Synthesis, Structure, and Function of PCP Pincer Transition-Metal-Complex-Bound Norvaline Derivatives

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Abstract: A PCP pincer palladium-complex-bound norvaline, Boc-L-[Pd]Nva-OMe, was synthesized and fully characterized by NMR, FT-ICR-MS, and X-ray crystallography. Selective N- and C-terminus transformations of Boc-L-[Pd]Nva-OMe were performed by conventional deprotection–condensation procedures to afford lipophilic palladium-bound norvaline derivatives without metal detachment. The N-/C-bisfunctionalized palladium-bound norvaline showed self-assembly properties, as evidenced by supramolecular gel formation. The catalytic activity of the supramolecular gel was assessed in the 1,4-conjugate addition of phenylboronic acid.

Keywords: amino acids, cross-coupling, catalysis, palladium, self-assembly

Metalated amino acids – hybrids of organometallic and biologically important molecules – have been considered as promising bioorganometallic materials.[1] The properties arising from the conjugation of amino acids and organometallic compounds exhibit naturally inaccessible new functions and activities without loss of the parents' inherent chemical, physical, and biological characteristics. For instance, the combination of amino acid bioaffinity and the photochemical, electrochemical, and radioactive properties of metal complexes has been widely investigated, providing various metalated amino acid-based bioimaging and biosensing reagents.[2] However, the application of metalated amino acids to functional materials remains a largely untouched subject, despite there having been several reports on metal array fabrication based on the self-assembly of metalated peptides[3] and a variety of research for fabricating functional materials based on the self-assembly of amino acids.[4] We recently found that metalated amino acids tethered to a NC-half-pincer platinum complex[5] and a NCN pincer palladium complex[6] self-assembled to form supramolecular fibrous aggregates with well-regulated metal arrays; some of these exhibited enhanced catalytic activity as supramolecular gel catalysts.[7] These findings demonstrate the potential of metalated amino acid-based fabrication of supramolecular functional materials, and led us to further exploit pincer transition-metal-complex-bound amino acids. Herein, we report the synthesis, characterization, and self-assembly properties of novel amino acids tethered to PCP pincer palladium and platinum complexes **1**–**5** (Figure 1). Further, we describe the catalytic activities of supramolecular gel of **4** in the 1,4-conjugate addition of arylboronic acid to cyclohexenone.

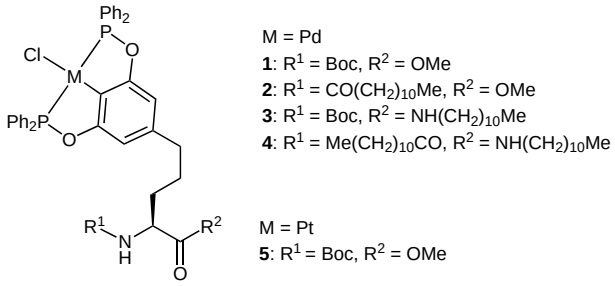

Figure 1 PCP pincer metal-complex-bound norvalines

We designed and synthesized the PCP pincer palladium-complex-bound norvaline derivatives **1**–**4** and their platinum analogue **5**. The robust cyclometalated PCP pincer structure was expected to tolerate acidic or alkaline conditions during various synthetic transformations without undesired metal leaching.[8,9] Additionally, the inert alkyl linkage between the palladium/platinum complex and the amino acid functionalities probably contributes to the prevention of undesirable metal-complex detachment, even under severe synthetic conditions.

The unreported parent PCP pincer complexes, [4-bromo-2,6-bis(diphenylphosphinoxy-κ*P*,κ*P*)phenyl-κ*C*]chloropalladium(II) (**6**) and [4-bromo-2,6-bis(diphenylphosphinoxy-κ*P*,κ*P*)phenyl-κ*C*]chloroplatinum(II) (**7**), were prepared in one pot, similarly to literature methods (Scheme 1).[10] The reaction of 1-bromo-3,5-dihydroxybenzene with excess chlorodiphenylphosphine (2.4 equiv) and triethylamine (3.0 equiv) was carried out in refluxing toluene for eight hours. Metalation of the resulting phosphinite intermediate was performed by the addition of $PdCl_2$ or $PtCl_2 \cdot SMe_2$ with additional refluxing for 18

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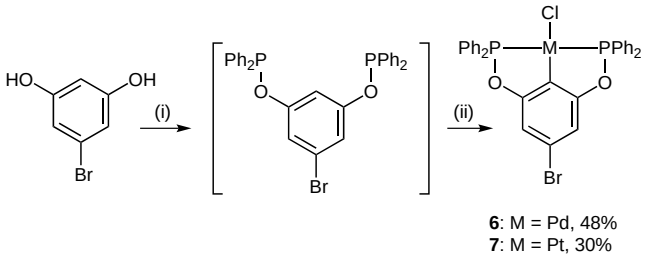


Scheme 1 Synthesis of PCP pincer palladium and platinum complexes. *Reagents and conditions*: (i) Ph_2PCl, Et_3N, toluene, reflux, 8 h; (ii) MCl_2 (M = Pd or Pt), toluene, reflux, 18 h.

hours to afford the corresponding PCP pincer complexes **6** and **7**, respectively. The PCP coordination geometry of complex **6** was unequivocally determined by single-crystal X-ray structure analysis as shown in Figure 2.[11] Conjugation of the PCP pincer complexes to the norvaline moiety was achieved by sequential hydroboration–Suzuki–Miyaura coupling starting from allylglycine – a route developed by Taylor[12] and van Koten,[13] and recently reconfirmed in effectiveness by us (Scheme 2).[6,7] The synthesis began with Boc-L-allylgly-OMe, which was quantitatively prepared from commercially available Boc-L-allylgly-OH·$HNCy_2$ by one-pot amine neutralization with HCl and trimethylsilyldiazomethane esterification. Cross-coupling of the 9-BBN adduct of Boc-L-allylgly-OMe with the PCP pincer complexes afforded mixtures of simultaneously formed halide-exchanged byproducts of M–Br and unreacted M–Cl complexes. Treatment with excess KCl reconverted the M–Br species into M–Cl species and afforded the desired PCP pincer palladium- and platinum-bound norvalines **1**[14] and **5**, respectively. No metal leaching was observed in the reaction mixture at any step of the process.[15] Preservation of the enantiomeric purity of the norvaline subunit during the coupling reaction in the presence of excess K_3PO_4 base was confirmed by chiral HPLC analysis, as in our previous study.[6] The absolute configuration of **1** was unequivocally determined by single-crystal X-ray crystallography,[16] in which the observed bond lengths and angles around the palladium complex subunit were essentially unchanged from those of the parent complex **6** (Figure 3).

Reactivity at the N-terminus was investigated on the palladium-bound norvaline **1**, as shown in Scheme 3. The Boc deprotection of **1** under acidic conditions using excess HCl afforded the palladium-bound norvaline-free amine **9**. Subsequent reaction with dodecanoic acid mediated by the condensing reagent DMTMM·PF_6[17] gave the corresponding *N*-alkanoyl palladium-complex-bound norvaline C_{12}-L-[Pd]Nva-OMe (**2**) in 89% yield without a metal-leaching byproduct. Conventional trifluoroacetic acid conditions were also applicable for the Boc deprotection of **1**, giving **9** in 68% yield, as revealed by NMR.

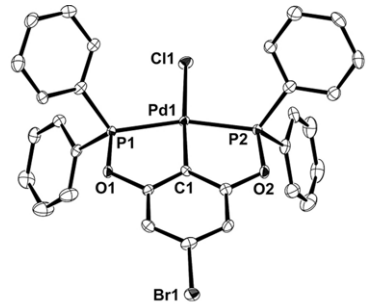
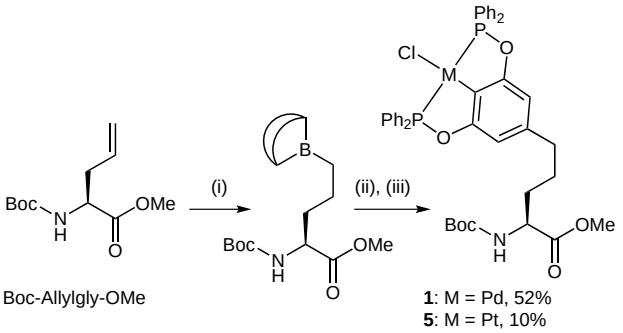


Figure 2 X-ray crystal structure of PCP pincer palladium complex **6**. Selected bond lengths (Å): Pd1–Cl1 = 2.3508(10), Pd1–C1 = 1.980(4), Pd1–P1 = 2.2597(12), Pd1–P2 = 2.2756(12); selected bond angles (°): P1–Pd1–P2 = 160.64(4), Cl1–Pd1–C1 = 177.08(13), Cl1–Pd1–P1 = 96.88(4), Cl1–Pd1–P2 = 102.47(4), C1–Pd1–P1 = 80.36(12), C1–Pd1–P2 = 80.28(12); selected dihedral angles (°): C11–Pd1–P1–O1 = –177.72(4), Cl1–Pd1–P2–O2 = –179.19(4), C1–Pd1–P1–O1 = 1.27(9), C1–Pd1–P2–O2 = 1.83(9).



Scheme 2 Synthesis of palladium- and platinum-complex-bound norvalines. *Reagents and conditions*: (i) 9-BBN, THF, 0 °C, 5 min, then r.t., 3 h; (ii) **6** or **7**, $Pd(OAc)_2$ (5 mol%), SPhos (10 mol%), K_3PO_4, THF–H_2O, r.t., 12 h; (iii) excess KCl, THF–H_2O, r.t., 6 h.

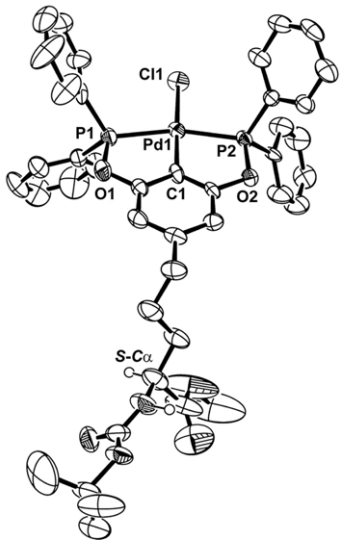


Figure 3 X-ray crystal structure of palladium-complex-bound norvaline **1**. Selected bond lengths (Å): Pd1–Cl1 = 2.376(1), Pd1–C1 = 1.991(4), Pd1–P1 = 2.276(1), Pd1–P2 = 2.266(1); selected bond angles (°): P1–Pd1–P2 = 159.49(5), Cl1–Pd1–C1 = 178.6(1), Cl1–Pd1–P1 = 99.63(5), Cl1–Pd1–P2 = 100.80(5), C1–Pd1–P1 = 79.3(1), C1–Pd1–P2 = 80.3(1); selected dihedral angles (°): C11–Pd1–P1–O1 = –174.02(9), Cl1–Pd1–P2–O2 = –177.4(1), C1–Pd1–P1–O1 = 5.0(2), C1–Pd1–P2–O2 = 3.5(2).

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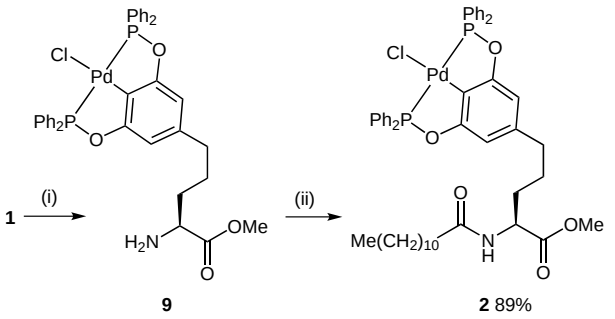
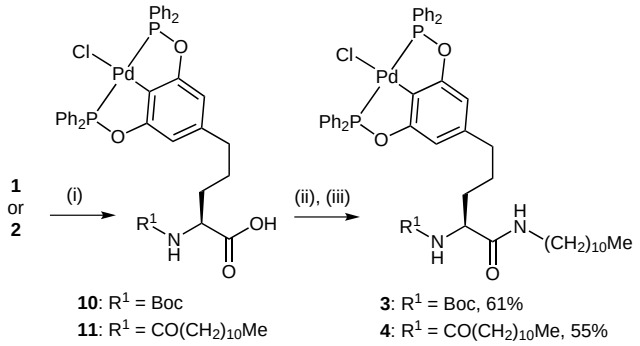


Scheme 3 N-Terminal functionalization of **1**. *Reagents and conditions*: (i) excess 4.0 M HCl, dioxane, r.t., 2 h; (ii) $Me(CH_2)_{10}CO_2H$, DMTMM·PF_6, Et_3N, DMF, r.t., 6 h.

The C-terminal convertibility was demonstrated by LiI-promoted C-deprotection,[18] followed by DMTMM·PF_6-mediated condensation with primary amines. Standard basic C-hydrolysis using LiOH or TMSOK failed and resulted in undesirable Boc deprotection and decomplexation of the PCP pincer palladium complex. As depicted in Scheme 4, condensation of the palladium-bound norvaline free acid **10** with undecylamine proceeded smoothly, and sequential halide exchange with $AgBF_4$/NaCl transformed the tentatively formed Pd–I byproduct to the Pd–Cl derivative, giving the desired *C*-alkylamido palladium-bound norvaline Boc-L-[Pd]Nva-C_{11} (**3**) in 61% yield. In addition, C-terminal amidation of **2** was also performed via the metalated free acid **11** to give the double-tailed palladium-bound norvaline C_{12}-L-[Pd]Nva-C_{11} (**4**) in 55% yield.



Scheme 4 C-Terminal functionalization of **1** and **2**. *Reagents and conditions*: (i) LiI, pyridine, reflux, 3 h; (ii) $Me(CH_2)_{10}NH_2$, DMTMM·PF_6, Et_3N, DMF, r.t., 6 h; (iii) $AgBF_4$, MeCN, r.t., 1 h, then NaCl, 1 h.

We have reported that NCN-pincer palladium-complex-bound *C*-alkylamido norvalines showed remarkable gelation properties in organic solvents, producing supramolecular gels.[6] Here, also, the PCP pincer palladium-bound norvaline **4** was found to be an efficient gelator in ethereal and aromatic solvents. Typically, a mixture of **4** in *tert*-butyl methyl ether (TBME) was heated until complete dissolution to afford a clear solution (Figure 4, a). Upon cooling to room temperature and allowing to stand for a few minutes, the TBME solution gradually thickened to form an opaque gel (Figure 4, b). Further, upon heating, the gel of **4** melted to afford the solution once again, and this sol–gel transition was completely reversible through heating and cooling cycles. Such a thermoreversible phase transition strongly suggested that the observed gelation was induced by a self-assembly process among the gelator molecules through noncovalent interactions such as hydrogen bonding and π–π interactions.[5,6] Scanning electron microscopy (SEM) analyses of dried gel particles (xerogels) of **4** showed an entangled network of beltlike microfibrils, which is typical of supramolecular gels prepared from lipophilic amino acids and peptides (Figure 5).[3]

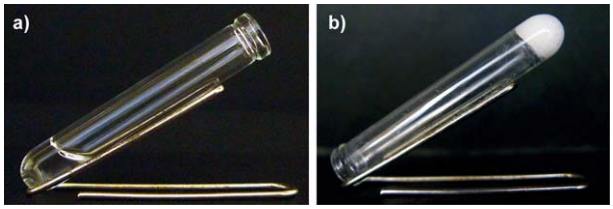


Figure 4 Thermoreversible gelation of **4** in TBME (3.010^{-2} M): a) TBME solution, and b) gel state.

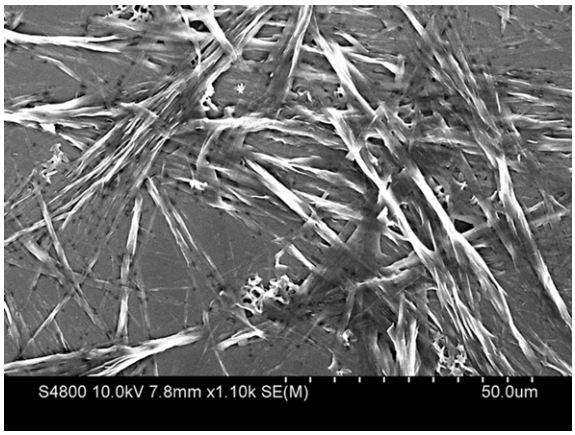


Figure 5 SEM image of TBME gel of **4** (× 11000).

We examined the catalytic activity of the supramolecular gel of **4** because palladium-complex-based supramolecular materials have recently been widely recognized as efficient supramolecular catalysts.[7,19] The xerogel particles of **4** prepared from the TBME gel showed catalytic activity for the 1,4-conjugate addition of phenylboronic acid to cyclohexenone under heterogeneous conditions (Scheme 5),[20] affording the corresponding adduct in 12% yield, despite that the parent complex, [2,6-bis(diphenylphosphinoxy-κ*P*,κ*P*)phenyl-κ*C*]chloropalladium(II) and catalysts **1**–**4** gave less than 3% yield of products under homogeneous nongelated conditions in $CHCl_3$ and THF. It is noteworthy that these types of PCP pincer palladium complexes have been reported as ineffective catalysts in the 1,4-conjugate addition of arylboron derivatives to enones in anhydrous toluene.[21]

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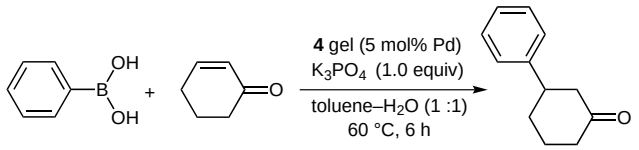

Scheme 5

In conclusion, we successfully synthesized chemically and physically robust novel PCP pincer palladium-bound norvaline derivatives. Self-assembly of the N-/C-double alkylated palladium-bound norvalines enabled us to prepare palladium-immobilized metallogels. We also found that a supramolecular gel of the palladium-bound norvaline showed catalytic activity in the 1,4-conjugate addition of phenylboronic acid. The palladium-immobilized metallogel acted as a heterogeneous catalyst for this reaction in the aqueous phase. Improvement of the catalytic efficiency of the PCP pincer palladium-bound norvaline gels and application of the supramolecular-gel-catalyzed reaction to asymmetric C–C bond formation are currently ongoing in our laboratory and will be reported in due course.

Acknowledgment

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Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(14) To a THF solution of Boc-L-allylglycine methyl ester (1.7 mmol) 9-BBN (3.4 mmol) was added at 0 °C and stirred at r.t. for 3 h. Pd-catalyzed cross-coupling with **6** (1.4 mmol) was carried out in the presence of 5 mol% of $Pd(OAc)_2$–SPhos with K_3PO_4 (3.3 mmol) followed by halide exchange of the resulting Pd–Br species by excess amount of KCl (170 mmol) to afford **5** (851 mg, 71%) after appropriate purification; mp 97.5–98.5 °C. ^{1}H NMR (392 MHz, $CDCl_3$): δ = 7.91–8.03 (m, 8 H, *m*-ArH), 7.42–7.54 (m, 12 H, ArH), 6.59 (s, 2 H, ArH), 5.00 (d, *J* = 8.2 Hz, 1 H, NH), 4.26–4.38 (m, 1 H, NHC*H*CO), 3.74 (s, 3 H, OCH_3), 2.47–2.63 (m, 2 H, $ArCH_2$), 1.58–1.90 (m, 4 H, $CHCH_2CH_2CH_2$), 1.43 [s, 9 H, $(CH_3)_3C$]. ^{13}C NMR (99.5 MHz, $CDCl_3$): δ = 173.2 (1 C, *C*$OOCH_3$), 164.3 (1 C, C_6H_2), 155.3 (1 C, OCONH), 143.6 (2 C, C_6H_2), 133.2 (4 C, C_6H_5), 131.9 (4 C, C_6H_5), 131.6 (8 C, C_6H_5), 128.9 (8 C, C_6H_5), 107.3 (2 C, C_6H_2), 53.1 (1 C, NHCH), 52.2 (1 C, $COOCH_3$), 35.2 (1 C, $CHCH_2CH_2CH_2$), 32.2 (1 C, $CHCH_2CH_2CH_2$), 28.2 [3 C, $OC(CH_3)_3$], 26.7 (1 C, $CHCH_2CH_2CH_2$). ^{31}P NMR (159 MHz, $CDCl_3$): δ =

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144.3. HRMS–FAB: *m/z* $[M - Cl]^+$ calcd for $C_{41}H_{42}NO_6P_2Pd$: 812.1522; found: 812.1502. Anal. Calcd for $C_{41}H_{42}ClNO_6P_2Pd \cdot 0.3CH_2Cl_2$: C, 56.75; H, 4.91; N, 1.60. Found: C, 56.95; H, 4.98; N, 1.64. $[\alpha]_D^{25}$ +8.67 (*c* 0.473, $CHCl_3$).

(15) Undesired aryl bromide reduction of **7** to [2,6-bis(diphenylphosphinoxy-κ*P*,κ*P*)phenyl-κ*C*]chloroplatinum(II) leads to low yields of platinum-bound norvaline **5**.

(16) X-ray diffraction measurements were obtained at SPring-8 (BL02B1: 2012B1109 and 2012B1790; BL40XU: 2011B1545, 2012A1161, 2012A1625, and 2012B1815). Flack parameter = –0.01(3). For the detailed crystallographic data of **1**, see Supporting Information and also, Yasuda, N.; Murayama, H.; Fukuyama, Y.; Kim, J. E.; Kimura, S.; Toriumi, K.; Tanaka, Y.; Moritomo, Y.; Kuroiwa, Y.; Kato, K.; Tanaka, H.; Takata, M. *J. Synchroton. Rad.* **2009**, *16*, 352.

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