The Pd-catalyzed semihydrogenation of alkynes to Z-alkenes: Catalyst systems and the type of active species
Drost, R.M.

Citation for published version (APA):
Chapter 4

Synthesis of Pd\textsuperscript{II}(allyl) Histidyldiene Complexes and their Application in Z-selective Transfer Semihydrogenation of Alkynes

Abstract

We have studied the amino acid histidine as a precursor for N-heterocyclic carbene (NHC) ligands. The natural amino acid histidine possesses an imidazole functional group, which makes it an interesting NHC precursor that contains an acid and amino functionality. These functionalities may be used for further tuning of NHC complexes. We have developed routes for the synthesis of symmetric and dissymmetric alkyl, benzyl and aryl substituted histidinium salts. Subsequently, the corresponding Ag and Pd histidyldienes were synthesized and the palladium complexes were tested in the Z-selective transfer semihydrogenation of alkynes. Histidyldiene palladium complexes that contain additional donor functionalities were found to display good selectivities. The best catalytic results were obtained with a Pd-histidyldiene complex that contains two picolyl functional groups.

4.1 Introduction

N-Heterocyclic carbenes (NHCs) have found application in functional materials, transition metal catalysis, organocatalysis, bioorganometallic chemistry and organometallic chemistry. The development of imidazolium salts, NHC ligands and methodologies that allow further modification of these compounds have a great impact on their applications.

Imidazolium and imidazolinium salts are the most common NHC precursors and are also the basis of many types of ionic liquids. An imidazole molecule contains four sites for ligand variation (Scheme 1). There are five methodologies for the synthesis of these imidazolium salts: I) multi-component synthesis of imidazolium compounds, II) multi-component synthesis of a substituted imidazole and its subsequent functionalization, III) two-step functionalization of imidazole (derivatives), IV) synthesis of a diamine compound and subsequent ring-closure with triethylorthoformate, and V) reacting formamidines with di-electrophiles, which provides an imidazolidine (Scheme 1).

Route I, II and III are the more standard methods, because of their simplicity. Route IV is mainly applied for symmetrically substituted diamines, and becomes problematic when the steric properties of the R1 and R2 groups become imposing. Additionally, synthesis of diimine compounds that are substituted on the backbone is challenging, and even more so for asymmetrically substitutions of this precursor. Route V is less applied in the synthesis of 5-membered ring imidazolinium salts, but it is a common route for expanded-ring NHC precursors. For the synthesis of R3 and R4 substituted compounds this route has been little investigated. In both route IV and V several functional groups cannot be applied and both methods are synthetically laborious. In the well-developed routes I-III, variation of the wingtips on the ligands is relatively easy, however, synthesis of backbone-functionalized NHCs is less trivial.

Hence, alternative strategies toward these compounds lead to a wider versatility in NHC ligands and options for the fine-tuning of catalyst reactivity. This makes development of such new strategies desirable.
Naturally abundant compounds are interesting starting materials for the synthesis and development of molecular catalysts, when these precursors circumvent laborious or challenging synthetic procedures. Therefore, abundant backbone-functionalized imidazoles are good starting materials for NHC ligands. The natural amino acid histidine is such an imidazole. Both its amine and acid functional group can be functionalized by well-established chemistry. Histidine can be converted into a histidinium salt via Route III (Scheme 1). This allows the synthesis of NHC precursors that possess four handles for further functionalization (Scheme 2). An additional reason why histidine is an interesting precursor for NHC ligands is that it is present in many biological molecules. Hence, the development of histidine as a precursor for NHC ligands is also relevant for bioinorganic and bioorganometallic applications.
Scheme 2. The natural amino acid histidine is a precursor for highly functionalized NHC transition metal complexes.

Histidylidenes, NHCs that are derived from histidine, have only recently been explored by Erker et al.\textsuperscript{27} and by Albrecht et al.\textsuperscript{28-31} The alkylation of histidine was also reported in studies toward chiral ionic liquids.\textsuperscript{32,33} The publications by Albrecht et al. and several other publications show that NHCs, histidylidenes, and other natural compound derived NHCs\textsuperscript{34-38} are highly interesting compounds for bioorganometallic applications.\textsuperscript{4,39} For instance, amino acid derived Au and Ag-NHC compounds have demonstrated to possess anti-tumor activity.\textsuperscript{40-42}

Aim

Up to now, only histidylidenes bearing simple alkyl wingtip substituents have been reported. The wing tips of the NHC are highly important for the fine-tuning of the catalytic performance of the transition metal complex. A wider variation in these precursors should increase the applicability of these compounds. Therefore, we set out to expand the synthetic methodologies for relevant precursors of histidylidene transition metal catalysts. We investigated methodologies that allow the synthesis of symmetric and dissymmetric alkyl-, benzyl- and aryl-substituted histidinium salts. Subsequently, the newly developed ligand precursors are applied in the synthesis of Ag\textsuperscript{1} and Pd\textsuperscript{0} histidylidene complexes. The catalytic properties of the palladium complexes in the Z-selective transfer semihydrogenation of alkynes are investigated.\textsuperscript{43} In these studies we focused on the influence of the NHC substitution pattern. We initially started these studies to use histidylidenes as precursors for the heterogenization of palladium NHC complexes in order to develop recoverable catalysts for the transfer semihydrogenation of alkynes to Z-alkenes. However, recent detailed studies concerning the use of [Pd(NHC)] systems in this catalytic reaction suggested that ill-defined palladium (nano)particles may be involved, rather than the originally anticipated, well-defined molecular complexes (Chapter 5). Hence, heterogenization of [Pd(NHC)] systems for this purpose is likely futile, and therefore we abandoned the intended heterogenization steps.
4.2 Methodologies for the Synthesis of Histidinium Salts

One of the reasons for our interest in histidine as a precursor for NHC complexes is that it provides four handles for functionalization: the two nitrogen atoms of the imidazolyl, the amine and the acid group (Scheme 2). The amine and the acid group are protected to allow the selective synthesis of the histidinium salts. We chose protecting groups that can be removed selectively so both the free acid and amine histidylidenes can be obtained. This design allows the incorporation of histidylidenes in, for instance, catalyst heterogenization or synthetic biomolecular scaffolds.44

The carboxylic acid group was protected in the form of a methyl ester, which can be removed under basic conditions. We chose a tert-butyloxycarbonyl (Boc) group for the protection of the amine. This group affords a carbamate that is unreactive under basic conditions, but may be cleaved by trifluoroacetic acid (TFA) or a 4 M solution of HCl in an organic solvent. Boc-protection of the histidine methyl ester is performed in a two-step reaction, which affords precursor 1 (Scheme 3).22

Scheme 3. Boc-histidine methyl ester, which is the chosen precursor for the synthesis of the histidinium salts.

Direct alkylation to afford symmetrically substituted histidinium halides

We employed three routes to obtain the target imidazolium salts. The first route was the direct benzylation of protected histidine 1 (Scheme 4). This route provides symmetrically substituted benzyl functionalized imidazolium bromides. When benzyl (Bn) bromide was used (D = CH), compound 2 was obtained in quantitative yields. When picoyl (Pic) bromide was used (D = N), formation of several side products was observed on TLC. Column chromatography allowed the isolation of the pure product 3 in a decent yield of 80%. The 1H NMR spectra show two separate A-B systems for the
diastereotopic benzylic \( \text{CH}_2 \) protons, indicating that these protons are not equivalent on NMR timescale.

**Scheme 4.** The synthesis of symmetrically substituted benzylic imidazolium bromides.

The cyclic urea approach to synthesize dissymmetrically functionalized histidinium halides

Synthesis of dissymmetrically substituted histidinium salts gives access to an even larger set of ligand precursors, which allows further tuning of the properties of the NHC metal complex. This is not straightforward because histidine has two tautomeric forms, which means that the \( \pi \)- and the \( \tau \)-nitrogen of the imidazole possess both imine and amine character (4, Scheme 5). Therefore, mixtures of regioisomers are obtained when the imidazole is reacted with one equivalent of an electrophile. To obtain the desired dissymmetrically substituted histidinium salts, we applied a route based on the report by Hodges and Chivikas that was improved by Brégeon et al. (Scheme 5).

**Scheme 5.** The cyclic urea route toward dissymmetrically substituted histidinium salts.
Table 1. Synthesized histidines and histidinium salts via the cyclic urea route.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Compound</th>
<th>R¹</th>
<th>R²</th>
<th>X</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>6</td>
<td>Bn</td>
<td></td>
<td></td>
<td>&gt;99</td>
</tr>
<tr>
<td>2</td>
<td>7</td>
<td>Pic</td>
<td></td>
<td></td>
<td>72</td>
</tr>
<tr>
<td>3</td>
<td>8</td>
<td>iPr</td>
<td></td>
<td></td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>9</td>
<td>Bn</td>
<td></td>
<td></td>
<td>30</td>
</tr>
<tr>
<td>5</td>
<td>10</td>
<td>Pic</td>
<td></td>
<td></td>
<td>25</td>
</tr>
<tr>
<td>6</td>
<td>11</td>
<td>Bn</td>
<td>Me</td>
<td>I</td>
<td>&gt;99</td>
</tr>
<tr>
<td>7</td>
<td>12</td>
<td>Bn</td>
<td>Pic</td>
<td>Br</td>
<td>68</td>
</tr>
<tr>
<td>8</td>
<td>13</td>
<td>Bn</td>
<td>iPr</td>
<td>I</td>
<td>0</td>
</tr>
<tr>
<td>9</td>
<td>14</td>
<td>Pic</td>
<td>Me</td>
<td>I</td>
<td>58</td>
</tr>
</tbody>
</table>

This cyclic urea route induces regioselectivity, as only the six-membered cyclic urea 5 can be formed. The other nitrogen atom can then be functionalized selectively through a nucleophilic substitution. Subsequently, the R¹-functionalized urea compounds can be ring-opened by reaction with an alcohol, which liberates the π-nitrogen atom of the imidazole, and provides a carbamate protected amine. The use of 4BuOH affords the Boc-protected histidine, which is the protection group we chose in the design of the general synthetic route (Scheme 3). A disadvantage of applying 4BuOH as ring-opening reagent is its poor nucleophilicity, which is the cause of the low yields. The report by Brégeon shows that the yields could be improved by using less sterically hindered alcohols, such as methanol.33 Therefore, the overall yields may be improved by a minor synthetic variation, if the deprotection of the amine is not required. Compounds 9 and 10 (Table 1) can then be alkylated, once more, with another electrophile (R²-X) to afford histidinium salts.

Via this cyclic urea route we synthesized compounds 6 and 7, R¹-functionalized imidazoles 9 and 10 and histidinium salts 11-14. However, we were unable to functionalize both the urea and the R¹-substituted imidazole compounds with isopropyl iodide (entries 3 and 8).

The Cham-Lam-Evans approach to yield dissymmetrically arylated, alkylated histidinium halides.

A synthetic route for NHC ligands that have an aryl substitution on the wingtips is also highly desirable, since many NHC compounds bearing aryl substituents display the best reactivities in catalytic applications.1,3 This is also true for our model reaction: the semihydrogenation of alkynes towards Z-alkenes.43,45 Several methods have been developed for the arylation of imidazoles, for instance, the Ullman46 and Buchwald47
coupling reactions. These methodologies have been applied in the arylation of imidazoles with aryl halides, \(^\text{48,49}\) arylllead(IV) reagents,\(^\text{50}\) arylboronic acids\(^\text{51,52}\) and trifluoroaryl borates\(^\text{53}\). Despite the tautomeric equilibrium of imidazoles, several N-arylation reactions were reported to have good chemoselectivities toward the \(\tau\)-nitrogen atom of backbone functionalized imidazoles.\(^\text{48,50}\) However, some of these methods are unpractical and may not be compatible with more functionalized histidine imidazoles.\(^\text{54,55}\) The Cham-Lam-Evans reaction with aryl boronic acids is an alternative reaction that operates under very mild conditions (Scheme 6).\(^\text{56,57}\) The regioselective \(N\)-arylation of a benzyl carbamate-protected histidine methyl ester with 4-methoxyphenylboronic acid gave yields of less than 10\%.\(^\text{57}\) However, the improved Cham-Lam-Evans method by Campagne and coworkers gave yields up to 31\% of the desired compound. We adapted this protocol by performing the reaction at room temperature and extending the reaction times. With these adjustments, we were able to obtain the \(para\)-methoxyphenyl 15 and mesityl 16 and \(N\)-arylated products in satisfactory yields of 84\% and 61\%, respectively.

Scheme 6. The Cham-Lam-Evans method to synthesize aryl-functionalized histidinium salts.

\[
\begin{align*}
\text{HN} & \equiv \text{N} \quad \text{CO}_2\text{Me} \\
\text{NHBoc} & \quad \text{H}_2\text{O} \\
\text{Cu(OAc)}_2\cdot\text{H}_2\text{O} & \quad \text{NaOAc} \\
\text{MeOH} & \quad \text{R}_2\text{X}
\end{align*}
\]

Subsequently, we alkylated these two aryl-functionalized histidines 15 and 16 with various electrophiles (\(R_2\text{-X}\)), which afforded another set of histidinium salts 17-20 (Table 2). This method was proven to be reliable and allows access to a wide variety of histidylidene precursors. Histidinium salts 19 and 20 were obtained in relatively low yields. They are synthesized through a reaction of histidine 16 with a Pic or lutidyl (Lut) bromide, which decompose during the reaction leading to the decrease in yield.\(^\text{58}\) NMR and mass spectrometry suggest that the decomposition product also gives rise to a trans-esterification of 16 and its product histidinium salts.
Table 2. \( N \)-arylation of histidine precursor 1 and its subsequent alkylation yielding aryl-substituted histidinium salts.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Compound</th>
<th>Ar</th>
<th>( R^2 )</th>
<th>X</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>15</td>
<td>p-OMePh</td>
<td>-</td>
<td>-</td>
<td>84</td>
</tr>
<tr>
<td>2</td>
<td>16</td>
<td>Mes</td>
<td>-</td>
<td>-</td>
<td>61</td>
</tr>
<tr>
<td>3</td>
<td>17</td>
<td>p-OMePh</td>
<td>Me</td>
<td>l</td>
<td>&gt;99</td>
</tr>
<tr>
<td>4</td>
<td>18</td>
<td>Mes</td>
<td>Me</td>
<td>l</td>
<td>&gt;99</td>
</tr>
<tr>
<td>5</td>
<td>19</td>
<td>Mes</td>
<td>Pic</td>
<td>Br</td>
<td>51</td>
</tr>
<tr>
<td>6</td>
<td>20</td>
<td>Mes</td>
<td>Lut</td>
<td>Br</td>
<td>80</td>
</tr>
</tbody>
</table>

Selective deprotection of histidinium salts

We chose the protection groups in such a way that the amine and/or the acid functionality could be deprotected selectively. That way, the free amine or acid compound can be prepared from a common precursor. Deprotection may either be performed after synthesis of the histidinium salt, or after the synthesis of the histidyldiene metal complex. NHCs generally lead to highly stable compounds. However, a wide range of transition metal complexes and precursors may not be stable under the conditions that are used in the deprotection step. Therefore, deprotection of the desired functionality before complexation to the metal may be desirable.

We have developed procedures for the deprotection of the acid as well as the amine of the histidine imidazolium salt. Boc-deprotection of an amino acid is a common organic synthetic procedure. It is usually performed with TFA, or a 4 M solution of HCl in dioxane. In general, the synthesis of the desired NHC transition metal complexes often involves a transmetallation step using a preformed silver-NHC complex, which is driven by the precipitation of a silver halide. The application of TFA in the Boc-deprotection step may cause scrambling of the counter ions of the imidazolium salt, which could give issues later on in the synthesis during the transmetallation step. Therefore, the application of HCl in dioxane is preferred over TFA. Because an excess of HCl is used, anion metathesis takes place concurrently with deprotection, yielding products with only chloride-anions. In the case of simple histidinium salts, which do not contain additional basic functionalities, the dicationic HCl salts are obtained. If additional basic functionalities are present in the compound (for instance picolyl moieties) tri- or tetracationic HCl salts are obtained (Scheme 7 and Table 3).

![Diagram of Scheme 7]

Table 3. Yields of Boc-deprotection.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Compound</th>
<th>R&lt;sup&gt;1&lt;/sup&gt;</th>
<th>R&lt;sup&gt;2&lt;/sup&gt;</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>21</td>
<td>Bn</td>
<td>Bn</td>
<td>&gt;99</td>
</tr>
<tr>
<td>2</td>
<td>22</td>
<td>Bn</td>
<td>Me</td>
<td>&gt;99</td>
</tr>
<tr>
<td>3</td>
<td>23</td>
<td>Pic</td>
<td>Pic</td>
<td>&gt;99</td>
</tr>
<tr>
<td>4</td>
<td>24</td>
<td>Pic</td>
<td>Me</td>
<td>&gt;99</td>
</tr>
<tr>
<td>5</td>
<td>25</td>
<td>Mes</td>
<td>Me</td>
<td>92</td>
</tr>
</tbody>
</table>

Subsequently, saponification of the methyl ester of 17 was performed by stirring it in a solution of MeOH with 10 equivalents of LiOH, which provided 26. TLC showed full conversion of the starting material, and after work up, <sup>1</sup>H-NMR showed the presence of the imidazolium proton as well as the complete disappearance of the characteristic methyl ester signal (Scheme 8).

Scheme 8. Methyl ester deprotection of 17.

![Diagram of Scheme 8]

**Summary of the histidinium salt synthesis**

We have developed three different methodologies for the synthesis of a wide variety of histidinium salts. Symmetrically substituted benzylated histidinium salts are obtained from the Boc-protected histidine methyl ester in a single reaction step. Dissymmetrically alkylated and benzylated products were obtained via the cyclic urea method, and a regioselective N-arylation via an adapted Cham-Lam-Evans coupling allowed the incorporation of aryl substituents into the histidylidene precursors. Subsequently, the obtained compounds can be deprotected selectively to obtain the free acid or free amine ligand, which is highly relevant for further applications.
4.3 Synthesis of Ag⁺ and [PdII(allyl)] Histidyldiene Complexes

We synthesized histidyldiene complexes of silver(I). These compounds are used as carbene transfer agents, and are generally relatively stable. We chose transmetallation as a method of complex synthesis for two reasons. Firstly, transmetallation from silver to the target precursor is a highly reliable and often applied method to obtain NHC complexes for a wide range of transition metals. Secondly, this is a very mild method that is highly tolerant towards a variety of functionalities in the ligand.

**Synthesis of Ag⁺ histidyldienes**

Ag⁺ NHCs are generally synthesized by the reaction of an imidazolium salt with silver(I) oxide, which functions as a base as well as a complexating agent. We synthesized a wide range of Ag⁺ histidyldienes by stirring the ligand with 0.55 equivalent of Ag₂O under inert conditions and exclusion of light (Scheme 9 and Table 4).

**Scheme 9. Synthesis of Ag⁺ histidyldienes.**

![Scheme 9](image)

The silver carbene is represented as an [Ag⁺(NHC)(halido)] complex. However, a multitude of [Ag⁺NHC] coordination compounds may be formed. For simplicity's sake this representation was chosen. ¹H NMR shows the absence of the imidazolium proton, and in the ¹³C NMR spectrum, signals were observed around 180 ppm, which is a typical value for a silver-carbene. For the Boc-protected histidinium salts, good to excellent yields were obtained for a range of R¹- and R²-substituents (Table 4, Entries 1-6).
Table 4. Synthesized Ag\textsuperscript{1} histidyldienes.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Compound</th>
<th>R\textsuperscript{1}</th>
<th>R\textsuperscript{2}</th>
<th>R\textsuperscript{3}</th>
<th>X</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>27</td>
<td>Bn</td>
<td>Bn</td>
<td>Boc</td>
<td>Br</td>
<td>95</td>
</tr>
<tr>
<td>2</td>
<td>28</td>
<td>Bn</td>
<td>Pic</td>
<td>Boc</td>
<td>Br</td>
<td>85</td>
</tr>
<tr>
<td>3</td>
<td>29</td>
<td>Pic</td>
<td>Pic</td>
<td>Boc</td>
<td>Br</td>
<td>80</td>
</tr>
<tr>
<td>4</td>
<td>30</td>
<td>3-0MePh</td>
<td>Me</td>
<td>Boc</td>
<td>I</td>
<td>78</td>
</tr>
<tr>
<td>5</td>
<td>31</td>
<td>Mes</td>
<td>Me</td>
<td>Boc</td>
<td>I</td>
<td>86</td>
</tr>
<tr>
<td>6</td>
<td>32</td>
<td>Mes</td>
<td>Lut</td>
<td>Boc</td>
<td>Br</td>
<td>89</td>
</tr>
<tr>
<td>7</td>
<td>33</td>
<td>Bn</td>
<td>Bn</td>
<td>H</td>
<td>Cl</td>
<td>96</td>
</tr>
<tr>
<td>8</td>
<td>34</td>
<td>Mes</td>
<td>Me</td>
<td>H</td>
<td>Cl</td>
<td>22</td>
</tr>
</tbody>
</table>

Complexes 27 and 29 display a high stability and can be stored in the solid for several weeks and manipulated in air as well. We also synthesized free-amine analogues 33 and 34. Their precursors are ammonium chloride salts of the histidinium salts. An ammonium proton is more acidic than a histidinium proton. Therefore, we applied an extra half equivalent of Ag\textsubscript{2}O as base in the synthesis of 33 and 34 (Table 4). The presence of the free amine, which is a better ligand for silver than a carbamate, does not seem to interfere in the synthesis of 33.

Synthesis of [Pd\textsuperscript{II}(η\textsuperscript{3}-allyl)] histidyldienes

[Pd\textsuperscript{II}(NHC)(η\textsuperscript{3}-allyl)Cl\textsubscript{2}] complexes are highly stable, readily synthesized, and good precatalysts for several reactions\textsuperscript{61} for instance the Z-selective semihydrogenation of alkynes\textsuperscript{62}. Therefore, we investigated the transmetallation of the silver(I) complexes to obtain the Pd\textsuperscript{II} histidyldienes (Scheme 10).

Scheme 10. Synthesis of Pd histidyldienes through transmetallation from their [Ag\textsuperscript{1}-histidyldiene precursors.

We successfully synthesized a variety of compounds (Table 5). In previous studies we found that the presence of hemilabile donors has a positive effect on the catalytic performance as well as the stability of the complexes\textsuperscript{45,62,63}. For the described ligands we find that the presence of a hemilabile picolyl or lutidyl group is also beneficial in the synthesis of the Pd complexes. Complexes 36, 37 and 39 could be purified by column chromatography. This is in contrast with compounds 35 and 38 that do not
possess a hemilabile moiety. They decomposed during column chromatography forming [Pd(allyl)Cl]₂, and a cationic bis-NHC [Pd(histidylidene)₂(allyl)]⁺Cl⁻ complex 41 (Figure 1). Similar complexes have been obtained with non-coordinating counterions.⁶⁴,⁶⁵

Table 5. Synthesized Pd(II)(allyl) histidylidenes.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Compound</th>
<th>R¹</th>
<th>R²</th>
<th>R³</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>35</td>
<td>Bn</td>
<td>Bn</td>
<td>Boc</td>
<td>41</td>
</tr>
<tr>
<td>2</td>
<td>36</td>
<td>Bn</td>
<td>Pic</td>
<td>Boc</td>
<td>53</td>
</tr>
<tr>
<td>3</td>
<td>37</td>
<td>Pic</td>
<td>Pic</td>
<td>Boc</td>
<td>&gt;99</td>
</tr>
<tr>
<td>4</td>
<td>38</td>
<td>Mes</td>
<td>Lut</td>
<td>Boc</td>
<td>93</td>
</tr>
<tr>
<td>5</td>
<td>39</td>
<td>p-OMePh</td>
<td>Me</td>
<td>Boc</td>
<td>0</td>
</tr>
<tr>
<td>7</td>
<td>40</td>
<td>Bn</td>
<td>Bn</td>
<td>H</td>
<td>31</td>
</tr>
</tbody>
</table>

Figure 1. Cationic bis-NHC [Pd(histidylidene)₂(allyl)]Cl complex 41.

The stability of 37 and 38 that possess hemilabile groups is not surprising. We previously reported a wide variety of highly stable NHCs bearing a triazole as secondary donor.⁶² The instability of complexes not bearing a hemilabile donor and concomitant formation of bis-histidylidene complexes is unexpected. In fact, similar NHC analogues that are not functionalized on the backbone (Chapter 2, Scheme 1) could be isolated by column chromatography without decomposition.⁶⁶,⁶⁷ The difference between those species and those described here is that the NHC complexes without backbone functionalization bear an N-mesityl-substituent. Possibly, the extra bulk of the mesityl group provides additional stabilization through a steric interaction. In this case, the incorporation of large (aryl) wingtips seems to be important for the stability of these compounds. Therefore, the Cham-Lam-Evans approach, which allows introduction aryl functionalities on the wingtips of the NHC, is extra relevant.

We investigated the viability of Boc-deprotection of Pd(II) histidylidene complexes to obtain free amine species. Subjecting compound 35 to a solution with TFA resulted in the decomposition of the complex. However, the free amine Pd(II) histidylidenes, such as
can be synthesized \textit{via} the previously developed route that uses free amine histidinium salts as ligand precursors (Scheme 10, Table 5).

**X-ray crystal structure of Pd$^{II}$(η$^3$-allyl) histidylidene complex 42**

The structure of the histidylidenes was further studied with X-ray crystallography. We obtained x-ray quality crystals through slow vapor diffusion of cyclohexane to a THF solution of compound 38 with a nitrate as a non-coordinating counter ion (42) (Figure 2).

The crystal structure contains co-crystalized cyclohexane and THF solvent molecules. Some of them were heavily disordered and were treated as diffuse electron density using the SQUEEZE algorithm.\textsuperscript{68} The asymmetric unit contains two independent Pd molecules, which are inverted with respect to each other (Figure 3).

The nitrate anions are involved by hydrogen bonds to the N-H donor groups. The η$^3$-coordinated allyl ligand was refined with a disorder model, which confirms previous observations that there is no preference for either conformation. The observed bond
lengths and geometry of 42 are normal for this type of compounds (Figure 4, Table 6). \textsuperscript{69-71}

Figure 4. A) ORTEP representation of 42 the cationic Pd\textsuperscript{II} histidine-derived NHC \(\eta^3\)-allyl complex 42. Ellipsoids are drawn at 50\% probability. Hydrogen atoms, nitrate anion and solvent molecules are omitted for the sake of clarity. Only one of two independent molecules is displayed. The disorder of the allyl ligand is not shown. B) The CPK model of 42 showing the interaction between the allyl and methyl group of the lutidyl donor.

We compared the structure of 42 to the previously reported complex 43\textsuperscript{62} (Figure 4, Table 6). These structures are highly similar, cationic, square planar [Pd\textsuperscript{II}(NHC)(\(\eta^3\)-allyl)] bidentate complexes that possess a non-coordinating counterion. The Pd–NHC and the Pd–N distances are significantly longer for 42 (Table 6, entries 1 and 2). The CPK model of 42 suggests a steric interaction between the methyl of the lutidyl donor and the allyl ligand, and an interaction between the allyl ligand and the mesityl wingtip substituent. We attribute the differences in bond lengths to this steric crowdedness around the Pd center. The large Boc-group may also contribute to the steric crowding around the Pd center.

The absolute structure determination using Bijvoet pairs confirmed the enantiopurity of the crystal (see Experimental Section). The observed enantiopurity is an indication that the chosen synthetic methodology does not cause racemization of chirality that is present in the starting material. The observation is in line with the methodology reported by Albrecht and coworkers for their adapted procedure.\textsuperscript{30}
Table 6. Selected bond lengths and angles of 42 and 43.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Bond lengths (Å)</th>
<th>42</th>
<th>43</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pd–NHC</td>
<td>2.015 (5)/1.999 (5)</td>
<td>2.044 (3)</td>
</tr>
<tr>
<td>2</td>
<td>Pd–N</td>
<td>2.135 (4)/2.148 (5)</td>
<td>2.098 (2)</td>
</tr>
<tr>
<td>3</td>
<td>Pd–C29</td>
<td>2.226 (6)/2.111 (7)</td>
<td>2.186 (4)</td>
</tr>
<tr>
<td>4</td>
<td>Pd–C30</td>
<td>2.139 (10)/2.101 (13)</td>
<td>2.163 (7)</td>
</tr>
<tr>
<td>5</td>
<td>Pd–C31</td>
<td>2.102 (5)/2.221 (7)</td>
<td>2.111 (5)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Entry</th>
<th>Angle (deg)</th>
<th>42</th>
<th>43</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>NHC–Pd–N</td>
<td>85.31 (16)/84.53 (17)</td>
<td>86.42 (11)</td>
</tr>
<tr>
<td>7</td>
<td>NHC–Pd–C31</td>
<td>100.0 (2)/166.1 (3)</td>
<td>103.05 (15)</td>
</tr>
<tr>
<td>8</td>
<td>N–Pd-C29</td>
<td>106.4 (2)/176.0 (3)</td>
<td>101.94 (11)</td>
</tr>
</tbody>
</table>

4.4 Palladium\(^{1}\) Histidylidenes as Precatalysts for the Z-selective Transfer Semihydrogenation of Alkynes

We tested complexes 35-39 as well as 44 and 45 (Chapter 2)\(^{67}\) in the transfer semihydrogenation of 1-phenyl-1-propyne toward Z-1-phenyl-1-propene (Scheme 11). We evaluated the influence of the (protected) amino acid functionality, and the hemilabile donors on the reaction with this set of precatalysts (Table 7). The performance of 35-39 was put into context by comparison with the previously discussed complexes 44 and 45.

Compounds 35, 36 and 38 give over-reduction and isomerization of the product Z-alkene after full consumption of the substrate. This was also observed for compounds 44 and 45. However, other systems were reported that do not display further conversion of the product Z-alkene.\(^{43,67,72-76}\) The substitution on the histidylidene ligand seems to be crucial for the performance of the catalyst. Incorporation of an aryl wingtip substituent on the ligand seems not only beneficial for the synthesis of these histidylidene complexes, but also for their catalytic performance. The bisbenzylc compound 35 loses activity during the reaction, most likely due to catalyst decomposition.

Table 7. The results of the Z-selective transfer semihydrogenation of 1-phenyl-1-propyne.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Cat.</th>
<th>TOF$_{15%}$a</th>
<th>Z-yield (%)b</th>
<th>Z-sel$^c$ (conv) (%)</th>
<th>Time to FC (h)$^d$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>35</td>
<td>9.6</td>
<td>38</td>
<td>94 (40)</td>
<td>f</td>
</tr>
<tr>
<td>1</td>
<td>36</td>
<td>12</td>
<td>80</td>
<td>95 (84)$^e$</td>
<td>10.3$^g$</td>
</tr>
<tr>
<td>3</td>
<td>37</td>
<td>7.2</td>
<td>91</td>
<td>92 (&gt;99)</td>
<td>28</td>
</tr>
<tr>
<td>4</td>
<td>38</td>
<td>18</td>
<td>68</td>
<td>68 (&lt;99)$^e$</td>
<td>18$^e$</td>
</tr>
<tr>
<td>5</td>
<td>44</td>
<td>38</td>
<td>88</td>
<td>92 (97)$^e$</td>
<td>5.6</td>
</tr>
<tr>
<td>6</td>
<td>45</td>
<td>8.5</td>
<td>61</td>
<td>94 (64)</td>
<td>&gt;&gt;24h$^f$</td>
</tr>
</tbody>
</table>

1 mol% catalyst, 2.7 mmol 1-phenyl-1-propyne, 70 °C. a in mol$_\text{cat.}$/mol$_\text{cat.}$·h. b GC-yields given for the Z-alkene. c Selectivity toward the Z-alkene in % ([response factor corrected GC area of Z-alkene]/[response factor corrected GC area of the total products]·100%) at the corresponding conversion, given in brackets. d Time to reach full conversion of the substrate. e Strong over-reduction and isomerization of the Z-alkene product was observed after full substrate conversion. f Reaction was stopped after 24 h. g Extrapolated time to full conversion.

In contrast, aryl substituted compounds 44 and 38 do reach full conversion. Incorporation of a hemilabile group in the ligand raises the initial selectivity and the turnover number as well. However, the hemilabile donor decreases the initial activity of the catalyst. This phenomenon is in agreement with previous studies. Compound 38 that bears both a mesityl and a lutidyl group shows a relatively high activity combined with a good selectivity. This compound does, however, display over-reduction and isomerization of the product Z-alkene. Therefore, samples at the exact time of full conversion of the substrate are required to fully assess the selectivity. The
selectivity of the catalyst up to 72% substrate conversion is excellent, a selectivity of 97% is observed. The over-reduction and isomerization reactions for this precatalyst are relatively slow compared to that of compounds 44 and 35. Noteworthy results are obtained with bispicolyl-substituted palladium complex histidyldiene 37. The incorporation of two hemilabile groups impairs the activity significantly. However, very good Z-selectivity is observed, and isomerization and over-reduction of the product after full consumption of the substrate is minimal. Precatalysts 37 and 45 both bear two hemilabile donors and display similar initial activities. However, 45 seems to deactivate over the course of the reaction. Hence, the picolyl substitution seems to be the best match for the optimum selectivity and reactivity in this reaction.

4.5 Conclusion

We have developed versatile and robust methodologies for the synthesis of symmetrically and dissymmetrically functionalized histidyldiene ligand precursors. Especially the methodology for arylation of histidine imidazoles, which are notoriously difficult, is improved. By careful selection of the protection groups, both the protected and selectively deprotected amino acid functionalities can be obtained. This allows facile access to various compounds via a single synthetic intermediate and provides a histidyldiene precursor with four handles for implementation of these ligands in complex systems. This is for instance important for the heterogenization of these compounds, or for the implementation in bioconjugates.\(^4\) Subsequently, we have synthesized a variety of \(\text{Ag}^I\) and \(\text{Pd}^{II}(\eta^1\text{-allyl})\) histidyldienes and we have investigated the activities of the palladium complexes in the Z-selective transfer semihydrogenation of an alkyne. We found that the substitution pattern of the ligand and especially the presence of hemilabile groups has significant effects on the reactivity of these compounds. Moreover, the presence of a mesityl substituent on the wingtips seems important for successful catalysts.
4.6 Experimental Section

Complex synthesis was performed using Schlenk techniques under an atmosphere of dry nitrogen. Synthesis of the histidinium salts was performed in air, unless stated otherwise. When dry solvents were used, these were prepared according to standard procedures and distilled prior to use. [Pd(η3-C3H5)Cl]2, triethyl amine, formic acid and potassium tert-butoxide were purchased from Sigma Aldrich. Compound 6 was synthesized according to the procedure reported by Jain et al. NMR spectra were recorded on Bruker AV 400 MHz, Bruker DRX 300, Bruker DRX 500 MHz, and Varian Mercury 300 MHz spectrometers. High-resolution mass spectra were recorded on a JEOL JMS SX/SX102A four-sector mass spectrometer; mass samples were loaded in a matrix solution (3-nitrobenzyl alcohol) onto a stainless steel probe and bombarded with xenon atoms with an energy of 3 keV. During the high-resolution FAB-MS measurements a resolving power of 10 000 (10% valley definition) was used.

1,3-Dibenzyl-4-2-(tert-butoxycarbonyl)amino-3-methoxy-3-oxopropyl)imidazol-3-ium bromide (2). 188 mg NaHCO₃ (2.23 mmol) was added to a stirred solution of 1 (547 mg, 2.03 mmol) and benzylbromide (725 µl, 6.09 mmol) in 20 mL MeCN. Subsequently, the suspension was stirred at reflux for 22 hours after which TLC (KMnO₄ indicator, 9:1; DCM:MeOH) showed the consumption of 1. The reaction mixture was filtered and volatiles were removed by rotary evaporation. The crude product was dissolved in a minimal amount of DCM and was added drop-wise to vigorously stirred Et₂O (200 mL). The white precipitate was filtered off, washed with Et₂O and dissolved in DCM. All volatiles were removed affording the title compound as a white foam (1.1 g, >99%). 1H NMR (400 MHz CD₂Cl₂): δ 10.62 (s, 1H, NC₃H₅N), 7.52-7.38 (m, 10H, Ar), 7.13 (bs, 1H, Im-bb), 5.75 (d, J = 6.1 Hz, 1H, NH), 5.56 (dd, J = 50.1, 15.2 Hz, 2H, NCH₂Ar), 5.52 (dd, J = 20.4, 14.6 Hz, 1H, NCH₂Ar), 4.46 (bs, 1H, α-C₃H₅), 3.68 (s, 3H, OCH₃), 3.13 (ddd, J = 15.9, 5.1, 0.7 Hz, 1H, β-CHH), 3.04 (ddd, J = 16.0, 7.8, 0.7 Hz, 1H, β-CHH). 13C-NMR (75 MHz CD₂Cl₂): δ 171.2 (CO(OMe)), 155.7 (CO(OtBu)), 153.6 (NCH₂Ph), 153.3 (C₃), 132.3 (C₆), 129.6 (ArCH), 129.6 (Ar(CH)), 129.4 (Ar(CH)), 129.2 (Ar(CH)), 128.5 (Ar(CH)), 120.9 (Im-bb(CH)), 80.5 (C(CH₃)₂), 53.3 (NCH₂Ph), 53.0 (α-CH), 52.3 (OMe), 51.3 (NCH₂Ph), 28.3 (C(CH₃)₂), 26.8 (β-CH₃). MS (FAB-TOF) calculated for C₂₆H₂₃O₄N⁺ 450.2387; found 450.2397.

4-2-(2-Tert-butoxycarbonyl)amino-3-methoxy-3-oxopropyl)-1,3-bis(pyridin-2-ylmethyl)imidazol-3-ium bromide (3). 439 mg NaHCO₃ (4.98 mmol) was added to a stirred suspension of 1 (134 mg, 0.50 mmol) and 2-(bromomethyl)-pyridine hydrobromide (264 mg, 1.05 mmol) in 10 mL MeCN. Subsequently, the suspension was stirred at reflux for 16 hours after which TLC (silica, KMnO₄ indicator, 9:1; DCM:MeOH) showed the consumption of 1. The reaction mixture was filtered and volatiles were removed by rotary evaporation. The crude product was dissolved in a minimal amount of DCM and was added drop-wise to vigorously stirred Et₂O (100 mL). The light brown precipitate was filtered off, washed with Et₂O and dissolved in DCM. The mixture was concentrated
and purified by column chromatography (95:5 → 9:1; DCM:MeOH) affording a light brown foam (219 mg, 80%). 1H NMR (400 MHz, CD$_3$CN) δ 10.52 (d, J = 1.1 Hz, 1H, NCHN), 8.62 – 8.50 (m, 2H, Py-H2 + Py-H2’), 7.78 (ddd, J = 15.9, 7.7, 1.8 Hz, 2H, Py-H4 + Py-H4’), 7.68 (t, J = 8.8 Hz, 2H, Py-H3 + Py-H3’), 7.47 (s, 1H, Im-bb), 7.34-7.30 (m, Py-H5 + Py-H5’), 5.99 (d, J = 6.5 Hz, 1H, NH), 5.68 (dd, J = 66.3, 15.5 Hz, 2H, NCH$_2$Py), 5.60 (s, 2H, NCH$_2$Py), 4.53 (d, J = 5.7 Hz, 1H, α-CH), 3.70 (s, 2H), 3.27 (dd, J = 14.6, 4.2 Hz, 1H, β-CHH), 3.22 (dd, J = 15.3, 6.4 Hz, 1H, β-CHHF), 1.37 (s, 9H, (CH$_3$)$_3$), $^{13}$C NMR (126 MHz, CD$_2$Cl$_2$) δ 171.6 (CO(OMe)), 155.9 (CO(OMe)), 153.4 (Py-C6 + Py-C6’), 150.5 (Py-C2), 150.4 (Py-C2’), 138.9 (NCHN), 138.0 (Py-C4), 138.0 (Py-C4’), 132.7 (Im-bb(Cq)), 124.4 (Py(CH)), 124.3 (Py(CH)), 124.0 (Py(CH)), 123.8 (Py(CH)), 121.6 (Im-bb(CH)), 80.7 (C(CH$_3$)$_3$), 54.9 (NCH$_2$Py), 53.3 (NCH$_2$Py), 53.0 (α-CH), 52.4 (OMe), 28.6, 27.1. MS (FAB-TOF) calculated for C$_{24}$H$_{30}$O$_4$N$_5^+$ 452.2298; found 452.2294.

Methyl 5-oxo-5,6,7,8-tetrahydroimidazo[1,5-c]pyrimidine-7-carboxylate (5).

A method adapted from Hodges et al. was applied.$^{20}$ 5.0 g L-histidine methyl ester dihydrochloride (20.7 mmol) and 3.68 g 1,1-dibromo-2-(bromomethyl)pyridine (0.56 mmol) were heated at 85 °C under vigorous mechanical stirring for 45 minutes. The slurry was allowed to cool to ambient temperature and was quenched with 5 mL H$_2$O. After 45 minutes of stirring the suspension was extracted with DCM (10 x 20 mL, each checked by TLC for content). Organic fractions were combined, dried with MgSO$_4$ and concentrated by rotary evaporation. The crude product was washed with Et$_2$O (2 x 100 mL) and dried in vacuo affording a white solid (2.8 g, 72%). 1H NMR (400 MHz, CD$_3$CN) δ 8.15 (d, J = 0.5 Hz, 1H, NCHN), 6.88 (d, J = 0.9 Hz, 1H, Im-bb), 6.47 (bs, 1H, NH), 4.37 (dd, J = 8.4, 5.4 Hz, 1H, α-CH), 3.81 (s, 3H, OMe), 3.38 (dd, J = 15.7, 5.3, 1.0 Hz, 1H, β-CHH), 3.15 (ddd, J = 15.7, 8.7, 1.3 Hz, 1H, β-CHHF).

7-(Methoxycarbonyl)-5-oxo-2-(pyridin-2-ylmethyl)-5,6,7,8-tetrahydroimidazol[1,5-c]pyrimidin-2-ium bromide (7).

142 mg 2-(bromomethyl)-pyridine hydrobromide (0.56 mmol) was neutralized with a saturated aqueous NaHCO$_3$ solution. The liberated 2-bromomethylpyridine was extracted with Et$_2$O (4 x 15 mL). Organic fractions were combined, dried with anhydrous MgSO$_4$ and filtered. The solution was concentrated to approximately 3 mL then added to a stirred solution of 142 mg 5 (0.56 mmol) in 5 mL MeCN. The diethyl ether was removed in vacuo and the reaction mixture was stirred for 5 days at room temperature and subsequently overnight at 50 °C, after which TLC showed the absence of 5. Volatiles were removed under reduced pressure and the crude product was dissolved in a minimal amount of DCM and was added drop-wise to vigorously stirred Et$_2$O (25 mL). The orange precipitate was filtered off, washed with Et$_2$O and dissolved in DCM. All volatiles were removed in vacuo affording the title compound as an orange solid (136 mg, 72%). 1H NMR (400 MHz, CD$_3$CN) δ 9.43 (d, J = 1.6 Hz, 1H, NCHN), 8.58 (dd, J = 4.8, 4.0 Hz, 1H, Py-H2), 8.00 (bs, 1H, NH), 7.87 (dt, J = 7.6, 2.0 Hz, 1H, Py-H4), 7.55 (d, J = 7.6 Hz, Py-H5), 7.44 – 7.42 (m, 3H, Im-bb + Py-H3), 5.57 (dd, J = 18.1, 16.0 Hz, 2H, NCH$_2$Py), 4.60-4.56 (m, 1H, α-CH), 3.73 (s, 3H, OCH$_3$), 3.38 (dd, J = 5.2 Hz, 2H, β-CH$_2$). $^{13}$C NMR (101 MHz, CD$_3$CN) δ 171.0 (CO(OMe)), 153.2 (Py(CH)$_3$), 150.8 (Py(CH)$_2$), 145.1 (N(CO)N), 138.6 (Ar), 136.0 (Ar), 129.6 (Ar), 125.0 (Ar), 124.3 (Ar), 54.9 (NCH$_2$Py), 53.3 (NCH$_2$Py), 53.0 (α-CH), 52.4 (OMe), 28.6, 27.1. MS (FAB-TOF) calculated for C$_{24}$H$_{30}$O$_4$N$_5$$^+$ 452.2298; found 452.2294.
Methyl 2-((tert-butoxycarbonyl)amino)-3-(1-pyridin-2-ylmethyl)-1H-imidazol-4-yl)propanoate (10). The method was adapted from Hodges et al.\(^{20}\) 65 µl DIPEA (0.39 mmol) was added to a suspension of 7 (130 mg, 0.35 mmol) in 2.5 mL dry \('\text{BuOH} under an argon atmosphere. The reaction mixture was stirred overnight at 85 °C. Volatiles were evaporated and the residue was dissolved in DCM (20 mL). The solution was washed with \(\text{H}_2\text{O} (2 \times 10\text{mL})\), washed with brine (1 \times 10 mL), dried with \(\text{MgSO}_4\) and concentrated yielding a brown oil. The oil was impregnated on silica and purified by column chromatography (95:5:10; DCM:MeOH:aceton) affording a brown oil (44 mg, 35%). \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 8.56 (m, 1H, Py-\(\text{H}4\)), 7.49 (d, \(J = 1.2\) Hz, NCHN), 7.26 – 7.22 (m, 1H, Py-\(\text{H}3\)), 6.89 (d, \(J = 7.6\) Hz, 2H, Py-\(\text{H}5\)), 6.73 (s, 1H, Im-\(\text{bb}\)), 5.90 (d, \(J = 8.0\) Hz, 1H, NCH2Py), 5.45 - 5.41 (m, 2H, \(\alpha\)-Ar), 5.01 (s, 2H, NCH2Ar), 4.51 (d, \(J = 6.7\) Hz, 2H, o-Ar), 4.44 (d, \(J = 8.2\) Hz, 1H, N\(\text{H}5\)), 5.01 (s, 2H, NCH2Ar), 4.54 – 4.46 (m, 1H, \(\alpha\)-CH), 3.83 (s, 3H, OMe), 3.04 (A-B, \(J = 14.8, 5.5\) Hz, 1H, \(\beta\)-CHH), 2.95 (dd, \(J = 14.6, 4.8\) Hz, 1H, \(\beta\)-CHH), 1.40 (s, 9H, C(CH\(_3\))\(_3\)). \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 172.7 (CO(OMe)), 156.2 (CO(O°Bu)), 155.7 (Py-C6), 149.8 (Py-C2), 138.3 (Im-bb(C\(_3\))), 137.6 (NCHN), 137.4 (Py-C4), 123.1 (Py-C5), 121.2 (Py-C3), 117.2 (Im-bb(CH)), 79.7 (C(CH\(_3\))\(_3\)), 53.7 (\(\alpha\)-CH), 52.6 (NCH2Py), 52.2 (OMe), 30.5 (\(\beta\)-CH2), 28.5 (C(CH\(_3\))\(_3\)). S (FAB-TOF) calculated for C\(_{18}\)H\(_{25}\)O\(_4\)N\(_4\)+ 361.1870; found 361.1875.

Methyl-3-(1-benzyl-1H-imidazol-4-yl)-2-((tert-butoxycarbonyl)amino)propanoate (9). The title compound was obtained as described for 10 characterization, and was previously reported by Hodges et al.\(^{20}\) \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.42 (d, \(J = 8.2\) Hz, 1H, NCHN), 7.35 - 7.25 (m, 3H, Ar), 7.08 (d, \(J = 6.7\) Hz, 2H, o-Ar), 6.62 (s, 1H, Im-\(\text{bb}\)), 5.94 (d, \(J = 8.2\) Hz, 1H, N\(\text{H}5\)), 5.01 (s, 2H, NCH2Ar), 4.54 – 4.46 (m, 1H, \(\alpha\)-CH), 3.60 (s, 3H, OMe), 3.04 (A-B, \(J = 14.8, 5.5\) Hz, 1H, \(\beta\)-CHH), 2.95 (dd, \(J = 14.6, 4.8\) Hz, 1H, \(\beta\)-CHH), 1.40 (s, 9H, C(CH\(_3\))\(_3\)).

1-Benzyl-4-((tert-butoxycarbonyl)amino)-3-methoxy-3-oxopropyl)-3-methyl-1H-imidazol-3-ium iodide (11). This compound was previously reported by Nakamura et al.\(^{70}\) 25 µl methyl iodide (0.39 mmol) was added to a stirred solution of 6 (48 mg, 0.13 mmol) in 3 mL MeCN. The mixture was stirred at reflux overnight. Volatiles were evaporated and the crude product was dissolved in a minimal amount of DCM. The mixture was added drop-wise to vigorously stirred Et\(_2\)O (50 mL). The white precipitate was collected by filtration, washed with Et\(_2\)O and dissolved in DCM. All volatiles were removed in vacuo, which afforded the title compound as a white foam (84 mg >99%). \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 10.01 (s, 1H (NCHN)), 7.54 – 7.42 (m, 2H, o-Ar), 7.42 – 7.35 (m, 3H, Ar), 7.11 (s, 1H, Im-\(\text{bb}\)), 5.62 (d, \(J = 6.6\) Hz, 1H, N\(\text{H}5\)), 5.45 (dd, \(J = 18.4, 14.5\) Hz, 2H, NCH\(_2\)Ar), 4.51 (d, \(J = 5.5\) Hz, 1H, \(\alpha\)-CH), 3.94 (s, 3H, NMe), 3.71 (s, 3H, OMe), 3.22 (dd, \(J = 15.8, 5.2\) Hz, 1H, \(\beta\)-CHH), 3.14 (dd, \(J = 15.8, 7.7\) Hz, 1H, \(\beta\)-CHH), 1.35 (s, 9H, C(CH\(_3\))\(_3\)).
3-Benzyl-5-(2-((tert-butoxycarbonyl)amino)-3-methoxy-3-oxopropyl)-1-(pyridin-2-ylmethyl)-1H-imidazol-3-ium bromide (12). 76 mg 2-(bromomethyl)pyridine hydrobromide was neutralized with a saturated aqueous NaHCO₃ solution. The liberated 2-bromomethylpyridine was extracted with Et₂O (4 x 15 mL). Organic fractions were combined, dried with anhydrous MgSO₄, and filtered. The solution was concentrated to approximately 3 mL and then added to a stirred solution of 97 mg 9 (0.27 mmol) in 5 mL MeCN. The Et₂O was removed in vacuo and the mixture was heated at 50 °C for 5 days after which TLC showed the absence of 9. Volatiles were evaporated in vacuo and the crude product was purified by column chromatography on a silica column (95:5; DCM/MeOH) affording the title compound as a white foam (101 mg, 71%). ¹H NMR (400 MHz, CDCl₃) δ 10.30 (s, 1H, NC=H), 8.54 (d, J = 4.4 Hz, 1H, Py-H2), 7.76 (td, J = 7.7, 1.8 Hz, 1H, Py-H4), 7.67 (d, J = 7.8 Hz, 1H, Py-H5), 7.51 – 7.36 (m, 5H, Ar), 7.33 – 7.19 (m, 2H, Ar), 6.22 (d, J = 7.0 Hz, 1H, NH), 5.83 (d, J = 15.6 Hz, 1H, NH-HPy), 5.67 (d, J = 15.6 Hz, 1H, NCH-HPy), 5.46 (s, 2H, NCH₃Ph), 4.48 (d, J = 6.4 Hz, 1H, α-CH), 3.64 (s, 3H, OCH₃), 3.26 – 3.14 (m, 2H, β-CH₂), 1.34 (s, 3H, C(CH₃)₃). ¹³C NMR (101 MHz, CDCl₃) δ 170.9 (CO(OMe)), 155.4 (CO(Bu)), 152.2 (Py-C6), 149.6 (Py-C2), 137.5 (Py-C4), 132.8 (C₆), 132.2 (C₆), 129.1 (Ar(CH)), 128.7 (Ar(CH)), 123.7 (Ar(CH)), 123.1 (Ar(CH)), 119.9 (Im-bb(CH)), 80.1 (C(CH₃)₃), 53.1 (Im-CH₂-Ar), 52.6 (α-CH), 52.1 (OMe), 51.4 (Im-CH₂-Ar), 28.0 (C(CH₃)₃), 26.2 (β-CH₂). MS (FAB-TOF) calculated for C₂₆H₃₃O₇N₄⁺ 451.2340; found 451.2351.

5-(2-((Tert-butoxycarbonyl)amino)-3-methoxy-3-oxopropyl)-1-methyl-3-(pyridin-2-ylmethyl)-1H-imidazol-3-ium iodide (14). Methyl iodide (21 µl, 0.33 mmol) was added to a stirred solution of 10 (40 mg, 0.11 mmol) in 2 mL MeCN. The mixture was stirred at reflux overnight. Volatiles were evaporated and the crude product was dissolved in a minimal amount of DCM and was added drop-wise to vigorously stirred Et₂O (50 mL). The white precipitate was filtered off, washed with Et₂O and dissolved in DCM. All volatiles were removed in vacuo yielding the title compound as a white foam (32 mg, 58%). ¹H NMR (400 MHz, CDCl₃) δ 10.10 (s, 1H, NCHN), 8.54 – 8.52 (m, 1H, Py-H2), 7.82 – 7.70 (m, 2H, Py-H4 + Py-H5), 7.40 (s, 1H, Im-bb), 7.33 – 7.26 (m, 1H, Py-H3), 5.63 (dd, J = 20.5, 14.7 Hz, 2H, NCH₂Py), 5.54 (d, J = 7.0 Hz, 1H, NH), 4.55 (dd, J = 5.3 Hz, 1H, α-CH), 3.94 (s, 3H, NCH₃), 3.76 (s, 3H, OMe), 3.26 (dd, J = 15.7, 5.2 Hz, 1H, β-CH₂), 3.15 (dd, J = 15.8, 7.2 Hz, 1H, β-CH₂), 1.37 (s, 9H, C(CH₃)₃). ¹³C NMR (101 MHz, CDCl₃) δ 170.7 (CO(OMe)), 152.3 (Py-C6), 150.0 (Py-C2), 137.9 (Py-C4), 131.2 (Im-bb(C₆)), 124.2 (Py-C5), 124.1 (Py-C3), 121.2 (Im-bb(CH)), 80.9 (C(CH₃)₃), 54.1 (NCH₃Py), 53.3 (α-CH), 52.3 (OMe), 34.6 (NMe), 28.3 (C(CH₃)₃), 26.7 (β-CH₂). MS (FAB-TOF) calculated for C₁₉H₂₁O₇N₄⁺ 375.2032; found 375.2037.

Methyl 2-((tert-butoxycarbonyl)amino)-3-(1-(4-methoxyphenyl)-1H-imidazol-4-yl)propanoate (15). To a stirred solution of 1 (0.103 g, 0.382 mmol), NaOAc (0.094 g, 1.15 mmol) and Cu(OAc)₂·H₂O (7.62 mg, 0.0382 mmol) in MeOH (2 mL), 4-methoxyphenylboronic acid (0.174 g, 1.15 mmol) was added. The mixture was stirred at 20 °C for 26 hours and concentrated in vacuo. The residue was dissolved
in DCM (35 mL), washed with H₂O (10 mL) and brine (10 mL), dried over MgSO₄ and concentrated in vacuo. Flash column chromatography of the residue (silica gel, 25% EtOAc in n-hexane) afforded the title product as a yellow oil. The yield was 120 mg (0.320 mmol, 84%). ¹H NMR (300 MHz, CDCl₃) δ 7.66 (s, 1H, NCH₃), 7.29 – 7.21 (m, 2H, Ar), 7.05 – 6.89 (m, 3H, Ar + Im·bb), 5.91 (d, J = 8.2 Hz, 1H, NH), 4.66 – 4.50 (m, 1H, α-CH), 3.83 (s, 3H, OMe), 3.72 (s, 3H, OMe), 3.11 (m, 2H, β-CH₂), 1.43 (s, 9H, CH₃). ¹³C NMR (101 MHz, CDCl₃) δ 172.57 (CO(OMe)), 158.84 (p-Ar), 155.61 (CO(OtBu)), 130.51 (i-Ar), 122.91 (Ar), 116.28 (Im·bb), 114.87 (Ar), 79.64 (C(CH₃)₃), 55.59 (Ar·OMe), 53.49 (α-CH), 52.25 (CO(OtMe)), 30.27 (β-CH₂), 28.34 (C(CH₃)₃). MS (FAB-TOF) calculated for C₁₉H₂₆N₃O₅⁺ 376.1872; found 376.1869.

Methyl-2-(((tert-butoxycarbonyl)amino)-3-(1-mesityl-1H-imidazol-4-yl)-propanoate (16). To a stirred solution of 1 (0.092 g, 0.342 mmol), NaOAc (0.080 g, 1.02 mmol) and Cu(OAc)₂·H₂O (6.8 mg, 0.0342 mmol) in MeOH (2 mL) 2,4,6-trimethylphenylboronic acid (0.166 g, 1.01 mmol) was added. The mixture was stirred at 20 °C for 6 days in an open air vessel. The mixture fell dry after 6 days and the green residue was then dissolved in DCM (35 mL), washed with H₂O (10 mL) and brine (5 mL), dried over MgSO₄ and concentrated in vacuo. Flash column chromatography of the residue (silica gel, 25% EtOAc in n-hexane) yielded the title compound as a yellow oil (80 mg, 0.206 mmol, 61%). ¹H NMR (300 MHz, CDCl₃) δ 7.33 (s, 1H, NCH₃), 6.94 (s, 2H, Mes), 6.64 (s, 1H, Im·bb), 6.03 (d, J = 8.5 Hz, 1H, NH), 4.78 – 4.54 (m, 1H, α-CH), 3.67 (s, 3H, OMe), 3.12 (m, 2H, β-CH₂), 2.32 (s, 3H, p-Mes(Me)), 1.96 (d, J = 8.7 Hz, 6H, o-Mes(Me)), 1.43 (s, 9H, C(CH₃)₃). ¹³C NMR (101 MHz, CDCl₃) δ 172.53 (CO(OMe)), 155.54 (CO(OtBu)), 138.89, 137.39, 137.22 (NCH₃), 135.30 (m-Ar), 135.18 (m-Ar), 132.89 (m-Ar), 128.82 (m-Ar), 117.55 (Im·bb(CH)), 79.62 (C(CH₃)₃), 53.48 (α-CH), 52.29 (OMe), 30.05 (β-CH₂), 28.22 (C(CH₃)₃), 17.27 (Mes(o-Me)), 14.14 (Mes(o-Me)). MS (FAB-TOF) calculated for C₂₁H₃₀N₃O₄⁺ 388.2236; found 388.2234.

4-(((2-((Tert-butoxycarbonyl)amino)-3-methoxy-3-oxopropyl)-1-para-metoxymethylphenyl-3-methyl-1H-imidazol-3-ium iodide (17). To a stirred solution of 15 (0.530 g, 1.41 mmol) in MeCN (12 mL) iodomethane (0.44 mL, 7.06 mmol) was added. The mixture was stirred at reflux for 6 hours, then concentrated in vacuo affording the title compound as a yellow solid (0.729 g, 1.41 mmol, 99% yield). ¹H NMR (300 MHz, CDCl₃) δ 10.22 (s, 1H, NC=NH), 7.65 (d, J = 8.9 Hz, 2H, Ar), 7.46 (s, 1H, Im·bb), 7.04 (d, J = 8.9 Hz, 2H, Ar), 5.71 (d, J = 7.3 Hz, 1H, NH), 4.66 (s, 1H, α-CH), 4.12 (s, 3H, NMe), 3.86 (s, 3H, OMe), 3.83 (s, 3H, OMe), 3.46 – 3.07 (m, 2H, β-CH₂), 1.41 (s, 9H, C(CH₃)₃). ¹³C NMR (75 MHz, CDCl₃) δ 170.68 (CO(OME)), 160.80 (Ar), 155.47 (CO(OBu)), 135.40 (NCH₃), 132.30, 127.33, 123.51 (Ar(CH)), 119.15 (Im·bb(CH)), 115.52 (Ar(CH)), 80.92 (C(CH₃)₃), 55.79 (p-Ar(OMe)), 53.24 (α-CH), 51.95 (CO(OMe)), 34.77 (NMe), 28.21 (C(CH₃)₃), 26.90 (β-CH₂). MS (FAB-TOF) calculated for C₂₆H₂₇N₃O₆⁺ 390.2029; found 390.2029.
4-(2-((Tert-butoxycarbonyl)amino)-3-methoxy-3-oxopropyl)-1-mesityl-3-methyl-1H-imidazol-3-ium iodide (18). To a stirred solution of 16 (0.500 g, 1.29 mmol) in MeCN (12 mL), iodomethane (0.40 mL, 6.45 mmol) was added. The mixture was heated to reflux overnight and then concentrated in vacuo yielding the title compound as a yellow solid (0.686 g, 1.29 mmol, >99% yield). 1H NMR (300 MHz, CDCl₃) δ 9.79 (s, 1H, NCH₃), 8.53 (d, J = 4.1 Hz, 1H, Pyr), 7.92 (d, J = 7.7 Hz, 1H, Pyr), 7.85 (t, J = 7.5 Hz, 1H, Pyr), 7.36 (m, 1H, Pyr), 7.12 (s, 1H, Im-bb), 6.98 (s, 2H, Mes), 6.18 (A-B system, 2H, Im-CH₂-Pyr), 4.64 - 4.63 (m, 1H, NH), 3.75 (s, 3H, OMe), 3.39 (d, J = 6.6 Hz, 2H, β-CH₃), 2.33 (s, 3H, Mes(Me)), 2.09 (s, 3H, Mes(Me)), 2.06 (s 3H, Mes(Me)). 13C NMR (101 MHz, CDCl₃) δ 178.29 (CO(OMe)), 160.08 (Pyr), 159.59 (Py), 155.47 (CO(OBu)), 151.86, 148.74, 141.10 (Ar), 138.59 (Ar), 138.25 (Ar), 134.21 (Ar), 134.12 (Ar), 132.80 (Ar), 130.55 (Ar), 129.65 (Ar), 124.08 (Ar), 124.03 (Ar), 120.87 (Ar), 80.44 ((C(CH₃)₃)), 52.85, 52.16, 50.84, 28.11 ((C(CH₃)₃)), 26.63 (β-CH₂), 20.97 (Mes(Me)), 17.39 (Mes(Me)). MS (FAB-TOF) calculated for C27H₃₆N₄O₄⁺ 452.2393; found 452.2389.

4-(2-((Tert-butoxycarbonyl)amino)-3-methoxy-3-oxopropyl)-1-mesityl-3-(pyridin-2-ylmethyl)-1H-imidazol-3-ium bromide (19). To a solution of 2-(bromomethyl)pyridine (0.234 g, 0.927 mmol) in cold H₂O (10 mL), a saturated aqueous solution of Na₂CO₃ (10 mL) was added in a drop-wise manner. The liberated 2-(bromomethyl)pyridine was extracted into Et₂O (10 mL, 3x) at 0 °C, dried with MgSO₄ and filtered. The filtrate was concentrated to ca. 2 mL and added to a solution of 16 (0.116 g, 0.299 mmol) in MeCN (8.5 mL) at 0 °C. The ether was removed under reduced pressure and the resulting solution was allowed to warm to room temperature. 4 Å molecular sieves were added after 2 hours, and the mixture was left to stir for 7 days. The molecular sieves were removed by filtration, followed by addition of Et₂O to the filtrate. This resulted in the precipitation of a red solid, which was removed by filtration. The organic layer was then concentrated in vacuo giving the title compound as a yellow oil. (86 mg, 0.154 mmol, 51% yield). 1H NMR (400 MHz, CDCl₃) δ 9.88 (s, 1H, NCH₃), 8.53 (d, J = 4.1 Hz, 1H, Pyr), 7.92 (d, J = 7.7 Hz, 1H, Pyr), 7.85 (t, J = 7.5 Hz, 1H, Pyr), 7.36 (m, 1H, Pyr), 7.12 (s, 1H, Im-bb), 6.98 (s, 2H, Mes), 6.18 (A-B system, 2H, Im-CH₂-Pyr), 4.64 - 4.63 (m, 1H, NH), 3.75 (s, 3H, OMe), 3.39 (d, J = 6.6 Hz, 2H, β-CH₃), 2.33 (s, 3H, Mes(Me)), 2.09 (s, 3H, Mes(Me)), 2.06 (s 3H, Mes(Me)). 13C NMR (101 MHz, CDCl₃) δ 178.29 (CO(OMe)), 160.08 (Pyr), 159.59 (Py), 155.47 (CO(OBu)), 151.86, 148.74, 141.10 (Ar), 138.59 (Ar), 138.25 (Ar), 134.21 (Ar), 134.12 (Ar), 132.80 (Ar), 130.55 (Ar), 129.65 (Ar), 124.08 (Ar), 124.03 (Ar), 120.87 (Ar), 80.44 ((C(CH₃)₃)), 52.85, 52.16, 50.84, 28.11 ((C(CH₃)₃)), 26.63 (β-CH₂), 20.97 (Mes(Me)), 17.39 (Mes(Me)). MS (FAB-TOF) calculated for C22H₂₂N₃O₄⁺ 402.2393; found 402.2389.

5-(2-((Tert-butoxycarbonyl)amino)-3-methoxy-3-oxopropyl)-3-mesityl-1-(6-methylpyridin-2-ylmethyl)-1H-imidazol-3-ium bromide (20). 410 mg of 16 (1.06 mmol) and 236 mg 2-(bromomethyl)-6-methylpyridine (1.27 mmol) were dissolved in 20 mL MeCN. The mixture was heated to reflux for 72 hours, after which TLC showed the full conversion of 16. All volatiles were removed in vacuo and the crude product was purified by column chromatography.
(silica, 95:5 to 9:1; DCM:MeOH) yielding the title compound as an off white foam (527 mg, 87% yield). 1H NMR (400 MHz, CD2Cl2) δ 9.87 (s, 1H, NCHN), 7.67 (t, J = 7.7 Hz, 1H, Py-H4), 7.54 (d, J = 7.7 Hz, 1H, Py-H3); 7.18 – 7.12 (m, 2H, Im-bb + Py-H5). 7.05 (s, 2H, Mes), 6.10 (d, J = 7.7 Hz, 1H, NH), 6.06-5.95 (A-B system, 2H, NCH2Py), 4.63 (bs, 1H, α-CH), 3.73 (s, 3H, OMe), 3.39-3.30 (m, 2H, β-CH2), 2.44 (s, 3H, Lut(Me)), 2.35 (s, 3H, Mes(p-CH3)), 2.12 (s, 3H, Mes(o-CH3)), 2.10 (s, 3H, Mes(o-Me), 1.37 (s, 9H, C(CH3)3).

13C NMR (126 MHz, CD2Cl2) δ 171.6 (CO(OMe)), 159.4 (Py-C6), 155.9 (CO(OtBu), 152.7 (Py-C2), 141.4 (Ar), 139.4 (Ar), 137.9 (Ar), 135.0 (Ar), 133.5 (Ar), 131.7 (Ar), 130.1 (Ar), 123.4 (Ar), 122.4 (Ar), 120.3 (Ar), 80.1 (C(CH3)3), 53.0 (NCH2Py), 52.7 (α-CH), 52.1 (OMe), 28.5 (C(CH3)3), 26.6 (β-CH2), 24.3 (Lut(CH3)), 21.1 (Mes(p-Me)), 17.7 (Mes(o-Me)).

MS (FAB-TOF) calculated for C28H37O4N4+ 493.2808; found 493.2818.

4-[(2-Aminoo-3-methoxy-3-oxopropyl)-1,3-dibenzyl-1H-imidazol-3-ium chloride](21). 265 mg of 2 (0.5 mmol) was dissolved in 5 mL of a 4.0 M HCl solution in dioxane. The reaction mixture was stirred overnight at room temperature. Volatiles were removed in vacuo and the residue was stripped with MeOH (3 x 10 mL). The crude product was dissolved in a small amount of MeOH and was added drop-wise to vigorously stirred Et2O (100 mL). The resulting white suspension was stirred for half an hour and then filtered. The residue was washed with Et2O and dissolved in MeOH. The mixture was concentrated and stripped with DCM yielding the title compound as a yellow foam (239 mg, >99%). 1H-NMR (400 MHz CD3OD) δ 9.16 (s, 1H, NCHN), 7.66 (s, 1H, Im-bb), 7.50-7.35 (m, 10H, Ar), 5.51 (s, 2H, NCH2Ph), 5.44 (s, 2H, NCH2Ph), 4.23 (s, 1H, α-CH), 3.72 (s, 3H, OMe), 3.40-3.18 (m, 2H, β-CH2).

13C NMR (100 MHz CD3OD) δ 169.1 (CO(OMe)), 135.0 (Ar(Cq)), 134.4 (Ar(Cq)), 130.9 (Im-bb(Cq)), 130.8 (Ar(CH)), 130.6 (Ar(CH)), 130.5 (Ar(CH)), 130.5 (Ar(CH)), 130.2 (Ar(CH)), 129.6 (Ar(CH)), 124.2 (Im-bb(CH)), 55.0 (Im-CH2-Ph), 54.6 (α-CH), 52.6 (Im-CH2-Ph), 26.0 (β-CH2). MS (FAB-TOF) calculated for C21H25O2N3+ 351.1936; found 351.1946.

5-[(2-Aminoo-3-methoxy-3-oxopropyl)-3-benzyl-1-methyl-1H-imidazol-3-ium chloride](22). The compound was prepared as described for 21. It was obtained as a red solid in a yield of 81%. 1H NMR (400 MHz, CD3OD) δ 9.08 (s, 1H, NCHN), 7.61 (s, 1H, Im-bb), 7.50 – 7.38 (m, 5H, Ar), 5.42 (s, 2H, NCH2Ph), 4.48 (t, J = 7.1 Hz, 1H, α-CH), 3.91 (s, 3H, NMe), 3.79 (s, 3H, OMe), 3.46 (dd, J = 16.1, 7.2 Hz, 1H, β-CH2), 3.37 (dd, J = 16.6, 7.1 Hz, 1H, β-CH2). 13C NMR (101 MHz, CD3OD) δ 169.2 (CO(OMe)), 139.6 (NCHN), 134.9 (Ar(Cq)), 131.0 (Im-bb(Cq)), 130.4 (Ar(CH)), 130.4 (Ar(CH)), 130.0 (Ar(CH)), 123.2 (Im-bb(CH)), 54.4 (NCH2Ph), 54.3 (α-CH), 52.2 (α-OMe), 34.9 (NCH3), 25.4 (β-CH2). HRMS (FAB) calculated for C15H21O2N3Cl2+ 345.1011; found 345.0983.
2-((5-(2-Ammonio-3-methoxy-3-oxopropyl)-1H-imidazol-3-ium-3-yl)methyl)-1,3-bispyridin-1-ium chloride. di-hydrochloride (23). The compound was prepared as described for 21. The title compound was obtained as an off-white foam in quantitative yield. $^1$H NMR (400 MHz, CD$_3$OD) $\delta$ 9.62 (s, 1H, NCHN), 8.93 (d, $J = 5.3$ Hz, 1H, Py-H2), 8.87 (d, $J = 5.1$ Hz, 1H, Py-H2'), 8.65 (t, $J = 7.6$ Hz, 1H, Py-H4), 8.51 (t, $J = 7.5$ Hz, 1H, Py-H4'), 8.23 (d, $J = 7.8$ Hz, 1H, Py-H5), 8.13 – 8.02 (m, 3H, Py-H5' + Im-bb + Py-H3), 8.00 – 7.92 (m, 1H, Py-H3'), 6.09 (s, 2H, NCH$_2$Py), 6.07 (s, 2H, NCH$_2$Py'), 4.62 (t, $J = 6.4$ Hz, 1H, $\alpha$-CH), 3.85 (s, 3H, OMe), 3.57 (dd, $J = 16.8$, 6.5 Hz, 1H, $\beta$-CH$\beta$H), 3.45 (dd, $J = 16.3$, 7.0 Hz, 1H, $\beta$-CH$\beta$H). $^{13}$C NMR (75 MHz, CD$_3$OD) $\delta$ 169.1 (CO(OMe)), 150.4 (Py-C6), 147.1 (Py-C2), 138.1 (NCN), 134.4, 130.94, 130.37, 129.30 (Mes(CH)), 123.23 (Im-bb(CH)), 122.78 (Py(CH)), 127.4 (Py(CH)), 124.6 (Im-bb(CH)), 54.4 (NCH$_2$Py), 52.2 (NCH$_2$Py'), 51.3 (CH$_2$CH), 25.5 (CH$_2$CH$_2$).

2-((5-(2-Ammonio-3-methoxy-3-oxopropyl)-1-methyl-1H-imidazol-3-ium-3-yl)methyl)pyridin-1-ium chloride. hydrochloride (24). The title compound was prepared as described for 23, and was obtained as a red solid in quantitative yield. $^1$H NMR (400 MHz, CD$_3$OD) $\delta$ 9.23 (s, 1H, NCHN), 8.80 (d, $J = 5.1$ Hz, 1H, Py-H2), 8.41 (t, $J = 7.8$ Hz, 1H, Py-H4), 7.95 (d, $J = 7.8$ Hz, 1H, Py-H5), 7.90 – 7.84 (m, 1H, Py-H3'), 7.79 (s, 1H, Im-bb), 5.85 (s, 2H, Im-CH$_2$-Py), 4.53 (t, $J = 7.0$ Hz, 1H, $\alpha$-CH), 3.97 (s, 3H, NMe), 3.87 (s, 3H, OMe), 3.54 (dd, $J = 16.2$, 6.4 Hz, 1H, $\beta$-CH$\beta$H), 3.38 (dd, $J = 16.3$, 7.6 Hz, 1H, $\beta$-CH$\beta$H). $^{13}$C NMR (101 MHz, CD$_3$OD) $\delta$ 169.1 (CO(OMe)), 150.4 (Py-C6), 147.1 (Py-C2), 145.3 (Py-C4), 131.6 (Im-bb(C$_2$)), 127.9 (Py-C5), 127.6 (Py-C3), 124.0 (Im-bb(CH)), 54.4 (CH$_3$), 52.2 (OMe), 51.5 (NCH$_2$Py), 35.1 (NMe), 25.4 ($\beta$-CH$_2$).

4-(2-Ammonio-3-methoxy-3-oxopropyl)-1-mesityl-3-methyl-1H-imidazol-3-ium chloride. hydrochloride (25). The title compound was prepared as described for 21, and isolated as an off white foam in 92% yield. $^1$H NMR (400 MHz, CD$_3$OD) $\delta$ 9.17 (s, 1H, NCHN), 7.70 (s, 1H, Im-bb), 7.13 (s, 2H, Mes), 4.61 (t, $J = 6.6$ Hz, 1H, $\alpha$-CH), 4.04 (s, 3H,NCH$_3$), 3.86 (s, 3H, OMe), 3.60 – 3.40 (m, 2H, $\beta$-CH$_2$), 2.36 (s, 3H, Mes(p-Me)), 2.11 (s, 6H, Mes(o-Me)). $^{13}$C NMR (75 MHz, CD$_3$OD) $\delta$ 167.85 (CO(OMe)), 141.20 (Mes), 138.16 (NCN), 134.43, 130.94, 130.37, 129.30 (Mes(CH)), 123.23 (Im-bb(CH)), 52.86 (OMe), 50.75 (o-Me), 33.67 (NMe), 24.10 ($\beta$-CH$_2$), 19.70 (Mes(Me)), 16.14 (Mes(Me)). MS (FAB-TOF) calculated for C$_{19}$H$_{24}$DN$_3$O$_2$ $^+$ 304.2010; found 304.2025.

4-(2-((Tert-butoxycarbonyl)amino)-3-carboxylate)-1-para-methoxyphenyl-3-methyl-1H-imidazol-3-ium (26). 17 (0.125 g, 0.24 mmol) was dissolved in 20 mL methanol. Subsequently, 2 mL H$_2$O and 60 mg LiOH (2.4 mmol) were added. The solution was stirred overnight. TLC showed the disappearance of the starting material. The solvent was removed in vacuo and the obtained yellow oil was stripped twice with methanol. The crude product was
further purified by column chromatography (silica, DCM MeOH 9:1) and 0.08 g of product was obtained in a yield of 65%. 1H NMR (400 MHz, CD2Cl2) δ 9.36 (s, 1H, NCHN), 7.72 (s, 1H, Im-bb), 7.62 (d, J = 8.9 Hz, 2H, Ar), 7.16 (d, J = 9.0 Hz, 2H, Ar), 4.36 – 4.11 (m, 1H, α-CH), 4.00 (s, 3H, NMe), 3.89 (s, 3H, OMe), 3.11 (m 2H, θ-CH2), 1.39 (s, 9H, (C(CH3)3). 13C NMR (101 MHz, MeOD) δ 174.72 (COO −), 160.71 (Ar), 157.87 (Ar), 155.99 (CO(Oe)), 133.53 (NCHN), 127.77 (Im-bb(Cq)), 114.15 (Ar), 114.15 (Me), 114.91 (Ar), 79.01 (C(CH3)3), 54.90 (Ar-Ome), 48.38 (α-CH), 33.10 (NMe), 27.36 (Β-CH2), 27.17 (C(CH3)3). MS (FAB-TOF) calculated for C19H24LiN3O5+ 383.2287.

(1,3-Dibenzyl-4-((tert-butoxycarbonyl)amino)-3-methoxy-3-oxopropyl)-1H-imidazol-2-(3H)-ylidene)silver(I) bromide (27). 2 (223 mg, 0.42 mmol) was dried azetropically by co-evaporation with toluene (3 x 3 mL). Ag2O (54 mg, 0.23 mmol) and 4 Å molecular sieves were added. The Schlenk flask was purged with argon twice. 10 mL DCM was added and the mixture was stirred overnight at room temperature with exclusion of light. The mixture was filtered through a pad of Celite in air and the residue was washed with 10 mL DCM. All volatiles were removed in vacuo affording the title compound as an off-white foam (203 mg, 96%). 1H NMR (400 MHz CD2Cl2) δ 7.48 – 7.08 (m, 10H, Ar), 6.82 (s, 1H, Im-bb), 5.47 (s, 2H, NCH2Ph), 5.33 (s, 2H, NCH2Ph'), 5.07 (s, 1H, NH), 4.42 (m, 1H, α-CH), 2.90-2.84 (m, 1H, β-CH2), 1.12 (s, 1H, β-CH2), 1.32 (d, J = 48.6 Hz, 9H, C(CH3)3). 13C NMR (75 MHz CD2Cl2) δ 183.2 (Ag-C), 171.5 (CO(Oe)), 155.4 (CO(Oe)Bu), 136.2 (Ar(Cq)), 136.2 (Ar(Cq)), 130.9 (Im-bb(Cq)), 129.4 (Ar(CH), 128.9 (Ar(CH), 128.6 (Ar(CH), 128.1 (Ar(CH), 127.1 (Ar(CH), 120.4 (Im-bb(CH)), 80.7 (C(CH3)3), 56.2 (NCH2Ph), 53.4 (NCH2Ph'), 52.9 (α-CH), 52.8 (Ome), 28.3 (β-CH2), 28.0 (C(CH3)3). MS (FAB-TOF) calculated for C52H42Li3O3N8109Ag+ 1007.3677; found 1007.3674.

(1-Benzyl-4-((tert-butoxycarbonyl)amino)-3-methoxy-3-oxopropyl)-3-(pyridin-2-ylmethyl)-1H-imidazol-2-(3H)-ylidene)silver(I) bromide (28). The title compound was prepared as described for 27. The compound was obtained as a mixture of species, which are presumably coordination oligomers. The compounds were applied in the transmetallation reactions and gave the desired Pd complex in good yields. 1H NMR (400 MHz, CD2Cl2) δ 8.55 (d, J = 2.9 Hz, 1H, Py-H2), 8.42 (d, J = 3.8 Hz, 0.5H, Py-H2'), 7.68 (t, J = 7.0 Hz, 1H, Py-H4), 7.55 (t, J = 7.6 Hz, 0.5H, Py-H4'), 7.38 – 7.08 (m, 12H, Ar), 6.89 (s, 0.5H, Im-bb'), 6.86 (s, 1H Im-bb), 6.02 (s, 1H, NH), 5.41 (m, 3H, NCH2Ar), 5.21 (s, 2H, NCH2Ar), 5.13 (s, 1H, NCH2Ar'), 4.64 (s, 0.5H, α-CH), 4.46 (s, 1H, α-CH'), 3.63 (s, 3H, OMe), 3.47 (s, 1.5H, OMe'), 3.14 (dd, J = 15.8, 4.8 Hz, 1H, β-CH2), 3.04 (dd, J = 15.9, 8.3 Hz, 1H, β-CH2), 2.87 – 2.61 (m, 1H, β-CH2'), 1.37 (s, 9H, (C(CH3)3), 1.26 (s, 4.5H, C(CH3)3'), 1.26 (s, 4.5H, C(CH3)3). 13C NMR (101 MHz, CDCl3) (13C CN signal was not observed) δ 170.88 (CO(Oe)Bu), 155.37, 152.20, 149.58, 137.50, 132.82, 132.15, 129.14, 128.73, 123.49, 123.08, 119.84 (Im-bb(CH), 80.07 (C(CH3)3), 53.09 (α-CH2), 52.60 (Im-Ch2-Ar), 52.07 (Im-Ch2-Ar), 51.35 (Ome), 27.99 (C(CH3)3), 26.21 (β-CH2).HRMS (FAB) calculated for C52H42Li3O3N8109Ag+ 1009.3582; found 1009.3591.
[(4-(2-((Tert-butoxycarbonyl)amino)-3-methoxy-3-oxopropyl)-1,3-bis(pyridin-2-ylmethyl)-1H-imidazol-2-(3H)-ylidene)silver(I) bromide] (29). The compound was prepared as described for compound 27. A white foam was obtained with a yield of 80%. 1H NMR (400 MHz, CDCl3) δ 8.56 (d, J = 3.6 Hz, 2H, Py-H2 + Py-H2'), 7.83 – 7.63 (m, 2H, Py-H4 + Py-H4'), 7.36 (d, J = 7.6 Hz, 1H, Py-H5), 7.32 – 7.19 (m, 4H, Py), 7.02 (s, 1H, Im-bb), 5.93 (d, J = 7.4 Hz, 1H, NH), 5.42 (AB system J = 28.7, 15.9 Hz, 2H, NCH3Py), 5.35 (s, 2H, NCH3Py'), 4.51 (s, 1H, α-CH), 3.68 (s, 3H, OMe), 3.17 (dd, J = 15.8, 4.9 Hz, 1H, β-CH3H), 3.06 (dd, J = 15.9, 8.0 Hz, 1H, β-CH3H), 1.37 (s, 9H, C(CH3)3).

13C NMR (126 MHz, CDCl3) δ 184.4 (NCN), 171.9 (CO(OMe)), 156.0 (Py-C6), 155.9 (Py-C6'), 155.7 (CO(OBu)), 150.2 (Py-C2 + Py-C2'), 137.8 (Py-C4), 137.6 (Py-C4'), 131.4 (Im-bb(C3)), 123.7 (Py(CH)), 123.6 (Py(CH)), 122.9 (Py(CH)), 122.9 (Py(CH)), 120.5 (Im-bb(CH)), 80.5 (C(CH3)3), 57.8 (NCH3Py), 54.4 (α-CH), 52.8 (OMe), 28.5 (C(CH3)3), 27.7 (β-CH3). MS (FAB-TOF) calculated for C28H35O4N5Ag+ 558.1270; found 558.1269.

[(4-(2-((Tert-butoxycarbonyl)amino)-3-methoxy-3-oxopropyl)-1-(4-methoxyphenyl)-3-methyl-1H-imidazol-3-ium-2-yl)silver(I) iodide] (30). The title compound was prepared as described for 27. The 1H spectrum was very broad and the 13C spectrum showed double peaks, probably due to coordination oligomers, or multiple coordination modes of the histidylidene to the silver. The compound was used, as obtained, and yielded the corresponding Pd-compound. 1H-NMR (400 MHz, CDCl3) δ 7.47 (d, J = 8.8 Hz, 2H, Ar), 7.12 (s, 1H, Im-bb), 6.96 (d, J = 8.8 Hz, 2H, Ar), 5.50 (s, 1H, NH), 4.63 (s, 1H, α-CH), 3.89 (s, 3H, NMe), 3.86 (s, 3H, OMe), 3.80 (s, 3H, OMe), 3.29 (AB-M system dd, J = 10.8, 4.8 Hz, 1H, β-CH2), 3.12 (AB-M system dd, J = 8.0, 7.6 Hz, 1H, β-CH2), 1.41 (s, 9H, C(CH3)3). 13C NMR (101 MHz, CDCl3) δ 180.87 (NCN), 171.31 (CO(OMe)), 159.60, 155.30 (CO(OBu)), 137.82, 133.17, 132.92, 130.80, 128.82, 128.01, 125.09 (Ar(CH)), 125.00 (Ar(CH)), 120.38 (Im-bb(CH)), 120.19 (Im-bb(CH)), 114.44 (Ar(CH)), 114.21 (Ar(CH)), 79.80 (C(CH3)3), 77.94 (C(CH3)3), 55.50 (Ar-OMe), 52.53 (CH3), 52.22 (CH3), 36.35 (NMe), 36.29 (NMe), 28.05 (C(CH3)3), 27.86 (C(CH3)3), 27.35 (β-CH2), 27.15 (β-CH2). MS (FAB-TOF) calculated for C31H34N4O10107Ag+ 887.2949, found 887.2964.

[Bis-(4-(2-((Tert-butoxycarbonyl)amino)-3-methoxy-3-oxopropyl)-1-mesityl-3-methyl-1H-imidazol-2-ylidene)silver(I) silver(I)diiodide] (31). The compound was prepared similar to 27 and was obtained as a yellow foam in a yield of 86%. 1H-NMR (400 MHz, CDCl3) δ 7.01 (s, 2H, Ar), 6.79 (s, 1H, Im-bb), 5.33 (d, J = 7.4 Hz, 1H, NH), 4.64 (m, 1H, α-CH), 3.87 (s, 3H, Me), 3.78 (s, 3H, Me), 3.12 (AB-M system, dd, J = 15.7, 5.1 Hz, 1H, α-CH), 2.38 (s, 3H, Mes), 1.96 (d, J = 4.2 Hz, 6H, Mes), 1.44 (s, 9H, C(CH3)3). 13C-NMR (400 MHz, CDCl3) δ 183.80 (NCN), 171.19 (CO(OMe)), 154.97 (CO(OBu)), 138.89, 135.43, 134.84, 130.19, 128.93, 120.57 (Im-bb(CH)), 80.03 (C(CH3)3),...
(32). The title compound was prepared similar to 27 and was obtained as a yellow foam in a yield of 89%. $^1$H NMR (400 MHz, CD$_2$Cl$_2$) $\delta$ 7.61 (t, $J = 7.7$ Hz, 1H, Py-H4), 7.27 – 7.02 (m, 2H, H-H3 + Py-H5), 6.99 (s, 2H, Mes), 6.82 (s, 1H, Im-bb), 5.81 (d, $J = 6.1$ Hz, 1H, H4), 5.4 (bs, 2H, NCH$_2$Py), 4.59 (d, $J = 5.1$ Hz, 1H, C(CH$_3$)$_3$), 3.69 (s, 3H, OMe), 3.21 (dd, $J = 15.9, 5.1$ Hz, 1H, C(CH$_3$)$_3$), 3.14 (dd, $J = 15.9, 7.3$ Hz, 1H, CH-$\beta$), 2.50 (s, 3H, C$_3$H$_6$O$_3$Ag). By co-evaporation with toluene (3 x 3 mL). 183 mg of 21 (0.43 mmol) was dried azeotropically by co-evaporation with toluene (3 x 3 mL). 125 mg Ag$_2$O (0.54 mmol) and molecular sieves were added. The Schlenk flask was purged twice and placed under an argon atmosphere. 10 mL DCM was added and the mixture was stirred overnight at room temperature with exclusion of light. The mixture was filtered through a pad of Celite in air and the residue was washed with 10 mL DCM. All volatiles were removed in vacuo providing the title compound as an off-white foam (203 mg, 96% yield). $^1$H NMR (400 MHz, CD$_2$Cl$_2$) $\delta$ 7.45 – 7.24 (m, 8H, Ar), 7.18 – 7.12 (m, 2H Ar), 6.91 (s, 1H, Im-bb), 5.43 (s, 2H, NCH$_2$Ph), 5.30 (s, 2H, NCH$_2$Ph$'$), 3.59 (s, 3H, OMe), 3.52 – 3.40 (m, 1H, C(CH$_3$)$_3$), 2.84 (dd, $J = 15.6, 5.2$ Hz, 1H, C(CH$_3$)$_3$), 2.61 (dd, $J = 15.6, 7.8$ Hz, 1H, C(CH$_3$)$_3$), 1.43 (d, $J = 7.2$ Hz, 2H, NH$_2$). $^{13}$C-NMR (126 MHz CD$_2$Cl$_2$) $\delta$ 181.19 (NCN), 174.9 (CO(OMe)), 136.6 (Ar(C$_3$)), 136.5 (Ar(C$_3$)), 132.3 (Im-bb(C$_3$)), 129.6 (Ar(CH)), 129.5 (Ar(CH)), 129.0 (Ar(CH)), 128.7 (Ar(CH)), 127.2 (Ar(CH)), 127.0 (Im-bb(CH)), 56.4 (NCH$_2$Ph), 54.2 (NCH$_2$Ph$'$), 53.7 (C(CH$_3$)$_3$), 53.5 (C(CH$_3$)$_3$), 52.5 (C(CH$_3$)$_3$), 30.2 (C(CH$_3$)$_3$). MS (FAB-TOF) calculated for C$_{42}$H$_{33}$N$_2$O$_2$+ x 107Ag $^+$ is 911.3677; found 911.3693. 

[(4-(2-Amino-3-methoxy-3-oxopropyl)-1,3-dibenzyl-1H-imidazol-2-(3H)-ylidene)silver(I) dichloride (34). The title compound was prepared as described for 33 and the isolated as an off-white oil/solid. The yield was 27 mg (22%). $^1$H NMR (400 MHz, CD$_2$Cl$_2$) $\delta$ 7.03 (s, 2H, Ar), 6.87 (s, 1H, Im-bb), 3.91 (s, 3H, OMe), 3.81 (s, 1H, C(CH$_3$)$_3$), 3.73 (s, 3H, OMe), 3.05 (dd, $J = 52.6, 15.5, 6.4$ Hz, 2H, C(CH$_3$)$_3$), 2.38 (s, 3H, Mes(p-Me)), 2.01 (s, 6H, Mes(o-Me)), 1.63 (s, 2H, NH$_2$). $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 185.24 (NCN), 171.89 (CO(OMe)), 136.6 (Ar(C$_3$)), 136.5 (Ar(C$_3$)), 132.3 (Im-bb(C$_3$)), 129.6 (Ar(CH)), 129.5 (Ar(CH)), 129.0 (Ar(CH)), 128.7 (Ar(CH)), 127.2 (Ar(CH)), 127.0 (Im-bb(CH)), 56.4 (NCH$_2$Ph), 54.2 (NCH$_2$Ph$'$), 53.7 (C(CH$_3$)$_3$), 53.5 (C(CH$_3$)$_3$), 52.5 (C(CH$_3$)$_3$), 30.2 (C(CH$_3$)$_3$). MS (FAB-TOF) calculated for C$_{32}$H$_{25}$N$_2$O$_2$+ x 107Ag $^+$ is 599.1787; found 599.1766.
(NCN), 174.48 (CO(OMe)), 139.36, 135.65, 134.88, 131.00, 129.17 (Ar(CH)), 120.70 (Im-bb(CH)), 53.80 (OMe/α-CH), 52.14 (OMe/α-CH), 36.55 (NCH3), 29.64 (β-CH2), 20.79 (Mes), 17.41 (Mes). MS (FAB-TOF) calculated for C34H46AgN6O4+ 711.2628; found 711.2634.

[(1,3-Dibenzyl-4-(2-((tert-butoxycarbonyl)amino)-3-methoxy-3-oxopropyl)-1H-imidazol-2-(3H)-ylidene) palladium(II)(allyl)chloride] (35). A solution of 28 (223 mg, 0.35 mmol) in 11 mL DCM was added drop-wise to a stirred solution of [Pd(allyl)Cl]2 (64 mg, 0.175 mmol) in 5.5 mL DCM. The mixture was stirred for one hour at room temperature. Subsequently, the mixture was filtered through a pad of Celite in air and the residue was rinsed with 10 mL DCM. Volatiles were evaporated and the crude product was purified by selective precipitation of the impurity by gradual cooling of a DCM/pentane solution providing the title compound as an off-white solid (90 mg, 41%). 1H NMR (400 MHz, CD2Cl2) δ 7.39 – 7.26 (m, 8H, Ar), 7.23 – 7.18 (m, 2H, Ar), 6.82 (s, 1H, Im-bb), 5.63 – 5.34 (m, 4H, NC2H2Ph), 5.12 – 5.00 (m, 2H, NH + allyl), 4.39 (bs, 1H, α-CH), 4.08 (dd, J = 7.5, 2.1 Hz, 1H, allyl), 3.62 (s, 3H, OMe), 3.12 (bs, 1H, allyl), 2.98 – 2.87 (m, 1H, β-CHH), 2.84 – 2.71 (m, 1H, β-CHH), 1.93 (d, J = 12.0 Hz, 1H, allyl), 1.38 (bs, 9H, C(CH3)3). 13C NMR (101 MHz, CD2Cl2) δ 182.7 (NCN), 171.8 (CO(OMe)), 155.3 (CO(OtBu)), 137.2 (Ar(Cq)), 137.1 (Ar(Cq)), 130.6 (Ar(CH)), 129.1 (Ar(CH)), 128.4 (Ar(CH)), 128.3 (Ar(CH)), 128.1 (Ar(CH)), 127.3 (Ar(CH)), 120.3 (Im-bb(CH)), 115.1 (allyl), 80.5 (C(CH3)3), 71.7 (allyl), 55.1 (NCH2Ph), 52.9 (α-CH), 52.6 (OMe), 52.4 (allyl), 28.3 (C(CH3)3), 28.1 (β-CH2). MS (FAB-TOF) calculated for C29H36O4N3Pd+ 596.1741; found 596.1743.

[(1-Benzyl-4-(2-((tert-butoxycarbonyl)amino)-3-methoxy-3-oxopropyl)-3-(pyridin-2-ylmethyl)-1H-imidazol-2-(3H)-ylidene) palladium(II)(allyl)chloride] (36). A solution of 29 (95 mg, 0.15 mmol) in 3 mL DCM was added drop-wise to a stirred solution of 23 mg [Pd(allyl)Cl]2 (0.075 mmol) in 2 mL DCM. The mixture was stirred for 24 hours at room temperature. Subsequently, the mixture was filtered through a pad of Celite in air and the residue was washed with 5 mL DCM. Volatiles were evaporated, and the crude product was purified by column chromatography (silica, DCM to 9:1; DCM:MeOH) providing the title compound as an off-white foam (70 mg, 74%). 1H NMR (400 MHz, CD2Cl2) δ 8.63 (d, J = 4.4 Hz, 1H, Py-H2), 7.84 – 7.67 (m, 2H, Ar), 7.40 – 7.19 (m, 6H, Ar), 6.81 (s, 1H, Im-bb), 6.56 (bs, 1H, NH), 5.73 – 5.47 (m, 2H, NCH2Py), 5.30 (s, 2H, NCH2Ph), 5.5.21-5.14 (m, 1H, allyl), 4.45 (dd, J = 13.1, 7.3 Hz, 1H, α-CH), 4.13 (d, J = 7.6 Hz, 1H, allyl), 3.65 (s, 3H, OMe), 3.16 (dd, J = 14.7, 10.0 Hz, 2H, β-CH2), 3.01 (bs, 2H, 2 x allyl), 2.0 (bs, 1H, allyl), 1.36 (s, 9H, C(CH3)3). 13C NMR (101 MHz, CD2Cl2) δ 180.9 (NCN), 172.0 (CO(OMe)), 156.1 (Py-C6), 155.9 (CO(OtBu)), 151.4 (Py-C2), 138.2 (Py-C4), 136.8 (Ar(Cq)), 131.9 (Im-bb(Cq)), 129.1 (Ar(CH)), 128.5 (Ar(CH)), 128.0 (Ar(CH)), 124.6 (Py-C5), 123.8 (Py-C3), 119.7 (Im-bb(CH)), 116.8 (allyl), 80.0 (C(CH3)3), 72.7 (allyl), 55.2 (NCH2Py), 53.7 (α-CH), 52.8 (NCH2Ph), 52.7 (OCH3), 48.6 (allyl), 28.4 (C(CH3)3), 27.2 (β-CH2). MS (FAB-TOF) calculated for C28H35O4N4Pd+ 597.1693; found 597.1697.
[(4-((Tert-butoxycarbonyl)amino)-3-methoxy-3-oxopropyl)-1,3-bis(pyridin-2-ylmethyl)-1H-imidazol-2-(3H-ylidene) palladium(II)] allyl chloride (37). The title compound was prepared as described for 36. It was obtained as an off-white foam in quantitative yield. $^1$H NMR (400 MHz, CD$_2$Cl$_2$) $\delta$ 8.62 (d, $J$ = 4.4 Hz, 1H, Py-H2), 8.59 (d, $J$ = 4.9 Hz, 1H, Py-H2'), 7.89 - 7.68 (m, 2H, Py-H4 + Py-H4'), 7.64 (d, $J$ = 7.5 Hz, 1H, Py-H5), 7.41 (d, $J$ = 7.6 Hz, 1H, Py-H5'), 7.34 - 7.24 (m, 2H, Py-H3 + Py-H3'), 7.17 (s, 1H, Im-bb), 6.56 (d, $J$ = 6.7 Hz, 1H, NH), 5.66 - 5.54 (m, 4H, NCH$_3$Py), 5.31 - 5.19 (m, 1H, allyl), 4.44 (d, $J$ = 4.9 Hz, 1H, $\alpha$-CH), 4.19 (d, $J$ = 7.6 Hz, 1H, allyl), 3.27 (d, $J$ = 13.6 Hz, 1H, allyl), 3.23 - 3.04 (m, 3H, $\beta$-CH$_2$ + allyl), 2.1 (bs, 1H, allyl), 1.34 (s, 9H, C(C$_3$H$_7$)$_3$), 13C NMR (126 MHz, CD$_2$Cl$_2$) $\delta$ 182.6 (Pd-C), 172.2 (CO(OMe)), 156.8 (Py-C6), 156.7 (Py-C6'), 155.8 (CO(OrBu)), 150.7 (Py-C2), 150.4 (Py-C2'), 137.7 (Py-C4), 137.6 (Py-C4'), 131.8 (Im-bb(C$_6$)), 123.8 (Py-CH), 123.8 (Py-CH), 123.5 (Py-CH), 123.4 (Py-CH), 120.7 (Im-bb(CH)), 116.4 (allyl), 80.5 (C(CH$_3$)$_3$), 72.8 (allyl), 57.1 (NCH$_3$Py), 53.5 ($\alpha$-CH), 52.8 (OMe), 48.7 (allyl), 28.6 (C(CH$_3$)$_3$), 27.8 ($\beta$-CH$_2$). MS (FAB-TOF) calculated for C$_2$H$_3$O$_3$N$_2$Pd$^+$ 598.1646; found 598.1646.

[(4-((Tert-butoxycarbonyl)amino)-3-methoxy-3-oxopropyl)-1-mesityl-3-(6-methylypyridin-2-ylmethyl)-1H-imidazol-2-(3H-ylidene)palladium(II)-(allyl)chloride (38). The title compound was prepared as described for 37. It was obtained as an off-white foam in 93% yield. $^1$H NMR (400 MHz, CD$_2$Cl$_2$) $\delta$ 7.61 (t, $J$ = 7.5 Hz, 1H, Py-H4), 7.40 (bs, 1H, Py-H5), 7.12 (d, $J$ = 7.6 Hz, 1H, Py-H3), 6.94 (bs, 2H, Mes), 6.84 (bs, 1H, Im-bb), 6.79 (s, 1H, NH), 5.83 - 5.40 (m, 2H, NCH$_3$Py), 4.66 (bs, 1H, allyl), 4.62 - 4.45 (m, 1H, $\alpha$-CH), 3.90 (d, $J$ = 7.2 Hz, 1H, allyl), 3.73 (s, 3H, OMe), 3.43 (d, $J$ = 4.1 Hz, 1H, allyl), 3.37 (dd, $J$ = 16.1, 6.1 Hz, 1H, $\beta$-CH$_2$), 3.22 (dd, $J$ = 14.9, 2.7 Hz, 1H, $\beta$-CH$_2$), 2.80 - 2.59 (m, 2H, 2 x allyl), 2.54 (s, 3H, Py-CH$_3$), 2.31 (s, 3H, Mes(p-Me)), 2.23 - 1.93 (m, 6H, Mes(o-Me)), 1.31 (s, 9H, C(CH$_3$)$_3$). $^{13}$C NMR (126 MHz, CD$_2$Cl$_2$) $\delta$ 184.1 (NCN), 172.1 (CO(OMe)), 159.3 (Py-C6), 156.9 (Py-C2), 155.9 (CO(OrBu)), 139.4 (Ar), 137.5 (Ar), 137.1 (Ar), 136.2 (Ar), 135.8 (Ar), 131.8 (Ar), 129.4 (Ar), 129.3 (Ar), 122.7 (Ar), 121.2 (Ar), 120.8 (Ar), 115.1 (allyl), 80.2 (C(CH$_3$)$_3$), 71.3 (allyl), 54.1 (NCH$_3$Py), 52.9 ($\alpha$-CH), 52.8 (OMe), 48.9 (allyl), 28.5 (C(CH$_3$)$_3$), 27.9 ($\beta$-CH$_2$), 24.7 (Lut(CH$_3$)), 21.3 (Mes(p-Me)), 18.5 (Mes(o-Me)), 18.2 (Mes(o-C$_6$H$_4$)). MS (FAB-TOF) calculated for C$_2$H$_3$O$_3$N$_2$Pd$^+$ 693.2163; found 639.2174.

[(4-((2-Amino-3-methoxy-3-oxopropyl)-1,3-dibenzyl-1H-imidazol-2-(3H-ylidene) palladium(II)] (allyl) chloride (40). This compound was prepared as described for 36. The title compound was obtained as a white solid in 31% yield. $^1$H NMR (400 MHz, CD$_2$Cl$_2$) $\delta$ 7.42 - 7.26 (m, 8H, Ar), 7.19 (d, $J$ = 7.1 Hz, 2H, Ar), 6.88 (s, 1H, Im-bb), 5.64 - 5.33 (m, 4H, NCH$_3$Ph), 5.13 - 5.02 (m, 1H, allyl), 4.07 (dd, $J$ = 7.5, 1.6 Hz, allyl), 3.60 (s, 3H, OMe), 3.45 (d, $J$ = 5.7 Hz, 1H, $\alpha$-CH), 3.08-3.02 (m, 2H, 2 x allyl), 2.89 - 2.80 (m, 1H, $\beta$-CH$_2$), 2.63 - 2.56 (m, 1H, $\beta$-CH$_2$), 1.92 (d, $J$ = 11.9 Hz, 1H, allyl), 1.4 (bs, 2H, N$_2$H$_2$). $^{13}$C NMR (101 MHz, CD$_2$Cl$_2$) $\delta$ 182.4 (NCN), 175.0 (CO(OMe)), 137.4 (Ar(C$_6$H$_4$)), 137.3 (Ar(C$_6$H$_4$)), 131.7 (Im-bb(C$_6$H$_4$)), 129.1 (Ar(CH)), 129.1.
(Ar(\text{CH})), 128.3 (\text{Ar(\text{CH})}), 128.3 (\text{Ar(\text{CH})}), 128.0 (\text{Ar(\text{CH})}), 127.3 (\text{Ar(\text{CH})}), 120.4 (\text{Im-}\beta\text{-CH}), 115.2 (\text{allyl}), 71.9 (\text{allyl}), 55.1 (N\text{CH}_2\text{Ph}), 52.5 (\alpha\text{-CH}), 52.4 (\text{OMe}), 49.3 (\text{allyl}), 30.2 (\beta\text{-CH}_2). MS (FAB-TOF) calculated for $\text{C}_{24}\text{H}_{28}\text{O}_2\text{N}_3\text{Pd}^+$ is 496.1216; found 496.1221.

\[
\text{[Bis-(4-[(2-((\text{tert-butoxycarbonyl)amino)-3-methoxy-3-oxopropyl)}]-1\text{-mesityl-1H-imidazol(3H)}-2-yldene-palladium(II)(allyl)] chloride (41).} \\
\]

5 mL of a solution of 30 (0.288 g, 0.46 mmol) in DCM was added drop-wise to a stirred 5 mL solution of $[\text{Pd(allyl)Cl}]_2$ (0.168 g, 0.46 mmol). Subsequently, the solution was stirred for an hour. The mixture was filtered over a pad of Celite in air, which was rinsed with an additional 5 mL of DCM. The volatiles were removed \textit{in vacuo} yielding a yellow foamy solid. The compound contained an excess of the Pd precursor. The crude product was purified by column chromatography (DCM to 95:5; DCM:MeOH to 9:1; DCM:MeOH). The fractions containing the product were combined. The solution was concentrated on a rotavap apparatus, and the remaining solvent was removed \textit{in vacuo} on a Schlenk line. A light yellow foamy solid was obtained (0.162 g, 0.17 mmol, 36% yield). $^1\text{H}$ NMR (400 MHz, CD$_2$Cl$_2$) $\delta$ 7.16 (s, 2H, Im-\beta\text{-bb}), 7.05 – 6.90 (m, 8H, Ar), 6.35 (s, 2H, NH), 5.34 – 5.20 (m, 1H, \alpha\text{-CH}), 4.55 – 4.36 (m, 2H, \alpha\text{-CH/(CO(O\text{Me}))}), 4.36 – 4.16 (m, 10H, \text{allyl} + \text{OMe}), 3.78 (s, 6H, OMe), 3.24 – 2.94 (m, 10H, \beta\text{-CH}_2 + N\text{Me}), 2.71 – 2.50 (m, 2H, allyl), 1.42 (s, 18H, CO(O\text{OtBu})). $^{13}\text{C}$ NMR (101 MHz, CD$_2$Cl$_2$) $\delta$ 175.90 (N\text{CN}), 171.52 (CO(\text{OMe})), 159.44 (p-Ar), 155.43 (CO(O\text{Bu})), 133.13 (Im-\beta\text{-bb(Cq)}), 130.79 (i-Ar), 125.83 (m-Ar), 121.40 (Im-\beta\text{-bb(CH)}), 118.00 (allyl), 114.13 (\alpha\text{-Ar}), 79.34 (CH$_3$), 58.45 (allyl), 55.57 (Ar-\text{OMe}), 52.25 (\alpha\text{-CH}/(\text{CO(\text{OMe})})), 51.90 (\alpha\text{-CH/CO(OMe)}), 34.78 (NMe), 27.84 (C(CH$_3$_3)), 26.57 (\beta\text{-CH}_2). MS (ESI-Goldspray) calculated for $\text{C}_{43}\text{H}_{59}\text{N}_6\text{O}_{10}\text{ClPd}^+$ 960.3016; found 960.3029.

\textbf{Catalytic transfer semihydrogenation of alkynes.} A Radleys’ twelve-place reaction station with integrated heating and cooling setup was used for all catalytic experiments. Samples were taken at regular time intervals by filtering \textit{aliquots} of the reaction mixture over short silica pads and eluting with DCM. Samples were analyzed on a Thermo Scientific Trace GC Ultra equipped with an R-Rxi 5m column (30 m, ID 0.25 mm) and quantified using the response factor corrected GC-area in respect to the internal standard. Samples were further analyzed by NMR-spectroscopy on a Bruker 400 MHz spectrometer.

\textbf{A standard catalytic experiment:} a stock solution was prepared, adding in their respective order: acetonitrile (320 mL, 250.3 g), 1-phenyl-1-propyne (6.4 g, 55 mmol), \textit{p}-xylene (internal standard, 5.68 g, 54 mmol), triethylamine (27.00 g, 267 mmol) and formic acid (11.48 g, 267 mmol), which was saturated with nitrogen gas by gently bubbling N$_2$ through the solution for 20 minutes. From the stock solution 20 mL was taken by a syringe and added to one of the twelve reaction vessels. The exact amount of added stock solution was determined by weighing; for this reason, molar and weight percentages were applied to determine quantities and further calculations. The Radleys’ station was heated to 70 °C, after which the appropriate amount of catalyst was added in aluminum weighing trays. Reaction rates were determined by taking the first order derivative of the conversion at 15%.
X-ray crystal structure determination of 42. C_{31}H_{41}N_{4}O_{4}Pd 0.5 C_{6}H_{12} 0.5 C_{4}H_{8}O + disordered solvent, Fw = 780.21[^{(*)}], pale brown block, 0.40 × 0.18 × 0.11 mm^3, monoclinic, P2₁ (no. 4), a = 14.5823(3), b = 14.2173(4), c = 20.5565(4) Å, β = 103.670(1)°, V = 4141.06(16) Å³, Z = 4, D_x = 1.251 g/cm³[^{(*)}], μ = 0.50 mm⁻¹[^{(*)}], 74792 reflections were measured on a Bruker Kappa Apex II diffractometer with sealed tube and Triumph monochromator (λ = 0.71073 Å) at a temperature of 150(2) K up to a resolution of (sin θ/λ)_{max} = 0.65 Å⁻¹. Intensity integration was performed with the software Eval15.79 Multiscan absorption correction and scaling was performed with SADABS[^{80}] (correction range 0.65-0.75). 19045 reflections were unique (R_{int} = 0.026), of which 16710 were observed [I>2σ(I)]. The structure was solved using the program SHELXT[^{81}]. Least-squares refinement was performed with SHELXL-2013[^{82}] against F² of all reflections. Because of large shifts of the structure along the polar b-axis, the y-coordinate of Pd1 were fixed in the refinement. All other non-hydrogen atoms were refined freely with anisotropic displacement parameters. The coordinated allyl groups, one of the non-coordinated nitrate ions and the cyclohexane molecule were refined with disordered models. The crystal structure additionally contains voids (526 Å³ / unit cell), filled with disordered cyclohexane and THF solvent molecules. Their contribution to the structure factors was secured by back-Fourier transformation using the SQUEEZE algorithm of PLATON[^{68}] resulting in 161 electrons / unit cell. All hydrogen atoms were introduced in calculated positions and refined with a riding model. 1011 Parameters were refined with 292 restraints concerning the disordered moieties. R1/wR2 [I>2σ(I)]: 0.0401 / 0.1029. R1/wR2 [all refl.]: 0.0492 / 0.1085. S = 1.037. The absolute structure was confirmed by a refinement as an inversion twin, resulting in a Flack parameter[^{83}] x = -0.02(2). Residual electron density between -1.58 and 1.33 e/Å³. Geometry calculations and checking for higher symmetry were performed with the PLATON program[^{68}].

[^{*}]: Derived values do not contain the contribution of the disordered solvent molecules.

### 4.7 Acknowledgements

Danny Broere, Jorin Hoogenboom and Simone de Baan are kindly acknowledged for their contributions to this work. The X-ray diffractometer has been financed by the Netherlands Organization of Scientific Research (NWO).

### 4.8 References

81. Sheldrick, G. M. SHELXT. 2013, Universität Göttingen, Germany.