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Direct functionalisation of group 10 N-heterocyclic carbene complexes for diversity enhancement†

Edith Chardon,[ab] Gian Luigi Puleo,[a] Georges Dahm,[a] Gilles Guichard*[b] and Stéphane Bellemin-Laponnaz*[a]

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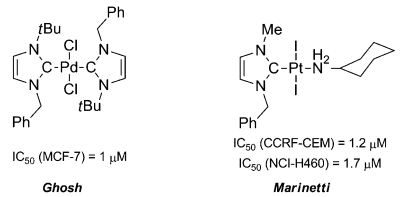
The synthesis of alkyne-substituted N-heterocyclic carbene complexes of Pd(II) and Pt(II) is reported. Catalyzed 1,3-dipolar cycloaddition with azides has been applied as a modular way of functionalisation of group 10 transition metal NHC complexes to generate potentially new metallodrugs.

Cisplatin which is effective against many forms of cancer is the quintessential transition metal-based chemotherapeutic agent. The formation of covalent crosslinks with DNA and subsequent disruption of the DNA structure are believed to account for its cytotoxic activity against cancer cells. Despite considerable benefits, the clinical use of cisplatin is limited by adverse side effects and resistance. Several approaches have been explored to overcome these hurdles. The search for new platinum complexes with different DNA binding properties and/or improved pharmacological profile has attracted considerable attention.[1]

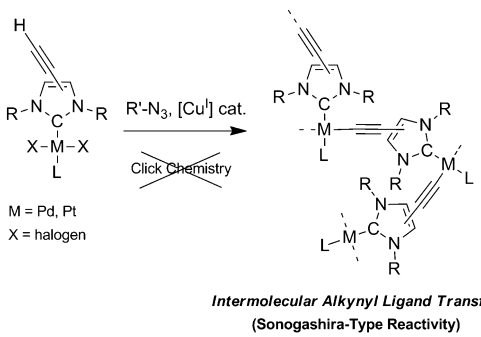
Very recently, several groups pointed to the importance of N-heterocyclic carbene (NHC)[2] ligand as a new structure for the development of transition metal-containing drug candidates. Remarkably, Ghosh *et al.* established that palladium complexes of general formula *trans*-$(NHC)_2PdX_2$ or *trans*-$(NHC)PdX_2$(pyridine) are potent inhibitors of the proliferation of cancer cells,[3] whereas Marinetti *et al.* showed the efficiency of *trans*-configured platinum complexes of general formula $(NHC)PtX_2(L)$ (with L = amine) towards cisplatin-resistant cell lines (Scheme 1).[4,5] Nevertheless, there is still a significant gap to be filled between this NHC-*proof of concept* and (pre)clinical developments. At this stage, a modular approach allowing the synthesis of functionalised and conjugated NHC metal complexes would be an asset to increase chemical diversity, introduce specific features (*i.e.* water solubility, specific cell recognition elements, delivery,



Scheme 1 Group 10 NHC complexes exhibiting cytoxicity against cancer cells (cell lines in brackets).

fluorescence...) and ultimately facilitate the development of this emerging class of cytotoxic molecules. However, the unavoidable strategy in organometallic synthesis, which consists in the coordination of the transition metal at the very last step of the synthesis, suffers from serious drawbacks: (i) forcing reaction conditions, (ii) low modularity and most importantly (iii) incompatibility with a large number of chemical functions (*i.e.* alcohols, amides...).[6] Although attractive, the chemoselective functionalisation of the NHC complex of late transition metals remains a challenging route and these transition metal complexes are potentially reactive molecules that usually do not tolerate further manipulation.[7,8]

We reasoned that *catalyzed 1,3-dipolar cycloadditions of terminal alkynes to azides* could be the solution of choice for that purpose. However, the copper(I)-catalyzed alkyne–azide cycloaddition (CuAAC)[9] is not compatible with the presence of halogens on a group 10 transition metal as shown in Scheme 2. Indeed, the reaction of dihalocomplexes of palladium (or platinum) with terminal alkyne in the presence of a copper(I) catalyst and an amine base is known as a method for



Scheme 2 The incompatibility of CuAAC: the reaction conditions lead to the formation of alkynyl complexes.

[a] *Institute of Physics and Chemistry of Materials of Strasbourg (IPCMS), University of Strasbourg – CNRS UMR7504, 23 rue du Loess, 67034 Strasbourg, France. E-mail: bellemin@unistra.fr; Fax: +33 (0)388107246; Tel: +33 (0)388107166*
[b] *European Institute of Chemistry and Biology (IECB), University of Bordeaux – CNRS UMR5248, 2 rue Escarpit, 33607 Pessac, France. E-mail: g.guichard@iecb.u-bordeaux.fr; Fax: +33 (0)540002200; Tel: +33 (0)540003020*
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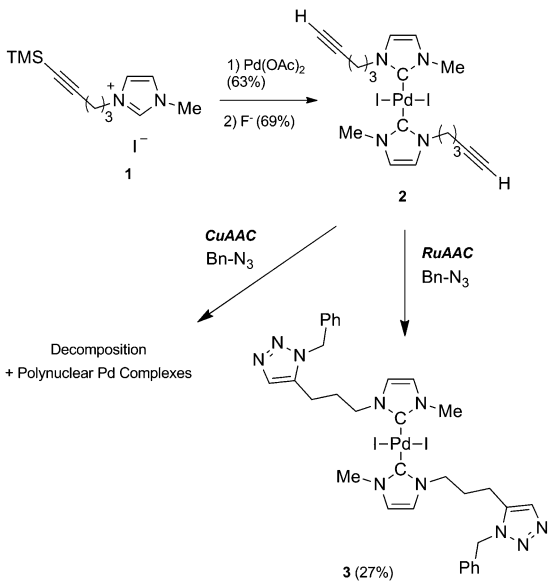
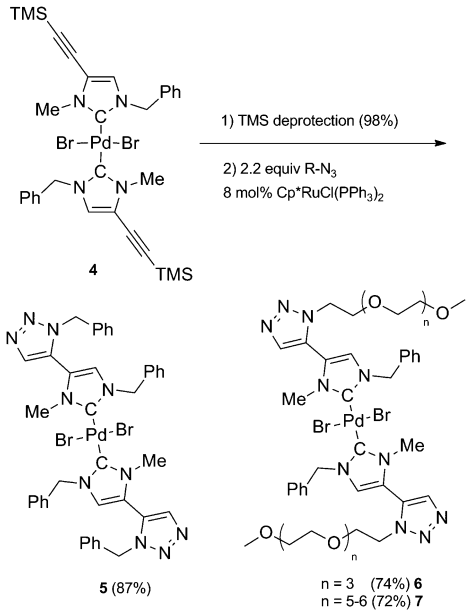
the preparation of dialkynyl complexes.[10] So far, the organic functionalisation of a sensitive group 10 transition metal complex (*i.e.* with potentially exchangeable ligands) in the presence of a transition metal catalyst remains elusive.[11] Herein, we report the successful functionalisation of alkyne-substituted NHC complexes of Pd(II) and Pt(II) with diverse azides as a direct and modular method for the development of elaborated NHC-based cytotoxic molecules.

The reaction of *N*-alkyne (TMS protected) functionalised imidazolium salt **1** with 0.5 equivalent of palladium acetate leads to the *trans*-bis(NHC) palladium complex in 63% yield.[12,13] Optimal deprotection of the TMS-alkyne was obtained with fluoride on a macroporous polymer support (2.0–3.0 mmol g^{-1} loading). The unmasked alkyne **2** was then subjected to reaction with 2.2 equivalents of benzyl azide in the presence of classical copper catalysts. Screening of various experimental conditions (copper source, solvent, temperature…) led to the conclusion that the reaction is not compatible with the presence of the Pd(II) complex derivative. Investigation of the reaction product composition revealed the presence of palladium black with insoluble orange/brown solids that may be assigned to coordination polymers by alkynyl complexes formation. Fortunately, an attempt to conduct the reaction with the ruthenium catalyst $Cp^*RuCl(PPh_3)_2$ afforded the long-awaited bis-cycloaddition product **3** (1,5-regioisomer), albeit in modest yield as shown in Scheme 3.

The ruthenium-catalyzed azide–alkyne cycloaddition (RuAAC)[14] was then successfully applied to the bis-*N*-heterocyclic carbene palladium complex **4** with remote TMS-alkyne tether in the backbone of the carbene ligand that accordingly offers a more significant degree of diversity (Scheme 4).[15] The double cycloaddition reaction with benzyl azide in the presence of 8 mol% of a Ru catalyst gave the desired product (**5**) in 87% isolated yield. Functionalisation with more



Scheme 3 Synthesis of complex **2** and 1,3-dipolar cycloaddition studies: (1) THF, Δ, 2 h; (2) fluoride on Amberlyst A-26, THF, rt; *RuAAC*: $Cp^*RuCl(PPh_3)_2$ as a catalyst; *CuAAC*: various copper sources, solvents and temperatures have been screened.

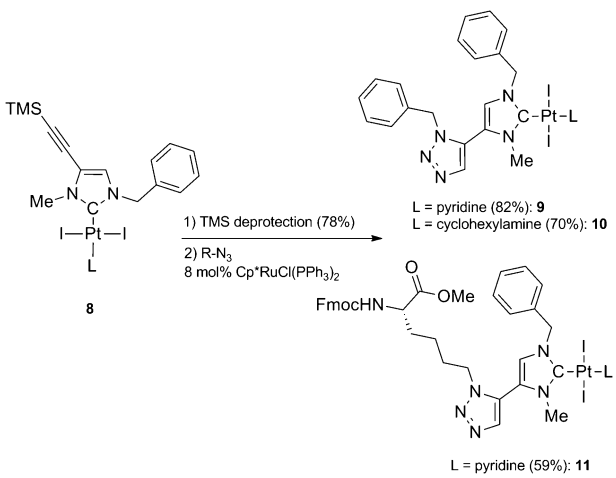


Scheme 4 Double functionalisation of *trans*-$(NHC)_2PdBr_2$ complex **4**. (1) Fluoride on Amberlyst A-26, THF, rt; (2) 8 mol% catalyst, THF, 60 °C, overnight.

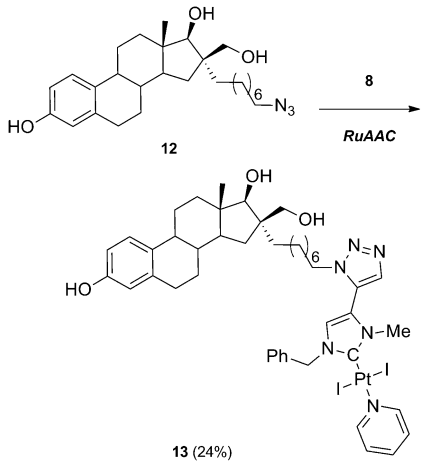
challenging azides like PEG derivatives was also possible. Noteworthily, compounds **6** and **7** were both obtained in good yields (74% and 72% respectively).[16]

Further investigation of the 1,3 dipolar cycloaddition reaction with platinum derivatives also proved the efficiency of ruthenium *vs.* copper catalysts towards square-planar NHC–platinum complexes such as **8**.[17] The cycloaddition products were obtained in 82% and in 70% with benzyl azide when L was pyridine (**9**) and cyclohexylamine (**10**) respectively. Following the same procedure the complex **8** gave the L-lysine derivative **11** in 59% yield (Scheme 5).

Finally, in order to possibly enhance selectivity and specificity towards cancer cells, we designed the oestrogen functionalised Pt(II) complex **13** as a possible candidate to target hormone-dependent diseases (*e.g.* breast cancer).[18] Complex **13** was obtained in 24% yield by reaction of **8** with the oestrogen



Scheme 5 Functionalisation of platinum complex **8** (L = pyridine or cyclohexylamine). (1) K_2CO_3, MeOH, rt; (2) 8 mol% catalyst, THF, Δ.



Scheme 6 Functionalisation of platinum complex **8** (L = pyridine) with oestrogen derivative **13** (8 mol% catalyst, THF, Δ).

derived azide **12** (Scheme 6) despite the presence of a 1,3-diol function in **12** susceptible to react either with the platinum complex or with the ruthenium catalyst.

In this work, we have investigated a modular approach to the functionalisation of a sensitive group 10 transition metal NHC complex using ruthenium-catalyzed azide–alkyne cycloaddition. Encouraged by these preliminary results, we are currently extending the scope of this method to a more diverse set of azides with the aim to generate chemical libraries and later to endow cytotoxic NHC complexes of transition metals with new properties (*e.g.* specific cell recognition, delivery, fluorescence…).

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12 Note that the alkyne has to be protected for the metal complexation with the NHC ligand.

13 The *trans*-configuration of the palladium complex was established by NMR studies. The ^{1}H NMR of the *trans*-bis(NHC) palladium complex (in $CDCl_3$ at RT) gives rise to two sets of signals due to the presence of rotational isomers. The interconversion between them has been confirmed by variable-temperature investigation (see ESI†).

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15 The *trans*-configuration of complex **4** was established by NMR studies and confirmed by an X-ray diffraction study (see ESI†). Two rotational isomers were observed at room temperature by ^{1}H NMR ($CDCl_3$ as a solvent), akin to palladium complex **2**.

16 NMR investigation of the regioselectivity of the cycloaddition revealed the selective formation of the 1,5-regioisomers as expected.

17 We found that the alkyne in **8** was optimally unmasked by treatment with K_2CO_3 in MeOH.

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