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A Chemoselective and Modular Post-Synthetic Multi-Functionalization of NHC–Platinum Complexes

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We report oxime ligation in combination with metal ligand exchange as a novel orthogonal and practical approach to the multifunctionalization of NHC–platinum complexes. This strategy, which enables strong diversity enhancement of metallodrug candidates, could also be applied to selective bioconjugation.

Introduction

The unique properties of metal ions can be used for the treatment of acute illnesses.[1] In this way, the serendipitous discovery of cisplatin by Rosenberg led to the most widely used anticancer drug, and this mainly paved the way for a new field of research that is medicinal inorganic chemistry.[2] Although widely used, cisplatin treatment is accompanied by several toxic side effects and tumor resistance.[3] Thus, chemists have tried to find alternative drugs in particular with potentially different mechanisms of action.[4] Nevertheless, the clinical success of the cisplatin drug still remains a driving force for the development of new platinum complexes with reduced side effects and/or (acquired) resistance. As such, organometallic complexes have been the subjects of exciting studies and offer many opportunities in the design of new drugs, not only as anticancer agent but also as antimicrobial, antimalarial and diagnostic agents.[5]

N-heterocyclic carbene (NHC) metal complexes are a class of organometallic complexes that have received recent interest in the context of cancer therapy.[6,7] In particular, several NHC-containing platinum compounds have shown efficacy in vitro against various cancer cell lines with cytotoxicities significantly higher than cisplatin.[8] However, the (pre)clinical development of these new molecules as anticancer agents still faces multiple challenges, including the clarification of their mode of action, the investigation of their selectivity profile, and the demonstration of their efficacy in vivo.[9] In vivo, the molecule should be inert towards the biological environment to avoid potential interference and deactivation before reaching the target cells. Parameters such as solubility and stability in aqueous solution thus become crucial in this respect. Ideally, NHC–metal complexes should also exhibit high selectivity towards cancer cells and rapid clearance from non-targeted cells. Active targeting by linking the anticancer agent to a suitable ligand that displays a high affinity for a specific receptor is thus needed. All these requirements should be pre-evaluated and possibly modulated by means of simple and highly modular synthetic pathways.[10]

The post-synthetic functionalization of organometallic complexes has long been understudied, mainly because these compounds, by their very nature, were thought to be incompatible with and too sensitive for such chemical transformations. Today, this concept is being revisited in light of the fast development of click chemistry and the copper-catalyzed azide-alkyne cycloaddition (CuAAC).[11] The high orthogonality, reliability and experimental simplicity of the CuAAC was exploited recently to access various transition metal conjugates including NHC complexes.[12,13]

However, creating a covalent and irreversible bond by azide-alkyne cycloaddition necessitates the insertion of potentially cleavable functionalities for an efficient release of the drug into the cancer cell. The reaction has also other limitations that have been noted in particular when considering post-functionalization of organometallic complexes.[13]

With such issues in mind, we describe here an efficient strategy for preparing multifunctionalized NHC–Pt complexes either by iterative assembly or by using orthogonal ligation reactions (Figure 1).

Among click-type reactions, the carbonyl condensation reactions, such as imine-, hydrazine- and oxime-bond formation, recently received considerable attention for ac-

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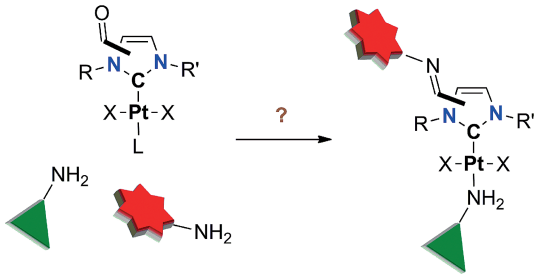
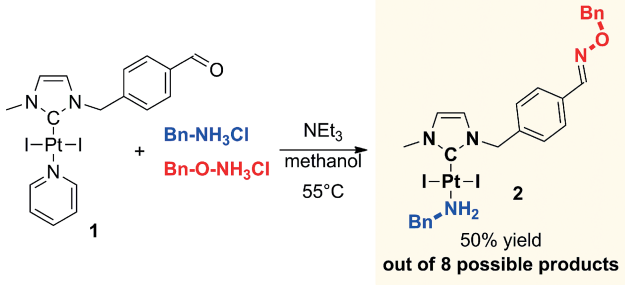


Figure 1. Schematic representation of a selective post-synthetic functionalization of NHC–platinum complexes by using possibly reversible reactions (exemplified with C=N-bond formation).

cessing bioconjugates.[11a,14,15] In addition of such post-synthetic functionalization, we envisioned that the introduction of additional functionalities through the coordination of a secondary relevant ligand would greatly enhance the diversity of the compounds. Such combination of chemoselective and orthogonal click techniques should considerably facilitate the preparation of Pt complexes that display multiple ligands.

Results and Discussion

It is known that oximes display a much higher stability compared to imines; thus, hydroxylamine derivatives (rather than amine derivatives) preferentially react with an aldehyde moiety. On the other hand, we found that in a competitive experiment with benzylamine and benzyl hydroxylamine an (NHC)(pyridine)platinum complex [(NHC)(pyridine)PtI_2] reacts preferentially with the amine in a ratio of 3:1 (see Supporting Information for details). This result suggests that the combination of oxime ligation with ligand exchange on the metal center could be exploited to access orthogonal bifunctionalized NHC complexes. To validate this hypothesis, we conducted the two reactions concurrently in a one-pot dual experiment with an (NHC)(pyridine)platinum complex bearing a benzaldehyde moiety (e.g. **1**) by just mixing all components (Scheme 1). NMR analysis showed the formation of a major product in ca. 50%, which was found to be the Pt complex **2** containing the



Scheme 1. One-pot chemoselective functionalization of NHC–Pt complex **1** by oxime ligation and ligand exchange, complex **2** indicating a self-sorting behaviour out of an eight-component dynamic combinatorial library (yield determined by NMR).

benzyloxime and the benzylamino ligand, thus confirming directional chemical reactivity.

The molecular structure of a related compound was confirmed by X-ray diffraction analysis. Figure 2 displays the molecular structure of the Pt complex **3** obtained by reaction with cyclohexylamine and *O*-benzylhydroxylamine. The platinum centre features the typical square-planar arrangement with a carbene–platinum bond length of 1.970(7) Å and the oxime in (*E*) configuration [C(11)–N(3) 1.385(9) Å].

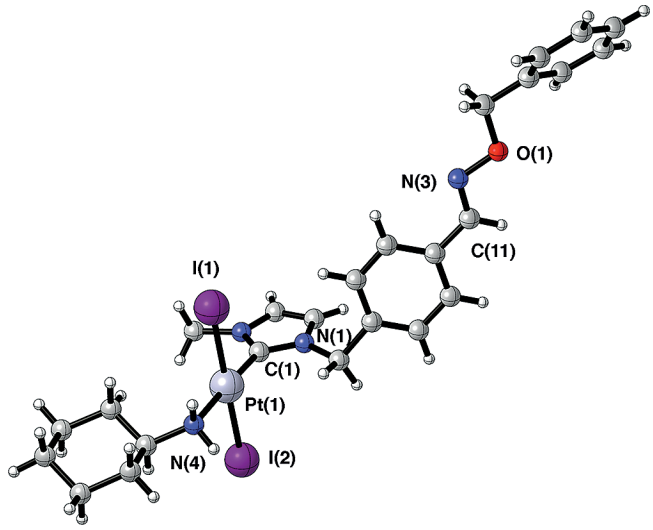
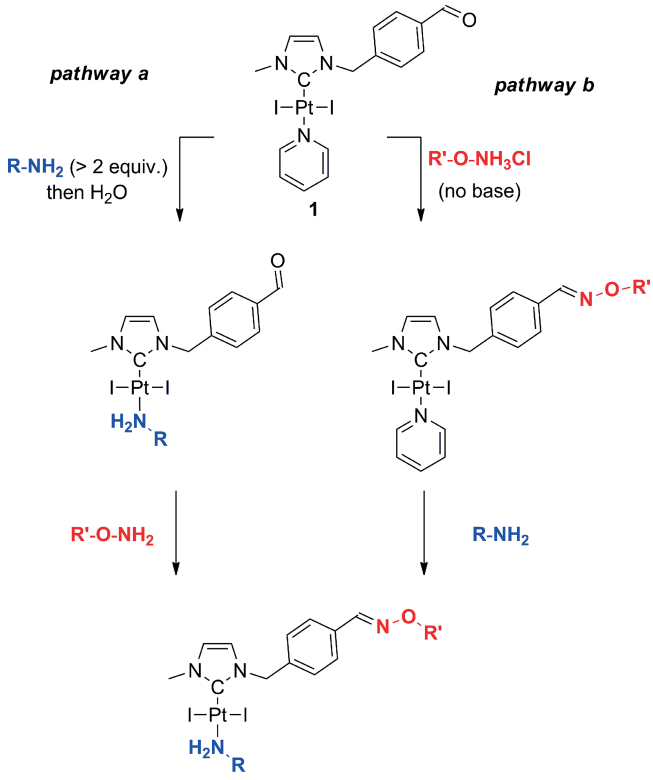


Figure 2. Molecular structure of complex **3**. Selected bond lengths [Å] and angles [°]: Pt(1)–C(1) 1.970(7), Pt(1)–N(4) 2.5901(6), Pt(1)–I(1) 2.6012(6), Pt(1)–I(2) 2.5901(6), C(11)–N(3) 1.283(12), N(3)–O(1) 1.385(9); I(1)–Pt(1)–I(2) 177.70(2), C(1)–Pt(1)–N(4) 177.7(3).

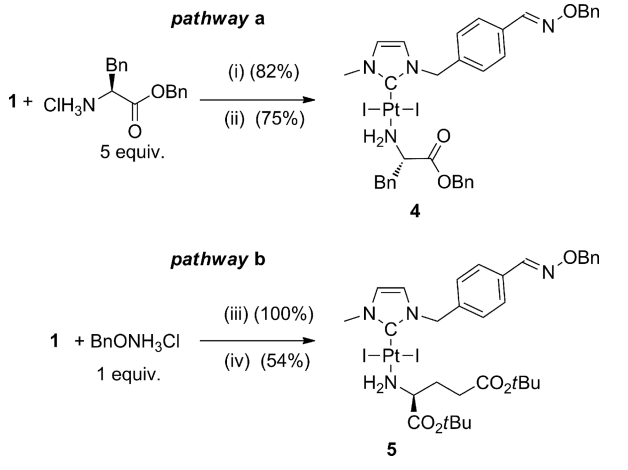
Sequential assembly by varying the order of addition of the reactants (Scheme 2) was also investigated to further optimize the process.[16] By introducing the amine first (*pathway a*), it was found that better conversion could be obtained in the presence of excess of amine reagent, thus giving the corresponding imine product as intermediate. Further treatment with wet silica led to the hydrolysis of the imine giving the aldehyde product in good yield. The hydroxylamine-functionalized compound could then be efficiently introduced. Alternatively, oxime ligation can be first done selectively (*pathway b*). Interestingly, the oxime ligation was found to be highly selective when the oxime was formed from the ammonium salt $RONH_3Cl$, whereas addition of a base such as triethylamine resulted in an unselective functionalization. Introduction of the amine afterwards resulted in a selective pyridine ligand exchange giving the expected product.

Scheme 3 displays two representative examples of such chemoselective molecular assembly. NHC–Pt complex **1** was first treated with an excess of D-phenylalanine benzyl ester followed by treatment with wet silica to give the corresponding aldehyde-containing amino complex in 82% isolated yield. Then, reaction with 1 equiv. of *O*-benzylhydroxylamine gave the expected Pt complex **4** in 62% yield. By



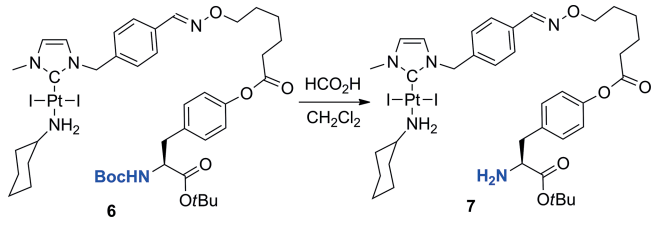
Scheme 2. The two possible pathways for double modification of NHC–Pt complex **1** by sequential oxime ligation/ligand exchange.

using *pathway b*, complex **1** was first treated with *O*-benzylhydroxylamine leading quantitatively to oxime ligation. Then, in a second step, the pyridine ligand could be selectively exchanged by L-glutamic acid di-*tert*-butyl ester to give complex **5** in 54% isolated yield.



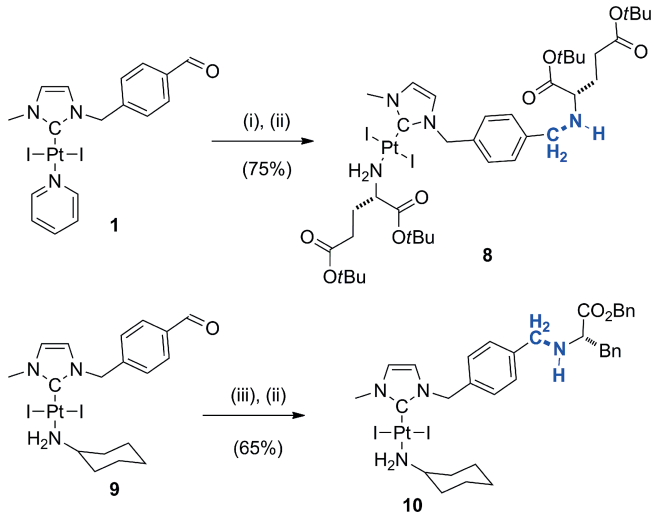
Scheme 3. Examples of one-pot double modification of NHC–Pt complex **1** by sequential oxime ligation and ligand exchange (*pathways a* and *b*). Reaction conditions: (i) NEt_3, MeOH then wet SiO_2; (ii) $BnONH_3Cl$, NEt_3; CH_2Cl_2; (iii) CH_2Cl_2; (iv) NEt_3, L-glutamic acid di-*tert*-butyl ester hydrochloride, EtOH.

The double functionalization by oxime ligation and metal ligand exchange offers products of remarkable stability that are potentially amenable to further chemical modification, thus offering an additional level of chemical diversity. For example, the NHC–platinum complex **6** containing the protected L-Boc-Tyr-O*t*Bu residue was obtained by oxime ligation in 60% yield under mild conditions. A selective deprotection of the *N*-Boc protecting group could then be achieved by treatment with formic acid in dichloromethane to give complex **7** in quantitative yield (Scheme 4).



Scheme 4. Selective *N*-Boc deprotection of an NHC–Pt complex **6** following chemoselective oxime bond functionalization.

Imine ligation shows lower stability than oxime or hydrazone ligations, in particular they are not stable at physiological pH.[14] Nevertheless, they can be used as intermediates and in situ reduced to generate the corresponding secondary amine. For example, doubly functionalized platinum complex **8** with L-glutamic acid di-*tert*-butyl ester was obtained by treatment of NHC–Pt complex **1** with an excess of the protected amino acid followed by $NaHB(OAc)_3$ (75% yield, two steps), featuring now an irreversible ligation with one glutamic acid derivative (Scheme 5). Due to the coordination of amino groups being thermodynamically stable, it is also possible to functionalize Pt complexes with two different nitrogen-containing ligands akin to previous complex **6**. As an example, complex **9** was treated with L-Phe-OBn followed by $NaHB(OAc)_3$ to give complex **10** in 65% overall yield.



Scheme 5. Post-modification of NHC–Pt complexes by tandem imine ligation/reduction. Reaction conditions: (i) L-glutamic acid di-*tert*-butyl ester hydrochloride (5 equiv.), K_2CO_3; (ii) $NaHB(OAc)_3$ (3 equiv.); (iii) L-Phe-OBn (1.1 equiv.).

Conclusions

Altogether these results demonstrate the efficiency of combining ligand substitution with oxime ligation to enhance the chemical diversity of (N-heterocyclic carbene)-platinum complexes. Although the directional chemical reactivities of amines and hydroxylamines allow the bis-functionalization of the (carbene)metal complex to be carried out in a one-pot process, we found it more practical to proceed sequentially in either way. The compatibility of the newly formed NHC–platinum complexes with further chemical transformations (e.g. Boc deprotection, reductive amination) brings added value. The examples reported herein thus validate a synthetic method that may prove useful in biology, allowing the cell targeting properties and cytotoxic activities and of NHC–metal complexes to be finely tuned.

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[1] *Medicinal Inorganic Chemistry* (Eds.: J. L. Sessler, S. R. Doctrow, T. J. McMurry, S. J. Lippard), ACS Symposium Series, Washington, DC, **2005**.
[2] B. Rosenberg, L. Van Camp, T. Krigas, *Nature* **1965**, *205*, 698.
[3] M. A. Fuertes, C. Alonso, J. M. Pérez, *Chem. Rev.* **2003**, *103*, 645.
[4] a) L. Ronconiand, P. J. Sadler, *Coord. Chem. Rev.* **2007**, *251*, 1633; b) P. C. A. Bruijnincx, P. J. Sadler, *Curr. Opin. Chem. Biol.* **2008**, *12*, 197; c) S. H. van Rijt, P. J. Sadler, *Drug Discovery Today* **2009**, *14*, 1089.
[5] a) G. Gasser, N. Metzler-Nolte, *Curr. Opin. Chem. Biol.* **2012**, *16*, 84; b) G. Gasser, I. Ott, N. Metzler-Nolte, *J. Med. Chem.* **2011**, *54*, 3; c) M. M. Jellicoe, S. J. Nichols, B. A. Callus, M. V. Baker, P. J. Barnard, S. J. Berners-Price, J. Whelan, G. C. Yeoh, A. Filipovska, *Carcinogenesis* **2008**, *29*, 1124; d) S. Ray, R. Mohan, J. K. Singh, M. K. Samantaray, M. M. Shaikh, D. Panda, P. Ghosh, *J. Am. Chem. Soc.* **2007**, *129*, 15042.
[6] a) A. Gautier, F. Cisnetti, *Metallomics* **2012**, *4*, 23; b) K. M. Hindi, M. J. Panzner, C. A. Tessier, C. L. Cannon, W. J. Youngs, *Chem. Rev.* **2009**, *109*, 3859; c) L. Mercs, M. Albrecht, *Chem. Soc. Rev.* **2010**, *39*, 1903; d) W. Liu, R. Gust, *Chem. Soc. Rev.* **2013**, *42*, 755.
[7] Recent general reviews on NHC complexes: a) M. N. Hopkinson, C. Richter, M. Schedler, F. Glorius, *Nature* **2014**, *510*, 485; b) S. Bellemin-Laponnaz, S. Dagorne, *Chem. Rev.* **2014**, *114*, 8747; c) K. Riener, S. Haslinger, A. Raba, M. P. Högerl, M. Cokoja, W. A. Herrmann, F. E. Kühn, *Chem. Rev.* **2014**, *114*, 5215; d) S. Díez-González, N. Marion, S. P. Nolan, *Chem. Rev.* **2009**, *109*, 3612.
[8] a) M. Skander, P. Retailleau, B. Bourrie, L. Schio, P. Mailliet, A. Marinetti, *J. Med. Chem.* **2010**, *53*, 2146; b) M. Chtchigrovsky, L. Eloy, H. Jullien, L. Saker, E. Ségal-Bendirdjian, J. Poupon, S. Bombard, T. Cresteil, P. Retailleau, A. Marinetti, *J. Med. Chem.* **2013**, *56*, 2074; c) E. Chardon, G. Dahm, G. Guichard, S. Bellemin-Laponnaz, *Chem. Asian J.* **2013**, *8*, 1232; d) E. Chardon, G. Dahm, G. Guichard, S. Bellemin-Laponnaz, *Organometallics* **2012**, *31*, 7618; e) E. Chardon, G. L. Puleo, G. Dahm, S. Fournel, G. Guichard, S. Bellemin-Laponnaz, *ChemPlusChem* **2012**, *77*, 1028; f) E. Chardon, G. L. Puleo, G. Dahm, S. Fournel, G. Guichard, S. Bellemin-Laponnaz, *Chem. Commun.* **2011**, *47*, 5864; g) R. W.-Y. Sun, A. L.-F. Chow, X.-H. Li, J. J. Yan, S. S.-Y. Chui, C.-M. Che, *Chem. Sci.* **2011**, *2*, 728.
[9] *Pharmaceutical Perspectives of Cancer Therapeutics* (Eds.: Y. Lu, R. I. Mahato), Springer, New York, **2009**.
[10] A. Monney, M. Albrecht, *Coord. Chem. Rev.* **2013**, *257*, 2420.
[11] For reviews, see: a) W. Tang, M. L. Becker, *Chem. Soc. Rev.* **2014**, *43*, 7013; b) P. Thirumurugan, D. Matosiuk, K. Jozwiak, *Chem. Rev.* **2013**, *113*, 4905; c) M. Meldal, C. W. Tornøe, *Chem. Rev.* **2008**, *108*, 2952; d) J. E. Moses, A. D. Moorhouse, *Chem. Soc. Rev.* **2007**, *36*, 1249.
[12] See, for example: a) S. Gauthier, N. Weisbach, N. Bhuvanesh, J. A. Gladysz, *Organometallics* **2009**, *28*, 5597; b) D. Urankar, J. Košmrlj, *Inorg. Chim. Acta* **2010**, *363*, 3817; c) J. D. White, M. F. Osborn, A. D. Moghaddam, L. E. Guzman, M. M. Haley, V. J. DeRose, *J. Am. Chem. Soc.* **2013**, *135*, 11680.
[13] F. Cisnetti, C. Gibard, A. Gautier, *J. Organomet. Chem.* **2014**, DOI: 10.1016/j.jorganchem.2014.10.012.
[14] S. Ulrich, D. Boturyn, A. Marra, O. Renaudet, P. Dumy, *Chem. Eur. J.* **2014**, *20*, 34.
[15] a) W. H. Ang, E. Daldini, L. Juillerat-Jeanneret, P. J. Dyson, *Inorg. Chem.* **2007**, *46*, 9048; b) Y. Q. Tan, P. J. Dyson, W. H. Ang, *Organometallics* **2011**, *30*, 5965; c) D. Y. Q. Wong, C. H. F. Yeo, W. H. Ang, *Angew. Chem. Int. Ed.* **2014**, *53*, 6752.
[16] The sequential rather than the one-pot assembly was found to give better overall yields. Moreover, one-pot assembly generates several possible products so that it is more difficult to purify the desired target.

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