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Platinum-pincer introduction using active ester chemistry

Bart M. J. M. Suijkerbuijk,[a] Martijn Q. Slagt,[a] Robertus J. M. Klein Gebbink,[a] Martin Lutz,[b] Anthony L. Spek[b] and Gerard van Koten[a,*]

[a]*Debye Institute, Department of Metal-Mediated Synthesis, Utrecht University, Padualaan 8, 3584 CH Utrecht, Netherlands*
[b]*Bijvoet Center for Biomolecular Research, Department of Crystal and Structural Chemistry, Utrecht University, Padualaan 8, 3584 CH Utrecht, Netherlands*

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Abstract—In search of a new way to attach organometallic pincer complexes to amines via an amide bond, the *N*-hydroxysuccinimide ester of 3,5-bis-[(dimethylamino)methyl]-4-(iodoplatino(II))-benzoic acid was synthesized. This compound reacts with several primary amines to form the corresponding amides cleanly and in high yields.

Since the first reports on the tridentate ligand $[2,6\text{-}(ECH_2)_2C_6H_3]^-$ (E = NR_2, SR, PR_2), now often referred to as 'pincer',[1] a large variety of metals have been incorporated into this chelating unit, providing novel catalysts.[2] These include catalytically active metals like ruthenium, nickel and palladium, of which the resulting organometallic materials can be applied in hydrogen transfer reactions,[3] Kharasch additions,[4] and C–C coupling reactions,[5] respectively. Recently, it was demonstrated that, via platinum incorporation, access can be gained to organometallic SO_2-sensors[6] and biomarkers.[7] Crucial to the latter application is the availability of easy routes to the *para*-functionalization of the pincer, eventually in the presence of the metal–carbon bond, in order to perform chemistry beyond the restrictions posed by the relatively small pincer.[2] Immobilization of the pincer on materials with complementary characteristics seems a promising way to combine the advantages of both. Two distinct approaches for the introduction of metalated pincer moieties via *para*-functionalization in or onto (organic) scaffolds are possible. Firstly, the organometallic pincer moiety can be introduced by metalation of the pincer ligand after its attachment. This procedure, however, does not ensure a full metalation of the product, especially in the case of a multi-ligand system (e.g. a metallodendrimer).[8] Secondly, metallated pincers can be introduced directly. This route, however, is not always accessible because of the limited stability of most organometallic fragments under the (harsh) coupling conditions. Recently, we set out to develop a gentle coupling chemistry for the attachment of the pincer moiety, with retention of the C–Pt bond, in order to attach it also to chemically less inert molecules.

One of the most stable heteroatomic bonds known to organic chemists is the amide bond. This bond is accessible via several synthetic routes, one of the most gentle being the activation of a carboxylic acid (i.e. synthesis of an activated ester) followed by reaction with an amine. Here, we describe the synthesis of such an 'activated pincer'-Pt **1** and its coupling chemistry with various amines.

Activated platinum-pincer **1** was synthesized according to the route depicted in Scheme 1. Bromo-iodo-compound **2** was obtained by a seven-step synthesis, starting from 3,5-dimethylaniline in 36% overall yield.[9] Platinum incorporation was accomplished via oxidative addition of **2** to $[Pt(p\text{-tol})_2(Et_2S)]_2$ using Canty's procedure,[10] which yielded 80% of **3** as a white, crystalline solid. The carboxylic acid derivative **4** was obtained by lithiation via exchange with the iodine and subsequent quenching of the resulting bimetallic species with CO_2.[11] In order to overcome halide-scrambling during this reaction, the resulting solid was treated with NaI in acetone, yielding 78% of **4** as a light yellow solid.[11] Making use of *N*,*N*′-dicyclohexylcarbodiimide (DCC) as a coupling agent, activated pincer **1** was synthesized from **4** and *N*-hydroxysuccinimide (NHS) with pyridine as a base to give a light yellow solid (98%).[12,13] Spectroscopic evidence for the formation of **1** includes low field shifts for the aromatic protons (7.58 ppm) compared to

* Corresponding author. Fax: (+31)30-2523615; e-mail: g.vankoten@chem.uu.nl

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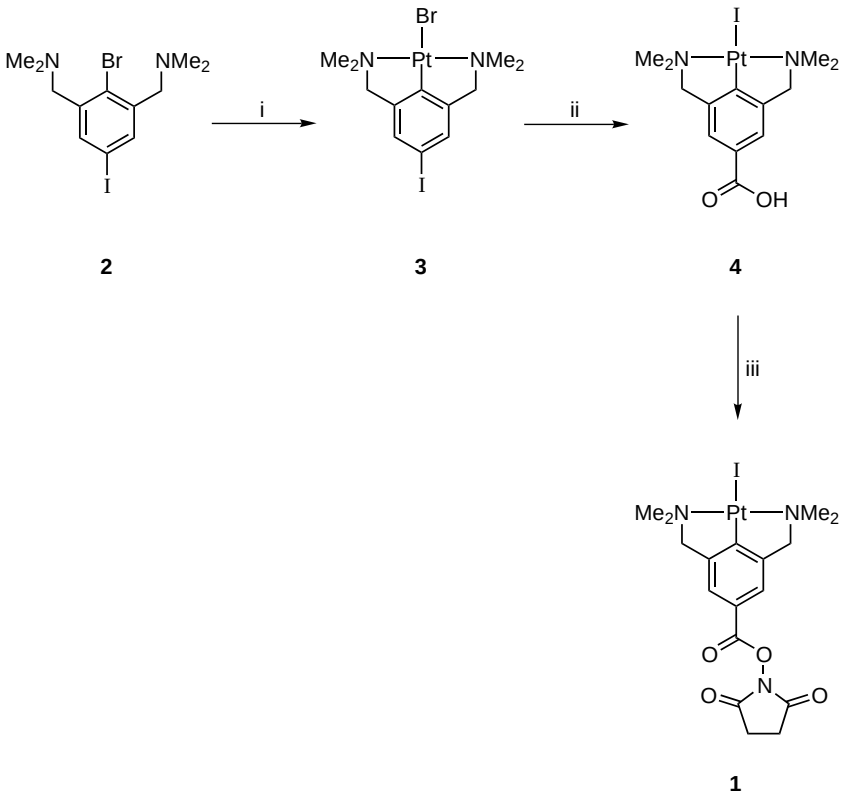


Scheme 1. *Reagents and conditions*: (i) $[Pt(p\text{-tol})_2(Et_2S)]_2$, C_6H_6, 2 h, reflux; (ii) (1) *t*-BuLi, THF, 2 min, −100°C, (2) $CO_{2(g)}$, 1 h, rt, (3) NaI, acetone, 1 h, rt; (iii) NHS, DCC, pyridine, THF, 16 h, rt.

the parent compound **4** (7.51 ppm). To unequivocally prove that **1** was obtained, crystals were grown by slowly diffusing Et_2O into a concentrated solution of **1** in methylene chloride. The crystal structure is shown in Fig. 1.[14–17]

The scope and reactivity of **1** toward several types of amines were investigated (Scheme 2).[18] First, **1** was reacted with *n*-butylamine by stirring both reagents in

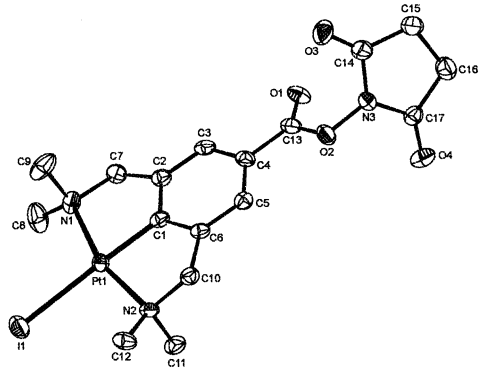
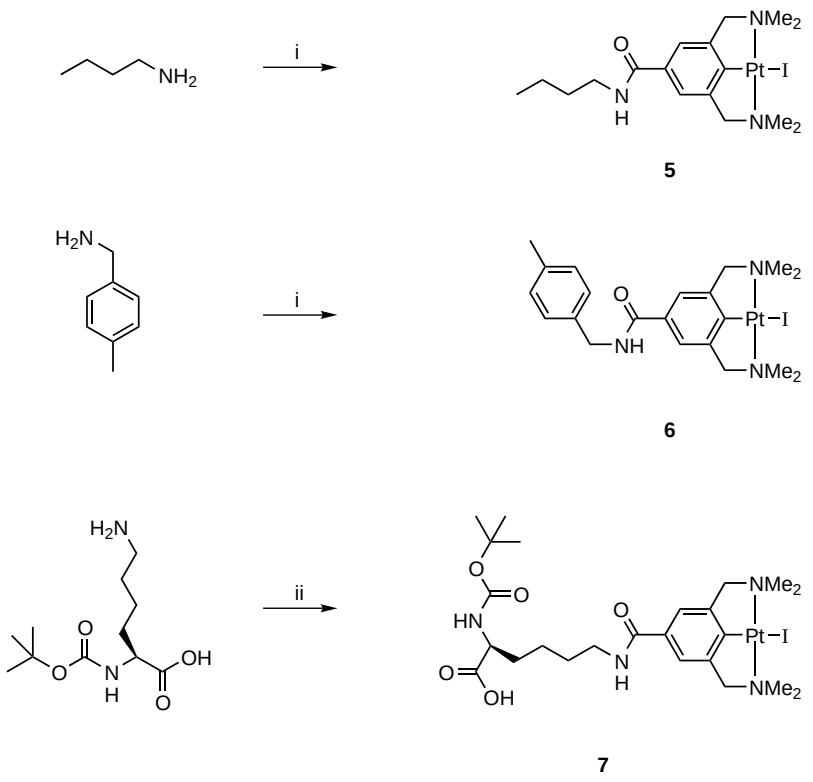


Figure 1. Displacement ellipsoid plot (50% probability) of **1**. Hydrogen atoms have been omitted for clarity. Selected bond lengths (Å), angles and torsion angles (°): Pt1–C1 1.923(5), Pt1–N1 2.108(4), Pt1–N2 2.102(4), Pt1–I1 2.7135(4), C4–C13 1.475(6), C13–O1 1.192(6), C13–O2 1.412(6), O2–N3 1.390(5), I1–Pt1–C1 177.83(13), N1–Pt1–N2 162.89(15), C1–Pt1–N1–C7 23.4(3), C1–Pt1–N2–C10 23.3(3), C3–C4–C13–O1 −9.4(7), C13–O2–N3–C14 74.0(5).

CH_2Cl_2 at room temperature for 16 hours. After a basic work-up, the product was precipitated from a CH_2Cl_2 solution with Et_2O, yielding 88% of **5**, without the need for additional purification steps. The formation of **5** was clearly indicated by the appearance of NMR resonances at $\delta = 7.48$ ppm (br t, N*H*C(O)) and $\delta = 3.36$ ppm (q, CH_2NHC(O)) and the change of the chemical shift of the aromatic protons from $\delta = 7.58$ ppm to $\delta = 7.36$ ppm. Applying the same procedure, **6** was synthesized using 4-methylbenzylamine as the amine. After work-up **6** was obtained in an 80% yield as a white solid (new NMR resonances at $\delta = 6.22$ ppm (br t, N*H*C(O)) and $\delta = 4.56$ ppm (d, CH_2NHC(O)), aromatic protons at $\delta = 7.28$). N^{α}-Boc-L-lysine was attached to the platinum pincer moiety following the procedure applied by Tampé and coworkers.[19] First, Boc-protected lysine was treated with chlorotrimethylsilane to enhance its solubility in the reaction medium. Next, **1** was added, the reaction mixture was stirred for 16 hours and after purification, including precipitation, a white solid **7** was obtained in 56% yield (new NMR resonances at $\delta = 7.58$ ppm (br t, N*H*C(O)) and $\delta = 3.38$ ppm (q, CH_2NHC(O)), aromatic protons at $\delta = 7.38$). Activated pincer **1** was shown not to react with less reactive amines like *p*-toluidine and diethylamine.

In conclusion, an organometallic active ester was synthesized and was shown to cleanly react with primary amines. The results are promising with regard to direct incorporation of metalated (organometallic platinum) pincer fragments in or onto large organic frameworks



Scheme 2. *Reagents and conditions*: (i) **1**, CH_2Cl_2, 16 h, rt; (ii) (a) TMSCl, Et_3N, CH_2Cl_2, 1 h, reflux; (b) **1**, 16 h, rt.

(i.e. without stepwise ligand incorporation followed by metalation). The reactivity of **1** towards other amines is currently under investigation. Furthermore, the incorporation of metals other than platinum into the activated pincer ligand is being pursued.

Acknowledgements

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in vacuo, the residue was taken up in $CHCl_3$ (200 mL) and washed with saturated NH_4Cl solution (2×10 mL). The organic layer was dried ($MgSO_4$) and the volatiles were removed. Next, the remaining solid was redissolved in acetone and treated with NaI (1.20 g, 8.00 mmol) and the yellow solution was stirred for 1 h. The solution was filtered over Celite and the volatiles were evaporated. The residue was redissolved in $CHCl_3$ (200 mL) and washed with H_2O (10 mL), the organic layer was dried ($MgSO_4$) and concentrated to 10 mL. Et_2O was added to induce precipitation. The light yellow product was collected by centrifugation. Yield: 1.96 g (78%). ^{1}H NMR (DMSO-d_6) δ = 7.41 (s, 2H, Ar*H*); 4.13 (s, $^3J_{PtH}$ = 39.0 Hz, 4H, CH_2); 3.07 (s, $^3J_{PtH}$ = 28.8 Hz, 12H, N(CH_3)$_2$) ppm. ^{13}C{^{1}H} NMR (DMSO-d_6) δ = 168.2, 156.0, 144.1, 125.6, 120.6, 75.4, 55.6 ppm.

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13. To a solution of **4** (538 mg, 0.97 mmol) in dry THF (50 mL) were added *N*-hydroxysuccinimide (112 mg, 0.98 mmol), DCC (202 mg, 0.98 mmol), and dry pyridine (1 mL). The clear yellow solution was stirred for 16 h and a white precipitate (dicyclohexylurea) was then filtered off. The solvent was evaporated and the remaining solid was redissolved in CH_2Cl_2 (5 mL) and a white precipitate was filtered off again. This cycle of dissolving the solid in CH_2Cl_2 and filtering off the white precipitate was repeated until no more white precipitate was detected. After evaporation of the solvent in vacuo, the yellow solid was taken up in CH_2Cl_2 (5 mL) and Et_2O was added to induce precipitation. The light yellow product was then collected by centrifugation. Further purification of **1** can be achieved by trituration with acetone. Yield: 613 mg (97%), after trituration 408 mg (65%). ^{1}H NMR ($CDCl_3$) δ = 7.61 (s, 2H, Ar*H*); 4.06 (s, $^3J_{PtH}$ = 45.9 Hz, 4H, ArCH_2); 3.17 (s, $^3J_{PtH}$ = 39.9 Hz, 12H, N(CH_3)$_2$); 2.89 (s, 4H, CH_2C(O)) ppm. ^{13}C{^{1}H} NMR ($CDCl_3$) δ = 169.5, 162.5, 160.2, 144.2, 122.0, 119.8, 76.3, 56.3, 25.7 ppm. Note: **1** undergoes halogen-exchange in chloroform. Elem. anal. found (calcd) for $C_{17}H_{22}IN_3O_4Pt$: C, 31.20 (31.09); H, 3.30 (3.45); N, 6.42 (6.31). ESI MS *m*/*z* 676.9 ([*M*+Na]$^+$), 527.3 ([*M*–I]$^+$).
14. *Crystal structure determination of* **1**. $C_{17}H_{22}IN_3O_4Pt$, M_r = 654.37, yellow plate, 0.12×0.12×0.03 mm^3, *T* = 125(2) K, monoclinic, space group $P2_1/c$ (No. 14), *a* = 6.1163(1), *b* = 23.3240(4), *c* = 14.4823(2) Å, β = 106.4139(7)°, *V* = 1981.80(5) Å^3. *Z* = 4, ρ = 2.193 g/cm^3. X-ray intensities were measured on a Nonius Kappa CCD diffractometer with rotating anode (λ = 0.71073 Å). Analytical absorption correction (μ = 8.66 mm^{-1}, 0.33–0.55 transmission). 27,598 measured reflections up to (sin $\theta/\lambda)_{max}$ = 0.65 Å^{-1}, of which 4524 were unique (R_{int} = 0.0459). The structure was solved with automated Patterson methods (DIRDIF97[15]) and refined with SHELXL97[16] against F^2 of all reflections. *R* [$I>2\sigma(I)$]: R_1 = 0.0275, wR_2 = 0.0614. *R* [all reflections]: R_1 = 0.0359, wR_2 = 0.0648. *S* = 1.020. Residual electron density between −1.13 and 2.90 e/Å^3. Molecular illustration, structure checking and calculations were performed with the PLATON package.[17]
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    5: White crystalline solid. ^{1}H NMR (acetone-d_6) δ = 7.48 (br t, 1H, N*H*); 7.36 (s, 2H, Ar*H*); 4.14 (s, $^3J_{PtH}$ = 45.6 Hz, 4H, ArCH_2); 3.36 (q, $^3J_{HH}$ = 6.6 Hz, 2H, CH_2NH); 3.15 (s, $^3J_{PtH}$ = 39.3 Hz, 12H, N(CH_3)$_2$); 1.57 (qui, $^3J_{HH}$ = 6.6 Hz, 2H, CH_2CH$_2$NH); 1.38 (sex, $^3J_{HH}$ = 6.6 Hz, 2H, CH_2CH$_2$CH$_2$NH); 0.92 (t, $^3J_{HH}$ = 6.6 Hz, 3H, CH$_2$CH_3) ppm. ^{13}C{^{1}H} NMR (acetone-d_6) δ = 168.1, 154.7, 144.8, 131.5, 119.2, 77.1, 56.5, 40.0, 32.7, 20.8, 14.1 ppm. Elem. anal. found (calcd) for $C_{17}H_{28}IN_3OPt$: C, 33.30 (33.34); H, 4.66 (4.61); N, 6.81 (6.86).
    6: White solid. ^{1}H NMR ($CDCl_3$) δ = 7.28 (s, 2H, Ar*H*); 7.24 (d, $^3J_{HH}$ = 8.1 Hz, 2H, Ar*H*); 7.16 (d, $^3J_{HH}$ = 8.1 Hz, 2H, Ar*H*); 6.22 (br t, 1H, N*H*); 4.56 (d, $^3J_{HH}$ = 5.4 Hz, 2H, CH_2NH); 4.03 (s, $^3J_{PtH}$ = 45.9 Hz, 4H, ArCH_2); 3.17 (s, $^3J_{PtH}$ = 38.7 Hz, 12H, N(CH_3)$_2$); 2.34 (s, 3H, ArCH_3) ppm. ^{13}C{^{1}H} NMR ($CDCl_3$) δ = 168.0, 154.7, 143.7, 137.3, 135.3, 130.0, 129.4, 127.9, 118.4, 76.2, 56.3, 43.9, 21.1 ppm. Elem. anal. found (calcd) for $C_{21}H_{28}IN_3OPt$: C, 38.26 (38.19); H, 4.34 (4.27); N, 6.31 (6.36).
    7: Off-white solid. ^{1}H NMR (acetone-d_6) δ = 7.58 (br, 1H, CH$_2$N*H*); 7.38 (s, 2H, Ar*H*); 6.16 (d, $^3J_{HH}$ = 8.4 Hz, 1H, CHN*H*C(O)O′Bu); 4.14 (s, $^3J_{PtH}$ = 44.7 Hz, 4H, ArCH_2 overlapping q, 1H, NHC*H*COOH); 3.38 (q, $^3J_{HH}$ = 6.6 Hz, 2H, CH_2NHC(O)); 3.15 (s, $^3J_{PtH}$ = 39.0 Hz, 12H, N(CH_3)$_2$); 1.80 (m, 2H, CH_2CH(C(O))(NH)); 1.62 (m, 2H, CH_2CH$_2$CH(C(O))(NH)); 1.51 (qui, 2H, 8.0 Hz, CH_2CH$_2$NHC(O)); 1.39 (s, 9H, Boc) ppm. ^{13}C{^{1}H} NMR ($CDCl_3$) δ = 174.3, 168.3, 156.6, 154.8, 144.8, 131.4, 119.2, 79.1, 77.1, 56.5, 54.3, 39.9, 32.2, 30.1, 28.6, 23.9 ppm. Elem. anal. found (calcd) for $C_{24}H_{39}IN_4O_5Pt$: C, 36.83 (36.69); H, 5.11 (5.00); N, 10.05 (10.19).
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