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The ability to perform "new-to-nature" chemical reactions within living cells and organisms is transforming the way in which scientists interrogate and/or manipulate biological processes. In recent years, the toolbox of bioorthogonal and cell-compatible reactions has been enriched with the incorporation of transition metal-mediated processes. Whereas the efficiency of these reactions is still low, the breadth and generality of organometallic catalysis promises to significantly impact the field of bioorthogonal chemistry. Particularly attractive is the possibility of using organometallic catalysis for performing bond-forming, synthetically relevant reactions, as this could allow to assemble biorelevant products at specific biological sites.

Cells are complex chemical factories in which thousands of chemical reactions are perfectly orchestrated to provide the food and energy required for life. These reactions can either break (catabolic) or build (anabolic) functional molecules, and most of them are promoted by enzymes, the catalysts of Nature [1]. **Enzymes** (see Glossary) exhibit excellent rates and turnovers, and present impressive selectivity and orthogonality, even under the complex environment of living cells and organisms. However, enzymes have evolved to catalyze only those reactions that are required by Nature, and therefore they usually present a limited scope in terms of breadth and generality. In contrast, human-invented catalysts, and especially those based on **transition metals**, tend to be much more general, and can promote an impressively broad range of reactions, well beyond those used by Nature [2,3]. However, organometallic catalysts present shortcomings when compared to enzymes, such as inferior kinetics, poorer orthogonality, and the usual requirement of water- and oxygen-free atmospheres to prevent the deactivation of the catalyst [4].

In recent years, there has been an increasing number of reports demonstrating that organometallic catalysts can operate under biological conditions, and even in living cells (Figure 1A) [5-7], although most of the reactions so far studied consist of uncaging/deprotection processes [8,9].

Transformations involving synthetic (anabolic) processes, namely, the building of large, complex molecules from smaller, exogenous reactants (Figure 1B), are only now starting to see the light [10]. These types of reactions are intrinsically relevant from a fundamental and conceptual perspective, but also promise to yield applications in biology and medicine, as they could be used to synthesize bioactive compounds or designed biomolecules *in situ*. In the present manuscript, we will review and discuss the progress in translating "synthetic" organometallic transformations to cellular and *in vivo* environments, presenting a brief perspective on this nascent/emerging field of **bioorthogonal synthetic chemistry**.

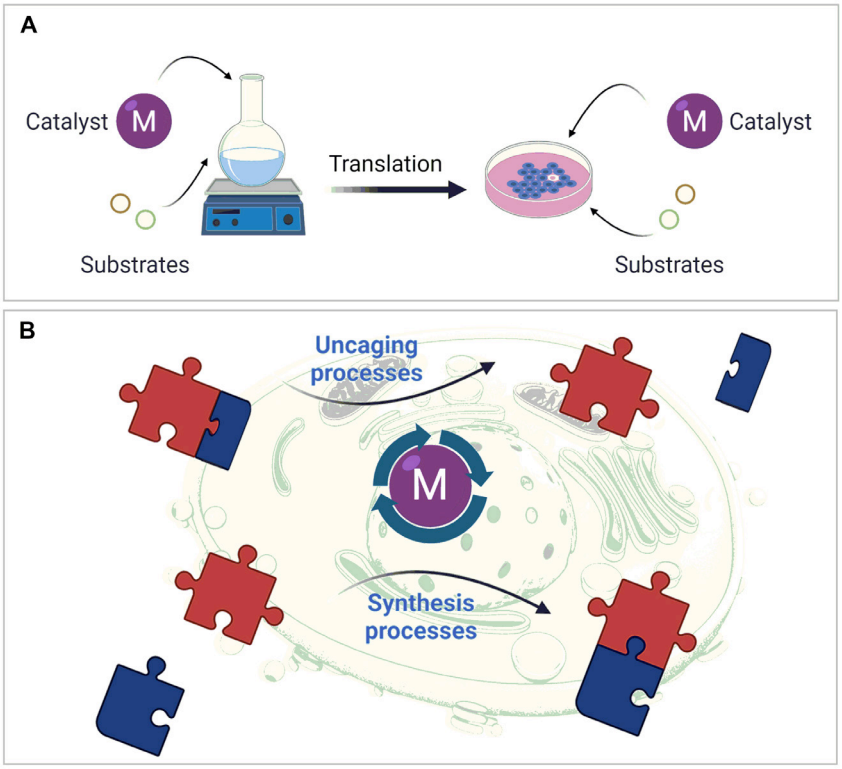

Figure 1. Merging transition-metal catalysis with cellular chemistry. A) Exporting organometallic transformations into cell cultures. B) Schematic representation of the type of metal-promoted reactions that can be performed in cellular environments.

Bioorthogonal ligations

A classical but enduring endeavor in the field of biological chemistry is the development of methods that enable the chemoselective modification of proteins or other biomolecules. This requires appropriate engineering of functional groups that exhibit a well-paired, orthogonal reactivity [11]. The conditions of chemoselectivity and orthogonality is especially challenging

when considering live cells, because they are complex reaction vessels, crowded with molecules and functional groups that could interfere with the desired reactivity.

Moreover, cells are highly compartmentalized, which can further hamper the necessary collision between reactants [1]. The branch of science devoted to inventing and studying biocompatible, non-natural reactions that can proceed effectively within the complex, biomolecular soup of living cells and organisms is called **bioorthogonal chemistry** [12-14]. The term was coined by C. Bertozzi in 2003 when working on the development of tools that could enable the study of glycans in a living organism [12]. The relevance of this field was recognized in 2022 with the Nobel prize awarded to Bertozzi.

From the very beginning, most of the reactions explored for bioorthogonal applications consisted of conjugations to modify biopolymers exhibiting reactive functional groups at specific sites [15-18], although their biological applications were essentially restricted to extracellular sites. An obvious sort of reaction to be used in these conjugations is the **copper-catalyzed azide-alkyne cycloaddition** (CuAAC). This is the benchmarking reaction of Click chemistry, and also deserved the Nobel prize recognition in 2022 to M. Meldal and B. Sharpless (https://www.nobelprize.org/prizes/chemistry/2022/press-release/). The reaction fitted almost perfectly in the field of bioorthogonal chemistry owing to its high rate and selectivity, especially when the copper is bound to tris-triazole ligands (Figure 2A) [19,20]. However, the redox lability and potential toxicity of copper somewhat discouraged the use of this reaction in living settings [21,22], and therefore other alternatives (metal-free) were pursued.

These efforts led to the development of the **strain-promoted azide-alkyne cycloaddition** (SPAAC, Figure 2B), although the reaction is slower than the CuAAC [23,24]. A faster alternative is the **inverse electron-demand Diels-Alder** (IEDDA), a cycloaddition between a 1,2,4,5-tetrazine and a strained alkyne/alkene (Figure 2C). This [4+2] cycloaddition shows excellent kinetics, and thus it is widely used, also in cellular settings and even in mice [25]. Despite the success of these reactions, the use of highly energetic reactants may generate problems of side reactivity, and the options for externally controlling the reactivity are limited. In this context, **metal-catalyzed reactions** are especially attractive because the reactants can be perfectly stable until they react with the catalyst, but mainly because they offer much higher versatility and transformative potential.

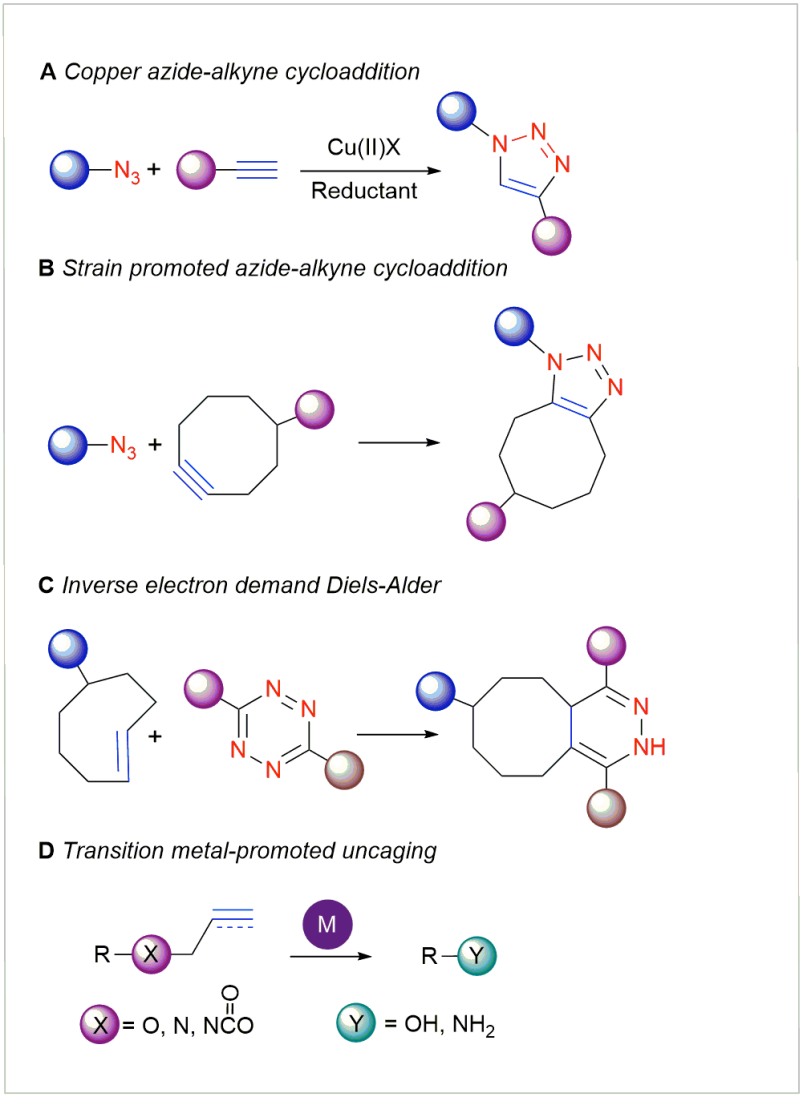

Figure 2. Canonical bioorthogonal ligations (A-C) and transition metal-promoted uncagings (D).

Metal catalysis in biological habitats: initial developments

A preliminary example demonstrating the viability of performing metal-promoted processes in biological environments was published in 1985, when Cséplö and co-workers reported the hydrogenation of unsaturated fatty acids in presence of mesophyll protoplast plant cells, by using a water-soluble ruthenium catalyst, although the process showed severe toxicity [26]. It wasn't until the 2000s that this field really took off with the discovery of the CuAAC reaction. The next groundbreaking advance in this field of metal-promoted bioorthogonal chemistry was reported by the group of Meggers in 2006 [27]. They claimed that the complex Cp*RuCl(COD) can promote the cleavage of allylcarbamates and release the parent amines, even in the cytoplasm of mammalian cells (Fig. 2D). Later, the same group found out that 2-carboxyquinoline-based Ru complexes are more efficient catalysts for similar uncaging/deprotection reactions [28]. In 2014, the group of Mascareñas demonstrated that this transformation could be applied to the controlled

release of DNA binders inside mammalian cells [29]. These preliminary results sparked new research in the area and led to a significant number of biological applications of related transition metal-promoted deprotections [30-32]. Although most of them employ discrete transition metal salts or complexes, some important contributions based on metal-supported nanoparticles [33-35], metal-organic frameworks (MOFs) [36,37], or even artificial metalloenzymes [38-40] have been published.

Transition-metal-promoted synthetic processes in living environments

As highlighted above, most of these advances trying to merge transition metal catalysis with cellular biology deal with deprotection/cleavage processes. Reactions of exogenous substrates involving bond-forming processes, aimed at the synthesis of specific products in live settings, are much more challenging and have been less explored.

Copper-catalyzed azide-alkyne cycloaddition

Initial reports dealing with biological applications of the CuAAC were focused on the modifications of biopolymers on/in bacteria [41,42] or even in mammalian cells [43,44]. Later, the reaction was also used for the intracellular synthesis of bioactive triazoles from exogenous reactants. In this sense, in 2016 Zimmerman and coworkers demonstrated that copper-containing metal-organic nanoparticles can catalyze the synthesis of antimicrobial tristriazoles inside *E. coli* bacteria, or of a fluorescent tristriazol-coumarin in NCI-H460 or MDA-MB-231 mammalian cells (Figure 3A) [45]. Apparently, embedding the copper salts into polymeric scaffolds was key for the success of the intracellular catalysis. Nonetheless, discrete copper catalysts can also be used inside living cells, as shown by Mascareñas and coworkers. These authors demonstrated in 2018 that predefined tristriazole or trispyrazole Cu(I) complexes could be used to promote the intracellular coupling of externally added anthracenyl azides and alkynes, without apparent toxicity, to generate fluorescent products [46].

Another interesting bioorthogonal synthetic application of the CuACC was reported by Zhang and co-workers. They demonstrate that it is possible to make a tristriazole analog of stilbenoid combretastatin A4, a tubulin polymerization inhibitor, inside HeLa cells, by using cross-linked lipoic acid nanoparticles doped with copper nanoparticles (Figure 3B) [47]. The drug-analog strategy was also applied by the group of Qu to make a tristriazole compound mimicking the apoptotic agent resveratrol, inside MCF-7 cells, using as reagents copper nanoparticles trapped into water-compatible MOFs (Figure 3C) [48]. The *in cellulo* generation of this resveratrol mimetic led to a considerable decrease in cell viability, even higher than when cells were directly incubated with the parent drug. Qu's group has also demonstrated that the CuAAC reaction can also be triggered by photoactivable Cu(0) nanoparticles trapped on mesoporous carbon nanospheres [49]. Under NIR irradiation these systems induce the production of ROS, which generate the copper(I) species required for catalysis. The processes were implemented not

only inside HeLa cells and nematodes but also in mice. The group has further expanded the strategies for different applications in anticancer therapy [50-52].

All these results confirm the viability of using the CuAAC for the "*in cellulo*" synthesis of bioactive products, and that The strategy could have long-term implications for biological and biomedical applications.

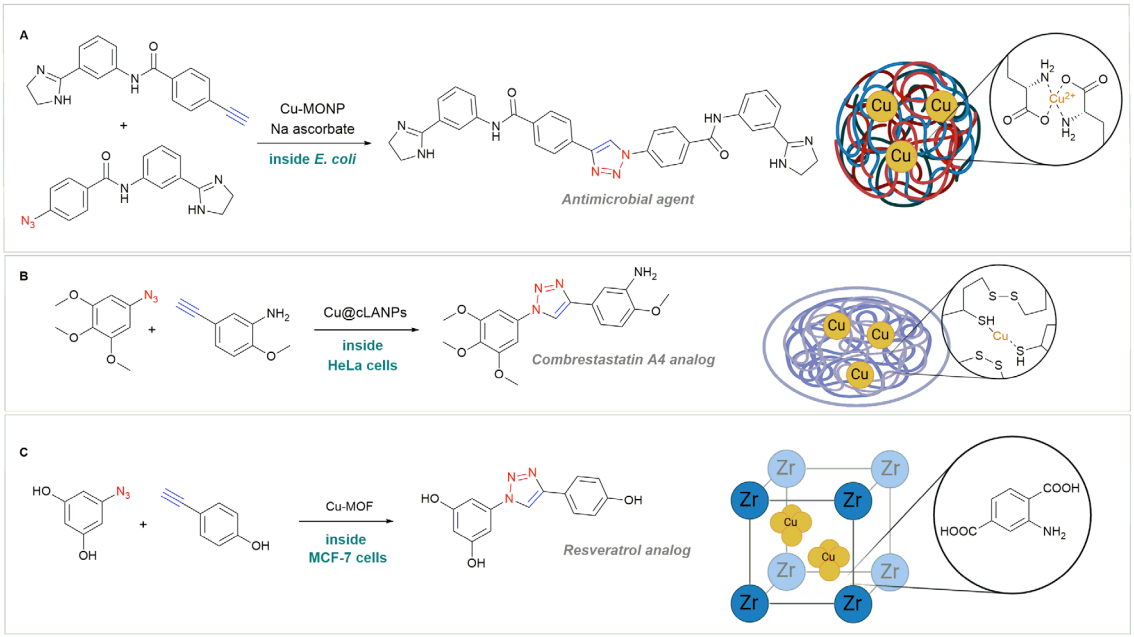

Figure 3. In cellulo synthetic assembly of bioactive triazole drug analogues using the CuAAC promoted by copper-containing nanostructures. A) Copper-containing single-chain nanoparticles (SCNP). B) Nanocopper-doped cross-linked lipoic acid nanoparticle (Cu@cLANP). C) Copper-functionalized MOF with a mitochondria targeting unit (TPP). Adapted with permission from [47].

Cross-couplings

Metal-catalyzed cross-couplings (Sonogashira, Suzuki-Miyaura, etc) are among the most important reactions in synthetic organic chemistry. Considering that some of these transformations can tolerate the presence of water [4], it was a matter of time before the methodologies were implemented under biologically relevant conditions. Initial applications in live settings focused on modifying bacterial proteins, using palladium catalysis [53-55]. In 2011, the group of Bradley and Unciti-Broceta claimed that Pd(0)-NPs can promote the cross-coupling of boronic esters with a fluoresceine derivative featuring an alkenyl triflate moiety, inside HeLa cells (Fig. 4A) [56]. A related cross-coupling was later described by Qu and co-workers, using Pd-nanoparticles embedded into microporous silica nanostructures functionalized with photoresponsive azobenzene units [57]. Discrete palladium catalysts have been less used, likely because they have a higher tendency to be deactivated in biological media. Nonetheless, the group of Tian has recently reported the use of $Pd(OAc)_2$/TPPTS for the localized synthesis of a push-pull fluorophore inside

the mitochondria of HeLa and HepG2 cells [58]. Finally, in a very recent example, the Rappsilber group employed a salicylate Pd-based metallopeptide to promote an intracellular Suzuki-Miyaura inside A549 cells for the synthesis of the anticancer drug linifanib [59]. Importantly, the metallopeptide performed better than the discrete Pd complex and was able to carry out the dual activation of a propargylated microtubule inhibitor paclitaxel, together with the synthesis of linifanib, which led to a synergetic therapeutic effect.

In a very nice example based on palladium catalysts, Weissleder and co-workers reported the synthesis of aminocoumarins inside HT1080 cells using an intramolecular Heck reaction [60]. For a successful outcome, the palladium catalyst had to be encapsulated in a biocompatible polymer, which improves its stability and cellular uptake.

Overall, *in cellulo* synthetic chemistry based on metal-catalyzed cross-coupling reactions is viable, but the number of examples is yet very scarce.

Alkene metathesis

Along with cross-coupling, metathesis reactions are among the most biocompatible methods to build molecules via C-C bond-forming processes. Ruthenium carbene catalysts have been long known to be quite compatible with water and, in this regard, in 2016, Ward and co-workers demonstrated that a streptavidin artificial metalloenzyme bearing a second-generation Hoveyda-Grubbs catalyst attached to a biotinylated moiety can catalyze ring-closing metathesis (RCM) reactions to generate fluorescent coumarins (Fig. 4B). The reaction needs to be carried out in the periplasm of *E. coli* bacteria cells, to avoid deactivation of the catalyst by native thiols [61]. Ru-promoted metathesis can also be performed in live mammalian cells, as shown by the group of Michel. A discrete ruthenium catalyst attached to a BODIPY-based fluorophore could react with ethylene or allyl alcohols in a cross-metathesis process [62], although the reaction was used for sensing rather than for synthetic applications.

In 2019, the group of Tanaka addressed the catalyst passivation issues by developing an artificial metalloenzyme in which a ruthenium catalyst attached to a coumarin moiety is located in the hydrophobic pocket of an albumin protein. The resulting hybrid was initially used as catalyst for the controlled generation of a coumarin-based umbelliprenin derivative via RCM, in different mammalian cell lines, and without disturbing endogenous biomolecules [63]. The methodology was later adapted for the biosensing of ethylene in fruits and plants [64]. Finally, the group could generate a combretastatin A4 analog in different cancer cell lines and even within the circulatory system of xenografted mice, corroborating the protecting effect of the albumin scaffold (Figure 4C) [65].

The first example of a new-to-nature organometallic transformation inside photoautotrophic cells (microalgae) was described by Mecking and co-workers. They took advantage of the high amounts of fatty acids present in these organisms to modify them via cross-metathesis reactions using a cyclic alkyl amino carbene-based ruthenium catalyst [66].

Altogether, these preliminary results indicate that Ru-based olefin-metathesis catalysts can be used in live settings to carry out synthetically relevant C-C bond formations, especially when embedded within protein scaffolds. Further applications will likely appear in the following years.

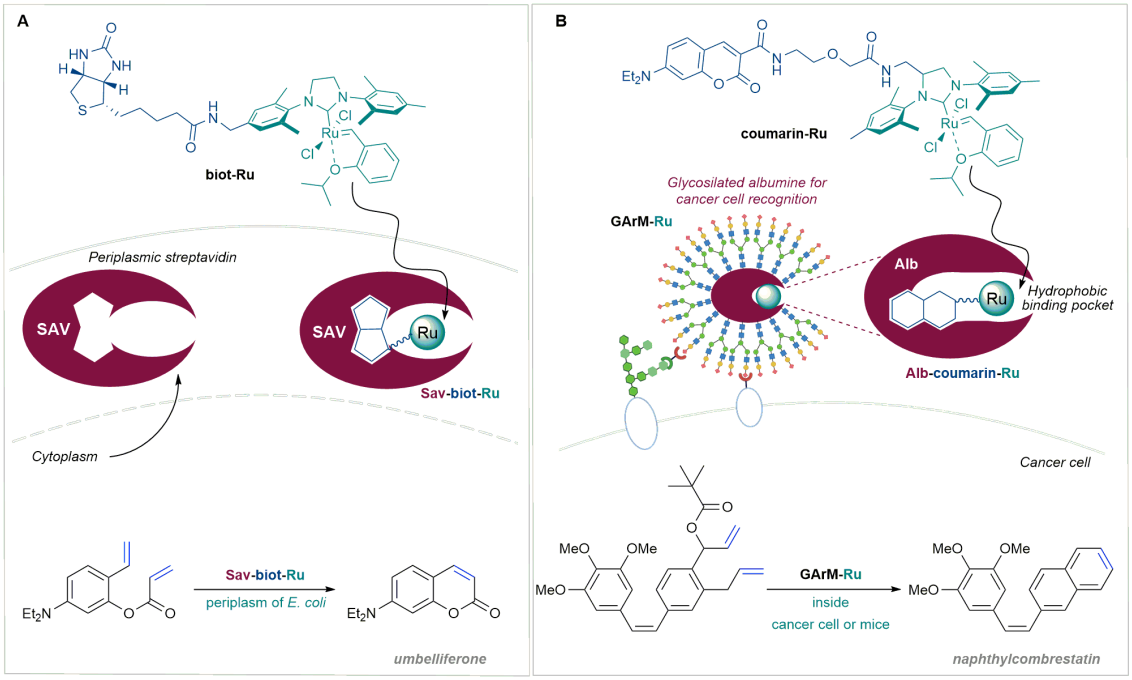

Figure 4. Olefin metathesis in cells promoted by artificial metalloenzymes: A) Catalyst based on a A Sav-biot construct. B) Ruthenium catalysts embedded in an albumin protein.

Cycloisomerizations

Gold complexes are well-known π acids with enormous synthetic potential, owing to their ability to bind and activate unsaturated functional groups, especially alkynes, in a chemoselective manner. Considering that alkynes are uncommon in Nature, gold catalysis seems very attractive for orthogonal synthetic chemistry in biological media, although deactivation of the gold reagents by native thiols could be a problem. An initial demonstration of the viability of a gold-promoted reaction in cellular settings was reported in 2009, with the design of fluorogenic probes for the detection of Au(III) salts [67]. Other related probes that provide fluorescent coumarin [68,69] or oxazol products [70,71] after a gold-catalyzed cyclization were later published. Tanaka and co-workers have recently described a Au(III)-promoted cyclization of 2-alkynylbenzamides inside different mammalian cell lines, a reaction that concomitantly releases the cytotoxic drug doxorubicin [72].

In 2018, the group of Mascareñas demonstrated that tailored gold(I) chloride complexes can promote alkyne hydroarylation reactions to build fluorescent coumarins inside living mammalian cells. Apparently, the gold chlorides behave as precatalysts that are activated in water to yield active aquo derivatives (Fig. 5A) [73]. This "precatalyst strategy" is beneficial to avoid a ready deactivation of the gold complexes by intracellular thiols. The reaction can be also carried out concurrently and orthogonally with a ruthenium-promoted allyl deprotection of other exogenous probes, suggesting the viability of building artificial metabolic circuits in live cells. Later, Zou and co-workers claimed that the gold(I) promoted cycloisomerization can also be carried out in zebrafish by using an organogold(I) complex made *in situ* by a Pd-triggered transmetallation [74].

A biomedical application of synthetic cycloisomerizations was described by Tanaka in 2021 (Figure 5B), and consisted of a gold-promoted synthesis of phenanthridinium moieties, known by their DNA-intercalating affinity and antitumoral properties [75]. The reaction was satisfactorily carried out in presence of A549 mammalian cells using a gold-containing albumin metalloenzyme. The albumin scaffold protects the gold catalytic site from deactivation and mitigates the toxicity of the metal.

All these results confirm that gold catalysts can be made biocompatible and are capable of promoting different type of reactions initiated by the activation of unsaturated reactants, especially alkynes. Considering the synthetic power of gold catalysis, it is very likely that many other synthetically relevant gold-promoted intracellular reactions will be developed.

Redox processes

The cell has a controlled redox environment, therefore, performing exogenous reduction or oxidation processes inside biological systems is intricate. Indeed, in work aimed at using iron catalysts for the reduction of aryl azides, Meggers and coworkers found that endogenous reductants could themselves promote the processes without the need of the catalyst [76]. However, several groups have firmly demonstrated that late transition metal catalysts can be used for the reduction of exogenous reactants in cellular settings.

Therefore, the group of Do reported the reduction of aldehydes to alcohols in NIH-3T3 cells, using Cp*Ir complexes as catalysts, in presence of the nicotinamide adenine dinucleotide cofactor (NADH) (Figure 5C) [77]. Sadler and co-workers have made significant contributions in the area. For instance, they carried out an enantioselective transformation of pyruvate into L- or D-lactate inside A2780 living cells by using a biocompatible *p*-cymene osmium catalyst, and sodium formate as exogenous reductant (Figure 5D) [78]. The final configuration of lactate was dependent on the catalyst configuration. Interestingly, sodium formate could be generated inside the cells from *N*-formylmethionine, the substrate of the peptide deformylase, overexpressed in

cancer cells such as PC3 cells. Unfortunately, both Do's and Sadler's processes seemed to present rather low efficiencies.

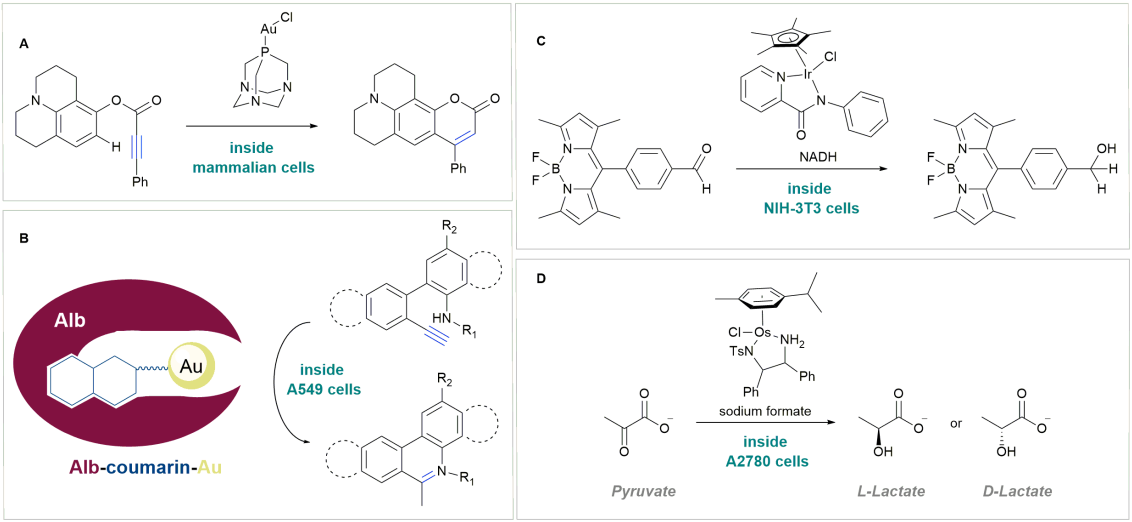

Figure 5. Metal-promoted cicloisomerization and redox processes inside living cells. A) Orthogonal cycloisomerization to generate fluorescent coumarins. B) Synthesis of phenanthridinium drugs promoted by gold-containing albumin derivatives. C) Iridium promoted reduction of an exogenous aldehyde. D) Enantioselective metal-catalyzed reductions inside cells.

Synthetically relevant reactions involving redox-neutral isomerizations are also viable in biological environments. Therefore, it is possible to perform ruthenium-catalyzed isomerizations of allylic alcohols into ethylketones inside HeLa cells, without generating major toxicity [79]. The mechanism of the reaction entails the formation of a ruthenium hydride intermediate, which seems to survive, at least partially, in the crowded environment of the cell. LC-MS techniques allowed to monitor the process and revealed a turnover >25, confirming the existence of catalytic cycles. Interestingly, the strategy was applied to the intracellular synthesis of bioactive products, such as glutathione (GSH) depleting α,β-unsaturated ketones. Remarkably, the biological effect is higher when this product is generated *in situ* than when it is externally added.

More recently, Qu and co-workers reported the use of mesoporous silica-Pd NPs with chiral modifiers for the enantioselective synthesis of ibuprofen, a well-known anti-inflammatory drug (pharmacological activity mainly attributed to *S*-enantiomer), through an asymmetric transfer hydrogenation process, using sodium formate as hydride source (ca. 75% ee). Remarkably, the reduction can be carried out intracellularly in mammalian cells or even mice, and the biological effect promoted (for instance, an anti-inflammatory action) depends on the use of the correct Pd-NP chirality [80].

Overall, a variety of metal-catalyzed, synthetically appealing redox transformations, most of which rely on hydrogen transfer processes, can be

promoted inside living cells. The reactions can also be designed to harness endogenous reducing agents or to alter intracellular redox equilibria.

Metal-carbene-mediated transformations

Carbenes are highly reactive intermediates that can be stabilized if bound to a transition metal, promoting many types of transformations, from cyclopropanations to C-H insertions. Metal carbenes, particularly of rhodium, have been extensively used for the modification of biomolecules, even in aqueous buffers [81]. They have also been used in reactions catalyzed by artificial metalloenzymes exhibiting metalloporphyrin cofactors (Cytochrome P450), for instance, for enantioselective cyclopropanations. Some of these reactions have been even performed inside *E. coli* [82-85].

An important study that involves the use of non-natural metalloenzymes to carry out cyclopropanations was reported by the group of Ward. An artificial metalloenzyme composed of a dirhodium complex core derivatized with biotin to anchor a streptavidin protein was expressed in the periplasm of *E. coli*, which exhibits turnovers of up to 20 in the cyclopropanation of styrene with ethyl diazoacetate [86]. Interestingly, the artificial metalloenzyme outperformed the free Rh complex in terms of uptake and TON.

In a different type of approach, Mascareñas et al. demonstrated the viability of performing N-H carbene insertions inside mammalian cells, promoted by catalysts as simple as copper (II) acetate (Figure 6A). The reactants were engineered to provide complex cyclic structures such as bioactive benzoquinoxalines from simple ortho-amino arylamines and α-keto diazocarbenes [87]. Importantly, using copper complexes anchored to an RGD motif there is a differential internalization of the catalysts depending on the cell line, which prompts well for a cell-selective generation of active products.

Considering the broad transformative power of metal carbenes, and the crescent demonstration of biocompatibility, other bioorthogonal synthetic applications will see the light in the near future.

Cycloadditions

Metal-catalyzed cycloadditions are among the most important reactions in terms of constructive, synthetic potential. Their use in biological synthetic chemistry is not restricted to the CuAAC. The group of Mahy claimed that conjugates between adenosine-receptor antagonists and copper-phenanthroline ligands can bind the surface of HEK-298 cells [88], where they catalyze the (4+2) cycloaddition between pentadiene and 2-aza-chalcones in moderate yields with a TON of up to 20. This type of Lewis-acid promoted Diels-Alder cycloaddition was also studied by Roelfes and co-workers with designed metalloenzymes [89]. The overexpression of the protein LmrR in the *E. coli* cytoplasm and the incubation of the cells with a Cu(II)-phenanthroline complex resulted in the formation of the intracellular metalloenzyme, which

can promote not only a Diels-Alder cycloaddition (Figure 6B), but also a Friedel-Craft alkynylation. Although yields were low, the reactions can be performed with a moderate enantiomeric excess (up to 45%).

In a synthetically relevant transformation, Teplý and collaborators reported an intramolecular Ru-promoted [2+2+2] cycloaddition of designed triynes in bacteria cell lysates, at room temperature, using commercially available Cp*RuCl(COD) as catalyst [90]. Several years later, it was demonstrated that this type of intriguing cycloadditions can be performed in live HeLa cells, either in intra- or even intermolecular formats to make anthraquinones (Figure 6C) [91], and even for the generation of aggregation-induced emission dyes, insoluble products that otherwise cannot be delivered to the cell.

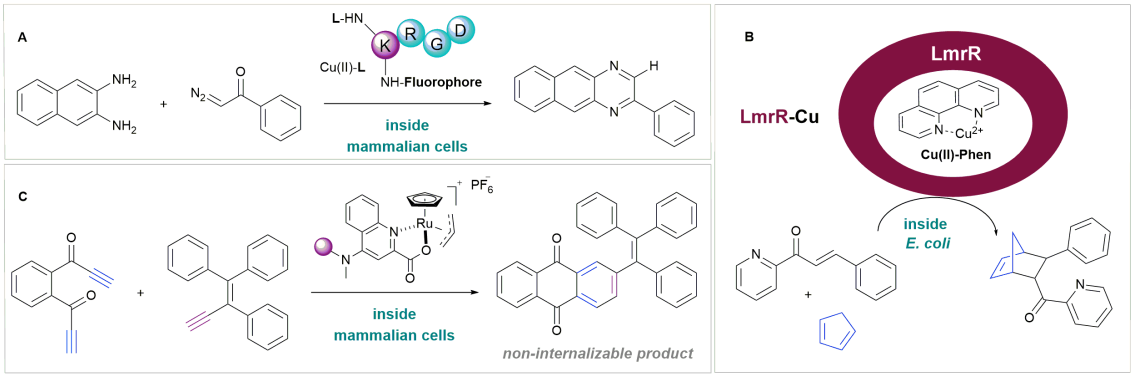

Figure 6. Metal carbene-mediated reactions, and cycloaddition processes inside living cells. A) Copper-promoted synthesis of a cytotoxic benzoquinoxaline. B) Diels-Alder cycloaddition mediated Cu(II)-artificial metalloenzymes. C) Synthesis of aggregation-induced emission dyes with anthraquinone skeletons.

Concluding remarks and future perspectives

In summary, despite the belief that transition metal catalysis is not compatible with aqueous and biological systems, an increasing number of evidences indicates that this notion is wrong, and that transition metal-catalyzed reactions can be performed in complex biological media and even in living contexts. It is true, however, that most of the transformations are yet poor in terms of catalytic efficiency, in great part because of the deactivation of the catalyst or of catalytic intermediates, but also as a consequence of transport, localization, and toxicity problems (see outstanding questions).

Recent contributions are demonstrating that catalytic reactions can be used not only for uncaging processes but, very importantly, for the intracellular synthesis of designed products from exogenous reactants. This ***in cellulo* synthetic chemistry** promises many applications in cell biology, for the interrogation and alteration of cells and their metabolism, but also in biomedicine, for the amplified localized synthesis of bioactive compounds, among others. We foresee a bright future for this never-thought relationship between organometallic chemistry and biology.

Acknowledgments

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Declaration of interests

No interest are declared.

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Glossary

Bioorthogonal synthetic chemistry: Emergent discipline of chemical biology that deals with the development of live-compatible bond-forming transformations for the synthesis of tailored products.

Copper-catalyzed azide-alkyne cycloaddition (CuAAC): Copper-promoted cycloaddition between a terminal alkyne and azide to give 1,4-disubstituted-1,2,3-triazoles.

Enzymes: Biological polymers constituted by amino acids, responsible for catalyzing chemical reactions in living cells and organisms. Some of them contain metal cofactors at their active site, and thus they are coined as metalloenzymes.

Inverse electron-demand Diels-Alder (IEDDA): (4+2) cycloaddition between a 1,2,4,5-tetrazines and strained alkenes that exhibit impressive reaction rates.

Strain-promoted azide-alkyne cycloaddition (SPAAC): Cycloaddition between a strained cyclooctyne and azide to give 1,4-disubstituted-1,2,3-triazoles.

Transition metals: Elements with partially filled d-orbitals and exhibiting several oxidation states, and capable of forming coordination complexes that can work as catalysts.

Figure legends

Figure 7. Merging transition-metal catalysis with cellular chemistry. A) Exporting organometallic transformations into cell cultures. B) Schematic representation of the type of metal-promoted reactions that can be performed in cellular environments.

Figure 8. Canonical bioorthogonal ligations (A-C) and transition metal-promoted uncagings (D).

Figure 9. In cellulo synthetic assembly of bioactive triazole drug analogues using the CuAAC promoted by copper-containing nanostructures. A) Copper-containing single-chain nanoparticles (SCNP). B) Nanocopper-doped cross-linked lipoic acid nanoparticle (Cu@cLANP). C) Copper-functionalized MOF with a mitochondria targeting unit (TPP). Adapted with permission from [47].

Figure 10. Cross-coupling and olefin metathesis in cells: A) Pd(0) nanoparticles trapped within polystyrene microspheres. B) Artificial metalloenzyme based on a Sav-biot construct. C) Artificial metalloenzyme based on a ruthenium catalyst embedded in an albumin protein.

Figure 11. Metal-promoted cicloisomerization and redox processes inside living cells. A) Orthogonal cycloisomerization to generate fluorescent coumarins. B) Synthesis of phenanthridinium drugs promoted by gold-containing albumin derivatives. C) Iridium promoted reduction of an exogenous aldehyde. D) Enantioselective metal-catalyzed reductions inside cells.

Figure 12. Metal carbene-mediated reactions, and cycloaddition processes inside living cells. A) Copper-promoted synthesis of a cytotoxic benzoquinoxaline. B) Diels-Alder cycloaddition mediated Cu(II)-artificial metalloenzymes. C) Synthesis of aggregation-induced emission dyes with anthraquinone skeletons.