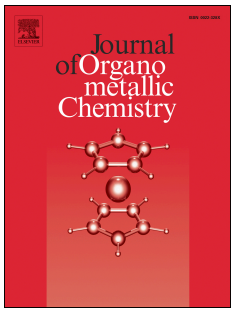

Rhodium(I) and Iridium(I) N-Heterocyclic carbene complexes of imidazolium functionalized amino acids and peptides

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PII: S0022-328X(19)30539-X

DOI: https://doi.org/10.1016/j.jorganchem.2019.121096

Reference: JOM 121096

To appear in: *Journal of Organometallic Chemistry*

Received Date: 1 November 2019

Revised Date: 20 December 2019

Accepted Date: 21 December 2019

Please cite this article as: I.M. Daubit, J. Wolf, N. Metzler-Nolte, Rhodium(I) and Iridium(I) N-Heterocyclic carbene complexes of imidazolium functionalized amino acids and peptides, *Journal of Organometallic Chemistry* (2020), doi: https://doi.org/10.1016/j.jorganchem.2019.121096.

Rhodium(I) and Iridium(I) N-Heterocyclic Carbene Complexes of Imidazolium Functionalized Amino Acids and Peptides

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Keywords: Bioorganometallic Chemistry, Iridium, Metal Peptide Bioconjugates, Non-natural amino acids, N-heterocyclic carbene complexes, Rhodium

Abstract

The conjugation of organometallic complexes to peptides is generally achieved through covalent organic linkages of the metal's ligand to the peptide. Examples of direct coordination to metal centers by amino acid side chain residues remain rare. In one such example, side chain methylation of the natural amino acid histidine (His) resulted in an imidazolium functionalized amino acid which was used for the synthesis of rhodium(I), iridium(I), iridium(III), palladium(II) and ruthenium(III) N-heterocyclic carbene (NHC) complexes of the single amino acid and peptides containing this amino acid. Here, we have synthesized two new, non-natural imidazolium functionalized amino acid derivatives, which were used for solid phase peptide synthesis and for the synthesis of [M(COD)(NHC)Cl] (COD=1,5 cyclooctadiene) complexes of Rh(I) and Ir(I). In total, six new complexes of the single amino acids and four complexes where the amino acids are present in a peptide environment were synthesized. Their characterization provides convincing evidence of conversion of the imidazolium moiety to an NHC ligand and thus the presence of a direct metal-carbon bond between the metal center and the amino acid side chain. Thus, our compounds represent unique examples of peptide-conjugated complexes that bear the potential to be used for the synthesis of N-heterocyclic carbene complexes conjugated to cancer cell targeting peptides.

Introduction

The discovery of cisplatin inspired the widespread investigation of metal complexes as potential anti-cancer drug candidates. For a long time, research in this area was limited to metal complexes without direct metal-carbon bonds, as they were considered too sensitive to oxygen and moisture to be suitable for an application in biological systems. However, recent advances in the field have shown a wide range of complexes suitable for this purpose, leading to the birth of medicinal organometallic chemistry.[1] Organometallic complexes of iridium and rhodium were identified as potential anti-cancer compounds as early as 1978.[2] Although in these first examples the complexes contained a metal center in the oxidation state +I, most of the recently investigated examples with these late group 8 metals comprise the metal center in the oxidation state +III, as these compounds are considered more stable than their lower oxidation state analogues.[3-8] A class of organometallic compounds of rhodium and iridium mainly known for their catalytic activities[9-14] are N-heterocyclic carbene (NHC) complexes of the type [M(COD)(NHC)Cl] (COD = 1,5-cyclooctadiene). They have only very recently gained attention in the field of organometallic anti-cancer research. Several examples of this compound class have been synthesized and their activities against different cancer cell lines have been assessed. [15-22] Besides of showing promising cytotoxic activities regarding their IC_{50} values, they were also shown to have very distinct mechanisms of action. These involve ligand displacement and interaction with biomolecules such as DNA[22] as well as influence on cellular signalling[18] in case of [Rh(COD)(NHC)Cl] compounds and proteins for [Ir(COD)(NHC)Cl] compounds.[19-21] Their most versatile structural element is the NHC ligand. Due to the possibility to substitute not only the nitrogen atoms but also the heterocycle backbone, the structure of the ligand can easily be designed in a way that suits the desired application, a feature which is heavily exploited for their catalytic applications.[23-25] In an attempt to increase the potential in catalytic conversions for the [Rh(COD)(NHC)Cl] complexes, the natural amino acid histidine (His) was converted to an imidazolium salt by alkylation of both nitrogen atoms.[26] These amino acid derivatives were then used in the synthesis of palladium(II), rhodium(I) and ruthenium(III) N-heterocyclic carbene complexes.[27-29] Furthermore, the synthesis and anti-proliferative activity of such metal complexes with Pt(II), Au(I) and Ir(III) was reported.[30] The ability of complex formation was not only evident for the single, fully protected amino acids, but was retained when the amino acid was included into a large, complex peptide scaffold.[31, 32] This system represents a very unique

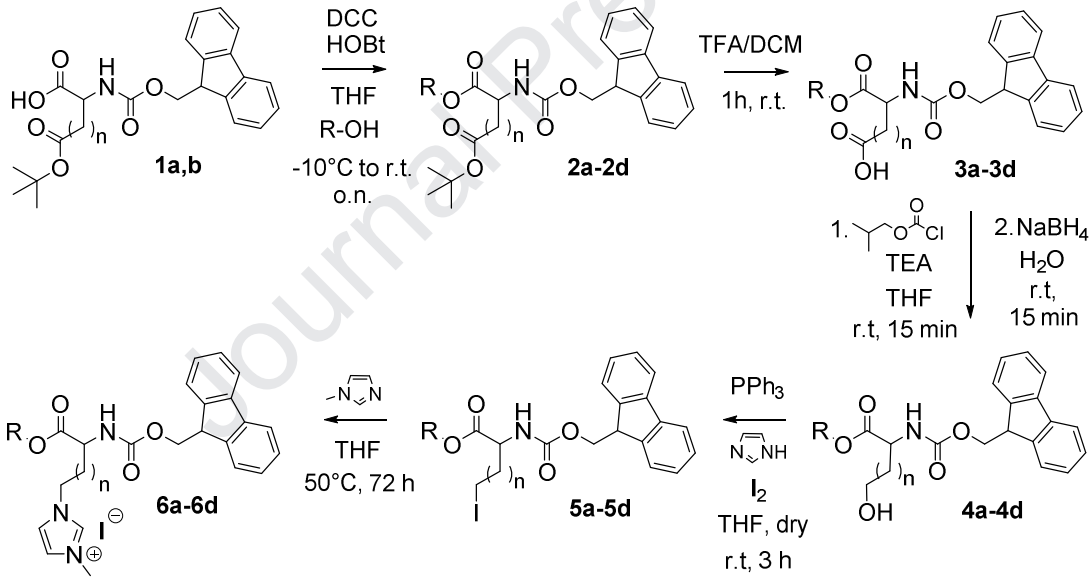
example of a peptide-conjugated organometallic complex: Instead of covalently attaching the peptide to a known ligand first, which then in turn coordinates to the metal center, as reported for a similar system [33], the coordination site in this case is directly included in the peptide chain without any additional functionality. This concept has recently been adapted for similar [Ir(COD)(NHC)Cl] complexes[34] and is so far the only reported example of peptide-conjugation for complexes of the [M(COD)(NHC)Cl] type by a direct metal-carbon bond with a natural amino acid present in the peptide chain. Herein, we report the synthesis of two new non-natural imidazolium functionalized amino acid derivatives, their use in peptide synthesis and their ability to form complexes of the [M(COD)(NHC)Cl] type for iridium and rhodium through the imidazolium side chain. The new imidazolium functionalized amino acids presented here are *not* derived from His, but rather formed from other amino acids and thus extend the synthetic toolbox for metal-NHC peptide complexes, providing defined anchoring points for the formation of metal complexes in more complex peptide scaffolds. Additionally, they can potentially be used in the synthesis of cancer cell-targeting complexes of iridium(I), rhodium(I) as well as several other metals which is an uprising field of research.[35]

Synthesis and Characterization

Synthesis of the amino acid derivatives was performed based on modified literature procedures starting from Fmoc-Glu(tBu)-OH and Fmoc-Asp(tBu)-OH (scheme 1). After esterification of the in situ activated C-terminal carboxylic acid with the respective alcohol,[36] the side chain protecting *tert*-butyl group was removed under acidic conditions. The progress of the reactions could be followed by ^{1}H- and ^{13}C-NMR, which showed subsequent appearance and disappearance of the signals for the respective protecting groups (see ESI). Subsequently, conversion of the carboxylic acid to the respective alcohol was performed by treatment with isobutylchloroformiate to form the respective anhydride *in situ*, followed by reduction of the anhydride using $NaBH_4$. [37, 38] It is important to note that the yield of the reaction was highly dependent on the reaction conditions, mainly the solvent and the dilution. In high dilution and a mixture of THF and water, the reaction proceeded towards the alcohol in moderate to good yields. In low dilution significant amounts of a side product were isolated. ^{1}H NMR and ESI-MS revealed the side product to be an amino acid dimer resulting from the reaction of the freshly

formed alcohol with the anhydride formed in the previous reaction step. In an attempt to improve the yield by choosing dry MeOH over water for the reduction step similarly low product yields were observed together with the reaction product of an esterification between the solvent and the *in situ* formed anhydride (see Fig. S1 in the ESI for the respective reaction conditions and side products).

Once obtained, the alcohols **4a-4d** were subjected to iodination by an Appel reaction as reported previously,[38] followed by substitution of iodine by 1-methylimidazole[19-21, 34] which led to the desired amino acid imidazolium salts **6a-6d**. The success of the reactions could again readily be followed by ^{1}H and ^{13}C NMR, which showed appearance of the new γ- and δ-CH_2 group respectively after formation of the alcohol, and most importantly a shift of the respective group depending on the nature of the adjacent functional group throughout each synthesis step (shown exemplarily for the series of compounds **2a-6a** in Fig. S4 in the ESI).

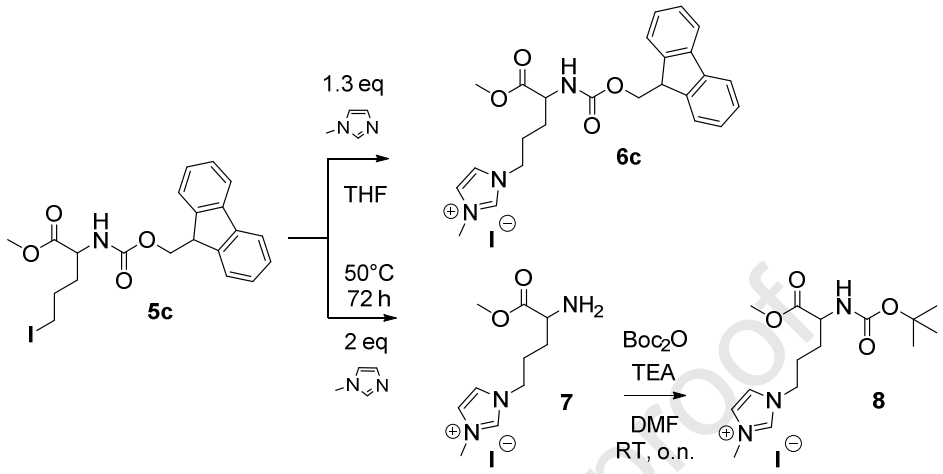


1a: n=1; **1b**: n=2 **2a-6a**: n=1, R= Me; **2b-6b**: n=1, R= Allyl; **2c-6c**: n=2, R= Me; **2d-6d**: n=2, R=Allyl

Scheme 1: *Synthesis scheme for the synthesis of amino acid imidazolium salts* ***6a-6d***

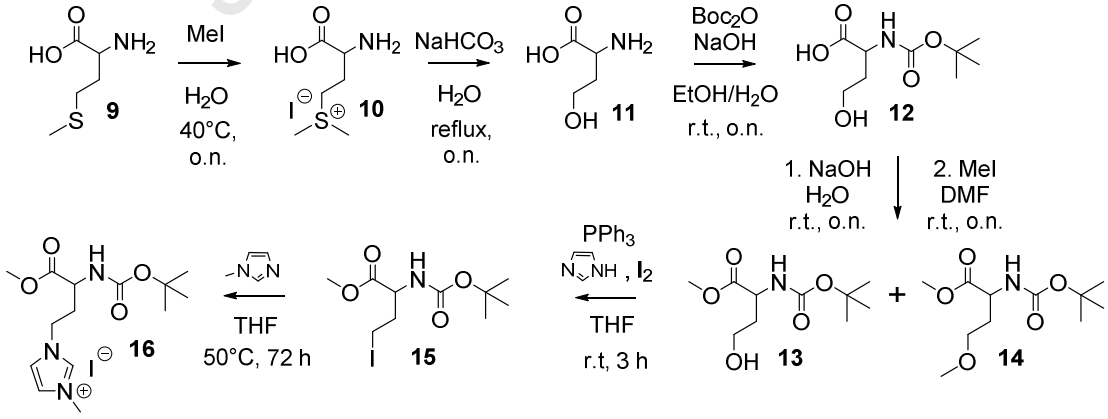
In an attempt to increase the yield of the reaction, the amount of 1-methylimidazole used for the preparation of **6c** was increased from 1.3 eq to 2 eq. However, the reaction did not proceed towards the desired product **6c**. Instead, ^{1}H-NMR and ESI-MS confirmed the nature of the obtained product to be the N-terminally deprotected amino acid **7** (scheme 2). Thus, the outcome of the reaction can easily be controlled by the amount of nucleophile that is used. With the N-

deprotected amino acid **7** in hand, N-terminal Boc protection was carried out with Boc_2O to yield compound **8**.



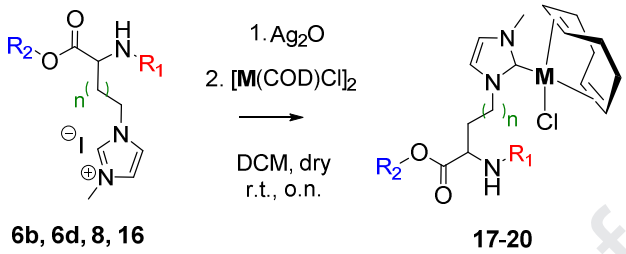
Scheme 2: *Reaction conditions leading to the products **6c** and **7** and synthesis of the Boc-protected amino acid imidazolium salt **8***

To obtain the Boc-protected derivative of **6a** a different synthetic pathway was chosen. After initial synthesis of homoserine (Hse) **11** it was N-terminally Boc-protected according to a literature known procedure[39-41] leading to protected compound **12**. The intended C-terminal methylation with MeI led to an inseparable mixture of the desired compound **13** and the double methylated side product **14**. The mixture was used without further purification to synthesize the desired amino acid imidazolium salt **16** following the route described in scheme 3.



Scheme 3: *Synthesis of the Boc protected amino acid imidazolium salt **16***

The fully protected amino acid derivatives **6b**, **6d**, **8** and **16** were used for the preparation of the respective [M(COD)(NHC)Cl] complexes of rhodium or iridium by the well established Ag_2O transmetalation route (scheme 4).[9, 19-21, 42]



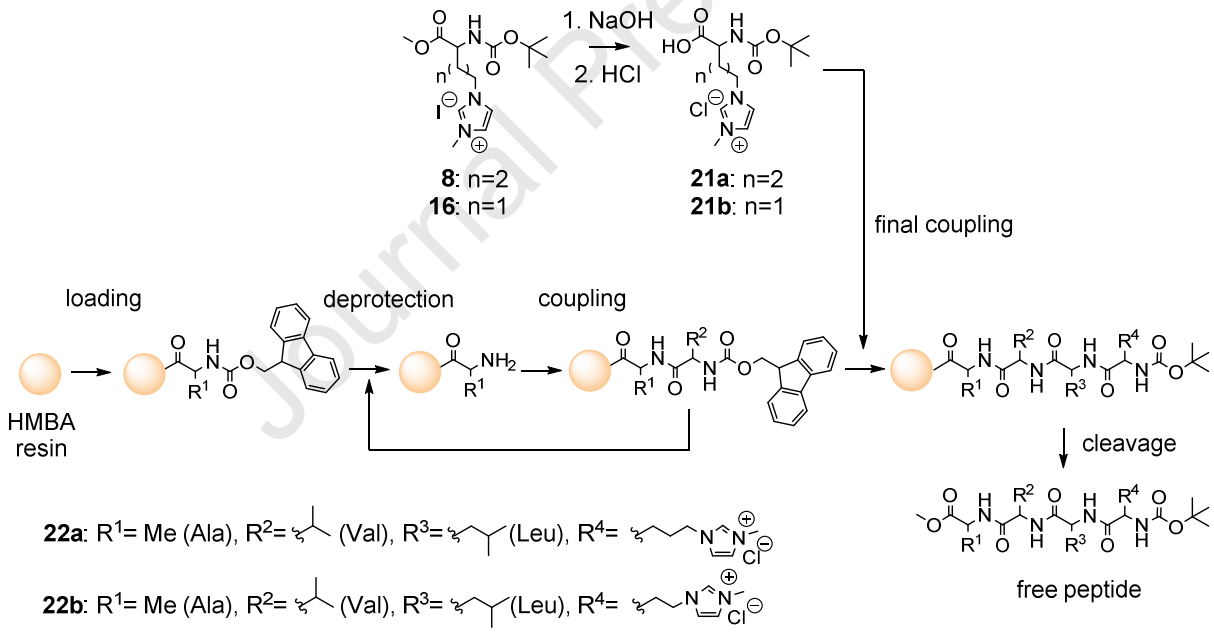
Metal center	*Compound*	*Length of C-chain n*	*N-term. protecting group R_1*	*C-term. protecting group R_2*
Rh	**17**	1	Fmoc	Alloc
	18a	1	Boc	Methyl
	18b	2	Boc	Methyl
Ir	**19a**	1	Boc	Methyl
	19b	2	Boc	Methyl
	20	2	Fmoc	Alloc

Scheme 4: *Synthesis of [M(COD)(NHC)Cl] amino acid complexes* ***17-20*** *by Ag_2O transmetalation*

The most significant sign of successful complex formation could be found in the NMR spectra. They did not only show disappearance of the imidazolium proton of the respective amino acids at around 9.80-9.95 ppm in the ^{1}H-NMR, but also a significant shift of the imidazolium carbon atom from around 136-137 ppm in the free amino acids to around 180-182 ppm after complexation in the ^{13}C-NMR.[43] This confirms that coordination of the amino acid to the metal center proceeds in the desired manner through the imidazolylidene carbon of the amino acid obtained by deprotonation of the imidazolium group and not through one of the other functional groups present in the molecule, which have been reported to be able to coordinate to metal centers in various ways.[44] Furthermore, it has to be noted that complexation works independently from the protective groups present in the amino acid. Therefore, the compounds represent a family of examples of bioconjugated organometallic complexes. The NMR spectra also show signs of formation of two isomers for the complexes due to the slow rotation around the metal-carbon bond, a phenomenon that has been reported for the His functionalized

[Rh(COD)(NHC)Cl] complexes earlier.[32] In complexes **18** and **19** this can be best observed for the signal of the C-terminal methyl ester which forms a doublet between 3.69 ppm and 3.76 ppm. For complexes **17** and **20** the heterocycle methyl group shows two signals between 3.95 ppm and 4.07 ppm. In comparison, the free ligands only show a singlet for the respective signals in the same chemical shift area (see NMR spectra in the ESI). Integration of the respective signals of the two isomers reveals a ratio of almost 1:1.

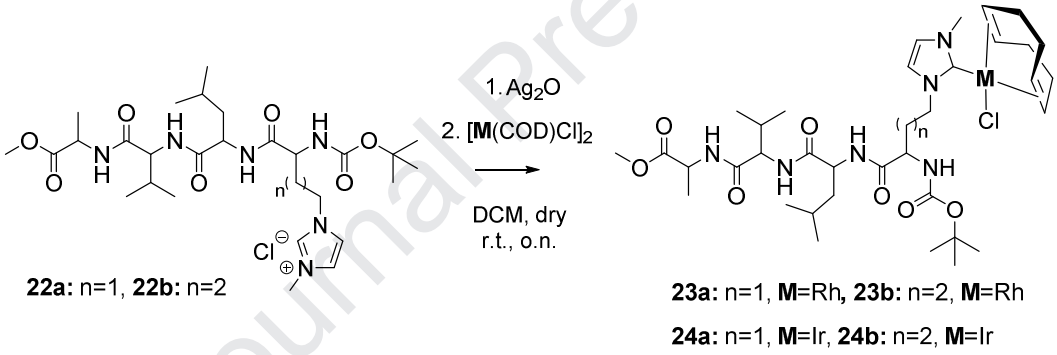
Going further, the potential of the amino acids to coordinate to metals as part of a larger peptide scaffold was assessed. To this end, the amino acid imidazolium salts **8** and **16** were C-terminally saponified by treatment with aqueous NaOH. This resulted in the respective carboxylic acids **21a** and **21b**, which were subsequently used for solid phase peptide synthesis (SPPS) based on a literature known procedure[34, 45, 46] to synthesize the peptide imidazolium salts **22a** and **22b** as depicted in scheme 5.



Scheme 5: *Synthesis of the carboxylic acids **21a** and **21b** and their subsequent use in SPPS. SPPS conditions were as follows for loading: Fmoc-Ala-OH, DCC, DMAP, DCM/DMF o.n., r.t., deprotection: 20% Piperidine in DMF, 25 min,r.t., coupling: Fmoc protected amino acid, TBTU, HOBt, DIPEA, DMF/NMP, 2x 45 min, r.t., final coupling (only **21a** and **21b**): amino acid, DCC, HOBT, DMF/NMP, o.n., r.t., cleavage: MeOH/DMF/DIPEA, 50°C, o.n.*

Peptides **22a** and **22b** were then used in the complexation of rhodium and iridium by Ag_2O transmetalation in a similar manner to the fully protected amino acids,[31, 32, 34] resulting in the

peptide complexes **23-24** as depicted in scheme 6. The success of the complexation was proven by ESI-MS, which confirmed the identity of the obtained complexes, but also by analytical HPLC which showed a significant shift in the retention time of the metal-peptide complexes in comparison to the free peptides (see Fig. S5-S8 in the ESI), and additionally established the purity of the compounds. Similar to the amino acid complexes, disappearance of the imidazolium proton at 8.97 ppm in the ^{1}H-NMR confirms the formation of a direct metal-carbon bond between the NHC moiety of the respective peptide and the metal center. In this examples as well, similar to the amino acid complexes, the formation of two isomers could be observed in the ^{1}H NMR. Thus, the amino acids **22a** and **22b** can coordinate to the metals even in the presence of a more complex peptide environment and, quite remarkably, complexation is not hampered by the presence of several other functional groups. These peptide-conjugates therefore represent rare examples of organometallic peptide conjugates of rhodium and iridium.



Scheme 6: *Synthesis of [M(COD)NHC)Cl] peptide complexes* ***23-24*** *by Ag_2O transmetalation*

Conclusion

In summary, we report the successful synthesis of a new set of amino acid imidazolium salts **6a-6d**, **8** and **16**, which contain different combinations of common amino acid protecting groups. The amino acids **6b**, **6d**, **8** and **16** were then used for the synthesis of complexes of the [M(COD)(NHC)Cl] type for rhodium and iridium, resulting in six new amino acid complexes **17-20.** The presence of a direct metal-carbon bond between the metal center and the imidazolium moiety of the amino acids could be unambiguously proven by ^{1}H and ^{13}C NMR spectroscopy, thus confirming the nature of the respective compounds as examples of organometallic complexes conjugated to small biomolecules. Furthermore, the amino acid imidazolium salts **8**

and **16** were converted to the respective C-terminally deprotected amino acids **21a** and **21b** suitable for SPPS and the synthesis of the peptide imidazolium salts **22a** and **22b** was successfully performed. Similar to the smaller amino acids, peptides **22a** and **22b** were used for the synthesis of [M(COD)(NHC)Cl] complexes of rhodium and iridium resulting in the peptide conjugated complexes **23** and **24**. Identical to the amino acid complexes, the peptide complexes feature a direct metal-carbon bond between the metal center and the imidazolium moiety which represents their most unique feature: A coordinative mode of conjugation through a direct bond with an amino acid side chain. The results show that complexation proceeds through the imidazolium-derived NHC moiety independently from any other functionality of either the amino acids or the peptides. This leads to the conclusion that neither the common amino acid protecting groups (Fmoc, Alloc or Boc) present in the amino acids nor the complex peptide environment have a negative effect on the complexation reaction. Our results pave the way towards a precise incorporation of rhodium and iridium into predefined small and medium sized peptides for therapeutic purposes. In future projects, the potential of the present imidazolium functionalized amino acids to be used in the synthesis of cancer cell targeting peptides and subsequent synthesis of cancer cell targeting rhodium and iridium complexes followed by the assessment of their cytotoxic potential in comparison to their non-peptide-conjugated parent compounds is envisioned.

Experimental section

General procedures for the main reactions are given in the following. Detailed synthetic procedures for all of the compounds and for solid phase peptide synthesis with the respective analytical data can be found in the ESI.

General procedures

*C-terminal esterification (**2a-2d**)*

In a heated Schlenk flask under N_2 atmosphere, 1 eq of the respective starting material and 1.5 eq of HOBt were dissolved in 4.5 ml of dry THF per mmol of starting material and cooled to -10°C.

In similar dry conditions, 1 eq of DCC was dissolved in 2.5 ml of dry THF per mmol and added dropwise to the first solution at -10°C. The reaction was stirred for 15-30 min and allowed to warm to room temperature. Afterwards, 35 eq of the respective alcohol were added dropwise and the reaction was refluxed over night at 75°C. After evaporation of the solvent under reduced pressure, the residue was taken up in 13 ml of DCM per mmol of starting material and the organic phase was extracted three times with saturated $NaHCO_3$ and brine respectively. The organic phase was separated, dried over $MgSO_4$ and the solvent was removed under reduced pressure. After Flash column chromatography over silica (n-hexane/EtOAc 1:0 → 7:3), the product was obtained as a white solid.

*tert-Butyl deprotection (**3a-3d**)*

1 eq of the respective starting material was dissolved in 10 ml of a 1:1 mixture of DCM and TFA per mmol. The solution was stirred at room temperature for 1 h until the gas evolution had ceased. The solvent was removed under reduced pressure and the oily residue was taken up in as little DCM as possible and precipitated from hexane, yielding a white precipitate which was identified as the product.

*Carboxylic acid reduction (**4a-4d**)*

In a heated Schlenk Flask under N_2 atmosphere, 1 eq of the respective starting material was dissolved in 65 ml of dry THF per mmol. 4 eq of isobutylchloroformiate were added dropwise, which resulted in the precipitation of a white solid and the reaction was stirred at room temperature for 15 min. 6 eq of $NaBH_4$ were dissolved in 20 ml of H_2O per mmol and the solution was added dropwise to the reaction mixture, resulting in gas evolution and temperature increase. The reaction was left to stir at room temperature for 15 min, during which time the gas development ceased. After completion, 10 ml of 1 M $KHSO_4$ per mmol of starting material were added to the reaction mixture and it was extracted three times with DCM. The combined organic phases were dried over $MgSO_4$ and the solvent was removed under reduced pressure. The oily residue was further purified by flash column chromatography over silica (n-hexane/EtOAc 1:0 → 0:1), yielding the product as a clear, slowly crystallizing oil.

*Appel reaction (**5a-5d**, **15**)*

In a heated Schlenk flask under N_2 atmosphere, 1.25 eq of PPh_3 and 2.5 eq of imidazole (with respect to the starting material) were dissolved in 20 ml of dry THF per mmol of starting material. 1.3 eq of I_2 (with respect to the starting material) were added and the reaction was stirred for 15 min at room temperature, which led the reaction mixture to turn brown. Under similarly dry conditions, the respective starting material was dissolved in 12 ml of dry THF per mmol and the reaction was left to stir at room temperature for 3 h. Afterwards, the reaction mixture was diluted with 50 ml of EtOAc per mmol of starting material and washed two times with 10% $Na_2S_2O_4$ to remove the remaining I_2 and two times with brine. The organic layer was dried over $MgSO_4$ and after evaporation of the solvent under reduced pressure, the remaining oily residue was purified by flash column chromatography over silica (n-hexane/EtOAc 1:0 → 0:1). The product was obtained as a white solid.

*Nucleophilic substitution with 1-methylimidazole (**6a-6d**, **16**)*

In a heated Schlenk flask under N_2 atmosphere, 1 eq of the respective starting material was dissolved in 15 ml of dry THF per mmol. 1.3 eq of 1-methylimidazole were added and the reaction mixture was heated to 50 °C and stirred for 72 h. The solvent was removed under reduced pressure and the remaining residue was purified by flash column chromatography over silica (DCM/MeOH 1:0 → 9:1). The product was obtained as a yellowish, foamy solid.

*Synthesis of [M(COD)(NHC)Cl] complexes (**17-20**, **23-24**)*

In a heated Schlenk flask under N_2 atmosphere, 1 eq of the respective imidazolium salt was dissolved in 5 ml of dry DCM (in case of ligands **6b, 6d, 8** and **16**) or dry ACN (in case of peptides **22a** and **22b**). The solution was degassed by three consecutive cycles of freeze-pump-thaw. After addition of 0.5 eq of freshly prepared Ag_2O the solution was left to stir at room temperature for 1 h in the dark, during which disappearance of the black Ag_2O could be seen, followed by addition of 0.5 eq of $[M(COD)Cl]_2$ (M=Ir or Rh) leading to a color change to bright yellow. The solution was then left to stir over night at room temperature. Afterwards the reaction mixture was filtered through Celite (DCM/MeOH 9:1) and the filtrate was concentrated under reduced pressure. Purification of the product was carried out by flash column chromatography over silica (n-hexane/EtOAc 0:1→1:0) yielding a bright yellow oily residue, which was taken up

in as little EtOAc as possible and precipitated from n-hexane to yield the products as bright yellow solids.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

We kindly acknowledge the work of our in-depth student Philipp Mathes who worked on the synthesis of complex **20**, and of Martin Gartmann, who helped recording the NMR spectra of all of the new metal-containing compounds.

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Rhodium(I) and Iridium(I) N-Heterocyclic Carbene Complexes of Imidazolium-functionalized Amino Acids and Peptides

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Highlights

- Synthesis of new imidazolium functionalized non-natural amino acids
- Use of imidazolium functionalized non-natural amino acids in SPPS
- Amino acid and peptide conjugation of iridium(I) and rhodium(I) NHC complexes
- Atachment of iridium(I) and rhodium(I) to amino acids and peptides through direct side chain coordination of imidazolium functionalized amino acids

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Keywords: Bioorganometallic Chemistry, Iridium, Metal Peptide Bioconjugates, Non-natural amino acids, N-heterocyclic carbene complexes, Rhodium

Declaration of Interest statement

The authors declare no conflicting interests.