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Green Catalysts: Solid-Phase Peptide Carbene Ligands in Aqueous Transition-Metal Catalysis

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A series of functionalized imidazolium ions containing a pyridine moiety and carboxylic acid functionality has been synthesized in solution. These compounds serve as *N*-heterocyclic carbene precursors and were attached to a dipeptide on solid support by means of standard peptide coupling techniques. Treatment with base generated the corresponding carbenes, which were directly complexed to palladium(II) and subsequently studied by mass spectrometry and NMR spectroscopy. The supported monocarbene catalyst **7** was successfully applied in Sonogashira and Suzuki cross-coupling reactions, and the cross-coupling products were isolated in excellent yield. Bis(carbene) catalyst **8** was successfully applied in solution in high-yielding Suzuki cross-coupling reactions. Furthermore, the catalysts proved to be stable in aqueous media, which allowed the Suzuki cross-coupling reactions to be performed in water. No loss of catalytic activity was observed when supported catalyst **7** was recycled and subjected to repetitive cycles of Suzuki cross-coupling reactions in water.

Introduction

N-Heterocyclic carbenes (NHCs) have attracted increasing attention since their emergence in the pioneering work of Öfele and Wanzlick[1] and, subsequently, in the work of Arduengo et al. on the isolation of a stable free carbene.[2] Since then, NHCs have proven to be a versatile and efficient class of ligands. They are easily synthesized, and the steric bulk on the two nitrogens neighbouring the carbene–carbon bond is easily modified. NHCs are often used as phosphane mimics, but the carbenes are stronger σ-donor ligands and, thus, provide a stronger metal binding site, which reduces the tendency of metal dissociation.[3] Phosphane ligands may suffer from degradation by phosphorus–carbon bond cleavage during catalysis, which requires the presence of an excess amount of ligand in the reaction.[4] Furthermore, phosphane complexes are water- and air-sensitive, a disadvantage not shared by NHCs. Metal complexes of mono- and polydentate NHCs have found widespread catalytic application in a number of reactions such as cross-coupling,[5] olefin metathesis,[6] hydrogenation,[7] hydroformylation,[8] hydrosilylation,[9] and olefin polymerization.[10,11] Further developments in this area have led to the generation of chelate carbenes, a class of ligands where neighbouring heteroatom donor functionalities take part in the metal binding. In particular, neighbouring *N*-heterocycles such as pyridine have attracted attention, and promising results have been obtained when they were applied in cross-coupling reactions.[12,13] In recent years, the development of polymer-supported ligands has improved significantly.[14] The majority of these ligands are phosphanes, but a few examples of polymer-supported palladium-NHC catalysts have also been reported.[15] When a catalyst is immobilized on solid support, a number of advantages can be gained such as easy recovery from reaction mixtures, no metal contamination of reaction solutions, easy handling of minute catalyst amount, and catalyst recycling. In addition, a combinatorial approach to catalyst design and optimization can be applied if catalysts are attached to a solid support. We have recently reported the first example of solid-phase-immobilized, peptide-based NHC ligands and their complexation to palladium.[16] Here we wish to extend the concept and report the synthesis of new solid-supported pyridine-NHC catalysts and their application in cross-coupling reactions.

Results and Discussion

Imidazolium ions can be generated by several methods comprising either one or several steps, depending on the requirements for the N substituents.[17] In the present work, we sought for a synthetic method that would give access to unsymmetrical, *N*-substituted, imidazolium ions containing a terminal, protected, carboxylic acid functionality.

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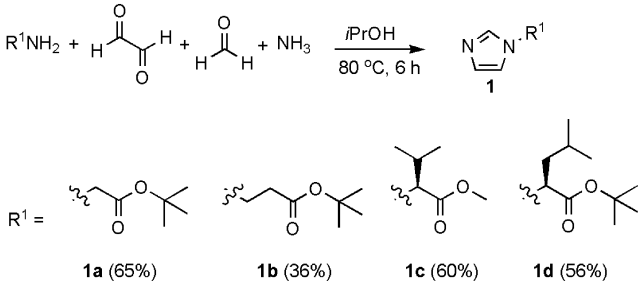
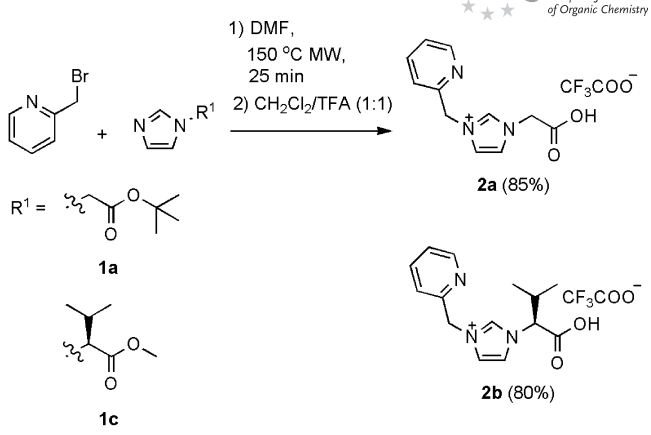
Such imidazolium ions would serve as *N*-heterocyclic carbene precursors and would be well suited for incorporation onto the solid phase. By using commercially available methyl or *tert*-butyl esters of different amino acids, four amino-acid-derived imidazoles were synthesized in a modified, one-pot, Arduengo condensation reaction,[18] in which the amino acid ester, glyoxal, formaldehyde, and aqueous ammonia were reacted to generate the *N*-substituted imidazole ring (Scheme 1).



Scheme 1. Synthesis of functionalized imidazoles by a four-component condensation reaction.

Two of the imidazoles **1** were treated with commercially available 2-(bromomethyl)pyridine with microwave (MW) heating (Scheme 2). Nucleophilic displacement of the bromide followed by TFA-mediated hydrolysis of the ester functionality generated imidazoles **2a**–**b** in good yield (80–85%).

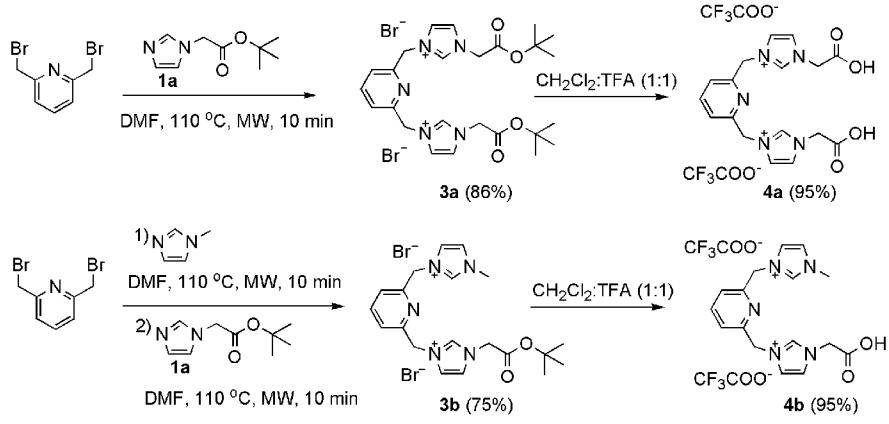
In order to allow for the formation of bis(imidazolium) salts, commercially available 2,6-bis(bromomethyl)pyridine was utilized (Scheme 3). Pyridines, symmetrically substituted with two imidazolium groups, were obtained by nucleophilic displacement of bromide upon the addition of 2 equiv. of imidazole **1a**, thus generating bis(imidazolium) salt **3a**. Unsymmetrically substituted salts were generated by the sequential addition of 1-methylimidazole and imidazole **1a**, which generated the bis(imidazolium) salt **3b**. Subsequent TFA-mediated hydrolysis of the ester functionalities afforded the corresponding carboxylic acids in excellent yield (95%).



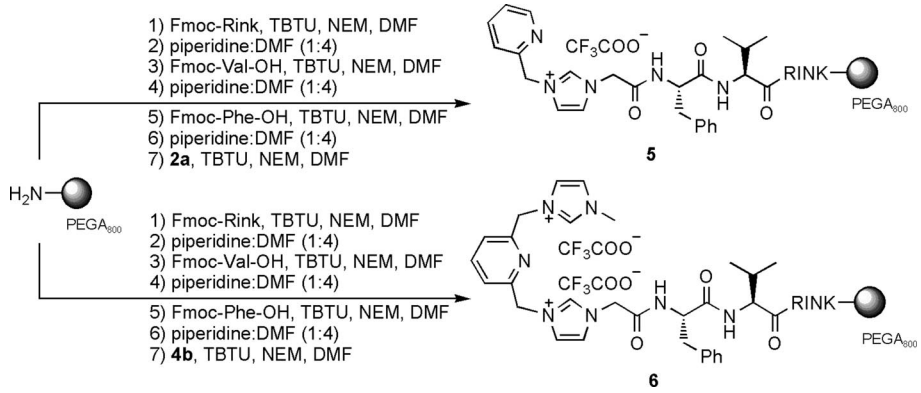
Scheme 2. Formation of pyridine-derivatized imidazolium salts.

In order to investigate the potential of the new imidazolium ion building blocks as *N*-heterocyclic carbene ligands on solid phase, two peptides were synthesized (Scheme 4). The synthesis commenced with the attachment of the acid-labile, Fmoc-protected, Rink-amide linker to amino-functionalized PEGA resin[19] with the standard TBTU activation procedure.[20] This was followed by piperidine/DMF-mediated Fmoc cleavage and TBTU coupling of Fmoc-Val-OH. After another Fmoc cleavage, Fmoc-Phe-OH was attached, followed by Fmoc cleavage and attachment of either imidazole **2a** or **4b**, thus generating the resin-bound mono- and bis(imidazolium) ligands **5** and **6**, respectively.

The dipeptide (Phe-Val) was chosen as a tether between the NHC and the solid support, thereby providing an anchorage point and a spacer toward the resin. The chiral architecture is based on readily available amino acids and their routine assembly, which allows for easy synthetic manipulation and variation at this position. A detailed study of the effects of substituting the tether has not been carried out, but different tethers have been applied previously.[16] Although the chirality of the catalysts are not exploited in the present work, the ability to easily provide chiral environment around the catalytic centre is obvious.



Scheme 3. Formation of pyridine-derivatized bis(imidazolium) salts.

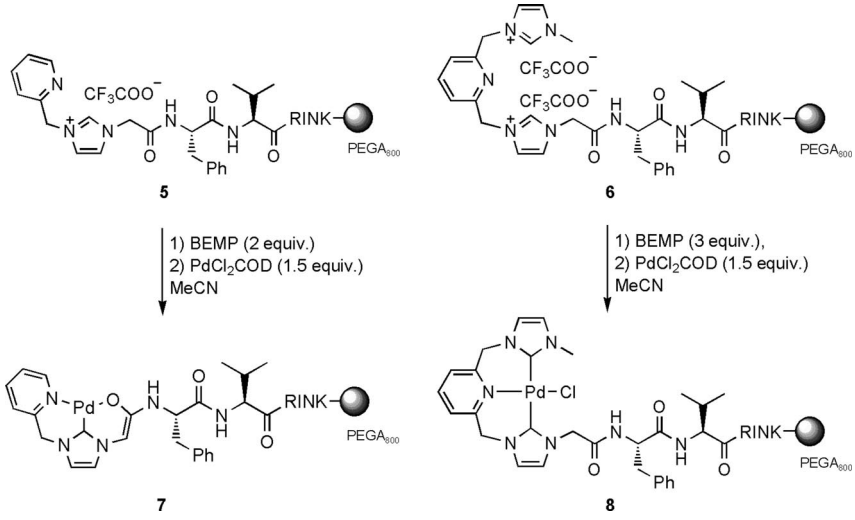


Scheme 4. Solid-phase synthesis of pyridine-derivatized mono- and bis(imidazolium) ligands.

With the resin-bound imidazolium ions in hand, carbene formation and subsequent palladium complexation was investigated directly on the resin. Carbene formation was accomplished by deprotonation of the imidazolium salt with the base 2-*tert*-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine (BEMP), directly followed by trapping of the NHC with $PdCl_2COD$[21] (Scheme 5). The optimized reaction conditions afforded a clean preparation of ligands **5** and **6** without any observation of palladium black precipitation. Upon release from the resin, it was discovered by HRMS (ESI) analysis that a β-enolate oxygen in compound **7** was coordinated to the palladium in addition to the carbene. This enolate was generated during the base treatment. Only a few examples of anionic ligands derived from NHCs are known,[22] but the formation of palladium-NHC-enolate complexes has been reported by Waymouth et al.[23] These results emphasize the preference for enolate formation when a carbonyl group is β to the carbene donor, thus enabling the formation of a stable six-membered chelate.

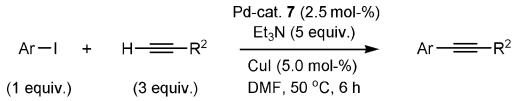
The properties of resin-bound catalyst **7** were evaluated in a series of Sonogashira cross-coupling reactions. Three different terminal alkynes (aromatic, aliphatic, and silyl) and two different aromatic iodides were used as coupling partners (Table 1). The reactions were performed at 50 °C in the presence of 2.5 mol-% catalyst and afforded the cross-coupling products in excellent yield (87–95%). Less activated halides have not been subjected to the current catalytic system.

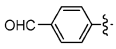
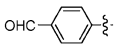
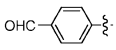
The successful Sonogashira cross-couplings prompted us to evaluate supported catalyst **7** in a series of Suzuki cross-coupling reactions. Ten different boronic acids were selected and coupled to both iodobenzene and bromobenzene. All the reactions were carried out in water and in the presence of 2.5 mol-% catalyst (Table 2). The ten reactions employing iodobenzene (Table 2, Entries 1a–4a and 6a–10a) were performed at 50 °C and afforded the cross-coupling products in excellent yield (90–96%). When the less reactive bromobenzene was applied (Table 2, Entries 1b–4b and 6b–10b), the reactions were performed at 65 °C, which afforded



Scheme 5. Base-mediated mono- and bis(carbene) formation, followed by in situ complexation to palladium.

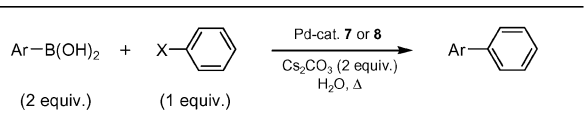
Table 1. Palladium-catalyzed Sonogashira cross-coupling reactions utilizing resin-bound catalyst **7**.

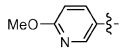
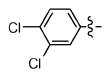
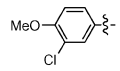
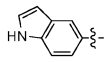


Entry	Ar	R^2	Product, % yield[a]
1			**9**, 94
2			**10**, 90
3			**11**, 91
4			**12**, 93
5			**13**, 87
6			**14**, 95

[a] Isolated yield after flash column chromatography.

Table 2. Palladium-catalyzed Suzuki cross-coupling reactions utilizing catalysts **7** and **8**.



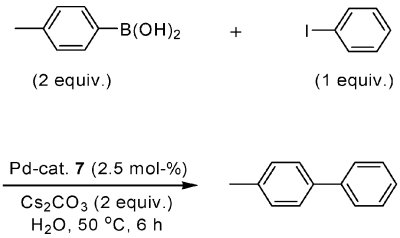
Entry	Ar	X	T [°C]	Pd-cat [mol-%]	Time	Product % yield[a]
1a		I	50	**7** (2.5)	6 h	**15**, 96
1b		Br	65	**7** (2.5)	6 h	**15**, 88
1c		I	90[b]	**8** (0.05)	10 min	**15**, 95
1d		Br	100[b]	**8** (0.05)	10 min	**15**, 92
2a		I	50	**7** (2.5)	6 h	**16**, 93
2b		Br	65	**7** (2.5)	6 h	**16**, 87
2c		I	90[b]	**8** (0.05)	10 min	**16**, 96
2d		Br	100[b]	**8** (0.05)	10 min	**16**, 91
3a		I	50	**7** (2.5)	6 h	**17**, 92
3b		Br	65	**7** (2.5)	6 h	**17**, 85
3c		I	90[b]	**8** (0.05)	10 min	**17**, 95
3d		Br	100[b]	**8** (0.05)	10 min	**17**, 91
4a		I	50	**7** (2.5)	6 h	**18**, 90
4b		Br	65	**7** (2.5)	6 h	**18**, 81
4c		I	90[b]	**8** (0.05)	10 min	**18**, 92
4d		Br	100[b]	**8** (0.05)	10 min	**18**, 90
5a		I	50	**7** (2.5)	6 h	**19**, 0
5b		Br	65	**7** (2.5)	6 h	**19**, 0
5c		I	90[b]	**8** (0.05)	10 min	**19**, 0
5d		Br	100[b]	**8** (0.05)	10 min	**19**, 0
6a		I	50	**7** (2.5)	6 h	**20**, 90
6b		Br	65	**7** (2.5)	6 h	**20**, 79
6c		I	90[b]	**8** (0.05)	10 min	**20**, 93
6d		Br	100[b]	**8** (0.05)	10 min	**20**, 90
7a		I	50	**7** (2.5)	6 h	**21**, 93
7b		Br	65	**7** (2.5)	6 h	**21**, 84
7c		I	90[b]	**8** (0.05)	10 min	**21**, 93
7d		Br	100[b]	**8** (0.05)	10 min	**21**, 91
8a		I	50	**7** (2.5)	6 h	**22**, 90
8b		Br	65	**7** (2.5)	6 h	**22**, 82
8c		I	90[b]	**8** (0.05)	10 min	**22**, 95
8d		Br	100[b]	**8** (0.05)	10 min	**22**, 92
9a		I	50	**7** (2.5)	6 h	**23**, 91
9b		Br	65	**7** (2.5)	6 h	**23**, 81
9c		I	90[b]	**8** (0.05)	10 min	**23**, 94
9d		Br	100[b]	**8** (0.05)	10 min	**23**, 91
10a		I	50	**7** (2.5)	6 h	**24**, 93
10b		Br	65	**7** (2.5)	6 h	**24**, 80
10c		I	90[b]	**8** (0.05)	10 min	**24**, 94
10d		Br	100[b]	**8** (0.05)	10 min	**24**, 92

[a] Isolated yield after flash column chromatography. [b] Microwave heating.

the cross-coupling products in good yield (79–88%). As expected, the most challenging (pentafluorophenyl)boronic acid did not couple under any of the reaction conditions employed (Table 2, Entries 5a–5d). The catalytic potential of bis(carbene) catalyst **8** was evaluated in an equivalent series of Suzuki cross-coupling reactions performed in water. This time, the catalyst was released from the solid support, purified, and employed in solution, while heating of the reaction mixtures was performed by microwave irradiation. The reaction temperature was increased to 90 °C and 100 °C for iodobenzene and bromobenzene, respectively, while the catalyst amount was reduced to only 0.05 mol-%. The application of catalyst **8** under elevated temperatures allowed for the cross-coupling reactions to run to completion within 10 min. When iodobenzene was applied (Table 2, Entries 1c–4c and 6c–10c), the cross-coupling products could be isolated in excellent yield (92–96%), and the application of bromobenzene (Table 2, Entries 1d–4d and 6d–10d) furnished the cross-coupling products in good yield (90–92%). No formation of cross-coupling product could be observed when the reactions were performed without a catalyst present. With respect to thermal stability, MS analysis revealed that the catalyst was still intact after the reactions had been performed at elevated temperatures (100 °C). Further heating to higher temperatures was not attempted.

After performing the cross-coupling reactions, supported catalyst **7** was analyzed by MS (ESI) and showed no sign of decomposition. Based on these results, an endurance test of the catalyst was set up, and the Suzuki cross-coupling between 4-methylphenylboronic acid and iodobenzene was chosen. Repetitive cycles of cross-coupling reactions were carried out with the same batch of supported catalyst **7**, and after each cycle, the product was purified and quantified, whereas the catalyst was washed and reused in the next reaction (Table 3). After eight cycles, the catalyst was still fully operational and showed no loss of activity. Overall, the combination of low catalyst amount, fast reaction times, high cross-coupling yields, and successful recycling of the catalyst is very encouraging and illustrates that the catalyst system can rival existing systems both in solution and on solid support.[14]

Table 3. Recycling experiment of resin-bound catalyst **7** in the palladium-catalyzed Suzuki cross-coupling reaction.



Run	1	2	3	4	5	6	7	8
% Yield[a]	94	96	93	95	92	96	93	94

[a] Isolated yield after flash column chromatography.

Conclusions

In summary, we have synthesized a series of functionalized imidazolium-ion building blocks, containing a pyridine moiety and carboxylic acid functionality. These compounds, which serve as NHC precursors, were easily attached to a dipeptide on solid support, with standard peptide-coupling chemistry. Subsequent carbene formation was accomplished by treatment with strong base, BEMP, followed by complexation to palladium(II) on solid support. These new and efficient palladium NHC catalysts were successfully applied in Sonogashira and Suzuki cross-coupling reactions. The catalysts proved stable toward TFA treatment when released from the solid support and stable in aqueous media, thus allowing for the Suzuki cross-coupling reactions to be performed in water. No loss of catalytic activity was observed when the catalyst was recycled and subjected to repetitive cycles of cross-coupling reactions in water.

Experimental Section

General Remarks. ^{1}H NMR (250 MHz, 600 MHz, or 800 MHz) and ^{13}C NMR (75 MHz, 150 MHz, or 200 MHz) were recorded with a Bruker DRX250, Bruker DRX600, or Bruker Avance 800 spectrometer. Chemical shifts are reported in ppm relative to the internal solvent peak (δ = 7.26 and 77.0 ppm, respectively, for $CDCl_3$). Coupling constants, *J*, are given in Hz. Multiplicities of peaks are given as: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), and br (broad). MS (ESI) spectra were recorded with a Bruker Esquire 3000plus mass spectrometer or a Micromass QTOF Global Ultima instrument. TLC plates were Merck silica gel 60 F254 on aluminum. Flash column chromatography was performed with silica 60H (230–400 mesh). Analytical RP-HPLC was performed with an HP1100 Series system, equipped with a Zorbax 300SB-C18 (3.5 μm, 4.6 × 50 mm) column. A solvent gradient system consisting of A (0.1% TFA in H_2O) and B (0.1% TFA in acetonitrile/H_2O, 9:1) was used in a linear gradient (100% A → 100% B in 25 min). Preparative RP-HPLC was performed with a Waters DeltaPrep system, equipped with a Waters 2487 detector and a XTerra® Prep MSC18 cartridge (5 μm, 19 × 10 mm). Monitoring was performed at 215 nm and 254 nm. Microwave reactions were carried out with a Biotage Initiator™ microwave system. All solvents were HPLC grade and stored over molecular sieves or distilled prior to use. Degassed solutions were obtained by bubbling argon through them for 10 min. For reactions on solid phase, $PEGA_{800}$ resin (loading: 0.30–0.35 mmol/g, Versamatrix A/S) was used. Prior to use, the resin was washed with methanol (5×), acetonitrile (5×), DMF (5×), and CH_2Cl_2 (5×) and dried overnight in vacuo. Solid-phase reactions were carried out in flat-bottomed polyethylene syringes equipped with sintered Teflon filters (50 μm pores), Teflon tubing, Teflon valves for flow control, and suction to drain the syringes from below. For solid-phase reactions carried out under argon, the syringes were equipped with a rubber septum and an argon inlet. Resin loading was determined by Fmoc cleavage and measurement of the optical density at 290 nm. Loadings were then calculated from a calibration curve. Starting materials purchased from commercial suppliers were used without further purification.

General Procedure for Peptide Couplings: TBTU-mediated couplings were performed by dissolving the carboxylic acid (3 equiv.) in DMF, followed by the addition of *N*-ethylmorpholine (NEM, 4.0 equiv.) and (TBTU, 2.88 equiv.). The resulting solution was allowed to react for 5 min and then added to the $PEGA_{800}$ resin and allowed to react for 2 h, followed by washing of the resin with DMF (5×) and CH_2Cl_2 (5×). To verify that full conversion of the free amine had taken place, the resin was checked by the Kaiser test.

General Procedure for Linker Attachment on Solid Phase: Attachment of the 4-[(2,4-dimethoxyphenyl)(Fmoc-amino)methyl]phenoxyacetic acid (Fmoc-Rink-amide) linker to the amino-functionalized resin ($PEGA_{800}$) was carried out by following the standard amino acid coupling procedure (Fmoc-AA-OH, TBTU, NEM, DMF). The linker (3.0 equiv.), NEM (4.0 equiv.), and TBTU (2.88 equiv.) were mixed in DMF and allowed to react for 5 min. The reaction mixture was added to the preswollen $PEGA_{800}$ resin and allowed to react for 2 h, followed by washing of the resin with DMF (5×) and CH_2Cl_2 (5×).

General Procedure for Fmoc Deprotection: The Fmoc group was removed by the addition of 20% piperidine in DMF for 2 min, and the resin was washed with DMF (3×), followed by the addition of 20% piperidine in DMF for 18 min. The resin was again washed with DMF (5×) and CH_2Cl_2 (5×).

General Procedure for Cleavage of Resin-Supported Peptides: Cleavage from the Rink-amide linker was achieved by treatment with 95% TFA (aqueous) for 2 h, followed by concentration in vacuo of the solution phase.

***tert*-Butyl (Imidazol-1-yl)acetate (1a):** Glyoxal (40 wt.-% solution in H_2O, 7.3 g, 50.0 mmol), and formaldehyde (37 wt.-% solution in H_2O, 4.1 g, 50.0 mmol) in *i*PrOH (50 mL) was added dropwise to a stirred suspension of H-Gly-O*t*Bu·HCl (8.4 g, 50 mmol), ammonia (28 wt.-% solution in H_2O, 55 mmol, 3.8 mL) and *i*PrOH (175 mL). After complete addition, the reaction mixture was heated to 80 °C and stirred for 6 h. The brownish solution was then cooled to 25 °C and diluted with CH_2Cl_2 (125 mL). The organic layer was separated, washed with NaOH (1.0 M, 125 mL), dried with Na_2SO_4, and concentrated in vacuo. Purification was performed by flash chromatography and yielded the title compound as a yellow solid. Yield 5.9 g (65%). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.49 (s, 1 H), 7.09 (s, 1 H), 6.94 (s, 1 H), 4.58 (s, 2 H), 1.47 (s, 9 H) ppm. ^{13}C NMR (63 MHz, $CDCl_3$): δ = 166.4, 137.8, 129.4, 119.9, 83.2, 48.8, 27.9 ppm. M.p. 110–112 °C (ref.[24] 111–113 °C). HRMS (ESI): calcd. for $C_9H_{15}N_2O_2$ $[M + H]^+$ 183.1128; found 183.1136.

***tert*-Butyl 3-(Imidazol-1-yl)propionate (1b):** A solution of glyoxal (40 wt.-% solution in H_2O, 1.5 g, 10.0 mmol) and formaldehyde (37 wt.-% solution in H_2O, 811.9 mg, 10.0 mmol) in *i*PrOH (10 mL) was added dropwise to a stirred suspension of H-β-Ala-O*t*Bu·HCl (1.8 g, 10 mmol), ammonia (28 wt.-% solution in H_2O, 11 mmol, 0.8 mL), and *i*PrOH (35 mL). After complete addition, the reaction mixture was heated to 80 °C and stirred for 6 h. The slightly yellow solution was then cooled to 25 °C and diluted with CH_2Cl_2 (25 mL). The organic layer was separated, washed with NaOH (1.0 M, 25 mL), dried with Na_2SO_4, and concentrated in vacuo. Purification was performed by kugelrohr distillation and yielded the title compound as a yellow oil. Yield 0.7 g (36%). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.49 (s, 1 H), 7.02 (s, 1 H), 6.92 (s, 1 H), 4.20 (t, J = 6.6 Hz, 2 H), 2.67 (t, J = 6.6 Hz, 2 H), 1.40 (s, 9 H) ppm. ^{13}C NMR (63 MHz, $CDCl_3$): δ = 169.7, 137.2, 129.4, 118.8, 81.6, 42.5, 37.1, 28.0 ppm. HRMS (ESI): calcd. for $C_{10}H_{17}N_2O_2$ $[M + H]^+$ 197.1285; found 197.1293.

Methyl 2-[(*S*)-2-Imidazol-1-yl]-3-methylbutyrate (1c): A solution of glyoxal (40 wt.-% solution in H_2O, 1.5 g, 10.0 mmol) and formaldehyde (37 wt.-% solution in H_2O, 811.9 mg, 10.0 mmol) in *i*PrOH (10 mL) was added dropwise to a stirred suspension of H-Val-OMe·HCl (1.7 g, 10 mmol), ammonia (28 wt.-% solution in H_2O, 11 mmol, 0.8 mL), and *i*PrOH (35 mL). After complete addition, the reaction mixture was heated to 80 °C and stirred for 6 h. The brownish solution was then cooled to 25 °C and diluted with CH_2Cl_2 (25 mL). The organic layer was separated, washed with NaOH (1.0 M, 25 mL), dried with Na_2SO_4, and concentrated in vacuo. Purification was performed by preparative HPLC and yielded the title compound as a slightly yellow oil. Yield 1.1 g (60%). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 8.91 (s, 1 H), 7.41 (s, 1 H), 7.40 (s, 1 H), 4.75 (d, J = 8.6 Hz, 1 H), 3.83 (s, 3 H), 2.53–2.39 (m, 1 H), 1.05 (d, J = 6.7 Hz, 3 H), 0.88 (d, J = 6.7 Hz, 3 H) ppm. ^{13}C NMR (63 MHz, $CDCl_3$): δ = 168.4, 135.9, 121.1, 120.5, 67.5, 53.3, 32.4, 18.9, 18.3 ppm. HRMS (ESI): calcd. for $C_9H_{15}N_2O_2$ $[M + H]^+$ 183.1128; found 183.1133.

***tert*-Butyl 2-[(*S*)-2-Imidazol-1-yl]-4-methylpentanoate (1d):** A solution of glyoxal (40 wt.-% solution in H_2O, 1.5 g, 10.0 mmol) and formaldehyde (37 wt.-% solution in H_2O, 811.9 mg, 10.0 mmol) in *i*PrOH (10 mL) was added dropwise to a stirred suspension of H-Leu-O*t*Bu·HCl (2.2 g, 10 mmol), ammonia (28 wt.-% solution in H_2O, 11 mmol, 0.8 mL), and *i*PrOH (35 mL). After complete addition, the reaction mixture was heated to 80 °C and stirred for 6 h. The brownish solution was then cooled to 25 °C and diluted with CH_2Cl_2 (25 mL). The organic layer was separated, washed with NaOH (1.0 M, 25 mL), dried with Na_2SO_4, and concentrated in vacuo. Purification was performed by flash chromatography and yielded the title compound as a slightly yellow oil. Yield 1.3 g (56%). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.53 (s, 1 H), 7.05 (s, 1 H), 7.00 (s, 1 H), 4.62 (t, J = 7.9 Hz, 1 H), 2.41–2.32 (m, 1 H), 1.88 (dd, J = 7.8, 7.2 Hz, 2 H), 1.42 (s, 9 H), 0.92 (d, J = 4.1 Hz, 3 H), 0.89 (d, J = 4.2 Hz, 3 H) ppm. ^{13}C NMR (63 MHz, $CDCl_3$): δ = 169.1, 136.8, 129.3, 117.3, 82.7, 59.0, 41.5, 27.8, 24.5, 22.6, 21.5 ppm. HRMS (ESI): calcd. for $C_{13}H_{23}N_2O_2$ $[M + H]^+$ 239.1754; found 239.1757.

3-(Carboxymethyl)-1-[(pyridin-2-yl)methyl]-3*H*-imidazol-1-ium Trifluoroacetate (2a): To a solution of imidazole **1a** (54.7 mg, 0.3 mmol) in DMF (1.5 mL) was added 2-(bromomethyl)pyridine hydrobromide (75.9 mg, 0.3 mmol), and the solution was heated to 150 °C for 25 min under microwave irradiation. The solvent was removed in vacuo, and the crude product was dissolved in CH_2Cl_2/TFA (1:1) and stirred for 1 h, after which time the reaction mixture was concentrated in vacuo. Purification was performed by preparative RP-HPLC to yield the title compound as a yellow oil. Yield 84.5 mg (85%). ^{1}H NMR (250 MHz, CD_3OD): δ = 9.18 (s, 1 H), 8.58 (ddd, J = 0.8, 1.5, 4.9 Hz, 1 H), 7.90 (dt, J = 1.7, 7.7 Hz, 1 H), 7.68 (td, J = 1.8, 11.2 Hz, 2 H), 7.52 (d, J = 7.8 Hz, 1 H) 7.42 (ddd, J = 1.0, 4.9, 7.7 Hz, 1 H), 5.59 (s, 2 H), 5.15 (s, 2 H) ppm. ^{13}C NMR (63 MHz, CD_3OD): δ = 169.0, 151.1 (2 C), 139.5, 139.3, 125.4, 125.3, 124.2, 124.0, 55.0, 50.9 ppm. HRMS (ESI): calcd. for $C_{11}H_{12}N_3O_2$ $[M - CF_3COO^-]^+$ 218.0924; found 218.0936.

3-[(*S*)-1-Carboxy-2-methylpropyl]-1-[(pyridin-2-yl)methyl]-3*H*-imidazol-1-ium Trifluoroacetate (2b): To a solution of imidazole **1c** (54.7 mg, 0.3 mmol) in DMF (1.5 mL) was added 2-(bromomethyl)-pyridine hydrobromide (75.9 mg, 0.3 mmol), and the solution was heated to 150 °C for 25 min under microwave irradiation. The solvent was removed in vacuo and the crude product was dissolved in CH_2Cl_2/TFA (1:1) and stirred for 4 h, after which time the solvent and TFA were removed in vacuo. Purification was performed by preparative RP-HPLC to yield the title compound as a brown oil. Yield 89.6 mg (80%). ^{1}H NMR (250 MHz, [D$_6$]DMSO): δ = 9.47 (s, 1 H), 8.53 (ddd, J = 0.9, 1.6, 4.8 Hz, 1 H), 7.91 (dd, J = 1.8, 7.7 Hz, 1 H), 7.85 (td, J = 1.7, 7.3 Hz, 2 H), 7.48 (d, J = 7.8 Hz, 1 H), 7.40 (ddd, J = 1.0, 4.9, 7.6 Hz, 1 H), 5.63 (s, 2 H), 5.17 (d, J = 7.4 Hz, 1 H), 2.51–2.49 (m, 1 H), 0.97 (d, J = 6.7 Hz, 3 H), 0.86 (d, J = 6.8 Hz, 3 H) ppm. ^{13}C NMR (63 MHz, [D$_6$]DMSO): δ = 169.1, 153.3, 149.5, 137.6, 137.4, 123.6, 122.9, 122.7, 122.3, 66.9, 53.1, 30.8, 18.7, 17.8 ppm. HRMS (ESI): calcd. for $C_{14}H_{18}N_3O_2$ $[M - CF_3COO^-]^+$ 260.1394; found 260.1399.

3,3′-(Pyridine-2,6-diyldimethanediyl)bis[1-(2-*tert*-butoxycarbonylmethyl)-1*H*-imidazol-3-ium] Dibromide (3a): To a solution of imidazole **1a** (136.7 mg, 0.75 mmol) in DMF (2.0 mL) was added 2,6-bis(bromomethyl)pyridine (79.5 mg, 0.3 mmol), and the solution was heated to 110 °C for 10 min under microwave irradiation. The solvent was removed in vacuo, and the crude product was purified by preparative RP-HPLC to yield the title compound as a colourless oil. Yield 162.4 mg (86%). ^{1}H NMR (250 MHz, [D$_6$]DMSO): δ = 9.21 (s, 2 H), 7.99 (t, J = 7.8 Hz, 1 H), 7.75 (d, J = 1.6 Hz, 1 H), 7.74 (d, J = 1.6 Hz, 1 H), 7.68 (d, J = 1.6 Hz, 1 H), 7.67 (d, J = 1.6 Hz, 1 H), 7.49 (d, J = 7.8 Hz, 2 H), 5.62 (s, 4 H), 5.19 (s, 4 H), 1.46 (s, 18 H) ppm. ^{13}C NMR (63 MHz, [D$_6$]DMSO): δ = 165.8, 153.4, 138.8, 137.9, 123.6, 122.9, 121.9, 83.0, 52.6, 50.0, 27.5 ppm. MS (ESI): calcd. for $C_{25}H_{35}N_5O_4$ $[M - 2Br^-]^{2+}$ 234.6; found 234.6.

1-(2-*tert*-Butoxycarbonylmethyl)-3-({6-[(1-methyl-1*H*-imidazol-3-ium-3-yl)methyl]pyridin-2-yl}methyl)-1*H*-imidazol-3-ium Dibromide (3b): To a solution of 1-methylimidazole (24.6 mg, 0.3 mmol) in DMF (2.0 mL) was added 2,6-bis(bromomethyl)pyridine (79.5 mg, 0.3 mmol), and the solution heated to 110 °C for 10 min under microwave irradiation. Imidazole **1a** (54.7 mg, 0.3 mmol) was then added, and the solution was heated to 110 °C for an additional 10 min under microwave irradiation. The solvent was removed in vacuo, and the crude product was purified by preparative RP-HPLC to yield the title compound as a yellow oil. Yield 119.1 mg (75%). ^{1}H NMR (250 MHz, [D$_6$]DMSO): δ = 9.29 (s, 1 H), 9.18 (s, 1 H), 7.97 (t, J = 7.7 Hz, 1 H), 7.80–7.67 (m, 4 H), 7.48 (d, J = 7.7 Hz, 2 H), 5.64 (s, 2 H), 5.54 (s, 2 H), 5.23 (s, 2 H), 3.89 (s, 3 H), 1.46 (s, 9 H) ppm. ^{13}C NMR (63 MHz, [D$_6$]DMSO): δ = 165.8, 153.5, 153.4, 138.7, 138.0, 137.1, 123.5, 123.4, 123.0, 122.9, 122.0, 121.9, 83.0, 52.6, 52.4, 50.0, 35.7, 27.5 ppm. MS (ESI): calcd. for $C_{20}H_{27}N_5O_2$ $[M - 2Br^-]^{2+}$ 184.6; found 184.6.

3,3′-(Pyridine-2,6-diyldimethanediyl)bis[1-(carboxymethyl)-1*H*-imidazol-3-ium] Bis(trifluoroacetate) (4a): The *tert*-butyl ester **3a** (126.0 mg, 0.2 mmol) was dissolved in CH_2Cl_2/TFA (1:1) and stirred for 4 h, after which time the solvent and TFA were removed

in vacuo, and the crude product was purified by preparative RP-HPLC to yield the title compound as a slightly yellow oil. Yield 110.8 mg (95%). ^{1}H NMR (800 MHz, [D$_6$]DMSO): δ = 9.17 (s, 2 H), 7.98 (t, J = 7.7 Hz, 1 H), 7.73 (s, 2 H), 7.66 (s, 2 H), 7.49 (d, J = 7.7 Hz, 2 H), 5.61 (s, 4 H), 5.17 (s, 4 H) ppm. ^{13}C NMR (201 MHz, [D$_6$]DMSO): δ = 168.2, 153.5, 138.8, 137.7, 123.7, 122.8, 122.0, 52.5, 49.8 ppm. HRMS (ESI): calcd. for $C_{17}H_{19}N_5O_4$ [M – 2 CF_3COO^-]$^{2+}$ 178.5713; found 178.5710.

1-(Carboxymethyl)-3-({6-[(1-methyl-1*H*-imidazol-3-ium-3-yl)methyl]pyridin-2-yl}methyl)-1*H*-imidazol-3-ium Bis(trifluoroacetate) (4b): The *tert*-butyl ester **3b** (119.0 mg, 0.2 mmol) was dissolved in CH_2Cl_2/TFA (1:1) and stirred for 4 h, after which time the solvent and TFA were removed in vacuo, and the crude product was purified by preparative RP-HPLC to yield the title compound as a slightly yellow oil. Yield 102.5 mg (95%). ^{1}H NMR (250 MHz, [D$_6$]-DMSO): δ = 9.20 (s, 1 H), 9.10 (s, 1 H), 7.98 (t, J = 7.7 Hz, 1 H), 7.77–7.65 (m, 4 H), 7.48 (d, J = 7.7 Hz, 2 H), 5.62 (s, 2 H), 5.52 (s, 2 H), 5.19 (s, 2 H), 3.88 (s, 3 H) ppm. ^{13}C NMR (63 MHz, [D$_6$]-DMSO): δ = 168.0, 153.5, 153.4, 138.7, 137.8, 137.0, 123.5, 123.4, 123.0, 122.8, 122.0, 121.9, 52.5, 52.4, 49.8, 35.7 ppm. HRMS (ESI): calcd. for $C_{16}H_{19}N_5O_2$ [M – 2 CF_3COO^-]$^{2+}$ 156.5764; found 156.5750.

***N*-{[3-(Pyridin-2-ylmethyl)-1*H*-imidazol-3-ium-1-yl]acetyl}-L-phenylalanyl-L-valine Trifluoroacetate (5):** Attachment of the Fmoc-Rink-amide linker followed the standard amino acid coupling procedure (Fmoc-Aa-OH, TBTU, NEM, DMF). The Fmoc-protecting group was removed under standard conditions by two successive additions of 20% piperidine in DMF. The amino acids Fmoc-Val-OH and Fmoc-Phe-OH were coupled to the resin with the above-mentioned standard coupling procedure with the standard Fmoc-deprotection steps in between. Imidazolium salt **2a** was then attached to the resin with the standard amino acid coupling procedure, and the final product was released from the resin by a 2 h treatment with 95% TFA (aqueous). After purification by preparative RP-HPLC (purity > 95%), the title compound was obtained as a white powder. Yield 22.5 mg (45%) obtained from 350 mg of $PEGA_{800}$ resin (loading: 0.25 mmol/g). ^{1}H NMR (800 MHz, [D$_6$]-DMSO): δ = 9.20 (s, 1 H), 8.74 (d, J = 8.2 Hz, 1 H), 8.10 (d, J = 9.0 Hz, 1 H), 7.88 (dt, J = 1.6, 7.6 Hz, 1 H), 7.75 (t, J = 1.5 Hz, 1 H), 7.56 (t, J = 1.5 Hz, 1 H), 7.45 (d, J = 7.8 Hz, 1 H), 7.40 (dd, J = 5.2, 7.2 Hz, 1 H), 7.35 (s, 1 H), 7.25–7.24 (m, 5 H), 7.19–7.17 (m, 1 H), 7.08 (s, 1 H), 5.58 (s, 2 H), 5.02 (d, J = 16.5 Hz, 1 H), 4.96 (d, J = 16.5 Hz, 1 H), 4.69 (dt, J = 4.6, 8.8 Hz, 1 H), 4.12 (dd, J = 6.7, 8.9 Hz, 1 H), 3.04 (dd, J = 4.5, 13.9 Hz, 1 H), 2.79 (dd, J = 9.4, 13.9 Hz, 1 H), 1.95 (qd, J = 6.8, 13.6 Hz, 1 H), 0.85 (d, J = 6.8 Hz, 3 H), 0.82 (d, J = 6.8 Hz, 3 H) ppm. ^{13}C NMR (201 MHz, [D$_6$]DMSO): δ = 173.2, 171.0, 165.0, 154.1, 150.1, 138.4, 138.1, 137.9, 129.8, 129.7, 128.6, 128.5, 126.9, 124.3, 124.2, 123.1, 123.0, 58.1, 54.6, 53.6, 51.1, 38.4, 31.0, 19.8, 18.6 ppm. HRMS (ESI): calcd. for $C_{25}H_{31}N_6O_3$ [M – CF_3COO^-]$^+$ 463.2452; found 463.2458.

***N*-{[3-({6-[(1-Methyl-1*H*-imidazol-3-ium-3-yl)methyl]pyridin-2-yl}methyl)-1*H*-imidazol-3-ium-1-yl]acetyl}-L-phenylalanylvaline Bis(trifluoroacetate) (6):** Attachment of the Fmoc-Rink-amide linker was performed following the standard amino acid coupling procedure (Fmoc-Aa-OH, TBTU, NEM, DMF). The Fmoc-protecting group was removed under standard conditions by two successive additions of 20% piperidine in DMF. The amino acids Fmoc-Val-OH and Fmoc-Phe-OH were coupled to the resin with the above-mentioned standard coupling procedure with the standard Fmoc-deprotection steps in between. Imidazolium salt **4b** was then attached to the resin with the standard amino acid coupling procedure, and the final product was released from the resin by a 2 h treatment with 95% TFA (aqueous). After purification by preparative RP-HPLC (purity > 95%), the title compound was obtained as a white powder. Yield 24.1 mg (41%) obtained from 300 mg of $PEGA_{800}$ resin (loading: 0.25 mmol/g). ^{1}H NMR (250 MHz, [D$_6$]-DMSO): δ = 9.15 (s, 1 H), 9.09 (s, 1 H), 8.87 (d, J = 8.1 Hz, 1 H), 8.12 (d, J = 8.9 Hz, 1 H), 7.96 (t, J = 7.7 Hz, 1 H), 7.66–7.58 (m, 4 H), 7.48 (t, J = 7.0 Hz, 2 H), 7.38 (br. s, 1 H), 7.28–7.20 (m, 5 H), 7.06 (br. s, 1 H), 5.58 (s, 2 H), 5.51 (s, 2 H), 5.04 (d, J = 5.7 Hz, 2 H), 4.71 (dt, J = 4.5, 8.9 Hz, 1 H), 4.13 (dd, J = 6.7, 8.8 Hz, 1 H), 3.84 (s, 3 H), 3.07 (dd, J = 4.4, 13.8 Hz, 1 H), 2.82 (dd, J = 9.4, 13.8 Hz, 1 H), 1.96 (qd, J = 6.7 Hz, 1 H), 0.85 (d, J = 6.5 Hz, 3 H), 0.82 (d, J = 6.5 Hz, 3 H) ppm. ^{13}C NMR (63 MHz, [D$_6$]-DMSO): δ = 172.6, 170.3, 164.6, 153.5, 153.4, 138.7, 138.0, 137.3, 137.0, 129.2 (2 C), 128.0 (2 C), 126.2, 123.4 (2 C), 123.0, 122.6, 122.0, 121.9, 57.5, 54.2, 52.4 (2 C), 50.5, 37.7, 35.7, 30.3, 19.2, 17.9 ppm. HRMS (ESI): calcd. for $C_{30}H_{38}N_8O_3$ [M – 2 CF_3COO^-]$^{2+}$ 279.1528; found 279.1528.

Pd Complex 7: Resin-bound **5** was swelled in MeCN and treated with BEMP (2.0 equiv.) for 15 min under an argon atmosphere followed by the addition of $PdCl_2COD$ (1.5 equiv.). The reaction was left for 5 h and then washed with MeCN (5×) and CH_2Cl_2 (5×). The final complex was released from the resin by a 2 h treatment with 95% TFA (aqueous). After purification by preparative RP-HPLC (purity > 95%), the title compound was obtained as a white powder. Yield 14.9 mg (35%) obtained from 250 mg of $PEGA_{800}$ resin (loading: 0.25 mmol/g). ^{1}H NMR (800 MHz, [D$_6$]DMSO): δ = 10.02 (d, J = 8.3 Hz, 1 H), 8.56 (d, J = 5.6 Hz, 1 H), 8.20 (dt, J = 1.4, 7.8 Hz, 1 H), 7.78 (d, J = 7.8 Hz, 1 H), 7.71 (s, 1 H), 7.63 (t, J = 6.5 Hz, 1 H), 7.58 (d, J = 1.9 Hz, 1 H), 7.56 (d, J = 1.9 Hz, 1 H), 7.38, (s, 1 H), 7.10–7.09 (m, 2 H), 6.99–6.98 (m, 1 H), 5.66 (d, J = 16.3 Hz, 1 H), 5.45 (dd, J = 4.0, 5.2 Hz, 1 H), 5.05 (d, J = 16.2 Hz, 1 H), 4.79 (d, J = 16.9 Hz, 1 H), 4.68 (d, J = 16.9 Hz, 1 H), 4.23 (t, J = 7.8 Hz, 1 H), 3.12 (dd, J = 5.5, 13.5 Hz, 1 H), 3.02 (dd, J = 3.7, 13.5 Hz, 1 H), 2.11 (qd, J = 6.8, 13.8 Hz, 1 H), 0.98 (d, J = 6.8 Hz, 3 H), 0.96 (d, J = 6.8 Hz, 3 H) ppm. ^{13}C NMR (151 MHz, [D$_6$]DMSO): δ = 182.2, 171.7, 164.7, 154.0, 151.6, 147.4, 141.6, 141.2, 138.4, 138.0, 136.5, 130.9, 127.9, 126.7, 126.2, 126.1, 122.9, 122.1, 66.4, 59.7, 53.4, 40.1, 30.5, 19.7, 18.6 ppm. HRMS (ESI): calcd. for $C_{25}H_{29}N_6O_3Pd$ [M – CF_3COO^-]$^+$ 567.1336; found 567.1337.

Pd Complex 8: Resin-bound **6** was swelled in MeCN and treated with BEMP (3.0 equiv.) for 15 min under an argon atmosphere, followed by the addition of $PdCl_2COD$ (1.5 equiv.). The reaction was left for 5 h and then washed with MeCN (5×) and CH_2Cl_2 (5×). The final complex was released from the resin by 2 h treatment with 95% TFA (aqueous). After purification by preparative RP-HPLC (purity > 95%), the title compound was obtained as a white powder. Yield 10.5 mg (26%) obtained from 200 mg of $PEGA_{800}$ resin (loading: 0.25 mmol/g). ^{1}H NMR (600 MHz, [D$_6$]-DMSO): δ = 10.08 (d, J = 7.2 Hz, 1 H), 9.18 (s, 1 H), 9.04 (s, 1 H), 8.01 (t, J = 7.6 Hz, 1 H), 7.73–7.72 (m, 1 H), 7.67 (s, 1 H), 7.49–7.46 (2 H), 7.38 (s, 1 H), 7.15 (m, 2 H), 6.95–6.93 (m, 3 H), 6.82 (d, J = 6.9 Hz, 2 H), 5.55 (s, 2 H), 5.48 (s, 2 H), 4.78–4.68 (m, 3 H), 4.00 (t, J = 7.7 Hz, 1 H), 3.90 (s, 3 H), 3.01 (m, 1 H), 2.91 (dd, J = 4.7, 13.1 Hz, 1 H), 2.03 (qd, J = 7.3, 13.9 Hz, 1 H), 0.92 (d, J = 6.0 Hz, 3 H), 0.91 (d, J = 6.0 Hz, 3 H) ppm. ^{13}C NMR (151 MHz, [D$_6$]DMSO): δ = 182.1, 182.0, 171.4, 171 ppm. 0, 164.5, 154.4, 153.8, 139.1, 137.2, 135.8, 130.5, 130.4, 127.6, 127.1, 126.6, 123.7, 123.2, 123.0, 122.3, 122.2, 64.8, 59.6, 54.7, 52.8, 52.5, 36.0, 29.7, 25.8, 19.1, 18.5 ppm. HRMS (ESI): calcd. for $C_{30}H_{36}ClN_8O_3Pd$ [M – CF_3COO^-]$^+$ 697.1634; found 697.1644.

General Procedure for Sonogashira Cross-Coupling Reactions: To a Nunc vial containing the solid-phase-immobilized palladium cata-

lyst (2.5 mol-%) was added the aryl iodide (0.2 mmol, 1.0 equiv.), alkyne (0.6 mmol, 3.0 equiv.), Et_3N (1.0 mmol, 5.0 equiv.), CuI (0.01 mmol, 0.05 equiv.), and DMF (1.0 mL). The solution was heated to 50 °C for 6 h and then cooled to room temp. and transferred to a polyethylene syringe, equipped with a sintered Teflon filter. The beads were washed with EtOAc (5 × 5 mL) to extract the product. The organic phase was concentrated in vacuo and purified by flash column chromatography on silica gel (EtOAc/hexane, 1:9).

1-Nitro-2-(phenylethynyl)benzene (9): The reaction was carried out as described in the general procedure for Sonogashira cross-coupling reactions. The product obtained was an orange oil. Yield 42 mg (94%). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 8.07 (dd, J = 1.3, 8.2 Hz, 1 H), 7.72 (dd, J = 1.5, 7.8 Hz, 1 H), 7.62–7.56 (m, 3 H), 7.45 (dd, J = 1.5, 7.8 Hz, 1 H), 7.36–7.41 (m, 3 H) ppm. ^{13}C NMR (63 MHz, $CDCl_3$): δ = 149.6, 134.5, 132.7, 132.0, 129.2, 128.5, 128.4, 124.7, 122.4, 118.7, 97.1, 84.7 ppm.

4-(Phenylethynyl)benzaldehyde (10): The reaction was carried out as described in the general procedure for Sonogashira cross-coupling reactions. The product obtained was a yellow solid. Yield 37 mg (90%). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 10.02 (s, 1 H), 7.88–7.85 (m, 2 H), 7.69–7.66 (m, 2 H), 7.58–7.54 (m, 2 H), 7.40–7.35 (m, 3 H) ppm. ^{13}C NMR (63 MHz, $CDCl_3$): δ = 191.3, 135.4, 132.1, 131.8, 129.5, 128.9, 128.4, 122.5, 93.4, 88.5 ppm. M.p. 98–99 °C (ref.[25] 98–100 °C).

Trimethyl(2-nitrophenylethynyl)silane (11): The reaction was carried out as described in the general procedure for Sonogashira cross-coupling reactions. Product obtained as a slightly yellow oil. Yield 40 mg (91%). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 8.00 (dd, J = 1.3, 8.1 Hz, 1 H), 7.65 (dd, J = 1.5, 7.7 Hz, 1 H), 7.54 (dt, J = 1.4, 7.5 Hz, 1 H), 7.44 (ddd, J = 1.6, 7.4, 8.1 Hz, 1 H), 0.28 (s, 9 H) ppm. ^{13}C NMR (63 MHz, $CDCl_3$): δ = 150.2, 135.1, 132.6, 128.8, 124.4, 118.4, 103.7, 99.3, –0.4 ppm.

4-[(Trimethylsilanyl)ethynyl]benzaldehyde (12): The reaction was carried out as described in the general procedure for Sonogashira cross-coupling reactions. The product obtained was a white solid. Yield 38 mg (93%). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 9.99 (s, 1 H), 7.81 (d, J = 8.4 Hz, 2 H), 7.59 (d, J = 8.3 Hz, 2 H), 0.26 (s, 9 H) ppm. ^{13}C NMR (63 MHz, $CDCl_3$): δ = 191.3, 135.6, 132.4, 129.4, 103.8, 99.0, –0.2 ppm. M.p. 67–68 °C (ref.[26] 66–67 °C).

1-(Hex-1-ynyl)-2-nitrobenzene (13): The reaction was carried out as described in the general procedure for Sonogashira cross-coupling reactions. The product obtained was a slightly yellow oil. Yield 35 mg (87%). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.95 (dd, J = 1.2, 8.2 Hz, 1 H), 7.57 (dd, J = 1.8, 7.7 Hz, 1 H), 7.50 (dt, J = 1.3, 7.4 Hz, 1 H), 7.38 (dt, J = 1.8, 8.3 Hz, 1 H), 2.48 (t, J = 6.9 Hz, 2 H), 1.68–1.42 (m, 4 H), 0.95 (t, J = 7.2 Hz, 3 H) ppm. ^{13}C NMR (63 MHz, $CDCl_3$): δ = 150.1, 134.7, 132.4, 127.8, 124.3, 119.3, 99.4, 30.4, 21.9, 19.5, 13.6 ppm.

4-(Hex-1-ynyl)benzaldehyde (14): The reaction was carried out as described in the general procedure for Sonogashira cross-coupling reactions. The product obtained was a yellow oil. Yield 35 mg (95%). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 9.97 (s, 1 H), 7.78 (d, J = 8.4 Hz, 2 H), 7.51 (d, J = 8.3 Hz, 2 H), 2.44 (t, J = 6.9 Hz, 2 H), 1.67–1.43 (m, 4 H), 0.95 (t, J = 7.2 Hz, 3 H) ppm. ^{13}C NMR (63 MHz, $CDCl_3$): δ = 191.4, 134.9, 132.0, 130.6, 129.4, 95.2, 80.1, 30.6, 22.0, 19.2, 13.6 ppm.

General Procedure for Suzuki Cross-Coupling Reactions: To a Nunc vial containing the solid-phase-immobilized palladium catalyst **7** (2.5 mol-%) was added the aryl halide (0.1 mmol, 1.0 equiv.), boronic acid (0.2 mmol, 2.0 equiv.), Cs_2CO_3 (0.2 mmol, 2.0 equiv.), and H_2O (1.0 mL). The solution was heated to 50 °C for 6 h and then cooled to room temp. The aqueous phase was decanted off, and the beads were transferred to a polyethylene syringe, equipped with a sintered Teflon® filter, and washed with EtOAc (50 mL) to extract the product. The organic phase was concentrated in vacuo and purified by flash column chromatography on silica gel (EtOAc/hexane, 1:9). Yields for the cross-coupling reactions performed with iodobenzene are given below, whereas yields from the cross-couplings with bromobenzene are given in Table 2. When catalyst **8** was applied, it was added in solution (0.05 mol-%), and the additional compounds were added as described above. Heating was performed by microwave irradiation for 10 min, and the reaction mixture was extracted with EtOAc (5× 1 mL), followed by purification of the concentrated extract by flash column chromatography on silica gel (EtOAc/hexane, 1:9). Yields are given in Table 2.

4-Methylbiphenyl (15): The reaction was carried out as described in the general procedure for Suzuki cross-coupling reactions. The product obtained was a white solid. Yield 16 mg (96%). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.61–7.57 (m, 2 H), 7.51 (d, J = 8.2 Hz, 2 H), 7.43 (t, J = 7.3 Hz, 2 H), 7.33 (t, J = 7.2 Hz, 1 H), 7.26 (d, J = 7.8 Hz, 2 H), 2.41 (s, 3 H) ppm. ^{13}C NMR (63 MHz, $CDCl_3$): δ = 141.2, 138.4, 137.0, 129.5, 128.7, 127.0, 126.8, 21.1 ppm. M.p. 48–49 °C (ref.[27] 49–50 °C).

3,5-Dimethoxybiphenyl (16): The reaction was carried out as described in the general procedure for Suzuki cross-coupling reactions. The product obtained was a colourless oil. Yield 20 mg (93%). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.61–7.56 (m, 2 H), 7.48–7.33 (m, 3 H), 6.75 (d, J = 2.3 Hz, 2 H), 6.49 (t, J = 2.3 Hz, 1 H), 3.86 (s, 6 H) ppm. ^{13}C NMR (63 MHz, $CDCl_3$): δ = 161.0, 143.5, 141.2, 128.7, 127.5, 127.2, 105.5, 99.3, 55.4 ppm.

2-Methoxy-5-phenylpyridine (17): The reaction was carried out as described in the general procedure for Suzuki cross-coupling reactions. The product obtained was a colourless oil. Yield 17 mg (92%). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 8.40 (dd, J = 0.6, 2.5 Hz, 1 H), 7.79 (dd, J = 2.6, 8.6 Hz, 1 H), 7.55–7.32 (m, 5 H), 6.82 (dd, J = 0.7, 8.6 Hz, 1 H), 3.99 (s, 3 H) ppm. ^{13}C NMR (63 MHz, $CDCl_3$): δ = 163.6, 145.0, 137.9, 137.5, 130.1, 129.0, 127.3, 126.7, 110.8, 53.5 ppm.

3-(Trifluoromethyl)biphenyl (18): The reaction was carried out as described in the general procedure for Suzuki cross-coupling reactions. The product obtained was a yellow oil. Yield 20 mg (90%). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.84–7.76 (m, 2 H), 7.62–7.37 (m, 7 H) ppm. ^{13}C NMR (63 MHz, $CDCl_3$): δ = 142.0, 139.8, 130.4, 129.2, 129.0, 128.0, 127.2, 124.0, 123.9, 123.8 ppm.

3,4-Dichlorobiphenyl (20): The reaction was carried out as described in the general procedure for Suzuki cross-coupling reactions. The product obtained was a white solid. Yield 20 mg (90%). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.68–7.38 (m, 8 H) ppm. ^{13}C NMR (63 MHz, $CDCl_3$): δ = 141.2, 138.8, 137.5, 130.7, 129.0, 128.1, 127.0, 126.3 ppm. M.p. 47–48 °C (ref.[28] 48–49 °C).

4-Fluorobiphenyl (21): The reaction was carried out as described in the general procedure for Suzuki cross-coupling reactions. The product obtained was a white solid. Yield 16 mg (93%). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.59–7.52 (m, 4 H), 7.44 (t, J = 7.3 Hz, 2 H), 7.35 (t, J = 7.2 Hz, 1 H), 7.13 (t, J = 8.7 Hz, 2 H) ppm. ^{13}C NMR (63 MHz, $CDCl_3$): δ = 162.5 (d, J = 246.3 Hz), 140.3, 137.4, 128.8, 128.7, 128.6, 127.2, 127.0, 115.6 (d, J = 21.4 Hz) ppm. M.p. 72–73 °C (ref.[29] 71–72 °C).

3-Nitrobiphenyl (22): The reaction was carried out as described in the general procedure for Suzuki cross-coupling reactions. The product obtained was a yellow solid. Yield 18 mg (90%). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 8.46 (t, J = 2.0 Hz, 1 H), 8.20 (ddd, J =

1.0, 2.3, 8.2 Hz, 1 H), 7.92 (ddd, J = 1.1, 1.7, 7.8 Hz, 1 H), 7.65–7.40 (m, 6 H) ppm. ^{13}C NMR (63 MHz, $CDCl_3$): δ = 148.8, 142.9, 138.7, 133.0, 129.7, 129.2, 128.5, 127.2, 122.0, 121.9 ppm. M.p. 59–60 °C (ref.[30] 60–61 °C).

3-Chloro-4-methoxybiphenyl (23): The reaction was carried out as described in the general procedure for Suzuki cross-coupling reactions. The product obtained was a white solid. Yield 20 mg (91%). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.63–7.30 (m, 7 H), 7.00 (d, J = 8.5 Hz, 1 H), 3.95 (s, 3 H) ppm. ^{13}C NMR (63 MHz, $CDCl_3$): δ = 154.4, 139.5, 134.7, 128.8, 127.2, 126.7, 126.2, 122.8, 112.3, 56.2 ppm. M.p. 91–92 °C (ref.[31] 93 °C).

5-Phenylindole (24): The reaction was carried out as described in the general procedure for Suzuki cross-coupling reactions. The product obtained was a yellow oil. Yield 18 mg (93%). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 8.15 (br. s, 1 H), 7.89 (s, 1 H), 7.68 (dd, J = 1.3, 8.3 Hz, 2 H), 7.49–7.43 (m, 4 H), 7.36–7.33 (m, 1 H), 7.24 (m, 1 H), 6.64–6.62 (m, 1 H) ppm. ^{13}C NMR (63 MHz, $CDCl_3$): δ = 142.5, 135.3, 133.4, 129.0, 128.6, 127.4, 126.3, 124.8, 121.9, 119.2, 111.2, 103.0 ppm.

Supporting Information (see also the footnote on the first page of this article): ^{1}H, ^{13}C and HPLC spectra of compounds **1**–**24**.

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