

# Unconventional Approaches in Coordination Chemistry and Organometallic Reactivity

Giovanni Salassa\* and Luca Salassa\*

Cite This: *ACS Omega* 2021, 6, 7240–7247

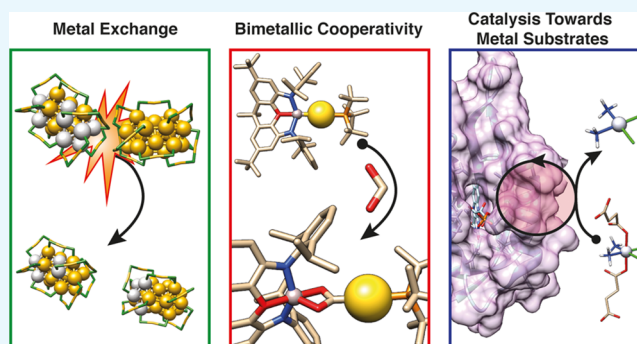
Read Online

ACCESS |

Metrics &amp; More

Article Recommendations

**ABSTRACT:** This contribution highlights a number of approaches developed by coordination and organometallic chemists that go beyond mainstream inorganic reactivity. A few of these strategies have been known for decades and are fundamental tools in synthesis and catalysis, while others are more recent and still belong to a niche. Through selected examples, we show herein how transmetalation, metal exchange, metal cooperativity, and catalytic transformation of metal complexes provide unique new opportunities to expand the reactivity arsenal of inorganic systems for synthetic and technological applications.



## INTRODUCTION

In coordination and organometallic chemistry, the choice, design, and preparation of ligands is pivotal to affording, upon coordination of transition metal ions, inorganic systems with desired physical and chemical properties. Therefore, the major synthetic challenge for inorganic chemists often resides in obtaining pure ligands and achieving their coordination to suitable metal salts or reactive metal precursors that allow mild reaction conditions, short reaction times, and most importantly high yields and a low level of impurities.

Frequently, postfunctionalization is the key step to tailor a metal complex to the application of choice (e.g., anchoring onto a surface/polymer, tagging with a biological vector). To this end, at least one of the coordinated ligands should contain suitable chemical groups to carry out further reactivity. However, ligand functionalization reactions typically rely on organic reactivity and are rarely innovative, since they follow procedures well-established for organic molecules. Obviously, the presence of metal ions can result in modified reaction outcomes and complications that lead to unsatisfying yields and purities.

As evidently demonstrated by the achievements of coordination chemistry over the decades, this mainstream *modus operandi* is undeniably successful and deserves no critique. Nevertheless, it has perhaps narrowed the interests of many inorganic chemists to the reactivity of a single metal complex or center, thus to plain ligand substitution/exchange reactions or oxidative addition and reductive elimination reactions involving solvent or (bio)-organic molecules.

Unquestionably, the scenario is more intricate, and inorganic reactivity goes well beyond the general picture described here. In fact, the inorganic chemistry community has developed

numerous unconventional approaches to exploit the uniquely rich chemistry of metals. Some of these have reached widespread use, while others, more recent, have specialized applications.

In this Mini-Review, we gather representative examples of what could be considered nonmainstream inorganic reactivity. This short overview is not a comprehensive description of the literature, but rather a first (and perhaps unusual) attempt to bring together different research areas with the aim of highlighting the potential of metal exchange reactions, metal cooperativity, and catalysis toward metal substrates as tools to advance inorganic chemistry toward new territories.

## METAL AND LIGAND EXCHANGE REACTIONS IN INORGANIC SYSTEMS

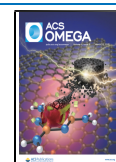
In this section, we illustrate selected examples of unconventional exchange reactions involving mono- and multimetallic metal complexes and clusters. The systems described undergo exchange of metal and/or ligand fragments between different metal-containing entities, thus enabling the formation of unique structures whose accessibility would be otherwise prevented or significantly more laborious.

**Transmetalation Reactions.** Transmetalation reactions are characterized by the transfer of ligands from one metal to

Received: December 2, 2020

Accepted: March 1, 2021

Published: March 11, 2021



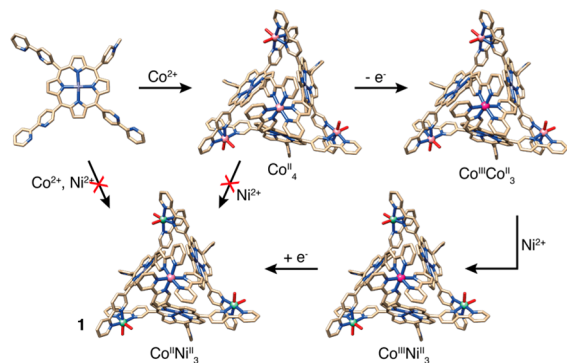
another and are well-known for their use in catalysis, sensing, and synthesis. They play a key role in catalytic cross-coupling as, for example, in the Stille reaction (that is, the Pd-catalyzed cross-coupling of organic electrophiles with organostannanes) in which Sn–Pd transmetalation controls the catalytic mechanism and the reaction stereoselectivity.<sup>1</sup>

Ag transmetalation reactions are, for instance, widely used in the preparation of Au–, Ir–, and Rh–carbene complexes,<sup>2,3</sup> while Zn–salphen complexes are regularly employed as starting materials in metal exchange reactions to obtain Ni, Cu, Pd, and Mn analogues.<sup>4</sup>

Transmetalation also provides convenient routes for the preparation of multimetallic and supramolecular structures. In such a context, Shaw et al. demonstrated in the 1980s that Pt–W bimetallic complexes such as  $[(RC\equiv C)_2Pt(\mu\text{-dppm})_2W(CO)_3]$  (dppm = bis(diphenylphosphino)methane, R = methyl, phenyl, and p-tolyl) were prepared in higher yields and with low amounts of side-products via transmetalation of  $[(RC\equiv C)_2Pt(\mu\text{-dppm})_2AgCl]$  with the  $[W(CO)_3(CH_3CN)_3]$  precursor.<sup>5</sup>

Ghosh et al. showed that transmetalation afforded heterometallic side-by-side  $Fe_2Zn$  helicates starting from either homometallic  $Zn_3$  or  $Fe_3$  structures and following distinct mechanisms.  $Zn^{II}$ -to- $Fe^{II}$  substitution occurred by the stepwise exchange of single ions on the  $Zn_3$  helicate. On the contrary, a high temperature and full dissociation were required by the  $Fe_3$  helicate to give the  $Zn_3$  analogue and subsequently the most thermodynamically stable  $Fe_2Zn$  structure.<sup>6</sup>

Similarly, Shionoya et al. reported a method based on redox and transmetalation reactions to obtain heteromultinuclear  $Co^{II}Ni^{II}_3$  complexes from their  $Co^{II}_4$  precursors (Figure 1).<sup>7</sup>



**Figure 1.** Supramolecular multimetallic complexes prepared via transmetalation. Red sticks denote a coordinating solvent molecule or a counteranion.

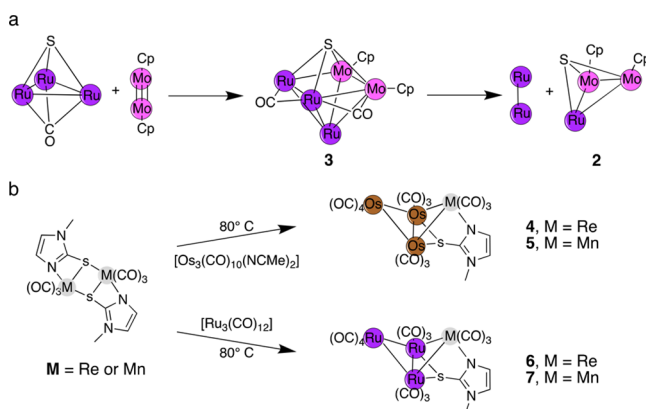
Accordingly, the starting homonuclear  $Co^{II}_4$  complex based on  $Zn^{II}$ -porphyrin-based tris-bidentate ligands was converted to the mixed-valence  $Co^{III}Co^{II}_3$  by selective oxidation with cerium(IV) ammonium nitrate. Subsequently,  $Co^{II}$  was transmetalated site-selectively with  $Ni^{II}$  to obtain  $Co^{III}Ni^{II}_3$ . After reduction (excess of  $n\text{-Bu}_4\text{N}^+\text{I}^-$ ), this species yielded the desired  $Co^{II}Ni^{II}_3$  derivative (1), a supramolecular complex not accessible by simple mixing of  $Co^{II}$  and  $Ni^{II}$  ions in a solution containing the ligand.

In addition, transmetalation has found applicability in sensing, as demonstrated by Cheng et al., who devised a colorimetric and turn-on fluorescence chemosensor for  $Al^{III}$  using salen-type Schiff base ligands. They demonstrated that the nature of the central metal in the transmetalation reaction was key in the  $Al^{III}$  detection, with  $Cu^{II}$  exhibiting the best performance.<sup>8</sup>

**Small Metal Clusters.** A few early examples of metal/ligand exchange reactions were reported during the 1980s for metal carbonyl clusters. This class of inorganic compounds is characterized by a core composed of few transition metal atoms stabilized by carbon monoxide (CO), and in some cases by other types of ligands (e.g., phosphines, unsaturated olefins, or aryl ligands).

Adams and co-workers reported several syntheses of mixed-metal (alloy) carbonyl cluster compounds by metal–metal exchange processes. In this type of reaction, the number of metal atoms present in the starting materials is retained in the product. Mechanistically, however, the reactions usually proceed through a sequence of metal-addition and elimination steps involving the formation of an intermediate of higher nuclearity.

In an illustrative example, Adams et al. prepared  $[RuMo_2(CO)_7Cp_2(\mu_3\text{-S})]$  (2, Figure 2a) from the reaction of



**Figure 2.** Metal exchange reactions between small carbonyl metal clusters and (a) Mo and (b) Re or Mn dinuclear carbonyl complexes. In a, only apical CO ligands are shown for clarity and Cp = cyclopentadienyl.

$[Ru_3(CO)_9(\mu_3\text{-CO})(\mu_3\text{-S})]$  with  $[CpMo(CO)_2]_2$  (where Cp = cyclopentadienyl).<sup>9</sup> The authors were able to demonstrate that the two Mo atoms of  $[CpMo(CO)_2]_2$  were added in one step to yield the pentanuclear intermediate  $[Ru_3Mo_2(CO)_{10}(\mu\text{-CO})_2Cp_2(\mu_3\text{-S})]$  (3), which then evolved to the trimetallic product. In this process, the sulfido ligand played a crucial role by creating Mo–S interactions with both the approaching Mo atoms, leading to the formation of 3.

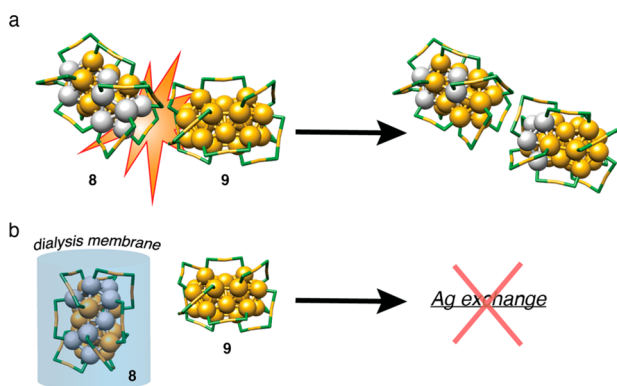
The same authors extended this approach to the synthesis of a series of trimetallic sulfido-W clusters containing each element of group VIII (Fe, Ru, and Os).<sup>10</sup> In particular, they reacted clusters of formula  $[M_3(CO)_9(\mu_3\text{-CO})(\mu_3\text{-S})]$  (where M = Fe, Ru and Os) with  $[W(CO)_5(PMe_2Ph)]$  under UV light irradiation, confirming the pivotal role of the bridging sulfide-ligand in the metal addition and elimination steps.

Ghosh et al. reported the synthesis of tetranuclear mixed-metal clusters  $[Os_3Re(CO)_{13}(\mu_3\text{-SN}_2C_4H_5)]$  (4) and  $[Os_3Mn(CO)_{13}(\mu_3\text{-SN}_2C_4H_5)]$  (5), characterized by a butterfly type of structure.<sup>11</sup> Such clusters were obtained by reaction of the dinuclear carbonyl complex  $[M_2(CO)_6(\mu\text{-SN}_2C_4H_5)_2]$  (where M = Re or Mn and  $SN_2C_4H_5 = 2\text{-mercapto-1-methylimidazole}$ ) with  $[Os_3(CO)_{10}(NCMe)_2]$  (Figure 2b). In a similar fashion, the reaction of  $[M_2(CO)_6(\mu\text{-SN}_2C_4H_5)_2]$  with  $Ru_3(CO)_{12}$  yielded the cluster analogues  $[Ru_3Re(CO)_{13}(\mu_3\text{-SN}_2C_4H_5)]$  (6) and  $[Ru_3Mn(CO)_{13}(\mu_3\text{-SN}_2C_4H_5)]$  (7). Compounds 4–7 have unique structures containing a noncrystallographic mirror

plane of symmetry with a butterfly core of four metal atoms and the M (Mn or Re) at a wingtip of the butterfly. These results provided a new method for the synthesis of a series of new group 7/8 mixed metal complexes containing a bifunctional heterocyclic ligand.

**Nanoclusters.** Noble metal nanoclusters (NCs) are a class of metal clusters composed by noble metals (*e.g.*, Au and Ag) with a core size of more than 15 atoms (diameter of  $\sim 1$  nm). NCs are usually stabilized by ligands such as thiolates and phosphines, and they have been investigated in the past 15 years for their unique physical and chemical properties. Recent data demonstrate that NCs also undergo metal and ligand exchange reactions, as reported for the first time by the group of Pradeep. They employed mass spectrometry to investigate the reaction between  $[\text{Au}_{25}(\text{2PET})_{18}]^{-}$  (where 2PET = 2-phenylethanethiolate) and the Ag analogue  $[\text{Ag}_{25}(\text{DMBT})_{18}]^{-}$  (where DMBT is 2,4-dimethylbenzenethiol).<sup>12</sup> Under ambient conditions, these NCs underwent spontaneous reactions in solution to form alloy nanoclusters of average formula  $[\text{Ag}_m\text{Au}_n(\text{2PET})_{18-x}(\text{DMBT})_x]^{-}$  ( $n = 1-24$ ;  $m + n = 25$ ). In line with what was observed for carbonyl clusters,<sup>9</sup> a dianionic adduct  $[\text{Ag}_{25}\text{Au}_{25}(\text{DMBT})_{18}(\text{PET})_{18}]^{2-}$  was detected in electrospray ionization mass spectrometry and proposed as the key intermediate in the exchange reaction.

The type of mechanism involved in NC metal exchanges was also investigated by Salassa et al.<sup>13-15</sup> Results indicated that Ag exchange between Ag-doped  $[\text{Ag}_x\text{Au}_{38-x}(\text{2PET})_{24}]$  (**8**) and  $[\text{Au}_{38}(\text{SR})_{24}]$  (**9**) nanoclusters occurred through a collision mechanism (Figure 3a).<sup>13</sup> When **8** and **9** were dissolved in



**Figure 3.** Metal exchange reactions in NCs. Schematic representation of Ag exchange reaction between **8** and **9** without (a) and with (b) a dialysis membrane. Color code for atoms: Au (yellow), Ag (gray), S (green), and C (light brown); for a and b, the aryl part of the thiolate ligand is omitted for clarity.

solution, redistribution of Ag among the two NCs occurred in only 10 min. On the other hand, when the two NCs were separated by a dialysis membrane, no Ag exchange could be observed (Figure 3b), thus discarding the hypothesis that **8** released small Ag containing species. Instead, mass spectrometry analysis confirmed that the structures of **8** and **9** were maintained throughout the reaction, indicating that the formation of adducts was rather induced by collisions between NCs. Using the same experimental approach, Salassa and co-workers examined the ligand exchange reaction between two different Au-NCs.<sup>14</sup> Once in solution,  $[\text{Au}_{25}(\text{2PET})_{18}]$  and  $[\text{Au}_{25}(\text{SBut})_{18}]$  (where SBut = butylthiolate) partially exchanged their protecting ligands, leading to the

formation of nanoclusters with an average formula of  $[\text{Au}_{25}(\text{2PET})_{18-x}(\text{SBut})_x]$  (where  $x = 5-13$ ). In such a case as well, the results pointed out that the two reacting NCs collide with each other forming short-living adducts that favor the ligand exchange.

These representative examples suggest that (nano)clusters can be treated exactly as molecules; they can substitute fragments without losing their original structure. Nevertheless, the actual level of control of metal exchange reactions is not yet satisfying, and new approaches are needed to advance the use of these processes in various research areas.

To this aim, Ghosh et al. reported a first promising step toward improving the control over exchange reactions in NCs.  $[\text{Ag}_{29}(\text{BDT})_{12}]$  or  $[\text{Ag}_{51}(\text{BDT})_{19}]$  NCs protected with the dithiolate ligand 1,3-benzenedithiol (BDT) were reacted with  $[\text{Au}_{25}(\text{SR})_{18}]$  (SR are monothiolate ligands, *e.g.* butanethiolate and octanethiolate),<sup>16</sup> observing only exchange of Ag and Au ions. Remarkably, no ligand or metal–ligand fragment exchanges were detected among these NCs, and reactions rates were significantly slower compared to what was observed between monothiolate analogues (*vide supra*). Both effects were ascribed to the increased rigidity conferred by the bidentate BDT ligands to the metal–thiolate framework of  $[\text{Ag}_{29}(\text{BDT})_{12}]$  with respect to its monothiolate-protected analogue. Hence, tuning of the rigidity of the metal–thiolate interface by the proper choice of polydentate ligands could potentially provide a structural handle to direct the reactivity of NCs toward specific reaction products.

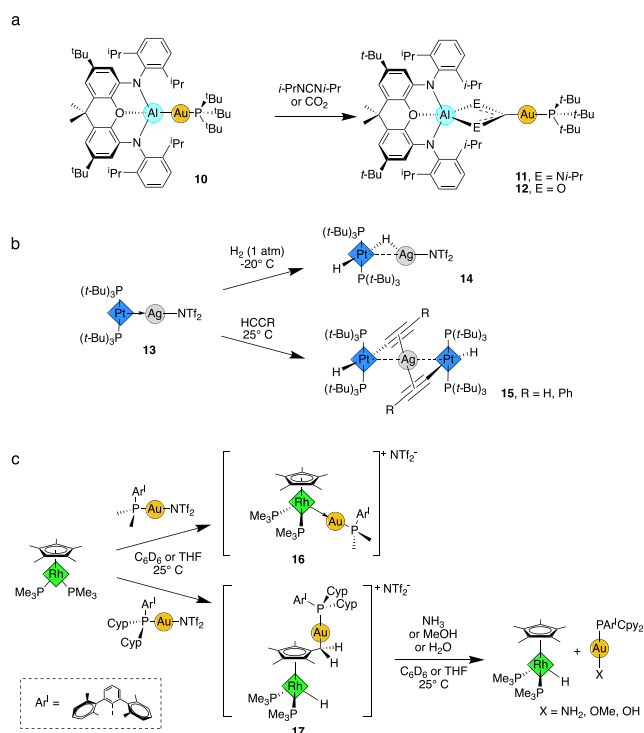
Exchange reactions do not occur only between Ag and Au nanoclusters. Few examples involving Cu- and Ir-NCs were reported recently.<sup>17</sup> For instance, Bhat et al. described the first case of an Ir-incorporation in a monolayer-protected noble metal NC, showing that  $[\text{Au}_{22}\text{Ir}_3(\text{2PET})_{18}]$  can be synthesized exclusively by the reaction between the  $[\text{Au}_{25}(\text{2PET})_{18}]$  and  $[\text{Ir}_3(\text{2PET})_6]$  clusters.

## ■ BIMETALLIC COOPERATING SYSTEMS

Bimetallic complexes are ideal and well-defined models to understand the fundamental role of metal–metal bonding and the reactivity that originates from it. Nature incorporates bimetallic active sites in many metalloenzymes to efficiently catalyze a wide variety of transformations. Artificial bimetallic complexes have often showed outstanding reactivities, and their study has also provided useful insights into the cooperative mechanisms between metals. However, we are still far from reaching the full potential that two (or more) cooperating metals can offer in terms of unconventional reactivity. In this section, we highlight selected examples of bimetallic complexes capable of activating and stabilizing small molecules that are usually arduous for their monometallic analogues, proving how metal–metal interactions could enable many new opportunities.

**Frustrate Lewis Pair.** Among the different types of bimetallic cooperating systems, frustrated Lewis pair (FLP) chemistry has emerged in the past decade as a new strategy that enables bimetallic compounds to activate small molecules.<sup>18</sup> An FLP is comprised of a Lewis acid and a base for which adduct formation is quenched by steric or geometric factors, leaving two reactive sites that can perform bond activation of a third species. Although the first FLPs reported were metal-free, FLPs featuring two transition-metal fragments largely increased the amount and structural diversity of Lewis acid/base combinations available, extending the catalytic usefulness of FLPs.<sup>19</sup>

In a recent groundbreaking study, Aldridge and co-workers used a strongly donating Al ligand for the preparation of a heterobimetallic complex featuring a highly polarized  $\text{Au}^{\delta-}-\text{Al}^{\delta+}$  bond.<sup>20</sup> The potassium Al complex  $[\text{K}\{\text{Al}(\text{NON})\}]_2$  (where NON = 4,5-bis(2,6-diisopropylanilido)-2,7-di-*tert*-butyl-9,9-dimethylxanthene) was reacted with phosphine-ligated complexes  $[(t\text{-Bu})_3\text{PAuI}]$ , to give the bimetallic  $[(\text{NON})\text{AlAuP}(t\text{-Bu})_3]$  (**10**, Figure 4a). Crystallographic and computational analyses of



**Figure 4.** Examples of bimetallic cooperation systems: (a) Al–Au, (b) Pt–Ag, and (c) Rh–Au and their reactivities toward small molecules such as (a) diisopropylcarbodiimide,  $\text{CO}_2$ ; (b)  $\text{H}_2$ , acetylene, phenylacetylene; (c) ammonia, methanol, and water. In c, Cyp = cyclopentyl.

**10** indicated that the Au and Al metal centers were characterized by effective charges of  $-0.82$  and  $+2.21$ , respectively. Therefore, the Al fragment appeared to transfer  $1.56 e^-$  during the formation of the Au–Al bond. In **10**, the  $\text{Au}^{\delta-}$  center exhibited a nucleophilic behavior as observed in the reaction with carbon-centered electrophiles. Heteroallenes such as diisopropylcarbodiimide ( $i\text{-PrN}=\text{C}=\text{Ni-Pr}$ ) and  $\text{CO}_2$  were selected as target reagents and both formed an insertion product (**11** and **12**) once mixed in toluene solution with **10** at room temperature. As shown in Figure 4a, **11** and **12** are characterized by a single molecule of  $i\text{-PrN}=\text{C}=\text{Ni-Pr}$  or  $\text{CO}_2$  reductively inserted into the Al–Au bond. The resulting metalla-amidinate/carboxylate fragment chelated the Al center through the two heteroatoms (N and O), with the Au center being bound to carbon in each case. This consisted of one of the first examples of a nucleophilic attack by Au at the electrophilic central carbon atom.

Campos and co-workers reported another fascinating example of a metal-only Lewis pair based on the combination of  $[\text{Pt}(\text{O})(\text{P}^t\text{Bu}_3)_2]$  with the sterically crowded electrophilic  $[\text{Ag}]^+[\text{NTf}_2]^-$  salt (where  $\text{NTf}_2 =$  bis-trifluoromethane sulfonimide).<sup>21</sup> The  $[(\text{P-}t\text{-Bu}_3)_2\text{Pt-AgNTf}_2]$  adduct obtained (**13**) is exclusively held together through a dative Pt→Ag interaction (Figure 4b). This bimetallic species was tested in the

activation of hydrogen and alkynes. In the presence of  $\text{H}_2$ , a heterobimetallic Pt(II)/Ag(I) dihydride complex (**14**) that contains a terminal and a bridging hydride was isolated. When **13** instead reacted with acetylene and phenylacetylene, a trinuclear  $[(\text{P-}t\text{-Bu}_3)_2(\text{H})\text{Pt}(\mu\text{-CCH})\text{Ag}(\mu\text{-CCH})\text{Pt}(\text{H})(\text{P-}t\text{-Bu}_3)_2]$  (**15**) was obtained in almost quantitative yield. Thus, while  $[\text{Pt}(\text{P-}t\text{-Bu}_3)_2]$  alone did not react with  $\text{H}_2$  or phenylacetylene, the presence of a silver salt readily facilitated the activation of these molecules, highlighting the efficacy of metal-only Lewis pairs systems for small molecule activation.

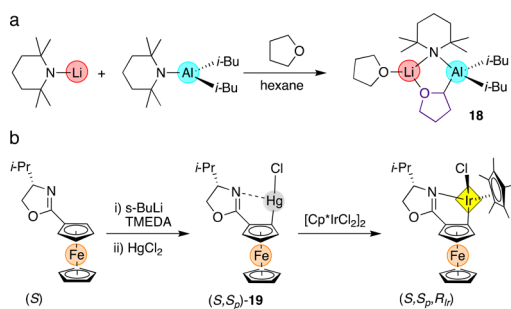
The same group also reported on metal-only FLPs based on a cyclopentadienyl Rh unit  $[(\eta^5\text{-Cp}^*)\text{Rh}(\text{PMe}_3)_2]$  (where  $\text{Cp}^* =$  pentamethylcyclopentadienyl) and electrophilic Au fragments of the type  $\text{AuPR}_2\text{Ar}^+$ .<sup>22</sup> When the R substituent on the Au fragment was a methyl group, complex **16**, displaying a  $2.59 \text{ \AA}$  Rh→Au dative bond, was obtained (Figure 4c). Conversely, when the R substituents were cyclopentyl (Cyp), **17** was formed quantitatively. The most hindered Au-fragment promoted a hydride migration from a methyl group of  $\text{Cp}^*$  to the Rh metal. Experiments employing a fully deuterated  $\text{Cp}^*$  ligand confirmed the origin of the hydride migration.

Campos and co-workers tested the reactivity of Rh/Au bimetallic compounds **16** and **17** toward polar E–H bonds, i.e., in  $\text{NH}_3$ , MeOH, and  $\text{H}_2\text{O}$ . Their activation by transition metal complexes is often challenging, especially for the case of the N–H bonds in ammonia. This is due to the formation of Werner-type complexes that typically quench any further reactivity at the metal site. Compound **16** exhibited no reactivity toward any of the explored E–H bonds, while **17** was active even under very mild conditions, particularly toward N–H bonds. During the reaction, **17** evolved into equimolar mixtures of the cationic  $[(\eta^5\text{-Cp}^*)\text{Rh}(\text{PMe}_3)_2\text{H}]^+$  and the corresponding neutral Au complex  $[(\text{PCyp}_2\text{Ar}^+)\text{Au}(\text{X})]$  (where  $\text{X} = \text{NH}_2$ , OMe, or OH). The rate of N–H bond activation ( $t_{1/2} \approx 30 \text{ min}$ ) was significantly faster than the activation of methanol and water (MeOH,  $t_{1/2} \approx 48 \text{ h}$ ;  $\text{H}_2\text{O}$ ,  $t_{1/2} \approx 5 \text{ days}$ ).

Organolithium compounds are common reagents that transmetalate with halogeno or pseudohalogeno complexes of transition metals. For this reason, they are widely employed in metal-mediated organic transformations. Among organolithium derivatives, Li amides are particularly useful when nucleophilic addition across unsaturated bonds is a competing reaction to lithiation. Importantly, transmetalation reactions of Li–N amides with organometallic Al compounds can stop before complete reaction is reached, giving origin to mixed heteroatomic complexes. These partial transmetalations are known in the literature as trans-metal-trapping, and they stabilize carbanions through cooperative bimetallic effects, affording lithiating agents apt for onward reactivity.<sup>23</sup>

Indeed, a problem often encountered in organolithium chemistry concerns the instability of the organic anions formed upon transmetalation. This is for example the case for THF, whose transmetalation can lead to ring opening and ethylene production. Mulvey showed that with mixing  $n\text{-BuLi}$ , TMP (TMP = 2,2,6,6-tetra-methylpiperidine),  $i\text{-Bu}_2\text{AlCl}$ , and THF, trans-metal-trapping took place, and the  $[(\text{THF})\text{Li}(\text{m-TMP})\text{-}(\text{m-OC}_4\text{H}_7)\text{Al}(i\text{-Bu})_2]$  (**18**) intermediate was formed preventing secondary reactions (Figure 5a). In **18**, the heterocyclic ring of the deprotonated THF did not open and was stabilized cooperatively through Li and Al binding to its O and deprotonated C atoms.<sup>23</sup>

Although trans-metal-trapping was successfully demonstrated also for Ga, using  $[\text{Ga}(\text{CH}_2\text{SiMe}_3)_3]$  as a reagent, the number of



**Figure 5.** Examples of cooperative effects in (a) trans-metal-trapping and (b) transmetalation reactions. In b, *sec*-BuLi = *sec*-butyllithium and TMEDA = tetramethylethylenediamine.

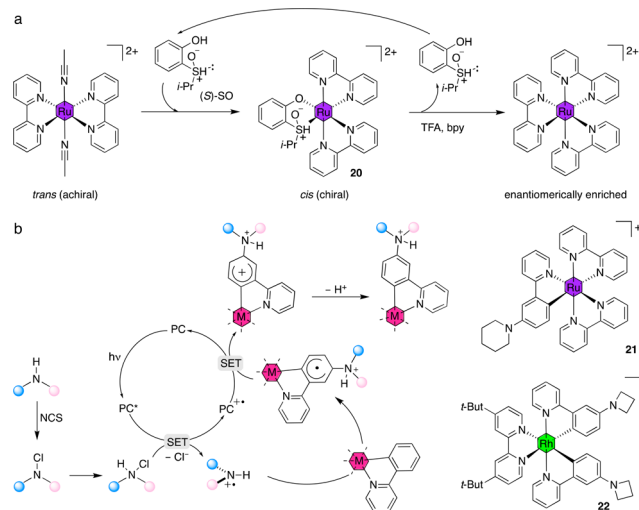
traps is still very limited, and trans-metal-trapping is in its infancy.<sup>24</sup> Hence, expanding the scope of this family of reactions has immense potential to deliver new synthetic approaches.

Lithiation and transmetalation were employed by Arthurs et al. to prepare metallacycles of Ir displaying planar chirality with application in asymmetric catalysis.<sup>25</sup> Generally, Ir derivatives with stereogenic centers are obtained by ortho-C–H activation mediated by a chiral auxiliary attached to a suitable ligand. Instead, they demonstrated that C–H activation of ferrocenyl-oxazoline followed by Hg transmetalation afforded the Hg-substituted compound **19** (Figure 5b) with almost complete diastereoselectivity (S,S<sub>p</sub>). This type of intermediate is stable in air and aqueous solution and upon addition of [Cp\*IrCl<sub>2</sub>]<sub>2</sub> and Bu<sub>4</sub>NCl resulted in a clean transmetalation and formation of the corresponding S,S<sub>p</sub>R<sub>Ir</sub> iridacycle as unique diastereoisomer. Importantly, direct mercuration (without preliminary lithiation) led to Hg-substituted ferrocenes, however with low diastereoselectivity. Although direct reaction between ferrocenyl-oxazoline and [Cp\*IrCl<sub>2</sub>]<sub>2</sub> successfully occurred via C–H activation, this was driven by the identity of the auxiliary ligand (i.e., oxazoline) of the ferrocene and limited the structure of the iridacycle with respect to relative stereochemistry of the product. Therefore, the lithiation/transmetalation strategy was more versatile for controlling the chirality this type of metallacycles. A drawback of the approach was associated with the toxicity of Hg. For this reason, the authors tried a transmetalation step with [PPh<sub>3</sub>AuCl], obtaining similar intermediates as for Hg, with high diastereoselectivity. Unfortunately, the following transmetalation with [Cp\*IrCl<sub>2</sub>]<sub>2</sub> did not occur.

## ■ CATALYSIS TOWARD METAL SUBSTRATES

Catalysis has enabled discovering and perfecting a myriad of sophisticated synthetic methods to access complex organic structures, including in stereoselective fashion. Instead, only few catalytic transformations capable of altering the structure of transition metal complexes have been studied and reported so far. This striking difference is intimately linked to the nature of organic and inorganic compounds and to the historical evolution of the methodologies employed in organic synthesis and coordination chemistry. Nevertheless, it is conceivable that application of catalysis concepts to coordination and organometallic chemistry could generate new and efficient methods to synthesize metal-based compounds as well as original strategies to exploit their chemical properties. In this section, we discuss the few examples of catalytic reactions in which, unconventionally, metal complexes behave as substrates to undergo chemical transformations.

Developing pioneering synthetic methods for the preparation of chiral-at-the-metal complexes, Meggers and co-workers employed the chiral (S)-(isopropylsulfinyl)phenol, (S)-SO, to achieve the catalytic asymmetric synthesis of the octahedral Δ-[Ru(bpy)<sub>3</sub>]<sup>2+</sup> (where bpy = 2,2'-bipyridine) starting from the achiral *trans*-[Ru(bpy)<sub>2</sub>(CH<sub>3</sub>CN)<sub>2</sub>](CF<sub>3</sub>SO<sub>3</sub>)<sub>2</sub> (Figure 6a).<sup>26</sup>

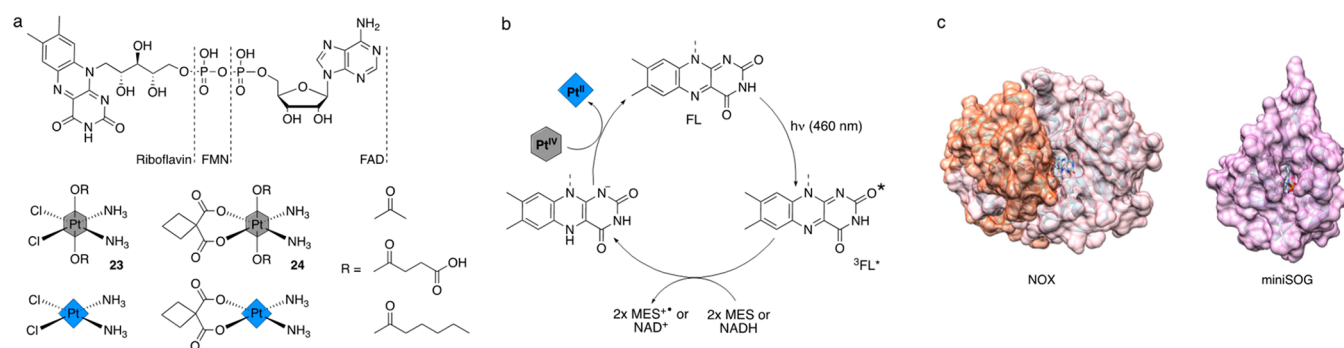


**Figure 6.** Catalytic reactions for the (a) asymmetric synthesis of Δ-[Ru(bpy)<sub>3</sub>]<sup>2+</sup> and (b) amination of Ru and Rh complexes. In a, TFA = trifluoroacetic acid and bpy = 2,2'-bipyridine; in b, NCS = N-chlorosuccinimide, SET = single-electron transfer, and PC = photoredox catalyst.

Unique in its kind, the reaction exploited the capacity of (S)-SO to selectively substitute the CH<sub>3</sub>CN ligands of the *trans*-Ru precursor and give the intermediate Δ-(R)-[Ru(bpy)<sub>2</sub>SO]<sup>+</sup> (**20**) with complete diastereoselectivity, in DMF and ethylene glycol. Removal of the chiral SO ligand proceeded smoothly upon the addition of trifluoroacetic acid (TFA), leading to Δ-[Ru(bpy)<sub>3</sub>]<sup>2+</sup> with retention of the configuration (99.4:0.6) when an excess of bpy was present in the reaction mixture. Crucially, the high selectivity for the Δ-(R)-[Ru(bpy)<sub>2</sub>SO]<sup>+</sup> diastereoisomer was rationalized by the favored orientation of the isopropyl substituent of SO, which avoided a steric clash with the CH group in the 6-position of the bpy ligand. Conversely, this interaction would occur for Λ-(R) analogue that was hence highly disfavored.

Optimizing the reaction conditions, Meggers demonstrated that 0.2 equiv of SO was sufficient for the reaction to proceed catalytically (with turnover numbers of more than 3) and afford 96% yields with an enantiomeric excess (e.r.) of 5.8:1. Using the more electron-rich methoxy derivative of SO as a catalyst further improved the e.r. (8:1) without any significant changes in the reaction yield (93%).

Another example of catalysis toward metal complexes was recently reported by the Leonori group.<sup>27</sup> They devised a photoredox strategy for the catalytic synthesis of aromatic amines by direct reaction of arenes and alkylamines. Their robust approach has merit to enable late stage functionalization of complex molecules such as drugs, enzyme inhibitors, and metal complexes as well. As outlined in Figure 6b, the organometallic complexes [Ru(ppy)(bpy)<sub>2</sub>]<sup>+</sup> (**21**) and [Rh(ppy)<sub>2</sub>(tbbpy)]<sup>+</sup> (**22**), where ppy = 2-phenylpyridine and tbbpy = 4,4'-di-*tert*-butyl-2,2'-dipyridyl, were selectively aminated on the 2-phenylpyridine ligand(s) using blue LEDs and [Ru-



**Figure 7.** Bioorthogonal photocatalytic activation of Pt(IV) prodrug complexes. (a) Selected flavin (FL) catalysts, Pt(IV) prodrugs, cisplatin, and carboplatin; (b) catalytic mechanism; and (c) structure of NOX and miniSOG. In b, MES = 2-(N-morpholino)ethanesulfonic acid.

(bpy)<sub>3</sub>]<sup>2+</sup> as a photoredox catalyst (PC). The amination occurred at the most nucleophilic position of the ppy, that is in para to the C atom coordinated to the transition metal. Reaction yields for the metal substrates were moderate (37% and 17% for the Ru and Rh complex, respectively, using 5% mol of catalyst). Nonetheless, these reactions are unique examples of catalytic functionalization of inert organometallic complexes that have relevance in solar energy storage and as anticancer agents.

In 2017, Salassa and co-workers exploited catalytic transformations of metal complexes for activating Pt(IV) anticancer prodrugs with visible light *in vitro* (Figure 7). The group showed that flavins (Fl) such as riboflavin, FMN, and FAD photocatalytically convert Pt(IV) complexes (23 and 24) in Pt(II) drugs such as cisplatin and carboplatin in the presence of electron donors (zwitterionic buffers, NADH, and ascorbate).<sup>28,29</sup> These catalytic reactions display unexpectedly high turnover numbers and frequencies (up to 500 and 26 min<sup>-1</sup>, respectively). Furthermore, they take place with the same efficiency in biological environments such as cell culture medium, where numerous chemical and biological components can interfere with the catalysis process.

The first step of the catalysis mechanism is triggered by light excitation and the subsequent formation of the <sup>3</sup>Fl excited state. This is a strong oxidant which is reduced by electron donors to afford the doubly reduced hydroquinone FlH<sup>-</sup> at pH 7. As evidenced by experimental and computational studies, FlH<sup>-</sup> can interact with Pt(IV) substrates via H-bonding, prompting the selective reduction of the metal complex and regeneration of the Fl catalyst.<sup>29</sup>

In cells, flavins are typically bound to proteins through strong noncovalent interactions constituting a variety of flavoprotein and flavoenzymes that participate in a myriad of fundamental processes for life. Remarkably, certain flavoproteins and flavoenzymes are also capable of bioorthogonally catalyzing these artificial Pt(IV) activation reactions. In 2018, Alonso-de Castro et al. demonstrated that miniSOG (mini singlet oxygen generator) and NOX (NADH oxidase) (photo)catalyzed the conversion of Pt(IV) prodrugs in Pt(II) active species in the presence of 2-(N-morpholino)ethanesulfonic acid (MES) and NADH.<sup>30</sup> In particular, NOX in combination with NADH prompted these transformations already in the dark with high efficiency (turnover frequency of 8.3 min<sup>-1</sup>). The catalytic activity of miniSOG and NOX was reasonably linked to the accessibility of their flavin binding pocket. Conversely, flavoenzymes such as glucose oxidase and glutathione reductase had much lower or no catalytic activity since FAD is deeply buried in their protein scaffold.

Mazzei et al. recently reported that this unconventional chemistry could be extended to the design of nanozymes. They developed a supramolecular photocatalyst by assembling FMN and Au nanoparticles decorated with a thiol bearing a 1,4,7-triazacyclononane headgroup and proved the photocatalytic conversion of a Pt(IV) anticancer complex to cisplatin.<sup>31</sup>

In 2019, Bradley reported a related approach using instead a Ru photosensitizer for the photocatalytic activation of oxaliplatin Pt(IV) prodrugs.<sup>32</sup> They demonstrated that 2 mol % loading of the photosensitizer achieved an 88% conversion of the Pt(IV) substrate after 1 h of irradiation with blue light, although no information on the catalysis mechanism was provided. When applied *in vitro*, the strategy was effective in reducing cell viability in both wild type and oxaliplatin resistant SKOV-3 cancer cells.

## CONCLUSIONS AND OUTLOOK

Coordination and organometallic chemistry strongly rely on traditional approaches in which the basic components, i.e., ligands and metals, are designed separately and hence combined. This contribution portrays a wealth of alternative reactivities centered on stoichiometric and catalytic transformations of metal components that are available for accessing exotic structures, synthesizing new metal-based materials, and activating small or biologically active molecules. Further systematic exploration of this type of nonmainstream inorganic reaction has the potential to greatly improve our understanding of several (bio)inorganic processes and inspire the development of ground-breaking technologies based on metal chemistry.

## AUTHOR INFORMATION

### Corresponding Authors

Giovanni Salassa – University Hospitals of Geneva (HUG), Geneva CH 1205, Switzerland; [orcid.org/0000-0002-2396-3884](https://orcid.org/0000-0002-2396-3884); Email: [giovanni.salassa@gmail.com](mailto:giovanni.salassa@gmail.com)

Luca Salassa – Donostia International Physics Center, Donostia 20018, Spain; Polimero eta Material Aurreratuak: Fisika, Kimika eta Teknologia, Kimika Fakultatea, Euskal Herriko Unibertsitatea UPV/EHU, Donostia 20018, Spain; Ikerbasque, Basque Foundation for Science, Bilbao 48011, Spain; [orcid.org/0000-0002-2112-9095](https://orcid.org/0000-0002-2112-9095); Email: [lsalassa@dipc.org](mailto:lsalassa@dipc.org)

Complete contact information is available at: <https://pubs.acs.org/10.1021/acsomega.0c05873>

## Author Contributions

The manuscript was written through contributions of all authors.

## Notes

The authors declare no competing financial interest.

## Biographies



Giovanni Salassa received his Ph.D. in chemistry at the Institute of Chemical Research of Catalonia (ICIQ) in 2013 under the supervision of Prof. A. W. Kleij. Afterwards, he became postdoctoral fellow in the group of Prof. F. Mancin at University of Padua. In 2016, he began his second postdoc in the group of Prof. T. Bürgi, where he was awarded a Marie Skłodowska-Curie Action fellowship (2017). Currently, funded by the BNF program, he is working at the University Hospital of Geneva (HUG). Giovanni's research mainly focuses on metal nanocluster characterization with NMR techniques and on the investigation of their chirality and reactivity on the nanoscale level.



Luca Salassa obtained his Ph.D. at the University of Turin (Italy) in 2004. Later, he was a postdoctoral fellow at the University of Montana (USA) and Marie Curie Fellow at the University of Warwick (UK). In 2012, he moved to San Sebastián (Spain) as a Ramón y Cajal Fellow (tenure-track) to join CIC biomaGUNE, and a few years later (2017) he became an Ikerbasque Professor at the Donostia International Physics Center and at the University of the Basque Country. Research in Luca's group principally focuses on the development of new strategies for the photoactivation of biologically relevant metal complexes.

## ACKNOWLEDGMENTS

L.S. acknowledges financial support from the Spanish State Research Agency for the grant PID2019-109111RB-I00 and the Spanish Multi-MetDrugs network (RED2018-102471-T) for fruitful discussions. This work was performed under the Severo

Ochoa Centres of Excellence Program of the Spanish State Research Agency, Grant No. CEX2018-000867-S (DIPC).

## DEDICATION

Dedicated to the memory of Prof. Carlo Lamberti.

## REFERENCES

- (1) Cordovilla, C.; Bartolomé, C.; Martínez-Illarduya, J. M.; Espinet, P. The Stille Reaction, 38 Years Later. *ACS Catal.* **2015**, *5* (5), 3040–3053.
- (2) Cure, J.; Poteau, R.; Gerber, I. C.; Gornitzka, H.; Hemmert, C. Dimeric Gold Bis(Carbene) Complexes by Transmetalation in Water. *Organometallics* **2012**, *31* (2), 619–626.
- (3) Chianese, A. R.; Li, X.; Janzen, M. C.; Faller, J. W.; Crabtree, R. H. Rhodium and Iridium Complexes of N-Heterocyclic Carbenes via Transmetalation: Structure and Dynamics. *Organometallics* **2003**, *22* (8), 1663–1667.
- (4) Escudero-Adán, E. C.; Benet-Buchholz, J.; Kleij, A. W. Expedient Method for the Transmetalation of Zn(II)-Centered Salphen Complexes. *Inorg. Chem.* **2007**, *46* (18), 7265–7267.
- (5) Blegg, A.; Hutton, A. T.; Pringle, P. G.; Shaw, B. L. Preparation of  $\mu$ -Ph<sub>2</sub>PCH<sub>2</sub>PPh<sub>2</sub> Platinum(II)-Tungsten(0), -Molybdenum(0) or -Chromium(0) Complexes by Transmetalation: Crystal Structure of [(p-MeC<sub>6</sub>H<sub>4</sub>C≡C)<sub>2</sub>Pt( $\mu$ -Ph<sub>2</sub>PCH<sub>2</sub>PPh<sub>2</sub>)<sub>2</sub>W(CO)<sub>3</sub>]. *Inorg. Chim. Acta* **1983**, *76* (C), L265–L266.
- (6) Akhuli, B.; Cera, L.; Jana, B.; Saha, S.; Schalley, C. A.; Ghosh, P. Formation and Transmetalation Mechanisms of Homo- and Heterometallic (Fe/Zn) Trinuclear Triple-Stranded Side-by-Side Helicates. *Inorg. Chem.* **2015**, *54* (9), 4231–4242.
- (7) Ube, H.; Endo, K.; Sato, H.; Shionoya, M. Synthesis of Hetero-Multinuclear Metal Complexes by Site-Selective Redox Switching and Transmetalation on a Homo-Multinuclear Complex. *J. Am. Chem. Soc.* **2019**, *141* (26), 10384–10389.
- (8) Cheng, J.; Ma, X.; Zhang, Y.; Liu, J.; Zhou, X.; Xiang, H. Optical Chemosensors Based on Transmetalation of Salen-Based Schiff Base Complexes. *Inorg. Chem.* **2014**, *53* (6), 3210–3219.
- (9) Adams, R. D.; Babin, J. E.; Tasi, M. Cluster Synthesis. 18. Metal-Metal Exchange Reactions. The synthesis and structural characterizations of Ru<sub>3</sub>Mo<sub>2</sub>(CO)<sub>10</sub>( $\epsilon$ -CO)<sub>2</sub>Cp<sub>2</sub>( $\epsilon_4$ -S) and Ru-Mo<sub>2</sub>(CO)<sub>7</sub>Cp<sub>2</sub>( $\epsilon_3$ -S). *Organometallics* **1988**, *7*, 219–227.
- (10) Adams, R. D.; Babin, J. E.; Mathur, P.; Natarajan, K.; Wang, J. G. Cluster Synthesis. 25. Synthesis and Characterization of New Mixed-Metal Cluster Complexes By Metal-Metal Exchange. Reactions of the sulfido cluster complexes M<sub>3</sub>(CO)<sub>9</sub>( $\epsilon_3$ -CO)( $\epsilon_3$ -S) (M = iron, ruthenium and osmium) with W(CO)<sub>5</sub>L (L = CO or PMe<sub>2</sub>Ph). *Inorg. Chem.* **1989**, *28* (8), 1440–1445.
- (11) Ghosh, S.; Kabir, S. E.; Pervin, S.; Raha, A. K.; Golzar Hossain, G. M.; Haworth, D. T.; Lindeman, S. V.; Bennett, D. W.; Siddiquee, T. A.; Salassa, L.; et al. Tetranuclear Group 7/8 Mixed-Metal and Open Trinuclear Group 7 Metal Carbonyl Clusters Bearing Bridging 2-Mercapto-1-Methylimidazole Ligands. *Dalton Trans.* **2009**, *3* (18), 3510–3518.
- (12) Krishnadas, K. R.; Baksi, A.; Ghosh, A.; Natarajan, G.; Pradeep, T. Structure-Conserving Spontaneous Transformations between Nanoparticles. *Nat. Commun.* **2016**, *7*, 13447.
- (13) Zhang, B.; Salassa, G.; Bürgi, T. Silver migration between Au<sub>38</sub>(SC<sub>2</sub>H<sub>4</sub>Ph)<sub>24</sub> and doped Ag<sub>x</sub>Au<sub>38-x</sub>(SC<sub>2</sub>H<sub>4</sub>Ph)<sub>24</sub> nanoclusters. *Chem. Commun.* **2016**, *52* (59), 9205–9207.
- (14) Salassa, G.; Sels, A.; Mancin, F.; Bürgi, T. Dynamic Nature of Thiolate Monolayer in Au<sub>25</sub>(SR)<sub>18</sub> Nanoclusters. *ACS Nano* **2017**, *11* (12), 12609–12614.
- (15) Zhang, B.; Safonova, O. V.; Pollitt, S.; Salassa, G.; Sels, A.; Kazan, R.; Wang, Y.; Ruppel, G.; Barrabés, N.; Bürgi, T. On the Mechanism of Rapid Metal Exchange between Thiolate-Protected Gold and Gold/Silver Clusters: A Time-Resolved In Situ XAFS Study. *Phys. Chem. Chem. Phys.* **2018**, *20* (7), 5312–5318.
- (16) Ghosh, A.; Ghosh, D.; Khatun, E.; Chakraborty, P.; Pradeep, T. Unusual Reactivity of Dithiol Protected Clusters in Comparison to

Monothiol Protected Clusters: Studies Using  $\text{Ag}_{51}(\text{BDT})_{19}(\text{TPP})_3$  and  $\text{Ag}_{29}(\text{BDT})_{12}(\text{TPP})_4$ . *Nanoscale* **2017**, *9* (3), 1068–1077.

(17) Bhat, S.; Baksi, A.; Kumar, S.; Natarajan, G.; Subramanian, V.; Mudedla, S. K.; Natarajan, G.; Subramanian, V.; Pradeep, T.  $\text{Au}_{22}\text{Ir}_3(\text{PET})_{18}$ : An Unusual Alloy Cluster through Intercluster Reaction. *J. Phys. Chem. Lett.* **2017**, *8* (13), 1–16.

(18) Campos, J. Bimetallic Cooperation across the Periodic Table. *Nat. Rev. Chem.* **2020**, *4*, 696.

(19) Hidalgo, N.; Moreno, J. J.; Pérez-Jiménez, M.; Maya, C.; López-Serrano, J.; Campos, J. Tuning Activity and Selectivity during Alkyne Activation by Gold(I)/Platinum(0) Frustrated Lewis Pairs. *Organometallics* **2020**, *39* (13), 2534–2544.

(20) Hicks, J.; Mansikkamäki, A.; Vasko, P.; Goicoechea, J. M.; Aldridge, S. A Nucleophilic Gold Complex. *Nat. Chem.* **2019**, *11* (3), 237–241.

(21) Hidalgo, N.; Maya, C.; Campos, J. Cooperative Activation of X-H (X = H, C, O, N) Bonds by a Pt(0)/Ag(I) Metal-Only Lewis Pair. *Chem. Commun.* **2019**, *55* (60), 8812–8815.

(22) Alférez, M. G.; Moreno, J. J.; Hidalgo, N.; Campos, J. Reversible Hydride Migration from  $\text{C}_3\text{Me}_5$  to  $\text{Rh}^I$  Revealed by a Cooperative Bimetallic Approach. *Angew. Chem., Int. Ed.* **2020**, *59*, 20863.

(23) Crosbie, E.; García-Álvarez, P.; Kennedy, A. R.; Klett, J.; Mulvey, R. E.; Robertson, S. D. Structurally Engineered Deprotonation/Alumination of THF and THTP with Retention of Their Cycloanionic Structures. *Angew. Chem., Int. Ed.* **2010**, *49* (49), 9388–9391.

(24) Uzelac, M.; Mulvey, R. E. Trans-Metal-Trapping: Concealed Crossover Complexes En Route to Transmetalation? *Chem. - Eur. J.* **2018**, *24* (31), 7786–7793.

(25) Arthurs, R. A.; Hughes, D. L.; Horton, P. N.; Coles, S. J.; Richards, C. J. Application of Transmetalation to the Synthesis of Planar Chiral and Chiral-at-Metal Iridacycles. *Organometallics* **2019**, *38* (5), 1099–1107.

(26) Gong, L.; Lin, Z.; Harms, K.; Meggers, E. Isomerization-Induced Asymmetric Coordination Chemistry: From Auxiliary Control to Asymmetric Catalysis. *Angew. Chem., Int. Ed.* **2010**, *49* (43), 7955–7957.

(27) Ruffoni, A.; Juliá, F.; Svejstrup, T. D.; McMillan, A. J.; Douglas, J. J.; Leonori, D. Practical and Regioselective Amination of Arenes Using Alkyl Amines. *Nat. Chem.* **2019**, *11* (5), 426–433.

(28) Alonso-De Castro, S.; Ruggiero, E.; Ruiz-De-Angulo, A.; Rezabal, E.; Mareque-Rivas, J. C.; Lopez, X.; López-Gallego, F.; Salassa, L. Riboflavin as a Bioorthogonal Photocatalyst for the Activation of a Pt IV Prodrug. *Chem. Sci.* **2017**, *8* (6), 4619–4625.

(29) Gurruchaga-Pereda, J.; Martínez-Martínez, V.; Rezabal, E.; Lopez, X.; Garino, C.; Mancin, F.; Cortajarena, A. L.; Salassa, L. Flavin Bioorthogonal Photocatalysis Toward Platinum Substrates. *ACS Catal.* **2020**, *10* (1), 187–196.

(30) Alonso-De Castro, S.; Cortajarena, A. L.; López-Gallego, F.; Salassa, L. Bioorthogonal Catalytic Activation of Platinum and Ruthenium Anticancer Complexes by FAD and Flavoproteins. *Angew. Chem., Int. Ed.* **2018**, *57* (12), 3143–3147.

(31) Mazzei, L. F.; Martínez, A.; Trevisan, L.; Rosa-Gastaldo, D.; Cortajarena, A. L.; Mancin, F.; Salassa, L. Toward Supramolecular Nanozymes for the Photocatalytic Activation of  $\text{Pt}^{IV}$  Anticancer Prodrugs. *Chem. Commun.* **2020**, *56* (72), 10461–10464.

(32) Norman, D. J.; Gambardella, A.; Mount, A. R.; Murray, A. F.; Bradley, M. A Dual Killing Strategy: Photocatalytic Generation of Singlet Oxygen with Concomitant Pt IV Prodrug Activation. *Angew. Chem., Int. Ed.* **2019**, *58* (40), 14189–14192.