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Optically Active (Peptido-carbene)palladium Complexes: Towards True Solid-Phase Combinatorial Libraries of Transition Metal Catalysts

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This work explores the potential of forming transition metal catalysts by combinatorial solid-phase peptide chemistry to produce catalysts with enzyme-like properties of stereoselectivity, regioselectivity and even substrate selectivity. A series of new functionalised carbene precursors/donors – imidazolium salts – each containing both amino acid and carboxylic acid functionality was synthesised in solution. The readily accessible carbene precursors were incorporated within the backbones of peptides attached to PEGA resin, by standard solid-phase peptide coupling techniques. The synthetic strategy gave easy access to both mono- and didentate ligand systems, providing folded structures around the central transition metal atoms, with different degrees of steric congestion and bite angles. Changing the number of incorporated amino acids between the two carbene donors facilitated variation of the properties of the complexes. Both ligand systems were complexed to palladium(II) by standard base treatment, and the Pd complexes were studied by mass spectrometry and NMR spectroscopy. The monodentate (carbene)palladium complexes were each the product of enolisation of a neighbouring carbonyl group and loss of a proton, followed by coordination of the oxy anion to the palladium atom. The established methods are suitable for the combinatorial synthesis of palladium catalysts on solid support.

Introduction

The development of polymer-bound organometallic complexes for homogeneous catalysis of organic reactions has progressed significantly in recent years.[1] The major contributions have been based on solid-supported phosphanes, which form complexes with the transition metals.[1] Only little attention has been paid to N-heterocyclic carbenes on solid supports, even though carbenes are emerging as an important family of ligands with electronic characteristics similar to those of the phosphanes.[2,3] However, the metal–carbon bonds in the carbene complexes have been shown to be much stronger than the metal–phosphorus bonds in common phosphane complexes, thus reducing the problems associated with weak ligand–metal interactions, which cause deposition of metal residues or metal leaching from the supported complex.[2,4]

Application of N-heterocyclic carbenes in catalysis can be traced back to two important events. Öfele and Wanzlick prepared the first examples of (N-heterocyclic carbene)-metal complexes.[5] Later and importantly, Arduengo and co-workers reported the synthesis of a stable free carbene,[6] which turned out to be an important feature for the development of new synthesis methods that facilitated applications of carbenes and their metal complexes in a broad variety of catalytic transformations, including cross-coupling,[7] olefin metathesis,[8,9] hydrosilylation,[10] telomerisation,[11] hydrogenation,[12] ethylene/CO copolymerisation[13] and ring-opening polymerisation.[14]

The efficiency of a given catalytic system depends crucially on subtle interplay between the metal atom and its coordinated ligand(s). Steric, geometric and electronic ligand parameters are important, but not easily predicted factors, especially in enantioselective catalysis. Therefore, the process of stepwise variation and selection is still commonly used in the discovery and optimisation of new catalysts.[15] With respect to the chiral carbene ligands and their metal complexes, both mono- and didentate chelate systems have been prepared by several groups.[2,16] At present, there are reports on solid-supported peptide-based chiral mono- and didentate N-heterocyclic carbene complexes, particularly because solid-phase synthesis of this type should facilitate combinatorial chemistry and give access to a diverse set of transition metal ligands. The well-developed nature of peptide chemistry and the great structural variety and functional diversity displayed by the amino acids provide a powerful tool for generating diverse on-bead libraries for the search for highly active and selective catalysts. So far, only a few research groups have applied peptides as transition metal ligands or as backbones for other attached ligand donors. Gilbertson,[17] Hoveyda[18] and Christensen[19] demonstrated that phosphane-containing peptides could be

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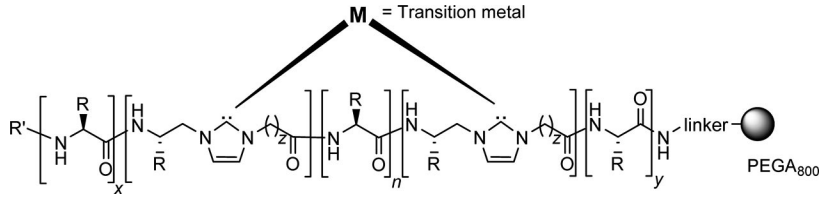


Figure 1. Schematic representation of the peptide-based carbene ligand system. Parameters *n*, *x*, *y* and *z* are variable.

applied effectively as ligands for transition-metal-catalysed (palladium and copper) asymmetric synthesis while the catalyst was still attached to the polymer. Recently, Adolfsson used dipeptide-derived ligands for ruthenium-catalysed enantioselective transfer hydrogenation.[20]

Inspired by these contributions, we now report the first solid-phase synthesis of carbene ligands and their palladium complexes with peptide backbones as chiral architectures. With a suitable carbene precursor containing the necessary functional groups for incorporation into the peptide chain, the combinatorial synthesis of carbene ligands is feasible.[21] The combinatorial strategy enables the generation of structurally diverse binding sites and allows the synthesis of monodentate, didentate and possibly polydentate ligands with a variety of different bite angles. In a didentate system, the bite angle itself may be varied by variation of the type (α-, β- and γ-) and number of amino acids incorporated between the ligand binding sites in the peptide chain, as outlined in Figure 1. The two flanking regions may similarly be optimised for substrate interaction by variation in length, constitution and stereochemistry.

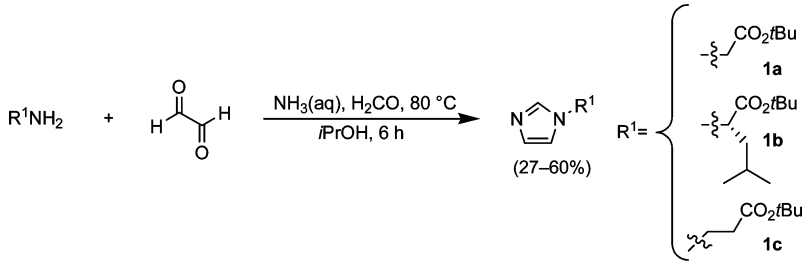
Results and Discussion

Preparation of Chiral Imidazolium Building Blocks as Precursors for N-Heterocyclic Carbenes

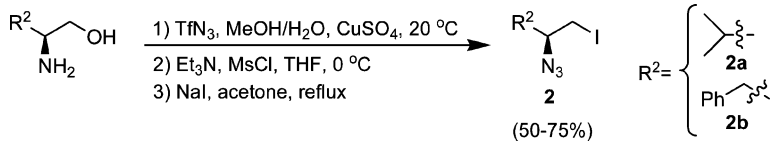
In previous studies it has been shown that imidazolium ions can be generated by several efficient methods, involving either one or several steps, depending on the requirement for the nature of *N*-substituents.[2] In this work we sought for a synthetic method that would give access to unsymmetrical *N*-substituted imidazolium ions each containing a masked/protected amino and acid functionality. Such carbene precursor building blocks would be well suited for standard solid-phase peptide chemistry. From the available *tert*-butyl esters of different amino acids, three amino-acid-derived imidazoles were synthesised in a modified one-pot Arduengo condensation,[22,23] in which the amino acid ester, glyoxal, formaldehyde and aqueous ammonia reacted to generate the *N*-substituted imidazole ring as outlined in Scheme 1.

The halide precursors for alkylation of the imidazoles to provide imidazolium ions were synthesised in two steps from commercially available amino alcohols as depicted in Scheme 2. The amino groups were protected as azides, and the alcohols were subsequently converted into the iodides via the mesylates with sodium iodide in acceptable yields and in agreement with previous synthesis of analogues.[24,25]

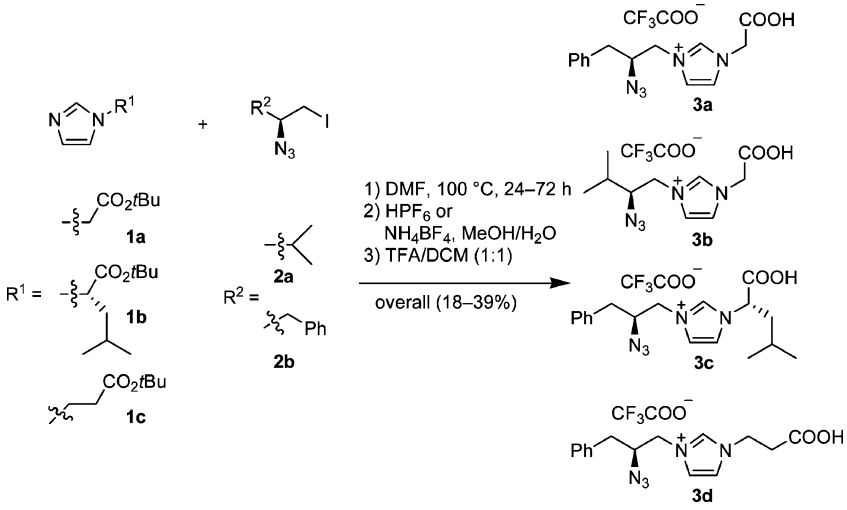
The imidazoles and alkyl iodides were employed in the synthesis of four different imidazolium salts as shown in Scheme 3. S_N2 iodide displacements in compounds **2** by the imidazoles **1** generated the imidazolium iodides in moderate yields (40–42%) after purification on silica gel. Before hydrolysis of the *tert*-butyl ester, iodide (I^-) was ion-exchanged either with hexafluorophosphate (PF_6^-) or with tetrafluoroborate (BF_4^-), which in our hands generated imidazolium salts more stable toward the subsequent TFA treatment, which completed the synthesis in good yields. MS analysis of the final compounds revealed that hexafluorophosphate



Scheme 1. Functionalised imidazole synthesis by a four-component condensation.



Scheme 2. 2-Azidoalkyl iodides synthesised from amino alcohols.



Scheme 3. Synthesis of imidazolium trifluoroacetate **3**.

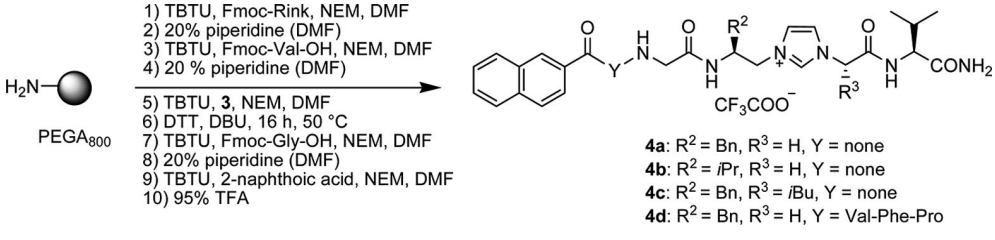
and tetrafluoroborate ions were exchanged during TFA treatment, thereby generating the corresponding imidazolium trifluoroacetates in acceptable yields.

Solid-Phase Synthesis and Characterisation of (Carbene)-palladium Complexes

In order to investigate the potential of the new imidazolium ion building blocks for the preparation of more elaborate carbene ligands for palladium complexation, both monodentate and didentate ligands with different distances between the two carbene donors were synthesised. The structural variation should provide a means of control of the bite angle.[26] Starting from amino-functionalised PEGA resin,[27] the acid-labile Fmoc-protected Rink amide linker was attached by the standard TBTU activation procedure,[28] followed by Fmoc cleavage effected with piperidine/DMF and another TBTU coupling of Fmoc-Val-OH. After Fmoc cleavage, each of the four different imidazolium ions **3** was attached to the PEGA-Rink-Val-NH_2 resin by activation with TBTU. Subsequently, the azide was reduced by treatment with a DMF solution of dithiothreitol (DTT, 0.25 M) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, 2 equiv.). The free amine was subjected to TBTU coupling,[29] followed by one additional cycle of Fmoc cleavage/TBTU coupling to afford four different resin-bound imidazolium ions as outlined in Scheme 4. The products were released from the resin with aqueous TFA (95%). ESMS revealed that trifluoroacetate was the counterion to the cationic imidazolium ion. However, when the synthesis was performed on a photolabile linker[30] instead of the Rink amide linker, it was possible to isolate the tetrafluoroborate (BF_4^-) salt.

Further analysis of the leucine-derived imidazolium ion **4c**, with a stereogenic centre in the α-position to the imidazolium ring and the carbonyl group, revealed, not surprisingly, that the product had racemised.

With the resin-bound imidazolium ions to hand, the carbene formation and complexation to palladium(II) was investigated directly on resin. Each imidazolium salt was treated with the base 2-(*tert*-butylimino)-2-(diethylamino)-1,3-dimethylperhydro-1,3,2-diazaphosphorine (BEMP) to deprotonate the imidazolium ion and to give the corresponding N-heterocyclic carbene, which was subsequently trapped with $PdCl_2COD$.[31] However, as revealed by HRMS (ESI) analysis of the palladium complex formed under these reaction conditions, a β-enolate oxygen atom was coordinated to the palladium atom in addition to the carbene coordination. This enolate was generated during the base treatment. The optimised reaction conditions afforded clean conversions of compounds **4** to **5**. According to HRMS (ESI), however, it was difficult to obtain quantita-



Scheme 4. Solid-phase synthesis of resin-bound peptides each containing one imidazolium ion.

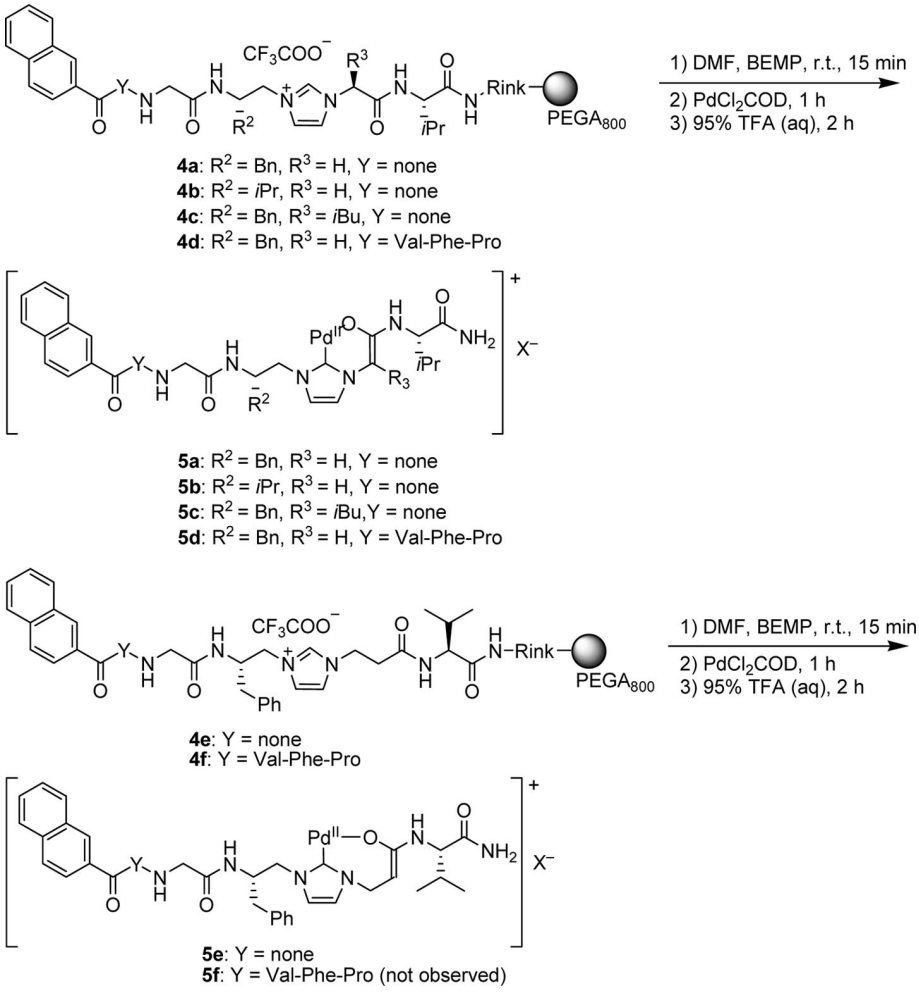
tive conversion, and conversion was further reduced with increased peptide chain length after the imidazolium ion (e.g., in **4d**). During initial experiments it had been observed that no complex formation took place with commonly used bases such as DBU and *t*BuOK.[32,33] Only a few examples of anionic ligands derived from carbenes are known,[34] but recent results from Waymouth et al.[35] demonstrated a preference for N-heterocyclic carbene enolate complexation when a carbonyl group is positioned β to the carbene donor, enabling the formation of very stable six-membered chelates. No decomposition of these complexes could be observed by MS (ESI) even after three months in a TFA buffer (0.1% aq.).

Chelate formation with enolates in similar systems could be avoided by formation of the (carbene)silver complexes and transmetallation with the appropriate palladium salts.[36,37] While this reaction works well with Ag_2O in solution reactions, experiments showed that the insoluble Ag_2O did not function with resin swollen in DCM.

Subjection of imidazolium ion **4e** to the same reaction conditions as described above resulted in some carbene enolate complexation, thereby generating the less favoured seven-membered chelate **5e**. However, MS analysis of the product mixture containing **5e** clearly demonstrated that this complex was less favoured than the six-membered chelates (**5a**–**5d**; Scheme 5). This was further substantiated by unsuccessful attempts to transform compound **4f** into **5f**.

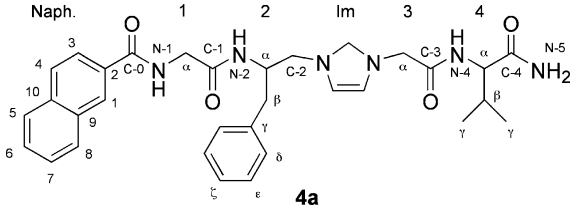
The imidazolium ion **4a** and the corresponding Pd-complexed chelate **5a** were studied by 1D and 2D NMR spectroscopy, and their chemical shifts, shown in Table 1, were structurally assigned to the two compounds. While the spectra of **4a** yielded sharp and well defined resonances, the spectra of **5a** showed a higher degree of line broadening, particularly of those protons in the vicinity of the palladium atom. Full interpretation of the NMR data could still be achieved, however, and both these and the HRMS data were in agreement with the structure **5a**.

Another, simpler way to generate (carbene)palladium complexes is through direct reactions between palladium(II) acetate and the imidazolium ions in the absence of base.[38] By this method, the resin-bound Fmoc-protected imidazolium ion **6** was treated with $Pd(OAc)_2$ at 75 °C in a solvent mixture of DMSO and THF for 2 h, as outlined in Scheme 6. After TFA cleavage from the resin, the structure



Scheme 5. Synthesis of N-heterocyclic carbene enolate palladium(II) complexes **5a**–**5e**.

Table 1. NMR spectroscopic data for compounds **4a** and **5a**.



4a

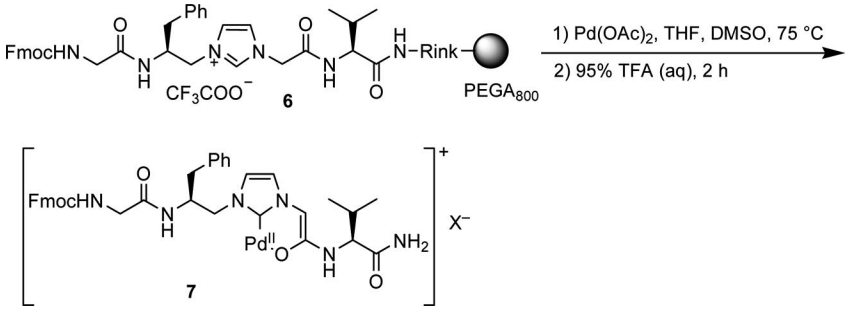
	Uncomplexed ligand **4a**		Pd-complexed ligand **5a**	
	^{1}H	^{13}C	^{1}H	^{13}C
Naph. C-1	8.498	127.5	8.529	127.6
Naph. C-2		130.8		131.1
Naph. C-3	7.979	124.0	7.998	124.0
Naph. C-4	8.015	127.6	7.982	127.4
Naph. C-5	7.997	127.4	7.980	127.4
Naph. C-6	7.633	127.5	7.633	127.5
Naph. C-7	7.615	126.6	7.615	126.6
Naph. C-8	8.028	128.6	8.015	128.6
Naph. C-9		131.9		132.0
Naph. C-10		134.0		134.0
C-0		166.6		166.6
N-1	8.935		8.909	
C-1$^\alpha$	3.775	42.7	3.795	42.6
	3.705		3.760	
C-1		168.9		168.6
N-2	8.013		7.977	
C-2$^\alpha$	4.362	50.2	4.475	51.9
C-2$^\beta$	2.887	36.7	2.889	37.8
	2.754		2.830	
C-2$^\gamma$		137.3		137.7
C-2$^\delta$	7.248	128.9	7.230	128.8
C-2$^\varepsilon$	7.288	128.0	7.245	128.0
C-2$^\zeta$	7.214	126.2	7.193	126.1
C-2	4.447	51.7	3.990	51.1
	4.252		3.827	
Im	8.971	137.6	–	–
Im	7.746	122.1	7.495	122.4
Im	7.698	123.4	7.381	122.7
C-3$^\alpha$	5.199	50.4	4.914	54.6
	5.097			
C-3		164.7		–
N-4	8.554		8.793	
C-4$^\alpha$	4.198	57.5	4.834	68.3
C-4$^\beta$	2.022	30.3	1.989	30.2
C-4$^{\gamma1}$	0.889	19.1	0.835	19.0
C-4$^{\gamma2}$	0.876	17.5	1.037	17.3
C-4		172.2		171.4
N-5	7.515		7.515	
	7.134		7.134	

of the formed complex **7** was determined and was found to be similar to the structures described above, with the formation of a six-membered chelate. On repetition of the reaction in solution, the same compound was obtained and characterised by ^{13}C NMR spectroscopy. According to MS (ESI), the solid-phase procedure forced the complexation to completion, although at the same time undesired precipitation of palladium black inside the PEGA beads was observed.

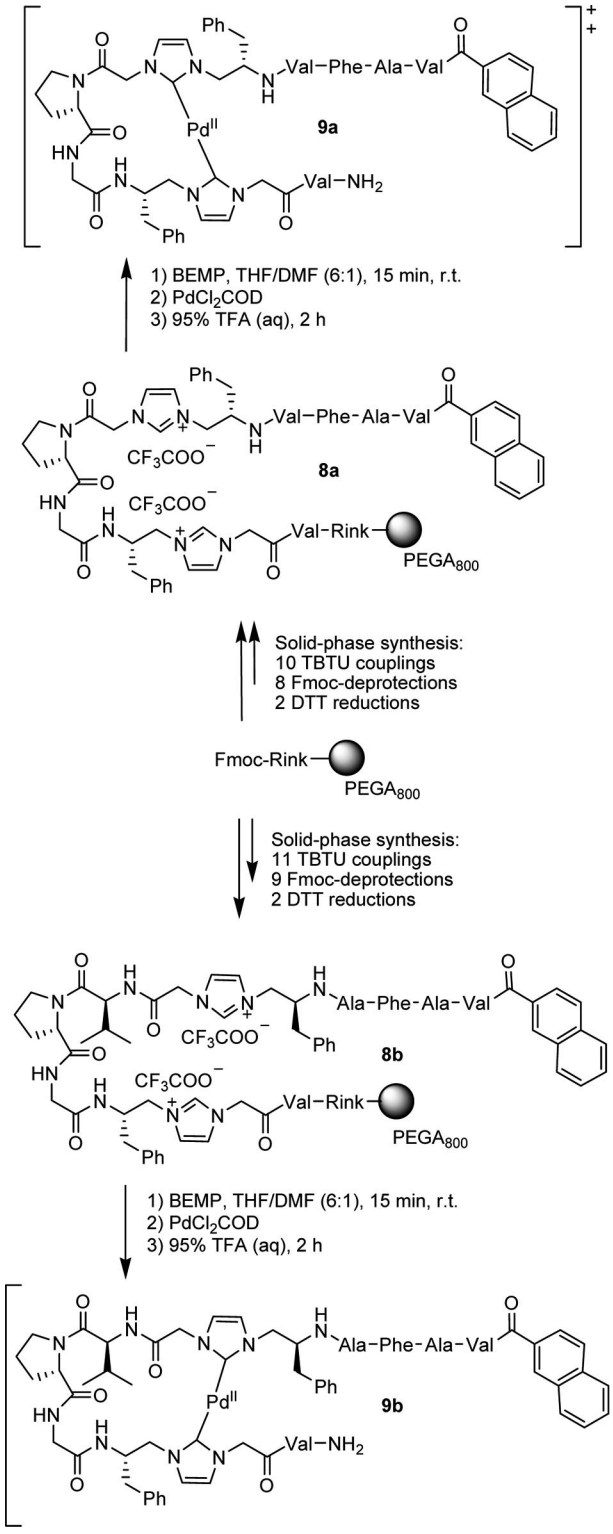
Palladium particles encapsulated inside the polymer are known to catalyze a range of less specific, unpredictable reactions, which is inconvenient when specific catalysts are prepared for use in solid-phase catalysis.[39] While the $Pd(OAc)_2$ procedure was useful for solution-phase synthesis of **7**, it was therefore not further employed in the synthesis of supported catalysts.

With these results to hand, the scope of the didentate ligand systems for complex formation was investigated. Three ligand precursors **8** for didentate complexation were synthesised in acceptable purity (>80%) by the TBTU coupling procedure as described in Schemes 7 and 8. The distance between the two imidazolium ions was modified by variation of the number (n = 2 or 3; see Figure 1) of amino acids between the carbenes. In two instances (**8a**, **8b**) proline was incorporated between the imidazolium ions, with the purpose of facilitating a β-turn, thereby spatially arranging the two donors for the complexation.[17a] In a mixture of THF and DMF as solvent, the didentate complexes were prepared by treatment with BEMP and $PdCl_2COD$. When DMF alone was used as solvent, approximately 30% of byproduct was formed, due to nucleophilic displacement α to the N1 atom of the imidazolium ion. After TFA cleavage, the palladium complexes could be characterised by electrospray ionisation HRMS in positive mode, showing clean ca. 80% conversions into **9a** and **9b**, respectively. Cleavage with 95% TFA showed that the complexes were acid-stable, and they could be stored for several months in a 0.1% TFA solution of water and acetonitrile. Only one palladium atom coordinated to each molecule, substantiating didentate complexation.

Finally, complexation with precursor **8c**, without a proline between the two potential donors, resulted in similar coordination of palladium(II) under the BEMP/$PdCl_2COD$

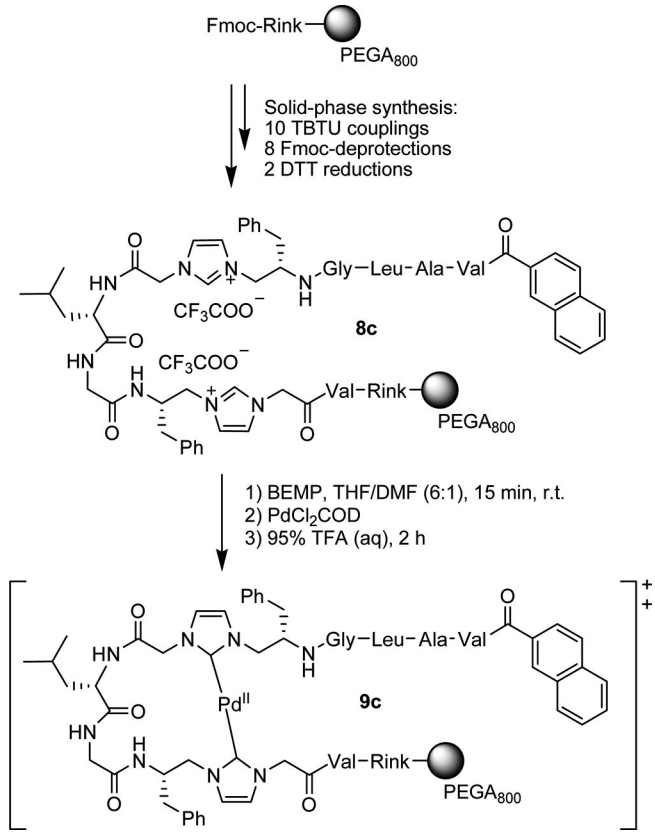


Scheme 6. Synthesis of a (carbene)palladium(II) complex with use of $Pd(OAc)_2$.



Scheme 7. Synthesis of (didentate carbene)palladium(II) complexes with induced turns in the peptides.

reaction conditions as shown in Scheme 8. Clearly, this result indicates that the strong effect of carbene coordination in the complex can force a turn in the flexible part of the peptide chain (n = 2), overcoming the loss in entropy upon complex formation.



Scheme 8. Synthesis of a (didentate carbene)palladium(II) complex without an induced turn.

Conclusions

We have succeeded in developing a new general synthetic procedure for highly functionalised imidazolium ion building blocks each containing both a masked amine (azide) and a carboxylic acid group. The readily available compounds, which serve as N-heterocyclic carbene precursors, were easily incorporated into peptide chains on solid phase, by standard peptide coupling chemistry. The developed strategy is well suited for combinatorial library synthesis. Nine different model compounds that provided the necessary structural variations for the first model studies of palladium(II) complexation were synthesised, and complexation was achieved on solid support. Palladium complexes of monodentate and didentate carbenes with different distances between the donors were generated by treatment with the strong base BEMP. The complexes formed were surprisingly stable towards air and moisture and could be characterised by mass spectrometry and by NMR spectroscopy. Currently, the combination of carbenes and phosphanes in the same peptide framework on PEG-based resins is being investigated for formation of combinatorial ligand libraries. The use of the resin-supported (carbene)palladium complexes in Suzuki reactions will be reported separately.

Experimental Section

General Remarks: All new compounds prepared in solution were characterised by ^{1}H and ^{13}C NMR (250 MHz, Bruker DRX 250 or 600 MHz, Bruker DRX 600), MS-ESI, and microanalysis or HRMS. New compounds prepared on $PEGA_{800}$ resins were cleaved off and characterised by HRMS electrospray (ESI) in positive mode with a Micromass QTOF instrument using a mixture of buffer (A) and buffer (B) (see below). MS (ESI) in negative mode was performed in a solvent mixture of water/acetonitrile (1:1) with a Bruker esquire3000plus mass spectrometer. Selected examples of carbene-peptides and precursors were fully characterised by ^{1}H NMR spectroscopy, and ^{13}C NMR spectroscopy was also employed. All solvents were of HPLC quality and were stored over molecular sieves or distilled from sodium before use (THF). For all reactions on solid support, PEGA800 resin (0.30–0.32 mmol g^{-1}, VersaMatrix A/S) was used. Prior to use, the resin was washed with methanol (6×), acetonitrile (6×), DMF (6×) and DCM (6×) and dried in vacuo overnight. All commercially available reagents were used as received without further purification. Analysis of solid-phase reactions was performed after cleavage of the products as their free amides from the resin. Analytical and preparative reversed-phase HPLC separations were performed with a Waters HPLC system using analytical chromolith speedrod RP-18E (50 × 4.6 mm) and delta PAK (25 × 200 mm) columns with flow rates of 5 and 10 cm^3 min^{-1}, respectively; detection ocurred at 215 nm with a multi-wavelength detector (Waters 490 E) for analytical purposes, and a photodiode array detector (Waters M991) was used for preparative separations. A solvent gradient system consisting of 0.1% TFA in water(A) and 0.1% TFA in acetonitrile/water (9:1) (B) was used.

***tert*-Butyl Imidazol-1-ylacetate (1a):** A solution of glyoxal (40% wt. solution in water, 17.30 g, 0.119 mol), formaldehyde (37% wt. solution in water, 9.70 g, 0.119 mol) and *i*PrOH (100 mL) was added dropwise at 20 °C to a stirred suspension of H-Gly-O*t*Bu·HCl (20.00 g, 0.119 mol), ammonia (25% wt. solution in water, 0.125 mol, 9.3 mL) and *i*PrOH (400 mL). After complete addition, the reaction mixture was heated to 80 °C and stirred for an additional 6 h. The final homogeneous and slightly yellow solution was cooled to 20 °C and diluted with DCM (300 mL). The organic layer was washed with NaOH (1.0 M, 300 mL) and dried (Na_2SO_4). Concentration in vacuo afforded a yellow oil. Purification by flash or VLC chromatography on silica gel (60H silica gel, 100% EtOAc) yielded *tert*-butyl imidazol-1-ylacetate (13.00 g, 60%) as a yellow solid. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.45 (dd, app [s], 1 H, CH), 7.05 (dd, app [s], 1 H, CH), 6.91 (dd, app [t], J = 1.2 Hz, 1 H, CH), 4.56 (s, 2 H, CH_2), 1.44 (s, 9 H, CH_3) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 166.39, 137.82, 129.41, 119.86, 83.13, 48.71, 27.84 ppm. HRMS (ESI): calcd. for $C_9H_{15}N_2O_2$ [M + H]$^+$ 183.1128; found 183.1134.

***tert*-Butyl (*S*)-2-(Imidazol-1-yl)-4-methylpentanoate (1b):** According to the procedure described above, the product was isolated as a light yellow oil, yield 25.00 g (58%). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.53 (br. s, 1 H, CH), 7.05 (br. s, 1 H, CH), 7.00 {dd, app [t], ^3J(H,H) = 1.2 Hz, 1 H, CH}, 4.62 [t, ^3J(H,H) = 7.9 Hz, 1 H, CH], 2.41–2.32 (m, 1 H, CH), 1.18 [dd, ^3J(H,H) = 7.9, ^3J(H,H) = 7.2 Hz, 2 H, CH_2], 1.42 (s, 9 H, CH_3), 0.92 [d, ^3J(H,H) = 4.1 Hz, 3 H, CH_3], 0.89 [d, ^3J(H,H) = 4.2 Hz, 3 H, CH_3] ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 169.11, 136.81, 129.29, 117.94, 82.75, 59.01, 41.49, 27.80, 24.52, 22.58, 21.52 ppm. HRMS (ESI): calcd. for $C_{13}H_{23}N_2O_2$ [M + H]$^+$ 239.1754; found 239.1757.

***tert*-Butyl Imidazol-1-ylpropionate (1c):** At 20 °C, a solution of glyoxal (40% wt. solution in water, 20.90 g, 0.144 mol), formaldehyde (37% wt. solution in water, 11.70 g, 0.144 mol) and *i*PrOH (100 mL) was added dropwise to a stirred suspension of H-β-Ala-O*t*Bu·HCl (25.00 g, 0.144 mol), ammonia (25% wt. solution in water, 0.144 mol, 10.7 mL) and *i*PrOH (250 mL). After complete addition, the reaction mixture was heated to 80 °C and stirred for an additional 6 h. The final homogeneous and slightly yellow solution was cooled to 20 °C and diluted with DCM (500 mL). The organic layer was washed with NaOH (1.0 M, 300 mL) and dried (Na_2SO_4). Concentration in vacuo afforded a yellow oil. Purification by kugelrohr distillation yielded *tert*-butyl imidazol-1-ylpropionate (7.20 g, 27%) as a yellow solid. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.49 (dd, app [br. s], 1 H, CH), 7.02 [dd, app [t], ^3J(H,H) = 1.3 Hz, 1 H, CH], 6.92 {dd, app [t], ^3J(H,H) = 1.3 Hz, 1 H, CH}, 4.21 [t, ^3J(H,H) = 6.6 Hz, 2 H, CH_2], 2.67 [t, ^3J(H,H) = 6.6 Hz, 2 H, CH_2], 1.41 (s, 9 H, CH_3) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 169.69, 137.17, 129.39, 118.82, 81.64, 42.50, 37.05, 28.05 ppm. HRMS (ESI): calcd. for $C_{10}H_{17}N_2O_2$ [M + H]$^+$ 197.1285; found 197.1293.

(*S*)-2-Azido-3-methylbutan-1-ol: TfN_3 was prepared as a DCM solution from NaN_3 and Tf_2O. (–)-L-Valinol (5.00 g, 0.049 mol) and $CuSO_4·H_2O$ (242 mg, 0.02 equiv.) were dissolved in H_2O (180 mL), and the pH was adjusted to 9–10 with K_2CO_3; MeOH (360 mL) and the crude TfN_3 in DCM (ca. 0.4 M, 1.5 equiv., 0.073 mol) was added, and the pH was readjusted to 9–10 with K_2CO_3. The two-phase system was stirred vigorously for 20 h. The layers were separated by addition of DCM, and the organic phase was washed with H_2O (2 × 200 mL). The combined aqueous phases were acidified with HCl (aq., 3 M) to pH ≈ 2. The aqueous phase was extracted with DCM (4 × 100 mL), and the combined organic phases were dried (Na_2SO_4), filtered and concentrated to 20 mL and purified directly by flash chromatography on silica gel (EtOAc/hexane, 1:9) to afford 2-azido-3-methylbutan-1-ol (5.16 g, 82%) as a slightly yellow oil. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 3.76 [dd, ^3J(H,H) = 3.5, ^3J(H,H) = 11.4 Hz, 1 H, CH], 3.60 [dd, ^3J(H,H) = 7.9, ^3J(H,H) = 11.4 Hz, 1 H, CH], 3.28 (m, 1 H, CH), 2.00 (br. s, 1 H, OH), 1.85 (m, 1 H, CH), [d, ^3J(H,H) = 6.8 Hz, 6 H, CH_3] ppm. ^{13}C NMR (62.9 MHz, CDCl3): δ = 70.71, 63.62, 29.84, 19.42, 18.47 ppm.

(*S*)-2-Azido-3-phenylpropan-1-ol: On application of the procedure described above to (–)-L-phenylalaninol (20.00 g, 0.132 mol), the reaction afforded (*S*)-2-azido-3-phenylpropan-1-ol (20.80 g, 89%) as a clear oil. ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 7.30–7.10 (m, 5 H), 3.60 (m, 2 H), 3.46 (m, 1 H), 2.76 (m, 2 H), 2.15 (s, 1 H) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 136.93, 129.17, 128.61, 126.84, 65.18, 64.32, 36.92 ppm.

(*S*)-2-Azido-1-iodo-3-methylbutane (2a): (*S*)-2-Azido-3-methylbutan-1-ol (5.06 g, 0.039 mol) and mesyl chloride (5.15 g, 1.15 equiv., 0.045 mol) were dissolved in THF (100 mL). The solution was cooled to 0 °C, before dropwise addition of triethylamine (5.14 g, 1.3 equiv., 0.051 mol). After complete addition, the reaction mixture was stirred at 0 °C for 1 h and then warmed to 20 °C. The precipitate was removed by filtration, and the residue was poured into water (40 mL) and DCM (100 mL). The organic layer was collected and dried (Na_2SO_4). Filtration and concentration in vacuo afforded the crude yellow mesylate as a yellow oil. The freshly prepared mesylate was dissolved in acetone (200 mL). NaI (17.50 g, 0.117 mol) was added in one portion, and the reaction mixture was heated to reflux. After 16 h at reflux, the reaction mixture was cooled to 20 °C, and the precipitate was removed by filtration. The solution was concentrated in vacuo to give a red oil. Further purifi-

cation by flash chromatography on silica gel (EtOAc/hexane, 1:18) yielded 2-azido-1-iodo-3-methylbutane (5.75 g, 61%) as a clear oil. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 3.30 (m, 2 H, CH_2), 1.95 (m, 1 H, CH), 0.99 [d, ^3J(H,H) = 5.9 Hz, 3 H, CH_3], 0.96 [d, ^3J(H,H) = 5.9 Hz, 3 H, CH_3] ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 69.35, 32.84, 19.46, 17.27, 6.82 ppm. $C_5H_{10}IN_3$ (239.06): calcd. C 25.12, H 4.22, N 17.58; found C 25.35, H 3.97, N 17.52.

(*S*)-(2-Azido-3-iodopropyl)benzene (2b): On application of the procedure described above to 2-azido-3-phenylpropan-1-ol (20.50 g, 0.116 mol), the reaction afforded (2-azido-3-iodopropyl)benzene (28.00 g, 84%) as a clear oil. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.44–7.24 (m, 5 H, CH), 3.70 {dt, app [q], ^3J(H,H) = 6.2 Hz, 1 H, CH}, 3.27 (m, 2 H, CH_2), 2.99 (m, 2 H, CH_2) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 136.24, 129.21, 128.69, 127.13, 63.43, 40.37, 7.99 ppm. $C_9H_{10}IN_3$ (287.10): calcd. C 37.65, H 3.51, N 14.64; found C 37.85, H 3.38, N 14.49.

1-[(*S*)-2-Azido-3-methylbutyl]-3-[(*tert*-butoxycarbonyl)methyl]-3*H*-imidazol-1-ium Iodide (Precursor to 3b): A solution of (*S*)-2-azido-1-iodo-3-methylbutane (5.65 g, 0.024 mol) and *tert*-butyl imidazol-1-ylacetate (4.30 g, 0.024 mol) in dry DMF (70 mL) was stirred at 100 °C for 72 h. The reaction mixture was concentrated in vacuo and purified by flash chromatography on silica gel [first 100% EtOAc, then EtOAc/acetone (1:1), and finally EtOAc/MeOH (9:1)] to yield 1-[(*S*)-2-azido-3-methylbutyl]-3-[(*tert*-butoxycarbonyl)-methyl]-3*H*-imidazol-1-ium iodide (3.95 g, 40%) as a red oil. ^{1}H NMR (250 MHz, [D$_6$]DMSO): δ = 9.22 {dd, app [t], ^3J(H,H) = 1.5 Hz, 1 H, CH}, 7.88 {dd, app [t], ^3J(H,H) = 1.6 Hz, 1 H, CH}, 7.80 {dd, app [t], ^3J(H,H) = 1.6 Hz, 1 H, CH}, 5.19 (s, 2 H, CH_2), 4.51 [dd, ^3J(H,H) = 3.6, ^3J(H,H) = 14.1 Hz, 1 H, CH], 4.29 [dd, ^3J(H,H) = 9.9, ^3J(H,H) = 14.1 Hz, 1 H, CH], 3.97 (m, 1 H, CH), 1.90 (m, 1 H, CH), 1.45 (s, 9 H, CH_3), 1.03 [d, ^3J(H,H) = 6.8 Hz, 3 H, CH_3], 0.97 [d, ^3J(H,H) = 6.8 Hz, 3 H, CH_3] ppm. ^{13}C NMR (62.9 MHz, DMSO): δ = 165.46, 137.84 (N^+=CN), 123.89, 122.36, 82.93, 66.80, 50.32, 50.07, 30.40, 27.51, 18.93, 17.27 ppm. HRMS (ESI): calcd. for $C_{14}H_{24}N_5O_2$ [M – I]$^+$ 294.1925; found 294.1916. MS (ESI): *m*/*z* = 127.4 [I]$^-$.

1-[(*S*)-2-Azido-3-phenylpropyl]-3-[(*tert*-butoxycarbonyl)methyl]-3*H*-imidazol-1-ium Iodide (Precursor to 3a): A solution of (*S*)-(2-azido-3-iodopropyl)benzene (8.00 g, 0.028 mol) and *tert*-butyl imidazol-1-ylacetate (5.08 g, 0.028 mol) in dry DMF (150 mL) was stirred at 100 °C for 72 h. The reaction mixture was concentrated in vacuo and purified by flash chromatography on silica gel [first 100% EtOAc, then EtOAc/acetone (1:1)] to yield 1-[(*S*)-2-azido-3-phenylpropyl]-3-[(*tert*-butoxycarbonyl)methyl]-3*H*-imidazol-1-ium iodide (5.56 g, 42%) as a red oil. ^{1}H NMR (250 MHz, [D$_6$]DMSO): δ = 9.24 {dd, app [t], ^3J(H,H) = 1.5 Hz, 1 H, CH}, 7.88 {dd, app [t], ^3J(H,H) = 1.6 Hz, 1 H, CH}, 7.80 {dd, app [t], ^3J(H,H) = 1.6 Hz, 1 H, CH}, 7.38–7.24 (m, 5 H, CH), 5.20 (s, 2 H, CH_2), 4.59 [dd, ^3J(H,H) = 2.2, ^3J(H,H) = 12.6 Hz, 1 H, CH], 4.40 (m, 1 H, CH), 4.34 (dd, app [m], overlap, 1 H, CH), 3.10 [dd, ^3J(H,H) = 3.6, ^3J(H,H) = 13.7 Hz, 1 H, CH], 2.74 [dd, ^3J(H,H) = 9.1, ^3J(H,H) = 13.7 Hz, 1 H, CH], 1.46 (s, 9 H, CH_3) ppm. ^{13}C NMR (62.9 MHz, [D$_6$]DMSO): δ = 165.48, 137.87 (N^+=CN), 136.44, 129.12, 128.49, 126.87, 123.82, 122.48, 120.81, 82.96, 62.16, 51.76, 50.32, 37.40, 27.51 ppm. HRMS (ESI): calcd. for $C_{18}H_{24}N_5O_2$ [M – I]$^+$ 342.1925; found 342.1912. MS (ESI): *m*/*z* = 126.9 [I]$^-$.

1-[(*S*)-2-Azido-3-methylbutyl]-3-(carboxymethyl)-3*H*-imidazol-1-ium Trifluoroacetate (3b): 1-(2-Azido-3-methylbutyl)-3-[(*tert*-butoxycarbonyl)methyl]-3*H*-imidazol-1-ium iodide (3.95 g, 9.38 mmol) was dissolved in MeOH (70 mL) and water (70 mL). At 20 °C the vigorously stirred solution was treated dropwise with HPF_6 (60% wt solution in water, 10 equiv., 0.094 mol, 22.90 g). After 1 h of stirring, the reaction mixture was diluted with DCM (300 mL). The organic layer was isolated and concentrated in vacuo and then treated with DCM (10 mL) and trifluoroacetic acid (10 mL). After 1 h of stirring at 20 °C, the reaction mixture was concentrated in vacuo. The crude product was dissolved in DCM (50 mL) and then concentrated in vacuo. This cycle was repeated three more times to give 1-(2-azido-3-methylbutyl)-3-(carboxymethyl)-3*H*-imidazol-1-ium trifluoroacetate (**3b**, 2.90 g, 88%) as a pure red oil. ^{1}H NMR (250 MHz, [D$_6$]DMSO): δ = 9.20 (dd, app [s], 1 H, CH), 7.85 {dd, app [t], ^3J(H,H) = 1.6 Hz, 1 H, CH}, 7.79 {dd, app [t], ^3J(H,H) = 1.6 Hz, 1 H, CH}, 5.17 (s, 2 H, CH_2), 4.49 [dd, ^3J(H,H) = 3.5, ^3J(H,H) = 14.1 Hz, 1 H, CH], 4.28 [dd, ^3J(H,H) = 9.9, ^3J(H,H) = 14.1 Hz, 1 H, CH], 3.95 (m, 1 H, CH), 1.90 (m, 1 H, CH), 1.03 [d, ^3J(H,H) = 6.6 Hz, 3 H, CH_3], 0.97 [d, ^3J(H,H) = 6.7 Hz, 3 H, CH_3] ppm. ^{13}C NMR (62.9 MHz, DMSO): δ = 167.91, 137.83 (N^+=CN), 123.96, 122.32, 66.94, 50.33, 49.72, 30.44, 18.95, 17.23 ppm. HRMS (ESI): calcd. for $C_{10}H_{16}N_5O_2$ [M – CF_3COO^-]$^+$ 238.1299; found 238.1301. MS (ESI): calcd. for $C_{12}H_{15}F_3N_5O_4$ [M – H]$^-$ 350.1; found 350.0.

1-[(*S*)-2-Azido-3-phenylpropyl]-3-(carboxymethyl)-3*H*-imidazol-1-ium Trifluoroacetate (3a): On application of the procedure described above to 1-(2-azido-3-phenylpropyl)-3-[(*tert*-butoxycarbonyl)methyl]-3*H*-imidazol-1-ium iodide (5.56 g, 11.85 mmol), the reaction afforded 1-(2-azido-3-phenylpropyl)-3-(carboxymethyl)-3*H*-imidazol-1-ium trifluoroacetate (**3a**, 4.10 g, 87%) as a red oil. ^{1}H NMR (250 MHz, [D$_6$]DMSO): δ = 9.20 (dd, app [s], 1 H, CH), 7.83 {dd, app [t], ^3J(H,H) = 1.6 Hz, 1 H, CH}, 7.78 {dd, app [t], ^3J(H,H) = 1.6 Hz, 1 H, CH}, 7.40–7.24 (m, 5 H, CH), 5.16 (s, 2 H, CH_2), 4.53 [dd, ^3J(H,H) = 2, ^3J(H,H) = 12 Hz, 1 H, CH], 4.36 (m, 1 H, CH), 4.30 (dd, app [m], overlap, 1 H, CH), 3.05 [dd, ^3J(H,H) = 3.6, ^3J(H,H) = 13.0 Hz, 1 H, CH], 2.74 [dd, ^3J(H,H) = 8.9, ^3J(H,H) = 13.9 Hz, 1 H, CH], 1.46 (s, 9 H, CH_3) ppm. ^{13}C NMR (62.9 MHz, [D$_6$]DMSO): δ = 167.94, 137.85 (N^+=CN), 136.57, 129.28, 128.60, 126.97, 123.92, 122.37, 62.29, 51.81, 50.36, 37.45 ppm. HRMS (ESI): calcd. for $C_{14}H_{16}N_5O_2$ [M – CF_3COO^-]$^+$ 286.1299; found 286.1322. MS (ESI): calcd. for $C_{16}H_{15}F_3N_5O_4$ [M – H]$^-$ 398.1; found 398.8.

1-[(*S*)-2-Azido-3-phenylpropyl]-3-(2-carboxyethyl)-3*H*-imidazol-1-ium Trifluoroacetate (3d): A solution of (*S*)-(2-azido-3-iodopropyl)-benzene (1.46 g, 5.1 mmol) and *tert*-butyl imidazol-1-ylpropionate (1.00 g, 5.1 mmol) in dry DMF (15 mL) was stirred at 105 °C for 24 h. The reaction mixture was concentrated in vacuo and purified by flash chromatography on silica gel [first 100% EtOAc, then EtOAc/acetone (1:1), then 10% MeOH in EtOAc]. Subsequently, the crude red oil was dissolved in MeOH (40 mL) and water (20 mL). At 20 °C the vigorously stirred solution was treated dropwise with HPF_6 (60% wt solution in water, ca. 10 equiv., 7.5 mL). After 1 h of stirring, the reaction mixture was diluted with DCM (100 mL). The organic layer was isolated, and the water phase was extracted with DCM (2 × 50 mL). The combined DCM phases were dried (Na_2SO_4), filtered, and concentrated in vacuo and were then treated with DCM (10 mL) and TFA (10 mL). After 1 h of stirring at 20 °C, the reaction mixture was concentrated in vacuo. The crude product was dissolved in DCM (50 mL) and then again concentrated in vacuo. This cycle was repeated three more times to give 1-(2-azido-3-methylbutyl)-3-(2-carboxyethyl)-3*H*-imidazol-1-ium trifluoroacetate (**3d**, 0.84 g, 39%) as a red oil. This sample was used without further purification for solid-phase synthesis (see below). A sample for further analysis was purified by prep. HPLC (reverse phase, acetonitrile/H_2O, 0.1% TFA). ^{1}H NMR (250 MHz, [D$_6$]DMSO): δ = 9.25 {dd, app [br. t], ^3J(H,H) < 1 Hz, 1 H, CH}, 7.84 {dd, app [t], ^3J(H,H) = 1.5 Hz, 1 H, CH}, 7.82 {dd, app [t],

^3J(H,H) = 1.5 Hz, 1 H, CH}, 7.41–7.25 (m, 5 H, CH), 4.52–4.18 (m, 5 H, CH, CH_2), 3.04 [dd, ^3J(H,H) = 3.9, ^3J(H,H) = 14.0 Hz, 1 H, CH], 2.92 [t, ^3J(H,H) = 6.6 Hz, 2 H, CH_2], 2.76 [dd, ^3J(H,H) = 9.1, ^3J(H,H) = 14.0 Hz, 1 H, CH] ppm. ^{13}C NMR (62.9 MHz, [D_6]-DMSO): δ = 171.55, 137.17 (N^+=CN), 136.45, 129.19, 128.51, 126.89, 122.82, 122.53, 62.11, 51.71, 44.84, 37.29, 33.58 ppm. HRMS (ESI): calcd. for $C_{15}H_{18}N_5O_2$ [M – CF_3COO^-]$^+$ 300.1455; found 300.1452. MS (ESI): calcd. for $C_{19}H_{18}F_6N_5O_6$ [M + CF_3COO^-]$^-$ 526.1; found 525.9.

1-[(*S*)-2-Azido-3-phenylpropyl]-3-[(*S*)-1-carboxy-3-methylbutyl]-3*H*-imidazol-1-ium Trifluoroacetate (3c): A solution of (2-azido-3-iodopropyl)benzene (2.40 g, 8.4 mmol) and *tert*-butyl (*S*)-2-(imidazol-1-yl)-4-methylpentanoate (2.00 g, 8.4 mmol) in dry DMF (20 mL) was stirred at 100 °C for 72 h. The reaction mixture was concentrated in vacuo and purified by flash chromatography on silica gel [first 100% EtOAc, then EtOAc/acetone (1:1), then 10% MeOH in EtOAc]. Subsequently, the crude red oil (1.90 g) was dissolved in MeOH (60 mL) and water (20 mL). The stirred solution was then treated with NH_4BF_4 (1.54 g, 14.7 mmol) in one portion. The final reaction mixture was stirred at 20 °C for 1 h and then diluted with DCM (100 mL). The organic phase was isolated and dried (Na_2SO_4), filtered, and concentrated in vacuo. DCM (10 mL) and trifluoroacetic acid (10 mL) were added to the *tert*-butyl ester and, after 1 h of stirring at 20 °C, the reaction mixture was concentrated in vacuo. The crude product was dissolved in DCM (50 mL) and then concentrated in vacuo. This cycle was repeated three more times to finally give 1-[(*S*)-2-azido-3-phenylpropyl]-3-[(*S*)-1-carboxy-3-methylbutyl]-3*H*-imidazol-1-ium trifluoroacetate (**3d**, 0.68 g, 18%) as a red oil. ^{1}H NMR (250 MHz, [D_6]DMSO): δ = 9.42 [t, ^3J(H,H) < 1 Hz, 1 H, CH], 7.96 [t, ^3J(H,H) < 1 Hz, 1 H, CH], 7.87 [t, ^3J(H,H) < 1 Hz, 1 H, CH], 7.43–7.23 (m, 5 H, CH), 5.31 [dd, ^3J(H,H) = 4.2, ^3J(H,H) = 11.1 Hz, 1 H, CH], 4.54 [dd, ^3J(H,H) = 3.0, ^3J(H,H) = 13.4 Hz, 1 H, CH], 4.40 (m, 1 H, CH), 4.25 (m, 1 H, CH), 3.05 [dd, ^3J(H,H) = 4.0, ^3J(H,H) = 13.9 Hz, 1 H, CH], 2.72 [dd, ^3J(H,H) = 9.1, ^3J(H,H) = 13.9 Hz, 1 H, CH], 2.12 (m, 1 H, CH), 1.95 (m, 1 H, CH), 1.26 (m, 1 H, CH), 0.89 [d, ^3J(H,H) = 6.7 Hz, 3 H, CH_3], 0.84 [d, ^3J(H,H) = 6.6 Hz, 3 H, CH_3] ppm. ^{13}C NMR (62.9 MHz, [D_6]DMSO): δ = 169.90, 137.22, 137.18, 136.42, 129.20, 128.52, 126.90, 122.66, 122.51, 122.46, 62.26, 60.36, 52.01, 37.40, 24.29, 22.36, 20.72, 20.65 ppm. HRMS (ESI): calcd. for $C_{18}H_{24}N_5O_2$ [M – CF_3COO^-]$^+$ 342.1925; found 342.1906. MS (ESI): calcd. for $C_{20}H_{23}N_5O_4$ [M – H]$^-$ 454.2; found 454.2.

Solid-Phase Synthesis

General Procedure for Monodentate Carbene Precursors. (Fmoc-Gly-{1-[(*S*)-2-amino-3-phenylpropyl]-3-(2-oxoethyl)-3*H*-imidazol-1-ium}-Val-NH_2)$^+$(CF_3COO)$^-$ (6): Attachment of the 4-[(2,4-dimethoxyphenyl)(Fmoc-amino)methyl]phenoxyacetic acid (Fmoc-Rink amide linker) to the amino-functionalised resin ($PEGA_{800}$) was carried out by the standard amino acid coupling procedure (Fmoc-AA-OH, TBTU, NEM, DMF). The Rink amide linker (3.0 equiv.), *N*-ethylmorpholine (NEM, 4.0 equiv.) and *N*-[(1*H*-benzotriazol-1-yl)(dimethylamino)methylene]-*N*-methylmethanaminium tetrafluoroborate *N*-oxide (TBTU, 2.88 equiv.) were mixed in DMF and allowed to react for 5 min. The reaction mixture was added to a preswollen $PEGA_{800}$ resin to give a volume of 1.5× the resin volume and allowed to react for 2 h, followed by washing with DMF (5×) and DCM (5×). The Fmoc protecting group was subsequently removed by double addition (2 and 18 min) of 20% piperidine in DMF. The first Fmoc-protected amino acid, Fmoc-Val-OH, was coupled to the Rink amide functionalised PEGA resin by the standard procedure described above. After washing with DMF (5×) and DCM (5×), the Fmoc group was removed by repeated addition of 20% piperidine in DMF as described above. 1-[(*S*)-2-Azido-3-phenylpropyl]-3-(carboxymethyl)-3*H*-imidazol-1-ium trifluoroacetate (**3a**) was subsequently coupled to the resin by the standard TBTU procedure. After the standard washing procedure, the resin was lyophilised. The azido group on the resin was reduced to an amino group by swelling of the resin in a DMF solution of dithiothreitol (DTT, 0.25 M) and subsequent addition of DBU (1,8-diazabicyclo[5.4.0]undec-7-ene, 2 equiv.). After 16 h at 50 °C, the resin was cooled to 20 °C and washed with DMF (6×) and DCM (6×). The free amino group was coupled with Fmoc-Gly-OH according to the standard coupling procedure. The final product was released from the resin by treatment with 95% TFA (aq.) (2 h). After purification by preparative HPLC, compound **6** was obtained as a white powder. ^{1}H NMR (250 MHz, [D_6]DMSO): δ = 8.98 (s, 1 H, CH), 8.54 [d, ^3J(H,H) = 8.9 Hz, 1 H, CH], 8.05 [d, ^3J(H,H) = 8.0 Hz, 1 H, CH], 7.90 {2 d, app [d], ^3J(H,H) = 7.3 Hz, 2 H, Fmoc aryl, CH_2}, 7.75–7.65 (m, 4 H, CH), 7.58–7.10 (m, 12 H, CH), 5.07 (br. s, 2 H, CH_2), 4.50–4.08 (m, 7 H, CH, CH_2), 3.45 (m, 2 H, CH_2), 2.87 [dd, ^3J(H,H) = 3.4, ^3J(H,H) = 13.7 Hz, 1 H, CH], 2.74 [dd, ^3J(H,H) = 8.6, ^3J(H,H) = 13.7 Hz, 1 H, CH], 2.00 (m, 1 H, CH), 0.84 (s, 6 H, CH_3) ppm. ^{13}C NMR (62.9 MHz, [D_6] DMSO): δ = 172.21, 169.11, 164.89, 164.71, 156.41, 143.69, 143.63, 140.59, 137.63, 137.34 (N^+=CN), 136.53, 128.92 (2 C), 128.13 (2 C), 127.51 (2 C), 126.92 (2 C), 126.26, 125.10, 123.42, 122.22, 119.98, 119.07, 65.61, 57.60, 51.58, 50.44, 50.23, 46.48, 43.27, 36.81, 30.39, 19.09, 17.56 ppm. HRMS (ESI): calcd. for $C_{36}H_{41}N_6O_5$ [M – CF_3COO^-]$^+$ 637.3133; found 637.3153. MS (ESI): calcd. for $C_{40}H_{41}F_6N_6O_9$ [M + CF_3COO^-]$^-$ 863.3; found 863.0.

The following monocarbene precursors were synthesised according to the peptide synthesis procedure described above. The compounds were finally capped with 2-naphthoic acid according to the standard TBTU coupling procedure.

(2-Naphthylcarbonyl-Gly-{1-[(*S*)-2-amino-3-phenylpropyl]-3-(2-oxoethyl)-3*H*-imidazol-1-ium}-Val-NH_2)$^+$(CF_3COO)$^-$ (4a): Crude purity ca. 85% after TFA cleavage, purity >95% after prep. HPLC; 21.0 mg (38%) was obtained from 350 mg of $PEGA_{800}$ resin (loading = 0.231 mmol/g resin). ^{1}H NMR ([D_6]DMSO, 600 MHz): δ = 8.97 (s, 1 H, CH), 8.94 [t, ^3J(H,H) = 6.0 Hz, 1 H, CH], 8.55 [d, ^3J(H,H) = 8.7 Hz, 1 H, CH], 8.50 (s, 1 H, CH), 8.04–7.97 (m, 5 H, CH), 7.75 (s, 1 H, CH), 7.70 (s, 1 H, CH), 7.65–7.60 (m, 2 H, CH), 7.51 (s, 1 H, CH), 7.31–7.19 (m, 5 H, CH), 7.11 (s, 1 H, CH), 5.21 [d, ^3J(H,H) = 16.3 Hz, 1 H, CH], 5.11 [d, ^3J(H,H) = 16.3 Hz, 1 H, CH], 4.45 [dd, ^3J(H,H) = 3.8, ^3J(H,H) = 13.7 Hz, 1 H, CH], 4.37 (m, 1 H, CH), 4.27 [dd, ^3J(H,H) = 9.1, ^3J(H,H) = 13.5 Hz, 1 H, CH], 4.20 [dd, ^3J(H,H) = 6.1, ^3J(H,H) = 8.7 Hz, 1 H, CH], 3.79 [dd, ^3J(H,H) = 5.7, ^3J(H,H) = 16.3 Hz, 1 H, CH], 3.72 [dd, ^3J(H,H) = 5.7, ^3J = 16.3 Hz, 1 H, CH], 2.89 [dd, ^3J(H,H) = 4.0, ^3J(H,H) = 13.9 Hz, 1 H, CH], 2.76 [dd, ^3J(H,H) = 9.4, ^3J(H,H) = 13.5 Hz, 1 H, CH], 2.04 (m, 1 H, CH), 0.88 {2 d, app [t], ^3J(H,H) = 6.3 Hz, 6 H, CH_3} ppm. ^{13}C NMR (150.9 MHz, [D_6]DMSO): δ = 172.23, 168.95 166.64, 164.71, 137.58, 137.32, 134.02, 131.94, 130.82, 128.91, 128.57, 128.03, 127.64, 127.53, 127.40, 126.64, 126.18, 124.03, 123.43, 122.07, 57.45, 51.67, 50.44, 50.21, 42.68, 36.65, 30.30, 19.08, 17.53 ppm. HRMS (ESI): calcd. for $C_{32}H_{37}N_6O_4$ [M – CF_3COO^-]$^+$ 569.2876; found 569.2875. MS (ESI): calcd. for $C_{36}H_{37}F_6N_6O_8$ [M + CF_3COO^-]$^-$ 795.3; found 795.2.

(2-Naphthylcarbonyl-Gly-{1-[(*S*)-2-amino-3-methylbutyl]-3-(2-oxoethyl)-3*H*-imidazol-1-ium}-Val-NH_2)$^+$(CF_3COO)$^-$ (4b): Crude purity ca. 80% after TFA cleavage. HRMS (ESI): calcd. for $C_{28}H_{37}N_6O_4$ [M – CF_3COO^-]$^+$ 521.2876; found 521.2878. MS

(ESI): calcd. for $C_{32}H_{37}F_6N_6O_8$ [M + CF_3COO^-]$^-$ 747.3; found 747.0.

(2-Naphthylcarbonyl-Gly-{1-[(*S*)-2-amino-3-phenylpropyl]-3-(1-formyl-3-methylbutyl)-3*H*-imidazol-1-ium}-Val-NH_2)$^+$(CF_3COO)$^-$ (4c): Crude purity ca. 90% after TFA cleavage. Product HPLC: t_R = 4.93 min. HRMS (ESI): calcd. for $C_{36}H_{45}N_6O_4$ [M – CF_3COO^-]$^+$ 625.3502; found 625.3502. MS (ESI): calcd. for $C_{40}H_{45}F_6N_6O_8$ [M + CF_3COO^-]$^-$ 851.3; found 851.1.

(2-Naphthylcarbonyl-Val-Phe-Pro-Gly-{1-[(*S*)-2-amino-3-phenylpropyl]-3-(2-oxoethyl)-3*H*-imidazol-1-ium}-Val-NH_2)$^+$(CF_3COO)$^-$ (4d): Crude purity >95% after TFA cleavage. HRMS (ESI): calcd. for $C_{51}H_{62}N_9O_7$ [M – CF_3COO^-]$^+$ 912.4767; found 912.4750. MS (ESI): calcd. for $C_{55}H_{62}F_6N_9O_{11}$ [M + CF_3COO^-]$^-$ 1138.4; found 1138.3.

(2-Naphthylcarbonyl-Gly-{1-[(*S*)-2-amino-3-phenylpropyl]-3-(3-oxopropyl)-3*H*-imidazol-1-ium}Val-NH_2)$^+$(CF_3COO)$^-$ (4e): Crude purity ca. 80% after TFA cleavage. HRMS (ESI): calcd. for $C_{33}H_{39}N_6O_4$ [M – CF_3COO^-]$^+$ 583.3033; found 583.3037. MS (ESI): calcd. for $C_{37}H_{39}F_6N_6O_8$ [M + CF_3COO^-]$^-$ 809.3; found 809.2.

(2-Naphthylcarbonyl-Val-Phe-Pro-Gly-{1-[(*S*)-2-amino-3-phenylpropyl]-3-(3-oxopropyl)-3*H*-imidazol-1-ium}-Val-NH_2)$^+$(CF_3COO)$^-$ (4f): Crude purity ca. 90% after TFA cleavage. HRMS (ESI): calcd. for $C_{52}H_{64}N_9O_7$ [M – CF_3COO^-]$^+$ 926.4929; found 926.4902. MS (ESI): calcd. for $C_{56}H_{64}F_6N_9O_{11}$ [M + CF_3COO^-]$^-$ 1152.5; found 1152.4.

Synthesis of Didentate Carbene Precursors

(2-Naphthylcarbonyl-Val-Ala-Phe-Val-{1-[(*S*)-2-amino-3-phenylpropyl]-3-(2-oxoethyl)-3*H*-imidazol-1-ium}-Pro-Gly-{1-[(*S*)-2-amino-3-phenylpropyl]-3-(2-oxoethyl)-3*H*-imidazol-1-ium}-Val-NH_2)$^{2+}$-2(CF_3COO)$^-$ (8a): After repetition of the procedure for the Fmoc-Gly-OH coupling described above (compound **6**), the free amino group was obtained by double treatment with 20% piperidine in DMF (2 and 18 min). The free amino group was coupled to Fmoc-Pro-OH by the standard coupling procedure. Usual washing and subsequent Fmoc removal with 20% piperidine in DMF were carried out. 1-(2-Azido-3-phenylpropyl)-3-(carboxymethyl)-3*H*-imidazol-1-ium trifluoroacetate (**3a**) was treated with the free amino group by the standard coupling procedure. The azido group on the resin was reduced to the amino group by swelling of the resin in a DMF solution of dithiothreitol (DTT, 0.25 M) and subsequent addition of DBU (1,8-diazabicyclo[5.4.0]undec-7-ene, 2 equiv.). After 16 h at 50 °C, the resin was cooled to 20 °C and washed with DMF (6×) and DCM (6×). Four Fmoc amino acids (Fmoc-Val-OH, Fmoc-Phe-OH, Fmoc-Ala-OH, Fmoc-Val-OH) were subsequently coupled to the resin according to the standard TBTU coupling and deprotection (piperidine) procedure. The last amino acid was (Fmoc-) deprotected and capped with 2-naphthoic acid by the standard TBTU coupling procedure. The final product was released from the resin by treatment with 95% TFA (aq) (2 h). Crude purity ca. 80%. Purity >95% after prep. HPLC; 16.6 mg (26%) was obtained from 360 mg of $PEGA_{800}$ resin (loading = 0.194 mmol/g resin). ^{1}H NMR (600 MHz, [D$_6$]DMSO): δ = 8.92 (s, 1 H, N$^+$CHN), 8.90 (s, 1 H, N$^+$CHN), 8.67 [d, ^3J(H,H) = 6.5 Hz, 1 H, CH], 8.59 (s, 1 H, CH), 8.51 [d, ^3J(H,H) = 8.8 Hz, 1 H, CH], 8.47 [d, ^3J(H,H) = 5.7 Hz, 1 H, CH], 8.26 [t, ^3J(H,H) = 5.9 Hz, 1 H, CH], 8.04–7.96 (m, 6 H, CH_3), 7.87 [d, ^3J(H,H) = 7.3 Hz, 1 H, CH], 7.72–7.53 (m, 7 H, CH), 7.54 (br. s, 1 H, NH), 7.48 (br. s, 1 H, NH), 7.29–7.07 (m, 15 H, CH, NH), 5.26 (s, 2 H, CH_2), 5.10 [d, ^3J(H,H) = 16.5 Hz, 1 H, CH], 5.02 [d, ^3J(H,H) = 16.5 Hz, 1 H, CH], 4.48 (m, 1 H, CH), 4.40 (m, 3 H, CH, CH_2), 4.27 (m, 4 H, CH_2), 4.16 [dd, ^3J(H,H) = 6.1, ^3J(H,H) = 18.6 Hz, 1 H, CH], 4.05 (m, 1 H, CH), 3.70–3.52 (m, 5 H, CH, CH_2), 3.50 (m, 2 H, CH_2), 3.40 [dd, ^3J(H,H) = 5.6, ^3J(H,H) = 16.5 Hz, 1 H, CH], 3.04 [dd, ^3J(H,H) = 4.8, ^3J(H,H) = 14.3 Hz, 1 H, CH], 2.96–2.84 (m, 2 H, CH_2), 2.74 (m, 2 H, CH_2), 2.47 (m, 1 H, CH), 2.22 (m, 1 H, CH), 2.10 (m, 1 H, CH), 2.00 (m, 3 H, CH, CH_2), 1.94 (m, 1 H, CH), 1.86 (m, 1 H, CH), 1.82–1.72 (m, 2 H, CH), 1.19 [d, ^3J(H,H) = 7.1 Hz, 3 H, CH_3], 1.04 [d, ^3J(H,H) = 6.7 Hz, 3 H, CH_3], 0.99 [d, ^3J(H,H) = 6.7 Hz, 3 H, CH_3], 0.88 [d, ^3J(H,H) = 7.1 Hz, 3 H, CH_3], 0.86 [d, ^3J(H,H) = 7.2 Hz, 3 H, CH_3], 0.73 [d, ^3J(H,H) = 6.7 Hz, 3 H, CH_3], 0.46 [d, ^3J(H,H) = 6.5 Hz, 3 H, CH_3] ppm. ^{13}C NMR (150.9 MHz, [D$_6$]DMSO): δ = 173.28, 172.21, 171.94, 171.35, 171.33, 170.51, 168.56, 167.67, 164.78, 164.34, 158.52, 158.28, 158.04, 157.78, 137.30, 137.23 (N$^+$=CN), 137.12 (N$^+$=CN), 134.17, 131.92, 131.11, 129.03, 128.87, 128.74, 128.68, 128.14, 128.05, 128.02, 127.95, 127.92, 127.88, 127.69, 127.65, 127.54, 126.70, 126.30, 126.26, 126.22, 124.37, 123.63, 123.47, 122.24, 122.17, 116.44, 114.51, 69.67, 60.65, 60.45, 57.72, 54.76, 52.06, 50.49, 50.31, 50.22, 49.47, 46.27, 41.83, 37.13, 36.94, 36.54, 30.37, 29.58, 29.52, 29.23, 24.05, 19.26, 19.12 (2 C), 18.73, 18.34, 17.62, 17.26 ppm. HRMS (ESI): calcd. for $C_{73}H_{92}N_{14}O_{10}$ [M – 2 CF_3COO^-]$^{2+}$/2 662.3558; found 662.3549. MS (ESI): calcd. for $C_{79}H_{92}F_9N_{14}O_{16}$ [M + CF_3COO^-]$^-$ 1663.7; found 1663.4.

(2-Naphthylcarbonyl-Val-Ala-Phe-Ala-{1-[(*S*)-2-amino-3-phenylpropyl]-3-(2-oxoethyl)-3*H*-imidazol-1-ium}-Val-Pro-Gly-{1-[(*S*)-2-amino-3-phenylpropyl]-3-(2-oxoethyl)-3*H*-imidazol-1-ium}-Val-NH_2)$^{2+}$2(CF_3COO)$^-$ (8b): Crude purity ca. 80% after TFA cleavage. Purity >95% after prep. HPLC; 27.3 mg (26%) was obtained from 360 mg of $PEGA_{800}$ resin (loading = 0.191 mmol/g resin). ^{1}H NMR (600 MHz, [D$_6$]DMSO): δ = 8.98 (s, 1 H, N$^+$CHN), 8.96 (s, 1 H, N$^+$CHN), 8.76 [d, ^3J(H,H) = 8.3 Hz, 1 H, CH], 8.61 [d, ^3J(H,H) = 7.1 Hz, 1 H, CH], 8.57 (s, 1 H, CH), 8.55 [d, ^3J(H,H) = 9.0 Hz, 1 H, CH], 8.40 [d, ^3J(H,H) = 5.9 Hz, 1 H, CH], 8.20 [t, ^3J(H,H) = 5.9 Hz, 1 H, CH], 8.03 [d, ^3J(H,H) = 7.5 Hz, 1 H, CH], 7.99 (m, 3 H, CH), 7.90 [d, ^3J(H,H) = 6.9 Hz, 1 H, CH], 7.86 [d, ^3J(H,H) = 7.40 Hz, 1 H, CH], 7.75–7.47 (m, 10 H, CH), 7.30–7.05 (m, 15 H, CH), 5.20–5.00 (m, 5 H, CH, CH_2), 4.48 (m, 2 H, CH), 4.41 (m, 2 H, CH), 4.27 (m, 3 H, CH, CH_2), 4.16 (m, 2 H, CH), 3.92 (m, 1 H, CH), 3.75 (m, 1 H, CH), 3.69 [dd, ^3J(H,H) = 6.3, ^3J(H,H) = 16.6 Hz, 1 H, CH], 3.62 (m, 1 H, CH), 3.50 (m, 1 H, CH), 3.40 [dd, ^3J(H,H) = 4.5, ^3J(H,H) = 16.3 Hz, 1 H, CH], 3.03 [dd, ^3J(H,H) = 4.5, ^3J(H,H) = 14.5 Hz, 1 H, CH], 2.91 (m, 2 H, CH_2), 2.84 [dd, ^3J(H,H) = 4.6, ^3J(H,H) = 13.9 Hz, 1 H, CH], 2.77 [dd, ^3J(H,H) = 9.4, ^3J(H,H) = 13.7 Hz, 1 H, CH], 2.68 [dd, ^3J(H,H) = 9.0, ^3J(H,H) = 13.6 Hz, 1 H, CH], 2.20 (m, 1 H, CH), 2.10–1.93 (m, 3 H, CH, CH_2), 1.80 (m, 2 H, CH), 1.20 [d, ^3J(H,H) = 7.3 Hz, 3 H, CH_3], 1.02 [d, ^3J(H,H) = 5.4 Hz, 3 H, CH_3], 1.01 [d, ^3J(H,H) = 5.4 Hz, 3 H, CH_3], 0.97 [d, ^3J(H,H) = 6.9 Hz, 3 H, CH_3], 0.94 [d, ^3J(H,H) = 6.7 Hz, 3 H, CH_3], 0.91 [d, ^3J(H,H) = 6.4 Hz, 3 H, CH_3], 0.88 [d, ^3J(H,H) = 6.9 Hz, 3 H, CH_3], 0.88 [d, ^3J(H,H) = 6.4 Hz, 3 H, CH_3] ppm. ^{13}C NMR (150.9 MHz, [D$_6$]DMSO): δ = 173.31, 172.22, 171.99, 172.90, 171.79, 172.10, 170.02, 168.66, 167.40, 164.92, 164.77, 158.32, 158.09, 156.64, 137.70, 137.24, 137.23 2 × (N$^+$=CN), 134.16, 131.95, 131.21, 129.10, 128.97, 128.93, 128.77, 128.70, 128.10, 128.07, 128.00, 127.91, 127.89, 127.88, 127.66, 127.52, 126.65, 126.30, 126.25, 126.22, 126.21, 124.42, 123.56, 122.28, 122.05, 116.49, 114.55, 69.67, 60.23, 59.96, 57.81, 56.21, 54.64, 52.04, 52.00, 51.95, 50.52, 50.34, 50.33, 50.18, 49.31, 49.09, 47.40, 42.08, 37.41, 37.17, 36.55, 36.46, 30.35, 30.23, 29.67, 28.99, 19.12, 18.70, 18.47, 17.63, 17.21 ppm. HRMS (ESI): calcd. for $C_{76}H_{97}N_{15}O_{11}$ [M – 2 CF_3COO^-]$^{2+}$/2 697.8746; found 697.8742. MS (ESI): calcd. for $C_{82}H_{97}F_9N_{15}O_{17}$ [M + CF_3COO^-]$^-$ 1734.7; found 1735.5.

(2-Naphthylcarbonyl-Val-Ala-Leu-Gly-{1-[(*S*)-2-amino-3-phenylpropyl]-3-(2-oxoethyl)-3*H*-imidazol-1-ium}-Leu-Gly-{1-[(*S*)-2-amino-3-phenylpropyl]-3-(2-oxoethyl)-3*H*-imidazol-1-ium}-Val-NH_2)$^{2+}$2(CF_3COO)$^-$ (8c): Crude purity ca. 70% after TFA cleavage. HRMS (ESI): calcd. for $C_{68}H_{92}N_{14}O_{10}$ [M – 2 CF_3COO^-]$^{2+}$/2 632.3561; found 632.3555; [M + CF_3COO^-]$^-$ not observed.

General Procedure for On-Resin Synthesis of (*N*-Heterocyclic carbene enolato)palladium Complexes. [(2-Naphthylcarbonyl-Gly-{1-[(*S*)-2-amino-3-phenylpropyl]-3-(eth-1-en-2-olato)-3*H*-imidazolin-2-ylidene}-Val-NH_2)palladium(II)]$^+$(CF_3COO)$^-$ (5a): 2-(*tert*-Butylimino)-2-(diethylamino)-1,3-dimethylperhydro-1,3,2-diazaphosphorin (BEMP, 2.5 equiv., 33.0 μL, 0.115 mmol) was added at 20 °C into a dry (under argon) Schlenk flask containing a shaken mixture of swollen resin **4a** (200 mg, 0.046 mmol) and DMF (5.0 mL). After complete addition, the reaction mixture was shaken for 15 min and then treated with $PdCl_2COD$ (1.5 equiv., 19.7 mg, 0.069 mmol) in one portion. The final yellow reaction mixture was shaken for 1 h and filtered. The resin was purified by the usual washing procedure with DMF (5 × 2 mL) and DCM (5 × 2 mL). The final complex (**5a**) was cleaved from the resin by treatment with TFA (aq., 95%) (2 h) and concentrated in vacuo. Purification by HPLC and lyophilisation yielded the title compound as a white solid. Yield: 12.0 mg (33%). NMR spectroscopic data are given in Table 1. HRMS (ESI): calcd. for $C_{32}H_{35}N_6O_4Pd$ [M – CF_3COO^-]$^+$ 673.1755; found 673.1762.

[(2-Naphthylcarbonyl-Gly-{1-[(*S*)-2-amino-3-methylbutyl]-3-(eth-1-en-2-olato)-3*H*-imidazolin-2-ylidene}-Val-NH_2)palladium(II)]$^+$(CF_3COO)$^-$ (5b): The final complex **5b** was cleaved from the resin (20.0 mg) by treatment with TFA (aq., 95%) (2 h). The solution of the complex was concentrated in vacuo and directly analyzed by HRMS (ESI) as the crude product. HRMS (ESI): calcd. for $C_{28}H_{35}N_6O_4Pd$ [M – CF_3COO^-]$^+$ 625.1755; found 625.1760.

[(2-Naphthylcarbonyl-Gly-{1-[(*S*)-2-amino-3-phenylpropyl]-3-(2-methylpent-4-en-5-olato)-3*H*-imidazolin-2-ylidene}-Val-NH_2)palladium(II)]$^+$(CF_3COO)$^-$ (5c): The final complex **5c** was cleaved from the resin (20.0 mg) by treatment with TFA (aq., 95%) (2 h). The solution of the complex was concentrated in vacuo and directly analyzed by HRMS (ESI) as the crude product. HRMS (ESI): calcd. for $C_{36}H_{43}N_6O_4Pd$ [M – CF_3COO^-]$^+$ 729.2381; found 729.2377.

[(2-Naphthylcarbonyl-Val-Phe-Pro-Gly-{1-[(*S*)-2-amino-3-phenylpropyl]-3-(eth-1-en-2-olato)-3*H*-imidazolin-2-ylidene}-Val-NH_2)-palladium]$^+$(CF_3COO)$^-$ (5d): The final complex **5d** was cleaved from the resin (20.0 mg) by treatment with 95% TFA (aq) (2 h). The solution of the complex was concentration in vacuo and directly analyzed by HRMS (ESI) as the crude product. HRMS (ESI): calcd. for $C_{51}H_{60}N_9O_7Pd$ [M – CF_3COO^-]$^+$ 1016.3645; found 1016.3695.

[(2-Naphthylcarbonyl-Gly-{1-[(*S*)-2-amino-3-phenylpropyl]-3-(2-ethen-3-olato)-3*H*-imidazolin-2-ylidene}-Val-NH_2)palladium(II)]$^+$(CF_3COO)$^-$ (5e): The final complex **5e** was obtained from the resin (20.0 mg) by treatment with TFA (95%, aq.) (2 h). The solution of the complex was concentrated in vacuo and directly analyzed by HRMS (ESI) as the crude product. HRMS (ESI): calcd. for $C_{33}H_{37}N_6O_4Pd$ [M – CF_3COO^-]$^+$ 687.1911; found 687.1884.

General Procedure for the Synthesis of Palladium Complexes with $Pd(OAc)_2$. a) On Solid Phase. [(Fmoc-NH-Gly-{1-[(*S*)-2-amino-3-phenylpropyl]-3-(eth-1-en-2-olato)-3*H*-imidazolin-2-ylidene}-Val-NH_2)palladium(II)]$^+$(CF_3COO)$^-$ (7): $Pd(OAc)_2$ (5.0 equiv., 5.1 mg) was added in air into a vial containing swollen resin **6** (20.0 mg, 0.229 mmol/g resin), THF (2 mL) and DMSO (0.25 mL). The final reaction mixture was heated to 75 °C for 4 h and then cooled to 20 °C. The final complex **7** was obtained from the resin by treatment with TFA (aq., 95%) (2 h). The solution of the complex was concentrated in vacuo and directly analysed by MS (ESI) as the crude product. MS (ESI): calcd. for $C_{36}H_{39}N_6O_5Pd$ [M – CF_3COO^-]$^+$ 741.2; found 741.2. **b) In Solution. [(Fmoc-NH-Gly-{1-[(*S*)-2-amino-3-phenylpropyl]-3-(eth-1-en-2-olato)-3*H*-imidazolin-2-ylidene}-Val-NH_2)palladium(II)]$^+$(CF_3COO)$^-$ (7):** A dry 100 mL Schlenk tube was charged under argon with imidazolium salt **6** (35.0 mg, 0.045 mmol), a solvent mixture of THF (4 mL)/DMSO (0.5 mL) and finally $Pd(OAc)_2$ (1.5 equiv., 15.1 mg). The final reaction mixture was heated to 80 °C and stirred for 16 h, followed by concentration in vacuo to afford a brown oil. The crude product was purified by prep. HPLC (0.1% aq. TFA/acetonitrile) to yield **7** (17.0 mg) as a brown solid. ^{1}H NMR (250 MHz, [D_6]DMSO): δ = 7.95–7.04 (m, 20 H, CH), 7.93 (s, 1 H, CH), 4.40–3.40 (m, 12 H, CH, CH_2), 0.80 (m, 6 H, CH_3) ppm. ^{13}C NMR (150.9 MHz, [D_6]-DMSO): δ = 185.67 (NCN), 168.95, 167.84, 165.03, 157.90, 156.40, 145.10, 143.70, 140.62, 137.50, 135.80, 128.93 (2 C), 128.15, 127.51, 127.01, 126.95 (2 C), 126.64, 126.26, 125.20, 122.34, 122.07, 120.00, 119.70, 69.66, 65.65, 63.66, 54.40, 49.98, 46.52, 43.25, 37.06, 33.64, 19.15, 17.73 ppm. HRMS (ESI): calcd. for $C_{36}H_{39}N_6O_5Pd$ [M – CF_3COO^-]$^+$ 741.2017; found 741.2015.

General Procedure for the Synthesis of Bis(N-heterocyclic carbene)-palladium Complexes with Base on Resin. [(2-Naphthylcarbonyl-Val-Ala-Phe-Val-{1-[(*S*)-2-amino-3-phenylpropyl]-3-(2-oxoethyl)-3*H*-imidazol-1-ium}-Pro-Gly-{1-[(*S*)-2-amino-3-phenylpropyl]-3-(2-oxoethyl)-3*H*-imidazol-1-ium}-Val-NH_2)palladium(II)]$^{2+}$($2CF_3COO$)$^{2-}$ (9a): A dry 10 mL Schlenk tube was charged under argon with resin-bound bis(imidazolium) salt **8a** (20 mg, loading = 0.191 mmol/g resin, 0.004 mmol), a solvent mixture of THF (1 mL)/DMF (0.16 mL) and finally BEMP (2.5 equiv., 2.7 mg). The mixture was deprotonated by shaking for 15 min and then treated with $PdCl_2COD$ (1.5 equiv., 1.6 mg) in one portion. After an additional 1 h of shaking at 20 °C, the resin was filtered and washed with DMF (5 × 1 mL) and DCM (5 × 1 mL). The final complex **9a** was obtained from the resin by treatment with TFA (95%, aq.) (2 h). The solution of the complex was concentrated in vacuo and directly analysed by HRMS (ESI) as the crude product. HRMS (ESI): calcd. for $C_{73}H_{90}N_{14}O_{10}Pd$ [Pd^{II}M – 2 CF_3COO^-]$^{2+}$/2 714.3000; found 714.3004.

[(2-Naphthylcarbonyl-Val-Ala-Phe-Ala-{1-[(*S*)-2-amino-3-phenylpropyl]-3-(2-oxoethyl)-3*H*-imidazol-1-ium}-Val-Pro-Gly-{1-[(*S*)-2-amino-3-phenylpropyl]-3-(2-oxoethyl)-3*H*-imidazol-1-ium}-Val-NH_2)-palladium(II)]$^{2+}$($2CF_3COO$)$^{2-}$ (9b): The final complex **9b** was cleaved from the resin by treatment with TFA (aq., 95%) (2 h). The solution of the complex was concentrated in vacuo and directly analyzed by HRMS (ESI) as the crude product. HRMS (ESI): calcd. for $C_{82}H_{95}N_{15}O_{17}Pd$ [Pd^{II}M – 2 CF_3COO^-]$^{2+}$/2 749.8185; found 749.8193.

[(2-Naphthylcarbonyl-Val-Ala-Leu-Gly-{1-(2-amino-3-phenylpropyl)-3-(2-oxoethyl)-3*H*-imidazol-1-ium}-Leu-Gly-{1-(2-amino-3-phenylpropyl)-3-(2-oxoethyl)-3*H*-imidazol-1-ium}-Val-NH_2)palladium(II)]$^{2+}$($2CF_3COO$)$^{2-}$ (9c): The final complex **9c** was cleaved from the resin by treatment with TFA (aq., 95%) (2 h). The solution of the complex was concentrated in vacuo and directly analyzed by HRMS (ESI) as the crude product. HRMS (ESI): calcd. for $C_{68}H_{90}N_{14}O_{10}Pd$ [Pd^{II}M – 2 CF_3COO^-]$^{2+}$/2 684.3000; found 684.2997.

Supporting Information (see footnote on the first page of this article): NMR spectra for the synthesised compounds, RP-HPLC chromatograms and ESI-HRMS spectra for selected compounds.

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