

COMMUNICATION

View Article Online
View Journal | View IssueCite this: *Dalton Trans.*, 2025, **54**, 11817Received 10th June 2025,
Accepted 16th July 2025

DOI: 10.1039/d5dt01364j

rsc.li/dalton

Chloride-to-(radio)iodide exchange on
NHC–metal complexes†Ginevra Giobbio,[‡] Killian Henault,[‡] Gauthier Foucras,[‡] Anais Prigent,[‡]
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Efficient chloride/iodide exchange on chloro-NHC–metal complexes was achieved under mild conditions using stable or radioactive iodide. The protocol enables simultaneous synthesis of radio-labeled compounds and their non-radioactive references, facilitating the development of chemically matched theranostic pairs.

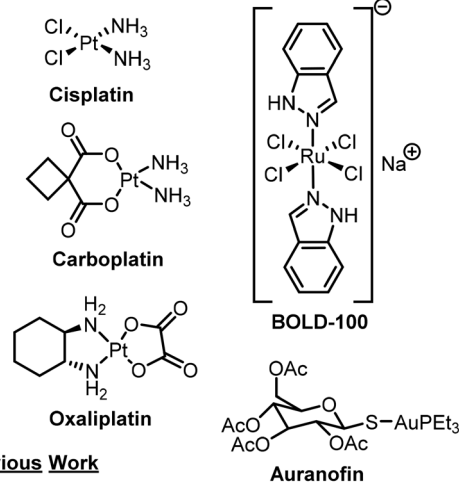
Introduction

Metallodrugs are an important class of therapeutic agents that have been used by humankind for centuries.^{1,2} To date, several of these drugs have been approved by the FDA, with the most commonly prescribed ones being lithium carbonate for mood disorder regulation, silver sulfadiazine as a topical antibiotic, bismuth subsalicylate for stomach pain relief, and, of course, cisplatin (Fig. 1). Since the approval of this anticancer chemotherapeutic drug in 1978, tremendous efforts have been made to discover better anticancer agents with improved pharmacological properties. Dedicated research teams have focused on the modification of ligands, leading to the development of carboplatin and oxaliplatin, while also exploring the use of other transition metals instead of platinum.³ A remarkable example of this latter approach is the discovery of BOLD-100,⁴ a ruthenium-based metallodrug currently in clinical development as an anticancer therapeutic. The recent repositioning of Auranofin, an antirheumatic agent, in clinical

trials for lung cancer or ovarian cancer is another noteworthy example.⁵

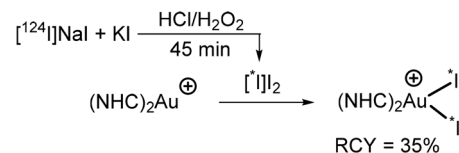
However, to date, aside from cisplatin and its derivatives, no anticancer metallodrug investigated in clinical trials has

Metallodrugs

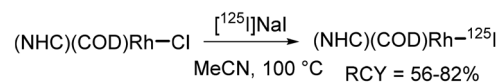


Previous Work

Berger, Llop, and Salassa



Gestin



This Work

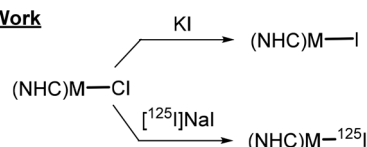


Fig. 1 Context and objectives.

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† Electronic supplementary information (ESI) available. See DOI: <https://doi.org/10.1039/d5dt01364j>

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received regulatory approval. The main limitations hindering the development of metal-based therapeutics in oncology are their low target selectivity, high off-target toxicity, and a therapeutic window that is often too narrow for safe and effective use.⁶ The use of radiolabeled metallodrugs as theranostic agents offers a distinct advantage by harnessing the emission properties of radionuclides, thereby enabling therapeutic applications at much lower doses. In this context, the therapeutic effect arises from the radioactive decay rather than the intrinsic chemical reactivity of the metal complex. Due to their outstanding anticancer potential, as well as their facile synthesis and stability, metallodrugs containing an *N*-heterocyclic carbene (NHC) ligands are now emerging as very promising chemotherapeutic agents.^{7–10} From a chemical point of view, these ligands possess donor properties similar to phosphines, along with strong σ -donating and weak π -back bonding capabilities, and they can be easily functionalized. In a drug design context, NHCs are also known for their low toxicity and stability under physiological conditions.^{11–14} These properties have led to the discovery of potent NHC–metal complexes incorporating various d-block metals, such as Au, Rh, Ru, Pd, Ag, Cu, Pt, and Ir. In many NHC–metal complexes, halogen atoms such as chloride or bromide are frequently coordinated to the metal center and can influence properties such as stability, solubility, or reactivity. In some systems, these factors have been associated with enhanced or modulated biological activity.¹⁵ In our view, the presence of these halogen atoms in many reported structures presents an opportunity to further improve these compounds and access new properties through substitution with an iodine radioisotope. Indeed, the introduction of radioactive isotopes would allow the conversion of halo-NHC–metal complexes into either a diagnostic tool -using iodine-123 for single photon emission computed tomography (SPECT) or iodine-124 for positron emission tomography (PET)- or a radiotherapeutic tool with iodine-131.

This approach was recently used by Berger, Llop, and Salassa to produce a diiodo-Au(III) PET imaging agent by synthesizing the diradioiodinated species from a (NHC)₂Au(I) complex.¹⁶ However, this synthesis provides the compound with a radiochemical yield (RCY) of 35% and requires the pre-oxidation of radioiodide (the only available chemical source for radioiodine) in the presence of KI, thus affording isotopic dilution. In this work, we aim to explore the more convenient conversion of chloro-NHC–metal complexes into their corresponding (radio)iodo-NHC–metal complexes. To the best of our knowledge, this type of halogen exchange on metallic center has been poorly explored using radioiodine isotopes. In 2014, Englert *et al.* described on a platinum complex a sequential approach for the conversion of iodine-127 to the corresponding hydroxy derivative, followed by hydroxyl-iodine-125 exchange.¹⁷ In 2008, Zalutsky's group proposed the preparation of Ir[16aneS4-diol]-^{125/131}I by reacting IrCl₃ with sulfur ligand and radioiodides.¹⁸ In 2007, Alberto *et al.* performed the radioiodination of a cisplatin adduct of vitamin B12 *via* a chloride/iodide exchange.¹⁹ In 2013, Gestin *et al.* described a direct chloride/iodide exchange on a Rh–NHC complex at high

temperature.²⁰ Establishing mild reaction conditions to obtain (radio)iodo-NHC–metal complexes from the corresponding chloro-NHC–metal will enable the simultaneous production of both HPLC standards and valuable theranostic tools.

Results and discussion

Firstly, the synthesis of the IPr metal chloride complexes (IPr = 1,3-bis(2,6-di-iso-propylphenyl)imidazol-2-ylidene) was achieved by known procedures reported in the literature. For complexes [CuCl(IPr)]²¹ (**1**) and [AgCl(IPr)]²² (**2**), **IPr-HCl** was engaged as precursor of the NHC in the presence of M₂O (M = Cu and Ag) to furnish [MCl(IPr)] complexes in 80 and 88% isolated yields, respectively (Scheme 1).

Complexes [AuCl(IPr)]²³ (**3**), [PdCl(IPr)(allyl)]²⁴ (**4**), [PtCl(IPr)(Me-allyl)]²⁴ (**5**), [RhCl(IPr)(cod)]²⁵ (**6**), and [IrCl(IPr)(cod)]²⁵ (**7**) were synthesized in 78 to 95% isolated yield starting from **IPr-HCl** in basic conditions (K₂CO₃ or ^tBuOK) in the presence of the specific metal precursor (Scheme 1). Finally, complexes [MnBr(IPr)(CO)₄] (**8**) and [ReCl(IPr)(CO)₄] (**9**) were obtained from the isolated free **IPr** in the presence of the metal precursors [M(CO)₅X]²⁶ (M = Mn or Re) and gave **8** and **9** in 69 and 46% isolated yield, respectively (Scheme 1). Of note, starting from **IPr-HCl** and the respective metal precursor to synthesize **8** and **9** led to the degradation of the starting material in our hands.

Once all the chloride complexes were obtained, the optimization of the iodide/chloride exchange was explored with complexes **1** and **2** inspired by the conditions reported by Gestin using dichloromethane as solvent for the exchange of the chloride atom by iodide onto a rhodium complex with KI (3.8 equiv.) as iodide source.²⁰

In these conditions, the complex [CuI(IPr)] (**10**) was obtained in 67% isolated yield (Table 1, entry 1) but complex [AgI(IPr)] (**11**) was obtained with the concomitant formation of [Ag(IPr)2][AgX2] (X = Cl or I) with yields estimated by ¹H NMR spectroscopy of 77 and 5% yield, respectively (Table 1, entry 6). To avoid the formation of this by-product, a screening of solvent was carried out for both complex **2** and **3**. Using **2**, the Cl/I exchange was observed in acetone, THF, methanol and acetonitrile furnishing **10** in 82, 85, 85, 77 and 86% isolated yield (Table 1, entries 2–5) whereas the synthesis of pure **11** was more complicated. In details, methanol or acetone led to no conversion or only formation of [Ag(IPr)2][AgX2] (X = Cl or I), respectively (Table 1, entries 7 and 9). In acetonitrile, **11** was observed as minor compound compared to [Ag(IPr)2][AgX2] (X = Cl or I) (Table 1, entry 10). Finally, THF appeared to be the best solvent as the sole formation of **11** was observed with 86% isolated yield (Table 1, entry 8). This last result was encouraging as THF would be compatible for the iodine-125 exchange.

Having this optimization in hands, we next applied them to complexes **3–9**. Gratefully, [AuI(IPr)] (**12**), [PdI(IPr)(allyl)] (**13**), [PtI(IPr)(Me-allyl)] (**14**), [RhI(IPr)(cod)] (**15**), [IrI(IPr)(cod)] (**16**), [MnI(IPr)(CO)₄] (**17**) and [ReI(IPr)(CO)₄] (**18**) were obtained as



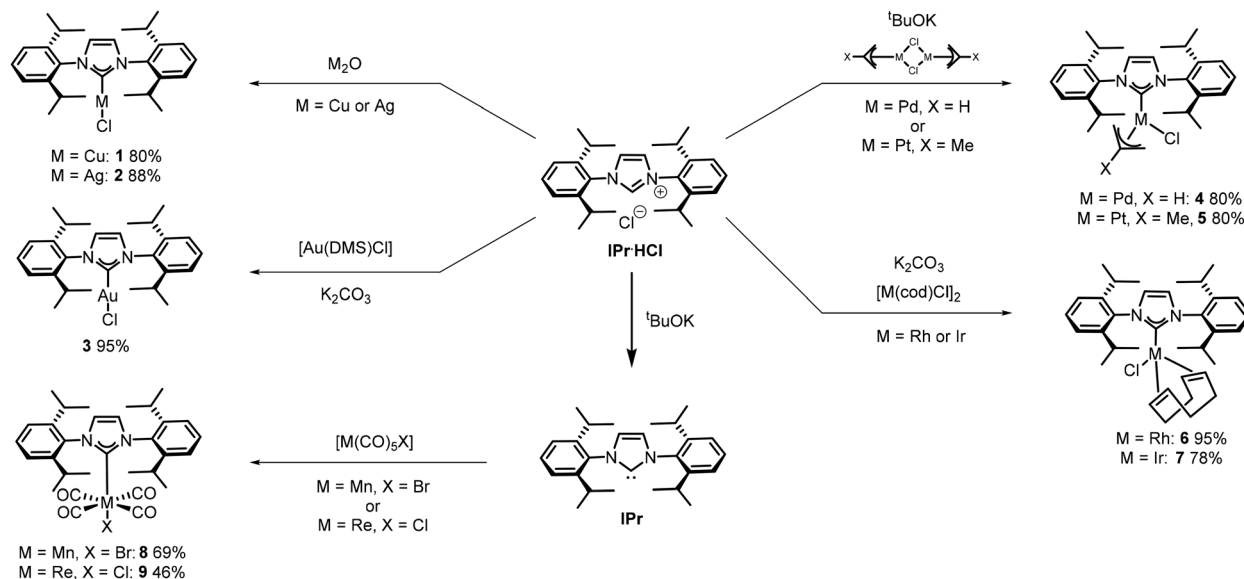


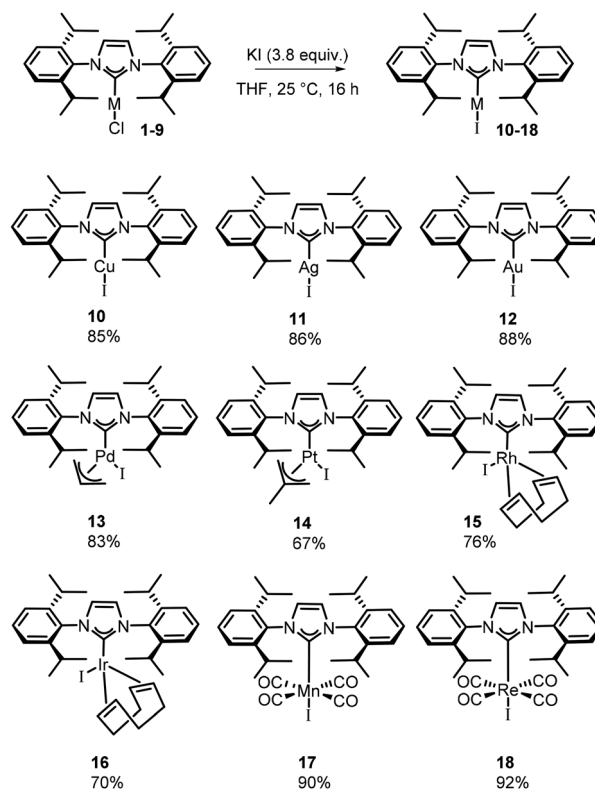
Table 1 Screening of solvent for the synthesis of [Cu(IPr)] **10** and [Ag(IPr)] **11**

Entry	Solvent	M	Product	Yield ^a (%)
1	Dichloromethane	Cu	10	67
2	Acetone	Cu	10	82
3	THF	Cu	10	85
4	MeOH	Cu	10	77
5	Acetonitrile	Cu	10	86
6	Dichloromethane	Ag	11	77 ^b (5)
7	Acetone	Ag	11	— ^b (45)
8	THF	Ag	11	86
9	MeOH	Ag	11	— ^c
10	Acetonitrile	Ag	11	12 ^b (40)

^a Isolated yield. ^b ¹H NMR yield using trimethoxybenzene as standard. The number between brackets is the NMR yield of [Ag(IPr)₂][AgX₂] in the crude. ^c Only starting material was recovered.

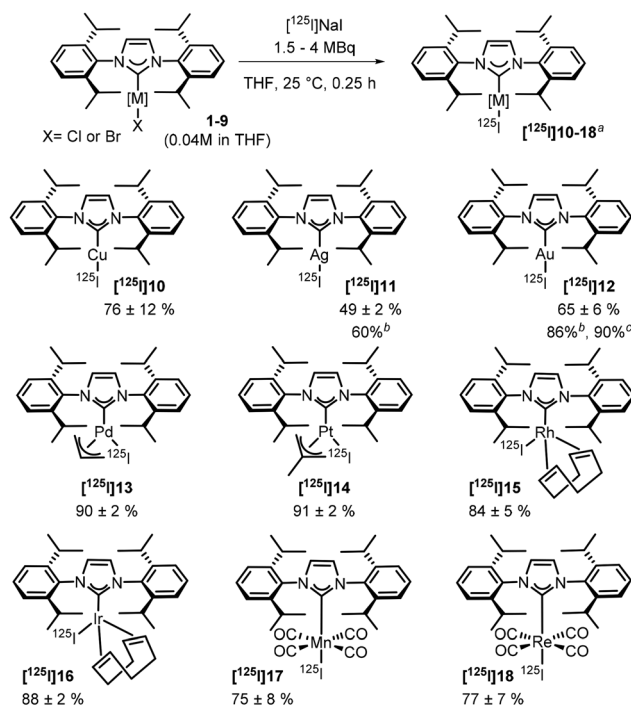
pure compounds in yield between 67 and 92% isolated yield (Scheme 2). Of note, some complexes did not present significant chemical shift in ¹H NMR spectroscopy to confirm the Cl⁻/I⁻ exchange and control of this exchange was confirmed by mass spectroscopy by detection of iodide.

We then turned our attention to adapting this protocol for radioiodination. For this purpose, iodine-125 was selected, as it is both the more readily available and safer radiochemical iodine isotope. Iodine-125 has a half-life of 60 days and emits predominantly low-energy X-rays (~30 keV). The only available chemical source of iodine-125 is [¹²⁵I]NaI, which we used directly at activity levels ranging from 1.5 to 4 MBq. Due to its



specific activity, 1 MBq of iodine-125 corresponds to approximately 12 picomoles. Reactions were therefore carried out using a large excess of chlorinated precursors (3.2 mmol). Reacting [CuCl(IPr)] (**1**) with [¹²⁵I]NaI in THF at room temperature for 15 minutes led to the formation of [¹²⁵I]**10** with a radiochemical conversion (RCC) of 76%, as determined by





Scheme 3 Scope of the chloride(bromide)/iodide-125 exchange.

^a Results are expressed as radiochemical conversions (RCC), assessed by radio-TLC analysis and reported as the mean of two experiments ($n = 2$).

^b Reaction was performed at 40 °C ($n = 1$). ^c Reaction time was extended to one hour ($n = 1$).

radio-TLC. Under the same conditions, starting from $[\text{AgCl}(\text{IPr})]$ (2) gave $[^{125}\text{I}]\mathbf{11}$ with an RCC of 49%, which increased to 60% upon heating to 40 °C. Applying the same protocol to $[\text{AuCl}(\text{IPr})]$ (3) yielded $[^{125}\text{I}]\mathbf{12}$ with an RCC of 65% at room temperature. Heating to 40 °C or extending the reaction time to one hour increased the RCC to 86% and 90%, respectively. High RCCs were also obtained from $[\text{PdCl}(\text{IPr}(\text{allyl}))]$ (4), $[\text{PtCl}(\text{IPr}(\text{Me-allyl}))]$ (5), $[\text{RhCl}(\text{IPr}(\text{cod}))]$ (6), and $[\text{IrCl}(\text{IPr}(\text{cod}))]$ (7), with the corresponding $[^{125}\text{I}]\mathbf{13-16}$ produced in RCCs ranging from 84% to 91% at room temperature. Slightly lower RCCs were observed with $[\text{MnBr}(\text{IPr})(\text{CO})_4]$ (8) and $[\text{ReCl}(\text{IPr})(\text{CO})_4]$ (9), affording $[^{125}\text{I}]\mathbf{17}$ and $[^{125}\text{I}]\mathbf{18}$ with RCCs of 75% and 77%, respectively and proving the efficacy of the process from a brominated derivative (Scheme 3).

Conclusions

In conclusion, we have demonstrated that chloride/iodide exchange can be carried out quite efficiently on a variety of chloro-NHC-metal complexes. This transformation proceeds under mild conditions, typically at room temperature in THF, and can be performed using either stable or radioactive iodide sources. Notably, in the radiochemical version of the reaction, radiochemical conversion (RCC) can be significantly improved by mild heating or by extending the reaction time. In a theranostic context, this protocol offers a distinct advantage: it

enables the simultaneous production of both the radioiodinated complex and its non-radioactive analytical reference from the same precursor. Furthermore, the methodology is compatible with different iodine radioisotopes, opening the door to applications in PET, SPECT, and radiotherapeutics. The methodology seems well-suited for the development of theranostic pairs, in which diagnostic and therapeutic agents share an identical chemical structure, ensuring consistent pharmacokinetics and facilitating regulatory and clinical translation.

Author contributions

GG and KH performed the chemistry experiments and wrote the article, GF and AP performed the radiochemistry experiments, SG conceived the experiments, and wrote the article, TC performed the radiochemistry experiments, conceived the experiments, and wrote the article.

Conflicts of interest

There are no conflicts to declare.

Data availability

The data supporting this article have been included as part of the ESI.†

Acknowledgements

This work was supported by the University of Caen, the “Ministère de l’Enseignement Supérieur et de la Recherche”, the CNRS (Centre National de la Recherche Scientifique) and the LABEX SynOrg (ANR-11-LABX-0029). S. G. acknowledges the “Région Normandie” (G. G. and K. H.), the Graduate School of Research XL-Chem (ANR-18-EURE-0020 XL-Chem) for funding. TC thanks the Normandy County Council and the European Union in the framework of the ERDF-ESF operational programme 2021–2027 for funding this project.

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