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Sustainable knowledge-driven approaches in transition metal-catalyzed transformations

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Dedicated to Prof. Pablo Espinet on the occasion of his 70th birthday

Abstract: The sustainable synthesis of relevant scaffolds for their use in the pharmaceutical, agrochemical and material sectors constitutes one of the most urgent challenges that the chemical community needs to overcome. In this context, the development of innovative and more efficient catalytic processes based on fundamental understanding of the underlying reaction mechanisms remains a largely unresolved challenge for academic and industrial chemists. Here, we cover selected examples of computational and experimental knowledge-driven approaches for the rational design of transition metal catalyzed transformations.

1. Introduction

In 1987, the World Commission on Environment and Development (WCED) published the report “Our Common Future”, also known as the Brundtland report, to alert on the most critical global issues: environmental protection, economic growth and social equity.^[1] This report also introduced the key concept of sustainable development as “development that meets the needs of the present without compromising the ability of future generations to meet their own needs.” It is undeniable that Chemistry is crucial for achieving a transition to a circular economy, by providing sustainable strategies for the use of raw materials (or building blocks) and energy sources.^[2] Over the past two decades, transition metal (TM) catalysis has played a key role in tackling some of the major problems that our world faces such as climate change, energy conversion or human health by

developing more efficient processes and/or designing new catalysts. In this regard, most advances have been accomplished based on trial-and-error approaches or serendipitous discoveries. Surprisingly, one strategy that has received very limited attention, despite its potential to provoke a paradigm shift in terms of sustainability, is the rational design of chemical transformations based on knowledge-driven approaches. Mechanistic investigations are typically applied as a posteriori tool, focused on understanding the reaction mechanism of successful transformations. However, this concept is beginning to evolve due to the employment of fundamental knowledge as reaction design resource. Over the past few years, computational methods have showed their tremendous capability, not only for predicting catalyst performance but also for improving their efficiency.^[3] Experimental mechanistic strategies can also facilitate tremendously the sustainable development of transition metal-catalyzed transformations. From our point of view, this paradigm-shift has to rely on the use of key reaction intermediates as “knowledge building blocks” (KBBs). The foundation of this approach is based on this conception: the success or failure of a whole chemical process relies on the performance of the reaction intermediates involved in each elementary step that constitutes the catalytic cycle. This may seem very obvious, but surprisingly, it is often overlooked and it can be a completely game-changer for non-efficient transformations, enabling gain in terms of money, time and human resources. Therefore, we envision to design efficient transformations by trapping these reaction intermediates and using them to overcome limitations and explore innovative reactivities.

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In this minireview, we discuss different computational and/or experimental knowledge-driven approaches, including the synergistic cooperation between them, for the rational design of TM-catalyzed transformations. In particular, to demonstrate the advantages of these approaches, herein we review their application in different relevant organic processes, including two cornerstones in modern organic chemistry: (i) TM-catalyzed cross-couplings, that emerged in the late 70s revolutionizing the way in which molecules are built,^[4] and (ii) C–H functionalization reactions, one of the “holy grails” in synthetic organic chemistry.^[5]

Figure 1. Rational design of chemical transformations based on knowledge-driven approaches.

Jesús Sanjosé-Orduna was born in Barcelona, Spain, in 1991. He received both his B.S.c. and M.S.c. from the University of Barcelona (UB) in 2014 and 2015, respectively. Shortly afterwards, he joined the Pérez-Temprano group at the Institute of Chemical Research of Catalonia (ICIQ) in Tarragona, Spain, to pursue his Ph.D. degree. Since then, he investigates the intricacies of Cp*Co-catalyzed C–H functionalization reactions, not only to provide a comprehensive mechanistic picture of these transformations but also to improve their efficiency based on fundamental knowledge.

Ángel L. Mudarra was born in Escacena del Campo (Huelva, Spain) in 1992. He received his B.S.c. degree in Chemistry from University of Huelva (Huelva, Spain) in 2014. In 2015, he got his M.S.c. degree from the University of Sevilla (Spain), and next he started his PhD studies at the Institute of Chemical Research of Catalonia (ICIQ) under the supervision of Dr. Mónica H. Pérez-Temprano and Prof. Feliu Maseras. His Ph.D. is focused on mechanistic investigations, combining computational and experimental approaches, to understand and develop bimetallic processes in the context of homogenous catalysis.

Sara Martínez de Salinas received her B.S.c. degree in Chemistry from the University of Oviedo in 2010. Then, she obtained her M.S.c. degree in Synthesis and Chemical Reactivity at the same university in 2011 under the supervision of Prof. Elena Lastra. In 2015, she got her Ph. D. in organometallic chemistry under the supervision of Prof. Elena Lastra working in rhodium systems. In December 2015, she joined the group of Dr. Mónica H. Pérez-Temprano as a postdoctoral researcher and she is currently working to obtain fundamental understanding of relevant organometallic processes in the context of bimetallic catalysis and trifluoromethylation.

Mónica H. Pérez-Temprano was born in Valladolid, Spain, in 1982. She received her PhD degree at the University of Valladolid, under the supervision of Prof. Espinet and Prof. Casares, in 2011. Next, she moved to the University of Michigan to work with Prof. Sanford on the synthesis and reactivity of high-valent palladium (IV) complexes. In 2015, she began her independent career as Junior Group Leader at the Institute of Chemical Research of Catalonia (ICIQ). Her research program is focused on the rational design of more sustainable approaches for the synthesis of organic molecules using fundamental organometallic chemistry.

2. Computational tools for rational design in homogeneous catalysis

Over the last two decades, computational chemistry has evolved into a key tool for unravelling the mechanistic intricacies of transition metal-catalyzed systems.^[6,3b] Currently, due to the major advances in the development of theoretical methods, software and hardware, it is possible to resolve Quantum

Mechanics (QM) systems at a reasonable time-scale. This allows the exploration and understanding at molecular level of chemical transformations, even without simplifying the systems. In this regard, Density Functional Theory (DFT) stands out as a powerful posteriori tool which provides virtual access to critical mechanistic information when experimental strategies exhibit intrinsic limitations. Indeed, modern DFT methods have reached such level of accuracy that can even quantitatively reproduce experimental outcomes, turning not only into a real-time complementary strategy for supporting mechanistic proposals but also into a truly predictive tool.^[6d-e,7] This later approach is particularly promising since it paves the way for the rational design of more efficient transition metal-catalyzed transformations and, subsequently, the development of sustainable organic processes. The ideal work-flow for computer-based discoveries involves the synergistic cooperation between DFT calculations and experiments. First, preliminary results and computation are essential to make an initial prediction. Next, this hypothesis is tested experimentally, and if the desired goal is not achieved, iterative calculation/experimental observation feedback loops are performed in order to fine-tune the initial guess (Figure 2). In this section, we will cover selected examples where it is shown the capability of computation to provide meaningful predictions and their impact on the development of innovative and more efficient TM-catalyzed reactions. We have classified the selected systems into two categories, depending on the computed data treatment: (i) the DFT-design of efficient catalysts; and (ii) the employment of statistical analysis of big data sets to predict a desired performance.

Figure 2. Work-flow for merging the capabilities of computational chemistry and experiments in the reaction optimization or discovery.

2.1 DFT calculations for enabling catalyst design

One of the main challenges associated to TM-catalyzed transformations is the potential formation of catalytically inactive species and/or off-cycle complexes, along with undesired side reactions, that can dramatically impact on the efficiency of these systems. Over the past few years, DFT calculations have been used to overcome these limitations by gaining mechanistic insights on certain intermediates and/or transition states (TSs) and, subsequently, predicting essential modifications on the catalyst design process.

2.1.1 Accessing virtual intermediates to understand key processes in nucleophilic trifluoromethylation reactions

An excellent example on the employment of computational predictions to promote challenging reactivities has been reported by Schoenebeck and co-workers in the context of Pd-catalyzed nucleophilic trifluoromethylation reactions (Scheme 1).^[8] Only few examples of bulky and/or wide-bite-angle phosphines have demonstrated their capability to promote the challenging formation of Ar–CF₃ from L_nPd^{II}(Ar)(CF₃) complexes.^[8c,i,m]

Scheme 1. Proposed catalytic cycle for Pd^{0/II}-catalyzed trifluoromethylations.

Between 2011 and 2014, Schoenebeck et al. explored the potential of computational chemistry in the design of an efficient phosphine ligand for facilitating challenging C–CF₃ bond-forming reductive eliminations.^[8d,f] Initially, they compared, theoretically, the efficiency of two synthetically accessible L_nPd(Ph)(CF₃) complexes bearing Xantphos and dppe as ligands. The former was known to promote the product release while the latter required high temperature even to afford Ph–CF₃ in low yield.^[8a-b] This computational investigation revealed that, instead of the bite angle of the phosphine, the crucial factor for facilitating the reductive elimination was the repulsive interaction between the ligand and the organic groups involved in the coupling. With this information in hand, they designed an unprecedented and experimentally efficient polytrifluoromethylated phosphine with a narrow bite angle (Scheme 2).^[8f] As mentioned above, the low barrier of the reductive elimination event can be explained due to the electrostatic repulsion between the ligand and both, the aryl and trifluoromethyl groups, on the palladium(II) complex. Other remarkable factor for the success of this reaction is the stabilization of Pd⁰ due to the electron-withdrawing nature of CF₃ substituent in the phosphine. This work stands out as a representative case of computational-guided ligand design.

Scheme 2. Computational study of phosphine ligand scaffolds.

2.1.2 Dissecting energy components in Cu-catalyzed anti-Markovnikov hydroamination reactions

Another interesting example of computer-based ligand design has been reported by Buchwald and Liu for the copper-catalyzed anti-Markovnikov hydroamination reactions of unactivated terminal alkenes.^[9] These transformations are particularly relevant for medicinal chemistry since the resulting organic scaffold is a prevalent motif in bioactive molecules.^[10] Previous mechanistic investigations demonstrated that, among the different elementary steps involved in the catalytic cycle, the hydrocupration is the rate-determining step (RDS) when using unactivated and/or terminal olefinic substrates (Scheme 3).

Scheme 3. Proposed catalytic cycle for the copper-catalyzed anti-Markovnikov hydroamination reactions.

Combining computational and experimental approaches, they were able to predict potential modifications on SEGPHOS-based ligand scaffolds to accelerate the hydrocupration step. Initially, preliminary kinetic studies revealed a promising and unexpected rate increase when using CF₃-SEGPHOS, a trifluoromethylated ligand. Next, the authors performed a computational ligand-substrate interaction analysis, between DTBM-SEGPHOS or CF₃-SEGPHOS and propene as model substrate, to rationally introduce further modifications into the ligand that could lead to an increase in the reaction rate (Scheme 4). At this point, they were able to identify and evaluate the main energy contributions to the activation barrier of the RDS, such as the distortion energy

necessary to reach the TS geometry or stabilizing through-space and/or through-bond interactions between the olefin and the LCuH moiety. The energy decomposition analysis disclosed a significantly stronger through-bond interaction for CF₃-SEGPHOS than for DTBM-SEGPHOS in the TS. This is likely due to the electron-withdrawing nature of the trifluoromethyl substituents, which increases the Lewis acidity of the copper catalyst and favors the binding of the alkene. For the through-space interactions, both ligands provided comparable energies but for different motives: TS_{DTBM-SEGPHOS} was more stabilized by attractive London dispersion forces whereas TS_{CF₃-SEGPHOS} exhibited more important through-space electrostatic interactions via C–F...H–C contacts between the fluorinated ligand and the olefin. With this information in hand, they predicted that the substitution of the CF₃ moiety by a larger perfluorinated chain, *i*-C₃F₇, could maintain the existing favorable through-space and through-bond interactions and increase the stabilizing London dispersion interactions. When the reactivity of the (*i*-C₃F₇-SEGPHOS)CuH catalyst was tested, the product formation was speed up at its initial stage, but the final yield did not improve. This experimental result pointed out the high activity of the catalyst along with its low stability. In order to find the perfect balance between the different stabilizing factors, the authors decided to design a hybrid SEGPHOS-based ligand, merging the high stability of DTBM-SEGPHOS and the high activity of *i*-C₃F₇-SEGPHOS. When using this new ligand, the reaction rate of the hydroamination product was 62 times faster than the one for DTBM-SEGPHOS but maintaining its stability. In addition, this catalyst system was successfully used for the transformation of a wide substrate scope under preparative conditions. This work showed the powerful combination of kinetic investigations, computer-driven catalyst design and experimental verification for the rational design and development of more efficient catalytic systems.

(a) Model reaction and kinetic studies

ligand	k_{rel}
DTBM-SEGPHOS R ¹ = ^t Bu R ² = OMe	1.0
CF ₃ -SEGPHOS R ¹ = CF ₃ R ² = H	6.7

Conclusion
 $k_{\text{CF}_3\text{-SEGPHOS}} > k_{\text{DTBM-SEGPHOS}}$

(b) Computation: Dissection in energy contributions

CF₃-SEGPHOS

- Strong through-bond interactions
- C–F...H–C interactions

Final design

Scheme 4. (a) Model system. (b) Ligand design.

2.1.3 Engineered iridacycles for the efficient formation of lactams

In 2018, Chang and co-workers reported a very elegant example of the synergistic cooperation between experimental and computational mechanistic investigations for the selective synthesis of γ -lactams, a prevalent scaffold in medicinal chemistry, via a key metal-nitrenoid intermediate.^[11a] Despite these cyclic amides are prevalent scaffolds in medicinal chemistry, this TM-catalyzed C–H amidation strategy had been hampered due to the inherent instability of the proposed carbonylnitrene intermediate. This highly reactive species tends to decompose affording an undesired isocyanate through a Curtius-type rearrangement (Scheme 5).^[11b,c,d]

Scheme 5. Reactivity of metal-nitrenoid intermediates.

The authors tackled this challenge by engineering $\text{Cp}^*\text{Ir}^{\text{III}}$ complexes that could block the decomposition route and facilitate the C–H insertion. Using the well-defined iridacycle **1_{Ir}-Ar^FCN**, they performed different stoichiometric reactions using phenyl-1,4,2-dioxazole derivatives as nitrogen source. They observed that 1,4,2-dioxazol-5-one reacts faster than (*o*-isopropyl)phenyldioxazole, affording the desired lactam in less than 5 minutes along with CO_2 extrusion. In sharp contrast, when they tested a dioxazolone containing a more flexible alkyl chain, instead of the corresponding lactam, they detected the formation of a six-membered $\text{Cp}^*\text{Ir}^{\text{III}}$ -amido complex formed via a C–N coupling. It should be noticed that the isocyanate by-product was not observed in these transformations (Scheme 6).

Scheme 6. Stoichiometric experiments using **1_{Ir}-Ar^FCN**.

To further understand the chemoselectivity dependence of the reaction depending on the nature of the substrate, they computed the energy barriers for the C–N coupling, the Curtius rearrangement and C–H insertion starting from an iridium(V)-nitrene intermediate and using the dioxazolone containing the flexible chain as substrate. DFT calculations unraveled that the most facile transformation from this high-valent $\text{Cp}^*\text{Ir}^{\text{V}}$ species is the C–N coupling. In order to prevent this side-reaction, the authors proposed the substitution of the phenylpyridine ligand by a monoanionic LX-donor ligand ($\text{X} = \text{O}, \text{N}$), since the N–O or N–N couplings would be more disfavored. Next, they performed a careful analysis of the computed natural bond orbitals (NBO) of every transition state (Scheme 7). These calculations revealed that the Curtius rearrangement transition state should be more sensitive to changes of the partial charge of the Ir center. Therefore, they hypothesized that the employment of electron-rich ligands could increase this energy barrier, shutting down this undesired decomposition route.

Scheme 7. Computational studies on the reactivity of $\text{Cp}^*\text{Ir}^{\text{V}}$ nitrenoid species.

Following this DFT-based rational design, the authors tested a new family of easily synthesized and air-stable $\text{Cp}^*\text{Ir}^{\text{III}}$ catalysts containing different LX-type ligands. The authors observed almost quantitative formation of the corresponding lactam when using LNR ligands, in less than 2 hours at room temperature. This benchmark reaction demonstrated the potential of this transformation since it allows the preparation of unprotected γ -lactams. Using these optimal reaction conditions, Chang and co-workers explored the intramolecular amidation of different types of C–H bonds, using a wide variety of dioxazolones derivatives (Scheme 8). They applied their amidation protocol for the late stage functionalization of complex molecules such as high-value amino acids to convert them into lactams.

Scheme 8. $\text{Cp}^*\text{Ir}^{\text{III}}$ -catalyzed synthesis of γ -lactams using readily available carboxylic acids as starting materials.

Related to this work, more recently, Chang et al. described a second generation of tailored iridacycles to enable the formation of asymmetric γ -lactams (Scheme 9).^[12] In this work, they evaluated different ligands, observing an excellent

enantioselectivity when using chiral diamine scaffolds. DFT studies demonstrated that the presence of transient intramolecular hydrogen bonding interactions between the substrate and NH substituent of the diamine ligand are responsible for the excellent stereoselectivity.

Scheme 9. Rational-driven tailoring of iridium catalysts.

2.2 Predictive statistical models for rational design

Despite the promising results shown in Section 2.1, the rational design of efficient catalytic systems based on computational chemistry present several challenges from a theoretical point of view. Among others, the necessity of time-demanding calculations for the evaluation of different reaction mechanisms, which can operate simultaneously, and the one-by-one analysis of certain key species, which could present different conformations, slows down the DFT-based rational design of TM-catalyzed organic transformations.^[13] An alternative strategy to overcome these limitations is the use of statistical modelling methods, which handle big amounts of data at a significant lower computational cost. These statistical approaches can predict reaction performances by correlating both calculated and experimental structural/physical organic molecular descriptors with reaction outputs such as activity or selectivity. Since the pioneering development of the Hammett parameter and its application in Linear Free Energy Relationships (LFERs), more complex multidimensional correlations and quantitative parameters have been generated by the organic chemistry community to predict experimental results.^[14] It should be noticed that not only the selection of a representative molecular descriptor is key for the success of this approach but also its statistical significance. Therefore, this strategy requires the treatment of relevant and abundant experimental data, including, if existed, negative outcomes. This is remarkable since both negative and positive results are equally valuable in the research procedure. Here, we will cover selected examples on the application of statistical correlations for predicting reaction outcomes where fundamental mechanistic information is provided as consequence of the LFERs.

2.2.1 Parametrization in Suzuki cross-couplings reactions

The Suzuki-Miyaura reaction is one of the most general and powerful methodologies used in the formation of C–C bonds in

medicinal and organic chemistry.^[15] In 2016, Sigman and co-workers described a multivariate correlation approach for examining and predicting the outcome of a previously-reported Pd-catalyzed cross-coupling reaction, where the nature of the ligand determined the product formation.^[16] In the literature precedent, Fu et al. controlled the regioselectivity in the Suzuki coupling of chloroaryl triflate derivatives by modifying the phosphine ligand (Scheme 10).^[17]

Scheme 10. Chemoselective Suzuki Cross-Couplings.

Given the dependence of the reaction outcome on the phosphine nature, Sigman et al. tackled the mathematical modelling by studying significant parameters of this ligand such as cone-angle measurements, Sterimol values, computed infrared values or experimental NMR measurements (Scheme 11). Based on previous computational studies by Schoenebeck and Houk,^[18] and their own experimental cyclic voltammetry (CV) measurements, Sigman and co-workers classified the ligands into two groups according to the speciation of the palladium(0) complex that undergoes the oxidative addition: large phosphines, which promote the oxidative addition to monoligated palladium (LPd) complexes, and “smaller” or Buchwald phosphines, which preferentially form the bis-ligated (L_2Pd) complexes that undergo the oxidative addition event. For larger phosphines, highly selective toward the oxidative addition of the C–Cl bond, the reaction outcome can be predicted using the phosphine selenide ^{31}P NMR chemical shift as a single descriptor for the model. For smaller and Buchwald biaryl phosphines, a more complex multivariate predictive model, which contains four different parameters, was found. They rationalized the relationship of these parameters with steric and electronic characteristics of the phosphines that explains the preferential oxidative addition of C–OTf bond.

Scheme 11. Statistical analysis of Suzuki-Miyaura reaction selectivity.

In 2018, Biscoe and Sigman were able to apply predictive statistical models to the rational design and development of stereospecific Pd-catalyzed Suzuki cross-coupling reactions,^[19] one of the limitations associated to these transformations. These reactions are typically hampered by a slow transmetalation step between $L_nPd(Ar)X$ and a sterically hindered alkylboron nucleophile and/or the tendency of the resulting alkyl-palladium(II) complex to undergo β -hydride elimination/reinsertion sequences that entail isomerization of the alkyl stereocenter (Scheme 12). Moreover, the transmetalation step can play a crucial role in the stereochemical outcome of the reaction when using a single-enantiomer organoboron nucleophile, since it can proceed via stereoretentive or stereoinvertive pathways depending on the reaction conditions.

Scheme 12. Mechanistic proposal for stereodivergent Suzuki cross-coupling.

The authors carried out initial investigations that provided additional relevant mechanistic observations: (i) they detected a loss on the stereofidelity of the resulting product when using electron-deficient aryl chlorides as coupling partners; and (ii) they did not observe a clear correlation between the stereoselectivity of the reaction and the steric properties of the different tested phosphines. Challenged by these results, they employed ligand parameterization tools to unravel the factors that control the transmetalation step in order to predict and rationally design a new ligand-controlled enantiodivergent process. Initial studies showed that larger ligands could suppress the undesired β -hydride elimination reaction. Further statistical analysis of the ligands that provided high enantiomeric excess (>30% ee), indicated that electron-rich phosphines promote invertive reactions while electron-poor phosphines favor the retentive ones (Scheme 13a). Based on this information, they were able to develop stereodivergent Suzuki coupling protocols using enantioenriched alkyl boron nucleophiles, depending on the selected phosphine ligand (Scheme 13b). The stereoretentive pathway was facilitated by designed biaryls phosphine ligands that combined a bulky substituent and an electron-poor group in their scaffolds. The stereoinvertive route was promoted by $PAAd_3$, a strongly σ -donating ligand. Finally, a multivariate regression analysis provided evidences for the origin of the enantiodivergent transmetalation step depending on the nature of the ligand.

Scheme 13. (a) Phosphine parameterization. (b) Stereodivergent Pd-catalyzed Suzuki cross-coupling using enantioenriched alkyl boron nucleophiles.

The parameterization of phosphine ligands has also been applied for the synthesis of benzylic ether derivatives by Ni-catalyzed Suzuki-Miyaura cross-coupling reactions. In this work, Doyle and Wu observed a clear dependence between the yield of the reaction and the steric size of the phosphine ligand.^[20] However, they revealed that presumably interchangeable descriptors for steric parameters, such as the cone angle (θ) and the buried volume (% V_{bur}), are not correlated. The cone angle, represents a virtual cone that encloses all the substituents on the phosphorous atom. This means the remote sterics at the distance from the metal center. In contrast, the buried volume only evaluates the proximal steric effect. The analysis of 17 bulky phosphine ligands established a positive direct correlation with the cone angle (θ) and an inverse one with the buried volume (% V_{bur}), establishing that the effectiveness of ligands relies on their remote steric hindrance (Scheme 14). A multivariate linear regression, combining both parameters, offered an excellent quantitative model for predicting ligand reactivity in Ni-catalyzed Suzuki-Miyaura couplings of benzylic acetals.

Scheme 14. (a) Ni-catalyzed Suzuki-Miyaura cross-coupling. (b) Crucial parameters according to the MLR model.

2.2.2 Analyzing TM-catalyzed C–H activation by using statistical analysis

Multivariate linear regressions (MLR) have been also applied for the rational design of TM-catalyzed C–H functionalization reactions. In 2017, Paton and Rovis demonstrated how subtle modifications in cyclopentadienyl (Cp^x) ligand structures can impact the reaction rate and/or the selectivity of Rh^{III}-catalyzed annulation reactions of 1-decene (Scheme 15a) or cyclopropene (Scheme 15b) with a benzohydroxamic acid derivative.^[21] They evaluated different electronic (IR stretching frequencies, NMR data, redox potential, charges) and steric (Tolman cone angles and Sterimol values) parameters of 22 different Cp^xRh^{III} complexes to develop a quantitative predictive model that could describe the performance of these catalysts.

Scheme 15. Selected Cp^xRh^{III}-catalyzed reactions to study the regioselectivity and stereoselectivity through MLRs.

They found that, in the case of 1-decene, the predictive model for the regioselectivity was composed by three electronic descriptors (³¹P chemical shift, antisymmetric CO stretching frequency and ¹⁰³Rh shielding tensor) and three steric parameters (Sterimol value, L, and Bondi cone angles). Regarding the selected cyclopropene as model substrate, the linear regression model that correlates the observed diastereoselectivity and the structure of the Cp^xRh^{III} complexes involved three electronic parameters (³¹P chemical shift, NBO charges at rhodium center and Rh^{III/II} redox potential) and a single steric descriptor (the minimum Bondi cone angle).

More recently, Rovis et al. performed a multivariate analysis to control the diastereoselectivity of Rh^{III}-catalyzed cyclopropanation of alkenes with N-enoxypthalimides.^[22] Using ethyl acrylate as coupling partner, they first evaluated the influence of 15 Cp^x-ligated Rh^{III} complexes and 8 N-enoxypthalimide derivatives in the diastereoselectivity of a model cyclopropanation reaction (Scheme 16a). While the *trans*-cyclopropane diastereomer was generally favored, sterically demanding Cp^x ligands and electron-deficient phthalimide combinations showed the highest *cis*-selectivities. When using NaOAc as base, a multivariate correlation of 96 catalyst/substrate pairs showed the existence of

two parallel mechanistic regimes, involving the formation of intermediate A or B (Scheme 16b). When using electron-rich phthalimides and small Cp^x ligands, the formation of the *trans*-product is favored via intermediate A. For more sterically-demanding Cp^x ligands, electron-deficient phthalimides and/or more strong Lewis acids, *cis*-product is favored. Based on this information, the authors developed a *cis*-cyclopropanation protocol using a wide range of enoxyphthalimide derivatives and alkenes, where the phthalimide ring-opening was presumably the rate-determining step (through Intermediate B).

Scheme 16. Rh^{III} -catalyzed cyclopropanation of alkenes with N-enoxyphthalimides.

Chang and co-workers have also used this physical organic approach for the rational design of regioselective $\text{Cp}^*\text{Ir}^{\text{III}}$ -catalyzed amidation of indoles using azides as coupling partners.^[23] They were able to selectively switch the C–H bond cleavage from the C7 to C2 position of N-acylindole derivatives by gaining insights of the effect of stereoelectronic properties of the substrate and the catalyst over the reaction outcome. Initially, the authors combined experimental and computational studies to evaluate the possible parameters that could affect the selectivity of the C–H metalation step. They observed that the C2-product formation is highly dependent on the size of the N-acyl group, increasing its ratio when reducing the size of the directing group. Moreover, they identified high selectivity towards the C2 functionalization when using silver trifluoroacetate in lieu of more basic carboxylates such as silver pivalate. With this information in hand, they evaluated the effect of different parameters of the substrate/carboxylate in the reaction outcome. First, the evaluation of different electronic (NBO charges of oxygens and CO stretching frequencies) and steric (Sterimol values) descriptors of 23 carboxylic acid surrogates, showed that a univariate model using $\text{NBO}_{\text{O-avg}}$ as parameter reproduces the experimental results. Then, they evaluated the effect of the size

of the N-acyl group (R^1 , Scheme 17) along with the nature of the carboxylate additive in the reaction outcome. Interestingly, they provided a predictive multivariate linear model which displays exclusively dependence on the aforementioned $\text{NBO}_{\text{O-avg}}$ parameter and the Sterimol B_1 value of the N-directing group. The authors carried out further experimental mechanistic investigations and confirmed the selective C2–H activation by the synthesis and characterization of the corresponding cyclometalated $\text{Cp}^*\text{Ir}^{\text{III}}$ species. They applied this mechanistic-driven approach, not only for developing a versatile and C2-selective C–H amidation protocol but also for inverting the selectivity of a previously described C7 alkenylation reaction.

Scheme 17. Regioselective $\text{Cp}^*\text{Ir}^{\text{III}}$ -catalyzed amidation of indoles

3. Experimental tools for rational design

Mechanistic experimental information has been historically used as a posteriori tool to understand how reactions work. However, recently, the isolation of putative intermediates in the catalytic cycle has been employed for boosting the rational design and development of new protocols. In this section, we have selected relevant examples in which the isolation of the key reaction intermediates and their use as “knowledge building blocks” has provided a hallmark in the improvement of the different methodologies.

3.1 Cross-coupling reactions

As mentioned in the introduction, the formation of C–C bonds using TM-catalyzed reactions is one of the most remarkable transformations in organic chemistry and it has received special attention since the second half of the 20th century.^[4] We highlight the potential of KBBs in two different reactivities: (i) palladium-catalyzed perfluoromethylation reactions using silver nucleophiles as transmetalating reagents and (ii) nickel-catalyzed Suzuki–Miyaura coupling.

3.1.1 Perfluoromethylation reactions mediated by Palladium and Silver Bimetallic Systems

Perfluoroalkyl groups such as CF_2H or CF_3 are privileged structural motifs due to their unique capability to modify the physical, chemical and biological properties of organic molecules. In this context, Pd/Ag bimetallic systems have demonstrated their ability to introduce these groups into organic scaffolds.^[24] The key step in these processes is the transmetalation between well-defined silver derivatives to oxidative addition palladium complexes. In this regard, in 2014 and later in 2017, Shen et al. accessed putative reactive intermediates to provide fundamental understanding of the pivotal steps of the mechanistic proposal shown in Scheme 18a to enable the rational design of efficient catalytic protocols. In their pioneering work, the authors initially investigated the reductive elimination step from $\text{L}_n\text{Pd}(\text{Ar})(\text{CF}_2\text{H})$. Remarkably, these complexes afforded the desired product in high yields in the presence of one equivalent of the ligand. Next, the authors investigated the viability of the transmetalation step, from $(\text{dppf})\text{Pd}(\text{Ph})\text{I}$ or $(\text{Xantphos})\text{Pd}(\text{Pyr})\text{Br}$, using a well-defined difluoromethyl silver complex, $\text{SiPrAg}(\text{CF}_2\text{H})$, stable enough to promote the CF_2H transference prior to its decomposition. In both cases the corresponding difluoromethylated products (palladium complexes or directly the organic molecules due to the fast reductive elimination) were obtained in quantitative yields. With this fundamental knowledge in hand, the authors developed a catalytic difluoromethylation protocol of aryl halides (using catalytic amounts of silver) while in the case of the heteroaryl halides a fine tuning of the ligand (DPePhos instead of XantPhos) was needed to obtain high yields of the corresponding organic products (Scheme 18b).^[25]

Scheme 18. (a) Proposed Pd/Ag synergistic cooperation in C– CF_2H bond-forming reactions. (b) Pd/Ag protocols.

Recently, in 2018, our group studied the reactivity of well-defined silver trifluoromethyl complexes in Pd-catalyzed trifluoromethylation reactions.^[8] From a long time, it had been

considered that the reductive elimination step is the only problem associated with these processes.^[8] However, in 2006, Grushin et al. reported that, when using Xantphos as ligand, a slow transmetalation reaction could promote undesired competitive reactions such as: mismatched transmetalations between aryl-palladium(II) complexes and/or ligand displacement by commercially available CF_3 nucleophiles (Scheme 19a).^[8a] For this reason, we decided to study the transmetalation step independently to overcome the aforementioned challenges. Initially, we used a model system to compare the reactivity as CF_3 shuttles of the well-defined silver (I) complexes with commercially available nucleophilic CF_3 sources. Notably, all these synthesized silver complexes, including a unique silver(I) ate-type complex, $(\text{Cs})[\text{Ag}(\text{CF}_3)_2]$, outperformed the widely used sources (Scheme 19b). These results were translated to a productive system, using Xantphos as ligand. Strikingly, the transmetalation reaction of $(\text{Xantphos})\text{Pd}(\text{Ph})\text{I}$ and $(\text{Cs})[\text{Ag}(\text{CF}_3)_2]$ afforded selectively $(\text{Xantphos})\text{Pd}(\text{Ph})(\text{CF}_3)$ in one pot in less than 10 min. This result was crucial to the thoughtful model of the one-pot formation of PhCF_3 using PhI as the starting material, under stoichiometric and catalytic conditions (Scheme 19c). This work is a proof-of-concept of the crucial role of the nucleophile in the success or failure of the coupling process.

Scheme 19. (a) Challenges in Pd-catalyzed trifluoromethylation reactions. (b) Model system. (c) Synthesis of PhCF_3 under stoichiometric and catalytic conditions.

3.1.2 Nickel-catalyzed decarbonylative Suzuki-Miyaura coupling of acyl fluorides and aryl boronic acids

As mentioned in Section 2.2.1., the Suzuki-Miyaura reaction is a powerful methodology for the formation of C–C bonds.^[15] A general feature in the Suzuki catalytic cycle is the use of an exogenous base to form a “transmetalation active species” that facilitates the transmetalation of the boronic acid. However, the presence of a base can promote undesired reactions that decomposes the organoboron nucleophile. In this regard, Sanford and co-workers envisioned the use of a combination of a nickel catalyst, a ligand and acid fluoride electrophile to generate a “transmetalation” active species that would react with the boronic acid in the absence of base (Scheme 20a)^[26] Initially, the authors evaluated the efficiency of each step involved in the catalytic cycle (Scheme 20b). Firstly, the oxidative addition and decarbonylation were investigated by performing the stoichiometric reaction of Ni(cod)₂, PCy₃ and benzoyl fluoride at room temperature. The benzoyl nickel fluoride complex was formed immediately, and subsequent decarbonylation gave rise the phenyl nickel fluoride species. The later, namely as “transmetalation active species” reacted with different boronic acids, including ones that undergo facile decomposition pathways, affording the biaryl products in high yields. This last experiment demonstrated the feasibility of the transmetalation and reductive elimination step within the catalytic cycle. When the authors tried the translation to catalytic conditions, they observed the formation of aryl ketone as by-product by the attack of the boronic acid directly to the acid fluoride. Fine tuning of the ligand (PPh₂Me instead of PCy₃) avoid this undesired competitive pathway. Further developments of this new methodology permitted the use of carboxylic acids as starting materials that are converted in the corresponding acyl fluorides using a fluoride source (TFFH) and a proton sponge.

(a) Strategies for Suzuki-Miyaura reaction

(b) Proposed catalytic cycle for base-free Ni-catalyzed decarbonylative Suzuki-Miyaura reaction

(c) Methodology

Scheme 20. (a) State-of-the-art of TM-catalyzed Suzuki-Miyaura cross-couplings. (b) Mechanistic proposal for base-free Ni-catalyzed reactions. (c) Synthetic protocol.

3.2 Knowledge-driven approach in TM-catalyzed C–H activation processes

The activation of typically inert C–H bonds to construct more complex scaffolds is one of the “holy grails” of modern synthetic chemistry and has received special attention since the second half of the 20th century.^[5a-b] In this context, ligand-directed transition metal-catalyzed transformations has emerged as a very powerful strategy since they offer the advantage of allowing the control site-selectivity in molecules that contain multitude of C–H bonds.^[5c-k]

3.2.1 Surpassing challenging elemental steps in Iridium-catalyzed C–H activation by an induced reductive elimination

In 2018, Chang and co-workers reported a very elegant example of the utilization of fundamental knowledge for enabling new reactivity patterns in Cp*Ir^{III}-catalyzed C–H functionalization reactions (Scheme 21a).^[27] In this work, they tackled a major challenge related to the development of efficient TM-catalyzed transformations: the high stability of some resulting reaction intermediates that can preclude the formation of the desired product. In their attempt to develop a Cp*Ir^{III}-catalyzed C–H arylation protocol using arylsilanes as coupling partners, the authors identified the reductive elimination step as the bottleneck of the process when involving traditional Ir^{III} catalytic cycles. In order to overcome this limitation, they proposed to modulate the electronics of the post-transmetalation Cp*Ir^{III} intermediate, by a selective oxidation, facilitating the challenging C–C bond-forming reaction from a high-valent Ir^{IV} or Ir^V species (Scheme 21b).

(a) Model reaction

(b) Mechanistic proposal

Scheme 21. Overview of the Cp*Ir^{III}-catalyzed C–H arylation.

For validating their working hypothesis, they used as platform well-defined $\text{Cp}^*\text{Ir}^{\text{III}}$ metallacycles, analogous to previously described reactive intermediates in iridium catalysis.^[28] As expected, the authors did not observe the corresponding C–C coupling from a post-transmetalation $\text{Cp}^*\text{Ir}^{\text{III}}$ complex **4_{Ir}-Ar**, confirming its high stability (Scheme 22a). Gratifyingly, they were able to oxidatively induce the reductive elimination event in the presence of different silver oxidants, and develop a catalytic version under similar reaction conditions. These preliminary results strongly supported, not only that the reductive elimination is the rate determining step, but also the accessibility of carbon–carbon bond-forming reductive elimination reaction from high-valent iridium intermediates. This experimental information agreed with DFT calculations, that showed a facile product formation from highly oxidized Ir^{IV} or Ir^{V} intermediates. Moreover, electrochemical studies confirmed the potential access to these high-valent iridium species using cyclic voltammetry (CV) (Scheme 22b). Stoichiometric experiments with different oxidants such as AgOTFA or acetylferrocenium tetrafluoroborate (AcFcBF_4), along with EPR spectroscopy measurements suggested that instead of a $\text{Ir}^{\text{III/IV}}$ pathway, a $\text{Ir}^{\text{IV/IV}}$ route is operative. Finally, the authors were able to develop an innovative $\text{Cp}^*\text{Ir}^{\text{III}}$ -catalyzed directed C–H arylation protocol using arylsilanes as nucleophilic coupling partners, based on fundamental mechanistic understanding (Scheme 22). This tailored reaction presented a wide substrate scope and a good group tolerance under mild reaction conditions.

Scheme 22. (a) Mechanistic investigation on oxidative induced C–C bond-forming reactions from a well-defined $\text{Cp}^*\text{Ir}^{\text{III}}$ metallacycle. (b) Catalytic protocol.

Inspired by these results, Chang and co-workers have extended their knowledge-driven approach to the development of TM-catalyzed C–H arylation reactions using arylboronic esters as transmetalating agents. In this work, apart from iridium systems, they also explored the potential of oxidative induced reductive elimination pathways from well-defined Rh and Ru complexes, in order to promote carbon–carbon bond-forming reactions.^[29]

3.2.2 Ruthenium-catalyzed C–H late-stage functionalization

The employment of knowledge-driven approaches for the synthesis of complex organic scaffolds represents one of its most promising applications. In 2018, Larrosa and co-workers described the rational design of a new family of ruthenium catalysts capable of promoting the late-stage C–H arylation of highly decorated N-chelating molecules, including pharmaceuticals, agrochemicals or natural products, with aryl(pseudo)halides.^[30] In this work, the authors demonstrated how fundamental mechanistic understanding can play a crucial role in the development of more efficient transformations. A thorough mechanistic investigation of the previously proposed $\text{Ru}^{\text{IV/IV}}$ catalytic cycle^[31] allowed them to uncover key unprecedented mechanistic features: (i) the *p*-cymene type-ligands, (e.g. **1_{Ru}-MeCN**, Scheme 23) widely used in these Ru-catalyzed transformations,^[32] inhibited the directed arylation reaction (ii) the employment of a *p*-cymene free ruthenacycle **2_{Ru}-MeCN** afforded a faster product formation;^[30,33] and (iii) they identified the formation of a bis-cycloruthenated Ru^{II} intermediate **3_{Ru}-MeCN**, prior to the oxidative addition step, revealing that a second C–H activation step occurs before accessing the high-valent Ru^{IV} (Scheme 23). Based on their experimental results, the authors proposed a new mechanistic hypothesis, involving a bis-cycloruthenated intermediate, as an alternative to the widely accepted catalytic cycle (Scheme 24).

(a) Literature precedents on Ru^{II}-catalyzed directed C–H arylation

(b) Stoichiometric experiments

Scheme 23. Precedents and mechanistic investigations of the ruthenium-mediated C–H arylation.

Scheme 24. Proposed catalytic cycles for the Ru^{II}-catalyzed C–H arylation.

With this information in hand, the authors investigated the catalytic activity of different ruthenium complexes. As expected, Ru catalysts containing *p*-cymene as ligand, like **1_{Ru}-MeCN** were inactive. When using **2_{Ru}-MeCN** as pre-catalyst, the authors observed an excellent combined yield of the mono and diarylated products, but unfortunately they also detected an undesired

“catalyst arylation” degradation derived from a mismatched coupling with the 2-phenylpyridine (2ppy) scaffold of the ruthenium pre-catalyst. In order to block this unproductive pathway, the authors tailored a new pre-catalyst, modifying the directing group, in order to differentiate the scaffold on the ruthenium and the targeted substrates. The *N,N*-dimethylbenzylamine-containing cycloruthenated complex **4_{Ru}-MeCN** showed an exquisite selectivity, giving rise exclusively the bis-arylated product in excellent yield (Scheme 25).

Scheme 25. Summary of the rational evolution of ruthenium-based catalysts.

Finally, they decided to explore the synthetic utility of this engineered ruthenium pre-catalyst in the late-stage functionalization of relevant drugs. They rationally designed a robust protocol for the C–H arylation of ligand-directed substrates with aryl(pseudo)halides, compatible with a wide range of functional groups that are prevalent in medicinal chemistry. The authors showed the potential of this methodology testing relevant molecules for drug discovery such as atazanavir (HIV treatment), diazepam (anxiolytic), sulfaphenazole (antibacterial) or bromantane (anxiolytic) derivatives. As a final proof-of-concept, they demonstrated the capability of their tailored ruthenium catalysts to couple organic drugs between them, as shown in Scheme 26.

Scheme 26. Overview of the capability of 4Ru-MeCN in different late-stage functionalizations.

3.2.3 Development of more efficient Cp^*Co -catalyzed C–H functionalization reactions based on knowledge-driven approaches

As shown above, the rational design of innovative transition metal-catalyzed transformations based on fundamental knowledge represents one of the most powerful strategies for the development of sustainable organic transformations. However, this approach can be completely prevented in emerging fields, such as cobalt catalysis, by the dramatic lack of mechanistic understanding.

Over the past few years, the employment of $\text{Cp}^*\text{Co}^{\text{III}}$ complexes, analogous to active Rh^{III} catalysts for C–H activation, has represented a tremendous advance in cobalt catalysis.^[34] When compared to noble metals, cobalt catalysts offer obvious advantages, including being earth-abundant and cheaper. Despite the significant growth in this field, these cobalt systems are still at their infancy when compared to Rh- and Pd-based catalysts, especially due to the limited fundamental organometallic understanding of these systems. The investigation of the underlying reaction mechanisms of $\text{Cp}^*\text{Co}^{\text{III}}$ -catalyzed C–H functionalization reactions has been hampered by the difficulty of trapping high reactive transient cobalt intermediates due to the proposed reversible nature of the C–H metalation step (Scheme 27).^[34]

Scheme 27. $\text{Cp}^*\text{Co}^{\text{III}}$ -catalyzed C–H activation reactions.

Intrigued by the lack of fundamental understanding, our group became interested in bringing light into the mechanistic “black box” of Cp^*Co -catalyzed directed C–H functionalizations in order to enable more sustainable transformations. As mentioned above, our knowledge-driven approach is based on trapping previously elusive highly reactive cobalt species and using them as “knowledge building blocks” (KBBs) for rational design. Considering the proposed reversible nature of the C–H activation step by $\text{Cp}^*\text{Co}^{\text{III}}$ complexes, our first challenge was to design a synthetic route for accessing catalytically relevant cobaltacycle complexes.

Using MeCN as stabilizing ligand, we were able to synthesize a direct analogue of one of the most widely invoked intermediates in $\text{Cp}^*\text{Co}^{\text{III}}$ -catalyzed C–H functionalization reactions, 1Co-MeCN , via a ligand-assisted oxidative addition followed by a halide abstraction.^[35a] We used this cyclometalated cobalt(III) complex to provide an unprecedented comprehensive picture on the most explored $\text{Cp}^*\text{Co}^{\text{III}}$ -catalyzed transformation, the oxidative alkyne annulation, including the first direct observation and full characterization of a cobalt resting state under catalytic conditions (Scheme 28). Our work revealed the higher catalytic activity of 1Co-MeCN compared to the widely used $[\text{Cp}^*\text{CoI}_2(\text{CO})]$ pre-catalyst; providing one of the lowest cobalt catalyst loading (1 mol%) reported to that date for this type of reactions in a short reaction time of 2 hours.

Scheme 28. (a) Synthesis and characterization of a previously elusive key cationic cobaltacycle via a ligand-assisted oxidative addition step. (b) Catalytic activity in a model oxidative alkyne annulation.

Inspired by these results, we took advantage of the unique stabilizing capability of MeCN to overcome the reversible nature of the C–H activation step and access two of the most widely invoked cationic cobaltacycles or KBBs which have been proposed in the literature as reactive intermediates after the C–H metalation step.

Moreover, we unveiled the dramatic accelerating effect of the perfluorinated alcohol 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) in the C–H metalation step.^[35b] Indeed, the beneficial impact of HFIP was not only limited to this elementary step. Our stoichiometric and catalytic studies revealed that the presence of HFIP also enhances the efficiency of two divergent reactivities, the hydroarylation of alkynes and oxidative alkyne annulation using as benchmark the reaction between diphenylacetylene and N-pyrimidinylindole (Scheme 29). These examples demonstrated the crucial role that mechanistic understanding can play for designing more efficient processes.

Scheme 29. (a) Synthetic route for key cationic cobaltacycles via C–H activation. (b) Beneficial effects of HFIP as additive under catalytic conditions.

4. Conclusions and Prospects

In summary, in this minireview we have covered examples that illustrate the potential of knowledge-driven approaches for the sustainable development of transition metal-catalyzed transformations. We anticipate that the selected computational and experimental strategies, including their synergistic cooperation, will pave the way for the employment of mechanistic investigations as reaction design resource. In this context, we envision that the next revolution in sustainable synthetic chemistry will be based on getting a deeper fundamental understanding of processes based on earth-abundant first-row metals or applying these knowledge-driven approaches for the rational design of innovative photoredox or electrochemical transition metal-catalyzed reactions. Moreover, the exploration of more statistical analysis methods such as Principal Component Analysis (PCA),^[36] can be crucial for enabling the sustainable development of efficient transformations. We encourage the scientific community to merge theoretical and experimental approaches, along with organic and organometallic understanding, to advance beyond the frontiers of knowledge and improve the catalytic performance of processes involving easily accessible raw materials as starting reagents.

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Entry for the Table of Contents (Please choose one layout)

Layout 1:

MINIREVIEW

The rational design of innovative and efficient chemical transformations based on fundamental knowledge constitutes one of the most promising sustainable strategies for the synthesis of organic scaffolds. Herein, we show the potential of theoretical and/or experimental knowledge-driven approaches for the sustainable development of transition metal-catalyzed transformations.

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