Covalently Bonded Platinum(II) Complexes of α-Amino Acids and Peptides as a Potential Tool for Protein Labeling

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Abstract: Arylplatinum(II) complexes have been covalently bonded to the N and C termini and to the α-carbon of various amino acid derivatives. These organometallic-functionalized amino acid compounds can be converted into the corresponding free amino acids under both basic and acidic conditions; this demonstrates the excellent stability properties of these biomolecules. Due to the NMR activity displayed by the ^{195}Pt nucleus (natural abundance 33.8%, $I = ½$) these compounds are functional biomarkers. Furthermore, the ability of the arylplatinum functional group to bind SO_2 gas, selectively and reversibly as indicated by changes in the spectroscopic properties (^{1}H, ^{13}C, ^{195}Pt NMR and UV spectra) of these compounds, allows for the potential use of these complexes as in vitro biosensors.

Keywords: amino acids · biomarkers · biosensors · NMR spectroscopy · platinum

Introduction

Labeling of peptides and/or proteins has furnished valuable insights into the structure and function of biomolecules. In addition to fundamental aspects, these insights also have an impact on medicinal research and applications.[1] Radioactive isotopes (RIs) have been widely used as biomarkers, because of their high detection sensitivity.[2] However, because of their hazardous nature and short shelf life, the development of an alternative detection system that is convenient and practical without relying on RIs is eagerly hoped for. In the last decade, improvements in fluorescence-based techniques have made fluorescence labels competitive with RI techniques.[3] Some biological molecules, such as proteins with high tryptophan residue contents, display an intrinsic fluorescence emission. To overcome their interference, new dyes with absorption in the near-infrared region have been developed. These new types of fluorescence labels, however, are normally large aromatic molecules that might modify the native structure of the labeled biomolecule.[4] Therefore, the use of organometallic compounds as an alternative method for the labeling of amino acids or peptides has recently been at the center of the attention of the scientific community.[5] Appropriate organometallic biomarkers must emit a characteristic signal remote from the signals of the biomolecule, they must be stable under physiological conditions, and they should not interfere with the labeled system. Moreover, the organometallic group must be left untouched under standard peptide chemistry conditions and, vice versa, the reaction that links the biomarker to the peptide may not affect the labeled biomolecule. Another essential requirement of the organometallic moiety is its chemoselectivity, that is, no doubt should remain either about the number of attached organometallic centers, or about their site of attachment to the biomolecule.

Recently, we have reported the potential application of organoplatinum(II) complexes of the type [PtX(NCN-R)] (NCN-R is the abbreviation for the terdentate coordinating monoanionic 2,6-bis(dimethylaminomethyl)-4-R-phenyl "pincer" ligand containing a functional group R: see Figure 1) for the labeling of biomolecules.[6] The use of these platinum(II) species as biomarkers is based on the NMR

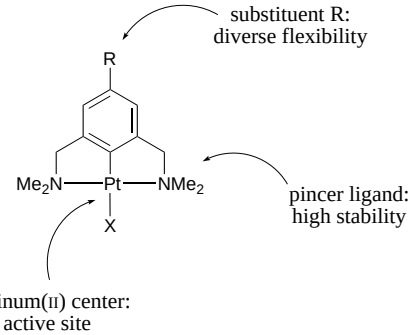

Figure 1. A diagnostic NCN "pincer" platinum(II) entity for α-amino acids. Various functional groups may be introduced into the aryl moiety of the ligand system.

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activity displayed by the ^{195}Pt nucleus (natural abundance 33.8 %, $I = ½$).[7] Chemical shift values and coupling constants are direct consequences of the steric and electronic environment around the observed nuclei, and different values are therefore usually obtained, depending on the R group attached to the organometallic site. Thus, peptide functionalization with these complexes provides a biomarker not only for biochemical purposes, but also for medical applications, since the potential use of the ^{195}Pt nucleus in MRI techniques has been demonstrated.[8]

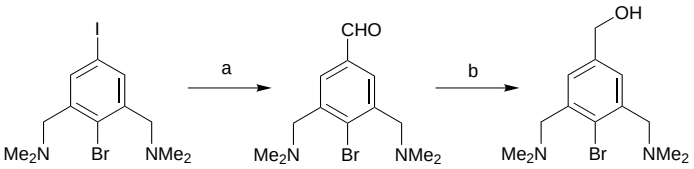
A further important property of the NCN platinum(II) complexes is their ability to bind SO_2 selectively and reversibly; this is readily indicated by a change in their spectroscopic properties, detectable by UV-visible spectroscopy even at very low concentrations (μm).[9] This provides functional biomarkers, which can be simultaneously used as biosensors.

Here we report on an extension of the application of NCN platinum(II) complexes as biomarkers and biosensors. We demonstrate the successful labeling of the N and C termini and the α-carbons of several amino acids and peptides with these organometallic sites, as well as the identification of the attachment by exploitation of the SO_2 recognition ability and NMR activity of the Pt^{II} center.

Results and Discussion

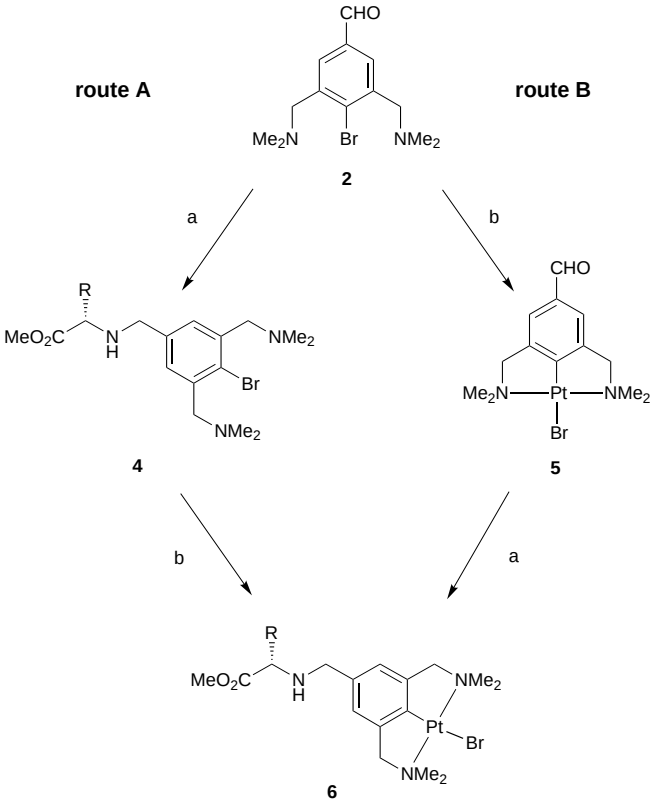
Synthesis of α-amino acids labeled at the N and C termini: To preserve the enantiomeric purity of the starting α-amino acid derivatives, standard peptide chemistry was applied to attach the "pincer" ligand [X(NCN-R)] to either the N or C termini. Furthermore, any synthetic method chosen had to be compatible with the organometallic functional group of the desired molecule.[10]

Aldehydes are valuable synthons, commonly used to functionalize or synthesize α-amino acids, and therefore we have used them to label the N termini of several amino acids (Scheme 1). Reduction of the carbonyl moiety to the corresponding alcohol could be achieved under mild conditions. This alcohol was used to introduce the ligand at the C terminus of an α-amino acid by a simple esterification procedure. The key molecule used to achieve this goal was the bifunctional ligand precursor [NC(Br)N-I-4] (**1**),[11] containing two carbon–halogen bonds (C_{aryl}–I and C_{aryl}–Br) with different reactivities. The selective lithiation of the *para* position was accomplished by iodine/lithium exchange at −100 °C, with *t*BuLi as base. The aryllithium intermediate formed was trapped with DMF; this afforded, after aqueous workup, aldehyde [NC(Br)N-CHO-4] (**2**) in 87 % yield. Reduction of **2** with sodium borohydride in methanol at room temperature yielded alcohol **3** (86 %).



Scheme 1. Reagents and conditions: a) *t*BuLi (2 equiv), THF, −100 °C, 10 min; then DMF, RT, 12 h; b) $NaBH_4$ (2 equiv), MeOH, RT, 1 h.

Condensation of aldehyde **2** with several α-amino esters in their hydrochloride forms[12] was performed in the presence of triethylamine and magnesium sulfate, yielding the corresponding Schiff bases.[13] In situ reduction of the imine intermediate with sodium cyanoborohydride afforded the N-substituted α-amino esters **4**, containing the required pincer ligand precursor for the direct introduction of the metallic site (Scheme 2, route A, Table 1). [{Pt(4-tol)$_2$(SEt$_2$)}$_2$][14] was used



Scheme 2. Synthesis of α-amino acids labeled at their N termini. Reagents and conditions: a) $MeO_2CCH(R)NH_3^+Cl^-$, $MgSO_4$, Et_3N, CH_2Cl_2, RT, 12 h; then $NaBH_3CN$, HOAc, MeOH, 10 °C to RT, 2 h; b) [Pt(4-tol)$_2$(SEt$_2$)]$_2$, C_6H_6, 50 °C, 3 h.

Abstract in Dutch: *Platina-gemarkeerde α-aminozuren werden gesynthetiseerd door NCN-platina complexen via de parapositie covalent te koppelen met de N, C termini en de α-koolstofterminus van verschillende α-aminozuren. Deze organometaal gefunctionaliseerde α-aminozuren kunnen eenvoudig omgezet worden in het vrije aminozuur door gebruik te maken van zure en basische reagentia, hetgeen de uitstekende stabiliteit van de NCN-platina groep in deze biomoleculen aantoont. Dankzij de NMR activiteit van de ^{195}Pt kern (natuurlijk voorkomen 33.8 %, I = 1/2) zijn deze verbindingen geschikt als biomarkers. Verder blijkt de NCN-platina groep ook in deze verbindingen selectief en reversibel met SO_2 gas te reageren, hetgeen tot uiting komt in een ogenblikkelijke verandering van hun spectroscopische eigenschappen (^{1}H, ^{13}C, ^{195}Pt en UV). Deze complexen kunnen tevens worden gebruikt als potentiele in vitro biosensoren.*

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Table 1. Synthesis of α-amino acids labeled at their N termini.

Entry	α-Amino ester	R	Route[a]	Product			
				No.	Yield (%)[b]	No.	Yield (%)[b]
1	L-ValOMe	$(CH_3)_2CH$	A	**4a**	87	**6a**	51
2	L-ValOMe	$(CH_3)_2CH$	B	**5**	76	**6a**	49
3	L-PheOMe	$PhCH_2$	A	**4b**	85	**6b**	52
4	GlyOEt	H	A	**4c**	–	**6c**	–
5	L-Asp$(OMe)_2$	CH_2CO_2Me	A	**4d**	61	**6d**	32

[a] See Scheme 2. [b] Overall yield of the isolated pure product after column chromatography.

Table 2. Synthesis of α-amino acids labeled at their C termini.

Entry	*N*-Boc α-amino acids	R	Route[a]	Product			
				No.	Yield (%)[b]	No.	Yield (%)[b]
1	L-Val	$(CH_3)_2CH$	A	**7a**	37	**9a**	15
2	L-Val	$(CH_3)_2CH$	B	**8**	59	**9a**	71
3	L-Phe	$PhCH_2$	A	**7b**	–	**9b**	47
4	Gly	H	A	**7c**	–	**9c**	44
5	L-Asp[c]	CH_2CO_2Me	B	**7d**	–	**9d**	61

[a] See Scheme 3. [b] Overall yield of the isolated pure product after column chromatography. [c] The carboxylic moiety at the 4-position was protected as a benzyl ester.

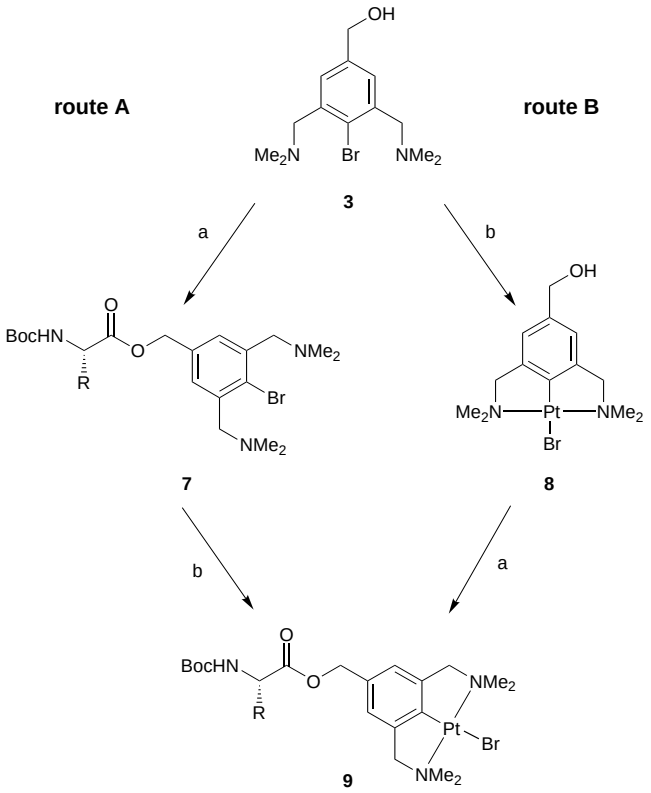
as a metalation reagent, affording the organoplatinum-labeled α-amino ester derivatives **6** (Scheme 2, Table 1). Similar yields were obtained when valine and phenylalanine methyl esters were used as starting materials (entries 1 and 3, Table 1). When glycine ethyl ester was used, condensation with **2** took place in a good yield, but only decomposition products were obtained in the subsequent reduction step (entry 4, Table 1). For the aspartic acid derivative, with both carboxylate functions protected, the yield for the formation of **4d** was lower than for the corresponding compounds **4a** and **4b** (cf. entry 5 with 1 and 2 in Table 1), while the metalation step proceeded equally well in all three cases.

Alternatively, a modular approach can be used for the direct attachment of the organometallic pincer derivative at the N termini of α-amino acids (route B, Scheme 2). Thus, platination of **2** by the same procedure as that used for the pincer-bound α-amino acids (vide supra) led to the metalated aldehyde **5** in 76% yield. Subsequently, **5** was treated with the respective α-amino esters in the presence of triethylamine and magnesium sulfate. Further reduction of the formed imines with sodium cyanoborohydride led to the labeled α-amino acids without affecting the organometallic site (Scheme 2). In the case of valine, **6a** was obtained by this method (entry 2, Table 1), the yield being similar to that obtained by route A. However, route B required more precise control both of reaction temperature (below 10 °C) and time (not longer than 2 hours). Despite these restrictions, this modular approach demonstrates the excellent stability properties of the organoplatinum unit.

α-Amino acids labeled at their C termini can also be obtained by both approaches: namely by chemical condensation between the pincer ligand alcohol derivative [NC(Br)N-CH_2OH] (**3**) by use of dicyclohexylcarbodiimide (DCC) and 4-dimethylaminopyridine (4-DMAP) and subsequent platination, or vice versa (Scheme 3, routes A and B, respectively).

Attempts to purify the intermediate ligand **7** that contains Boc-protected ester derivatives by column chromatography led to lower overall yields in the case of valine (entry 1, Table 2). Hence, the platination step was carried out with crude **7**, and the obtained organoplatinum α-amino acids derivatives **9** were then isolated by column chromatography. Despite this, the isolated yields for **9** were always superior when route B was followed (entry 5, Table 2).

The organometallic unit in an α-amino acid labeled at the C terminus is bound through a methylene linker. To study the possible electronic and chemical influence of this CH_2 unit (vide infra) in the arylplatinum moiety, we prepared two



Scheme 3. Synthesis of α-amino acids labeled at their C termini. Reagents and conditions: a) $HO_2CCH(R)NHBoc$, DCC, 4-DMAP, CH_2Cl_2, RT, 12 h; b) $[Pt(4\text{-}tol)_2(SEt_2)]_2$, C_6H_6, 50 °C, 3 h.

examples of C-termini-labeled α-amino acids directly bound to the organometallic unit (Scheme 4).

Thus, direct introduction of the platinated alcohol derivative **10**, again by means of DCC coupling, allowed the synthesis of the desired phenolic ester derivatives **11**. In this way, valine and phenylalanine C-terminus-platinated phenolic derivatives were obtained in 57 and 55% yields, respectively (Scheme 4).

Synthesis of labeled free α-amino acids: Conversion of the N- and C-labeled α-amino esters into the corresponding free α-amino acids would widen the applicability of the [PtX(NCN)] unit as a biomarker, since this would offer the possibility to include these labeled α-amino acids in peptide chemistry. Interestingly, **6a** and **6b** were easily hydrolyzed by treatment of solutions of **6a** and **6b** in THF/H_2O with lithium hydroxide, without affecting the platinum(II) center (Scheme 5).[15] The deprotected derivatives were first obtained as lithium salts

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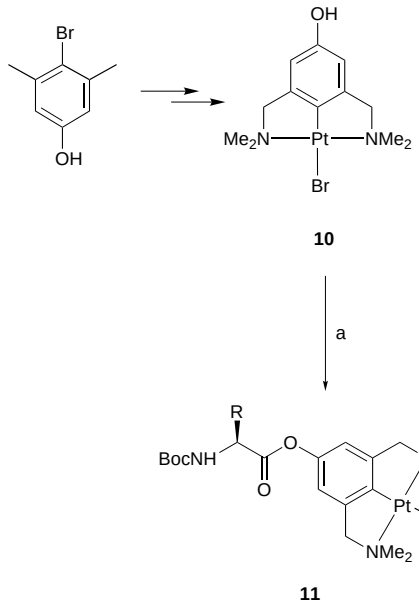
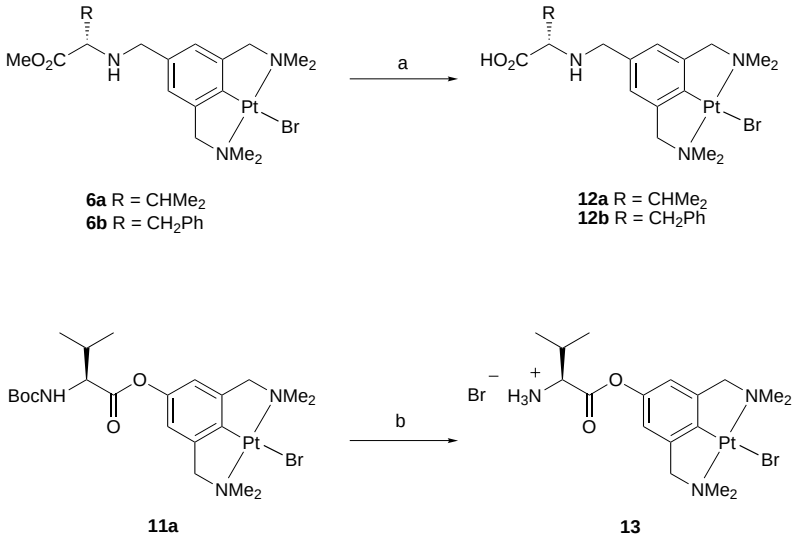


Scheme 4. Synthesis of α-amino acids labeled at their C termini. Reagents and conditions: a) $HO_2CCH(R)NHBoc$, DCC, 4-DMAP, CH_2Cl_2, RT, 12 h.



Scheme 5. Deprotection of α-amino acids bound to platinum "pincer" markers. Reagents and conditions: a) LiOH, MeOH, RT, 12 h; b) HBr/AcOH or HBr/Et_2O, RT, 1 h.

and then transformed into the acids by ion-exchange chromatography, affording **12a** and **12b** each in 70% yield.

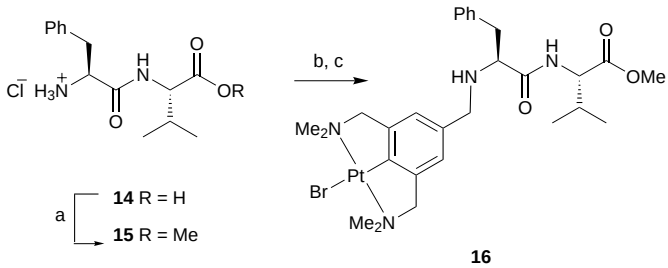
Deprotection of Boc-protected α-amino acids is normally accomplished by treatment with trifluoroacetic acid (TFA). When this method was applied to the C-terminus-labeled α-amino acids **9** or **11**, only decomposition products were obtained, probably due to initial displacement of the bromine atom attached to the platinum center by trifluoroacetate, leading to reactive platinum derivatives. Consequently, an alternative deprotection method had to be used. Thus, **11a** was treated with a solution of HBr/HOAc at room temperature, yielding **13** as its ammonium salt. Although the platinum–carbon bond remained intact, about 10% of the bromine was replaced by acetate. However, pure **13** was obtained by treatment of **11a** with a solution of HBr/Et_2O (Scheme 5).

When the same deprotection methods were applied to **9a**, the benzylic bond between the amino acid and the NCN-Pt entity was cleaved, affording the free α-amino acid and the starting platinated alcohol **8**. However, this result is also potentially useful for those studies in which the recovery of the nonplatinated amino acid or peptide is required.

Labeling of peptides: We studied the introduction of the biomarker into peptides by the methodology developed in this work for the attachment of the [PtX(NCN)]-unit to α-amino acids.

To show the feasibility of this approach, the dipeptide L-Phe-L-Val was attached to the pincer ligand. Treatment of a methanol solution of L-Phe-L-Val with $SOCl_2$ afforded the methyl ester-protected dipeptide **15**.[16] This was followed by the introduction of the ligand and the metal center (vide supra, Scheme 2, route A). The obtained product was purified by column chromatography to give **16** in 31% overall yield (Scheme 6).

Synthesis of α-labeled α-amino acids: Even more challenging would be the introduction of the organometallic site at the α-position of an amino acid. This new labeled α-amino acid would allow the insertion of the biomarker at any position in a peptide chain. To this end we followed a recently reported procedure for the preparation of enantiomerically pure α-amino acids bearing an aryl moiety in the side chain.[17] Eventually, protected racemic allyl glycine ester[18] was used as a substrate for the hydroboration/Suzuki coupling reaction with the bifunctional precursor [NC(Br)N-I-4] (**1**). The reaction was accomplished with [$PdCl_2$(dppf)] as a catalyst, affording **18** after 12 h at reflux. The metalation of the obtained product was carried out with [{Pt(4-tol)$_2$(SEt$_2$)}$_2$], yielding



Scheme 6. Synthesis of a dipeptide labeled at the N terminus. Reagents and conditions: a) $SOCl_2$, MeOH, Δ, 1 h; b) **2**, $MgSO_4$, Et_3N, CH_2Cl_2, RT, 12 h, then $NaBH_3CN$, HOAc, MeOH, 10 °C to RT, 2 h; c) [Pt(4-tol)$_2$(SEt$_2$)]$_2$, C_6H_6, 50 °C, 3 h.

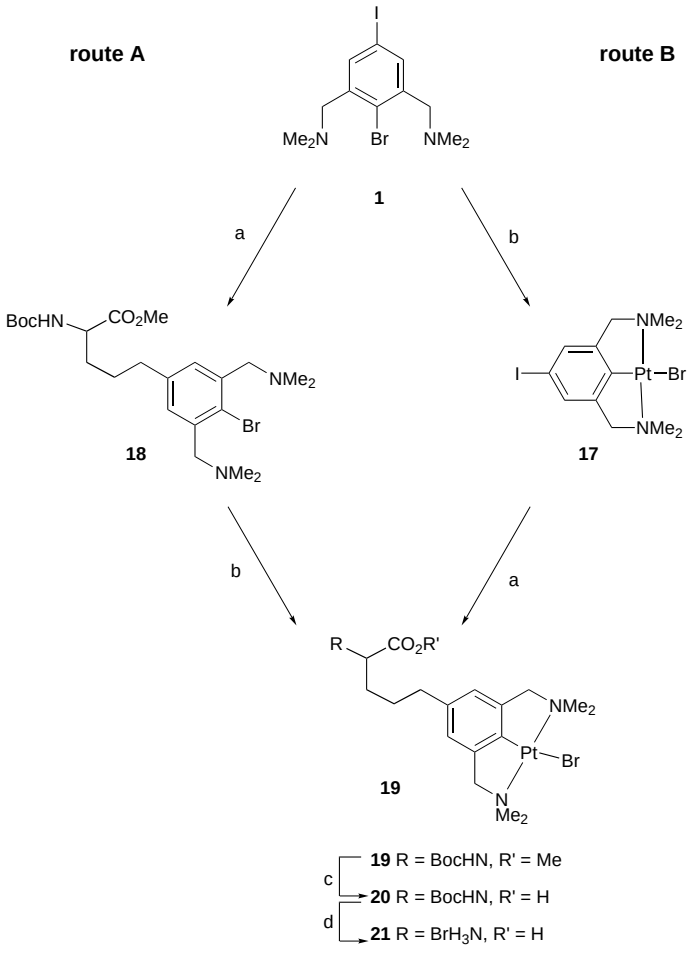
the expected α-labeled amino acid **19** in 45% overall yield after purification (Scheme 7).

Even the metalated compound [PtBr(NCN-I-4)] **17** could be used as starting material in the hydroboration/Suzuki coupling reaction, which took place at room temperature (i.e., under very mild conditions) in only 3 h. In this way, **19** was obtained in 29% overall yield (Scheme 7).

The hydrolysis of the product to give the free α-metalated amino acid was accomplished in two steps (Scheme 7). Treatment of **19** with LiOH in a THF/H_2O mixture gave acid **20** (77%), and subsequent treatment with HBr/Et_2O yielded the free α-labeled amino acid **21** (75%).

^{195}Pt NMR measurements on the pincer-Pt^{II} labeled α-amino acids: To study whether functionalization of NCN-pincer platinum(II) complexes with α-amino acids would provide diagnostic organometallic biomarkers for biochemical applications,[19] ^{195}Pt NMR spectra of the various NCN-pincer platinum(II)-labeled α-amino acid derivatives were recorded in $CDCl_3$ (0.1M) (Table 3). The chemical shifts for the N-terminus derivatives amounted to $\delta = -1973$ to -1980 ppm, while for the C-terminus complexes these values were found in a somewhat narrower range of $\delta = -1963$ to -1967 ppm. The absence of the methylene linker in **11** does not have any influence on the platinum chemical shifts of these complexes. Furthermore, spectra of **6b** recorded at various concentrations in the range of 0.01–0.1M showed an almost constant ^{195}Pt chemical shift value. However, the ^{195}Pt NMR shifts are dependent on the nature of the solvent, as has been shown for **6a** (entry 5, Table 3). These results suggest that it is possible to distinguish between NCN-Pt^{II} N- and/or C-labeled α-amino acids and acid derivatives. The α-functionalized compounds have ^{195}Pt NMR shifts at $\delta = -1997$ to -1980 ppm.

Large ^{195}Pt NMR chemical shifts were observed upon coordination of SO_2, which also produced an instantaneous change of the color of the solution from colorless to orange.[20] The downfield shift points to a strong deshielding of the platinum nucleus upon SO_2 binding and is in accordance with a platinum-to-ligand charge transfer. As expected, the observed chemical shifts were also dependent on the concentration of SO_2 in solution.



Scheme 7. Synthesis of an α-amino acid labeled at the α-carbon. Reagents and conditions: a) Boc-allylOMe, 9-BBN, THF, 2 h RT, then K_3PO_4, DMF, 10% [$PdCl_2$(dppf)], **1**, Δ, 12 h or K_3PO_4, DMF, 10% [$PdCl_2$(dppf)], **17**, RT, 3 h; b) [Pt(4-tol)$_2$(SEt_2)]$_2$, C_6H_6, 50°C, 3 h; c) LiOH, MeOH, RT, 12 h; d) HBr/Et_2O, RT, 1 h.

Conclusion

A new methodology, involving covalent linking of an NCN "pincer" platinum(II)-entity, has been developed for the labeling of α-amino acids, and possibly also peptides, at either their N or their C termini, or at the α-carbon. The excellent chemical stability of the [PtX(NCN)]-entity under physiological conditions provides a route to peptide labeling with a broad application potential. The ability of the [PtX(NCN)] entity to bind SO_2, changing the spectroscopic properties and the color of the labeled systems, both in solution and in solid phase,[21] allows their application in combinatorial and solid-phase in vitro biochemistry studies.

Experimental Section

General: Syntheses involving organolithium compounds were carried out under nitrogen atmosphere by using standard Schlenk techniques. THF, benzene, and Et_2O were dried from Na/benzophenone and distilled prior to use. CH_2Cl_2 was distilled from CaH_2. DMF and NEt_3 were flash distilled from CaH_2 and stored over molecular sieves. The platinum salt [{Pt(4-tol)$_2$(SEt_2)}$_2$],[14a] the ligand precursor [NC(Br)N-I-4] (**1**),[11] and compounds **2**,[6] **4a**,[6] **5**,[6] **6a**,[6] and **17**[11] were prepared by published procedures. All other reagents were obtained commercially and used without further purification. The ^{1}H and ^{13}C NMR spectra were recorded at 25°C at 300 and 75 MHz, respectively, and were referenced to external $SiMe_4$ ($\delta = 0.00$ ppm, J in Hz). ^{195}Pt NMR spectra (64.5 MHz) were referenced to external Na_2PtCl_6 ($\delta = 0$ ppm).[11b] Elemental analyses were performed by Kolbe, Mikroanalytisches Laboratorium (Mülheim, Germany). ES-MS were obtained from the Biomolecular Mass Spectrometry Department of Utrecht University. MALDI-TOF-MS spectra were acquired with a Voyager-DE BioSpectrometry Workstation (PerSeptive Biosystems, Framingham, MA) mass spectrometer equipped with a nitrogen laser emitting at 337 nm. The instrument was operated in the linear mode at an accelerating voltage in the range of 22000 V. External calibration was performed with C_{60}/C_{70}, and detection was performed with a linear detector and digitizing oscilloscope operating at 500 MHz. Sample solutions of ≈ 10 mg mL^{-1} in THF were used, and the matrix was either 3,5-dihydroxybenzoic acid or 5-chlorosalycilic acid in THF (10 mg mL^{-1}). A solution of silver(I) trifluoroacetate in THF was in some cases added to the

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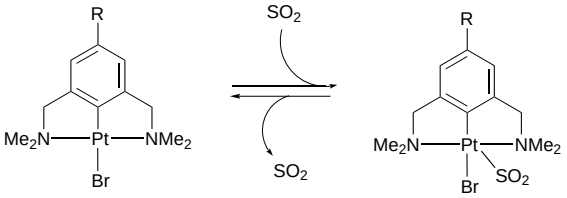
Table 3. ^{195}Pt NMR data for platinum complexes.[a]



Entry	Compound	R	Solvent	δ_{Pt}	$\delta_{Pt/SO_2adduct}$	$\Delta\delta$
1	[PtBr(NCN)]	H	$CDCl_3$	−1982	−743	1239
2	**17**	I	$CDCl_3$	−1942	−901	1041
3	**5**	CHO	$CDCl_3$	−1960	−1156	804
N termini						
4	**6a**	CH_2-L-Val-OMe	$CDCl_3$	−1982	−751	1231
5			C_6D_6	−1944	−830	1114
6	**6b**	CH_2-L-Phe-OMe	$CDCl_3$	−1973	−732	1241
7			$CDCl_3$[b]	−1980	–	–
8	**6d**	CH_2-L-Asp-OMe[c]	$CDCl_3$	−1983	−954	1029
9	**12a**	CH_2-L-Val-OH	CD_3OD	−1972	−1170	802
10	**12b**	CH_2-L-Phe-OH	CD_3OD	−1973	−1170	803
11	**16**	CH_2-L-Phe-L-Val-OMe	$CDCl_3$	−1983	−954	1029
C termini						
12	**9a**	CH_2-L-Val-Boc	$CDCl_3$	−1964	−870	1094
13	**9b**	CH_2-L-Phe-Boc	$CDCl_3$	−1963	−1219	744
14	**9c**	CH_2-Gly-Boc	$CDCl_3$	−1964	−776	1188
15	**9d**	CH_2-L-Asp-Boc[c]	$CDCl_3$	−1964	−1152	812
16	**11a**	L-Val-Boc	$CDCl_3$	−1967	−790	1177
17	**11b**	L-Phe-Boc	$CDCl_3$	−1967	−883	1084
18	**13**	L-Val-NH_3Br	CD_3OD	−1982	–	–
α-labeled						
19	**19**	BocHN{$CH(CH_2)_3$}CO_2Me	$CDCl_3$	−1997	−1078	919
20	**20**	BocHN{$CH(CH_2)_3$}CO_2H	$CDCl_3$	−1982	−998	984
21	**21**	BrH_3N{$CH(CH_2)$}CO_2H	DMSO	−1980	–	–

[a] 0.01 M solutions; δ (ppm). [b] 0.1 M solutions. [c] The carboxylic acid moiety at the 4-position was protected as a methyl ester in **6d** and as a benzyl ester in **9d**.

sample in order to improve the peak resolution. The sample solution (0.2 μL) and the matrix solution (0.2 μL) were combined and placed on a gold MALDI target and analyzed after evaporation of the solvents.

[NC(Br)N-CH_2OH-4] (3): $NaBH_4$ (0.23 g, 6.2 mmol) was added to a solution of **2** (0.93 g, 3.1 mmol) in MeOH (40 mL). The solution was stirred for 1 h at room temperature. The solvent was removed in vacuo, and the resulting residue was dissolved in CH_2Cl_2 (25 mL) and washed with H_2O and brine. The organic layer was dried over $MgSO_4$, and solvent was removed under reduced pressure to afford **3** as a yellowish oil (0.80 g, 86 %). ^{1}H NMR ($CDCl_3$): $\delta = 2.29$ (s, 12H; NCH_3), 3.40 (br s, 1H; CH_2OH) 3.55 (s, 4H; CH_2NMe_2), 4.62 (s, 2H; CH_2OH), 7.35 (s, 2H; ArH); ^{13}C NMR ($CDCl_3$): $\delta = 45.5$ (NCH_3), 63.7 (CH_2NMe_2), 64.3 (CH_2OH), 97.2, 125.6, 127.9 (ArH), 138.4; elemental analysis calcd (%) for $C_{13}H_{21}BrN_2O$ (301.23): C 51.83, H 7.03, N 9.30; found: C 51.91, H 6.97, N 9.19.

General procedure for the synthesis of α-amino acids 6, labeled at their N termini—Route A: A mixture of α-amino acid hydrochloride, protected as an ester (12 mmol), triethylamine (1.63 mL, 12 mmol), and an excess of $MgSO_4$ (8 g) were stirred in CH_2Cl_2 (25 mL) at room temperature for 16 h. All solids were filtered off, and the volatile components were removed under reduced pressure to yield a yellow oil, which was dissolved in MeOH (20 mL) and HOAc (0.33 mL, 5.85 mmol). This solution was cooled below 10 °C, and $NaBH_3CN$ (0.73 g, 12 mmol) was added in portions. The reaction mixture was allowed to warm to room temperature and stirred for an additional 2 h. All volatile components were removed in vacuo, and the resulting residue was diluted with NaOH (2 M, 50 mL) and extracted with EtOAc (3 × 30 mL). The combined organic layers were washed with brine (30 mL) and dried over $MgSO_4$. Volatile components were removed, and the resulting oil was purified by column chromatography (SiO_2, EtOAc/MeOH/NH_4OH, 80:8:2) to yield **4**. A mixture of **4** (0.43 mmol) and [{Pt(4-tol)$_2$(SEt_2)}$_2$] (200 mg, 0.22 mmol) in dry benzene (30 mL) was heated at 50 °C for 3 h. Volatile components were removed at reduced pressure, and the resulting oil was washed with pentane (2 × 30 mL). The formed precipitate was removed by centrifugation and decanting of the clear supernatant. The solid residue was concentrated and purified by gradient column chromatography (SiO_2, CH_2Cl_2/acetone). The platinum-containing fractions were collected and evaporated to dryness, yielding **6** as a solid.

Route B: A mixture of **5** (110 mg, 0.23 mmol), L-valine methyl ester hydrochloride (75 mg, 0.45 mmol), triethylamine (0.06 mL, 0.45 mmol), and $MgSO_4$ (1.0 g) was stirred in CH_2Cl_2 (10 mL) at room temperature for 24 h. All solids were filtered off, volatile components were removed under reduced pressure, and the residue was dissolved in MeOH (10 mL) and HOAc (0.02 mL, 0.23 mmol). This solution was kept below 10 °C while portions of $NaBH_3CN$ (27.9 mg, 0.44 mmol) were added. The reaction mixture was then warmed to room temperature and stirred for 2 h. All volatile components were removed in vacuo, and the residue was extracted with NaOH (2 M, 20 mL) and CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with brine (20 mL) and dried over $MgSO_4$. The $MgSO_4$ was filtered off, and the volatile components from the filtrate were removed in vacuo. The resulting oil was purified as described in route A. Yield of **6a**: 85 mg (49 %).

[NC(Br)N-(CH_2-L-Val-OMe)-4] (4a): ^{1}H NMR ($CDCl_3$): $\delta = 0.91$ (d, ^3J(H,H) = 5.6 Hz, 3H; $CH(CH_3)_2$), 0.94 (d, ^3J(H,H) = 5.2 Hz, 3H; $CH(CH_3)_2$), 1.88 (m, 1H; $CH(CH_3)_2$), 2.24 (s, 1H; NH), 2.31 (s, 12H; NCH_3), 2.96 (d, ^3J(H,H) = 6.2 Hz, 1H; NH-C*H*-CO), 3.52 (downfield part of AB signal, ^3J(H,H) = 6.2 Hz, 1H; Ar-CH_2-NH), 3.53 (s, 4H; CH_2NMe_2), 3.71 (s, 3H; OCH_3), 3.81 (upfield part of AB signal, ^3J(H,H) = 6.2 Hz, 1H; Ar-CH_2-NH), 7.29 (s, 2H; ArH); ^{13}C NMR ($CDCl_3$): $\delta = 18.6$ ($CH(CH_3)_2$), 19.3 ($CH(CH_3)_2$), 31.7 ($CH(CH_3)_2$), 45.6 (NCH_3), 51.3 (OCH_3), 51.7 (Ar-CH_2-NH), 64.0 (CH_2NMe_2), 66.4 (NH-CH-CO), 125.3 (C), 129.3, 138.5 (C), 138.6 (C), 175.6 (COOMe); elemental analysis calcd (%) for $C_{19}H_{32}BrN_3O_2$ (414.39): C 55.07, H 7.78, N 10.14; found: C 55.21, H 7.85, N 9.96.

[NC(Br)N-(CH_2-L-Phe-OMe)-4] (4b): $[\alpha]_D^{25} = -3.0°$ ($c = 1.7$ in $CHCl_3$); ^{1}H NMR ($CDCl_3$): $\delta = 2.29$ (s, 12H; NCH_3), 2.93 (d, ^3J(H,H) = 6.5 Hz, 2H; CH_2Ph), 3.47–3.64 (m, 5H; CH_2NMe_2, NH-CH-CO), 3.58 (downfield part of AB signal, ^3J(H,H) = 13.4 Hz, 1H; Ar-CH_2-NH), 3,64 (s, 3H; OCH_3), 3.80 (upfield part of AB signal, ^3J(H,H) = 13.4 Hz, 1H; Ar-CH_2-NH), 7.20 (m, 7H; ArH); ^{13}C NMR ($CDCl_3$): $\delta = 39.7$ (CH_2Ph), 45.2 (NCH_3), 51.1 (OCH_3), 51.6 (Ar-CH_2-NH), 61.9 (NH-CH-CO), 63.8 (CH_2NMe_2), 125.4 (C), 126.6, 128.3, 129.1, 129.3, 129.7 (C), 137.1 (C), 138.2 (C), 174.8 (COOMe); MS (MALDI-TOF): m/z calcd: 461.2 [M^+]; found: 461.1; elemental analysis calcd (%) for $C_{23}H_{32}BrN_3O_2$ (462.42): C 59.74, H 6.98, N 9.09; found: C 59.59, H 7.01, N 8.94.

{NC(Br)N-[CH_2-L-Asp-($OMe)_2$]-4} (4d): $[\alpha]_D^{25} = -0.6°$ ($c = 0.5$ in $CHCl_3$); ^{1}H NMR ($CDCl_3$): $\delta = 2.24$ (s, 1H; NH), 2.33 (s, 12H; NCH_3), 2.67–2.71 (m, 2H; CH_2CO_2Me), 3.55 (m, 1H; NH-CH-CO), 3.60 (s, 4H; CH_2NMe_2), 3.66 (s, 3H; OCH_3), 3.67 (downfield part of AB signal, ^3J(H,H) = 13.4 Hz, 1H; Ar-CH_2-NH), 3.71 (s, 3H; OCH_3), 3.85 (upfield part of AB signal, ^3J(H,H) = 13.4 Hz, 1H; Ar-CH_2-NH), 7.31 (s, 2H; ArH); ^{13}C NMR ($CDCl_3$): $\delta = 37.8$ (CH_2CO_2Me), 45.3 (NCH_3), 51.1 (OCH_3), 51.7 (OCH_3), 52.0 (Ar-CH_2-NH), 56.9 (NH-CH-CO), 63.6 (CH_2NMe_2), 125.1 (C), 129.7, 137.9 (C), 138.5 (C), 171.2 (COOMe), 173.8 (COOMe); MS (MALDI-

TOF): *m*/*z* calcd: 443.4 [M^+]; found: 445.3; elemental analysis calcd (%) for $C_{19}H_{30}BrN_3O_4$ (444.38): C 51.35, H 6.81, N 9.46; found: C 51.49, H 6.90, N 9.49.

[PtBr(NCN-{CH$_2$-L-Val-OMe}-4)] (6a): $[\alpha]_D^{25} = -7.7^\circ$ ($c = 1$ in $CHCl_3$); ^{1}H NMR ($CDCl_3$): $\delta = 0.88$ (d, ^3J(H,H) = 3.4 Hz, 3H; CH(CH_3)$_2$), 0.92 (d, ^3J(H,H) = 3.8 Hz, 3H; CH(CH_3)$_2$), 1.90 (m, 1H; CH(CH$_3$)$_2$), 2.28 (s, 1H; NH), 3.07 (s, ^3J(Pt,H) = 37.8 Hz, 12H; NCH$_3$), 3.05 (d, ^3J(H,H) = 17.2 Hz, 1H; NH-CH-CO), 3.39 (downfield part of AB signal, ^3J(H,H) = 13.4 Hz, 1H; Ar-CH_2-NH), 3.61 (upfield part of AB signal, ^3J(H,H) = 13.4 Hz, 1H; Ar-CH_2-NH), 3.69 (s, 3H; OCH$_3$), 3.97 (s, ^3J(Pt,H) = 46.0 Hz, 4H; CH_2NMe$_2$), 6.77 (s, 2H; ArH); ^{13}C NMR ($CDCl_3$): $\delta = 18.7$ (CH(CH_3)$_2$), 19.1 (CH(CH_3)$_2$), 31.6 (CH(CH$_3$)$_2$), 51.4 (OCH$_3$), 53.3 (Ar-CH_2-NH), 55.0 (NCH$_3$), 66.6 (NH-CH-CO), 77.4 (^3J(Pt,C) = 53.6 Hz, CH_2NMe$_2$), 119.6, 135.0 (C), 143.3 (^2J(Pt,C) = 78.4 Hz, (C)), 145.0 (C), 175.4 (COOMe); ES-MS: *m*/*z* calcd: 610.5 [M^++H]; found: 610.4; elemental analysis calcd (%) for $C_{19}H_{32}BrN_3O_2Pt$ (609.48): C 37.44, H 5.29, N 6.89; found: C 37.30, H 5.22, N 6.78.

[PtBr(NCN-{CH$_2$-L-Phe-OMe}-4)] (6b): $[\alpha]_D^{25} = -3.6^\circ$ ($c = 1$ in C_6H_6); ^{1}H NMR ($CDCl_3$): $\delta = 2.70 - 2.75$ (m, 2H; CH_2Ph), 3.07 (s, ^3J(Pt,H) = 37.8 Hz, 12H; NCH$_3$), 3.45 (downfield part of AB signal, ^3J(H,H) = 7.0 Hz, 1H; Ar-CH_2-NH), 3.54 (t, ^3J(H,H) = 7.0 Hz, 1H; NH-CH-CO), 3.61 (upfield part of AB signal, ^3J(H,H) = 7.0 Hz, 1H; Ar-CH_2-NH), 3.63 (s, 3H; OCH$_3$), 3.93 (s, ^3J(Pt,H) = 45.8 Hz, 4H; CH_2NMe$_2$), 6.64 (s, 2H; ArH), 7.14 – 7.26 (m, 5H; ArH); ^{13}C NMR ($CDCl_3$): $\delta = 39.0$ (C$H$$_2$Ph), 51.9 (OCH$_3$), 52.4 (Ar-C$H_2$-NH), 55.0 (NCH$_3$), 61.7 (NH-C$H$-CO), 77.4 (C$H_2NMe_2$), 119.9, 126.9, 128.5, 129.3 (C), 136.7 (C), 143.5 (C), 145.2 (C), 174.5 (COOMe); MS (MALDI-TOF): *m*/*z* calcd: 577.2 [M^+ – Br]; found: 577.7; elemental analysis calcd (%) for $C_{23}H_{32}BrN_3O_2Pt$ (656.13): C 42.01, H 4.91, N 6.39; found: C 42.13, H 4.85, N 6.31.

[PtBr(NCN-{CH$_2$-L-Asp-(OMe)$_2$}-4)] (6d): $[\alpha]_D^{25} = -0.5^\circ$ ($c = 3$ in $CHCl_3$); ^{1}H NMR ($CDCl_3$): $\delta = 2.34$ (br, 1H; NH), 2.73 (t, ^3J(H,H) = 7.0 Hz, 2H; CH_2CO$_2$Me), 3.09 (s, ^3J(Pt,H) = 36.6 Hz, 12H; NCH$_3$), 3.54 (downfield part of AB signal, ^3J(H,H) = 12.5 Hz, 1H; Ar-CH_2-NH), 3.56 – 3.66 (m, 1H; NH-CH-CO), 3.66 (s, 3H; OCH$_3$), 3.72 (upfield part of AB signal, ^3J(H,H) = 12.5 Hz, 1H; Ar-CH_2-NH), 3.73 (s, 3H; OCH$_3$), 3.98 (s, ^3J(Pt,H) = 44.8 Hz, 4H; CH_2NMe$_2$), 6.77 (s, 2H; ArH); ^{13}C NMR ($CDCl_3$): $\delta = 37.6$ (CH_2CO$_2$Me), 51.8 (OCH$_3$), 52.1 (OCH$_3$), 52.6 (Ar-CH_2-NH), 55.0 (NCH$_3$), 56.8 (NH-CH-CO), 77.3 (CH_2NMe$_2$), 119.6, 134.3 (C), 143.3 (C), 145.2 (C), 171.2 (COOMe), 173.8 (COOMe); MS (MALDI-TOF): *m*/*z* calcd: 559.2, [M^+ – Br], 364.2 [M^+ – PtBr]; found: 557.3, 362.3; elemental analysis calcd (%) for $C_{19}H_{30}BrN_3O_4Pt$ (639.47): C 35.69, H 4.73, N 6.57; found: C 35.87, H 4.70, N 6.38.

General procedure for the synthesis of α-amino acids 9, labeled at their C termini—Route A: A solution of Boc-protected α-amino acid (0.5 mmol) in CH_2Cl_2 (5 mL) was slowly added at room temperature to a solution of DCC (0.156 g, 0.75 mmol), 4-DMAP (0.012 g, 0.01 mmol), and the alcohol **3** (0.180 g, 0.6 mmol) in CH_2Cl_2 (20 mL). The mixture was stirred at this temperature for 16 h. All solids were filtered off, and the organic layer was washed with a saturated solution of NH_4Cl, water, and brine, and dried over $MgSO_4$. Volatile components were removed, and the resulting oil was purified by column chromatography (SiO_2, EtOAc/MeOH/NH_4OH, 70:29:1) to afford compound **7a**. Compounds **7b** and **7c** were used without further purification. A mixture of **7** (0.40 mmol) and [{Pt(4-tol)$_2$(SEt$_2$)}$_2$] (188 mg, 0.20 mmol) in dry benzene (30 mL) was heated at 50 °C for 3 h. All volatile components were removed at reduced pressure and the resulting oil was washed with pentane (2 × 30 mL). The formed precipitate was removed by centrifugation and decanting of the clear supernatant. The solid residue was concentrated and purified by gradient chromatography (SiO_2, CH_2Cl_2/acetone). The platinum-containing fractions were collected and evaporated to dryness, yielding compounds **9** as solids.

Route B: A solution of Boc-protected α-amino acid (0.33 mmol) in CH_2Cl_2 (5 mL) was slowly added at room temperature to a solution of DCC (0.103 g, 0.5 mmol), 4-DMAP (0.005 g, 0.03 mmol), and the alcohols **8** or **10** (0.4 mmol) in CH_2Cl_2 (20 mL). The mixture was stirred at room temperature for 16 h. All solids were filtered off, and the organic layer was washed with a saturated solution of NH_4Cl, water, and brine, and dried over $MgSO_4$. Volatile components were then removed and the resulting oil was purified by column chromatography as described in route A.

[NC(Br)N-(CH$_2$-L-Val-Boc)-4] (7a): $[\alpha]_D^{25} = -2.1^\circ$ ($c = 2.3$ in $CHCl_3$); ^{1}H NMR ($CDCl_3$): $\delta = 0.82$ (d, ^3J(H,H) = 7.0 Hz, 3H; CH(CH_3)$_2$), 0.90 (d, ^3J(H,H) = 7.0 Hz, 3H; CH(CH_3)$_2$), 1.41 (s, 9H; OC(CH$_3$)$_3$), 2.10 – 2.14 (m, 1H; CH(CH$_3$)$_2$), 2.29 (s, 12H; NCH$_3$), 3.55 (s, 4H; CH_2NMe$_2$), 4.22 – 4.26 (m, 1H; NH-CH-CO), 5.03 – 5.10 (br s, 1H; NH), 5.07 (downfield part of AB signal, ^3J(H,H) = 12.2 Hz, 1H; Ar-CH_2-O), 5.16 (upfield part of AB signal, ^3J(H,H) = 12.2 Hz, 1H; Ar-CH_2-O), 7.35 (s, 2H; ArH); ^{13}C NMR ($CDCl_3$): $\delta = 17.5$ (CH(CH_3)$_2$), 18.9 (CH(CH_3)$_2$), 28.2 (O(CH_3)$_3$, C(CH_3)$_3$), 31.3 (CH(CH$_3$)$_2$), 45.5 (NCH$_3$), 58.5 (Ar-CH_2-NH), 63.6 (CH_2NMe$_2$), 66.2 (NH-CH-CO), 79.7 (OCMe$_3$), 126.8 (C), 129.4, 134.1 (C), 138.8 (C), 155.6 (NHCOO), 172.1 (COOMe); MS (MALDI-TOF): *m*/*z* calcd: 442.1 [M^+ – *t*Bu], 398.1 [M^+ – CO_2*t*Bu]; found: 441.6, 398.0; elemental analysis calcd (%) for $C_{23}H_{38}BrN_3O_4$ (500.48): C 55.20, H 7.65, N 8.40; found: C 55.28, H 7.60, N 8.32.

[PtBr(NCN-{CH$_2$-L-Val-Boc}-4)] (9a): $[\alpha]_D^{25} = -15.0^\circ$ (c = 1.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$): $\delta = 0.83$ (d, ^3J(H,H) = 6.7 Hz, 3H; CH(CH_3)$_2$), 0.92 (d, ^3J(H,H) = 6.7 Hz, 3H; CH(CH_3)$_2$), 1.42 (s, 9H; OC(CH_3)$_3$), 2.10 – 2.14 (m, 1H; CH(CH$_3$)$_2$), 3.10 (s, ^3J(Pt,H) = 38.5 Hz, 12H; NCH$_3$), 4.00 (s, ^3J(Pt,H) = 44.3 Hz, 4H; CH_2NMe$_2$), 4.20 – 4.25 (m, 1H; NH-CH-CO), 4.94 (downfield part of AB signal, ^3J(H,H) = 11.9 Hz, 1H; Ar-CH_2-O), 5.02 (upfield part of AB signal, ^3J(H,H) = 11.9 Hz, 1H; Ar-CH_2-O), 6.80 (s, 2H; ArH); ^{13}C NMR ($CDCl_3$): $\delta = 17.3$ (CH(CH_3)$_2$), 19.0 (CH(CH_3)$_2$), 28.2 (C(CH_3)$_3$), 31.3 (CH(CH$_3$)$_2$), 55.0 (NCH$_3$), 58.4 (NH-CH-CO), 67.7 (Ar-CH_2-O), 77.2 (CH_2NMe$_2$), 79.6 (C(CH$_3$)$_3$), 120.1, 130.4 (C), 143.5 (C), 147.1 (C), 155.6 (NHCO$_2$), 172.3 (CO$_2$); MS (MALDI-TOF): *m*/*z* calcd: 694.2 [M^+], 615.3 [M^+ – Br]; found: 695.0, 616.3; elemental analysis calcd (%) for $C_{23}H_{38}BrN_3O_4Pt \cdot 0.5\,C_3H_6O$ (723.10): C 40.70, H 5.51, N 5.81; found: C 40.50, H 5.74, N 6.04.

[PtBr(NCN-{CH$_2$-L-Phe-Boc}-4)] (9b): $[\alpha]_D^{25} = -7.3^\circ$ ($c = 1$ in $CHCl_3$); ^{1}H NMR ($CDCl_3$): $\delta = 1.40$ (s, 9H; C(CH$_3$)$_3$), 3.06 (AB signal overlapped, 2H; CH_2Ph), 3.11 (s, ^3J(Pt,H) = 33.0 Hz, 12H; NCH$_3$), 4.00 (s, ^3J(Pt,H) = 45.4 Hz, 4H; CH_2NMe$_2$), 4.57 – 4.64 (m, 1H; NH-CH-CO), 4.94 (s, 2H; Ar-CH_2-O), 6.80 (s, 2H; ArH), 7.02 – 7.21 (m, 5H; Ph); ^{13}C NMR ($CDCl_3$): $\delta = 28.2$ (C(CH_3)$_3$), 40.5 (CH_2Ph), 54.3 (NH-CH-CO), 55.0 (NCH$_3$), 67.9 (Ar-CH_2-O), 77.2 (CH_2NMe$_2$), 80.2 (C(CH$_3$)$_3$), 120.3, 126.8 (C), 128.4, 128.6 (C), 129.3, 130.2 (C), 135.9, 143.5 (C), 155.0 (NHCO$_2$), 171.7 (CO$_2$); MS (MALDI-TOF): *m*/*z* calcd: 662.2 [M^+ – Br]; found: 664.8; elemental analysis calcd (%) for $C_{27}H_{38}BrN_3O_4 \cdot 0.3\,C_6H_6$ (768.18): C 45.26, H 5.24, N 5.46; found: C 45.59, H 5.97, N 5.58.

[PtBr(NCN-{CH$_2$-Gly-Boc}-4)] (9c): ^{1}H NMR ($CDCl_3$): $\delta = 1.40$ (s, 9H; C(CH$_3$)$_3$), 3.08 (s, ^3J(Pt,H) = 41.5 Hz, 12H; NCH$_3$), 3.89 (d, ^{3}J(H,H) = 5.5, 2H; NH-CH_2-CO), 3.98 (s, ^{3}J(Pt,H) = 49.7, 4H; CH_2NMe$_2$), 4.99 (s, 2H; Ar-CH$_2$-O), 5.03 (s, 1H; NH-CH$_2$-CO), 6.80 (s, 2H; ArH); ^{13}C NMR ($CDCl_3$): $\delta = 28.2$ (C(CH_3)$_3$), 42.4 (NH-CH_2-CO), 55.0 (NCH$_3$), 67.9 (Ar-CH_2-O), 77.2 (CH_2NMe$_2$), 79.9 (C(CH$_3$)$_3$), 120.2, 130.2 (C), 143.6 (C), 147.3 (C), 155.6 (NHCO$_2$), 170.2 (CO$_2$); MS (MALDI-TOF): *m*/*z* calcd: 572.2 [M – Br]$^+$; found: 573.6; elemental analysis calcd (%) for $C_{27}H_{38}BrN_3O_4$ (652.12): C 37.67, H 5.42, N 6.28, Br 11.93; found: C 37.76, H 5.37, N 6.27, Br 11.79.

[PtBr(NCN-{CH$_2$-L-Asp-Boc 4-benzyl ester}-4)] (9d): $[\alpha]_D^{25} = +8.0^\circ$ ($c = 1$ in $CHCl_3$); ^{1}H NMR ($CDCl_3$): $\delta = 1.41$ (s, 9H; C(CH$_3$)$_3$), 2.84 (downfield part of ABX signal, ^3J(H,H) = 4.6, 16.7 Hz, 1H; NH-CH-CH_2), 3.09 (upfield part of ABX signal overlapped with a s, ^3J(Pt,H) = 36.6 Hz, 13H; NCH$_3$ and NH-CH-CH_2), 3.98 (s, ^3J(Pt,H) = 44.6 Hz, 4H; CH_2NMe$_2$), 4.58 (m, 1H; NH-CH-CO); 4.92 (downfield part of AB signal, ^3J(H,H) = 11.9 Hz, 1H; CH_2Ph), 5.00 (upfield part of AB signal, ^3J(H,H) = 11.9 Hz, 1H; CH_2Ph), 5.07 (s, 2H; Ar-CH_2-O), 5.46 (br d, 1H; NH-CH$_2$-CO), 6.75 (s, 2H; ArH), 7.34 (m, 5H; Ph); ^{13}C NMR ($CDCl_3$): $\delta = 24.9$ (NH-CH-CH_2), 28.5 (C(CH_3)$_3$), 50.3 (NH-CH-CO), 55.3 (NCH$_3$), 66.9 (Ar-CH_2-O), 68.7 (Ph-CH_2-O), 77.5 (CH_2NMe$_2$), 80.4 (C(CH$_3$)$_3$), 120.4, 128.4, 128.6 (C), 128.9, 130.4 (C), 135.6, 143.8 (C), 147.5 (C), 155.6 (NHCO$_2$), 170.9 (CO$_2$), 171.2 (CO$_2$); MS (MALDI-TOF): *m*/*z* calcd: 720.2 [M^+ – Br]; found: 721.9; elemental analysis calcd (%) for $C_{27}H_{38}BrN_3O_4 \cdot C_2H_6O$ (874.25): C 45.26, H 5.75, N 4.80; found: C 45.03, H 5.39, N 4.97.

[PtBr(NCN-{L-Val-Boc})-4] (11a): $[\alpha]_D^{25} = -11.6^\circ$ ($c = 1$ in $CHCl_3$); ^{1}H NMR ($CDCl_3$): $\delta = 0.98$ (d, ^3J(H,H) = 7.2 Hz, 3H; CH(CH_3)$_2$), 1.04 (d, ^3J(H,H) = 7.2 Hz, 3H; CH(CH_3)$_2$), 1.44 (s, 9H; OC(CH$_3$)$_3$), 2.24 – 2.30 (m, 1H; CH(CH$_3$)$_2$), 3.09 (s, ^3J(Pt,H) = 36.3 Hz, 12H; NCH$_3$), 3.98 (s, ^3J(Pt,H) = 44.1 Hz, 4H; CH_2NMe$_2$), 4.39 (m, 1H; NH-CH-CO), 5.03 (d, ^3J(H,H) = 8.9 Hz, 1H; NH-CH-CO), 6.53 (s, 2H; ArH); ^{13}C NMR ($CDCl_3$): $\delta = 17.7$ (CH(CH_3)$_2$), 19.0 (CH(CH_3)$_2$), 28.3 (C(CH_3)$_3$), 31.3 (CH(CH$_3$)$_2$), 55.0 (NCH$_3$), 58.6 (NH-CH-CO), 77.2 (CH_2NMe$_2$), 79.9 (C(CH$_3$)$_3$), 112.7,

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143.6 (C), 143.9 (C), 147.1 (C), 155.6 ($NHCO_2$), 171.4 (CO_2); MS (MALDI-TOF): *m/z* calcd: 681.15 [M^+], 601.4 [$M^+ - Br$]; found: 681.3, 600.6; elemental analysis calcd (%) for $C_{22}H_{36}BrN_3O_4Pt$ (681.52): C 38.77, H 5.32, N 6.08; found: C 38.63, H 5.28, N 6.08.

[PtBr(NCN-{L-Phe-Boc}-4)] (11b): $[\alpha]_D^{25} = -10.6°$ (c = 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$): $\delta = 1.43$ (s, 9H; $C(CH_3)_3$), 3.10 (s, ^3J(Pt,H) = 43.8 Hz, 12H; NCH_3), 3.16–3.21 (m, 2H; CH_2Ph), 3.98 (s, ^3J(Pt,H) = 43.2 Hz, 4H; CH_2NMe_2), 4.76–4.78 (m, 1H; NH-CH-CO), 5.03 (d, ^3J(H,H) = 7.9 Hz, 1H; NH-CH-CO), 6.44 (s, 2H; ArH), 7.22–7.36 (m, 5H; Ph); ^{13}C NMR ($CDCl_3$): $\delta = 28.2$ ($C(CH_3)_3$), 38.3 (CH_2Ph), 54.6 (NH-CH-CO), 55.1 (NCH_3), 77.2 (CH_2NMe_2), 80.2 ($C(CH_3)_3$), 112.6, 127.2 (C), 128.6 (C), 129.4, 135.8, 143.6, 143.9 (C), 147.1 (C), 155.1 ($NHCO_2$), 170.9 (CO_2); MS (MALDI-TOF): *m/z* calcd: 649.2 [$M^+ - Br$]; found: 647.7; elemental analysis calcd (%) for $C_{26}H_{36}BrN_3O_4Pt$ (729.59): C 42.80, H 4.97, N 5.76; found: C 42.95, H 5.08, N 5.68.

General procedure for the deprotection of α-amino acids 6, labeled at their N termini: A solution of **6** (0.05 mmol) and $LiOH \cdot H_2O$ (8 mg, 0.35 mmol, 56%) in THF/H_2O (2:1, 3 mL) was stirred at room temperature overnight. After this time an aqueous solution of HBr was carefully added until pH = 6. Dowex® resin was added to this solution, and the mixture was stirred overnight at room temperature. Dowex® resin was filtrated off. The filtrate was concentrated to afford **12** (0.035 mmol, 70%).

[PtBr(NCN-{CH_2-L-Val-OH}-4)] (12a): ^{1}H NMR (CD_3OD): $\delta = 1.02$ (d, ^3J(H,H) = 6.8 Hz, 3H; $CH(CH_3)_2$), 1.14 (d, ^3J(H,H) = 6.8 Hz, 3H; $CH(CH_3)_2$), 2.31–2.38 (m, 1H; $CH(CH_3)_2$), 3.00 (s, 12H; NCH_3), 3.83 (d, 1H; NH-CH-CO), 4.10 (m, 6H; CH_2NMe_2 and Ar-CH_2-NH), 6.96 (s, 2H; ArH); ^{13}C NMR (CD_3OD): $\delta = 17.9$ ($CH(CH_3)_2$), 19.6 ($CH(CH_3)_2$), 30.6 ($CH(CH_3)_2$), 51.4 (NH-CH-CO), 55.0 (NCH_3), 55.2 (Ar-CH_2-NH), 77.9 (CH_2NMe_2), 122.7, 126.7 (C), 145.9 (C), 149.7 (C), 170.4 (CO_2); MS (MALDI-TOF): *m/z* calcd: 515.2 [$M^+ - Br$], 320.2 [$M^+ - PtBr$]; found: 514.4, 320.4.

[PtBr(NCN-{CH_2-L-Phe-OH}-4)] (12b): $[\alpha]_D^{25} = -3.0°$ (*c* = 1 in CH_3OH); ^{1}H NMR (CD_3OD): $\delta = 3.05$ (s, ^3J(Pt,H) = 37.8 Hz, 12H; NCH_3), 3.22 (dd, ^3J(H,H) = 6.0, 15.3 Hz, 2H; CH_2Ph), 3.66–3.71 (m, 1H; NH-CH-CO), 3.86 (downfield part of AB signal, ^3J(H,H) = 12.6 Hz, 1H; Ar-CH_2-NH), 3.95 (upfield part of AB signal, ^3J(H,H) = 12.6 Hz, 1H; Ar-CH_2-NH), 4.05 (s, ^3J(Pt,H) = 43.2 Hz, 4H; CH_2NMe_2), 6.79 (s, 2H; ArH), 7.25–7.33 (m, 5H; Ph); ^{13}C NMR (CD_3OD): $\delta = 37.0$ (CH_2Ph), 52.4 (Ar-CH_2-NH), 54.5 (NH-CH-CO), 55.0 (NCH_3), 77.9 (CH_2NMe_2), 122.4, 126.7 (C), 128.8, 130.0, 130.5, 135.7 (C), 146.0 (C), 149.5 (C), 171.5 (COOH); MS (MALDI-TOF): *m/z* calcd: 562.2 [$M^+ - Br$]; found: 561.3; elemental analysis calcd (%) for $C_{22}H_{29}BrN_3O_2Pt \cdot 2H_2O$ (678.52): C 38.94, H 4.90, N 6.16; found: C 38.81, H 4.93, N 6.09.

[PtBr(NCN-{L-Val-NH_3Br}-4)] (13): A solution of HBr/HOAc (0.8 mL, 0.14 mmol, 10%) was added to a solution of **11a** (100 mg, 0.014 mmol) in glacial HOAc (0.8 mL). The mixture was stirred at room temperature for 1 h. After this time, a yellow solid had precipitated from the reaction mixture. The solid was triturated twice with 5 mL of Et_2O, and the solvent was removed by decantation to afford **13** (76 mg, 76%). ^{1}H NMR ($CDCl_3$): $\delta = 0.97$ (d, ^3J(H,H) = 6.8 Hz, 3H; $CH(CH_3)_2$), 1.03 (d, ^3J(H,H) = 6.8 Hz, 3H; $CH(CH_3)_2$), 2.12–2.16 (m, 1H; $CH(CH_3)_2$), 3.07 (s, ^3J(Pt,H) = 33.0 Hz, 12H; NCH_3), 3.47 (m, ^3J(H,H) = 4.9 Hz, 1H; NH-CH-CO), 3.97 (s, ^3J(Pt,H) = 35.4 Hz, 4H; CH_2NMe_2), 4.05 (downfield part of AB signal, ^3J(H,H) = 7.3 Hz, 1H; Ar-CH_2-O), 4.09 (upfield part of AB signal, ^3J(H,H) = 7.3 Hz, 1H; Ar-CH_2-O), 6.52 (s, 2H; ArH); ^{13}C NMR ($CDCl_3$): $\delta = 17.1$ ($CH(CH_3)_2$), 19.1 ($CH(CH_3)_2$), 32.2 ($CH(CH_3)_2$), 54.9 (NCH_3), 59.8 (NH-CH-CO), 77.1 (CH_2NMe_2), 112.6, 143.4 (C), 143.8 (C), 147.2 (C), 174.3 (CO_2); ES-MS: *m/z* calcd: 582.4 [$M^+ - Br$]; found: 582.1; elemental analysis calcd (%) for $C_{17}H_{29}Br_2N_3O_2Pt$ (662.35): C 30.83, H 4.41, N 6.35; found: C 30.75, H 4.36, N 6.28.

[PtBr(NCN-{CH_2-L-Phe-L-Val-OMe}-4)] (16): $[\alpha]_D^{25} = -16°$ (*c* = 1 in $CHCl_3$); ^{1}H NMR ($CDCl_3$): $\delta = 0.94$ (d, ^3J(H,H) = 6.7 Hz, 3H; $CH(CH_3)_2$), 0.91 (d, ^3J(H,H) = 6.7 Hz, 3H; $CH(CH_3)_2$), 2.16–2.23 (m, 1H; $CH(CH_3)_2$), 2.65 (dd, 2H; ^3J(H,H) = 10.0, 13.7 Hz, 2H; CH_2Ph), 3.01 (s, ^3J(Pt,H) = 37.8 Hz, 12H; NCH_3), 3.24–3.60 (m, 1H; NH-CH-CO), 3.67 (downfield part of AB signal, ^3J(H,H) = 7.6 Hz, 1H; Ar-CH_2-NH), 3.62 (upfield part of AB signal, ^3J(H,H) = 7.6 Hz, 1H; Ar-CH_2-NH), 3.75 (s, 3H; OCH_3), 3.93 (s, ^3J(Pt,H) = 43.9 Hz, 4H; CH_2NMe_2), 4.57 (dd, ^3J(H,H) = 4.9, 9.5 Hz, 1H; NH-CH-CO), 6.52 (s, 2H; ArH), 7.15–7.31 (m, 5H; Ph), 7.89 (d, ^3J(H,H) = 9.5 Hz, 1H; NH); ^{13}C NMR ($CDCl_3$): $\delta = 17.8$ ($CH(CH_3)_2$), 19.1 ($CH(CH_3)_2$), 31.0 ($CH(CH_3)_2$), 38.8 (CH_2Ph), 52.1 (OCH_3), 52.6 (Ar-CH_2-NH), 55.0 (NCH_3), 56.9 (NH-CH-CO), 62.7 (NH-CH-CO), 77.2 (CH_2NMe_2), 119.8, 127.0, 128.6 (C), 128.7, 129.2, 134.2 (C), 136.1 (C), 143.7 (C), 153.0 (NHCO), 172.2 (CO); MS (MALDI-TOF): *m/z* calcd: 676.3 [$M^+ - Br$]; found: 673.7; elemental analysis calcd (%) for $C_{28}H_{41}BrN_4O_3$ (756.6): C 44.45, H 5.46, N 7.40; found: C 44.36, H 5.57, N 7.35.

Synthesis of α-labeled α-amino acid 19—Route A: 9-Borabicyclo[3.3.1]-nonane (9-BBN; 0.5 M in THF, 6.0 mL, 3.00 mmol) was added at 0 °C to a solution of Boc-allylglycine methyl ester (0.343 g, 1.5 mmol) in degassed THF (7 mL), and the reaction mixture was warmed to RT and stirred for 2 h. Degassed DMF (4 mL) was added, followed by careful addition (H_2 evolution) of aq. K_3PO_4 (3 M, 1.0 mL, 3.1 mmol), followed by a quick addition of **1** (0.510 g, 1.3 mmol) and, finally, [$PdCl_2$(dppf)] (0.109 g, 0.15 mmol). The reaction mixture was heated under reflux overnight and the solvent was removed in vacuo. The residue was taken up in diethyl ether (20 mL) and washed with sat. $NaHCO_3$ (15 mL). The aqueous layer was re-extracted twice with diethyl ether (20 mL), and the combined organic layers were dried over $MgSO_4$. The volatile components were removed, and the resulting oil was percolated by column chromatography (SiO_2, Et_2O and Et_2O/MeOH 1:1) to yield compound **18** (0.530 g, 72% yield), which was used in the next step without further purification. A mixture of **18** (0.377 g, 0.76 mmol) and [{Pt(tol-4)$_2$(SEt$_2$)}$_2$] (355 mg, 0.76 mmol) in dry benzene (30 mL) was heated at 50 °C for 3 h. All volatile components were removed at reduced pressure and the resulting oil was washed with pentane (2 × 30 mL). The formed precipitate was removed by centrifugation and decanting of the clear supernatant. The solid residue was concentrated and purified by gradient chromatography (SiO_2, CH_2Cl_2/acetone). The platinum-containing fractions were collected and evaporated to dryness, yielding **19** as white solid (0.470 g, 45%).

Route B: The procedure was similar to that used above, but instead of **1**, **17** was used as alkyl iodide. After addition of all reagents, the reaction mixture was stirred for 3 h at RT and the solvent was removed in vacuo. The residue was taken up in diethyl ether (20 mL) and washed with sat. $NaHCO_3$ (15 mL). The aqueous layer was re-extracted twice with diethyl ether (20 mL), and the combined organic layers were dried over $MgSO_4$. The volatile components were removed, and the resulting oil was purified by gradient chromatography (SiO_2, Et_2O and then CH_2Cl_2/acetone). The platinum-containing fractions were collected and evaporated to dryness, yielding **19** as a white solid (yield 29%).

[PtBr(NCN-{BocHN[$CH(CH_2)_3$]CO_2Me}-4)] (19): ^{1}H NMR ($CDCl_3$): $\delta =$ 1.43 (s, 9H; $OC(CH_3)_3$), 1.48–1.85 (m, 4H; CH_2CH_2), 2.44–2.51 (m, 2H; CH_2CH), 3.10 (s, ^3J(Pt,H) = 36.9 Hz, 12H; NCH_3), 3.71 (s, 3H; OCH_3), 3.98 (s, ^3J(Pt,H) = 44.4 Hz, 4H; CH_2NMe_2), 4.29–4.31 (m, 1H; NH-CH-CO), 4.98 (d, ^3J(H,H) = 8.0 Hz, 1H; NH), 6.60 (s, 2H; ArH); ^{13}C NMR ($CDCl_3$): $\delta = 27.3$ (CH_2CH_2), 28.3 ($OC(CH_3)_3$), 32.3 (CH_2CH_2), 35.7 (CH_2CH), 52.2 (OCH_3), 53.2 (NH-CH-CO), 53.6 (NCH_3), 77.4 (CH_2NMe_2), 79.9 ($OC(CH_3)_3$), 119.3, 136.9 (C), 143.3 (C), 145.0 (C), 155.3 (NHCO), 173.3 (CO_2); MS (MALDI-TOF): *m/z* calcd: 615.7 [$M^+ - Br$]; found: 614.7; elemental analysis calcd (%) for $C_{23}H_{38}BrN_3O_4Pt$ (694.17): C 39.72, H 5.51, N 6.04; found: C 39.85, H 5.62, N 6.08.

Hydrolysis of compound 19: A solution of **19** (85 mg, 0.14 mmol) and $LiOH \cdot H_2O$ (29 mg, 0.7 mmol, 56%) in THF/H_2O (4:1, 5 mL) was stirred at room temperature overnight. After this time the reaction mixture was treated with 1 M HCl (aq.) The aqueous phase was extracted with EtOAc (3 × 20 mL) and the collective organic layer were washed with brine and dried over $MgSO_4$ to afford **20** (62 mg, 77%). ^{1}H NMR (CD_3OD): $\delta = 1.43$ (s, 9H; $OC(CH_3)_3$), 1.67–1.85 (m, 4H; CH_2CH_2), 2.44–2.51 (m, 2H; CH_2CH), 3.10 (s, ^3J(Pt,H) = 23.8 Hz, 12H; NCH_3), 3.98 (s, ^3J(Pt,H) = 39.1 Hz, 4H; CH_2NMe_2), 4.29–4.31 (m, 1H; NH-CH-CO), 4.98 (d, ^3J(H,H) = 8.0 Hz, 1H; NH), 6.62 (s, 2H; ArH); ^{13}C NMR ($CDCl_3$): $\delta =$ 27.3 (CH_2CH_2), 28.3 ($OC(CH_3)_3$), 31.9 (CH_2CH_2), 35.7 (CH_2CH), 53.2 (NH-CH-CO), 53.6 (NCH_3), 77.4 (CH_2NMe_2), 80.2 ($OC(CH_3)_3$), 119.4, 136.8 (C), 143.3 (C), 145.3 (C), 155.3 (NHCO), 177.3 (CO_2); MS (MALDI-TOF): *m/z* calcd: 600.25 [$M^+ - Br$]; found: 600.4.

Synthesis of compound 21: A solution of HBr/HOAc (0.5 mL, 0.10 mmol, 10%) was added to a solution of **20** (60 mg, 0.10 mmol) in glacial HOAc (0.5 mL). The mixture was stirred at room temperature for 1 h. After this time, a brown solid had precipitated from the reaction mixture. The solid was triturated twice with Et_2O (5 mL), and the solvent was removed by decantation to afford **21** (50 mg, 75% yield). ^{1}H NMR (DMSO): $\delta = 1.75 -$

1.89 (m, 4H; CH_2CH_2), 2.48–2.50 (m, 2H; CH_2CH), 2.93 (s, 12H; NCH_3), 3.87–3.92 (m, 1H; NH-C*H*-CO), 4.00 (s, 4H; CH_2NMe_2), 6.60 (s, 2H; ArH), 8.2 (brs, 3H; NH_3); ^{13}C NMR ($CDCl_3$): $\delta = 27.5$ (CH_2CH_2), 30.7 (CH_2CH_2), 36.3 (CH_2CH), 53.0 (NH-*C*H-CO), 55.4 (NCH_3), 77.4 (CH_2NMe_2), 120.1, 137.1 (C), 143.3 (C), 144.6 (C), 172.1 (CO_2); ES-MS: *m*/*z* calcd: 582.44 [$M^+ - Br$]; found: 582.1.

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[19] The influence of *para* substituents in several [PtX(NCN-R)] complexes on the platinum NMR chemical shift has previously been studied in our group.[11b] It has been shown that a linear correlation exists between platinum NMR chemical shift and the σ_p Hammett constants.

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