (1.0 eq) were added. An oxygen filled-balloon was placed on top of the flask, and the mixture was stirred vigorously. The progress of the reaction was monitored by GC-MS. After completion, CH₂Cl₂ (10 mL) and H₂O (10 mL) were added. The aqueous layer was extracted with CH₂Cl₂ (3 x 10 mL), the combined organic layers washed with saturated NaHCO₃ solution and H₂O, and dried over MgSO₄. The solvent was evaporated in vacuum.
Synthesis of Pd(MeCN)₂Cl(NO₂): **AgNO₂** (0.154 g, 1.00 mmol) in MeCN (2.0 mL) was added to Pd(MeCN)₂Cl₂ (0.260 g, 1.00 mmol) in MeCN (4.4 mL). After stirring overnight, the precipitate was filtered and the filtrate concentrated in vacuum to yield a light orange solid (0.263 g, 0.97 mmol, 97%). m.p. 108-110°C; IR (KBR): ν=2771 (NO), 2661 (NO). Data were according to literature.

4-Methoxy-N-(1-phenylallyl)aniline 4.40. Preparation of vinyllithium¹⁴: n-BuLi (6.4 mL, 10 mmol, 5.0 eq) was added to tetravinyltin (0.36 mL, 2.0 mmol, 1.0 eq) in dry n-hexane. After 2h of stirring the solvent was removed with a syringe, and the residue was washed four times with dry n-hexane. The solid was dried in vacuum and dissolved in dry THF. The imine (0.43 g, 2.0 mmol, 1.0 eq) was dissolved in dry toluene, TMEDA (0.33 mL, 2.2 mmol, 1.1 eq) was added and the mixture was cooled to -72°C. The solution of vinyllithium (4.3 mmol, 2.2 eq) in dry THF (1.5 mL) was added dropwise over 30 min. The mixture was stirred for 24 h, quenched with MeOH, and warmed slowly to room temperature. The solvent was evaporated in vacuum, and the crude allylic amine purified by flash column chromatography (pentane:EtOAc 90:10) to yield a reddish oil (0.44 g, 1.83 mmol, 92%).¹³ Data were according to literature³³: ¹H NMR (400 MHz, CDCl₃): δ= 3.72 (s, 3H; CH₃), 3.81 (bs, 1H; NH), 4.85 (d, ²J=6.0 Hz, 1H; CH), 5.20 (d, ³J=10.4 Hz, 1H; CH), 5.26 (d, ³J=17.2 Hz, 1H; CH), 6.03 (ddd, ³J=16.8 Hz, ³J=10.2 Hz, ³J=6.2 Hz, 1H; CH), 6.56 (d, ²J=8.8 Hz, 2H; CH₂), 6.73 (d, ³J=9.2 Hz, 1H; CH), 7.24-7.40 (m, 5H; CH Ar). ¹³C NMR (100 MHz, CDCl₃): δ=55.5(CH₃), 55.6 (CH₃), 61.6 (CH), 61.7 (CH), 114.6 (CH₂), 114.8 (CH₂), 115.7 (CH), 127.0 (CH), 127.2 (CH), 128.6 (CH), 139.4 (CH), 141.3 (C), 142.0 (C), 152.0 (C).

Benzyl 1-phenylallyl carbamate 4.42. To 1-phenylprop-2-en-1-amine (0.27 g, 2.0 mmol) in EtOAc (6.15 mL) was added saturated NaHCO₃ solution (6.15 mL) and benzyl chloroformate (0.29 mL, 2.0 mmol) at 0°C. The reaction was stirred over night at room temperature. The aqueous layer was extracted with EtOAc (3 x 10mL), the combined organic layers washed with 1M HCl (2 x 20 mL), dried over MgSO₄, and concentrated in vacuum. The product was purified by flash column chromatography (pentane/EtOAc 3:1) to a white solid (0.50 g, 1.9 mmol, 94%).¹⁵ Data according to literature³⁴: ¹H NMR (300 MHz, CDCl₃): δ= 5.08-5.20 (m, 2H; CH₂), 5.22-5.23 (m, 3H; CH+CH₂), 5.40 (bs, 1H; NH), 5.96-6.10 (m, 1H; CH), 7.28-7.42 (m, 10H; CH₆).¹³C NMR (75 MHz, CDCl₃): δ=57.0 (CH), 68.8 (CH₂), 115.7 (CH₂), 126.9 (CH), 127.6 (CH), 128.0 (CH), 128.4 (CH), 128.6 (CH), 136.3 (C), 137.5 (CH), 140.6 (C), 155.5 (CO).
4-Methyl-N-(1-phenallyl)benzenesulfonamide 4.44. p-Toluenesulfonyl chloride (0.41 g, 2.12 mmol) was added to 1-phenylprop-2-en-1-amine (0.27 g, 2.0 mmol) and NEt₃ (0.64 mL, 4.59 mmol) in CH₂Cl₂ (1.6 mL) and stirred at room temperature overnight. H₂O was added, and the aqueous layer extracted with CH₂Cl₂ (3 x 5 mL), the organic layer dried over MgSO₄ and concentrated in vacuum. The product was purified by flash column chromatography (n-pentane/EtOAc 3:1) to a yield white solid (0.38 g, 1.31 mmol, 66%). Data according to literature35: ¹H NMR (400 MHz, CDCl₃): δ= 2.37 (s, 3H; CH₃), 4.94 (t, 3J=6.0 Hz, 1H; CH), 5.06-5.13 (m, 2H; CH+CH), 5.59 (d, 3J=6.8 Hz, 1H; NH), (ddd, 3J=16.8 Hz, 3J=10.3 Hz, 3J=6.3 Hz, 1H; CH), 7.09-7.21 (m, 7H; CH Ar), 7.62-7.67 (m, 2H; CH Ar). ¹³C NMR (100 MHz, CDCl₃): δ=21.4 (CH), 59.8 (CH₃), 116.5 (CH), 126.9 (CH), 127.0 (CH), 127.5 (CH), 128.4 (CH), 129.2 (CH), 137.0 (CH), 137.5 (C), 139.3 (C), 143.0 (C).

tert-Butyl 1-phenallylcarbamate 4.46. 1) To oxalyl chloride (0.27 mL, 3.2 mmol) in CH₂Cl₂ (3 mL) was added DMSO (0.23 mL, 3.3 mmol) at -63°C, and the solution was stirred for 20 min at -63°C, and the solution was stirred for 20 min at -63°C. The alcohol (0.48 g, 2.0 mmol) in DMSO/CH₂Cl₂ (0.17 mL/3 mL) was added over 5 min. The mixture was stirred at -35°C for 20 min. Then, NEt₃ (1.72 mL, 12.3 mmol) was added dropwise. After stirring for 5 min at room temperature it was cooled to -78°C. 2) HMDS (0.87 mL, 4.2 mmol) was added dropwise to KH (30% in mineral oil, 0.50 g, 3.74 mmol) in dry THF (14 mL) at 0°C, and stirred for 1 h at 0°C. The mixture was added via cannula to MePPh₃Br (1.5 g, 4.58 mmol) at 0°C, and stirred for 1 h. After cooling to -78°C the aldehyde in THF (4 mL) was added. The mixture was stirred for 5 min at -78°C, then warmed to room temperature over 1 h and heated to 40°C overnight. MeOH (0.1 mL) and potassium tartrate (1.5 mL of saturated solution and 7 mL H₂O) were added. The aqueous layer was extracted with EtOAc (3 x 10 mL), the combined organic layers washed with H₂O and brine, and dried over MgSO₄. The crude allylic amine was purified by flash column chromatography (n-pentane/EtOAc 6:1) to a colourless oil (0.09 g, 0.4 mmol, 20%). Data according to literature17: ¹H NMR (400 MHz, CDCl₃): δ=1.44 (s, 9H; CH₃), 4.85 (bs, 1H; NH), 5.15-5.34 (m, 3H; CH+CH+CH), 5.99 (ddd, 3J=15.6 Hz, 3J=10.1 Hz, 3J=5.5 Hz, 1H; CH), 7.22-7.38 (m, 5H: CH Ar). ¹³C NMR (75 MHz, CDCl₃): δ=28.3 (CH₃), 56.6 (CH), 79.7 (C), 115.4 (CH₂), 127.0 (CH), 127.5 (CH), 128.6 (CH), 137.9 (CH), 141.0 (C), 155.0 (C).

N-(But-3-en-2-yl)benzamide 4.49. Bis(1,5-cyclooctadiene)diiridium(I) dichloride (0.02 g, 0.03 mmol, 1.5 mol%) and phosphoramidite 4.50 (0.02 g, 0.06 mmol, 3.0 mol%) were stirred in DMF for 15 min. Then, the allylic alcohol (0.17 mL, 2.0 mmol) and sulfamic acid (0.19 g, 2.00 mmol) were added. The sealed tube was heated to 50°C over night. After cooling to room temperature NEt₃ (1.1 mL, 7.8 mmol) and freshly distilled benzoylchloride (0.47 mL, 4.1
mmol) were added. The mixture was stirred for 3.5 h, CH₂Cl₂ (40 mL) and H₂O added, and the aqueous layer extracted with CH₂Cl₂ (3 x 30 mL). The combined organic layers were dried over MgSO₄, concentrated in vacuum, and the product was purified by flash column chromatography (n-pentane/EtOAc 3:1) to a white solid (0.27 g, 1.5 mmol, 76%).¹⁸ Data according to literature¹⁸: mp. 55-57°C; ¹H NMR (300 MHz, CDCl₃): δ=1.35 (d, ³J=6.6 Hz, 3H; CH₃), 4.73-4.86 (m, 1H; CH), 5.14 (d, ³J=10.2 Hz, 1H; CH), 5.24 (d, ³J=17.4 Hz, 1H; CH), 5.86-6.04 (m, 2H; NH+CH), 7.40-7.53 (m, 3H; CH₉), 7.72-7.80 (m, 2H; CH₉). ¹³C NMR (75 MHz, CDCl₃): δ=20.3 (CH₃), 47.1 (CH), 114.4 (CH₂), 126.8 (CH), 128.5 (CH), 131.4 (CH), 134.7 (C), 139.4 (CH), 166.6 (CO).

tert-Butyl 2-nitrophenylsulfonyl(phenylallyl)carbamate 4.51. To PPh₃ (0.79 g, 3.01 mmol), amine (0.60 g, 2.0 mmol) and allylic alcohol (0.18 mL, 2.0 mmol) in dry THF (8 mL) was added DEAD (40% in toluene, 1.4 mL) at 0°C. After stirring overnight at room temperature the mixture was concentrated in vacuum. The product was purified by flash column chromatography (n-pentane/EtOAc 3:1) to a colourless oil (0.65 g, 1.82 mmol, 91%).²¹ ¹H NMR (400 MHz, CDCl₃): δ= 1.35 (s, 9H; CH₃), 1.59 (d, ³J=6.8 Hz, 3H; CH₃), 4.97 (quin, ³J=6.4 Hz, 1H; CH), 5.18 (d, ³J=10.4 Hz, 1H; CH), 5.26 (d, ³J=17.2 Hz, 1H; CH), 6.12 (ddd, ³J=16.9 Hz, ³J=10.9 Hz, ³J=5.7 Hz, 1H; CH), 7.70-7.76 (m, 3H; CH₉), 8.25-8.30 (m, 1H; CH₉). ¹³C NMR (100 MHz, CDCl₃): δ=18.7 (CH₃), 27.8 (CH₃), 56.6 (CH), 84.9 (C), 115.9 (CH₂), 124.3 (CH), 131.8 (CH), 132.9 (CH), 133.9 (CH), 134.1 (C), 138.0 (C), 147.7 (C), 150.2 (CO). HR-ESI-MS: m/z calcd for C₁₅H₂₁N₂O₆S [M+H]+ 357.1115, found 357.1115.

General procedure for the Mitsunobu-reaction. The corresponding allylic alcohol (1.0 eq) was dissolved in dry THF (0.25M), triphenylphosphine (1.5 eq), and phthalimide (1.0 eq) were added. DEAD (40% in toluene, 1.5 eq) was added dropwise to the ice-cooled mixture. After stirring overnight at room temperature, the solvent was removed in vacuum. The crude product was purified by flash column chromatography (n-pentane/EtOAc) on silica gel.²²

2-(1-Methyl-allyl)-isoindole-1,3-dione 4.52. Column chromatography (n-pentane/EtOAc 4:1) yielded the phthalimide as white solid (75%); m.p. 86-87°C; ¹H NMR (400 MHz, CDCl₃): δ=1.58 (d, ³J=7.2 Hz, 3H; CH₃), 4.93 (quin, ³J=7.0 Hz, 1H; CH), 5.16 (d, ³J=10.0 Hz, 1H; CH), 5.23 (d, ³J=17.2 Hz, 1H; CH), 6.20 (ddd, ³J=17.1 Hz, ³J=10.3 Hz, ³J=6.7 Hz, 1H; CH), 7.70 (dd, ³J=5.2 Hz, ³J=3.2 Hz, 2H; CH₉), 7.83 (dd, ³J=6.4 Hz, ³J=3.2 Hz, 2H; CH₉). ¹³C NMR (75 MHz, CDCl₃): δ=18.2 (CH₃), 48.9 (CH), 116.3 (CH₂), 123.1 (CH), 132 (C), 133.8 (CH), 136.8 (CH), 167.9 (CO). HRMS calcd for C₁₂H₁₁NO₂ 201.0790, found 201.0799.
2-(1-Vinyl-hexyl)-isoindole-1,3-dione 4.53. Column chromatography (n-pentane/EtOAc 5:1) yielded the phthalimide as colourless oil (76%). \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta=0.80-0.88\) (m, 3H; CH\(_3\)), 1.20-1.34 (m, 6H, CH\(_2\)), 1.86-1.93 (m, 1H, CH\(_2\)), 2.02-2.12 (m, 1H, CH\(_2\)), 4.72 (q, \(^3J=7.7\) Hz, 1H; CH), 5.16 (dt, \(^3J=10.5\) Hz, \(^2J=0.8\) Hz, 1H; CH), 5.22 (d, \(^3J=17.2\) Hz, \(^2J=1.2\) Hz, 1H; CH), 6.21 (ddd, \(^3J=17.4\) Hz, \(^2J=5.8\) Hz, \(^1J=9.9\) Hz, 1H; CH), 6.54 (d, \(^2J=17.2\) Hz, \(^1J=10.5\) Hz, 1H; CH), 5.22 (d, \(^3J=5.4\) Hz, \(^2J=3.0\) Hz, 2H; CH\(_{\text{aryl}}\)), 7.82 (dd, \(^3J=5.6\) Hz, \(^2J=3.2\) Hz, 2H; CH\(_{\text{aryl}}\)). \(^{13}\)C NMR (75 MHz, CDCl\(_3\)): \(\delta=13.9\) (CH\(_3\)), 22.4 (CH\(_2\)), 26.0 (CH\(_2\)), 31.2 (CH\(_2\)), 31.9 (CH\(_2\)), 54.1 (CH), 117.2 (CH\(_2\)), 123.1 (CH), 131.9 (C), 133.8 (CH), 135.8 (CH), 168.0 (CO). HR-ESI-MS: m/z calcd for C\(_{16}\)H\(_{20}\)NO\(_2\) [M+H]\(^+\) 258.1489, found 258.1489.

2-(4-Methylhex-1-en-3-yl)isoindoline-1,3-dione 4.54. Column chromatography (n-pentane/EtOAc 9:1) gave the aldehyde as a 60:40 mixture of diastereomers (52%). \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta=0.80-0.87\) (m, 6H; 2 x CH\(_3\)), 0.90-0.96 (m, 6H; 2 x CH\(_3\)), 0.97-1.17 (m, 2H; 2 x CH\(_2\)), 1.32-1.43 (m, 1H; CH\(_2\)), 1.59-1.71 (m, 1H; CH\(_2\)), 2.24-2.38 (m, 2H; 2 x CH), 4.33-4.40 (m, 2H; 2 x CH), 5.80-5.90 (m, 2H; 2 x CH), 5.80-5.90 (m, 2H; 2 x CH), 6.24-6.34 (m, 2H; 2 x CH), 7.68-7.73 (m, 4H; 2 x CH\(_{\text{aryl}}\)), 7.80-7.85 (m, 4H; 2 x CH\(_{\text{aryl}}\)). \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta=10.5\) (CH\(_3\)), 10.7 (CH\(_3\)), 15.4 (CH\(_3\)), 16.1 (CH\(_3\)), 25.5 (CH\(_2\)), 26.0 (CH\(_2\)), 36.9 (CH), 35.2 (CH), 59.7 (CH), 59.8 (CH), 118.8 (CH\(_2\)), 118.9 (CH\(_2\)), 123.0 (CH), 131.8 (C), 133.9 (CH), 135.0 (CH), 135.1 (CH), 168.0 (C). HR-ESI-MS: m/z calcd for C\(_{15}\)H\(_{18}\)NO\(_2\) [M+H]\(^+\) 244.1328, found 244.1332.

2-(1,1-Dimethyl-allyl)-isoindole-1,3-dione 4.55. Column chromatography (n-pentane/EtOAc 3:1) yielded the phthalimide as colourless oil (12%). \(^1\)H NMR (300 MHz, CDCl\(_3\)): \(\delta=1.70-1.75\) (m, 6H, CH\(_3\)), 4.99-5.13 (m, 2H; CH+CH), 6.12-6.26 (m, 1H; CH), 7.58-7.65 (m, 2H; CH\(_{\text{aryl}}\)), 7.66-7.75 (m, 2H; CH\(_{\text{aryl}}\)). \(^{13}\)C NMR (75 MHz, CDCl\(_3\)): \(\delta=26.7\) (CH\(_3\)), 59.8 (CH), 111.1 (CH\(_2\)), 122.5 (CH), 131.8 (C), 133.6 (CH), 143.2 (CH), 168.9 (CO). ESI-MS: m/z calcd for C\(_{13}\)H\(_{14}\)NO\(_2\) [M+H]\(^+\) 216.1017, found 216.1019.

2-(1-Benzyl-allyl)-isoindole-1,3-dione 4.56. Column chromatography (n-pentane/EtOAc 95:5) yielded the phthalimide as white solid (62%). m.p. 92-93\(^\circ\); \(^1\)H NMR (300 MHz, CDCl\(_3\)): \(\delta=3.20\) (dd, \(^2J=13.8\) Hz, \(^3J=6.6\) Hz, 1H; CH\(_3\)), 3.42 (dd, \(^2J=13.8\) Hz, \(^3J=9.9\) Hz, 1H; CH\(_2\)), 4.99-5.09 (m, 1H; CH), 5.16-5.27 (m, 2H; CH\(_3\)), 6.27 (dd, \(^3J=17.4\) Hz, \(^2J=10.1\) Hz, \(^1J=7.1\) Hz, 1H; CH), 7.07-7.23 (m, 5H; CH\(_{\text{aryl}}\)), 7.62-7.70 (m, 2H; CH\(_{\text{aryl}}\)), 7.71-7.79 (m, 2H; CH\(_{\text{aryl}}\)). \(^{13}\)C NMR (75 MHz, CDCl\(_3\)): \(\delta=38.2\) (CH\(_2\)), 55.1

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2-(1-Benzoxymethyl-allyl)-isoindole-1,3-dione 4.57. Column chromatography (n-pentane/EtOAc 9:1) yielded the phthalimide as colourless oil (88%).

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\text{\textsuperscript{1}H NMR (300 MHz, CDCl}_3\text{: }\delta=3.77 (dd, 2J=9.9 Hz, 3J=5.7 Hz, 1H; CH), 4.13 (dd, 2J=9.8 Hz, 3J=9.8 Hz, 1H; CH), 4.49 (d, 2J=12.3 Hz, 1H; CH), 4.58 (dd, 2J=12.3 Hz, 1H; CH), 5.05-5.15 (m, 1H; CH), 5.26 (d, 3J=10.5 Hz, 1H; CH), 5.26 (d, 3J=16.2 Hz, 1H; CH), 6.17 (ddd, 3J=17.1 Hz, 3J=10.1 Hz, 3J=7.1 Hz, 1H; CH), 7.21-7.30 (m, 5H; CHAr), 7.67-7.74 (m, 2H; CHAr), 7.79-7.86 (m, 2H; CHAr).}
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\text{\textsuperscript{13}C NMR (75 MHz, CDCl}_3\text{: }\delta=53.1 (CH), 68.8 (CH), 72.7 (CH), 118.9 (CH), 123.1 (CH), 127.5 (CH), 128.2 (CH), 131.8 (C), 132.2 (CH), 133.8 (CH), 137.8 (C), 168.0 (CO).}
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HR-ESI-MS: m/z calcd for C\textsubscript{19}H\textsubscript{18}NO\textsubscript{3} [M+H]+ 308.1276, found 308.1281.

2-(1-Phenyl-allyl)-isoindole-1,3-dione 4.58. Column chromatography (n-pentane/EtOAc 4:1) yielded the phthalimide as white solid (16%). m.p. 59-61\degree C; \textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}): \delta=5.36 (d, 2J=17.7 Hz, 1H; CH), 5.38 (d, 2J=10.2 Hz, 1H; CH), 5.97 (d, 2J=7.5 Hz, 1H; CH), 6.66 (ddd, 2J=17.4 Hz, 3J=10.1 Hz, 3J=7.4 Hz, 1H; CH), 7.24-7.37 (m, 3H; CHAr), 7.43-7.48 (m, 2H; CHAr), 7.70 (dd, 2J=5.2 Hz, 3J=3.2 Hz, 2H; CHAr), 7.83 (dd, 2J=6.4 Hz, 3J=3.2 Hz, 2H; CHAr). \textsuperscript{13}C NMR (75 MHz, CDCl\textsubscript{3}): \delta=56.8 (CH), 119.0 (CH), 123.3 (CH), 127.6 (CH), 127.7 (CH), 128.5 (CH), 131.8 (C), 133.9 (CH), 134.1 (CH), 138.4 (C), 167.6 (CO). HR-ESI-MS: m/z calcd for C\textsubscript{17}H\textsubscript{14}NO\textsubscript{2} [M+H]+ 264.1019, found 264.1019.

2-(1-(Thiophen-2-yl)allyl)isoindoline-1,3-dione 4.59. Column chromatography (n-pentane/EtOAc 10:1) yielded the phthalimide as yellow oil (45%). \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}): \delta=5.35 (d, 2J=10.8 Hz, 1H; CH), 5.38 (d, 2J=18.4 Hz, 1H; CH), 6.17 (d, 2J=7.6 Hz, 1H; CH), 6.64 (ddd, 2J=17.4 Hz, 3J=9.8 Hz, 3J=7.6 Hz, 1H; CH), 6.94 (dd, 2J=4.8 Hz, 3J=3.6 Hz, 1H; CH), 7.10 (d, 2J=2.8 Hz, 1H; CH), 7.23 (d, 2J=5.2 Hz, 1H; CH), 7.66-7.72 (m, 2H; CH), 7.79-8.75 (m, 2H; CH). \textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}): \delta=52.2 (CH), 119.0 (CH), 123.3 (CH), 125.4 (CH), 126.3 (CH), 126.7 (CH), 131.7 (C), 134.0 (CH), 141.3 (C), 167.1 (CO). HR-ESI-MS: m/z calcd for C\textsubscript{15}H\textsubscript{12}NO\textsubscript{2}S [M+H]+ 270.0583, found 270.0580.
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2-(E)-1-Methyl-2-enyl)-isoindole-1,3-dione 4.60. Column chromatography \((n\text{-pentane/EtOAc 3:1})\) yielded the phthalimide as colourless oil (49%). \(^1\)H NMR (300 MHz, CDCl\(_3\)): \(\delta=1.50\) (d, \(J=7.2\) Hz, 3H; CH\(_3\)), 1.63 (d, \(J=6.6\) Hz, 3H; CH\(_3\)), 4.84 (quin, \(J=7.2\) Hz, 1H; CH), 5.65 (dq, \(J=15.3\) Hz, \(J=7.5\) Hz, 1H; CH\(_3\)), 7.63-7.67 (m, 2H; CH\(_{Ar}\)), 7.73-7.78 (m, 2H; CH\(_{Ar}\)). \(^13\)C NMR (75 MHz, CDCl\(_3\)): \(\delta=17.5\) (CH\(_3\)), 18.8 (CH\(_3\)), 48.7 (CH), 122.9 (CH), 127.8 (CH), 129.8 (C), 132.0 (CH), 133.6 (CH), 167.9 (CO). ESI-MS: m/z calcd for C\(_{13}H_{14}NO_2\) [M+H\(^+\)] 216.1019, found 216.1019.

2-(1,2-Dimethyl-allyl)-isoindole-1,3-dione 4.61. Column chromatography \((n\text{-pentane/EtOAc 4:1})\) yielded the phthalimide as colourless oil (64%). \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta=1.64\) (d, \(J=7.2\) Hz, 3H; CH\(_3\)), 1.74 (s, 3H; CH\(_3\)), 4.85 (q, \(J=7.1\) Hz, 1H; CH), 4.99 (s, 1H; CH), 5.01 (s, 1H; CH), 7.71 (dd, \(J=5.4\) Hz, \(J=3.0\) Hz, 2H; CH\(_{Ar}\)), 7.83 (dd, \(J=5.4\) Hz, \(J=3.0\) Hz, 2H; CH\(_{Ar}\)). \(^13\)C NMR (75 MHz, CDCl\(_3\)): \(\delta=16.0\) (CH\(_3\)), 20.3 (CH\(_3\)), 50.3 (CH), 112.0 (CH\(_2\)), 122.9 (CH), 131.7 (C), 133.7 (CH), 142.7 (CH), 167.9 (CO). HR-ESI-MS: m/z calcd for C\(_{13}H_{14}NO_2\) [M+H\(^+\)] 216.1019, found 216.1019.

3-(1,3-Dioxo-1,3-dihydro-isoindol-2-yl)-butyraldehyde 4.68. Column chromatography \((n\text{-pentane/EtOAc 1:1})\) gave the aldehyde as white solid (94%). m.p. 106-107\(^\circ\)C; \(^1\)H NMR (300 MHz, CDCl\(_3\)): \(\delta=1.47\) (dd, \(J=7.2\) Hz, \(J=1.2\) Hz, 3H; CH\(_3\)), 2.99 (dd, \(J=18.0\) Hz, \(J=6.0\) Hz, 1H; CH\(_3\)), 3.28 (dd, \(J=18.0\) Hz, \(J=8.1\) Hz, 1H; CH\(_2\)), 4.89 (sextet, \(J=6.9\) Hz, 1H; CH), 7.65-7.72 (m, 2H; CH\(_{Ar}\)), 7.76-7.81 (m, 2H; CH\(_{Ar}\)), 9.73 (s, 1H; CHO). \(^13\)C NMR (75 MHz, CDCl\(_3\)): \(\delta=18.8\) (CH\(_3\)), 42.3 (CH\(_3\)), 47.3 (CH), 123.2 (CH\(_{Ar}\)), 131.8 (C), 134.0 (C), 168.0 (CO), 199.2 (CHO). ESI-MS: m/z calcd for C\(_{12}H_{12}NO_3\) [M+H\(^+\)] 218.0809, found 218.0812.

3-(1,3-Dioxo-1,3-dihydro-isoindol-2-yl)-octanal 4.69. Column chromatography \((n\text{-pentane/EtOAc 2:1})\) gave the aldehyde as colourless oil (91%). \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta=0.83\) (t, \(J=6.8\) Hz, 3H; CH\(_3\)), 1.20-1.31 (m, 6H; CH\(_3\)), 1.66-1.75 (m, 1H; CH\(_3\)), 2.00-2.11 (m, 1H; CH\(_2\)), 2.95 (\(J=18.0\) Hz, \(J=5.6\) Hz, \(J=1.1\) Hz, 1H; CH\(_3\)), 3.30 (dd, \(J=17.6\) Hz, \(J=8.8\) Hz, \(J=1.5\) Hz, 1H; CH\(_3\)), 4.76 (m, 1H; CH), 7.70 (dd, \(J=5.6\) Hz, \(J=3.2\) Hz, 2H; CH\(_{Ar}\)), 7.82 (dd, \(J=5.4\) Hz, \(J=3.0\) Hz, 2H; CH\(_{Ar}\)), 9.74 (s, 1H; CHO). \(^13\)C NMR (100 MHz, CDCl\(_3\)): \(\delta=13.8\) (CH\(_3\)), 22.3 (CH\(_3\)), 25.8 (CH\(_3\)), 31.1 (CH\(_2\)), 32.3 (CH\(_2\)), 45.7 (CH\(_3\)), 46.3 (CH), 123.2 (CH\(_{Ar}\)), 131.6 (C), 133.9 (C), 168.2 (CO), 199.4 (CHO). HR-ESI-MS: m/z calcd for C\(_{16}H_{20}NO_3\) [M+H\(^+\)] 274.1438, found 274.1438.
3-(1,3-Dioxoisoindolin-2-yl)-4-methylhexanal 4.70. Column chromatography (n-pentane/EtOAc 9:1) gave the aldehyde as a 60:40 mixture of diastereomers (88%). $^1$H NMR (300 MHz, CDCl$_3$): δ= 0.79-0.86 (m, 6H; 2 × CH$_3$), 0.89-1.00 (m, 6H; 2 × CH$_3$), 1.01-1.24 (m, 2H; 2 × CH$_2$), 1.29-1.44 (m, 1H; 2 × CH), 1.48-1.64 (m, 1H; 2 × CH), 2.01-2.21 (m, 2H; 2 × CH), 2.84-2.96 (m, 2H; 2 × CH$_2$), 3.35-3.49 (m, 2H; 2 × CH$_2$), 4.43-4.50 (m, 2H; 2 × CH), 7.65-7.72 (m, 4H; 2 × CH), 7.75-7.82 (m, 4H; 2 × CH), 7.97 (s, 2H; 2 × CHO). $^{13}$C NMR (75 MHz, CDCl$_3$): δ= 10.7 (CH$_3$), 10.9 (CH$_3$), 15.4 (CH$_3$), 16.0 (CH$_3$), 25.6 (CH$_2$), 26.1 (CH$_2$), 36.4 (CH), 36.8 (CH), 43.7 (CH$_2$), 43.8 (CH$_2$), 50.3 (CH), 50.5 (CH), 123.2 (CH), 131.5 (C), 134.0 (CH), 168.4 (CO), 168.5 (CO), 199.7 (CHO), 199.8 (CHO). HR-ESI-MS: m/z calcd for C$_{15}$H$_{18}$NO$_3$ [M+H]$^+$ 260.1282, found 260.1281.

3-(1,3-Dioxoisoindolin-2-yl)-3-methylbutanal 4.71. The reaction was completed after 2 days. Column chromatography (n-pentane/EtOAc 2:1) gave the aldehyde as colourless oil (74%). $^1$H NMR (300 MHz, CDCl$_3$): δ=1.77 (s, 6H; CH$_3$), 3.18 (s, 2H; CH$_2$), 7.66 (dd, $^2$J=5.4 Hz, $^4$J=3.0 Hz, 2H; CH Ar), 7.76 (dd, $^2$J=5.3 Hz, $^4$J=3.2 Hz, 2H; CH$_2$), 9.78 (s, 1H; CHO). $^{13}$C NMR (75 MHz, CDCl$_3$): δ= 27.7 (CH$_3$), 53.0 (CH$_2$), 57.1 (CH), 122.8 (CH), 131.8 (C), 133.9 (C), 169.4 (CO), 199.5 (CHO). HR-ESI-MS: m/z calcd for C$_{12}$H$_{14}$NO$_3$ [M+H]$^+$ 232.0967, found 232.0968.

3-(1,3-Dioxo-1,3-dihydro-isoindol-2-yl)-4-phenyl-butyraldehyde 4.72. Column chromatography (n-pentane/EtOAc 95:5) gave the aldehyde as colourless oil (94%). $^1$H NMR (400 MHz, CDCl$_3$): δ=3.00 (dd, $^2$J=18.0 Hz, $^3$J=5.2 Hz, 1H; CH$_2$), 3.13 (dd, $^2$J=13.6 Hz, $^3$J=6.8 Hz, 1H; CH$_2$), 3.25 (dd, $^2$J=13.4 Hz, $^3$J=9.0 Hz, 1H; CH$_2$), 3.39 (ddd, $^2$J=9.0 Hz, $^4$J=1.0 Hz 1H; CH$_2$), 4.99-5.08 (m, 1H; CH), 7.11-7.25 (m, 5H; CHAr), 7.63-7.71 (m, 2H, CH$_2$), 7.72-7.78 (m, 2H; CH$_2$), 9.71 (s, 1H; CHO). $^{13}$C NMR (100 MHz, CDCl$_3$): δ=38.5 (CH$_2$), 45.5 (CH$_2$), 47.0 (CH), 123.2 (CH), 126.9 (CH), 128.6 (CH), 129.0 (CH), 131.5 (C), 134.0 (CH), 138.4 (C), 170.0 (CO), 199.0 (CHO). HR-ESI-MS: m/z calcd for C$_{18}$H$_{16}$NO$_3$ [M+H]$^+$ 294.1130, found 294.1125.

4-Benzylx-3-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-butyraldehyde 4.73. Column chromatography (n-pentane/EtOAc 9:1) gave the aldehyde as colourless oil (93%). $^1$H NMR (400 MHz, CDCl$_3$): δ=3.04 (ddd, $^2$J=18.0 Hz, $^3$J=5.8 Hz, $^3$J=1.0 Hz, 1H; CH$_3$), 3.27 (ddd, $^2$J=18.0 Hz, $^3$J=8.6 Hz, $^3$J=1.4 Hz, 1H; CH$_2$), 3.74 (dd, $^2$J=9.6 Hz, $^3$J=6.6 Hz, 1H; CH$_2$), 3.86 (dd, $^2$J=9.6 Hz, $^3$J=8.0 Hz, 1H; CH$_2$), 4.48 (d, $^2$J=12.0 Hz, 1H; CH$_2$), 5.03-5.11 (m, 1H; CH), 7.20-7.30 (m, 5H; CHAr).
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3-(1,3-Dioxo-1,3-dihydro-isoindol-2-yl)-3-phenyl-propionaldehyde 4.66. Column chromatography (n-pentane/EtOAc 1:1) gave the aldehyde as colourless oil (95%). ¹H NMR (400 MHz, CDCl₃): δ=3.39 (dd, 2J=18.4 Hz, 3J=5.6 Hz, 1H; CH₂), 3.96 (dd, 2J=18.4 Hz, 3J=9.6 Hz, 1H; CH₂), 4.89 (dd, 2J=9.6 Hz, 3J=5.6 Hz, 1H; CH), 7.24-7.35 (m, 2H; CHAr), 7.51 (d, 3J=7.6 Hz, 2H; CH₂), 7.6-7.68 (m, 2H; CH₂), 7.71-7.80 (m, 2H; CH₂), 9.78 (s, 1H; CHO). ¹³C NMR (100 MHz, CDCl₃): δ=45.0 (CH₂), 48.7 (CH), 123.2 (CH), 127.6 (CH), 128.1 (CH), 128.7 (CH), 131.5 (C), 134.0 (CH), 138.4 (C), 167.9 (CO), 198.7 (CHO). HR-ESI-MS: m/z calcd for C₁₇H₁₄NO₃ [M+H]⁺ 280.0968, found 280.0968.

3(1,3-Dioxoisindolin-2-yl)-3-(thiophen-2-yl)propanal 4.74. Column chromatography (n-pentane/EtOAc 3:1) gave the aldehyde as a yellow oil (77%). ¹H NMR (400 MHz, CDCl₃): δ=1.41 (d, 3J=6.8 Hz, 3H; CH₃), 2.11 (s, 3H; CH₃), 2.98 (dd, 2J=17.6 Hz, 3J=6.4 Hz, 1H; CH₂), 3.27 (dd, 2J=17.6 Hz, 3J=8.0 Hz, 1H; CH₂), 4.81 (sextett, 3J=7.0 Hz, 1H; CH₂), 7.64-7.69 (m, 2H; CH₂), 7.73-7.80 (m, 2H; CH₂). ¹³C NMR (100 MHz, CDCl₃): δ=18.8 (CH₂), 30.1(CH₃), 42.5 (CH₂), 46.7 (CH), 123.1 (CH), 131.9 (C), 133.8 (CH), 168.1 (CO), 205.7 (CO). HR-ESI-MS: m/z calcd for C₁₃H₁₂NO₃S [M+H]⁺ 286.0534, found 286.0532.

2-(1-Methyl-3-oxo-butyl)-isoindole-1,3-dione 4.75. The reaction was completed after 2 days. Column chromatography (n-pentane/EtOAc 1:1) gave the product as white solid (89%). m.p. 74-76 °C; ¹H NMR (400 MHz, CDCl₃): δ=1.41 (d, 3J=6.8 Hz, 3H;CH₃), 2.11 (s, 3H; CH₃), 2.98 (dd, 2J=17.6 Hz, 3J=6.4 Hz, 1H; CH₂), 3.27 (dd, 2J=17.6 Hz, 3J=8.0 Hz, 1H; CH₂), 4.81 (sextett, 3J=7.0 Hz, 1H; CH₂), 7.64-7.69 (m, 2H; CH₂), 7.73-7.80 (m, 2H; CH₂). ¹³C NMR (100 MHz, CDCl₃): δ=18.8 (CH₂), 30.1(CH₃), 42.5 (CH₂), 46.7 (CH), 123.1 (CH), 131.9 (C), 133.8 (CH), 168.1 (CO), 205.7 (CO). HR-ESI-MS: m/z calcd for C₁₃H₁₄NO₃ [M+H]⁺ 232.0968, found 232.0973.
2-(1-Phenyl-allyl)-isoindole-1,3-dione 4.66. Under Argon, TBD (0.011 g, 0.08 mmol) was added to a solution of ([Ir(COD)Cl]$_2$) (0.013, 0.02 mmol) and (R,R,R)-4.65 (0.022, 0.04 mmol) in dry and degassed THF (0.5 mL). After stirring for 2 h at room temperature cinnamyl carbonate 4.64 (0.140 g, 1.0 mmol) was added, and the mixture was stirred for 5 min at room temperature. Then the phthalimide was added (0.177 g, 1.2 mmol) and the mixture was stirred for 24 h at room temperature. The reaction mixture was concentrated in vacuum and the residue was purified by flash column chromatography (n-pentane/EtOAc 95:5), yielding the product as a colorless oil (0.108 g, 0.41 mmol, 41%). HPLC Chiralcel OD-H, n-hexane/i-PrOH 95:5, $T_r$ = 18.5 min (major), 22.5 min (minor). 96% ee.

3-(1,3-Dioxoisoindolin-2-yl)-3-phenylpropane-1,1-diyl diacetate 4.67. Aldehyde 4.66 (0.08 g, 0.30 mmol) was dissolved in acetic anhydride (1.0 mL, 13.6 mmol) at 0°C. Then anhydrous FeCl$_3$ (2.43 g, 0.015 mmol) was added and the reaction mixture was stirred for 15 min at 0°C and subsequently for 12 h at room temperature. The solvent was removed in vacuum and the residue was purified by flash column chromatography (n-pentane/EtOAc 9:1) yielding the product as colorless oil (0.09 g, 0.24 mmol, 83%).

$\text{1H NMR (400 MHz, CDCl}_3\text{): } \delta_1=1.94 \text{ (s, 3H; CH}_3\text{), } \delta_2=1.99 \text{ (s, 3H; CH}_3\text{), } \delta_3=2.68 \text{ (ddd, } J_1=14.3 \text{ Hz, } J_2=6.0 \text{ Hz, } J_3=6.0 \text{ Hz, 1H; CH}_2\text{), } \delta_4=3.29 \text{ (ddd, } J_1=14.5 \text{ Hz, } J_2=10.5 \text{ Hz, } J_3=3.9 \text{ Hz, 1H; CH}_2\text{), } \delta_5=5.55 \text{ (ddd, } J_1=10.4 \text{ Hz, } J_2=5.2 \text{ Hz, 1H; CH), } \delta_6=6.95 \text{ (ddd, } J_1=6.0 \text{ Hz, } J_2=4.4 \text{ Hz, 1H; CH), } \delta_7=7.24-7.36 \text{ (m, 3H; CH}_3\text{), } \delta_8=7.53 \text{ (dd, } J_1=7.2 \text{ Hz, 2H; CH}_2\text{), } \delta_9=7.69 \text{ (dd, } J_1=5.0 \text{ Hz, } J_2=3.0 \text{ Hz, 2H; CH}_2\text{), } \delta_{10}=7.81 \text{ (ddd, } J_1=5.2 \text{ Hz, } J_2=3.2 \text{ Hz, 2H; CH}_2\text{).}$

$\text{13C NMR (50 MHz, CDCl}_3\text{): } \delta_1=20.5 \text{ (CH}_3\text{), } \delta_2=20.6 \text{ (CH}_3\text{), } \delta_3=34.0 \text{ (CH}_2\text{), } \delta_4=49.7 \text{ (CH), } \delta_5=88.2 \text{ (CH), } \delta_6=123.3 \text{ (CH), } \delta_7=127.9 \text{ (CH), } \delta_8=128.1 \text{ (CH), } \delta_9=128.7 \text{ (CH), } \delta_{10}=131.8 \text{ (C), } \delta_{11}=134.0 \text{ (CH), } \delta_{12}=138.5 \text{ (C), } \delta_{13}=168.0 \text{ (CO), } \delta_{14}=168.5 \text{ (CO), } \delta_{15}=168.6 \text{ (CO).}$

HR-ESI-MS: m/z calcd for C$_{21}$H$_{19}$NO$_6$ [M+H]$^+$ 404.1105, found 404.1102. HPLC Chiralcel AS-H, n-heptane/i-PrOH 98:2, $T_r$ = 30.0 min (minor), 31.8 min (major).

3-(1,3-Dioxoisoindolin-2-yl)butanoic acid 4.76. Mn-tmtacn (1.92 mg, 0.0026 mmol, 0.5 mol%), trichloroacetic acid (6 mg, 0.031 mmol, 6.23 mol%), H$_2$O (0.046 mL) and H$_2$O$_2$ (50% in H$_2$O, 0.020 mL) in MeCN (6.40 mL) were stirred at 0°C for 20 min. The aldehyde 4.68 (0.108 g, 0.497 mmol) and additional H$_2$O$_2$ (50% in H$_2$O, 0.020 mL) were added. The reaction mixture was stirred at 0°C, and four portions of H$_2$O$_2$ (50% in H$_2$O, 4 x 0.020 mL) were added every 30 min. After warming to room temperature, EtOAc (20 mL) and H$_2$O (10 mL) were added. The aqueous layer was extracted with EtOAc (3 x 10 mL), the combined organic layers were dried over MgSO$_4$, and concentrated in vacuum. The crude acid was purified by flash column chromatography (n-pentane/EtOAc 1:1) to a white oil (0.101 g, 0.433 mmol, 87%).

$\text{1H NMR (400 MHz, CDCl}_3\text{): } \delta_1=1.94 \text{ (s, 3H; CH}_3\text{), } \delta_2=1.99 \text{ (s, 3H; CH}_3\text{), } \delta_3=2.68 \text{ (ddd, } J_1=14.3 \text{ Hz, } J_2=6.0 \text{ Hz, } J_3=6.0 \text{ Hz, 1H; CH}_2\text{), } \delta_4=3.29 \text{ (ddd, } J_1=14.5 \text{ Hz, } J_2=10.5 \text{ Hz, } J_3=3.9 \text{ Hz, 1H; CH}_2\text{), } \delta_5=5.55 \text{ (ddd, } J_1=10.4 \text{ Hz, } J_2=5.2 \text{ Hz, 1H; CH), } \delta_6=6.95 \text{ (ddd, } J_1=6.0 \text{ Hz, } J_2=4.4 \text{ Hz, 1H; CH), } \delta_7=7.24-7.36 \text{ (m, 3H; CH}_3\text{), } \delta_8=7.53 \text{ (dd, } J_1=7.2 \text{ Hz, 2H; CH}_2\text{), } \delta_9=7.69 \text{ (dd, } J_1=5.0 \text{ Hz, } J_2=3.0 \text{ Hz, 2H; CH}_2\text{), } \delta_{10}=7.81 \text{ (ddd, } J_1=5.2 \text{ Hz, } J_2=3.2 \text{ Hz, 2H; CH}_2\text{).}$
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NMR (300 MHz, CDCl3): \( \delta = 1.49 \) (d, \( J = 6.9 \) Hz, 3H; CH₃), 2.85 (dd, \( J = 16.7 \) Hz, \( J = 6.2 \) Hz, 1H; CH₂), 3.21 (dd, \( J = 16.7 \) Hz, \( J = 8.6 \) Hz, 1H; CH₂), 4.78 (dqd, \( J = 8.4 \) Hz, \( J = 6.8 \) Hz, \( J = 6.8 \) Hz, 1H; CH₂), 7.71 (dd, \( J = 5.4 \) Hz, \( J = 3.0 \) Hz, 2H; CH₃), 7.81 (dd, \( J = 5.6 \) Hz, \( J = 3.2 \) Hz, 2H; CH₃). ¹³C NMR (75 MHz, CDCl₃): \( \delta = 19.0 \) (CH₃), 37.8 (CH₂), 43.4 (CH), 123.5 (CH), 132.0 (C), 134.2 (C), 168.3 (CO), 167.3 (CO₂H). HR-ESI-MS: m/z calcd for C₁₂H₁₂NO₄ [M+H⁺] 234.0761, found 234.0761.

3-Aminobutanoic acid 4.69. Hydrazine monohydrate was added to the phthalimide protected acid 4.76 (20 mg, 0.09 mmol) in EtOH (1.5 mL). After heating to 110°C for 2.5 h, the solvent was evaporated in vacuum. Aqueous 4M HCl (1 mL) was added, the resulting precipitate was filtered, and the filtrate concentrated in vacuum. The solid was dissolved in EtOH and Et₂O added to precipitate the amino acid. After standing overnight at 4°C the precipitate was filtered and dried in vacuum (12 mg, 0.09 mmol, 100%). Spectral data were according to the literature: ¹H NMR (400 MHz, CDCl₃): \( \delta = 1.06 \) (d, \( J = 6.4 \) Hz, 3H, CH₃), 2.42-2.51 (m, 2H; CH₂), 3.40-3.50 (m, 1H; CH). ¹³C NMR (75 MHz, CDCl₃): \( \delta = 17.7 \) (CH₃), 37.7 (CH₂), 44.4 (CH), 164.1 (CO).

2-(4-Hydroxybutan-2-yl)isoindoline-1,3-dione 4.77. To a solution of the corresponding aldehyde 4.68 (0.065 g, 0.300 mmol) in MeOH (1.5 mL) at 0°C sodium borohydride (0.011 g, 0.3 mmol) was added. After stirring for 1 h at 0°C the reaction was quenched with a saturated solution of ammonium chloride (10 mL) and extracted with CH₂Cl₂ (3 x 5 mL). The organic layers were dried over MgSO₄, the solvent was removed in vacuum and the residue was purified by flash column chromatography (CH₂Cl₂/acetone 95:5), yielding the product as white solid (0.062 g, 0.285 mmol, 95%). Spectral data were according to the literature: m.p. 72-74°C; ¹H NMR (300 MHz, CDCl₃): \( \delta = 1.51 \) (d, \( J = 6.9 \) Hz, 3H; CH₃), 1.82-2.00 (m, 2H; CH₂), 2.12-2.29 (m, 2H; CH₂), 3.46-3.66 (m, 2H; CH₂), 4.48-4.61 (m, 1H; CH), 7.68 (dd, \( J = 5.4 \) Hz, \( J = 3.0 \) Hz, 2H; CH₃), 7.78 (dd, \( J = 5.5 \) Hz, \( J = 3.2 \) Hz, 2H; CH₃). ¹³C NMR (75 MHz, CDCl₃): \( \delta = 18.8 \) (CH₃), 36.6 (CH₂), 44.4 (CH₂), 59.9 (CH), 123.4 (CH), 132.1 (C), 134.2 (C), 169.0 (CO). HR-ESI-MS: m/z calcd for C₁₂H₁₄NO₃ [M+H⁺] 220.0968, found 220.0968.

3-Aminobutan-1-ol 4.70. Hydrazine monohydrate (56 µL, 1.3 mmol) was added to the corresponding protected alcohol 4.77 (30 mg g, 0.13 mmol) in EtOH (2.0 mL). After heating to reflux for 3 h, the solvent was evaporated in vacuum. 1M aq. HCl (5 mL) was added, and the suspension stirred for 1h. The resulting precipitate was filtered, and aq. NaOH (40%) added until the solution was basic. The solution was extracted with hot CHCl₃ (4 x 5 mL), dried over MgSO₄, and concentrated in vacuum to a colourless oil (11 mg, 0.12 mmol, 90%). Spectral data were according to the literature: ¹H NMR (400 MHz, C₃DOD): \( \delta = 1.22 \) (d, \( J = 6.8 \) Hz,
3H; CH₃), 1.58-1.69 (m, 1H; CH₂), 1.70-1.81 (m, 1H; CH₂), 3.19 (bs, 1H; OH), 3.29-3.40 (s, 1H; CH), 3.53-3.69 (m, 2H; CH₂). ¹³C NMR (75 MHz, CDCl₃): δ=25.0 (CH₃), 39.2 (CH₂), 46.9 (CH), 61.3 (CH₂).

4.7 References

5 The crystal structure was determined for [Pd₂Cl₂(C₁₀H₁₂NO₂)₂] CH₂Cl₂, a metallacycle derived from a substituted norbornene dicyclopentadiene, see Ref. 6c.
23 Catalyst C was not tested for this substrate.
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25 Similar selectivities have been observed in catalytic hydrogenation of α-phthalimido ketones, see: Wang, Y.-Q.; Lu, S.-M.; Zhou, Y.-G. *Org. Lett.* **2005**, 7, 3235.
28 No supporting information is available for this publication, see Ref. 26.
36 Synthesized from cinnamyl alcohol and methylchloro formate and cat. DMAP in CHCl₃ and pyridine in 93% yield.

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