Coordination Chemistry Reviews 359 (2018) 57–79

Contents lists available at ScienceDirect

Coordination Chemistry Reviews

journal homepage: www.elsevier.com/locate/ccr

Review

Organometallic catalysis in biological media and living settings

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ARTICLE INFO

Article history:
Received 12 October 2017
Accepted 7 January 2018

Keywords:
Organometallic
Bioorthogonal
Transition metal catalysis
Living cells
Artificial metalloenzymes

ABSTRACT

Organometallic catalysis has allowed the development of an impressive number of chemical transformations that could not be achieved using classical methodologies. Most of these reactions have been accomplished in organic solvents, and in many cases in the absence of water, and under air-free conditions. The increasing pressure to develop more sustainable transformations has stimulated the discovery of metal-catalyzed reactions that can take place in water. A particularly attractive extension of this chemistry consists of the use of biological relevant aqueous solvents, as this might set the basis to translate catalytic metal complexes to biological settings. While this research field is in its infancy, along the last ten years there have been an increasing number of reports demonstrating the viability of achieving metal-promoted transformations in biologically relevant contexts. In this review, that does not intend to be comprehensive, we summarize the most significant advances in the area, and highlight some of the more important difficulties that must be faced when trying to design biocompatible organometallic catalysts, such us stability, cell uptake, bioorthogonality and toxicity. We will manly focus on transition metal systems which have been shown to keep their activity in complex aqueous buffers and inside living cells.

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Contents

Abbreviations: CuAAC, Copper-Catalyzed Azide–Alkyne Cycloadditions; PhSH, thiophenol; alloc, allylcarbamate group; DAPI, 4′,6-diamidine-2′-phenylindole; EtBr, ethidium bromide; TON, turnover number; GSH, glutathione; PBS, phosphate buffered saline; TPP, triphenylphosphonium; IMM, mitochondrial inner membrane; TMRE, tetramethylrhodamine, ethyl ester; ICP-MS, inductively coupled plasma mass spectrometry; RuAtAC, Ruthenium-Catalyzed Azide–Thioalkyne Cycloadditions; GFP, Green Fluorescent Protein; proc, propargylic-carbamate; *Neu*, neuramic acid; PdNPs, palladium nanoparticles; **5FU**, 5-fluoro-1-propargyl-uracil; TFP, ligand tri-2-furylphosphine; HBSS, Hank's Balanced Salt Solution; PEG, polyethylene glycol; PLGA, poly lactic acid-co-glycolic acid; ROS, reactive oxygen species; THPTA, *tris*-(hydroxypropyltriazolylmethyl)amine; BTTAA, *bis*[(tert-butyltriazoyl)methyl]-[(2-carboxymethyltriazoyl)methyl]-amine; TBTA, *tris*[(1-benzyl-1H-1,2,3-triazol-4-yl)methyl]amine; HPG, homopropargylglycine; TCEP, *tris*(2-carboxyethyl)phosphine hydrochloride; NaAsc, sodium ascorbate; HEK, human embryonic kidney; FITC, Fluorescein isothiocyanate; OVCAR5, human ovarian cancer cells; CuNPs, copper nanoparticles; E–Cu–NPs, embedded copper nanoparticles; Cu-MONPs, Cu-containing organic nanoparticles; FRET, fluorescence resonance energy transfer; AuNPs, gold nanoparticles; TPP, 5,10,15,20-tetraphenyl-21H,23H-porphine; bPPs, bovine pancreatic polypeptides; ee, enantiomeric excess; PIX, porphyrin IX; TOF, turnover frequency; ATHase, artificial transfer hydrogenase; biot–Sav, biotin–streptavidin; NaPi, sodium phosphate solution.

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https://doi.org/10.1016/j.ccr.2018.01.011
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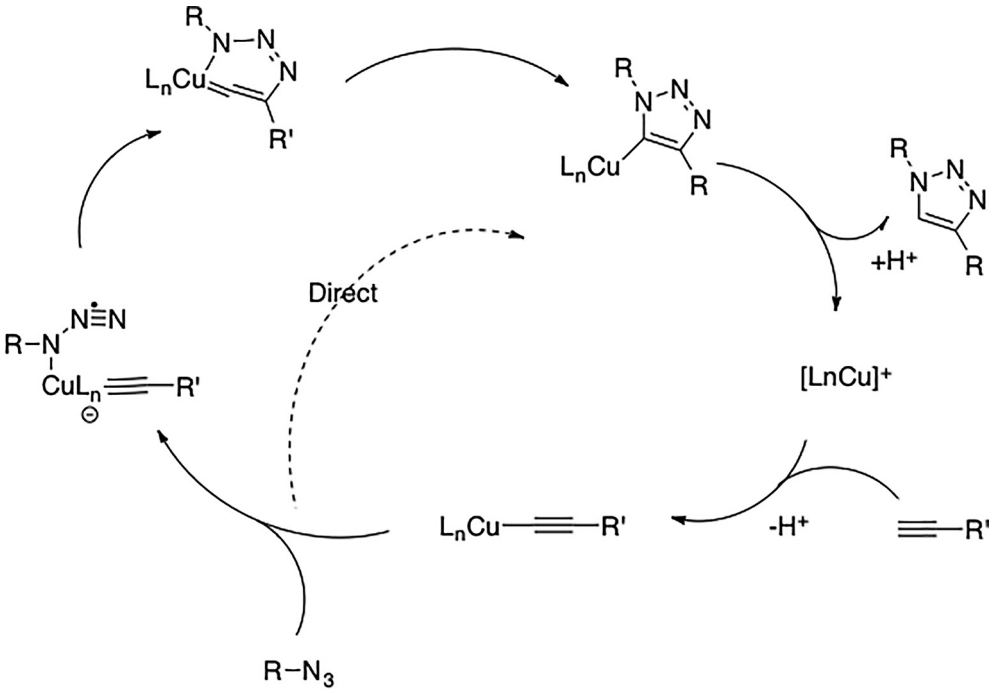
1. Introduction

Organometallic catalysis in water is itself a quite new field of research which has been mainly developed within the context of "Green chemistry" [1–6]. In recent years, there have been many reports on metal-catalyzed reactions that can take place in water, including couplings, isomerizations, cyclizations, cycloadditions or hydrolysis processes. Despite this progress, the number of water-compatible organometallic reactions is still very small when compared with transformations achieved in organic solvents [7,8]. Thus, one should expect many new contributions in the coming years.

Given that the basic solvent of biological habitats is water, it is not difficult to envision that some of these transformations might be achieved in bio-relevant media. However, the complexity of biological solvents, owing to the presence of a high concentration of biomolecules such as thiols or amines which can poison the metal and kill the catalytic activity, makes extremely challenging to translate metal-catalyzed reactions to such media. Even more difficult is the transfer to *living cells*, as in this case additional issues such as cell uptake and transport, and especially, side biological effects [9–12], need to be taken into account. In addition, transition metal speciation should be considered, as this could influence the reactivity as well as the toxicity of the metals [13,14]; however, studies in this area, in the context of metal-promoted reactions in cell culture, are yet lacking. Anyhow, in recent years there have been many reports on the use of metal complexes in complex aqueous buffers, and even *in vivo* settings [15–18]. While organometallic catalysis in biological media is yet an emerging discipline, it seems clear that being able to achieve non-natural catalytic transformations of exogenous substrates in bio-settings might unleash a new world of opportunities for biological and medicinal research. This can be of great relevance for instance for the *in situ* generation of drugs, the amplification of optical signals for the detection of biomarkers, or the metal-promoted modification of biomolecules, among others.

Undoubtedly, one of the key discoveries that has had a more significant impact on the development of biocompatible metal-catalyzed transformations was the report by Sharpless and by Meldal of the famous Copper-Catalyzed Azide–Alkyne Cycloadditions (**CuAAC**, Scheme 1) [19,20]. This reaction has changed our capability to transform and monitor biomolecules, in some cases even in living atmospheres, in the presence of many other native molecular components. This type of reactions belongs to what Bertozzi coined as *Bioorthogonal Chemistry* [21,22]. The copper-promoted annulations can be considered as the first metal-catalyzed reactions that could be achieved in complex aqueous media and even in cell culture media for the modification of cell surface sugars [23–25] and proteins [26]. The cytotoxicity of Cu(I) ions, however, has significantly hindered the application of this reaction in the internal space of living cells.

After these ground-breaking and inspiring developments in bioorthogonal chemistry, other research groups started to investigate the applicability of other metals in this new field of research. Nevertheless, moving to cells is not trivial, as the living cell is a very complex, compartmentalized and dynamic entity, with a very high concentration of biomolecules, including thiols. Despite this, recent data suggest that certain transition metal derivatives can



Scheme 1. Initial mechanism proposed by Sharpless for the CuAAC [19].

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