Computer-Aided Mechanism Elucidation of Acetylene Hydrocarboxylation to Acrylic Acid Based on a Novel Union of Empirical and Formal Methods

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In the elucidation of complex multistep reactions, it is easy to overlook significant mechanistic hypotheses. Hence, the use of computer programs to search for mechanisms is attractive, but these programs must respect the prior knowledge held by the investigator. Virtually all knowledge-based programs accommodate prior knowledge of either *what can* or *what cannot* happen, but there are advantages in exploiting both types of knowledge simultaneously. We report a novel alliance of two programs that enables these advantages and which represents an advance in the capabilities of computational chemistry, as illustrated here on the complex synthesis of acrylic acid from acetylene, CO, and water catalyzed by palladium complexes. The pathways reported by the programs were categorized as hydride, hydroxycarbonyl (alcoholate-like), and metallocyclic, the mechanistic types that are known from publications on hydrocarboxylation and hydrocarbalkoxylation of unsaturated molecules in solutions of transition metal complexes. Many specific pathways were not considered before in the absence of comprehensive computerized searches.

Introduction

Mechanism elucidation in organic chemistry and catalysis is among the most interesting and challenging tasks of chemical inference. Over the past 20−30 years, rapid progress in experimental techniques has led to a better understanding of the fine details of many reaction mechanisms. Such progress, however, has led researchers to study ever more complex mechanisms. To compound the problem, a catalytic reaction is often believed to occur via different mechanisms, which may vary with experimental conditions and the nature of the catalyst.

It has become increasingly apparent to us, based on our experiences with the computer programs to be described and applied here, that it is very easy for the investigator to overlook important hypotheses that are worth testing. Computer programs may assist a chemist to perform a systematic search of these possibilities. A number of (knowledge-based) computer programs have been already developed.[1−3] These programs can be roughly divided into two major types. The empirical programs (CAMEO,[4] TAMREAC,[5] ChemNet,[1] etc.) employ reaction libraries or libraries of transforms that summarize expert knowledge about elementary steps of complex multistep reactions. The formal−logical programs (RAIN,[6] GRACE,[7] MECHEM,[8] etc.), on the other hand, work without transforms and reaction libraries. Instead, their emphasis is on a search based on basic chemical principles, that is, by consideration of what is, a priori, the space of possible mechanisms. In most cases, both types of programs are based on a constrained combinatorial search. Constraints are used

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to restrict the combinatorics and to let the output make chemical sense.

The task of mechanism elucidation is fundamentally to explain a given phenomenon rather than to synthesize new phenomena. In organic synthesis (the latter case), it may be quite feasible to develop a largely autonomous program which, given a target molecule, will suggest highly plausible and efficient synthetic plans. Indeed, this is the goal of, for example, the SYNGEN program.[9] However, for mechanism elucidation, the chemist will bring to the table a variety of prior knowledge whose origin may be directly experimental or may be background or theoretical knowledge concerning the class of reactions of which the particular one under study is a member. Computer programs should respect this prior knowledge if they are to avoid overwhelming the chemist/user with mechanisms that are clearly wrong to the chemist but not to the program.

There are several types of prior knowledge: what can happen (e.g., the reaction transforms of empirical programs) and what cannot happen (the constraints of logical/empirical programs). To the extent that knowledge of what can and cannot happen is reliable, ideally a computer-aided approach should make use of both types of prior knowledge. Indeed, on very complex reactions there may be little alternative, since otherwise the programs will be overwhelmed by the sheer combinatorics of mechanistic possibilities.

The aim of this paper is to describe an alliance of empirical and formal/logical approaches to computational chemistry, as embodied in the programs ChemNet and MECHEM developed by the authors. This alliance permits making use of quite a broad range of prior knowledge to analyze a rather complex reaction: synthesis of acrylic acid from acetylene, CO, and water catalyzed by palladium complexes. To our knowledge, coupling an empirical approach to a logical one within computer-aided mechanism elucidation has not been done previously.

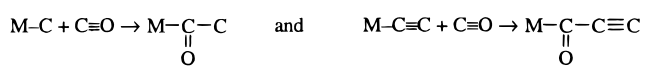
We chose the synthesis of acrylic acid via hydrocarboxylation of acetylene catalyzed by palladium complexes because (1) there is a great deal of experimental data on hydrocarboxylation and hydrocarbalkoxylation of unsaturated organic molecules catalyzed by transition metal complexes, which allows comparing the computer-generated mechanisms with the published ones and (2) the synthesis of products based on carbonylation reactions is of practical and industrial interest.

Overview of ChemNet.[1] ChemNet is an organometallic-catalysis-oriented program (although applicable to any reactions) for generating the list of elementary steps (reaction network) given a set of user-defined constraints, a set of generic transforms, and a list of initial species. Constraints and transforms within ChemNet summarize the chemist/user's knowledge about the reaction to be studied with ChemNet, which may come from preliminary experimental work or literature data. The species and transforms are inputted through the graphical interface using a mouse and a keyboard. The internal representation of species and reactions is unrelated to the purpose of this paper. On the screen, a species looks like a structural formula and an elementary reaction is displayed as a transformation of species. The generation of elementary steps of the network proceeds by applying the transforms (elementary-reaction templates) to the user-defined initial species, then to the enlarged "pot" of initial species joined by the newly-generated species, then to the still-larger pot, and so on. All transforms express either unimolecular or bimolecular steps as a good compromise between combinatorics and chemistry. Of course, not every combination of species and transform is a match; that is, a transform T is applicable to a pair of species S1 and S2 when (1) *S*1 and *S*2 together contain all fragments (substructures) described in T as "starting materials"; (2) the resulting products meet the constraints (e.g., they contain minimum/maximum numbers of atoms specified by a user and do not contain prohibited substructures); (3) the resulting products are different from S1 and S2, that is, degenerate elementary steps are thus excluded, although one of the products may be the same as S1 or S2. Thus, a transform acts as an operator T(S1, S2) = S3 + S4. If the resulting products S3 and S4 are new, they augment the current pot of species. If S3 and S4 are already in the pot, then no new reactions are enabled. In any case, the new elementary reaction is added to the reaction network.

After applying the first transform, the program proceeds to the second, third, and so on. When all transforms are matched and applied to the species pot, ChemNet repeats this procedure on all reactants that involve at least one newly added species. The growth of the reaction network stops when conditions 1−3 cannot be fulfilled. The result is a list of conjectured species and a list of conjectured elementary steps. If the user is dissatisfied with the output, the transforms and constraints may be corrected and the run repeated.

Elementary reactions in ChemNet have a definite direction, i.e., the presence of a reaction S1 + S2 → S3 + S4 does not by itself imply that S3 + S4 → S1 + S2 is also feasible. The reverse direction would need to be explicit in the transforms.

Generic transforms are a powerful tool for articulating the user's knowledge about chemical reactions, which tends to be specific, and also represent one of the most common ways of heuristic chemical reasoning about reactions. Transforms offer the chemist a way to fine tune the plausible reaction network that is eventually reached by the combinatorial generation of elementary steps. A transform is a skeleton of a set of chemical reactions, which may include more or less detail about them. The more details specified by the user in any specific transform, the fewer the reactions in the resulting reaction network. For instance, consider the choice of two possible transforms in a carbonylation reaction involving a metal complex



One should realize the difference in the level of generality. The first transform will result in a network where each carbon−metal bond undergoes the CO insertion reaction, which may result in among other reactions double CO insertion, the probability of which is very low if at all. The second transform will result in CO insertion only into the carbon−metal bonds adjacent to a triple C≡C bond.

Overview of MECHEM. MECHEM[8] is a formal/

(9) Hendrickson, J. B. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 1286−1295.

logical program that is generally usable on any reaction, although its application has so far focused on catalysis (heterogeneous and homogeneous). Given the set of reaction starting materials, any observed products and intermediates, and user-defined constraints, the program searches comprehensively for all of the simplest reaction mechanisms, i.e., containing the fewest number of species *S* and steps *R*. The user can override this default search behavior to explore the next simplest mechanisms, i.e., the simplest mechanisms that were not already generated by the program. This enables a systematic and comprehensive examination of mechanisms across a wide range of possible complexity, and this capability is exploited below.

The prior knowledge about a reaction, whether empirical or theoretical, is expressed via a rich array of constraints that serve to discard implausible branches of the comprehensive search. Experimental knowledge about any reaction products and intermediates is one type of prior knowledge. This and other information serve to constrain the search, as well as to ensure that the mechanisms found are not incompatible with prior knowledge held by the user/chemist.

The user formulates a small initial set of constraints and runs the program, which then reports the simplest satisfactory mechanisms, i.e., mechanisms having the smallest values for *S* and *R* and which do not violate any constraints. Typically, inspection of the mechanisms that appear will prompt objections, which the user then articulates via the interface in the form of a new constraint, such that the program will not at its next run consider any mechanisms that violate the constraint. This style of interaction continues for a few more rounds until either the user does not object to the mechanisms that are found or the problem becomes too complex to handle within the scope of a comprehensive combinatorial search. Hence, not all problems are within the program's scope, but many of the typical reactions of homogeneous and heterogeneous catalysis can be handled.

MECHEM is currently a 14k-line Lisp program that has taken a number of years to design and improve. Much of the early algorithm design involved minimization of search redundancy by recognizing and eliminating symmetries (in the combinatorial sense) from the search space, e.g., by devising a canonical representation of multistep pathways.[8d,e,h] Work in recent years has focused on providing a rich array of constraints with which to express the user's prior knowledge, together with an interface to make this process convenient. Any detailed discussion of algorithms is beyond the scope of this paper, but one can describe briefly how the program generates elementary steps.

Given a current pot of species to draw from (initially, just the reaction starting materials and the catalyst, if any), the program generates a list of all possible pairs and singletons of reactants. For each entry reactants in this list, all possible elementary steps are formed, thus, reactants $\rightarrow$ X, reactants $\rightarrow$ 2X, reactants $\rightarrow$ X + Y, reactants $\rightarrow$ P_i, reactants $\rightarrow$ $2P_i$, reactants $\rightarrow$ $P_i + P_j$, reactants $\rightarrow$ X + P_i, where P_i and P_j are any nonconjectured species, that is, user-input species that are taken from the starting materials or from the known products and intermediates. If the step's products are both known, then the program just verifies that the number of changes to the molecular-graph topology is no more than the user-defined ceiling, which is a variable parameter. If the step's products are both unknowns (e.g., X and Y), then the program constructs all possible products that result in no more topology changes than the current ceiling. The remaining case (X + P_i) is a hybrid of the two procedures.

It is important to realize that at many stages within this process of generating steps and of adding these steps to form mechanisms, the user-input constraints serve to interrupt fruitless search directions. For example, if the user declares that the topological link in CO is never to be cleaved, then many reaction steps that would cleave CO are never even generated. As a second example, the constraint that a known intermediate P is necessarily a precursor of a known product Q will result in the immediate pruning of any partially built mechanism in which the pathway to Q does not pass through P.

MECHEM is best seen as an aid for the elucidation of reaction mechanisms, not for mechanism prediction nor target synthesis. If the user knows little about a reaction, hence can formulate few constraints, then one expects that the resulting mechanisms will not be very credible. If the user is very knowledgeable, then the program's comprehensive search can still help by finding simple mechanisms that the investigator may well overlook without a computerized search. Earlier, we reported one example where the program found a simple, seemingly overlooked mechanism for ethane hydrogenolysis in heterogeneous catalysis.[8b]

Expression of Prior Knowledge in MECHEM and ChemNet. ChemNet allows the chemist/user to formulate a set of transforms that will be applied repeatedly to the starting materials until no new products can be formed. This procedure is potentially endless if, for example, the transforms include insertion steps; so at a minimum, the user should place a ceiling on the size of possible products. Here is the current list of constraints available in ChemNet: (1) set of transforms; (2) maximum number of any atom in conjectured species; (3) maximum/minimum oxidation state of a metal atom; (4) maximum/minimum coordination number of a metal atom; (5) maximum/minimum number of valence electrons of a metal atom; (6) prohibit substructures of a conjectured species or the entire conjectured species.

Currently, MECHEM captures prior knowledge by means of about 80 constraint types, in addition to the prior knowledge of which products and intermediates have been observed experimentally. Also, virtually all parameters can be adjusted by the user, except for two that are fixed for the foreseeable future: at most two reactants and at most two products per elementary step. This molecularity constraint is very common in chemical computing in order to deal with the potentially explosive combinatorics.

In general, a MECHEM constraint tests some aspect of a partially-built reaction pathway P. If the test fails, then P is discarded, i.e., no more steps will be added to it. The constraint types are organized according to what aspect of a pathway they pertain to. The following pairs indicate the organizational scheme and a constraint example: atom (prohibit new bonds onto a specified atom), formula (ceiling or floor on the coefficient of an

element), topology (unbreakable bonds), structure (prohibit a certain substructure), reactants (a specified element or catalyst site must be present), products (a given species cannot be formed), steps (prohibit transfer of a terminal element from one species to another), sets-of-steps (one species is a necessary precursor of another), and full pathway (overall stoichiometry).

In terms of the demands they make of a user, ChemNet and MECHEM differ in that ChemNet asks the user to specify *what can happen* (transforms) and MECHEM asks *what cannot happen* (constraints). It is instructive to consider the result if both programs are given the initial starting materials and nothing else. If no transforms are specified, then ChemNet will conclude that nothing happens because it cannot generate any steps. If no constraints, products, or intermediates are specified, MECHEM likewise concludes that nothing happens, but not because it cannot generate any steps, but because nothing in the input rules out a zero-step pathway, which is the simplest solution that it finds. A second scenario that still considers the case of only specifying the starting materials is also instructive. If the user arbitrarily requests, say, a five-step mechanism, then ChemNet cannot comply because without transforms it can generate no steps. MECHEM, on the other hand, will generate all possible five-step mechanisms, but these will likely be very numerous in the absence of constraints or stipulated products and intermediates.

There is nothing fundamentally incompatible between the two types of prior knowledge of what can and cannot happen. For example, if the chemist comprehensively and reliably states the set of reactions that can occur, then what cannot occur is any reaction that fails to appear in the set. Therefore, one can conceive of a single program that is able to build on all of a chemist's prior knowledge (stating what can and cannot happen) and which possesses the best algorithms to carry out a comprehensive search for simple reaction mechanisms within the large combinatorial space. The fact of logical compatibility does not mean, however, that there is not a marked difference in the emphases of the two types of prior knowledge and of corresponding approaches to knowledge-based chemical computer programs.

In this paper, we report the coupling of these two different approaches as embodied in the two distinct programs ChemNet (empirical or inclusive, user states what can happen) and MECHEM (formal/logical or exclusive, user states what cannot happen).

Typically, ChemNet produces a long list of reactions whereas MECHEM produces a list of pathways consisting of short sets of reactions. Any short set from this list is what is called a reaction mechanism or pathway.

To perform the study, we modified ChemNet with the capability to save ChemNet output in MECHEM format and to read MECHEM output. The second capability was not necessary for our study and is irrelevant to this paper but it is useful for viewing species as structural formulas in the graphical form. MECHEM, in turn, was enhanced with new constraints that allow rejecting any species or step that is not contained in input lists. Here, these lists consist of ChemNet output, although any other source could be used as well.

Prior Knowledge about Test Reaction

The reaction of acrylic acid synthesis by acetylene hydrocarboxylation was chosen as a test case, eq 1. This

$$C_2H_2 + CO + H_2O \longrightarrow H_2C{=}CH{-}COOH \qquad (1)$$

reaction forms the basis of a commercial process, which is carried out under high pressures (4.5−8 MPa) at 160−200 °C in a solution of nickel salts or complexes.[10] For example, in the BASF process, the catalytic system $Ni(CO)_4$−CuBr−THF is used.[10] The limitations of the commercial application of nickel complexes are as follows: (1) the formation or use of $Ni(CO)_4$, which is toxic and volatile, and (2) the presence of acetylene and high reactor pressure, which make it difficult to meet the requirements of explosion safety.[11] All these facts stimulated the search for other active catalysts for this reaction.[11] To date, a new catalyst for the synthesis of acrylic acid has not been found. It is known, however, that the reaction shown in eq 2, which is similar to eq

$$C_2H_2 + CO + ROH \longrightarrow CH_2{=}CHCOOR \qquad (2)$$

1, occurs in solutions of palladium complexes;[11−13] e.g., in butanol solutions of *cis*-$Pd[P(OPh)_3]_2Br_2$, reaction (2) occurs under mild conditions (∼70 °C, atmospheric pressure) at a high rate. In this system, the selectivity to acrylate is unsatisfactory because of the formation of acrylate dimer at long contact times.

Methylacetylene undergoes a similar reaction in the presence of palladium catalysts with (2-pyridyl)diphenylphosphine ligands.[14] This is an industrial-scale reaction which occurs with a high selectivity and turnover frequency,[15] although the mechanism of this process is not yet well understood.

The mechanistic data on carbonylation of unsaturated substrates in the presence of transition metal complexes

$$RC{\equiv}CR + CO + XOH \longrightarrow HRC{=}CR{-}COOX$$

$$R_2C{=}CR_2 + CO + XOH \longrightarrow R_2HC{-}CR_2{-}COOX$$

(X = H, R), especially on hydrocarbalkoxylation of olefins, are abundant.[12,16,17] These data suggest three principal types of mechanisms,[11,12] two of which, involving the formation of M−H and M−COOR groups in intermediate species and their addition to a double or triple bond, are cited more frequently than others.[18]

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(15) Beller, M.; Cornils, B.; Frohning, C. D.; Kohlpainter, C. W. *J. Mol. Catal.* **1995**, *104*, 17−85.

(16) (a) Parshall, G. W. *Homogeneous Catalysis;* Wiley: New York, 1980. (b) Pino, P.; Piacenti, F.; Bianchini, M. In *Organic Synthesis via Metal Carbonyls;* Wender, I., Pino, P., Eds.; Wiley: New York, 1977; pp 233−296. (c) Tsuji, J. *Organic Synthesis with Palladium Compounds;* Springer: New York, 1980; pp 81−84.

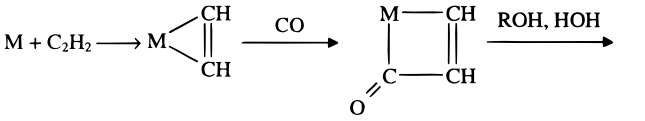
(17) Collman, P. J.; Hegedus, L. S.; Norton, J. R.; Finke, P. *Principles and Applications of Organotransition Metal Chemistry*; University Science Books: Mill Valley, CA, 1987.

Generally, the mechanisms of carbonylation reactions are reasonable to classify according to the nature of an intermediate species: M−COOR (R = alkyl or H), M−R (R= alkyl or vinyl), and a cycle involving a metal atom and the carbon atoms from the carbonyl group and substrate.

M−COOR (Case 1). The formation of intermediate alkoxycarbonyl or hydroxycarbonyl complexes occurs via CO insertion into an M−OR bond or the attack of an alcohol or water molecule onto the metal carbonyl. Further insertion of the substrate (alkyne or alkene) into the M−COOR bond results in the formation of the C−C bond of carbonylation products. A mechanism of this type was reported for the first time by Kaliya *et al.*[19] and further supported by Heck[20] and Zhir-Lebed' *et al.*[21] Convincing evidence for the participation of an M−COOR intermediate was found only for acetylene in the hydrocarbalkoxylation reactions. Correspondingly, the mechanisms involving M−COOR as a key intermediate were called *alcoholate.* When an alcohol is replaced by water, the mechanism may be referred to as *hydroxycarbonyl.*

M−R (Case 2). The formation of this intermediate usually occurs via insertion of an unsaturated substrate into an M−H bond of a metal hydride complex. The mechanisms of this sort were called *hydride* mechanisms, although the formation of C−H and M−H bonds may be the result of the attack of the H^+ ion from the solution onto the π-complex of substrate. For instance, $M(C_2H_2) + HX \rightarrow X-M-CH=CH_2$. The formation of a C−C bond occurs via CO insertion into an M−R bond. The hydride mechanisms were considered for the hydrocarboxylation and hydrocarbalkoxylation reactions of alkynes and alkenes in solutions of nickel, cobalt, rhodium, and iridium complexes[17,22,23] and are proposed more frequently than other types of mechanisms.

Metallocyclic Intermediate (Case 3). In this case, the formation of a C−C bond is not mediated by H−OR or HO−H. Instead, the metallocycle is formed. Therefore, this mechanism was called *metallocyclic.*[11,12] It is most likely that CO undergoes the insertion into an M−C bond of the metallacyclopropene. Metallacyclopropene is an intermediate of many reactions of cyclocarbonylation. When the catalyst is a metal cluster, a −HC=CH−C(O)− fragment is formed by CO and C_2H_2

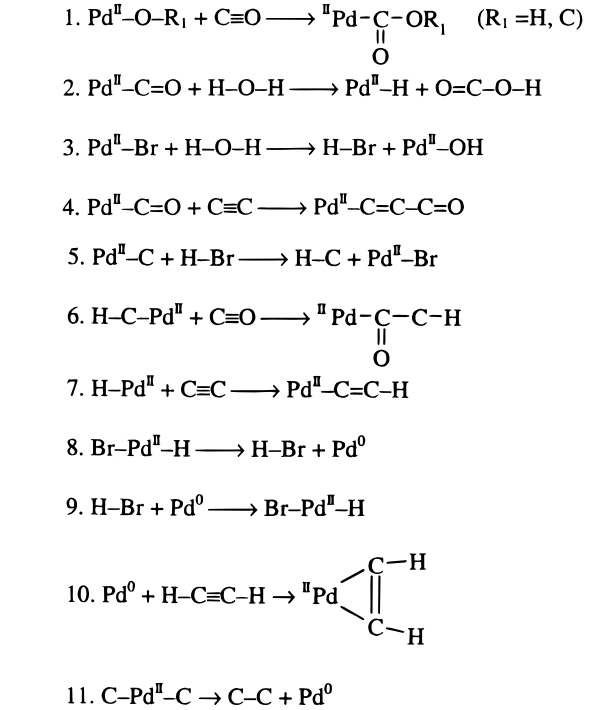


(or in the reverse order) insertions into an M−M bond. Intermediates of this sort were conjectured for the synthesis of maleic anhydride in solutions of Pd(I) complexes.[11,12,29]

It was also conjectured that hybrid variants of the above mechanistic types are also possible.[12] Thus, a characteristic feature of homogeneous reactions catalyzed with metal complexes is the possibility of several mechanisms that involve different key intermediates. One of several plausible mechanisms of the same reaction may dominate over others. In other cases, several different pathways have a comparable influence. For instance, when studying the mechanism of acrylic acid ester (and other products) formation in solutions of Pd(I) clusters, Bruk *et al.* failed to explain the experimental data by conjecturing a single pathway to the acrylate.[24] The problem was removed by conjecturing that the mechanism contains two pathways to the main product, which proved sufficient to account for the process kinetics.[25] The situation was complicated by the existence of many plausible pathways. All of this clearly motivated the use of computer programs like ChemNet and MECHEM to assist in conjecturing reaction pathways.

Formulation of the Task for the Computer

ChemNet Input. Prior knowledge about the reaction was summarized in the form of the following transforms:



The reasoning behind the choice of these transforms was as follows. Firstly, we included the transforms that

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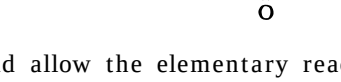
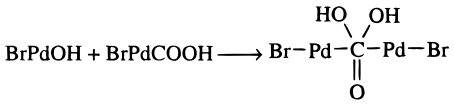
describe the elementary steps proposed earlier for the mechanism of the synthesis of acrylic acid and its esters (transforms 1−7 and 10). Secondly, we included the transforms describing the steps of a variety of catalytic processes over transition metal complexes, in particular palladium, the evidence for which, in our opinion, is beyond question (transforms 8, 9, and 11). Some other transforms (e.g., oxidative addition of C−Br bonds to Pd(0) and the reverse reaction, reductive elimination of a H−C bond from H−Pd−C, etc.) were not included for simplicity. In fact, they could be included if one strived for a more complete reaction network. Generally, the choice of transforms is the most questionable point in the entire procedure. One may formulate transforms and constraints by using reaction databases and any other reference information or, otherwise, by relying upon the expert's knowledge.

To better understand how these transforms affect the generation of elementary reactions, some comments are needed here. The difference between C=O and C≡O (compare transforms 1 and 2) allows the program to distinguish between the CO of carbonyl groups and carbon monoxide. If transform 1 was



then it would allow the elementary reactions of all species containing $PdOR_1$ and C=O, e.g.,



where the valence of the carbon atom exceeds its normal value. This can be avoided by using different bond orders between carbon and oxygen. A similar expedient is used in transform 4, where the order of a carbon−oxygen bond is two. This transform allows the insertion of any species that contain a triple carbon−carbon bond to any species containing a palladium−carbon bond adjacent to C=O and prohibits the insertion into a palladium bond with a carbonyl ligand (if any). In contrast to transform 4, where C≡C is one of the reacting fragments, transform 10 contains "full" acetylene. This restricts the combinatorial generation of steps by stipulating that no other triple bond except that of acetylene can undergo the oxidative addition to palladium. Transform 6 allows the insertion of carbon monoxide into a Pd−C bond adjacent to a C−H bond and prohibits CO insertion into a Pd−C bond adjacent to other atoms. For example, a Pd−C−C fragment will not insert CO. Thus, double CO insertion is avoided, whereas alternating CO and acetylene insertions are allowed.

The level of generality used in the transforms' description significantly affects the output. Transforms 8 and 11 describe the reductive elimination reactions. Instead, one may use a single transform with substituents for R_1 and R_2. Obviously, such a reduction in the

$$R_1–Pd^{II}–R_2 \rightarrow R_1–R_2 + Pd^0, \qquad R_1 = H, C; R_2 = Br, C$$

number of transforms by considering another (higher) level of generality entails an increase in the number of transforms of the lower level. The new transform is equivalent to four transforms of the same level as transforms 8 and 11: $H−Pd^{II}−C \rightarrow H−C + Pd^0$, $H−Pd^{II}−Br \rightarrow H−Br + Pd^0$, $C−Pd^{II}−C \rightarrow C−C + Pd^0$, $C−Pd^{II}−Br \rightarrow Br−C + Pd^0$.

When formulating a transform, one should try to picture the consequences of their use. A more general transform will result in a larger number of conjectured reactions and species. If a transform is less general, the program will report fewer reactions and species, but this may reduce the potential of finding novel unsuspected pathways.

To constrain the generation of the reaction network, we rejected any conjectured species containing more than 15 atoms. The maximum numbers of carbon, oxygen, and palladium atoms were set to 6, 4, and 1, respectively. We also required that the oxidation state of Pd range from 0 to II. The ceiling on the number of valence electrons in palladium was set to 18. The maximum coordination number of palladium was set to 2, considering that other coordination vacancies are filled with neutral ligands L, which add up to the coordination number 4. The $Pd(OH)_2$ complex was specifically prohibited.

All atoms in the initial species were at normal valence, and the transforms did not form species that violated these normal valencies.

ChemNet Output (MECHEM Input). ChemNet generated 77 species and 160 elementary reactions. Twenty-one organic byproducts are shown in Scheme 1. The list of reactions is given in Scheme 2.

The ability of a transform to generate elementary reactions within a certain system depends on the level of generality of the transform formulation and on the specific set of initial species and constraints. Table 1 measures this fertility in terms of the number of elementary reactions generated by a transform. As can be seen, transform 5 demonstrates the greatest "generating power". This can be explained by three facts: (1) There are many conjectured species containing palladium−carbon bonds; (2) This transform never increases the number of atoms in conjectured species; (3) Palladium does not change the oxidation state, the number of valence electrons, and the coordination number in this transform. That is, the constraints do not affect the species generated by this transform, and the transform is applicable to many reactant pairs.

MECHEM Final Output (Results). All conjectured species and steps were automatically converted into the format recognized by MECHEM, whose task was to find simpler pathways within the overall reaction network. At this stage, the only constraints used were as follows. (1) The overall stoichiometry $C_2H_2 + H_2O + CO \rightarrow$ Acrylic acid. This constraint is implemented with matrix computations that test whether there exist Horiuti stoichiometric numbers that yield the given overall stoichiometry. For each mechanism below, these stoichiometric numbers will be displayed with each step. (2) The initial species were C_2H_2, H_2O, CO, and $PdBr_2$, and the final species was acrylic acid. All other species were to be conjectured by the program. Note the difference between the starting materials in the overall equation and species listed in this constraint. The list of initial species includes all reactive species added to the system, including the catalyst. (3) Prohibit any species or step not contained in the ChemNet output

Scheme 1

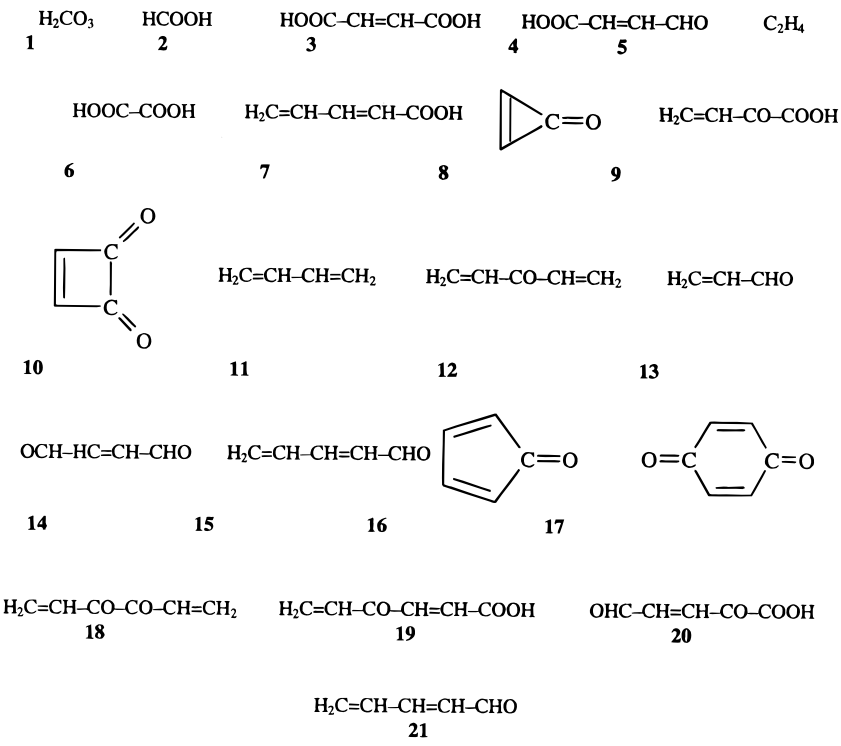


Table 1. Number of Elementary Reactions Generated by a Transform

transform no.	list of elementary reactions (numbered as in the text)	total no. of elementary reactions
1	2, 19−22, 72, 132, 133	8
2	3, 23−29, 73−81, 119−122, 134−138, 155	27
3	1, 4, 5, 30−32, 82, 123−125	10
4	6, 7, 33−35, 83−87, 126, 139,	12
5	8−11, 36−50, 88−109, 127−130, 140−146, 156−159	56
6	12, 13, 51−57, 110−115, 131, 147, 148, 160	19
7	14, 15, 58−62, 149, 150	9
8	16	1
9	17	1
10	18	1
11	63−71, 116−118, 151−154	16

(MECHEM input). (4) Prohibit superfluous steps with zero stoichiometric number. In this run, pathways containing steps with stoichiometric numbers of zero (in the sense of Horiuti) were allowed. This made it possible to generate pathways that included the steps of the formation of active catalyst entities (e.g., palladium hydride). However, we prohibited steps if they were unnecessary both for the overall stoichiometry (meaning that they have zero stoichiometric number) and for the pathway (meaning that the reduced pathway obtained by removing the step still satisfies all the given constraints). This prohibition avoids steps that are irrelevant to the pathway, that is, are not steps of catalyst deactivation or transformation of a catalyst precursor into the actual catalyst.

This input to MECHEM does not make use of its capability to constrain the search at various stages using its rich array of constraints. Rather, the main role for MECHEM here will be to carry out the combinatorial search for simpler pathways with maximum efficiency.

The program found 35 mechanisms of varying complexity, listed as follows according to their number S of conjectured species and number R of elementary steps.

(A) $S = R = 4$. ⟨1⟩ The simplest pathway conjectured by the program and the simplest *hydroxycarbonyl* mechanism, because it includes the addition of Pd−COOH to a triple bond.

1. $H_2O + PdBr_2 \xrightarrow{(1)} HBr + BrPdOH$
2. $CO + BrPdOH \xrightarrow{(1)} BrPdCOOH$
3. $C_2H_2 + BrPdCOOH \xrightarrow{(1)} BrPd–CH=CH–COOH$
4. $HBr + BrPd–CH=CH–COOH \xrightarrow{(1)} PdBr_2 +$ *Acrylic acid*

(B) $S = R = 5$. ⟨2⟩ *Hydroxycarbonyl* mechanism; here, BrPdOH acts as $PdBr_2$ does in mechanism ⟨1⟩, while $PdBr_2$ plays the role of a catalyst precursor.

1. $H_2O + PdBr_2 \xleftarrow{(0)} HBr + BrPdOH$
2. $CO + BrPdOH \xrightarrow{(1)} BrPd–COOH$
3. $C_2H_2 + BrPd–COOH \xrightarrow{(1)} BrPd–CH=CH–COOH$
4. $H_2O + BrPd–CH=CH–COOH \xrightarrow{(1)} HBr + HOPd–CH=CH–COOH$
5. $HBr + HOPd–CH=CH–COOH \xrightarrow{(1)}$ *Acrylic acid* $+ BrPdOH$

⟨3⟩ *Hydroxycarbonyl* mechanism similar to ⟨2⟩.

1. $H_2O + PdBr_2 \xleftarrow{(0)} HBr + BrPdOH$
2. $CO + BrPdOH \xrightarrow{(1)} BrPd–COOH$
3. $H_2O + BrPd–COOH \xrightarrow{(1)} HBr + HOPd–COOH$
4. $C_2H_2 + HOPd–COOH \xrightarrow{(1)} HOPd–CH=CH–COOH$
5. $HBr + HOPd–CH=CH–COOH \xrightarrow{(1)}$ *Acrylic acid* $+ BrPdOH$

(C) $S = R = 6$. ⟨4⟩ *Hydroxycarbonyl* mechanism; here, BrPd−COOH acts in a catalytic cycle, while steps 1 and 2 are necessary to produce this species.

1. $H_2O + PdBr_2 \xleftarrow{(0)} HBr + BrPdOH$
2. $CO + BrPdOH \xleftarrow{(0)} BrPd–COOH$
3. $C_2H_2 + BrPd–COOH \xrightarrow{(1)} BrPd–CH=CH–COOH$
4. $H_2O + BrPd–CH=CH–COOH \xrightarrow{(1)} HBr + HOPd–CH=CH–COOH$
5. $CO + HOPd–CH=CH–COOH \xrightarrow{(1)} HOOC–Pd–CH=CH–COOH$
6. $HBr + HOOC–Pd–CH=CH–COOH \xrightarrow{(1)}$ *Acrylic acid* $+ BrPd–COOH$

⟨5⟩ *Hydroxycarbonyl* mechanism.

1. $H_2O + PdBr_2 \leftarrow(0)\rightarrow HBr + BrPdOH$
2. $CO + BrPdOH \leftarrow(0)\rightarrow BrPd–COOH$
3. $H_2O + BrPd–COOH \text{—}(1)\rightarrow HBr + HOPd–COOH$
4. $C_2H_2 + HOPd–COOH \text{—}(1)\rightarrow HOPd–CH=CH–COOH$
5. $CO + HOPd–CH=CH–COOH \text{—}(1)\rightarrow HOOC–Pd–CH=CH–COOH$
6. $HBr + HOOC–Pd–CH=CH–COOH \text{—}(1)\rightarrow$ *Acrylic acid* + $BrPd–COOH$

⟨6⟩ *Hydroxycarbonyl* mechanism.

1. $H_2O + PdBr_2 \leftarrow(0)\rightarrow HBr + BrPdOH$
2. $CO + BrPdOH \leftarrow(0)\rightarrow BrPd–COOH$
3. $H_2O + BrPd–COOH \text{—}(1)\rightarrow HBr + HOPd–COOH$
4. $CO + HOPd–COOH \text{—}(1)\rightarrow Pd(–COOH)_2$
5. $C_2H_2 + Pd(–COOH)_2 \text{—}(1)\rightarrow HOOC–Pd–CH=CH–COOH$
6. $HBr + HOOC–Pd–CH=CH–COOH \text{—}(1)\rightarrow$ *Acrylic acid* + $BrPd–COOH$

(D) $S = 7$, $R = 6$. ⟨7⟩ The simplest *hydride* mechanism, involves Pd−H addition to a triple bond.

1. $H_2O + PdBr_2 \leftarrow(0)\rightarrow HBr + BrPdOH$
2. $CO + BrPdOH \leftarrow(0)\rightarrow BrPdCOOH$
3. $H_2O + BrPdCOOH \leftarrow(0)\rightarrow HPdBr + H_2CO_3$
4. $C_2H_2 + HPdBr \text{—}(1)\rightarrow BrPd–CH=CH_2$
5. $CO + BrPd–CH=CH_2 \text{—}(1)\rightarrow BrPd–CO–CH=CH_2$
6. $H_2O + BrPd–CO–CH=CH_2 \text{—}(1)\rightarrow$ *Acrylic acid* + $HPdBr$

(E) $S = 8$, $R = 7$. ⟨8⟩ *Hydride* mechanism, involves Pd−H addition to a triple bond; differs from mechanism ⟨7⟩ in the structure of a metal hydride.

1. $H_2O + PdBr_2 \leftarrow(0)\rightarrow HBr + BrPdOH$
2. $CO + BrPdOH \leftarrow(0)\rightarrow BrPd–COOH$
3. $H_2O + BrPd–COOH \leftarrow(0)\rightarrow HPdBr +$ **1**
4. $H_2O + HPdBr \leftarrow(0)\rightarrow HBr + HPdOH$
5. $C_2H_2 + HPdOH \text{—}(1)\rightarrow HOPd–CH=CH_2$
6. $CO + HOPd–CH=CH_2 \text{—}(1)\rightarrow HOPd–CO–CH=CH_2$
7. $H_2O + HOPd–CO–CH=CH_2 \text{—}(1)\rightarrow$ *Acrylic acid* + $HPdOH$

⟨9⟩ *Hydroxycarbonyl* mechanism; the steps of the active catalyst formation differ from those in the previous alcoholate mechanisms.

1. $H_2O + PdBr_2 \leftarrow(0)\rightarrow HBr + BrPdOH$
2. $CO + BrPdOH \leftarrow(0)\rightarrow BrPd–COOH$
3. $H_2O + BrPd–COOH \leftarrow(0)\rightarrow HPdBr +$ **1**
4. $H_2O + HPdBr \text{—}(1)\rightarrow HBr + HPdOH$
5. $CO + HPdOH \text{—}(1)\rightarrow HPd–COOH$
6. $C_2H_2 + HPd–COOH \text{—}(1)\rightarrow HPd–CH=CH–COOH$
7. $HBr + HPd–CH=CH–COOH \text{—}(1)\rightarrow$ *Acrylic acid* + $HPdBr$

⟨10⟩ *Hydride* mechanism; the steps of the active catalyst formation differ from those in the previous hydride mechanisms.

1. $H_2O + PdBr_2 \leftarrow(0)\rightarrow HBr + BrPdOH$
2. $CO + BrPdOH \leftarrow(0)\rightarrow BrPd–COOH$
3. $H_2O + BrPd–COOH \leftarrow(0)\rightarrow HBr + HOPd–COOH$
4. $H_2O + HOPd–COOH \leftarrow(0)\rightarrow HPdOH +$ **1**
5. $C_2H_2 + HPdOH \text{—}(1)\rightarrow HOPd–CH=CH_2$
6. $CO + HOPd–CH=CH_2 \text{—}(1)\rightarrow HOPd–CO–CH=CH_2$
7. $H_2O + HOPd–CO–CH=CH_2 \text{—}(1)\rightarrow$ *Acrylic acid* + $HPdOH$

(F) $S = R = 8$. ⟨11⟩ *Hydroxycarbonyl* mechanism.

1. $H_2O + PdBr_2 \text{—}(1)\rightarrow HBr + BrPdOH$
2. $CO + BrPdOH \leftarrow(0)\rightarrow BrPd–COOH$
3. $H_2O + BrPd–COOH \leftarrow(0)\rightarrow HBr + HOPd–COOH$
4. $C_2H_2 + HOPd–COOH \text{—}(1)\rightarrow HOPd–CH=CH–COOH$
5. $CO + HOPd–CH=CH–COOH \text{—}(1)\rightarrow HOOC–Pd–CH=CH–COOH$
6. $HBr + HOOC–Pd–CH=CH–COOH \text{—}(1)\rightarrow$ **2** + $BrPd–CH=CH–COOH$
7. $HBr + BrPd–CH=CH–COOH \text{—}(1)\rightarrow PdBr_2 +$ *Acrylic acid*
8. $BrPdOH +$ **2** $\text{—}(1)\rightarrow HBr + HOPd–COOH$

⟨12⟩ *Hydroxycarbonyl* mechanism.

1. $H_2O + PdBr_2 \text{—}(1)\rightarrow HBr + BrPdOH$
2. $CO + BrPdOH \text{—}(1)\rightarrow BrPd–COOH$
3. $H_2O + BrPd–COOH \leftarrow(0)\rightarrow HBr + HOPd–COOH$
4. $CO + HOPd–COOH \leftarrow(0)\rightarrow Pd(–COOH)_2$
5. $C_2H_2 + Pd(–COOH)_2 \text{—}(1)\rightarrow HOOC–Pd–CH=CH–COOH$
6. $HBr + HOOC–Pd–CH=CH–COOH \text{—}(1)\rightarrow$ **2** + $BrPd–CH=CH–COOH$
7. $HBr + BrPd–CH=CH–COOH \text{—}(1)\rightarrow PdBr_2 +$ *Acrylic acid*
8. $BrPd–COOH +$ **2** $\text{—}(1)\rightarrow HBr + Pd(–COOH)_2$

⟨13⟩ *Hydroxycarbonyl* mechanism.

1. $H_2O + PdBr_2 \text{—}(1)\rightarrow HBr + BrPdOH$
2. $CO + BrPdOH \leftarrow(0)\rightarrow BrPd–COOH$
3. $H_2O + BrPd–COOH \leftarrow(0)\rightarrow HBr + HOPd–COOH$
4. $CO + HOPd–COOH \text{—}(1)\rightarrow Pd(–COOH)_2$
5. $C_2H_2 + Pd(–COOH)_2 \text{—}(1)\rightarrow HOOC–Pd–CH=CH–COOH$
6. $HBr + HOOC–Pd–CH=CH–COOH \text{—}(1)\rightarrow$ **2** + $BrPd–CH=CH–COOH$
7. $HBr + BrPd–CH=CH–COOH \text{—}(1)\rightarrow PdBr_2 +$ *Acrylic acid*
8. $BrPdOH +$ **2** $\text{—}(1)\rightarrow HBr + HOPd–COOH$

⟨14⟩ *Hydroxycarbonyl* mechanism.

1. $H_2O + PdBr_2 \leftarrow(0)\rightarrow HBr + BrPdOH$
2. $CO + BrPdOH \leftarrow(0)\rightarrow BrPd–COOH$
3. $H_2O + BrPd–COOH \text{—}(1)\rightarrow HBr + HOPd–COOH$
4. $C_2H_2 + HOPd–COOH \text{—}(1)\rightarrow HOPd–CH=CH–COOH$
5. $CO + HOPd–CH=CH–COOH \text{—}(1)\rightarrow HOOC–Pd–CH=CH–COOH$
6. $HBr + HOOC–Pd–CH=CH–COOH \text{—}(1)\rightarrow$ **2** + $BrPd–CH=CH–COOH$
7. $PdBr_2 +$ **2** $\text{—}(1)\rightarrow HBr + BrPd–COOH$
8. $HBr + BrPd–CH=CH–COOH \text{—}(1)\rightarrow PdBr_2 +$ *Acrylic acid*

⟨15⟩ *Hydroxycarbonyl* mechanism.

1. $H_2O + PdBr_2 \leftarrow(0)\rightarrow HBr + BrPdOH$
2. $CO + BrPdOH \leftarrow(0)\rightarrow BrPd–COOH$
3. $H_2O + BrPd–COOH \text{—}(1)\rightarrow HBr + HOPd–COOH$
4. $CO + HOPd–COOH \text{—}(1)\rightarrow Pd(–COOH)_2$
5. $C_2H_2 + Pd(–COOH)_2 \text{—}(1)\rightarrow HOOC–Pd–CH=CH–COOH$
6. $HBr + HOOC–Pd–CH=CH–COOH \text{—}(1)\rightarrow$ **2** + $BrPd–CH=CH–COOH$
7. $PdBr_2 +$ **2** $\text{—}(1)\rightarrow HBr + BrPd–COOH$
8. $HBr + BrPd–CH=CH–COOH \text{—}(1)\rightarrow PdBr_2 +$ *Acrylic acid*

(G) $S = 9$, $R = 8$. ⟨16⟩ *Hydroxycarbonyl* mechanism.

1. $H_2O + PdBr_2 \leftarrow(0)\rightarrow HBr + BrPdOH$
2. $CO + BrPdOH \leftarrow(0)\rightarrow BrPd–COOH$
3. $H_2O + BrPd–COOH \text{—}(1)\rightarrow HBr + HOPd–COOH$
4. $H_2O + HOPd–COOH \text{—}(1)\rightarrow$ **1** + $HPdOH$
5. $CO + HPdOH \text{—}(1)\rightarrow HPd–COOH$
6. $C_2H_2 + HPd–COOH \text{—}(1)\rightarrow HPd–CH=CH–COOH$
7. $HBr + HPd–CH=CH–COOH \text{—}(1)\rightarrow$ *Acrylic acid* + $HPdBr$
8. $HPdBr +$ **1** $\text{—}(1)\rightarrow H_2O + BrPd–COOH$

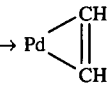
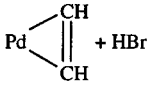
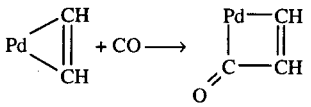
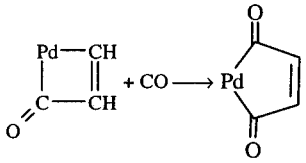
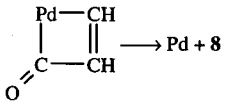
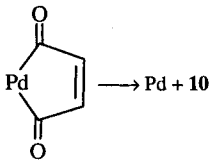
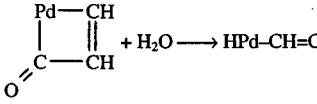
⟨17⟩ *Hydroxycarbonyl* mechanism.

1. $H_2O + PdBr_2 \leftarrow(0)\rightarrow HBr + BrPdOH$
2. $CO + BrPdOH \leftarrow(0)\rightarrow BrPd–COOH$
3. $H_2O + BrPd–COOH \text{—}(1)\rightarrow HBr + HOPd–COOH$
4. $CO + HOPd–COOH \text{—}(1)\rightarrow Pd(–COOH)_2$
5. $C_2H_2 + Pd(–COOH)_2 \text{—}(1)\rightarrow HOOC–Pd–CH=CH–COOH$
6. $H_2O + HOOC–Pd–CH=CH–COOH \text{—}(1)\rightarrow$ **1** + $HPd–CH=CH–COOH$
7. $HBr + HPd–CH=CH–COOH \text{—}(1)\rightarrow$ *Acrylic acid* + $HPdBr$
8. $HPdBr +$ **1** $\text{—}(1)\rightarrow H_2O + BrPd–COOH$

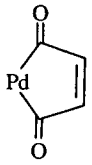
⟨18⟩ *Hydroxycarbonyl* mechanism.

1. $H_2O + PdBr_2 \leftarrow(0)\rightarrow HBr + BrPdOH$
2. $CO + BrPdOH \leftarrow(0)\rightarrow BrPd–COOH$
3. $H_2O + BrPd–COOH \text{—}(1)\rightarrow HBr + HOPd–COOH$
4. $CO + HOPd–COOH \text{—}(1)\rightarrow Pd(–COOH)_2$
5. $H_2O + Pd(–COOH)_2 \text{—}(1)\rightarrow$ **1** + $HPd–COOH$
6. $C_2H_2 + HPd–COOH \text{—}(1)\rightarrow HPd–CH=CH–COOH$
7. $HBr + HPd–CH=CH–COOH \text{—}(1)\rightarrow$ *Acrylic acid* + $HPdBr$
8. $HPdBr +$ **1** $\text{—}(1)\rightarrow H_2O + BrPd–COOH$

Scheme 2

1. $PdBr_2 + H_2O \longrightarrow BrPdOH + HBr$
2. $BrPdOH + CO \longrightarrow BrPd{-}COOH$
3. $BrPd{-}COOH + H_2O \longrightarrow \mathbf{1} + HPdBr$
4. $BrPd{-}COOH + H_2O \longrightarrow HBr + HOPd{-}COOH$
5. $HPdBr + H_2O \longrightarrow HBr + HPdOH$
6. $BrPd{-}COOH + C_2H_2 \longrightarrow BrPd{-}CH{=}CH{-}COOH$
7. $HOPd{-}COOH + C_2H_2 \longrightarrow HOPd{-}CH{=}CH{-}COOH$
8. $BrPd{-}COOH + HBr \longrightarrow PdBr_2 + \mathbf{2}$
9. $HOPd{-}COOH + HBr \longrightarrow BrPdOH + \mathbf{2}$
10. $BrPd{-}CH{=}CH{-}COOH + HBr \longrightarrow PdBr_2 +$ *Acrylic acid*
11. $HOPd{-}CH{=}CH{-}COOH + HBr \longrightarrow BrPdOH +$ *Acrylic acid*
12. $BrPd{-}CH{=}CH{-}COOH + CO \longrightarrow BrPd{-}CO{-}CH{=}CH{-}COOH$
13. $HOPd{-}CH{=}CH{-}COOH + CO \longrightarrow HOPd{-}CO{-}CH{=}CH{-}COOH$
14. $HPdBr + C_2H_2 \longrightarrow BrPd{-}CH{=}CH_2$
15. $HPdOH + C_2H_2 \longrightarrow HOPd{-}CH{=}CH_2$
16. $HPdBr \longrightarrow HBr + Pd$
17. $Pd + HBr \longrightarrow HPdBr$
18. $Pd + C_2H_2 \longrightarrow$ 
19. $HOPd{-}COOH + CO \longrightarrow Pd(-COOH)_2$
20. $HPdOH + CO \longrightarrow HPd{-}COOH$
21. $HOPd{-}CH{=}CH{-}COOH + CO \longrightarrow HOOC{-}Pd{-}CH{=}CH{-}COOH$
22. $HOPd{-}CH{=}CH_2 + CO \longrightarrow HOOC{-}Pd{-}CH{=}CH_2$
23. $HOPd{-}COOH + H_2O \longrightarrow \mathbf{1} + HPdOH$
24. $BrPd{-}CO{-}CH{=}CH{-}COOH + H_2O \longrightarrow HPdBr + \mathbf{3}$
25. $HOPd{-}CO{-}CH{=}CH{-}COOH + H_2O \longrightarrow HPdOH + \mathbf{3}$
26. $Pd(-COOH)_2 + H_2O \longrightarrow \mathbf{1} + HPd{-}COOH$
27. $HPd{-}COOH + H_2O \longrightarrow \mathbf{1} + PdH_2$
28. $HOOC{-}Pd{-}CH{=}CH{-}COOH + H_2O \longrightarrow \mathbf{1} + HPd{-}CH{=}CH{-}COOH$
29. $HOOC{-}Pd{-}CH{=}CH_2 + H_2O \longrightarrow \mathbf{1} + HPd{-}CH{=}CH_2$
30. $BrPd{-}CH{=}CH{-}COOH + H_2O \longrightarrow HBr + HOPd{-}CH{=}CH{-}COOH$
31. $BrPd{-}CO{-}CH{=}CH{-}COOH + H_2O \longrightarrow HBr +$ $HOPd{-}CO{-}CH{=}CH{-}COOH$
32. $BrPd{-}CH{=}CH_2 + H_2O \longrightarrow HBr + HOPd{-}CH{=}CH_2$
33. $Pd(-COOH)_2 + C_2H_2 \longrightarrow HOOC{-}Pd{-}CH{=}CH{-}COOH$
34. $HPd{-}COOH + C_2H_2 \longrightarrow HPd{-}CH{=}CH{-}COOH$
35. $HOOC{-}Pd{-}CH{=}CH_2 + C_2H_2 \longrightarrow H_2C{=}CH{-}Pd{-}CH{=}CH{-}COOH$
36. $BrPd{-}CO{-}CH{=}CH{-}COOH + HBr \longrightarrow PdBr_2 + \mathbf{4}$
37. $HOPd{-}CO{-}CH{=}CH{-}COOH + HBr \longrightarrow BrPdOH + \mathbf{4}$
38. $BrPd{-}CH{=}CH_2 + HBr \longrightarrow PdBr_2 + \mathbf{5}$
39. $HOPd{-}CH{=}CH_2 + HBr \longrightarrow BrPdOH + \mathbf{5}$
40.  $+ HBr \longrightarrow BrPd{-}CH{=}CH_2$
41. $Pd(-COOH)_2 + HBr \longrightarrow BrPd{-}COOH + \mathbf{2}$
42. $HPd{-}COOH + HBr \longrightarrow HPdBr + \mathbf{2}$
43. $HOOC{-}Pd{-}CH{=}CH{-}COOH + HBr \longrightarrow BrPd{-}COOH +$ *Acrylic acid*
44. $HOOC{-}Pd{-}CH{=}CH{-}COOH + HBr \longrightarrow BrPd{-}CH{=}CH{-}COOH + \mathbf{2}$
45. $HOOC{-}Pd{-}CH{=}CH_2 + HBr \longrightarrow BrPd{-}COOH + \mathbf{5}$
46. $HOOC{-}Pd{-}CH{=}CH_2 + HBr \longrightarrow \mathbf{2} + BrPd{-}CH{=}CH_2$
47. $HPd{-}CH{=}CH{-}COOH + HBr \longrightarrow HPdBr +$ *Acrylic acid*
48. $HPd{-}CH{=}CH_2 + HBr \longrightarrow HPdBr + \mathbf{5}$
49. $H_2C{=}CH{-}Pd{-}CH{=}CH{-}COOH + HBr \longrightarrow$ *Acrylic acid* $+$ $BrPd{-}CH{=}CH_2$
50. $H_2C{=}CH{-}Pd{-}CH{=}CH{-}COOH + HBr \longrightarrow BrPd{-}CH{=}CH{-}COOH + \mathbf{5}$
51. $BrPd{-}CH{=}CH_2 + CO \longrightarrow BrPd{-}CO{-}CH{=}CH_2$
52. $HOPd{-}CH{=}CH_2 + CO \longrightarrow HOPd{-}CO{-}CH{=}CH_2$
53. 
54. $HOOC{-}Pd{-}CH{=}CH_2 + CO \longrightarrow HOOC{-}Pd{-}CO{-}CH{=}CH_2$
55. $HPd{-}CH{=}CH{-}COOH + CO \longrightarrow HPd{-}CO{-}CH{=}CH{-}COOH$
56. $HPd{-}CH{=}CH_2 + CO \longrightarrow HPd{-}CO{-}CH{=}CH_2$
57. 
58. $HPd{-}COOH + C_2H_2 \longrightarrow HOOC{-}Pd{-}CH{=}CH_2$
59. $PdH_2 + C_2H_2 \longrightarrow HPd{-}CH{=}CH_2$
60. $HPd{-}CH{=}CH{-}COOH + C_2H_2 \longrightarrow H_2C{=}CH{-}Pd{-}CH{=}CH{-}COOH$
61. $HPd{-}CH{=}CH_2 + C_2H_2 \longrightarrow Pd(-CH{=}CH_2)_2$
62. $HPd{-}CO{-}CH{=}CH_2 + C_2H_2 \longrightarrow H_2C{=}CH{-}Pd{-}CO{-}CH{=}CH_2$
63. $Pd(-COOH)_2 \longrightarrow Pd + \mathbf{6}$
64. $HOOC{-}Pd{-}CH{=}CH{-}COOH \longrightarrow Pd + \mathbf{3}$
65. $HOOC{-}Pd{-}CH{=}CH_2 \longrightarrow$ *Acrylic acid* $+ Pd$
66. $H_2C{=}CH{-}Pd{-}CH{=}CH{-}COOH \longrightarrow Pd + \mathbf{7}$
67.  $\longrightarrow Pd + \mathbf{8}$
68. $HOOC{-}Pd{-}CO{-}CH{=}CH_2 \longrightarrow Pd + \mathbf{9}$
69.  $\longrightarrow Pd + \mathbf{10}$
70. $Pd(-CH{=}CH_2)_2 \longrightarrow Pd + \mathbf{11}$
71. $H_2C{=}CH{-}Pd{-}CO{-}CH{=}CH_2 \longrightarrow Pd + \mathbf{12}$
72. $HOPd{-}CO{-}CH{=}CH_2 + CO \longrightarrow HOOC{-}Pd{-}CO{-}CH{=}CH_2$
73. $BrPd{-}CO{-}CH{=}CH_2 + H_2O \longrightarrow HPdBr +$ *Acrylic acid*
74. $HOPd{-}CO{-}CH{=}CH_2 + H_2O \longrightarrow HPdOH +$ *Acrylic acid*
75. 
76. $HOOC{-}Pd{-}CO{-}CH{=}CH_2 + H_2O \longrightarrow$ *Acrylic acid* $+ HPd{-}COOH$
77. $HOOC{-}Pd{-}CO{-}CH{=}CH_2 + H_2O \longrightarrow \mathbf{1} + HPd{-}CO{-}CH{=}CH_2$
78. $HPd{-}CO{-}CH{=}CH{-}COOH + H_2O \longrightarrow \mathbf{3} + PdH_2$
79. $HPd{-}CO{-}CH{=}CH_2 + H_2O \longrightarrow$ *Acrylic acid* $+ PdH_2$

Scheme 2 (Continued)

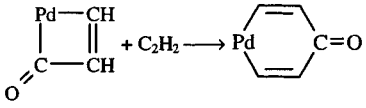
80.  + H_2O ⟶ HPd–CO–CH=CH–COOH

81. H_2C=CH–Pd–CO–CH=CH_2 + H_2O ⟶ *Acrylic acid* + HPd–CH=CH_2

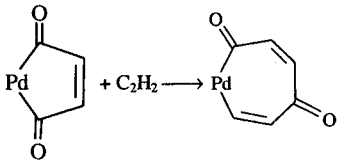
82. BrPd–CO–CH=CH_2 + H_2O ⟶ HBr + HOPd–CO–CH=CH_2

83. BrPd–CO–CH=CH_2 + C_2H_2 ⟶ BrPd–CH=CH–CO–CH=CH_2

84. HOPd–CO–CH=CH_2 + C_2H_2 ⟶ HOPd–CH=CH–CO–CH=CH_2

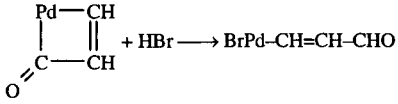
85. 

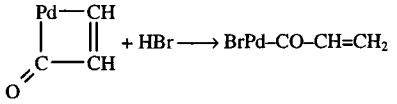
86. HPd–CO–CH=CH_2 + C_2H_2 ⟶ HPd–CH=CH–CO–CH=CH_2

87. 

88. BrPd–CO–CH=CH_2 + HBr ⟶ $PdBr_2$ + **13**

89. HOPd–CO–CH=CH_2 + HBr ⟶ BrPdOH + **13**

90. 

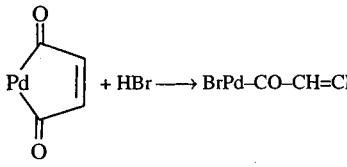
91. 

92. HOOC–Pd–CO–CH=CH_2 + HBr ⟶ BrPd–COOH + **13**

93. HOOC–Pd–CO–CH=CH_2 + HBr ⟶ **2** + BrPd–CO–CH=CH_2

94. HPd–CO–CH=CH–COOH + HBr ⟶ HPdBr + **4**

95. HPd–CO–CH=CH_2 + HBr ⟶ HPdBr + **13**

96. 

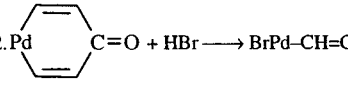
97. Pd(–CH=CH_2)$_2$ + HBr ⟶ BrPd–CH=CH_2 + **5**

98. H_2C=CH–Pd–CO–CH=CH_2 + HBr ⟶ BrPd–CH=CH_2 + **13**

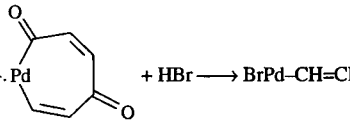
99. H_2C=CH–Pd–CO–CH=CH_2 + HBr ⟶ **5** + BrPd–CO–CH=CH_2

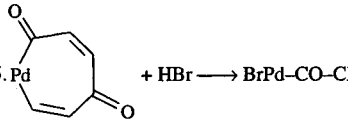
100. BrPd–CH=CH–CO–CH=CH_2 + HBr ⟶ $PdBr_2$ + **12**

101. HOPd–CH=CH–CO–CH=CH_2 + HBr ⟶ BrPdOH + **12**

102. 

103. HPd–CH=CH–CO–CH=CH_2 + HBr ⟶ HPdBr + **12**

104. 

105. 

106. BrPd–CH=CH–CHO + HBr ⟶ $PdBr_2$ + **13**

107. BrPd–CO–CH=CH–CHO + HBr ⟶ $PdBr_2$ + **14**

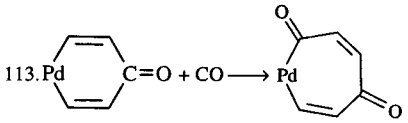
108. BrPd–CH=CH–CO–CH=CH–CHO + HBr ⟶ $PdBr_2$ + **15**

109. BrPd–CO–CH=CH–CO–CH=CH_2 + HBr ⟶ $PdBr_2$ + **15**

110. Pd(–CH=CH_2)$_2$ + CO ⟶ H_2C=CH–Pd–CO–CH=CH_2

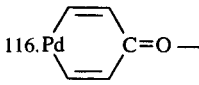
111. H_2C=CH–Pd–CO–CH=CH_2 + CO ⟶ Pd(–CO–CH=CH_2)$_2$

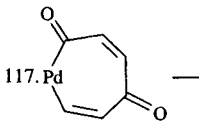
112. BrPd–CH=CH–CO–CH=CH_2 + CO ⟶ BrPd–CO–CH=CH–CO–CH=CH_2

113. 

114. HPd–CH=CH–CO–CH=CH_2 + CO ⟶ HPd–CO–CH=CH–CO–CH=CH_2

115. BrPd–CH=CH–CHO + CO ⟶ BrPd–CO–CH=CH–CHO

116.  ⟶ Pd + **16**

117.  ⟶ Pd + **17**

118. Pd(–CO–CH=CH_2)$_2$ ⟶ Pd + **18**

119. BrPd–CO–CH=CH–CHO + H_2O ⟶ HPdBr + **4**

120. BrPd–CO–CH=CH–CO–CH=CH_2 + H_2O ⟶ HPdBr + **19**

121. Pd(–CO–CH=CH_2)$_2$ + H_2O ⟶ *Acrylic acid* + HPd–CO–CH=CH_2

122. HPd–CO–CH=CH–CO–CH=CH_2 + H_2O ⟶ PdH_2 + **19**

123. BrPd–CH=CH–CO–CH=CH_2 + H_2O ⟶ HBr + HOPd–CH=CH–CO–CH=CH_2

124. BrPd–CH=CH–CHO + H_2O ⟶ HBr + HOPd–CH=CH–CHO

125. BrPd–CO–CH=CH–CHO + H_2O ⟶ HBr + HOPd–CO–CH=CH–CHO

126. BrPd–CO–CH=CH–CHO + C_2H_2 ⟶ BrPd–CH=CH–CO–CH=CH–CHO

127. Pd(–CO–CH=CH_2)$_2$ + HBr ⟶ BrPd–CO–CH=CH_2 + **13**

128. HPd–CO–CH=CH–CO–CH=CH_2 + HBr ⟶ HPdBr + **15**

129. HOPd–CH=CH–CHO + HBr ⟶ BrPdOH + **13**

130. HOPd–CO–CH=CH–CHO + HBr ⟶ BrPdOH + **14**

131. HOPd–CH=CH–CHO + CO ⟶ HOPd–CO–CH=CH–CHO +

132. HOPd–CH=CH–CHO + CO ⟶ HOOC–Pd–CH=CH–CHO

133. HOPd–CO–CH=CH–CHO + CO ⟶ HOOC–Pd–CO–CH=CH–CHO

134. HOPd–CO–CH=CH–CHO + H_2O ⟶ HPdOH + **4**

135. HOOC–Pd–CH=CH–CHO + H_2O ⟶ **1** + HPd–CH=CH–CHO

136. HOOC–Pd–CO–CH=CH–CHO + H_2O ⟶ HPd–COOH + **4**

137. HOOC–Pd–CO–CH=CH–CHO + H_2O ⟶ **1** + HPd–CO–CH=CH–CHO

138. HPd–CO–CH=CH–CHO + H_2O ⟶ PdH_2 + **4**

139. HPd–CO–CH=CH–CHO + C_2H_2 ⟶ HPd–CH=CH–CO–CH=CH–CHO

140. HOOC–Pd–CH=CH–CHO + HBr ⟶ BrPd–COOH + **13**

141. HOOC–Pd–CH=CH–CHO + HBr ⟶ **2** + BrPd–CH=CH–CHO

142. HOOC–Pd–CO–CH=CH–CHO + HBr ⟶ BrPd–COOH + **14**

143. HOOC–Pd–CO–CH=CH–CHO + HBr ⟶ **2** + BrPd–CO–CH=CH–CHO

144. HPd–CH=CH–CHO + HBr ⟶ HPdBr + **13**

145. HPd–CO–CH=CH–CHO + HBr ⟶ HPdBr + **14**

Scheme 2 (Continued)

146. HPd–CH=CH–CO–CH=CH–CHO + HBr ⟶ HPdBr + **15**
147. HOOC–Pd–CH=CH–CHO + CO ⟶ HOOC–Pd–CO–CH=CH–CHO
148. HPd–CH=CH–CHO + CO ⟶ HPd–CO–CH=CH–CHO
149. HPd–CH=CH–CHO + C_2H_2 ⟶ H_2C=CH–Pd–CH=CH–CHO
150. HPd–CO–CH=CH–CHO + C_2H_2 ⟶ H_2C=CH–Pd–CO–CH=CH–CHO
151. HOOC–Pd–CH=CH–CHO ⟶ Pd + **4**
152. HOOC–Pd–CO–CH=CH–CHO ⟶ Pd + **20**
153. H_2C=CH–Pd–CH=CH–CHO ⟶ Pd + **21**
154. H_2C=CH–Pd–CO–CH=CH–CHO ⟶ Pd + **15**
155. H_2C=CH–Pd–CO–CH=CH–CHO + H_2O ⟶ HPd–CH=CH_2 + **4**
156. H_2C=CH–Pd–CH=CH–CHO + HBr ⟶ BrPd–CH=CH_2 + **13**
157. H_2C=CH–Pd–CH=CH–CHO + HBr ⟶ **5** + BrPd–CH=CH–CHO
158. H_2C=CH–Pd–CO–CH=CH–CHO + HBr ⟶ BrPd–CH=CH_2 + **14**
159. H_2C=CH–Pd–CO–CH=CH–CHO + HBr ⟶ **5** + BrPd–CO–CH=CH–CHO
160. H_2C=CH–Pd–CH=CH–CHO + CO ⟶ H_2C=CH–Pd–CO–CH=CH–CHO

⟨19⟩ *Hydroxycarbonyl* mechanism.

1. H_2O + $PdBr_2$ ←(0)→ HBr + BrPdOH
2. CO + BrPdOH ←(0)→ BrPd–COOH
3. H_2O + BrPd–COOH —(1)→ HBr + HOPd–COOH
4. C_2H_2 + HOPd–COOH —(1)→ HOPd–CH=CH–COOH
5. CO + HOPd–CH=CH–COOH —(1)→ HOOC–Pd–CH=CH–COOH
6. H_2O + HOOC–Pd–CH=CH–COOH —(1)→ **1** + HPd–CH=CH–COOH
7. HBr + HPd–CH=CH–COOH —(1)→ *Acrylic acid* + HPdBr
8. HPdBr + **1** —(1)→ H_2O + BrPd–COOH

⟨20⟩ *Hydroxycarbonyl* mechanism.

1. H_2O + $PdBr_2$ ←(0)→ HBr + BrPdOH
2. CO + BrPdOH ←(0)→ BrPd–COOH
3. H_2O + BrPd–COOH ←(0)→ HBr + HOPd–COOH
4. H_2O + HOPd–COOH ←(0)→ HPdOH + **1**
5. CO + HPdOH —(1)→ HPd–COOH
6. C_2H_2 + HPd–COOH —(1)→ HPd–CH=CH–COOH
7. HBr + HPd–CH=CH–COOH —(1)→ *Acrylic acid* + HPdBr
8. H_2O + HPdBr —(1)→ HBr + HPdOH

⟨21⟩ *Hydride* mechanism.

1. H_2O + $PdBr_2$ ←(0)→ HBr + BrPdOH
2. CO + BrPdOH ←(0)→ BrPd–COOH
3. H_2O + BrPd–COOH ←(0)→ HBr + HOPd–COOH
4. H_2O + HOPd–COOH ←(0)→ HPdOH + **1**
5. CO + HPdOH ←(0)→ HPd–COOH
6. C_2H_2 + HPd–COOH —(1)→ HOOC–Pd–CH=CH_2
7. CO + HOOC–Pd–CH=CH_2 —(1)→ HOOC–Pd–CO–CH=CH_2
8. H_2O + HOOC–Pd–CO–CH=CH_2 —(1)→ *Acrylic acid* + HPd–COOH

⟨22⟩ *Hydride* mechanism.

1. H_2O + $PdBr_2$ ←(0)→ HBr + BrPdOH
2. CO + BrPdOH ←(0)→ BrPd–COOH
3. H_2O + BrPd–COOH ←(0)→ HBr + HOPd–COOH
4. CO + HOPd–COOH ←(0)→Pd(–COOH)$_2$
5. H_2O + Pd(–COOH)$_2$ ←(0)→ HPd–COOH + **1**
6. C_2H_2 + HPd–COOH —(1)→ HOOC–Pd–CH=CH_2
7. CO + HOOC–Pd–CH=CH_2 —(1)→ HOOC–Pd–CO–CH=CH_2
8. H_2O + HOOC–Pd–CO–CH=CH_2 —(1)→ *Acrylic acid* + HPd–COOH

⟨23⟩ *Hydroxycarbonyl* mechanism.

1. H_2O + $PdBr_2$ ←(0)→ HBr + BrPdOH
2. CO + BrPdOH ←(0)→ BrPd–COOH
3. C_2H_2 + BrPd–COOH —(1)→ BrPd–CH=CH–COOH
4. H_2O + BrPd–CH=CH–COOH —(1)→ HBr + HOPd–CH=CH–COOH
5. CO + HOPd–CH=CH–COOH —(1)→ HOOC–Pd–CH=CH–COOH
6. H_2O + HOOC–Pd–CH=CH–COOH —(1)→ **1** + HPd–CH=CH–COOH
7. HBr + HPd–CH=CH–COOH —(1)→ *Acrylic acid* + HPdBr
8. HPdBr + **1** —(1)→ H_2O + BrPd–COOH

⟨24⟩ *Hydride* mechanism.

1. H_2O + $PdBr_2$ ←(0)→ HBr + BrPdOH
2. CO + BrPdOH ←(0)→ BrPd–COOH
3. H_2O + BrPd–COOH ←(0)→ HPdBr + **1**
4. C_2H_2 + HPdBr —(1)→ BrPd–CH=CH_2
5. CO + BrPd–CH=CH_2 —(1)→ BrPd–CO–CH=CH_2
6. H_2O + BrPd–CO–CH=CH_2 —(1)→ HBr + HOPd–CO–CH=CH_2
7. H_2O + HOPd–CO–CH=CH_2 —(1)→ *Acrylic acid* + HPdOH
8. HBr + HPdOH —(1)→ H_2O + HPdBr

⟨25⟩ *Hydride* mechanism.

1. H_2O + $PdBr_2$ ←(0)→ HBr + BrPdOH
2. CO + BrPdOH ←(0)→ BrPd–COOH
3. H_2O + BrPd–COOH ←(0)→ HPdBr + **1**
4. C_2H_2 + HPdBr —(1)→ BrPd–CH=CH_2
5. H_2O + BrPd–CH=CH_2 —(1)→ HBr + HOPd–CH=CH_2
6. CO + HOPd–CH=CH_2 —(1)→ HOPd–CO–CH=CH_2
7. H_2O + HOPd–CO–CH=CH_2 —(1)→ *Acrylic acid* + HPdOH
8. HBr + HPdOH —(1)→ H_2O + HPdBr

⟨26⟩ *Hydride* mechanism.

1. H_2O + $PdBr_2$ ←(0)→ HBr + BrPdOH
2. CO + BrPdOH ←(0)→ BrPd–COOH
3. H_2O + BrPd–COOH ←(0)→ HPdBr + **1**
4. H_2O + HPdBr ←(0)→ HBr + HPdOH
5. CO + HPdOH ←(0)→ HPd–COOH
6. C_2H_2 + HPd–COOH —(1)→ HOOC–Pd–CH=CH_2
7. CO + HOOC–Pd–CH=CH_2 —(1)→ HOOC–Pd–CO–CH=CH_2
8. H_2O + HOOC–Pd–CO–CH=CH_2 —(1)→ *Acrylic acid* + HPd–COOH

⟨27⟩ This is the simplest mechanism of the hybrid *hydride−hydroxycarbonyl* type, where acetylene undergoes the insertion into a H−Pd bond and a Pd−COOH bond is formed independently. Acrylic acid is formed by coupling of the vinyl and hydroxycarbonyl groups via the reductive elimination from a palladium complex.

1. H_2O + $PdBr_2$ ←(0)→ HBr + BrPdOH
2. CO + BrPdOH ←(0)→ BrPd–COOH
3. H_2O + BrPd–COOH ←(0)→ HPdBr + **1**
4. H_2O + HPdBr —(1)→ HBr + HPdOH
5. CO + HPdOH —(1)→ HPd–COOH
6. C_2H_2 + HPd–COOH —(1)→ HOOC–Pd–CH=CH_2
7. HOOC–Pd–CH=CH_2 —(1)→ *Acrylic acid* + Pd
8. HBr + Pd —(1)→ HPdBr

⟨28⟩ Hybrid *hydride−hydroxycarbonyl* type; differs from mechanism ⟨27⟩ in the order of CO and acetylene insertions.

1. $H_2O + PdBr_2 \leftarrow(0)\rightarrow HBr + BrPdOH$
2. $CO + BrPdOH \leftarrow(0)\rightarrow BrPd–COOH$
3. $H_2O + BrPd–COOH \leftarrow(0)\rightarrow HPdBr + \mathbf{1}$
4. $H_2O + HPdBr \text{—}(1)\rightarrow HBr + HPdOH$
5. $C_2H_2 + HPdOH \text{—}(1)\rightarrow HOPd–CH=CH_2$
6. $CO + HOPd–CH=CH_2 \text{—}(1)\rightarrow HOOC–Pd–CH=CH_2$
7. $HOOC–Pd–CH=CH_2 \text{—}(1)\rightarrow$ *Acrylic acid* + Pd
8. $HBr + Pd \text{—}(1)\rightarrow HPdBr$

⟨29⟩ Hybrid *hydride*−*hydroxycarbonyl* type.

1. $H_2O + PdBr_2 \leftarrow(0)\rightarrow HBr + BrPdOH$
2. $CO + BrPdOH \leftarrow(0)\rightarrow BrPd–COOH$
3. $H_2O + BrPd–COOH \leftarrow(0)\rightarrow HPdBr + \mathbf{1}$
4. $C_2H_2 + HPdBr \text{—}(1)\rightarrow BrPd–CH=CH_2$
5. $H_2O + BrPd–CH=CH_2 \text{—}(1)\rightarrow HBr + HOPd–CH=CH_2$
6. $CO + HOPd–CH=CH_2 \text{—}(1)\rightarrow HOOC–Pd–CH=CH_2$
7. $HOOC–Pd–CH=CH_2 \text{—}(1)\rightarrow$ *Acrylic acid* + Pd
8. $HBr + Pd \text{—}(1)\rightarrow HPdBr$

⟨30⟩ *Hydroxycarbonyl* mechanism, where $BrPd–CH{=}CH_2$ acts as an active species being formed at the preliminary stages before the catalytic cycle.

1. $H_2O + PdBr_2 \leftarrow(0)\rightarrow HBr + BrPdOH$
2. $CO + BrPdOH \leftarrow(0)\rightarrow BrPd–COOH$
3. $H_2O + BrPd–COOH \leftarrow(0)\rightarrow HPdBr + \mathbf{1}$
4. $C_2H_2 + HPdBr \leftarrow(0)\rightarrow BrPd–CH=CH_2$
5. $H_2O + BrPd–CH=CH_2 \text{—}(1)\rightarrow HBr + HOPd–CH=CH_2$
6. $CO + HOPd–CH=CH_2 \text{—}(1)\rightarrow HOOC–Pd–CH=CH_2$
7. $C_2H_2 + HOOC–Pd–CH=CH_2 \text{—}(1)\rightarrow H_2C=CH–Pd–CH=CH–COOH$
8. $HBr + H_2C=CH–Pd–CH=CH–COOH \text{—}(1)\rightarrow$ *Acrylic acid* + $BrPd–CH=CH_2$

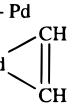
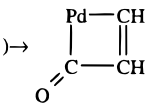
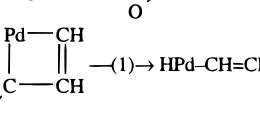
⟨31⟩ *Hydride* mechanism.

1. $H_2O + PdBr_2 \leftarrow(0)\rightarrow HBr + BrPdOH$
2. $CO + BrPdOH \leftarrow(0)\rightarrow BrPd–COOH$
3. $H_2O + BrPd–COOH \leftarrow(0)\rightarrow HPdBr + \mathbf{1}$
4. $C_2H_2 + HPdBr \leftarrow(0)\rightarrow BrPd–CH=CH_2$
5. $H_2O + BrPd–CH=CH_2 \leftarrow(0)\rightarrow HBr + HOPd–CH=CH_2$
6. $CO + HOPd–CH=CH_2 \text{—}(1)\rightarrow HOPd–CO–CH=CH_2$
7. $H_2O + HOPd–CO–CH=CH_2 \text{—}(1)\rightarrow$ *Acrylic acid* + HPdOH
8. $C_2H_2 + HPdOH \text{—}(1)\rightarrow HOPd–CH=CH_2$

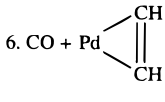
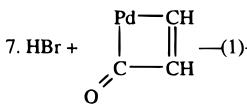
⟨32⟩ *Hydride* mechanism.

1. $H_2O + PdBr_2 \leftarrow(0)\rightarrow HBr + BrPdOH$
2. $CO + BrPdOH \leftarrow(0)\rightarrow BrPd–COOH$
3. $C_2H_2 + BrPd–COOH \leftarrow(0)\rightarrow BrPd–CH=CH–COOH$
4. $CO + BrPd–CH=CH–COOH \leftarrow(0)\rightarrow BrPd–CO–CH=CH–COOH$
5. $H_2O + BrPd–CO–CH=CH–COOH \leftarrow(0)\rightarrow HPdBr + \mathbf{3}$
6. $C_2H_2 + HPdBr \text{—}(1)\rightarrow BrPd–CH=CH_2$
7. $CO + BrPd–CH=CH_2 \text{—}(1)\rightarrow BrPd–CO–CH=CH_2$
8. $H_2O + BrPd–CO–CH=CH_2 \text{—}(1)\rightarrow$ *Acrylic acid* + HPdBr

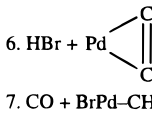
⟨33⟩ *Metallocyclic* mechanism.

1. $H_2O + PdBr_2 \leftarrow(0)\rightarrow HBr + BrPdOH$
2. $CO + BrPdOH \leftarrow(0)\rightarrow BrPd–COOH$
3. $H_2O + BrPd–COOH \leftarrow(0)\rightarrow HPdBr + \mathbf{1}$
4. $HPdBr \text{—}(1)\rightarrow HBr + Pd$
5. $C_2H_2 + Pd \text{—}(1)\rightarrow$ 
6. $CO +$  $\text{—}(1)\rightarrow$
7. $H_2O +$  $\text{—}(1)\rightarrow HPd–CH=CH–COOH$
8. $HBr + HPd–CH=CH–COOH \text{—}(1)\rightarrow$ *Acrylic acid* + HPdBr

⟨34⟩ *Metallocyclic* mechanism.

1. $H_2O + PdBr_2 \leftarrow(0)\rightarrow HBr + BrPdOH$
2. $CO + BrPdOH \leftarrow(0)\rightarrow BrPd–COOH$
3. $H_2O + BrPd–COOH \leftarrow(0)\rightarrow HPdBr + \mathbf{1}$
4. $HPdBr \text{—}(1)\rightarrow HBr + Pd$
5. $C_2H_2 + Pd \text{—}(1)\rightarrow$ 
6. $CO +$  $\text{—}(1)\rightarrow$
7. $HBr +$  $\text{—}(1)\rightarrow BrPd–CO–CH=CH_2$
8. $H_2O + BrPd–CO–CH=CH_2 \text{—}(1)\rightarrow$ *Acrylic acid* + HPdBr

⟨35⟩ A vinyl group is formed via steps 4−6, which do not imply the direct insertion of acetylene into a Pd−H bond. Other steps of the mechanism resemble the hydride mechanism, where CO is inserted into the vinyl complex. Because in this mechanism metallacyclopropene is formed and then is attacked by H^+, this can be regarded as a hybrid *metallocyclic*−*hydride* mechanism.

1. $H_2O + PdBr_2 \leftarrow(0)\rightarrow HBr + BrPdOH$
2. $CO + BrPdOH \leftarrow(0)\rightarrow BrPd–COOH$
3. $H_2O + BrPd–COOH \leftarrow(0)\rightarrow HPdBr + \mathbf{1}$
4. $HPdBr \text{—}(1)\rightarrow HBr + Pd$
5. $C_2H_2 + Pd \text{—}(1)\rightarrow$ 
6. $HBr +$  $\text{—}(1)\rightarrow BrPd–CH=CH_2$
7. $CO + BrPd–CH=CH_2 \text{—}(1)\rightarrow BrPd–CO–CH=CH_2$
8. $H_2O + BrPd–CO–CH=CH_2 \text{—}(1)\rightarrow$ *Acrylic acid* + HPdBr

We stopped requesting more complex pathways after MECHEM found mechanisms of all three types (hydride, hydroxycarbonyl, and metallocyclic). The program generated 35 pathways to acrylic acid, among which 20 pathways belong to hydroxycarbonyl mechanisms, 2 pathways are metallocyclic, 10 pathways are hydride mechanisms, 2 pathways are of a hydride−hydroxycarbonyl hybrid, and 1 mechanism is of a metallocyclic−hydride type hybrid.

Let us first analyze Scheme 1, which is an important result of the ChemNet run. As can be seen, a variety of unsaturated aldehydes were reported by the program, which have not yet been observed in solutions of palladium complexes, although a special study is needed that would confirm or disprove their formation. Among the double carbonylation products, oxalic acid (**6**) in the form of oxalate was experimentally observed. Cyclobutanedione (**10**) was observed in solutions of iron complexes. Products **16** and **17** were found to be formed in solutions of rhodium, iron, and other complexes.[9] The procedure of coupling of the two programs can be used to isolate the pathways to each of these products. However, to avoid the inclusion of palladium-containing species in the overall stoichiometry of these pathways, the appearance of redox reactions in the network will be needed. Hence, in that case, one would need to add the transforms of Pd(0) oxidation and Pd(II) reduction.

Our analysis of the chemical implications of the computer-generated pathways suggests that the specific feature of these pathways is the presence of the steps

of the formation of catalytically active species (palladium complexes). These are the steps with zero stoichiometric numbers. For example, five of the eight steps of hydride mechanism ⟨22⟩ possess stoichiometric numbers of zero. Conjecturing the catalyst formation pathways is very useful for both mechanistic studies and catalyst design, because the program reports all conceivable pathways of the catalyst precursor transformation to the actual catalysts. In particular, hydroxycarbonyl mechanisms contain the following species serving as actual catalysts: $PdBr_2$, BrPdOH, BrPdCOOH, HOPdCOOH, $Pd(COOH)_2$, $BrPdCH{=}CH_2$, HPdOH, HPdCOOH, and HPdBr. Among these active complexes, only $PdBr_2$ was considered for the alcoholate mechanism of acrylate synthesis.[1,19] Interestingly, the hydride complexes of palladium may participate in the hydroxycarbonyl mechanism (see ⟨6⟩ and ⟨16⟩−⟨19⟩). Hydroxycarbonyl complexes, in turn, may act as intermediate species in the hydride mechanisms both in the steps of a catalyst formation and in the body of a catalytic cycle (see ⟨21⟩, ⟨22⟩, and ⟨26⟩). Even vinyl derivatives may be the catalysts of the process, where the vinyl group simply acts as a ligand rather than a synthon of a target molecule, ⟨30⟩. The effect of the formation of extraneous fragments in catalytic species should be taken into account when designing experiments to test mechanistic hypotheses. To our knowledge, no study has been devoted to this effect.

The simplest hydroxycarbonyl mechanism, ⟨1⟩, was well-documented for the acetylene hydrocarbalkoxylation reactions (reaction 2). Step 3 is considered as a rate-limiting step, whereas steps 1 and 2 are fast pseudoequilibrium steps.[26] Drent proposed this mechanism for the commercial synthesis of methylmethacrylate in the methanol solution of cationic palladium complexes, although no convincing evidence for the formation of a key intermediate was reported.[14]

The hydroxycarbonyl mechanisms largely contain the steps of the Pd−Br bond hydrolysis. These steps (except for hydrolysis of $PdBr_2$ in the first step that produces BrPdOH or BrPdOR) were not proposed earlier. Pd−Br hydrolysis steps were prominent in the pathways conjectured by the program. Because the ligands

$$BrPdCOOH + H_2O \longrightarrow HBr + HOPdCOOH$$

$$BrPdCH{=}CHCOOH + H_2O \longrightarrow HBr + HOPdCH{=}CHCOOH$$

$$BrPdH + H_2O \longrightarrow HBr + HPdOH$$

−COOH, −CH=CHCOOH, and −H are highly *trans*-activating, substitution of Br^- in these intermediates by a water molecule followed by deprotonation of the coordinated water molecule may be even more favorable than with $PdBr_2$.

An interesting result of the computer-aided generation of mechanistic hypotheses is the conjecture of $Pd(COOH)_2$ as an intermediate of acrylic acid synthesis (pathways ⟨6⟩, ⟨12⟩, ⟨13⟩, ⟨15⟩, ⟨17⟩, and ⟨22⟩). The formation of this kind of species was considered in the synthesis of oxalates by oxidative carbonylation of alcohols in the presence of palladium(II) complexes.[27] However, the possibility of acetylene insertion into a Pd−COOH bond was not even discussed.

$$Pd(COOH)_2 + C_2H_2 \longrightarrow HOOCPdCH{=}CHCOOH$$

The reaction of nucleophilic substitution of Pd by a water molecule with electrophilic assistance of H^+ in the bis(hydroxycarbonyl)palladium complex (pathways ⟨18⟩ and ⟨22⟩) is plausible, although earlier it was overlooked.

$$Pd(COOH)_2 + H_2O \longrightarrow HOCOOH + HPdCOOH$$

A similar reaction in the backward direction for a slightly different complex seems less plausible (pathways ⟨16⟩−⟨19⟩ and ⟨23⟩) because the basicity of the hydroxy group of the carbonic acid is too low to withdraw a proton from the palladium hydride.

$$HPdBr + HOCOOH \longrightarrow H_2O + BrPdCOOH$$

The acidolysis step involving the Pd−C bond in the case of the strong electrophilic hydroxycarbonyl group and nucleophilic acryloyl group is hardly probable (pathways ⟨11⟩−⟨15⟩).

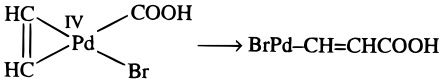
$$HBr + HOOC{-}Pd{-}CH{=}CH{-}COOH \longrightarrow HCOOH + BrPdCH{=}CHCOOH$$

Analysis of the hydroxycarbonyl mechanisms shows that the list of transforms should be supplemented with the transform $C{-}Pd^{II}{-}H \rightarrow C{-}H + Pd^0$ because, in a number of mechanisms, the intermediate HPdCH=CH−COOH is formed which can immediately transform into acrylic acid via reductive elimination.

In all generated pathways, $PdBr_2$ is the precursor of catalytically active species, e.g., even the simplest hydride mechanism ⟨7⟩ involves three steps of catalyst (HPdBr) formation. The hydride mechanism in the presence of palladium complexes was experimentally proven by a number of studies.[23,26,28,29] In the case of nickel carbonyl complexes, kinetic arguments are available in favor of this mechanism.[30] The complex $HNi(CO)_3CN$, which is active in the carbonylation, is well-characterized.[31]

The catalysts in the hydride mechanisms proposed by the computer program are HPdBr, HPdOH, and HPdCOOH. The intermediate HPdOH is formed via several steps wherever it appears, because there was no transform for the step $Pd^0 + H_2O \rightarrow HPdOH$. Although this step is theoretically quite possible[28] and also convenient for model building, we elected to exclude it because of the lack of sufficient experimental evidence in its favor.

The list of conjectured pathways is useful also because it contains two types of hybrid mechanisms: hydride−hydroxycarbonyl ⟨27⟩−⟨29⟩ and metallocyclic−hydride ⟨35⟩. The metallocyclic−hydroxycarbonyl mechanisms were not generated because the maximum oxidation state of palladium was restricted to II. Hybrid mechanisms were hypothesized by Bruk,[25] although the procedure was not formal.



Consideration of the list of hypothetical mechanisms (which within the framework of transforms, constraints, and chosen pathway complexities should be exhaustive) will allow a researcher to be more correct in interpreting the experimental findings. Thus, the fact that a hydride

(30) Bruk, L. G.; Temkin, O. N. *Khim. Prom-st.* **1993**, 57−63.
(31) Amer, I.; Alper, H. *J. Organomet. Chem.* **1990**, *383*, 573−577.

(hydroxycarbonyl, metallocyclic) species is found in the solution does not by itself mean that the mechanism is hydride (hydroxycarbonyl, metallocyclic). The list in Scheme 2 serves as a good illustration of this idea, which is also supported by the possibility of hybrid pathways.

Conclusion

Knowledge-based programs for the elucidation of reaction mechanisms must respect the prior knowledge possessed by the chemist/user if they are to be useful in chemistry practice. We have distinguished two types of prior knowledge: knowledge of what can and cannot occur. To the extent that this knowledge is reliable, one should ideally make use of both types. If the reaction is complex, then either approach alone may be insufficient to overcome the potentially explosive combinatorics.

This paper has demonstrated how to ally these two approaches as embodied in the programs ChemNet and MECHEM. The protocol is that the empirical program ChemNet is charged with applying user-formulated transforms to find all conceivable elementary steps, intermediates, and byproducts. The logical program MECHEM has been modified to use this information (i.e., any absent step or species is to be rejected) in order to find, from within the large reaction network, simpler pathways that meet the overall stoichiometry, contain no superfluous steps, and include the needed steps of catalyst formation.

Our computer-aided approach turned up pathways belonging to the types known from the literature: hydride, hydroxycarbonyl (alcoholate-like), and metallocyclic. We also found hybrid pathways. Some of these pathways were earlier overlooked due to the absence of comprehensive computerized searches. Our results suggest which intermediates species should be sought within solutions of palladium complexes in order to test these hypothetical pathways.

Our further work will include (1) applying this methodology to other reaction systems and (2) testing the feasibility of a purely constraint-based approach to acrylic-acid synthesis and comparison of the outcome.

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