

Guideline for Elucidating Catalysts

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Abstract: In the last decades, numerous efforts have been made to replace metal catalysts with cheaper and earth-abundant alternatives or the complete exclusion of metals in cross-coupling reactions, maintaining high efficiency of the target transformation. However, follow-up studies often revealed the role of metal impurities in the catalytic process. Thus, active metal impurities lead to mechanistic misinterpretations, could initiate erroneous research directives, and can lead to severe reproducibility problems. Milestone precedents of impurity effect in cross-coupling reactions are well documented in the literature. Interestingly, this fallacy has occurred repeatedly over the years due to the lack of thorough mechanistic studies and the appropriate research study scheme for identifying the impurity effect. Herein, we propose a guideline elucidating the real catalyst of future catalytic transformations that could eliminate mechanistic misinterpretation and help exclude the role of impurities in novel catalytic processes. Although this guideline mainly focuses on problems related to trace transition metals, it also offers the base for more general catalyst research.

Noble metal catalysts are so efficient and versatile that they shape our perceptions when we think about catalysis. However, they also have drawbacks, such as their price and environmental impact, and, in some cases, health effects. There is a tremendous amount of research aimed at minimizing the presence of these noble metals by optimizing reaction conditions and ligands or replacing them with more abundant metals or organic materials. In these latter two research directions, a critical issue must be considered in order to establish the proper mechanistic picture and develop robust and reproducible catalytic transformations: the impurity effect.

The impurity effect plays a double role in research. In some cases, when it is discovered and managed at an early stage of research, it leads to highly beneficial discoveries, such as an efficient industrial catalyst for polymerization,¹ or to more reliable catalysis by eliminating an inhibiting trace impurity.² However, when the focus of development is to replace a metal catalyst of a known transformation with another metal or even an organocatalyst, the potential participation of the original metal in the novel procedure as a trace contaminant should be considered for reproducibility and mechanistic interpretations.

In many cases, a significant reduction or replacement of a known catalyst by another metal or the complete omission can result in substantial economic and sustainability benefits.³ On the other hand, realizing alternative and improved methods is sometimes a really challenging task, and the greater the deviation from the original method, the more important it is to demonstrate experimental and computational mechanistic proof of the new concept.

I. Catalyst reduction, replacement and omission

Reducing catalyst loading is the easiest to achieve, considering reproducibility and robustness. In this regard, there are many palladium-catalyzed methods that were efficiently

performed with “homeopathic”⁴ ppb-ppm⁵ level of palladium loading,⁶ including the utilization of well-characterized palladium complexes⁷⁻⁹ and nano-particles with different sizes.¹⁰⁻¹⁴ In this case, one can assume the same mechanistic pathways are relevant in the reaction.

Depending on the reaction type, replacing a known transition metal catalyst with an alternative one is a more challenging task. In this situation, it should be proved that a metal can be replaced with another nonconventional one, defining its exact role in the catalytic cycle. Delightfully, there are examples where relatively cheap and sustainable nickel,^{13, 15-20} and copper,²¹⁻²⁵ are able to act as a catalyst in cross-coupling reactions in a broad spectrum, replacing more expensive metals.

However, in certain cases, the impurity of the applied catalyst and additives participate in the reactions. A representative and edifying example of this effect is the attempted replacement of copper with iron in C-heteroatom bond-forming coupling reactions.²⁶⁻²⁸ Shortly after the disclosure of some “iron-catalyzed” -couplings, Bolm and Buchwald revealed that ppm level copper impurity was responsible for the transformation, and ultra-pure iron salts did not catalyze the reaction (Fig. 1a).²⁹ The beneficial conclusion of these studies is that the couplings can be achieved with ppm level of copper catalysts.³⁰

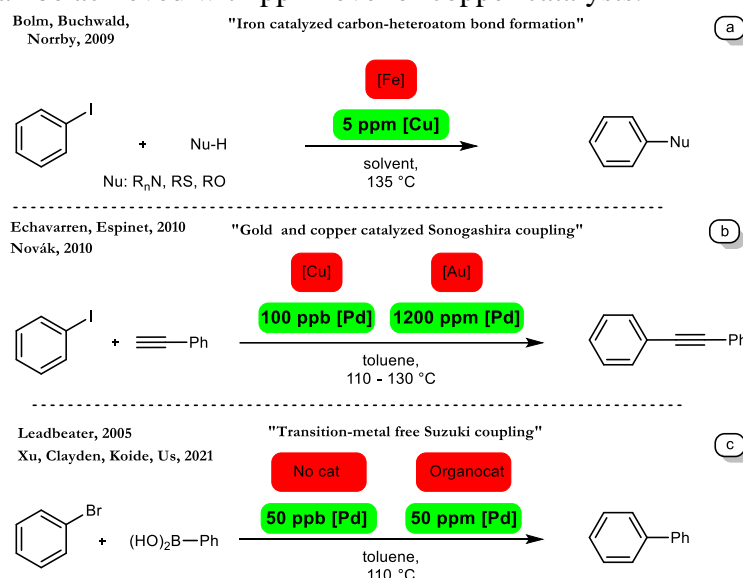


Figure 1. Contamination catalysis in the literature

Similarly, copper³¹⁻³² and gold³³ catalyzed Sonogashira coupling of terminal alkynes and aryl halides are well-documented in the literature. However, in both cases, ppm/ppb level of palladium impurities³⁴ was proved as the actual catalyst (Fig. 1b).³⁵⁻³⁶

The impurities could be present in the catalyst, in the base, or even in the solvent. Special care should be taken to exclude ppb-ppm level cross-contamination, especially in the labs where palladium is present in any form. In our previous study,³⁶ we showed, in the case of the Sonogashira reaction, that the stir bar previously used in the Pd-catalyzed reaction could transfer enough palladium into another reaction to reach complete conversion, even after cleaning (not with aqua regia). The stir bar problem as a technical contamination source was deeply studied by Janiak³⁷ and Ananikov³⁸ and co-workers, who made solid scientific statements on the role of metal impurities transported by this common laboratory accessory.

The potentially most rewarding but synthetically most challenging is the complete omission of noble metals. This approach was also attempted earlier in cross-coupling reactions,³⁹ but after the first examples of the Pd-free Suzuki reaction, Leadbeater and co-workers reassessed their previous results (Fig. 1c) and demonstrated that even ppb level of palladium is able to catalyze the reaction under optimal conditions.⁴⁰ These findings reverse

the problem to benefit: a hyperactive catalytic system and useful method were discovered for the C-C bond formation with the utilization of a minute amount of palladium catalyst. Due to the possible benefits, these kinds of catalytic developments are still in focus; hence, researchers are experiencing the same problems, challenges, and difficulties. Recently, Yu, Xu, and co-workers developed an amine-catalyzed Suzuki-Miyaura-type coupling reaction (Fig. 1d).⁴¹ In their work, it was demonstrated that specially functionalized aniline derivatives could be a catalyst for this reaction. Considering the importance of these findings, the catalysis community was interested in using this new catalyst type, leading to synthetic applications.⁴² Unfortunately, the palladium contamination that occurred during the preparation of the catalyst was exceptionally stable and difficult to remove using many techniques. These results have invalidated even some published results, resulting in later retractions.⁴³⁻⁴⁴

The examples above demonstrate that it is of utmost importance to identify contamination effects in catalysis. This is the most crucial and difficult task, and a healthy suspicion should always be maintained. With that said, there are warning signs that we have to examine. Below, we provide the most common indications that should always be inspected experimentally and computationally to identify potential cases of “contamination catalysis”.

II. The signs of possible contamination effect:

It is important to know when to consider scrutinizing the role of the catalyst. Based on earlier examples, the below phenomenon can be a sign of contamination catalysis.

I. The same reaction exists with another catalyst.

There is a very similar transformation with similar conditions.

II. The reaction has the same scope profile as a literature precedence.

While investigating the scope, it might be recognized that there is a correlation for the same pairs of reactions (e.g. electron donating-electron withdrawing).

III. High temperature is needed for the transformation.

It seems to be a common aspect that, to utilize trace amounts of catalyst, considerably higher than similar transformations.

IV. There are particular batches of starting materials that outperform others, or instances where the reaction proceeds much faster than usual.

This can be a sign of a non-intentionally added catalyst. One source can be an additive that was added in higher equivalent, including the solvent. Other sources might come from the equipment, especially from the stir bar.

V. The impurity profile of reaction mixtures contains the same compounds as another reaction with another catalyst.

The same side reactions can be a sign of the same unintentional catalyst.

VI. There is an unusually high barrier according to the theoretical calculation.

The computed barriers are not consistent with the experimentally observed reaction rates at the utilized temperatures.

VII. The computationally predicted activity of substrates does not match the experimental ones.

Current computational methods are providing robust predictions in terms of the relative trends of activities. Large deviations in trends should not be expected when the correct mechanism is considered.

If all the above-mentioned points are negative, one might proceed with the presumption that contamination is not relevant in the given reaction. However, if suspicion is raised, there is a three-step procedure that can effectively minimize the risk of falling in misinterpretation

due to contamination catalysis. First, it is required to establish a laboratory setup and starting materials that systematically minimize all potential sources of contamination. We provide a detailed description of suitable laboratory practices in the section "Contamination minimization".

Having the usual synthetic setup and minimally contaminated catalytic system in hand, their overall contamination levels have to be estimated via analytical procedures. We have collected step-by-step instructions to be followed in order to obtain reliable results in the section "Analytical procedures".

Having access to the reaction setups and the corresponding contamination levels, one can study the effect of the contamination on the reaction and its mechanism both experimentally and computationally. To this end, we have gathered the directly implementable suggestions in the section "Systematic mechanistic examinations" to guide readers in this regard.

The above-described three-step procedure can be of help for future methodology development, as well as a reference for future doubtful referees and editors.

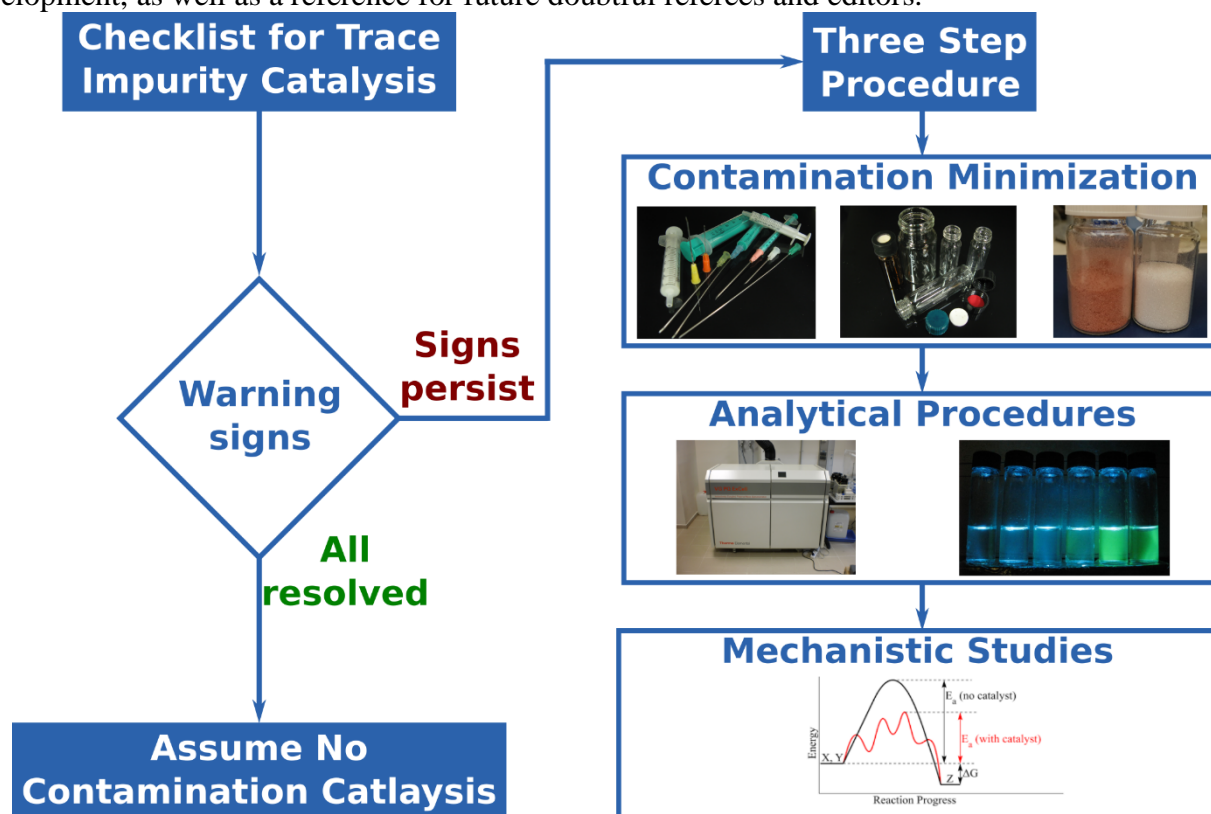


Figure 2. Methods and guideline for elucidating catalyst

III. Contamination minimization

III.1 General

A common main problem is equipment and general laboratory purity. Laboratories, where transition metals were extensively used, can be a possible source of contamination and should be avoided. Even more so, the glove box is usually a concentrated storage and utilization space of extremely active catalysts of various types; therefore, it should be avoided or, if not possible, treated with the utmost suspicion.

Residual trace metal impurities on reaction vessels, vacuum lines, and glove boxes can originate from previous reactions and even tap water.⁴⁵⁻⁴⁷ Therefore, we generally advise new glassware, especially stir bars, but equipment can be washed in some cases. Glassware should be fully submerged in freshly prepared *Aqua Regia* overnight. After, it should be rinsed with distilled water and submerged in distilled water for 30 minutes. After rinsing with distilled water, drying in a clean oven is recommended.⁴⁸ Polyethylene vessels can be purified by nitric acid.⁴⁹ In the case of a vacuum line, we advise for a throughout cleaning by the method above and using brand new tubes and connectors. As for the spatulas and spoons, marking and separating those for each material for each purity level or using single-use new plastic ones is a good practice.

With pure equipment in hand, we must ensure that the main components (by weight) are as pure as possible. These are usually the solvent(s), the additives/bases, and the starting materials. The solvent(s) should be adequately distilled, or at least known high purity should be utilized.

In general, different metals come hand-in-hand together during the production process of inorganic chemicals, and simple metal salts with acceptable purity for organic chemistry (>95%) are not appropriate for catalytic studies. Any possible contamination should be minimized for these critical reaction components, and the metal source should be in the highest purity available (>99.99%). Here, it should be stated that a material with a purity of 99.999% still has 10 $\mu\text{g/g}$ impurity. Depending on the reaction setup, this alone can result in 10 ppm of unknown catalyst added, which can divert the reaction route in many cases. Utilization of w/w % as a sign of purity can be misleading, as materials with high molecular weight can contain significantly larger amounts of impurity. For example, cesium carbonate is very useful due to its relatively good solubility in organic solvents. Still, it has more than three times more impurity than its sodium counterpart with the same w/w %.

Even with the effort made on equipment and material purity, contamination can not be ruled out, and it is not enough to compare the new conditions to some existing protocols. A blank reaction without the catalyst candidate should be examined to exclude that the reaction proceeds without the intended catalyst (background reaction/catalyst).

Especially for such challenging reactions, reproducibility should be ensured.⁵⁰⁻⁵¹ First, batch-to-batch reproducibility should be ensured (a new batch of starting materials for catalyst, substrates, and solvent from different suppliers). Subsequently, robustness should be confirmed in as independent circumstances as possible, preferably in an independent research group. Optimally, the results should be replicated from the least synthetically advanced locally sourced starting materials in another laboratory.

Unfortunately, “contamination catalysis” can not be excluded even in this scenario.

III.2 Purity of surrogate metal catalyst

In the case of a surrogate metal catalyst, in-process purifications can be difficult due to the chemical similarities between the two metals. These metals can co-occur in nature and might even be extracted from the same ore. This might be even worse when the occurrence of a similar metal is not high enough for the metal manufacturer to extract it, and then it stays there as an impurity.

There are several possibilities and reasons for unexpected metals to be present in our reaction mixtures. For example, most platinum group metals come from nickel mining. These metals are extracted together, and the first steps in order of purification to obtain platinum metals are to remove nickel and then copper. Then, by mostly solution refining, silver, gold, palladium ruthenium, osmium, platinum, iridium, and rhodium are separated in this order.⁵² In this sense, we can legitimately expect cross-contamination among these metals. Platinum and

palladium metals are part of our everyday life through automotive catalysts, and concentrations might exceed 100 $\mu\text{g}/\text{kg}$ in road dust on some busy roads.⁵³ Even potatoes can contain $\mu\text{g}/\text{kg}$ quantities of Pt and ng/kg quantities of Rhodium.⁵⁴ Similarly to the co-extracted platinum metals, cobalt is also extracted from copper and nickel ore.⁵⁵

High-purity gold might contain Pd, Fe, Cu, and Ag in the 10 $\mu\text{g}/\text{g}$ range. The exact amount is highly variable due to macroscopic inhomogeneities resulting from different melting points.⁵⁶⁻⁵⁷ Other pure metals (Hg, Ga, In, Sn, Zn, Al, Ag, Au, Cu) used as melting standards for temperature scales can contain several impurities.⁵⁸ Iron can contain copper,²⁹ lead and zinc,⁵⁹ calcium aluminum, and manganese.⁶⁰ 98+% lithium carbonate might contain, over the expected alkali and alkali-earth metals, copper, iron, and nickel as well, at hundreds of mg/kg .⁶¹

III.3 Purity of organocatalyst

Achieving a good organocatalyst is highly beneficial for many applications, especially in industrial (pharmaceutical) setups. However, in the preparation of organocatalysts, it is extremely important to avoid the usage of any transition metal catalysts, especially the ones that could be applied as a catalyst in the target reaction. Furthermore, the source of chemicals should be carefully selected, as in most cases, traces of metals are carried forward through several steps in a multi-step synthesis. Once synthesized, purification of the catalyst candidate is an instrumental but challenging task.

Chromatographic techniques are a well-known and useful method for the purification of organic chemicals. On the other hand, on its own, it is not recommended as the exclusively applied method for purification. In this case, where a very minor component might be present, there is a high risk for co-elution, as interactions with the desired organic compound can hinder the separation process.

Contrary to chromatography, careful recrystallization(s), where medium-size crystals are formed, is an adequate technique to reach purity. Distillation and sublimation might also work, but they are usually not a practical solution below a certain sample mass.

In addition to general purification techniques, transition metal scavengers can be applied to decrease the content of these elements. This method has limitations that have to be considered. Namely, these processes have to be heavily optimized for the given application, and even then, the remaining ppm quantities of metal are still present.⁶² This is due to the fact that there are two remaining obstacles. First, if the organic compound in question has the ability to form even weak complexes with the metal, it will be in the complex form, given that the concentration of the organic compound is orders of magnitude higher. Second, the mixture might have a very stable pre-formed complex, barely affected by the scavenger.

It is also possible to purify organic materials by electrochemical means by depositing them to an electrode. This method can be helpful in qualitative analysis as well because the deposited metal concentrates on the electrode that can be analyzed.⁶³

If the organic catalyst is a polymeric material, it is an especially difficult task to purify it properly. One possibility is to use GPC. Using this technique for the purification of a suspected polymeric photocatalyst, Kosco and co-workers were able to bring down the Pd level of their polymer made by Suzuki coupling from 1170 ppm to below their detection limit of 1 ppm.⁶⁴

Molecules with more polar functional groups are more susceptible to collect metal impurities. Consequently, amino acids are prone to high amounts of metal contaminations, including iron, nickel, copper, and chromium.⁶⁵

IV. Analytical procedures

ICP is the main tool for the identification of possible transition metal contaminants, but sample preparation can be overseen if the samples are not prepared carefully. Here, we list our advice for proper sample preparation.

1. Very clean dishes and high-purity acids are essential for proper sample preparation. The vessels used in the digestion must be pre-washed with ultrapure water (18.2 M Ω / cm) using dilute acids (nitric acid and/or hydrochloric acid) (acidic wash).
2. Samples should be prepared with complete digestion, and the best method for this is microwave-assisted acidic digestion⁶⁶ (for example, Anton Paar Microwave 3000 system). For this, high-purity concentrated nitric acid and hydrochloric acid must be used in a ratio of inverse aqua regia (3 parts of HNO₃ and 1 part of HCl). Thus, nitric acid can oxidize the organic part of the sample, and palladium (transition metal) can be kept in solution due to the presence of hydrochloric acid.
3. The solutions obtained by microwave digestion must be completed to the given volume with ultrapure water (18.2 M Ω / cm), and the solutions thus obtained measured with an ICP-OES or ICP-MS instrument. Depending on the metal concentration, one or both techniques have to be used.
4. Using external calibration (single- or multi-element ICP standard solutions), a 3-4-point calibration curve should be measured to calculate the Pd content of the samples. For ICP measurements, it is advisable to perform 2 or 3 parallel measurements (with 2 or 3 independent sample preparations) if the sample amount allows it.
5. With concentrations close to the detection limit execute a spiking experiment and report spike recovery

An other very useful tool in the search for transition metal is the utilization of fluorescent sensors. Even quantitative measurements to the ppm level can be achieved for certain metals by relatively simple sensors and equipment. A drawback could be that some sensors are specific to certain elements, so one has to know what to look for.

There are several ways to detect transition metals via fluorescence,⁶⁷⁻⁶⁸ even in living cells,⁶⁹⁻⁷⁰ A more organic chemistry centered application for Pd is developed by the group of Koide.⁷¹⁻⁷⁴

NMR, as synthetic chemists use it, is not a particularly good tool for the identification of very minor unknown impurities, but it might give some clue. Pay attention to minor peaks and try to trace back their origin. Try to run NMR for nuclei that are not apparently present. In some cases, strongly binding ligands might be present and visible to a keen observer.

V. Systematic mechanistic examinations

One possible approach to determine whether (transition-) metal contamination plays a substantial role in a given transformation is systematically studying the given reaction's mechanism. The most often used options to this end are the experimental or computational kinetics and estimates of isotope- and substituent effects.

Conceptually, one must study the contamination-free and the on-purpose contaminated (spiked) reactions to exclude the catalytic activity of the contaminant. Technically, a contamination-free system experimentally is never granted, although purity can be pursued (See section Contamination minimization).

In excluding the possibility that the reaction is driven by impurities, conveying decent kinetic experiments would be an extremely valuable, but tedious process. Fortunately, a lot of information can be achieved from simplified experiments. Following the reaction in time to compare time-yield curves can reveal mechanistic similarities. One reaction might be faster, but the shape of the curve might provide insight. For a quick estimate, one might choose a certain point at intermediate conversion (ie, 70% yield) for comparison.

The above-mentioned spiking experiments should be done carefully, as there is a general lack of information on the actual catalytic quantity. If there is already too much catalyst from the reaction matrix present, adding too little might not affect the reaction outcome. This can be on the ppm or even the ppb scale. Therefore, spiking a blank reaction with various amounts of suspicious metal from ppb to low mol% should be examined. Even with such a careful approach, one has to keep in mind that an additional layer of difficulty appears if there is a high synergistic effect between the surrogate or assumed catalyst and the contaminating active catalytic centrum.

Contrarily to experiments, in a computational setup, one can and should examine both the typical metal-catalyzed pathways and the proposed alternative mechanisms. It should be proven that at the maximal possible experimental contamination level, the dopant could not effectively catalyze the reaction with respect to the contamination-free catalyst. This procedure is subject to some of the usual tricks of the trade,⁷⁵ such as the general requirement for conformational analysis,⁷⁶ proper concentration corrections, including implicit and, if necessary, explicit solvation, and the identification of resting states and rate-determining states for both mechanisms.⁷⁷

However, some special issues are arising due to the nature of the problem. First, given the presence and absence of the extremely low concentration dopant in the two mechanisms, barrier heights can only be directly compared if the dopant concentration is explicitly taken into account instead of using the usual 1 mol/dm³ concentration.

Second, due to the often-applied insoluble reactants (i.e., solid alkaline compounds), special attention has to be paid to their handling. Ideally, one should consider computer simulation of the solid-liquid interfaces via *ab initio* molecular dynamics simulations (AIMD). As an alternative approach, cluster-continuum calculations have been suggested and complemented by AIMD determination of the solution phase structure.⁷⁸ Despite the theoretical rigor of these approaches, such involving computations is rarely feasible. Therefore, more pragmatic but approximate solutions have been suggested to estimate the Gibbs free energy of these solid additives on a consistent scale with the quantum chemical calculations. One option is to combine thermodynamic cycles with experimental and computational data.⁷⁹ Although this approach is very straightforward, it is prone to sizeable errors due to handling species with highly different electronic structures⁸⁰ Further options might include purely computational approaches to thermodynamic cycles, including solid state, gas phase, and implicit solvent calculations⁷⁹ or extrapolations by providing a lower bound to the solvation free energies via increasing size cluster models,⁸¹⁻⁸² Ultimately, the replacement of the solid reactants should be experimentally attempted to obtain a model reaction that can be examined in homogenous phase via NMR spectroscopy and computational chemistry as well.

Third, given the uncertainty from the above-mentioned challenges, we suggest studying substituent effects or kinetic isotope effects if applicable. Substituent effects might provide different trends for the two mechanisms. Therefore, if an existing transformation with another catalyst is similar to the newly developed method, it is highly recommended that the two reactions be compared. To this goal, multiple compounds from the substrate scope of the other reaction with versatile substitution patterns should be selected. Then, both reactions'

conversions (NMR or GC yield) should be compared with each other and the corresponding computational estimates.

Even in the absence of well-defined contamination-free or metal-catalyzed analogous reactions, we suggest considering quantities depending on relative rates since trends are more robust with respect to technical issues than absolute rate constants. The same applies to kinetic isotope effect measurements and calculations, which benefit considerably from error cancellation.

VI. Conclusion

We composed a guideline as a recommendation for future methodology developments to highlight the importance of appropriately handling materials and equipment, purification, and analysis of products to avoid any mechanistic misinterpretations. We are aware that complying with all our recommendations is a resourceful task, but adhering to the presented guidelines and reporting the corresponding results will highly increase the credibility of newly suggested catalysts. Consideration of the critical issues could save time and energy by the on-time termination of studies misled by contamination catalysis. We hope this approach could turn the curse of any impurity effect into the blessing of novel and highly efficient catalyst systems developed in chemical research.

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VIII. Supplementary material

An interactive “Contamination Catalysis Checklist” is the part of the manuscript.

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