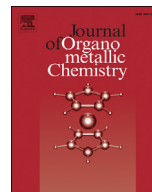




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Review

Post-functionalization of metal–NHC complexes: A useful toolbox for bioorganometallic chemistry (and beyond)?

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ABSTRACT

Post-functionalization of metal *N*-heterocyclic carbene complexes (metal NHCs) is described in this focused review. As metal NHCs are nowadays prominent in organometallic chemistry, functionalization methods for these scaffolds are of high importance for numerous applications of these organometallic compounds, ranging from catalysis to medicinal chemistry. Recently, post-functionalization – *i.e.* chemical modification of a preformed metal complex – has emerged as a set of divergent and modular methods for metal NHC modification. Examples chosen herein highlight that in a near future such methods may increase the number and diversity of biocompatible and bioconjugated metal–NHC complexes.

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Introduction

Metal *N*-heterocyclic carbene complexes have entered chemistry first as chemical curiosities in the 1960s [1,2] before becoming part of mainstream research after the isolation of the free carbenes in the 1990s [3,4]. They are currently the focus of a great deal of

research, as their coordination properties are now well understood [5]. Nowadays, this family of complexes is one of the most broadly considered for all the applications of organometallic chemistry [6–8]. The first applications of metal–NHC complexes were considered in the context of catalysis where NHCs replaced phosphine ligands for a broad range of catalytic applications [9]. Indeed, the desirable characteristics for ancillary ligands in catalysis – strong binding, low chemical reactivity of the ligand scaffold, control of metal redox states, simple speciation, tailored steric crowding etc... – are quite similar to the general requirements for

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metal-based molecular compounds in biological media. Hence, not unsurprisingly NHC ligands have also been considered for the design of metal-based drug candidates [10–15].

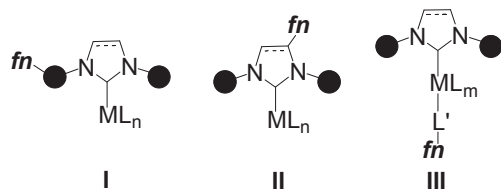
While several authors have reported functionalized NHCs [16] as structures of interest for specific purposes, the concept of “functionalization” is generally only implicitly defined. In this review, we will define functionalization as the synthetic modification of “reference” ligand scaffolds bearing only alkyl- or aryl-substituents – as exemplified in Scheme 1 with the most frequently encountered metal complexes of imidazol(in)-2-ylidenes – with a moiety providing the complex with new properties. These could be: reactivity through added functional groups, modification of solubility polar/charged pendants, chirality, biomolecular recognition... In this review, we will consider both the modification of the ligand scaffold (cases I and II) as well as the case where the added function is carried by a non-NHC ligand (case III).

To obtain functionalized metal–NHC complexes, straightforward and modular synthetic routes permitting easy variation of the grafted functional group are highly desirable. In this short review, we will focus on post-functionalization of metal–NHC complexes to obtain well-defined molecular complexes; solid-supported complexes (see a review [17] and a recent example [18]) will not be discussed herein. Post-functionalization consists in performing the synthetic step allowing the introduction of the extra functionality on preformed metal complexes. The obvious advantage of post-functionalization methods is that a single complex precursor may allow the divergent access to a family of functionalized complexes. While this topic is quite recent (<10 years), several synthetic approaches have now attained sufficient maturity to consider them as a toolbox to achieve molecular diversity in an efficient manner, which is highly desirable in many areas, in particular for biological applications.

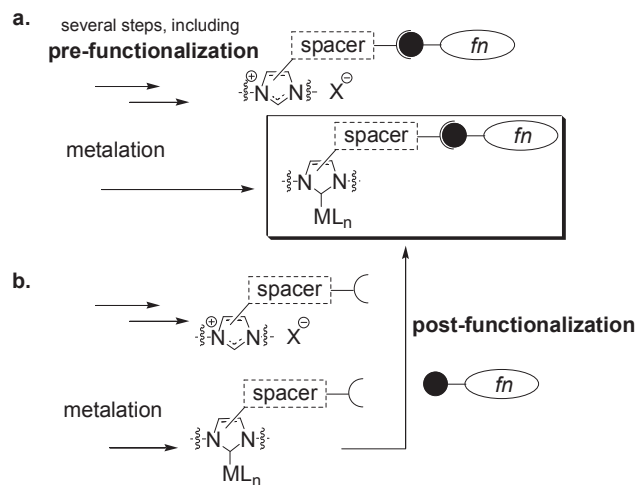
Chemical modification of the NHC ligand scaffold

Generally, two strategies exist to obtain functionalized metal–NHC complexes where the extra function is carried by the organic scaffold (Scheme 2). In the pre-functionalization strategy, the desired functionality is added at some point in the multistep preparation of the azolium salt [19] (often linked to the imidazol(in)-2-ylidene ring via a spacer), then the compound is metalated to yield the functionalized complex. On the contrary, in the post-functionalization strategy, an azolium salt carrying functionalizable groups is metalated and the function is introduced thanks to a reaction performed on the resulting complex precursor.

Obviously, this strategy will be successful provided that reactive groups required for post-functionalization are compatible with the preparation of azolium salts and that general conditions may be found for the functionalization step. As it will be apparent by examination of the examples discussed hereafter, this constitutes a limitation that has impeded a broader use of post-functionalization methods. On the other hand, for the pathway relying on pre-



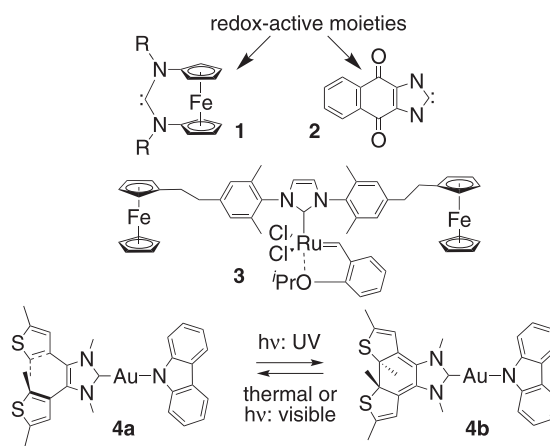
Scheme 1. Various types of functionalized metal–NHC scaffolds. Black disks denote alkyl- or aryl-substituents. I: functionalization on *N*-substituents (alkyl or aryl). II: imidazol(in)-2-ylidene cycle functionalization. III: non-NHC ligand substitution. For the sake of simplicity, cases I–III are exemplified with imidazol(in)-2-ylidene scaffolds.



Scheme 2. Insert: functionalized metal–NHC complexes obtained by modification of NHC ligands. Pre- and post-functionalization strategies to access them are shown in panels a and b, respectively.

functionalized ligand precursors, several synthetic steps need to be adapted when changing the added functionality. Tedious synthetic optimization of organic and organometallic synthetic steps may be required for each compound, because the properties of the final complex and its precursors may vary significantly due to the added functional groups. Moreover, as steps requiring harsh conditions conclude frequently imidazol(in)ium salt preparations (typically: cyclizations in acidic conditions) [19], further limitations of synthetic nature may appear if the additional functionality is introduced in the early stages of the synthetic sequence.

Strategies aimed at appending functional groups by modification of NHC ligands within metal complexes have been explored by a few research groups worldwide since a handful of years. However, this was preceded by NHC ligands switchable (*i.e.* modifiable) by other types of external stimuli. Redox- or photo-induced post-modifications of metal–NHC complexes were described by several groups (Scheme 3). Redox (either electrochemically or by chemical reagents) modifications of metal–carbene complexes are more widespread. By analogy with extensive works performed in various areas of inorganic chemistry with *N*-, *P*-, *O*- and *S*-ligands, early and



Scheme 3. Top: NHC scaffolds fused with oxidizable or reducible groups; center: reduced form of a redox switchable (dissolved/precipitated) olefin metathesis catalyst by Süßner and Plenio [24]; bottom: photochemical post-modification of metal–NHC complexes as reported by Yam et al. [27] Example shown for gold.

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