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Harnessing the Power of the Water-Gas Shift Reaction for Organic Synthesis

Andrea Ambrosi and **Scott E. Denmark**[*]
Department of Chemistry, University of Illinois at Urbana-Champaign Urbana, IL 61801 (USA)

Abstract

Since its original discovery over a century ago, the water-gas shift reaction (WGSR) has played a crucial role in industrial chemistry, providing a source of H_2 to feed fundamental industrial transformations such as the Haber–Bosch synthesis of ammonia. Although the production of hydrogen remains nowadays the major application of the WGSR, the advent of homogeneous catalysis in the 1970s marked the beginning of a synergy between WGSR and organic chemistry. Thus, the reducing power provided by the CO/H_2O couple has been exploited in the synthesis of fine chemicals; not only hydrogenation-type reactions, but also catalytic processes that require a reductive step for the turnover of the catalytic cycle. Despite the potential and unique features of the WGSR, its applications in organic synthesis remain largely underdeveloped. The topic will be critically reviewed herein, with the expectation that an increased awareness may stimulate new, creative work in the area.

Graphical Abstract

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[*] sdenmark@illinois.edu.

Keywords

carbon monoxide; heterogeneous catalysis; homogeneous catalysis; reduction; transition metals

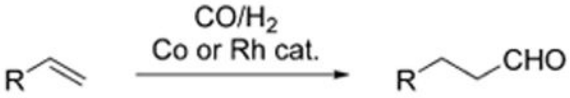
1. Introduction

The water-gas shift reaction (WGSR) is a transformation of long-standing industrial relevance that converts a mixture of carbon monoxide and water into hydrogen and carbon dioxide [Eq. (1)].

$$CO+H_2O \rightleftharpoons CO_2 + H_2 \quad (1)$$

Many industrial manufacturing processes rely on synthesis gas ($CO + H_2$) as the raw material.[1] This mixture can be obtained either by coal gasification or, more commonly, from steam reforming of natural gas. Depending upon the method of production, synthesis gas will constitute different ratios of CO and H_2. The WGSR is employed to adjust this ratio to the optimal value, or to remove CO altogether by converting it to CO_2. Thus, the WGSR finds application in the Haber–Bosch process for ammonia synthesis,[2] in which high purity H_2 is obtained from synthesis gas by removal of CO (which would poison the Fe-based ammonia synthesis catalyst). Also, it is used to tune the H_2/CO ratio in the production of methanol[3] and in the Fischer–Tropsch process for the synthesis of hydrocarbons.[4]

The WGSR is not limited to industrial applications, but has also been used sporadically in organic synthesis as a method to carry out reductive processes. In these instances, H_2 is not a direct product of the reaction, but rather, the reductive potential of the WGSR is channeled toward the reduction of organic substrates, or exploited to insure turnover of catalytic cycles. The hydroformylation reaction is an excellent example to illustrate this concept. In its original incarnation, the hydroformylation reaction converts terminal alkenes into homologous aldehydes utilizing a mixture of CO and H_2 over a Co or Rh catalyst [Eq. (2)].[5] In 1953, Reppe and Vetter introduced a modified protocol that used H_2O in lieu of H_2, and $Fe(CO)_5$ as the catalyst in basic media [Eq. (3)].[6] Under these conditions, the WGSR generates intermediate metal-hydride complexes that account for the overall reductive process. Formally, this can be seen as formation of H_2 in situ.



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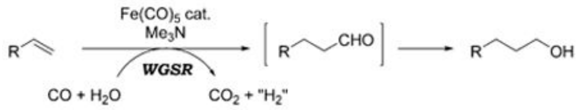

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In addition to hydroformylation, the operation of the WGSR has also been documented in several other reductive processes, including nitro reduction, reductive amination, hydrogenation of carbonyls and alkenes.[7]

Our group became interested in the WGSR in 2008, after the serendipitous discovery that the WGSR was operative in a transformation being studied in our laboratories.[8] At that time, the goal was to develop an allylation reaction of aldehydes that was truly catalytic in metal (i.e. without stoichiometric amounts of metal reducing agents). Two decades earlier, Watanabe and co-workers had reported the formation of homoallylic alcohols from allyl acetate and aldehydes under ruthenium catalysis using triethylamine as the stoichiometric reducing agent (Scheme 1a).[9] The reaction required harsh conditions and high pressures of CO to stabilize the low-valent ruthenium carbonyl catalyst, but nevertheless suited our requirement of being catalytic in metal. In an attempt to identify a more practical protocol, reaction conditions were surveyed in our laboratories using a six-well autoclave. To our surprise, it was found that the reaction proceeded much faster after the autoclave had been cooled and opened in air for sampling and monitoring, a fact that was attributed to the presence of oxygen or water. Control experiments showed indeed that addition of water significantly accelerated the reaction and allowed for milder conditions to be employed (Scheme 1b). Moreover, it was found that the conversion improved using a substoichiometric amount of triethylamine (0.1 equiv), whereas the use of excess amine was detrimental. Evidently, in our case the base was not the stoichiometric reducing agent, as initially shown by Watanabe et al.[10] Thus, it was concluded that the turnover of the catalytic cycle was originating instead from the combined action of CO and H_2O in the WGSR.

The topic of the WGSR in its developments and industrial facets has been reviewed extensively.[11] However, only one review, dating back to 1985, describes the application of the WGSR to organic synthesis.[7] The purpose of this review is to fill this gap and provide a compendium of examples wherein, knowingly or not, the WGSR has been used as a way of promoting organic reactions. To ensure a better understanding of the context, the discussion of the WGSR in organic synthesis will be preceded by a historical and mechanistic prelude.

2. The Water-Gas Shift Reaction

2.1. Historical Overview

The WGSR was first reported by Ludwig Mond in 1888,[12] but its importance was not recognized until the development of the Haber–Bosch process for the synthesis of ammonia.[2,13] The water gas (a mixture of CO and H_2 obtained from steam and incandescent coal) was employed as the source of hydrogen. However, removal of excess CO by liquefaction proved to be challenging on a large scale. The WGSR provided an efficient method for the removal of CO by conversion to CO_2 (more easily removed by dissolution in water), with the benefit of producing additional H_2 for ammonia synthesis. In an attempt to optimize the process, researchers at BASF initiated an intensive research program in the early 1910s and eventually settled on a Fe_2O_3-Cr_2O_3 heterogeneous catalyst. This system, named the high temperature (HT) shift catalyst, operated above 400 °C and could achieve CO levels of 2–4 % at the exit of the reactor.[14] In the early 1960s, the CO conversion was further improved by the discovery of a series of Cu-ZnO catalysts, called low temperature (LT) shift catalysts, which operated at lower temperature (200 °C) and afforded an exit CO concentration of 0.1–0.3 %.[15] The higher efficiency observed at lower temperature is a direct consequence of the thermodynamics of the WGSR (see below). Consequently, further research efforts focused on the identification of more active catalysts that could operate at still lower temperatures.

In 1932 Hieber et al. reported that metal carbonyl complexes reacted with aqueous bases to form metal carbonyl hydrides. Following acidification, H_2 and CO_2 were released [Eq. (4)].[16]

$$\begin{aligned} & \mathrm{Fe(CO)_5} + 2\mathrm{OH^-} \rightarrow \mathrm{H_2Fe(CO)_4} + \mathrm{CO_3}^{2-} \\ & \xrightarrow{+2\mathrm{H}^+} 1/2\,\mathrm{Fe(CO)_5} + 1/2\,\mathrm{Fe(CO)_3} + \mathrm{H_2} + \mathrm{CO_2} + \mathrm{H_2O} \end{aligned} \tag{4}$$

In the 1970s, the analogy between these observations and the steps in the WGSR was eventually recognized. Thus, metal carbonyls were investigated as potential low-temperature, homogeneous WGSR catalysts, leading to a series of patents[17] and four independent publications in 1977. Ford et al.[18] and Pettit et al.[19] reported that several transition metal carbonyl complexes are active WGSR catalysts when combined with organic or inorganic bases at temperatures as low as 100 °C. In contrast, Eisenberg et al.[20] and Zudin et al.[21] were able to show that the WGSR can also take place in acidic media. These seminal reports launched decades of intensive research aimed at identifying more efficient homogeneous catalysts. Hundreds of soluble transition metal complexes, representing over 20 d-block elements, have been examined for their ability to catalyze the WGSR and the results have been thoroughly chronicled.[22]

More recently, a renewed interest in heterogeneous WGSR catalysis led to the discovery of extremely active, supported gold catalysts. The initial investigations by Andreeva et al. showed that Fe_2O_3-supported Au catalyzes the WGSR in the 160–200 °C range, whereas Fe_2O_3 alone is poorly reactive.[23] Titania (TiO_2)-,[24] ceria (CeO_2)-,[25] and zirconia (ZrO_2)-supported[26] gold catalysts are equally reliable. The activity of supported gold catalysts is highly dependent on the method of deposition, the structure and size of the nanoparticles. Investigation in the area is still ongoing, especially with regard to the reaction mechanism, the nature of active sites and their relationship to catalytic activity.[27]

Remarkably mild conditions for the WGSR have been achieved through the use of photocatalysis.[28] In 1980, Sato and White reported that UV-irradiated Pt/TiO_2 catalyzed the WGSR at room temperature and below![29] Following this initial disclosure, a number of soluble transition metal complexes were found to be active photocatalysts for the WGSR at ambient pressure and temperature.[30] Ir-bipyridine complexes, which are widely utilized for their photocatalytic properties, have been investigated by Ziessel in their capacity to promote the WGSR.[31]

Despite the advances in the low temperature WGSR brought about by the use of homogeneous and photocatalysis, these systems have yet to match the levels of performance and robustness of heterogeneous catalysts. Thus, the HT and LT shift catalysts, originally intended for the synthesis of ammonia and improved over the course of the years, still represent today the basis for the catalysis of the WGSR on an industrial scale.

2.2. Thermodynamics and Mechanism

The WGSR is a reversible, moderately exothermic reaction ($\Delta H^0 = -9.8$ kcalmol^{-1}). As such, according to the Van 'tHoff equation, the equilibrium constant decreases with increasing temperature. This aspect, demonstrated experimentally by Haber as early as 1909,[32] explains the higher efficiency of the LT shift catalysts, although at the expense of the reaction rate. In accordance with Le Châtelier's principle, the equilibrium constant is not affected by the pressure since the number of moles of reactant and products is independent of the position of the equilibrium.

The kinetics and mechanism of the WGSR under heterogeneous catalysis have been widely investigated and have been the subject of debate over decades.[33] Two limiting mechanisms have been proposed: 1) the associative mechanism, which involves the adsorption of H_2O and CO, the formation of an intermediate on the surface of the catalyst, and its decomposition into CO_2 and H_2, and 2) the regenerative or redox mechanism, which entails reduction of H_2O to H_2 with concomitant oxidation of the catalytic surface, followed by oxidation of CO to CO_2. Although the consensus mechanism for the HT catalysts is the regenerative, redox proposal, the mechanistic scenario for LT catalysts appears much less well understood and is highly dependent upon the metal and the experimental conditions.[34]

The discovery of homogeneous catalysts has opened up the possibility for the detection and characterization of reactive intermediates, leading to a more refined and relatively well understood mechanistic picture.[22b] The catalytic cycle shown in Scheme 2 represents the generally accepted mechanism for the WGSR catalyzed by a metal–carbonyl complex (**i**) under basic conditions. The cycle consists of five steps: A) nucleophilic activation of coordinated CO to form hydroxycarbonyl complex **ii**, B) decarboxylation to form metal hydride **iii**, C) protonation, D) reductive elimination of H_2 from the dihydrido complex **iv**, and E) binding of CO to the coordinatively unsaturated intermediate **v**.

In the $Fe(CO)_5$ system investigated by King et al., the mechanism follows the general catalytic cycle with step A being turnover limiting.[35] DFT studies also support this catalytic cycle, although alternative proposals have been formulated.[36] The mechanism appears to be more complex with Ru, Os, Rh and Ir carbonyl complexes due to the formation of metal clusters.[37] A different pathway has been suggested for Group 6 (Cr, Mo, W) metal–carbonyl complexes. Activation of free CO forms anionic formate (F), which coordinates to the metal (G). Decarboxylation then takes place from a formate–metal complex **vi** rather than a hydroxycarbonyl–metal complex **ii**.[38]

The occurrence of the WGSR under acidic conditions is a much less general phenomenon. For instance, whereas $Ir_4(CO)_{12}$, $Fe(CO)_5$ and $Ru_3(CO)_{12}$ are all active catalysts in alkaline solution, only the latter is active in the presence of H_2SO_4.[22a,39] A plausible mechanism was proposed by Ford et al. using $Ru_3(CO)_{12}$, which generates the active $Ru_2(CO)_9$ catalyst **vii** in situ (Scheme 3).[40]

Under acidic conditions, coordinated CO must be sufficiently activated toward nucleophilic attack by water rather than hydroxide (step J, as opposed to A). This activation can be achieved if protonation of the metal center (H) occurs prior to nucleophilic attack of CO. Protonation raises the oxidation state by two, decreases the extent of CO back-bonding and therefore renders CO more susceptible to nucleophilic attack. Similar mechanistic proposals have been formulated for related acid-catalyzed processes.[41]

The mechanism of the WGSR under *photocatalysis* has been described for $[Ir(bipy)Cp^*Cl]^+Cl^-$ (**xii**, R = COOH) in a landmark study by Ziessel (Scheme 4).[31c] Following the initial CO coordination and activation steps (M and N), turnover-limiting decarboxylation yields the neutral, coordinatively unsaturated complex **xv**, the intermediacy of which has been established by direct isolation. Protonation of the metal center furnishes the hydrido intermediate **xvi**, which is prone to photoexcitation and protonation of the excited state **xvii**, and reductive elimination of H_2 thereby (R). The requirement for light in the final protonation step was demonstrated by the lack of reactivity of complex **xvi** in the dark.

3. The Water-Gas Shift Reaction in Organic Synthesis

The vast amount of research done since the 1970s on homogeneous catalysis has demonstrated the possibility of harnessing the reducing potential of the WGSR to drive reductive organic transformations. The obvious advantages of this synergy include low impact of waste, scalability and availability of precursors. However, despite all of the research into improving the efficiency of the WGSR, the process nowadays is mainly utilized for the generation of hydrogen using heterogeneous catalysis, while its applications to the synthesis of fine chemicals remain underdeveloped. The following sections will illustrate the potential for application of the WGSR to a myriad of organic transformations and identify areas of future development.

The reduction potential of the WGSR can be exploited in organic synthesis in two different ways. In the first approach, the WGSR provides reducing equivalents that can be directly incorporated into the final product (Figure 1a). Essentially this corresponds to the delivery of H_2 as would be achieved through a hydrogenation reaction, although free H_2 is not directly involved. In the second approach, the reducing potential of the WGSR is applied to a metal catalyst that has to be reduced to its active form to reenter the catalytic cycle (Figure 1b). In the absence of the WGSR, transformations of this type would require a stoichiometric amount of a reducing agent, usually a low-valent metal (Mn, Zn, SmI_2, $SnCl_2$, etc.). It should be highlighted that, whereas in the former case the WGSR offers modest to no practical advantage over a standard hydrogenation, the latter case eliminates the need for a stoichiometric amount of metal, thus reducing the waste stream and enhancing atom economy.

Another important distinction involves the type of transformation that is accomplished. The vast majority of reactions employing the WGSR entail the reduction of a functional group without a carbon–carbon bond forming event. These transformations usually fall into the category of incorporation of H_2 (as in the reduction of nitro groups, imines, alkenes and carbonyls), although there are exceptions (deoxygenation of epoxides). Only a limited number of WGSR-promoted reactions accomplish the formation of a carbon–carbon bond. Among those, some rely on CO as both the reducing agent and the source of carbon (hydroformylation and other carbonylation reactions), whereas others utilize an external building block to forge the new carbon-carbon bond (allylation, alkylation). The following sections are arranged on the basis of this classification.

This review covers only transformations that employ the CO/H_2O couple as the reducing agent in the presence of a metal catalyst. Reductions carried out with CO alone (without water and/or hydroxide) will not be covered. Likewise, reactions that employ a metal carbonyl complex in stoichiometric amounts are not included in this review.

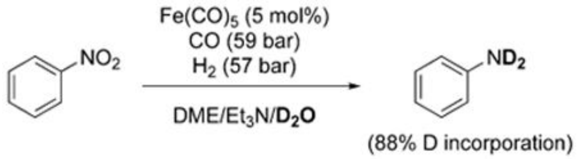
3.1. Non-C–C Bond Forming Reactions

3.1.1. Nitro Reduction—The reduction of nitroarenes to anilines represents the most common application of the WGSR to organic synthesis. Traditionally, this transformation is carried out using stoichiometric amounts of reducing agents (such as Fe or Zn powder, Na_2S, $SnCl_2$), or catalytic hydrogenation over Pd, Pt or Ni.[42] The use of the WGSR as the source of reducing equivalents allows for a mild and chemoselective process. The nitro-to-amine transformation is a $6e^-$-reduction, therefore three equivalents of CO are required per mole of nitro compound [Eq. (5)]

$$\mathrm{Ar{-}NO_2 + 3CO + H_2O \rightarrow Ar - NH_2 + 3CO_2} \quad (5)$$

The reduction of nitrobenzene to aniline with CO/H_2O was first reported by Iqbal in 1971 using Rh catalysts and organic bases (Scheme 5a).[43] More systematic studies were undertaken by Pettit et al. in 1978 using Fe, Rh, Ru, Os, Ir carbonyl complexes and aqueous solutions of trialkylamines (Scheme 5b).[44]

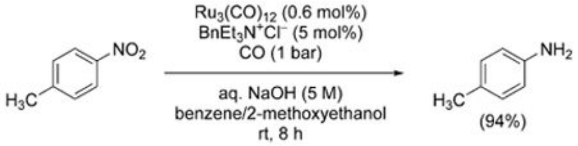
The metal complexes under examination are active catalysts for the WGSR and do generate H_2 when exposed to CO/H_2O. However, Pettit et al. suggested the involvement of a metal-hydride intermediate $[HM(CO)_n]^-$ as the reducing agent (formed via CO activation/decarboxylation, as **iii** in Scheme 2),[45] as opposed to in situ generation of H_2. This point was demonstrated by the incorporation of deuterium in the product when the reaction was carried out in the presence of CO/D_2O/H_2 [Eq. (6)]. From these results, it appears



(6)

evident that H_2 is not causing the reduction of nitrobenzene, even though it may be generated under the reaction conditions.

In 1980, Alper and Amaratunga described a system capable of operating under mild conditions (ambient pressure and temperature).[46] The system is comprised of $Ru_3(CO)_{12}$ and $BnEt_3N^+Cl^-$ as the phase transfer catalyst in a mixture of 5M aqueous NaOH/benzene/2-methoxyethanol [Eq. (7)]. The increased reactivity is attributed to the solubility of the putative ammonium–ruthenate intermediate $[BnEt_3N]^+$ $[HRu_3(CO)_{11}]^-$ in the organic phase.



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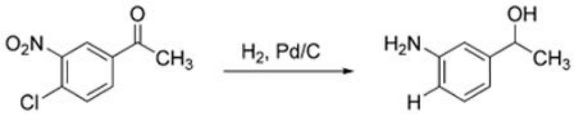
These initial reports stimulated dozens of further elaborations,[47] and the topic is still an active field of research. A summary of catalysts and reaction conditions that have been reported is provided in Table 1. Most of the protocols employ basic or neutral conditions, although there are examples of acidic media (entries 12 and 14). Generally, the reaction conditions have been optimized for nitrobenzene as a benchmark and extended to a limited number of nitroarenes, making it impossible to come to conclusions regarding their generality. A few methods, however, possess remarkable generality and functional group tolerance, and will be discussed separately (entries 6, 17, 22, 35, 39). The most user-friendly protocols appear to be those that employ phase-transfer catalysis (entries 4 and 11) or additives such as amines and phosphines (entries 15 and 16), as they operate under mild conditions (room temperature and ambient pressure) with readily available reagents. The use of selenium as the catalyst, which generates H_2Se under WGSR conditions, is also well established (entries 5, 26, 32).

One of the remarkable features of the nitro reduction under WGSR conditions is the high chemoselectivity, which often cannot be guaranteed using other reduction protocols.[96] For example, all three reduction-susceptible functional groups of 4-chloro-3-nitroacetophenone are reduced unselectively by a standard hydrogenation over Pd/C [Eq. (8)].[97] Conversely, under WGSR conditions, reduction of the nitro group occurs selectively even in the presence of other



(8)

functional groups prone to reduction (alkenes, alkynes, halides, nitriles, ketones, aldehydes, esters, etc., Figure 2).[53,68,73,90,94]

A noteworthy sequence of complementary reduction methods allows for the preparation of **5**, a tritiated photoaffinity ligand for the dopamine reuptake transporter protein (Scheme 6).[98] Reduction of the nitro group in **1** under Alper's phase-transfer conditions affords amine **2** without reduction of the unsaturated amide. Lithium aluminum hydride was used to carry out the deoxygenation of the amide, followed by the introduction of the tritium label by hydrogenation of 3 (T_2, Pd/C).

WGSR conditions display a marked preference for the reduction of aromatic as compared to aliphatic nitro groups; aliphatic nitro groups are normally unreactive (Figure 3a).[49,55] However, conditions have been developed that can effect the reduction of aliphatic nitro groups to amines (Figure 3b)[46,90] or the partial reduction to nitriles (Figure 3c).[52,99]

Mechanistic investigations of the reduction of nitro groups by CO/H_2O are abundant. From a qualitative standpoint, the participation of H_2 is clearly excluded on the basis of important facts: 1) the reduction is often less efficient if H_2 is used instead of CO/H_2O ;[61] 2) some of the systems used for the nitro reduction are not active WGSR catalysts and do not produce CO_2 and H_2 in the absence of a nitro compound;[68,86,95] 3) even for those systems that are capable of producing H_2, competition/labelling experiments demonstrate that the nitro group is not directly reduced by H_2;[44] 4) functional groups that are susceptible to reduction by H_2 do not react (Figure 2).

The generally accepted catalytic cycle, supported by the isolation of some reactive intermediates,[100] involves two sequential deoxygenation steps (Scheme 7). Following the formation of cycloadduct **xviii** between the nitro group and ligated CO decarboxylation produces the η^2-nitrosoarene complex **xix**. Insertion of CO leads to the four-membered cycloadduct **xx** which decarboxylates to form the nitrenoid complex **xxi**. The nitrenoid affords the aniline product after a further $2e^-$-reduction, either WGSR-driven (via metal-hydride **xxii**),[101] or via formation of an isocyanate and its subsequent hydrolysis/decarboxylation.[56,68,102] An exception to this general catalytic cycle is the reduction using the Se/amine system. The reaction of selenium with CO/aqueous amine produces H_2Se,[103] which is believed to be the actual reducing agent.[50,87b]

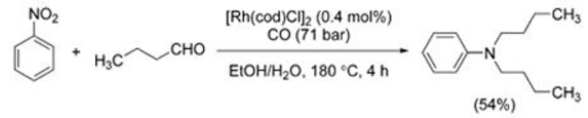
3.1.2. Downstream Reactions From Nitro Reduction—

The reduction of nitro groups to amines represents only a small portion of the vast amount of reductive processes that can be accomplished from nitro compounds using CO as the reducing agent. As illustrated in Scheme 7, the reaction of a nitro group with CO generates a nitrenoid intermediate **xxi** which, in the absence of water, may undergo different reaction pathways.[97,104,105] Thus, depending on the reaction conditions, nitro compounds can be converted into isocyanates, azo compounds, imines, ureas, or carbamates (Figure 4a). The nitrenoid can also react intramolecularly with a tethered functional group (olefinic or aromatic C–H, alcohol, amine, etc.), lending itself to the synthesis of heterocycles (Figure 4b).

These sets of reductive transformations, which do not rely on the CO/H_2O couple, are outside the scope of this review. However, similar approaches have been used to combine the WGSR-driven nitro reduction with a tandem transformation.

The reductive amination reaction from nitroarenes and carbonyl compounds falls into this category, and proceeds through the in situ formation of an imine, which is reduced under WGSR conditions. The first example was reported by Watanabe et al. in 1980.[106] In the presence of $[Rh(cod)Cl]_2$ or $[Rh(nbd)Cl]_2$, nitroarenes and linear, aliphatic aldehydes furnish reductive amination products in moderate yield [Eq. (9)]. Under these conditions, *N,N*-dialkylated anilines result.

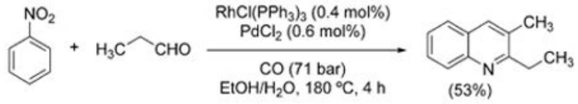
An improved variant possessing increased synthetic utility was recently reported by Park and Chung.[107] The use of a Co_2Rh_2/C heterogeneous catalyst enabled the synthesis of a number of secondary amines from nitroarenes, aromatic aldehydes and ketones (Figure 5). These conditions avoid double alkylation, but the substrate scope remains limited to aromatic nitro compounds and benzaldehydes.



(9)

It might be tempting to assume that the nitro compound is reduced to the aniline first and condensation with the aldehyde follows, but this appears not to be the case. Indeed, imines form readily from nitroarenes and aldehydes by a CO-mediated reduction without the need for H_2O.[108] In addition, control experiments wherein the aldehyde is combined directly with the aniline yield no product, showing that the aniline is not a competent intermediate.[106b] Therefore, it was suggested that the imine is formed directly from the nitrenoid intermediate **xxiii** (Scheme 8) via oxaziridine **xxiv** and nitrone **xxv**, which is reduced by CO to the imine.[109] The reductive amination product is then obtained via WGSR reduction (Section 3.1.3).

Over the course of their studies on reductive amination from nitroarenes, Watanabe et al. also found that, under modified conditions ($RhCl(PPh_3)_3$ and $PdCl_2$), the formation of dialkylated anilines was suppressed and quinolines were obtained instead [Eq. (10)].[106] Although the transformation is overall redox-neutral, the aniline formed via WGSR reduction of the nitroarene is along the reaction pathway. Quinoline formation occurs by self-condensation of the aldehyde, conjugate addition of the aniline, and oxidative cyclization (Skraup quinoline synthesis).



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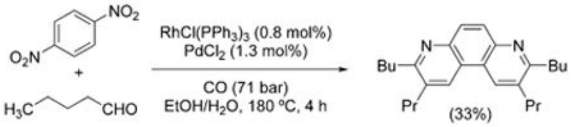
Similarly, the syntheses of phenanthrolines [Eq. (11)][110] and quinolines from 2-nitrochalcones [Eq. (12)][111,112] have been reported. In the latter case, the intermediacy of the



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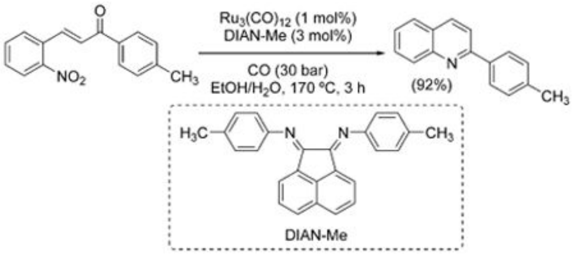
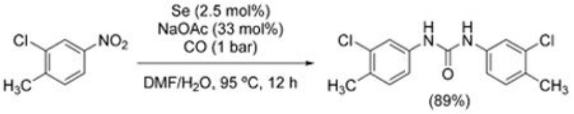


(12)

aniline obtained via WGSR reduction was suggested by a set of clever competition experiments.[113]

Lastly, although ureas are generally synthesized from nitroarenes and amines under anhydrous conditions (Figure 4), symmetrical arylureas can be obtained directly from the corresponding nitroarenes via CO/H_2O reduction/carbonylation, using selenium as the catalyst [Eq. (13)].[114]



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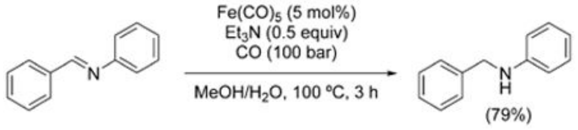
3.1.3. Reduction of Imines and Reductive Amination—The reductive amination employing nitroarenes and carbonyl compounds was discussed in Section 3.1.2. In addition to this approach, the synthesis of substituted amines by reductive amination can be achieved directly from an amine precursor and a carbonyl compound, thus bypassing the first nitro-to-amine reduction step. The obvious advantage is the wider range of products that can be produced. Whereas reductive amination from nitro compounds can lead only to secondary anilines (or tertiary anilines with two identical substituents), no such limitations exist when a primary or secondary amine is used as the starting material.

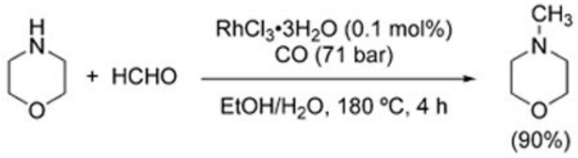
As is the case with the reductive amination from nitro compounds, the reaction relies on the in situ generation of an imine (or iminium ion) that is reduced under WGSR conditions. This crucial step has been documented in the reduction of *N*-benzylideneaniline with catalytic amounts of $Fe(CO)_5$ [Eq. (14)].[115]



(14)

The first example of reductive amination under WGSR conditions was reported by Watanabe et al. in 1978.[116] A number of amines combined with formaldehyde or benzaldeyde to produce the corresponding methylated or benzylated amines in variable yield using Rh catalysts [Eq. (15)]. The same process can be carried out in the presence of $Co_2(CO)_8$/dppe with comparable results.[117] Ketones can participate in the reaction, as well [Eq. (16)].[52]

The last two years have witnessed a renewed interest in the WGSR-driven reductive amination. Several improved variants have been developed that allow for the alkylation of primary and secondary amines with aldehydes and ketones, using homogeneous[118,119] or heterogeneous catalysts.[107,120]



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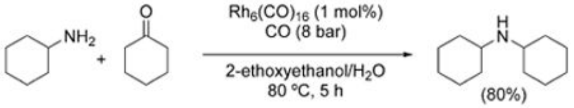


(16)

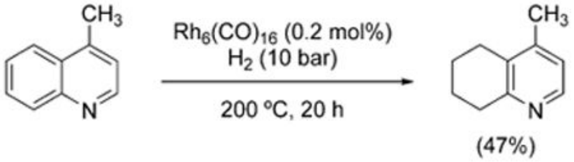
Quite surprisingly, none of the recent reports acknowledge the pioneering cases mentioned above. Reaction conditions and illustrative examples are provided in Figure 6.

Since the reaction protocols employ little to no water, the role of water deserves a comment. The condensation between a carbonyl compound and an amine liberates one equivalent of water, which in principle should suffice to carry out the subsequent reduction of the imine bond. The formation of reduction products even in the absence of added water is therefore justified (Figure 6c). In the presence of molecular sieves, which sequester the water originating from imine condensation, the reaction stops at the imine stage.[107] On the other hand, addition of a superstoichiometric amount of water is detrimental.[118]

By means of labeling and competition experiments, Chusov and List ruled out the involvement of free H_2. The reaction proceeded at a much lower rate when CO was replaced by H_2. Only 11% D incorporation was measured when D_2 (1 bar) was added to the reaction mixture, whereas D incorporation reached 74% when *N,N*-deuterated aniline was used. In addition, a Rh-hydride complex was detected by ^{1}HNMR reaction monitoring. On the basis of these observations, the authors proposed a catalytic cycle involving oxidative addition of a Rh carbonyl complex into the C-OH bond of the intermediate hemiaminal.[118] This step seems rather unlikely, given the tendency of hemiaminals to lose water and the fact that oxidative addition of Rh into C–OH bonds is unknown. It seems more reasonable that the intermediate imine would undergo reduction by a Rh—H complex (observed in situ!) generated via the WGSR.

3.1.4. Reduction of Heterocycles

3.1.4. Reduction of Heterocycles—The reduction of nitrogen-containing heterocycles can be driven by the WGSR under forcing conditions. Murahashi et al. reported that quinolines and isoquinolines are reduced to the corresponding 1,2,3,4-tetrahydroquinolines and 1,2,3,4-tetrahydroisoquinolines (with concomitant *N*-formylation in the latter case) in the presence of $Rh_6(CO)_{16}$ at 150 °C and 55 bar of CO (Figure 7).[121] Only the *N*-containing ring undergoes reduction. This feature offers complementarity to direct hydrogenation methods, which provide 5,6,7,8-tetrahydroquinolines selectively [Eq. (17)].



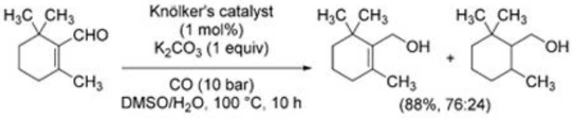
(17)

Other nitrogen-containing heterocycles undergo reduction under WGSR conditions as well, but the reported methods have little synthetic utility due to the low turnover numbers or complexity of the reaction mixtures.[122–124] Oxygen- and sulfur-containing heterocycles, as well as polynuclear aromatic hydrocarbons, are unreactive or poorly reactive under WGSR conditions.[123,124]

3.1.5. Reduction of Carbonyls—The reduction of carbonyls to primary and secondary alcohols is a relatively facile transformation under WGSR conditions and several catalytic systems have been investigated in this capacity (Table 2). The early reports described harsh conditions with limited applicability (entries 1–4). While aromatic and branched aliphatic aldehydes were reduced to the corresponding alcohols, linear aldehydes underwent aldol condensation/1,2-reduction (entry 1). Improved results were obtained with the $Rh_6(CO)_{16}$/TMPDA system described by Kaneda et al., which allowed for a milder process compatible with several classes of aldehydes, but not as widely applicable in the case of ketones (entry 5 and Figure 8a). Recently, Beller et al. reported the efficient and scalable reduction of aldehydes using Knölker's catalyst (entry 7 and Figure 8b). Ketones are not reactive under these conditions.

The reduction of α,β-unsaturated aldehydes is more challenging due to the competition between the 1,2- and 1,4-reduction modes (see Section 3.1.6). For example, the reduction of α,β-unsaturated aldehydes using Knölker's catalyst afforded mixtures of saturated and allylic alcohols [Eq. (18)].[130]

Kaneda et al. were able to obtain selective carbonyl reduction by fine tuning of the reaction conditions. In the case of $Rh_6(CO)_{16}$, it was shown that the site-selectivity is highly dependent on the base used in the reaction. The use of TMPDA is crucial for the achievement of 1,2-reduction (even the similar TMEDA gives poorer results), whereas 4-DMAP reverses the selectivity in favor of 1,4-reduction [Eq. (19)].[129b] Good 1,2-selectivity is also displayed by ceria-supported gold nanoparticle catalysts [Eq. (20)].[125] In contrast, direct hydrogenation using the same catalyst is unselective.



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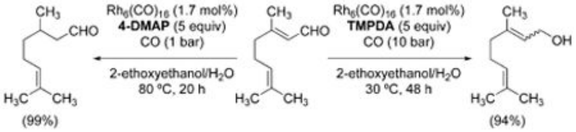

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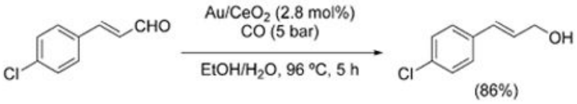
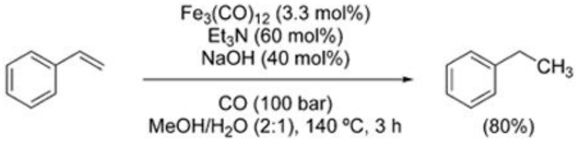


(20)

3.1.6. Reduction of Alkenes and Alkynes—

The hydrogenation of unactivated olefins under WGSR conditions is rather unexplored and only two cases have been reported. Ethylene is hydrogenated to ethane using $K_2PtCl_4/SnCl_2$ in acidic medium (HCl/acetic acid) under CO (0.4 bar) at 88 °C.[132] However, the same conditions failed to provide clean hydrogenation of propylene. Hydrogen added to the reaction mixture remained unconsumed, thus lending support to the intermediacy of a Pt–H intermediate formed from H_2O. Styrene is reduced to ethylbenzene in good yields using $Fe_3(CO)_{12}$ and basic conditions, though with competing hydrohydroxymethylation (Section 3.2.1) depending upon the solvent mixture [Eq. (21)].[133]

Conversely, the hydrogenation of activated olefins (α,β-unsaturated aldehydes, ketones, esters, amides, and nitriles) has been investigated more thoroughly. Already in 1973, Joh et al. had shown that the C–C double bond of a variety of unsaturated carbonyl compounds underwent selective 1,4-reduction, whereas unactivated olefins were unreactive.[134]



(21)

The initial conditions were quite harsh (98 bar, 130 °C, Figure 9a), but the addition of Et_3N allowed for a milder process to be developed (1 bar, 30 °C, Figure 9b).[135] Selenium, often used as an alternative to transition metals in WGSR-driven reductions, is also effective in the selective reduction of activated olefins (Figure 9c).[136] Other Rh-based catalytic systems were studied in the 1,4-reduction of conjugated olefins, however with limited exploration of the substrate scope. [58b, 128, 129b, 137, 138]

The only reported example of alkyne hydrogenation under WGSR conditions involves heterogeneous catalysis. Using TiO_2-supported gold nanoparticle catalysts, Cao et al. were able to achieve the chemo- and stereoselective reduction of a wide range of alkynes to (*Z*)-alkenes in high yields and without overreduction. (Figure 10).[139]

3.1.7. Deoxygenation of Epoxides—

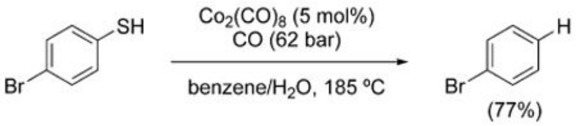
The deoxygenation of epoxides to the corresponding alkenes under WGSR conditions has been known since 1968, when Watanabe et al. reported the reduction of styrene oxide with $K_2Fe(CO)_4$.[140] However, the development of synthetically useful reduction protocols occurred only in the last decade with the advent of nanoparticle catalysts. Hydrotalcite-supported silver[141] and gold,[142] as well as titania-supported gold nanoparticles,[143] are efficient promoters of the reduction of a variety of epoxides (Figure 11). Thanks to these contributions, the use of WGSR conditions represents one of the mildest and most efficient catalytic methods to date for this transformation.

From a mechanistic standpoint, it should be emphasized that the deoxygenation of epoxides is conceptually different from the reactions discussed above because it does not lead to the incorporation of reducing equivalents (H) into the substrate. The reducing power provided by the CO/H_2O couple ensures turnover of the catalytic cycle by reducing the putative metal–oxo intermediate **xxvii** to the active form of the metal **xxvi** (Scheme 9). Metal–oxo intermediates are believed to be involved in the deoxygenation of epoxides.[144] However, their intermediacy in the deoxygenation reaction under WGSR conditions has not been explicitly documented and, therefore, alternative mechanisms cannot be discounted at this time.

Regardless of the mechanistic pathway, an important aspect concerns the role of water. Although water does not appear in the balanced equation, its presence is of course required for the occurrence of the WGSR. Control experiments demonstrated that the reaction did not proceed in the absence of water (Scheme 10a). However, a catalytic amount of water is needed to initiate the reaction (Scheme 10b).[143]

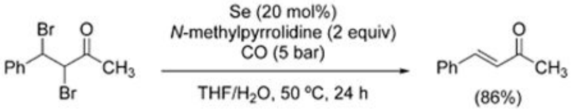
3.1.8. Other Deoxygenation Reactions—Several other deoxygenation reactions have been carried out using CO/H_2O as the reducing agent. A summary is provided in Table 3.

3.1.9. Desulfurization—The desulfurization of thiophenols and benzylic mercaptans was described by Alper et al. in 1985 using $Co_2(CO)_8$ under rather forcing conditions [Eq. (22)].[147] Interestingly, the proposed mechanistic pathway involves generation of carbonyl sulfide, rather than carbon dioxide, and is supported by its direct observation.



(22)

3.1.10. Dehalogenation—The examples shown in Figure 2 and thereafter illustrate the reluctance of carbon-halogen bonds to undergo reduction under WGSR conditions. Indeed, only a handful of cases of hydrodehalogenation have been reported. In 1990, Sonoda et al. described the use of Se/Et_3N for the debromination/elimination of vicinal dibromides [Eq. (23)], as well as the dehalogenation of α-halo ketones [Eq. (24)].[148] Similarly, α-chloroacetophenone undergoes dechlorination in the presence of $PdCl_2(PPh_3)_2$ [Eq. (25)].[149]



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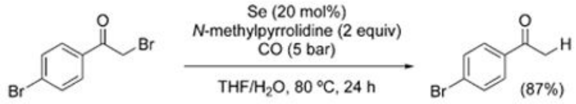

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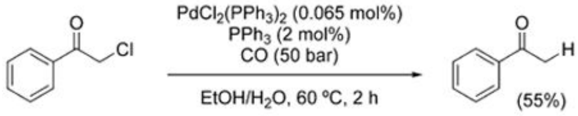
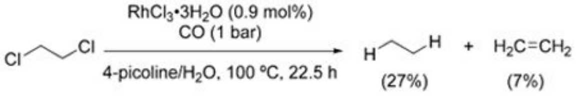


(25)

Ford et al. showed that 1,2-dichloroethane can be dechlorinated to a mixture of ethane and ethylene with $RhCl_3$/4-picoline [Eq. (26)].[150] From the observation that the ethylene/ethane ratio decreases as the reaction progresses, it was suggested that ethylene forms first via a reduction/elimination pathway and is then further reduced to ethane by the same catalytic system.



(26)

Harsh conditions are needed for the dechlorination of chlorobenzene, which has been achieved, albeit in low yield, using $CuCl_2$ supported on poly(4-vinylpyridine) (Scheme 11a).[151] In contrast, deiodination of aryl iodides occurs readily at 60 °C and 1 bar of CO (Scheme 11b).[152]

3.2. C–C Bond Forming Reactions

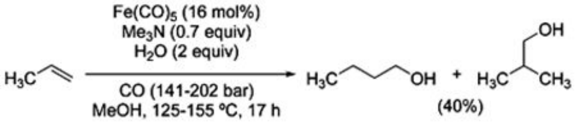
3.2.1. Hydroformylation and Hydrohydroxymethylation—

The hydroformylation reaction is a powerful C–C bond forming process with extensive industrial applications. The traditional Co- and Rh-based catalysts for this transformation are capable of converting alkenes into homologous aldehydes using syngas.[5] The possibility of using the CO/H_2O couple was investigated by Reppe and Vetter as early as 1953.[6] Besides being one of the earliest applications of the WGSR to organic synthesis, the Reppe-type hydroformylation reaction represents an exception in the landscape of WGSR-driven organic reactions, because CO acts both as carbon source and reducing agent (Scheme 12).

The seminal report by Reppe, part of a thorough study on the chemistry of hydrido-metal-carbonyl complexes, illustrates the conversion of terminal alkenes into homologated alcohols (via the corresponding aldehydes) using $Fe(CO)_5$ in combination with trimethylamine [Eq.

(27)]. Strictly speaking, therefore, the term hydrohydroxymethylation would be more appropriate for this transformation.

These results established the basis for further elaborations that took place beginning in the 1970s, contemporaneous with the development of homogeneous catalysis for the WGSR. Thus, Pettit et al. investigated the use of other metal–carbonyl complexes in the Reppe-type hydroformylation of propylene

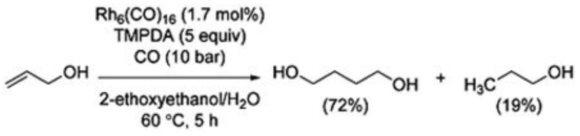


(27)

and obtained higher efficiency and selectivity for the linear aldehyde **6** relative to the $Fe(CO)_5$ system (Table 4).[19]

Similarly, Laine compared the performance of Ru and Rh carbonyls in alkaline solution and found that, whereas Ru carbonyls display a higher selectivity for the linear aldehyde, Rh carbonyls are less selective, and capable of reducing the aldehyde product to the alcohol.[153] Numerous other variations of the Reppe-type hydroformylation reaction have been reported, encompassing a wide array of metal catalysts and using either basic, neutral, or acidic conditions (Table 5.). However, unlike some other WGSR-driven reactions, the hydroformylation under WGSR conditions has not risen to the status of a well-established synthetic method. In most cases, harsh conditions are needed and the desired aldehyde is obtained in low yield even from simple, linear olefins. The process is fraught with multiple challenges, ranging from the control of the site selectivity, to the occurrence of hydrogenation of the alkene, overreduction of the aldehyde to the alcohol, or aldol condensation. In contrast, traditional hydro-formylation approaches (with CO/H_2) appear much more robust and synthetically useful.[154]

The boundary between hydroformylation and hydrohydroxymethylation is not clear-cut. The hydroformylation reaction is often accompanied by overreduction of the aldehyde to the alcohol. The ease of carbonyl reduction under the forcing conditions required for hydroformylation has been exploited in the formulation of protocols that yield hydrohydroxymethylation products predominantly. This is true for the original report by Reppe, as well as a number of other cases.[133,155,156] For example, allyl alcohol can be converted to 1,4-butanediol under WGSR conditions in the presence of $Rh_6(CO)_{16}$ and TMPDA [Eq. (28)].[155a] Again, however, these methods are of little synthetic utility due to the limited substrate scope and poor efficiency.



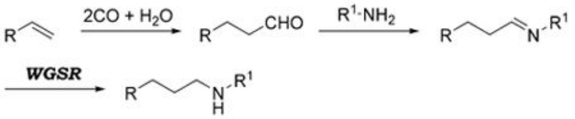
(28)

The mechanism of Reppe-type hydroformylation has been examined by means of identification of reactive intermediates and kinetic studies. The proposed mechanism parallels the earlier proposal by Heck and Breslow for the hydroformylation with $Co_2(CO)_8$ and CO/H_2,[157] the only difference being that the reactive metal hydride **iii** is generated via WGSR rather than by oxidative addition of H_2 (Scheme 13).[19] Besides being involved in the coordination/migratory insertion of the olefin to form **xxx**, intermediate **iii** is accountable for the reduction of the aldehyde to the alcohol.[153] Intermediate **iii** can also react along the traditional WGSR manifold to produce H_2, which is detected in the reaction mixtures.[164,165]

One of the key observations is that, in the case of $Fe(CO)_5$, the reaction displays second order kinetic behavior with respect to $Fe(CO)_5$.[161] This fact is consistent with an alternative mechanistic proposal whereby the acyl iron intermediate **xxxiii** liberates the product not by means of protonation/reductive elimination (as in Scheme 13), but by attack of iron hydride **xxxiv** (Scheme 14).[168]

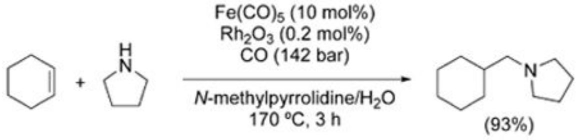
3.2.2. Hydroaminomethylation—

If the aldehyde produced by hydroformylation is intercepted by an amine, the imine (or iminium ion) formed in situ can undergo reduction, resulting in an overall hydroaminomethylation process [Eq. (29)].



(29)

Interestingly, the hydroaminomethylation sequence was first reported by Reppe and Vetter in the context of their seminal work on the CO/H_2O-mediated hydroformylation reaction,[6] and only later revisited (and vastly elaborated) using syngas.[169] The initial conditions used by Reppe were quite harsh ($Fe(CO)_5$, 105–145 °C, 100–200 bar) and the process was inefficient, but further studies identified more effective catalysts and reaction conditions. Iqbal obtained improved results with a mixed $Fe(CO)_5/Rh_2O_3$ system [Eq. (30)].[170]



(30)

Other catalysts (metal carbonyls[171,172] and cationic Rh complexes)[173] behave similarly. However, the control of the site-selectivity (linerar vs. branched) and the forcing conditions remained the major issues which hampered further synthetic developments for decades.

Significant advances have been achieved in the last two years thanks to the contributions of Beller and co-workers. Using a combination of $Ru_3(CO)_{12}$ and K_2CO_3, the hydroaminomethylation reaction proceeds cleanly with a wide range of olefins and primary/ secondary amines (Figure 12a).[174] Remarkably, the site-selectivity for the linear product is high (typically > 95:5) even in the absence of ligands. Under these conditions, the catalyst displays selectivity for terminal olefins, whereas internal olefins are unreactive. However, in a modified approach, which employs a phosphinoimidazole ligand, internal olefins become reactive and undergo isomerization to furnish the linear amine product when possible (Figure 12b).[175]

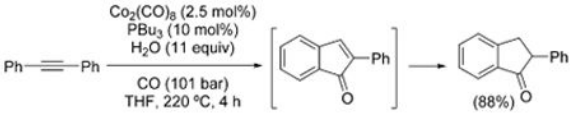
3.2.3. Other Carbonylation Reactions—A large number of carbonylation reactions are carried out using mixtures of CO and H_2O, namely hydroxycarbonylation of alkenes,[176] alkynes,[177] and halides[47b] (including the Monsanto process).[178] However, a careful distinction must be made as to the role of CO and H_2O. The aforementioned transformations are redox-neutral and employ CO and H_2O as reactants, not as a reducing couple. Since the WGSR is not involved, those transformations will not be covered here. Besides hydroformylation and related processes, only a limited number of carbonylation reactions employing CO/H_2O are reductive and rely on the WGSR. These include cyclocarbonylation reactions and the carbonylation of alkenes to symmetrical ketones.

The reductive cyclocarbonylation under WGSR conditions was pioneered and considerably developed by Takahashi and co-workers. In an initial report, the reaction of internal alkynes with CO and $Rh_4(CO)_{12}$ under basic conditions afforded furanones (Figure 13a).[179] The reaction was subsequently extended to terminal alkynes under modified conditions (Figure 13b).[180] This pathway is a prerogative of the CO/H_2O system, as the use of CO/H_2 caused hydrogenation of the alkyne and hydrohydroxymethylation.[181] The site-selectivity under these conditions is poor and mainly substrate-induced, but it was later shown that the selectivity could be significantly improved using more polar solvents, although at the expenses of the conversion.[182]

The involvement of the WGSR as the source of reducing equivalents was initially established by carrying out the reaction with D_2O, which resulted in full incorporation of D at the 5-position of the furanone.[179] A mechanistic proposal was then put forward which proceeds by double carbonylation of the alkyne and rearrangement to form **xxxviii**, generation of a Rh-hydride intermediate **xl** via WGSR, and subsequent reductive elimination to the product (Scheme 15).[182]

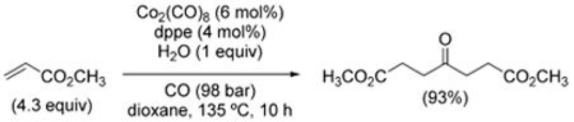
Similar approaches to the synthesis of furanones were also described by other research groups, using PdI_2,[183] Co_2Rh_2/C,[184] and $Ru_3(CO)_{12}$.[185] Interestingly, Takahashi et al. found that, while $Co_2(CO)_8$ is inactive in the formation of furanones, at higher temperatures it promotes the formation of indanones from aryl-substituted alkynes, through a C–H insertion process [Eq. (31)].[186] The reaction proceeds via the corresponding indenone, which undergoes reduction under WGSR conditions and was shown to be a competent intermediate.[187]

The propensity of alkynes toward reductive cyclocarbonylation has been pivotal to achieve the synthesis of various other cyclic structures.[188] In particular, by introducing a reactive, tethered functional group, fused cycles such as indolones,[189] tricyclic lactones,[190] isocoumarins,[191] benzofuranones,[192] and isochromanones[193] could be synthesized (Scheme 16).



(31)

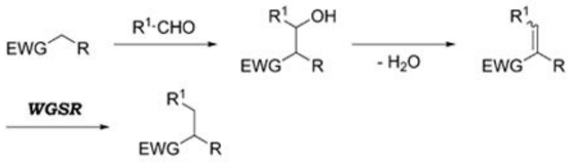
The synthesis of symmetrical ketones from alkenes is another instance of reductive carbonylation reaction that can be carried out under WGSR conditions. The reaction represents an alternative pathway to hydroformylation that becomes predominant when operating in an excess of the olefin. Being related to hydroformylation, it suffers from limitations such as need for harsh conditions and poor control over site-selectivity. Indeed, the method is largely underdeveloped and only a few cases have been reported.[194] For example, dimethyl-4-oxopimelate has been synthesized from methyl acrylate using $Co_2(CO)_8$/dppe in 93% yield with respect to H_2O (the limiting reagent) [Eq. (32)].[194d]



(32)

3.2.4. Reductive Alkylation

—As was illustrated for reductive amination reactions, stabilized carbanions can be alkylated with aldehydes under WGSR conditions. The reaction proceeds via formation of an

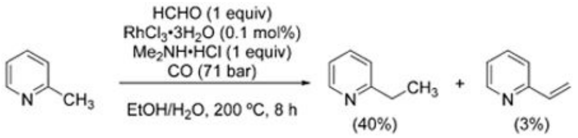


(33)

aldol adduct, elimination of water, and reduction of the activated double bond [Eq. (33)].

The first example of this transformation was reported by Watanabe et al. in 1978.[195] Several ketones were α-methylated with aqueous formaldehyde in the presence of $RhCl_3 \cdot 3H_2O$. Yields were low and mixtures of mono- and dimethylated products were obtained (Scheme 17).

In a similar fashion, picolines can be homologated with formaldehyde to afford ethylpyridines [Eq. (34)],[196] and arylacetonitriles are α-methylated to arylpropionitriles [Eq. (35)].[197]



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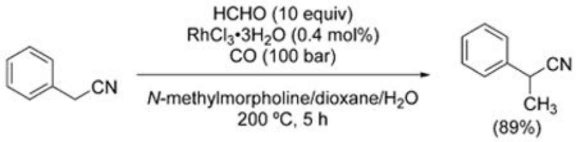
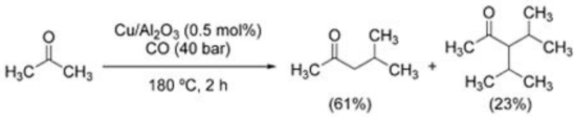


(35)

In an attempt to streamline the synthesis of methyl isobutyl ketone from acetone, Rossi et al. discovered that WGSR conditions can be employed to this end using a Cu/Al_2O_3 catalyst [Eq. (36)].[198]



(36)

A more useful synthetic protocol involves the reaction of active methylene compounds with carbonyls in what is formally a reductive Knoevenagel condensation. Chusov et al. reported that methyl cyanoacetate can be alkylated in good yield with aldehydes and ketones using homogeneous (Figure 14a)[199] or heterogeneous (Figure 14b)[120] Rh catalysts.

As is the case in the reductive amination, addition of water is not necessary because one equivalent of water is liberated from the condensation reaction. Indeed, it was shown that decarboxylation of the ester moiety in the product takes place when water is added to the reaction mixture (Figure 14c). The authors again propose a catalytic cycle which involves oxidative addition of Rh into the C–OH bond of the aldol adduct,[199] but this proposal is arbitrary and lacks experimental evidence, as discussed in Section 3.1.3. More likely, the Knoevenagel condensation adduct undergoes reduction by a Rh–H species formed via the WGSR.

3.2.5. Carbonyl Allylation—The allylation of carbonyl compounds is a fundamental reaction in organic synthesis owing to its versatility and capacity to build adjacent stereogenic centers with high levels of stereocontrol.[200] The reaction is generally conducted with a pre-formed allylmetal species, typically an allylic borane, silane, or stannane. Catalytic variants have also been developed. Some of the catalytic protocols employ an allylic halide or alcohol derivative in combination with a metal catalyst and a sacrificial metal reducing agent in stoichiometric amount. An example is represented by the allylation under Nozaki–Hiyama–Kishi/Fürstner conditions, which combines catalytic amounts of $CrCl_2$ (or $CrCl_3$) and superstoichiometric amounts of Mn.[201] Although catalytic in the metal that carries out the allylation reaction itself, protocols of this kind are de facto not catalytic, because a stoichiometric amount of metal reducing agent is still required. Truly catalytic methods include the transfer hydrogenation approach described by Krische.[202] Given the prominence and abundant use of allylation reactions in total synthesis endeavors, the discovery that catalysis is possible by means of the WGSR represents an important advance, especially from the point of view of atom economy and environmental concerns. In fact, under WGSR conditions, the only byproducts are CO_2 and the conjugate base of the allyl nucleofuge!

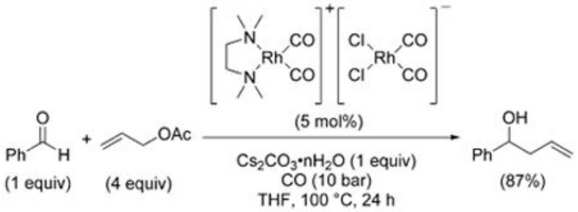
The first report from these laboratories, in 2008, identified optimal reaction conditions for the allylation of aldehydes with allyl acetate, using $RuCl_3$ hydrate.[8] Under mild conditions (70–80 °C and 2 bar of CO), a variety of aromatic, aliphatic and α,β-unsaturated aldehydes could be allylated with excellent functional group compatibility (Figure 15).

One of the key findings is that only 10 mol% of Et_3N is needed. The use of a stoichiometric or superstoichiometric amount of base is detrimental. On the other hand, the reaction does not proceed in the absence of base. These results clearly rule out the participation of triethylamine as the stoichiometric reducing agent. Rather, it seems that the base may be involved in the reduction of $RuCl_3$ to the catalytically active Ru^0, and/or act as a buffer for the acid liberated as the byproduct. Another important observation concerns the role of halide. The reaction proceeds at a much reduced rate when $Ru_3(CO)_{12}$ is employed instead of $RuCl_3 \cdot n\,H_2O$, but the rate is restored upon addition $Bu_4N^+Cl^-$. It seems that the neutral Ru^0–carbonyl complex is not effective in the formation of a π-allylruthenium intermediate, but it can be converted into a more reactive anionic Ru^0–Cl complex by the addition of a chloride source. On the basis of these observations, the catalytic cycle shown in Scheme 18 was formulated.

The suggested catalytically active species **xli** is produced either by chloride displacement of CO in $Ru_3(CO)_{12}$, or reduction of $RuCl_3$ to Ru^0 by WGSR or perhaps Et_3N.[203] Oxidative addition of allyl acetate into Ru^0 forms π-allylruthenium(II) complex **xlii**, which adds to the aldehyde (**xliii**) and generates the product after protonolysis. This process leaves behind a Ru^{II}–hydroxide complex **xliv**, which is prone to CO migratory insertion to form the Ru-hydroxycarbonyl intermediate **xlv**. From **xlv**, the usual WGSR steps (decarboxylation, reductive elimination) regenerate the active Ru^0 catalyst along with carbon dioxide and acetic acid as the byproducts.

Recently, the scope of the allylation reaction has been expanded to include substituted allylic acetates. Under similar reaction conditions, allylic acetates bearing a variety of substituents at the 2-position (methyl, phenyl, ester, ketone, acetal) react with aldehydes in good yield (Figure 16).[204] Ketones are not suitable electrophilic partners under these conditions.

In addition, a recent report by Vasylyev and Alper describes the use of $[Rh(TMEDA)(CO)_2]^+[RhCl_2(CO)_2]^-$ as an allylation catalyst in the presence of $Cs_2CO_3 \cdot n\, H_2O$ serving both as the base and the water source [Eq. (37)].[205]



(37)

3.3. Future Opportunities

The water-gas shift reaction has found application in a diverse set of organic reactions. One of the most intriguing, yet underdeveloped aspects is the capacity of the CO/H_2O couple to act as a terminal reductant, therefore enabling turnover of catalytic cycles. The carbonyl allylation reaction embodies this approach, resulting in an atom-economic process which is essentially waste-free. In this capacity, the WGSR is aligned with the first of the "grand challenges" identified by the NRC report "*Sustainability in the Chemical Industry*", which calls for the reduction of waste and the identification of environmentally benign strategies.[206] Given the number of reductive transformations currently carried out with pre-formed organometallic species or (super)stoichiometric amounts of reducing agents, the impact of the WGSR could be broad, especially in process chemistry.

In the design of new methods that capitalize on the WGSR, one has to keep in mind the electrochemical limits posed by the CO/H_2O couple. With a half-cell reduction potential $E°= −0.53$ V, the WGSR has approximately the same reducing power as gallium(0). Therefore, it is not likely to be successful in regenerating highly electropositive metals ($E° < 0$ V). On the other hand, metals with positive reduction potentials are good candidates, as they generate an overall positive (hence thermodynamically favorable) electromotive force $\Delta E°$ (Scheme 19).

This range corresponds roughly to the right half of the d-transition metal block, and explains why the allylation reaction worked efficiently with Ru ($E°_{Ru(II)/Ru(0)} = 0.45$ V, $\Delta E° = 0.98$ V), but failed with Fe ($E°_{Fe(II)/Fe(0)} = -0.45$ V, $\Delta E° = 0.08$ V) or Mn ($E°_{Mn(II)/Mn(0)} = -1.19$ V, $\Delta E° = -0.66$ V).[207] In view of such electrochemical requirements, opportunities for expanding the range of applicability of the WGSR to many other reductive processes can be envisioned, including additions to carbonyls and imines, conjugate addition, opening of epoxides, pinacol coupling, reductive homocoupling and heterocoupling of halides, etc.

4. Summary and Outlook

Aside from its industrial use in the production of hydrogen, the potential of the WGSR is still underappreciated. This review has highlighted the broad applicability of the WGSR in organic synthesis, ranging from bulk reductions to the synthesis of fine chemicals. Nevertheless, the methods that involve the WGSR are often underdeveloped and lack robustness. The scarcity of interest into developing improved methods with CO/H_2O is motivated by the fact that their hydrogenative (or stoichiometric) counterparts are so reliable and well established that there is no need to seek opportunities elsewhere. In addition, the conditions required to initiate the WGSR are often harsh and incompatible with sensitive substrates, although the fine tuning of reaction conditions and the revival of heterogeneous catalysis (in the form of nanoparticle catalysts) have demonstrated the achievability of mild, practical and operationally simple protocols.

Nevertheless, several desirable features are unique to the WGSR. First, is the ability to act as an atom-economic, non-wasteful terminal reductant, which could be leveraged in a variety of reductive transformations. Second, is the high degree of chemoselectivity, as illustrated in the reduction of nitroarenes, conjugated carbonyls, and alkynes. Third, is the access to reaction pathways that are not available using traditional methods, as in cyclocarbonylation reactions.

In our view, opportunities abound for creative applications of the WGSR in organic synthesis. We hope that this overview achieves its intended goal of capturing the imagination of researchers and stimulating new avenues of investigation that leverage the potential of the WGSR.

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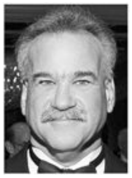
Biographies

Andrea Ambrosi obtained a Laurea Triennale (B.S.) from the University of Torino (Italy) and a Laurea Magistrale (M.S.) from the University of Milano in 2010. While in Milano, he worked under the direction of Prof. Cesare Gennari on the total synthesis of dictyostatin. He is currently a member of the Denmark group at the University of Illinois, where his research interests include the cross-coupling of organosilicon compounds as well as other organometallic reactions.



Scott E. Denmark obtained an S.B. degree from MIT in 1975 and his D.Sc.Tech. (under the direction of Albert Eschenmoser) from the ETH Zürich in 1980. That same year he began his career at the University of Illinois and since 1991 he has been the Reynold C. Fuson Professor of Chemistry. His research interests include the invention of new synthetic reactions, exploratory organoelement chemistry and the origin of stereocontrol in fundamental carbon–carbon bond forming processes.

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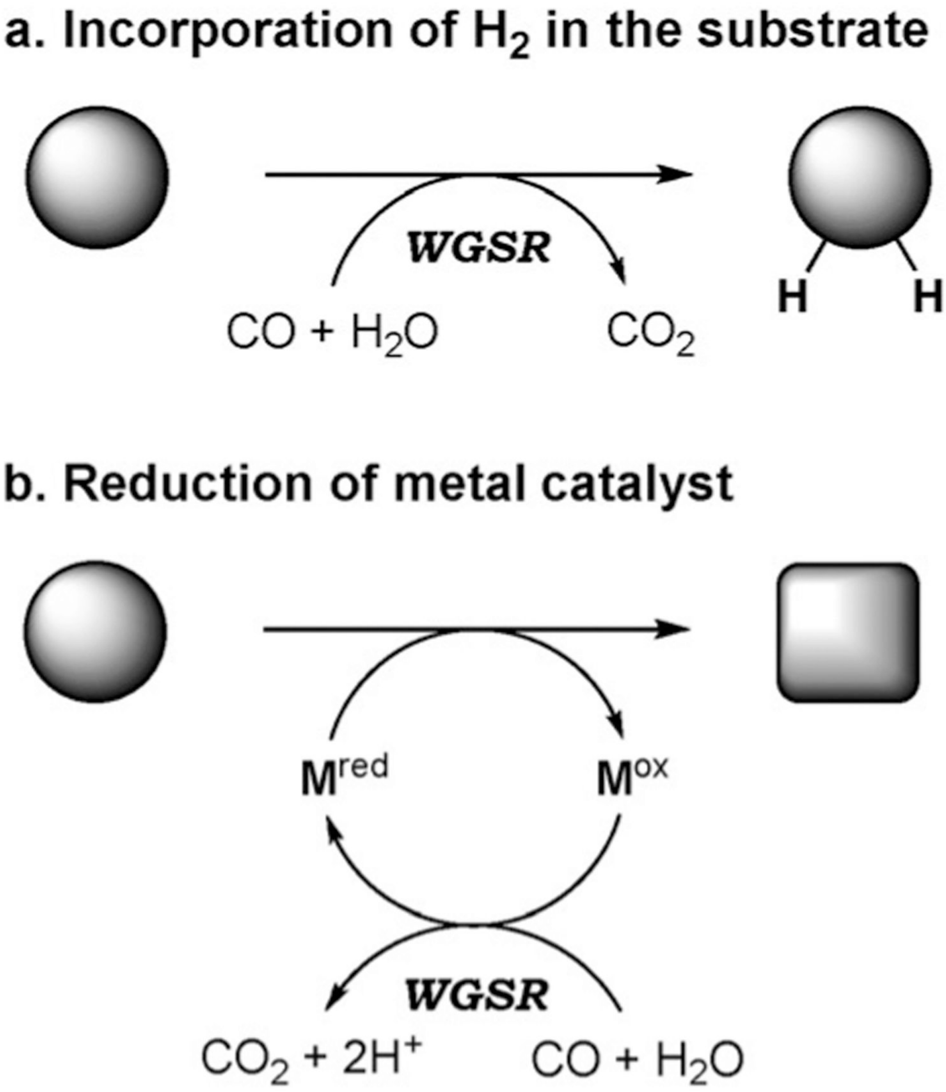


Figure 1.

WGSR in organic transformations.

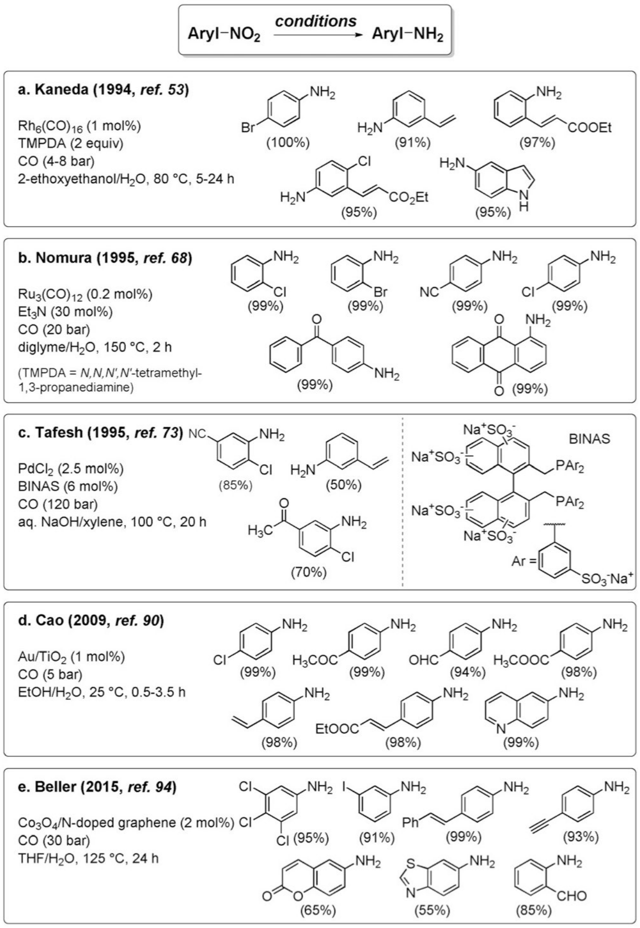


Figure 2.

Chemoselective reduction of nitroarenes.

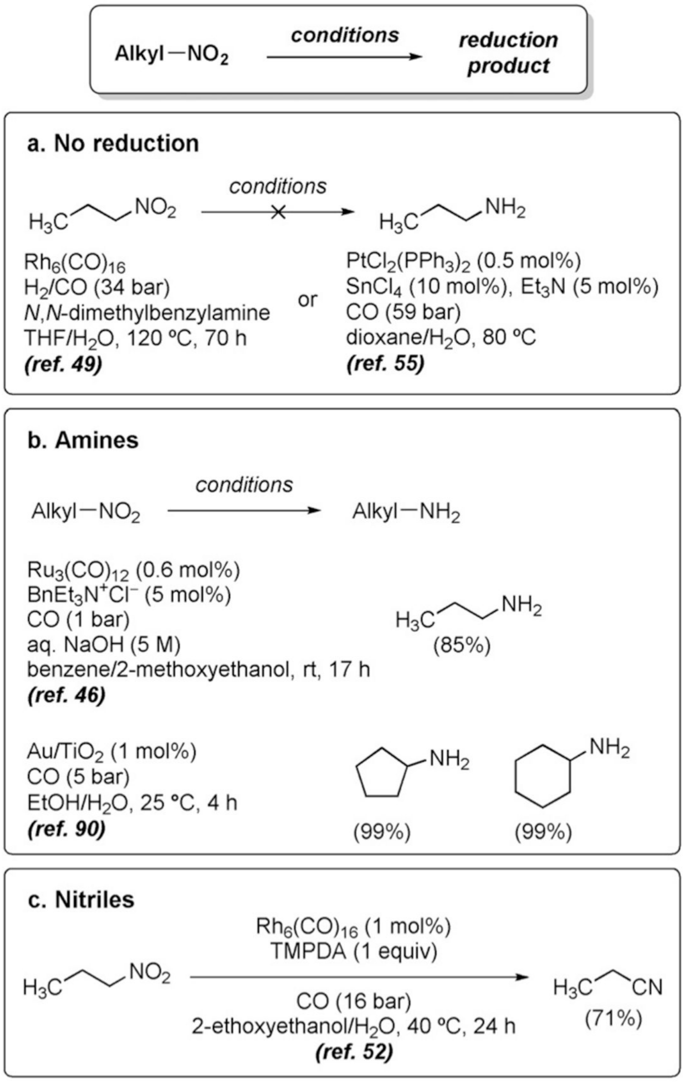


Figure 3.

Reduction of aliphatic nitro groups.

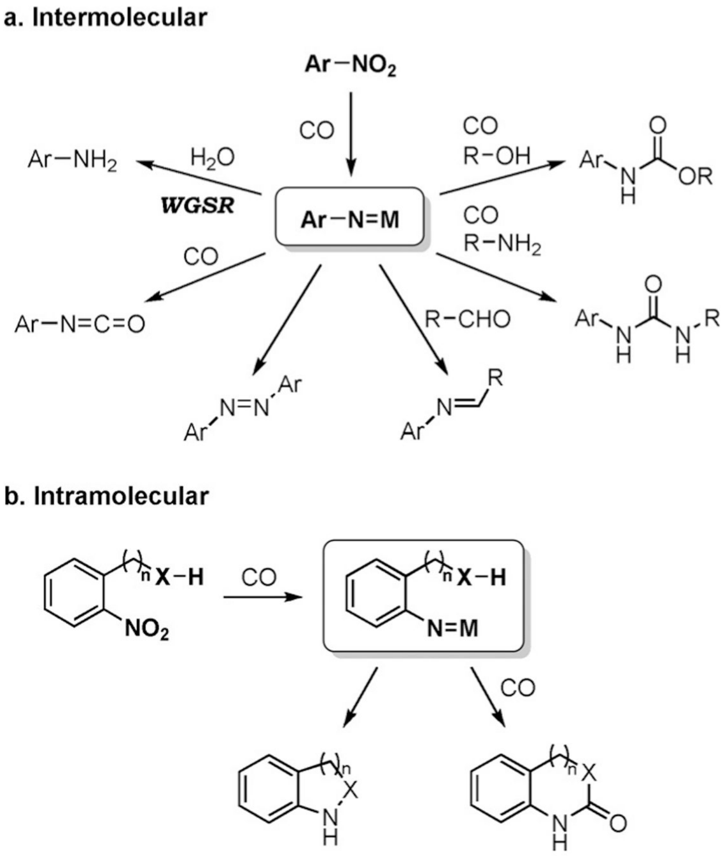


Figure 4.

Possible reaction pathways following the CO-mediated reduction of nitroarenes.

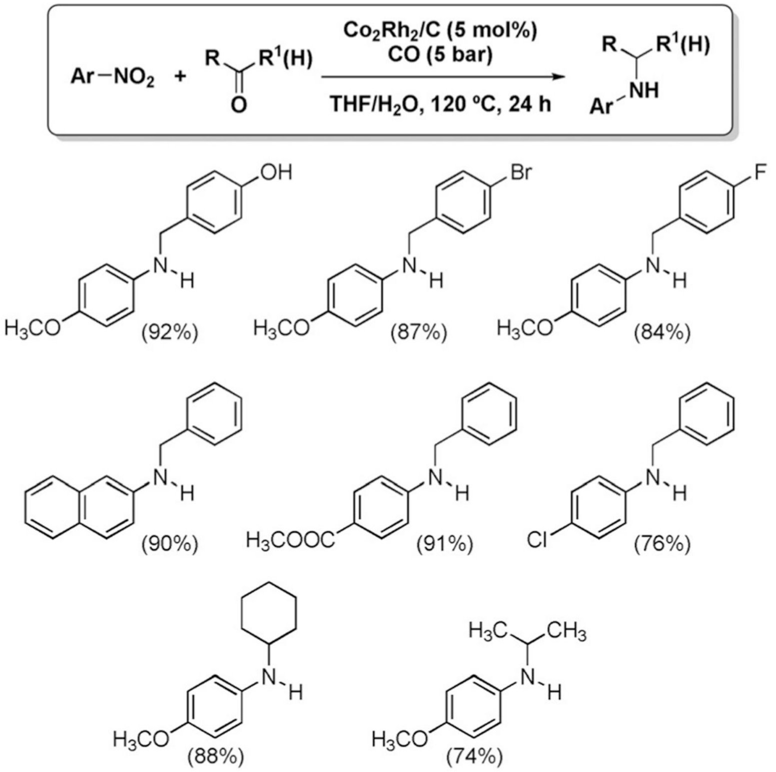


Figure 5.

Reductive amination from nitroarenes and carbonyls.

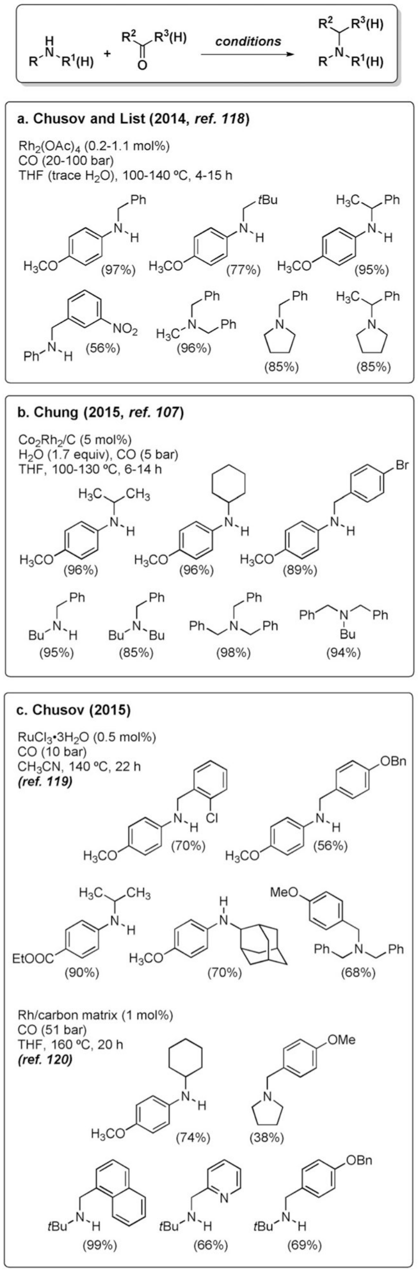


Figure 6.

Reductive amination under WGSR conditions.

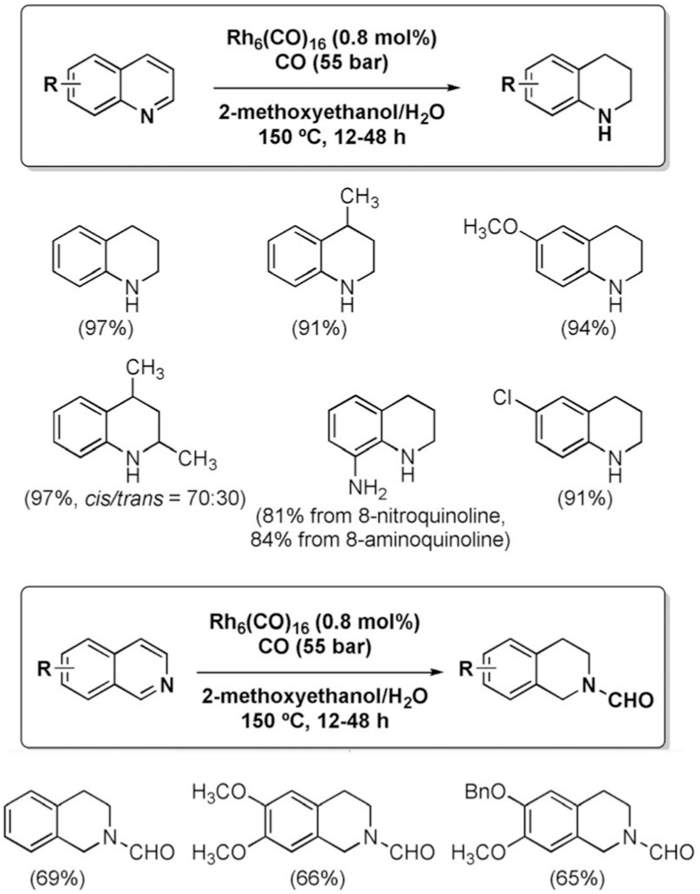


Figure 7.

Reduction of quinolines and isoquinolines.

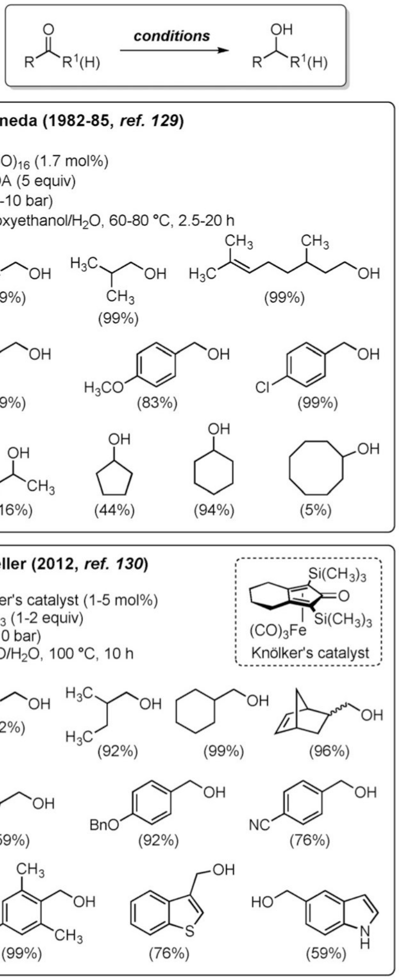


Figure 8.

Reduction of aldehydes and ketones.

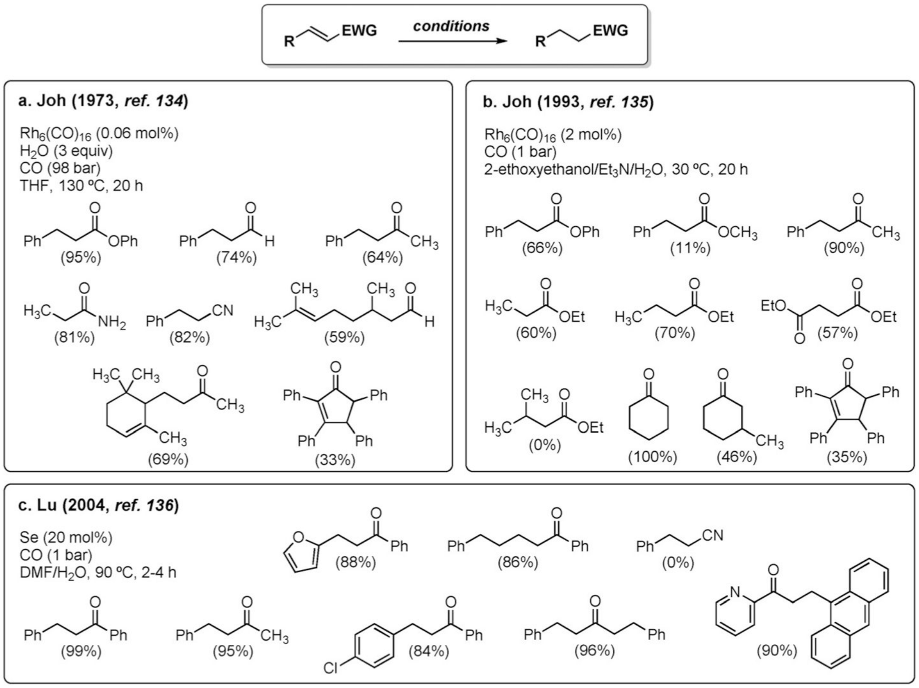


Figure 9.

Selective 1,4-reduction of conjugated olefins.

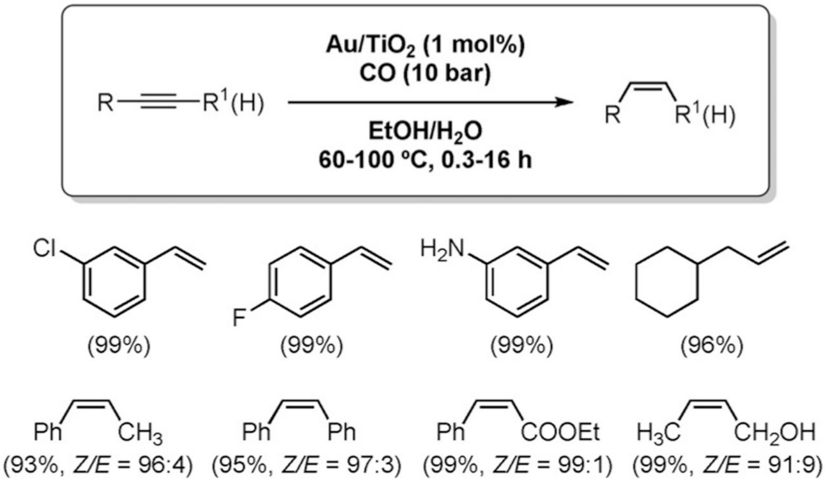


Figure 10.

Selective reduction of alkynes to alkenes.

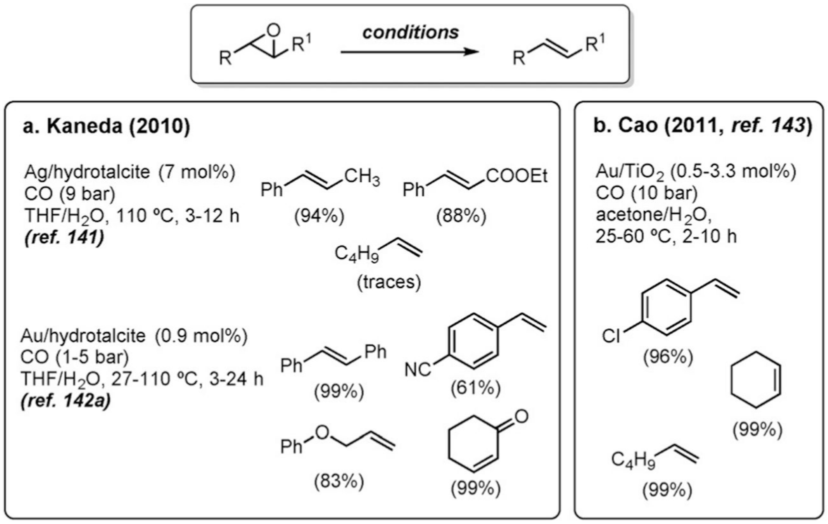


Figure 11.

Deoxygenation of epoxides with nanoparticle catalysts.

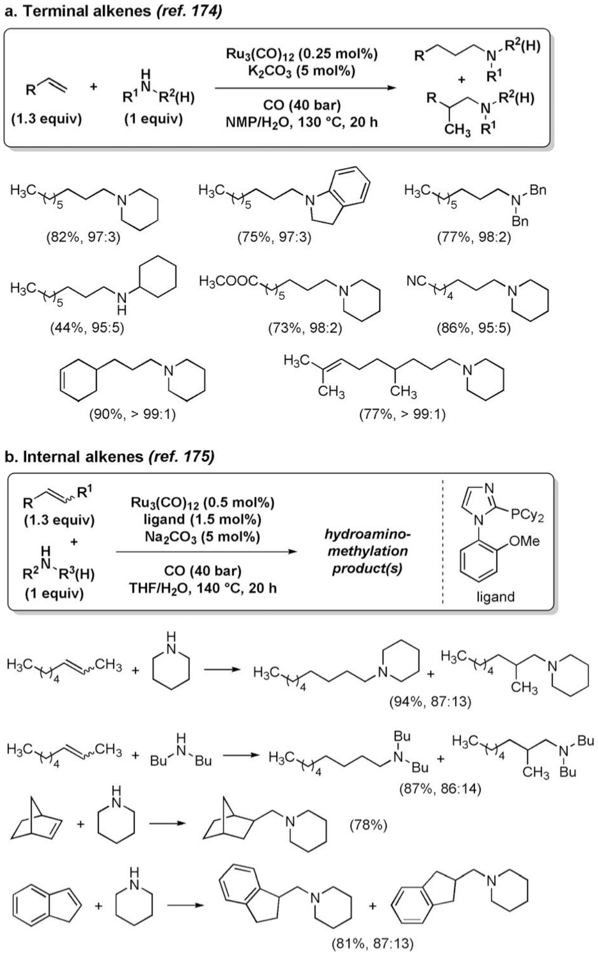


Figure 12.

Hydroaminomethylation reaction under WGSR conditions.

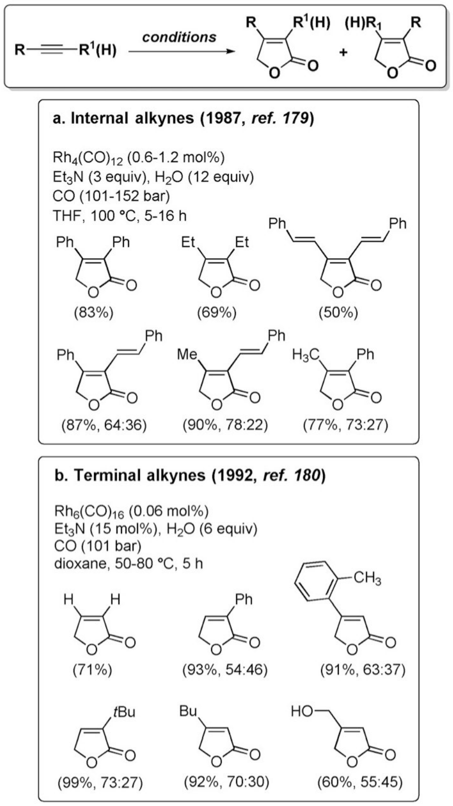


Figure 13.

Synthesis of furanones by reductive cyclocarbonylation.

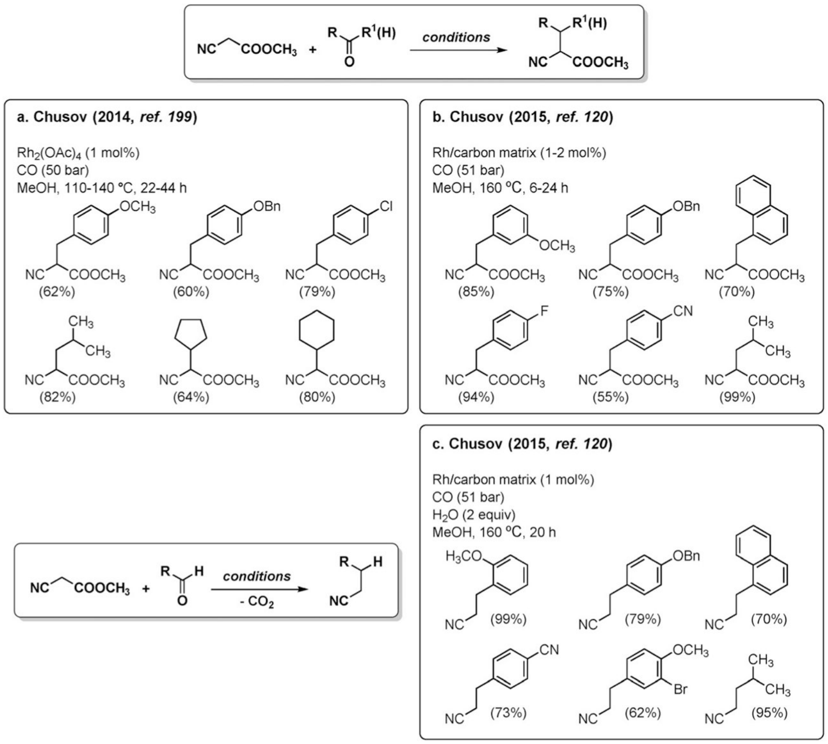


Figure 14.

Reductive Knoevenagel condensation.

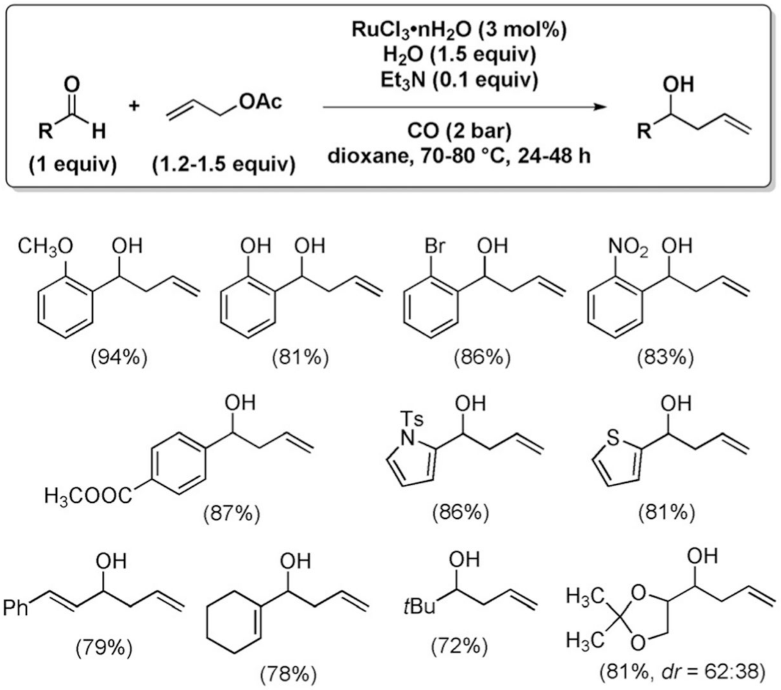


Figure 15.

Allylation of aldehydes.

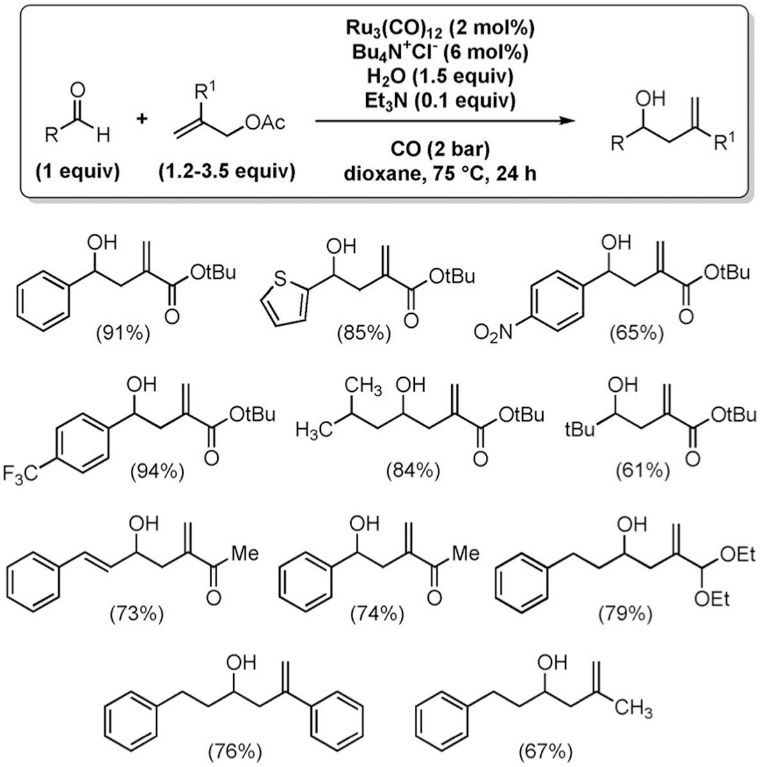
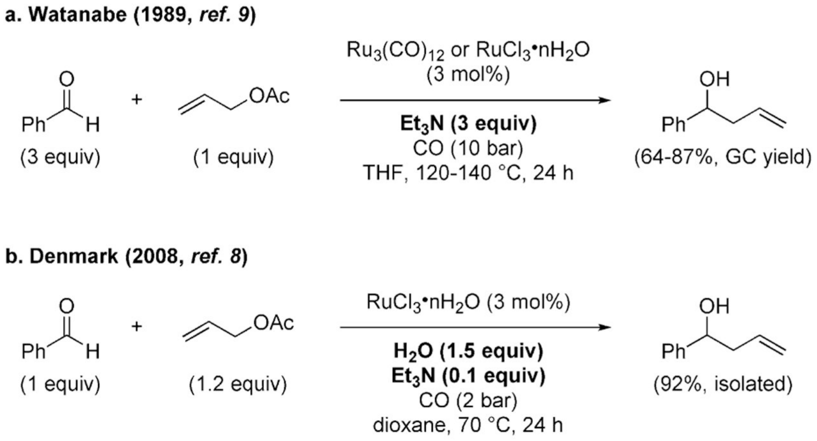


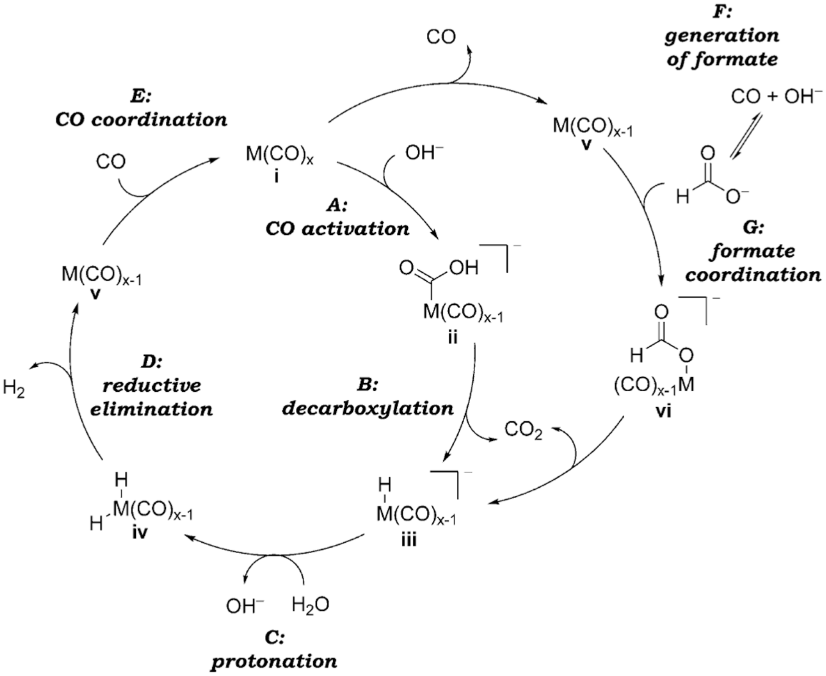
Figure 16.

Extension to 2-substituted allylic acetates.



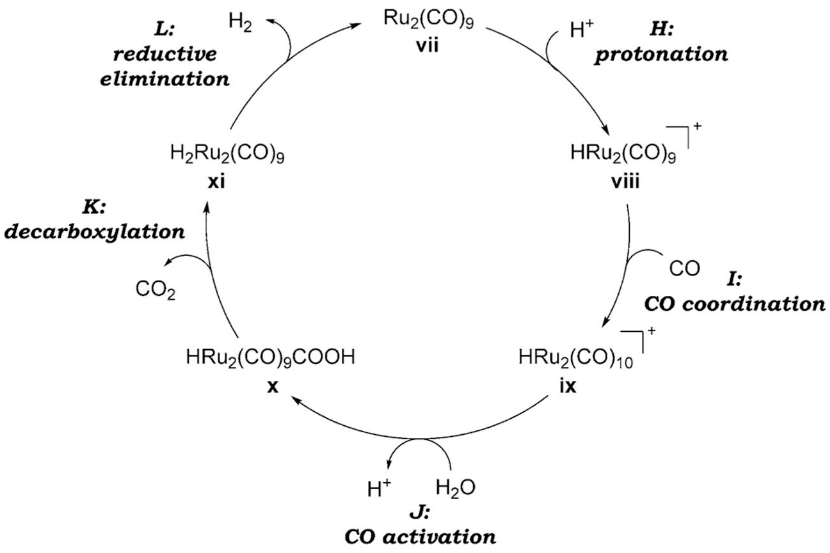
Scheme 1.

Catalytic allylation of aldehydes.



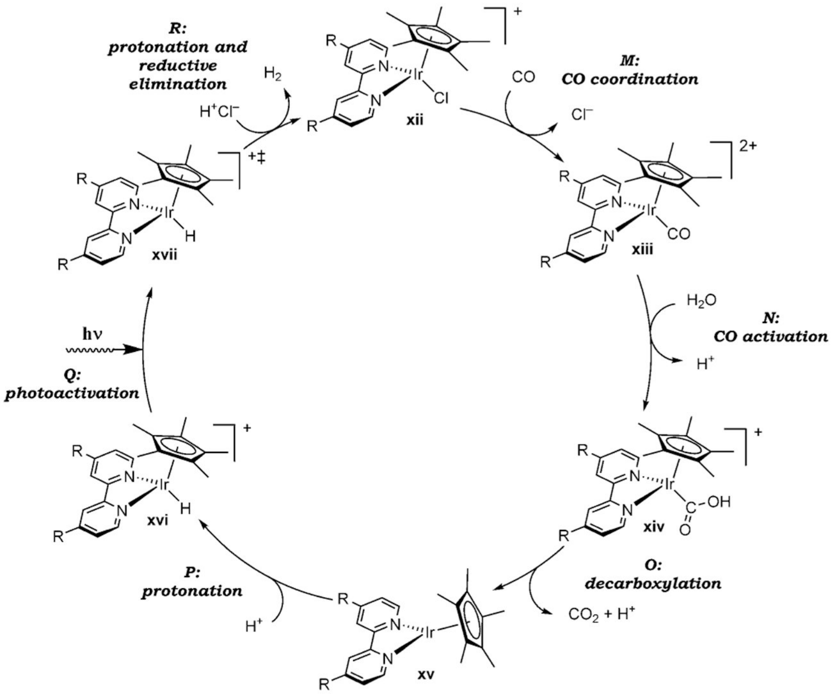
Scheme 2.

General catalytic cycle of the WGSR under basic conditions.



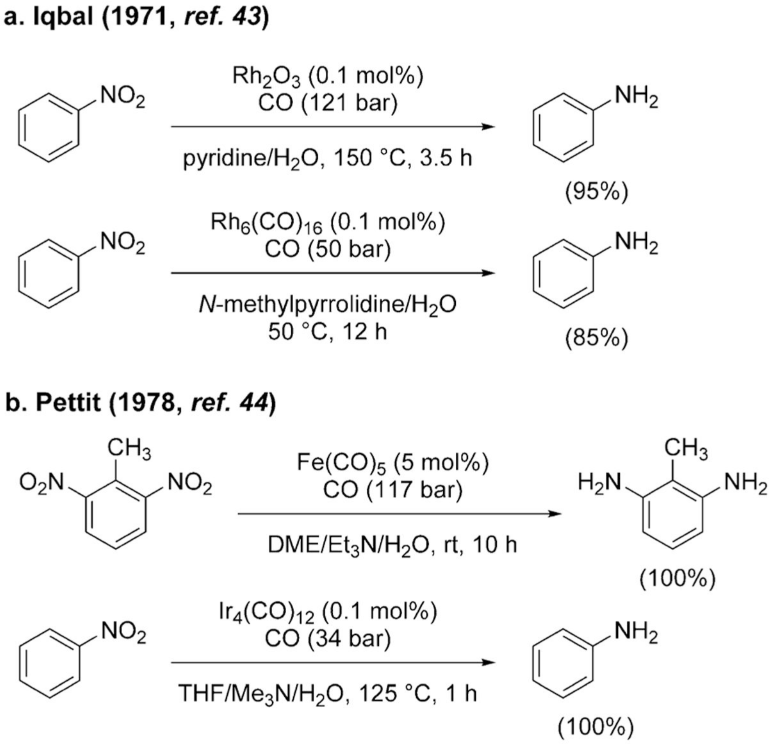
Scheme 3.

Catalytic cycle of the WGSR under acidic conditions using Ru3(CO)$_{12}$/H$_2$SO$_4$.



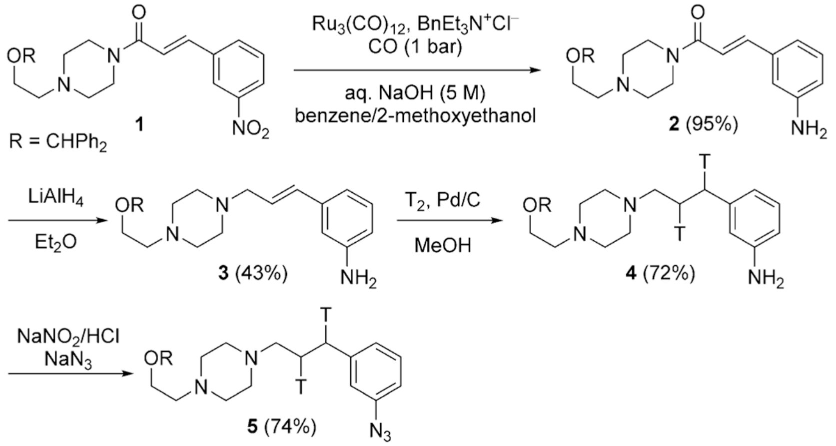
Scheme 4.

Catalytic cycle of the WGSR under photocatalysis using **xii**.



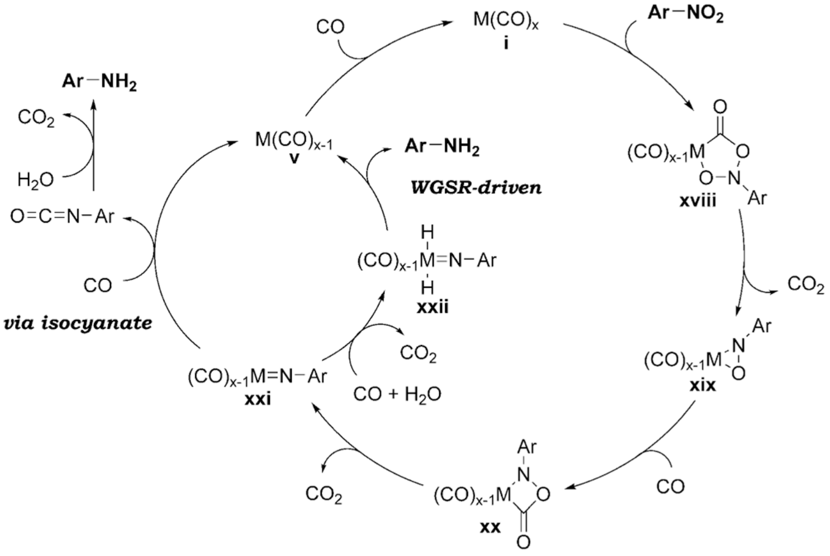
Scheme 5.

Initial reports on nitroarene reduction using WGSR conditions.



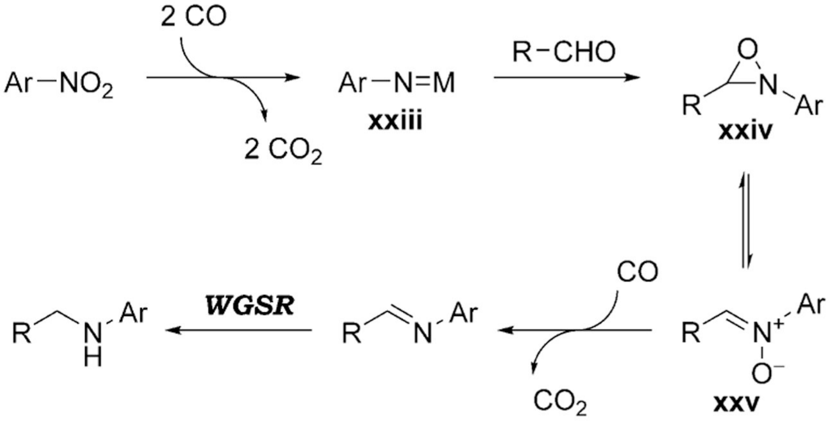
Scheme 6.

Sequential reduction reactions for the synthesis of **5**.



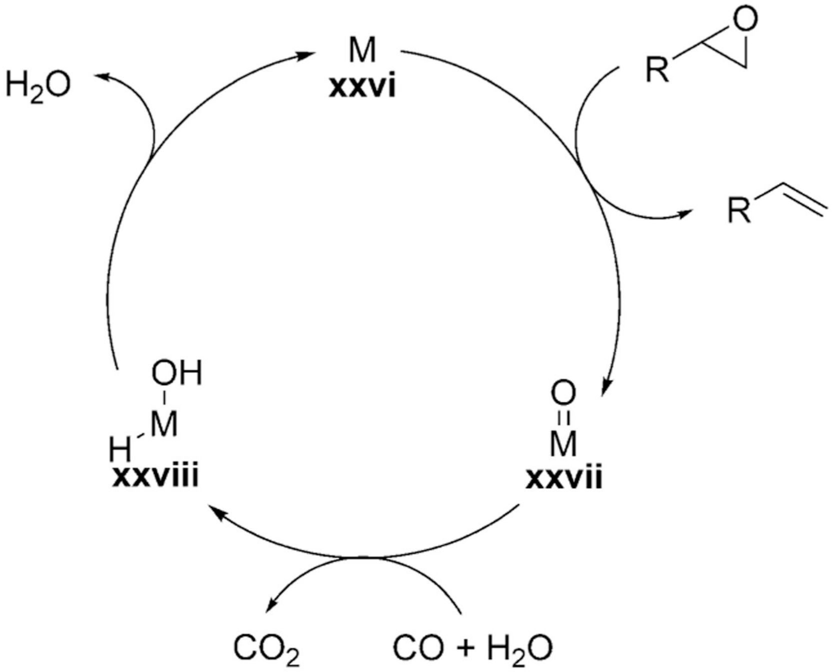
Scheme 7.

Catalytic cycle for the reduction of nitroarenes.

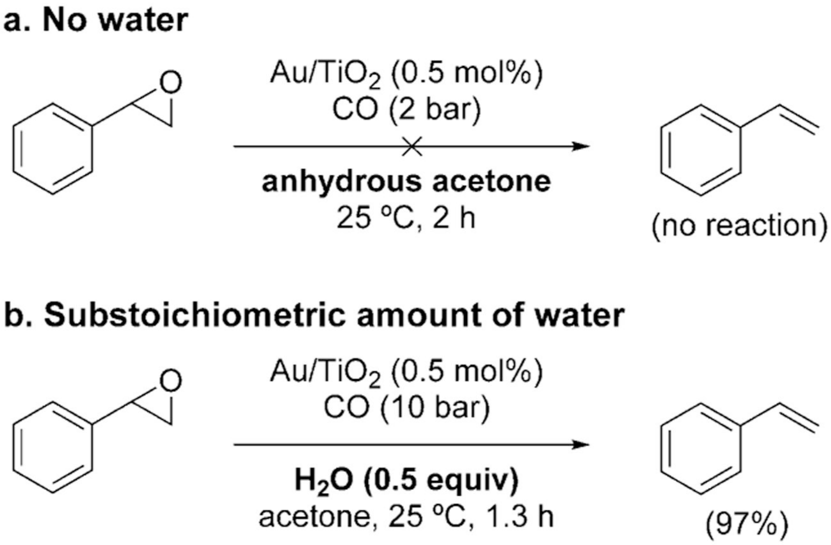


Scheme 8.

Mechanism for the formation of an imine by CO reduction of a nitro compound.

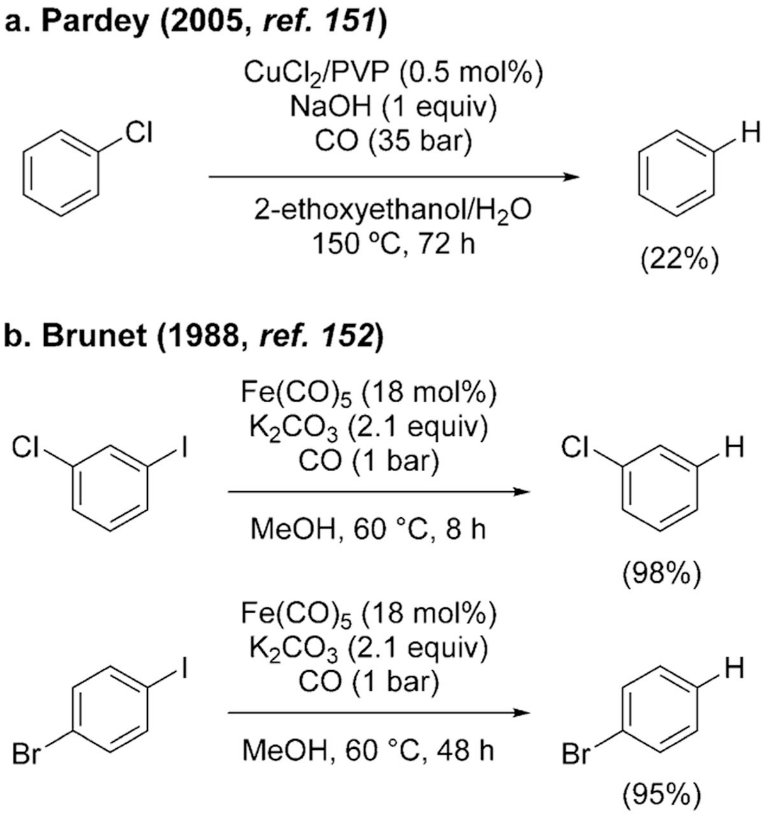


Scheme 9.
WGSR in the deoxygenation of epoxides.

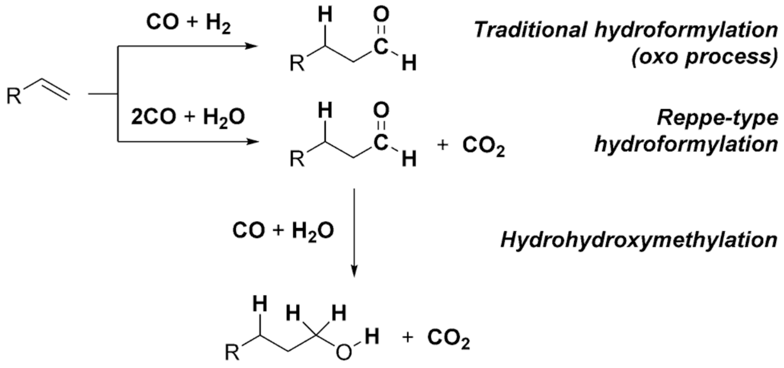


Scheme 10.

Control experiments with water.

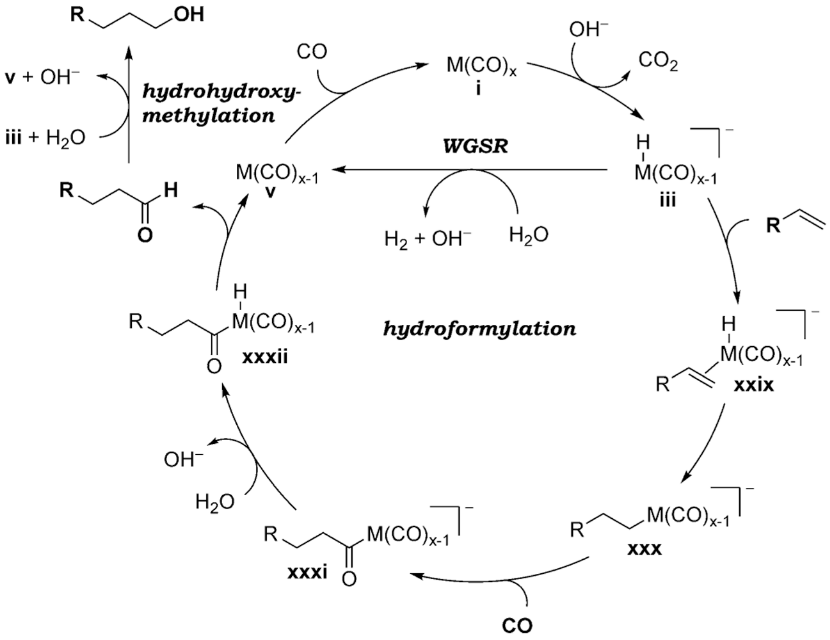


Scheme 11.
Hydrodehalogenation of aryl halides.



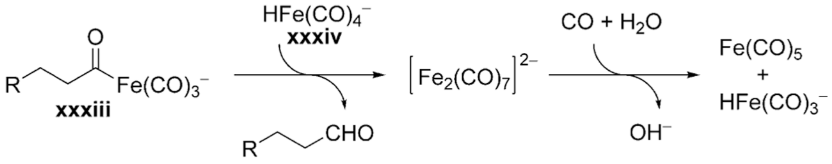
Scheme 12.

Reducing equivalents in hydroformylation reactions.



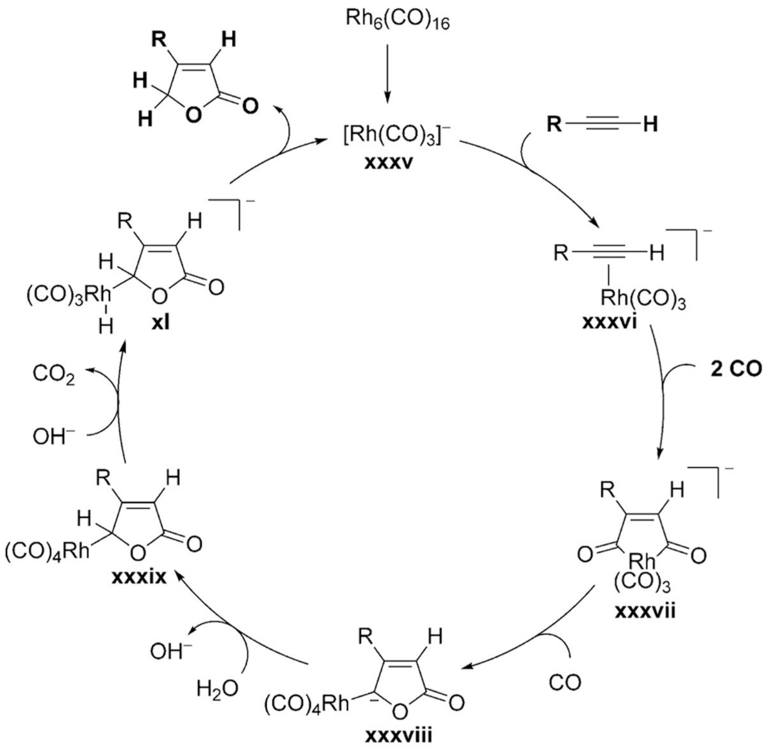
Scheme 13.

Catalytic cycle for the Reppe-type hydroformylation reaction.



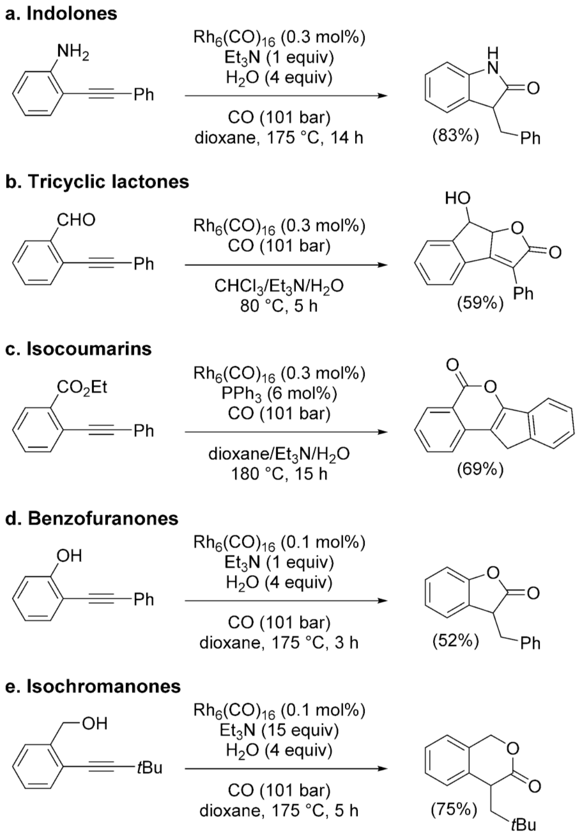
Scheme 14.

Alternative binuclear mechanism for hydroformylation.



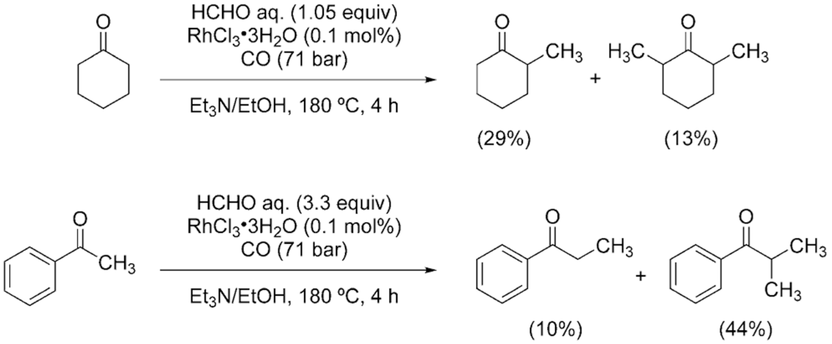
Scheme 15.

Catalytic cycle for the formation of furanones.



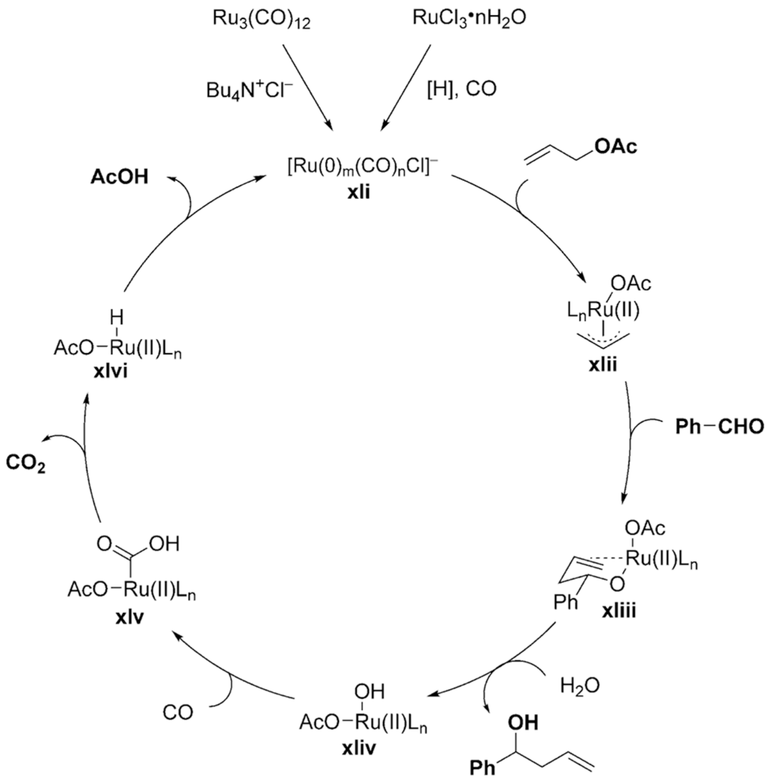
Scheme 16.

Synthesis of other fused cycles by cyclocarbonylation.



Scheme 17.

Reductive alkylation of ketones.



Scheme 18.

Catalytic cycle for the allylation reaction.

$$\mathrm{CO} + \mathrm{H_2O} \longrightarrow \mathrm{CO_2} + 2\mathrm{H^+} + 2e^- \qquad E^\circ_{\mathrm{ox}} = +0.53\ \mathrm{V}$$

$$\mathrm{M^{2+}} + 2e^- \longrightarrow \mathrm{M^0} \qquad E^\circ_{\mathrm{red}} = x$$

$$\mathbf{M^{2+} + CO + H_2O \longrightarrow M^0 + CO_2 + 2H^+} \qquad \boldsymbol{\Delta E^\circ = (x + 0.53)\ \mathrm{V}}$$

If $E^\circ_{red} > -0.53$ V,
the reaction can, in principle,
be driven by the WGSR

Scheme 19.

Electrochemical limitations for WGSR-driven reductions.

Table 1:

Reaction conditions for the reduction of aromatic nitro groups.

Entry	Metal catalyst	Additives	*T* [°C]	P_{co} [bar]	Ref.
1	Rh_2O_3, $RhCl_3{\cdot}3H_2O$, Rh carbonyl complexes	pyridine, *N*-methylpyrrolidine	50–150	50–121	[43]
2	Mn, Re, Fe, Ru, Os, Rh, Ir, Pt carbonyl complexes	Me_3N, Et_3N	25–187	34–117	[44, 48]
3	$Rh_6(CO)_{16}$	*N*,*N*-dimethylbenzylamine (DMBA), polymer-bound DMBA	80–120	7–55	[49]
4	$Ru_3\,(CO)_{12}$	$NaOH/BnEt_3N^+Cl^-$	25	1	[46]
5	Se	Et_3N	80	30	[50]
6	Rh carbonyl complexes	aliphatic amines and diamines, pyridine, substituted pyridines, polymer-bound amines	80	1–8	[51–53]
7	$[Ru(cod)py_4](BPh_4)_2$	–	80–145	15–61	[54]
8	$PtCl_2(PPh_3)_2$	$Et_3N/SnCl_4$	20–100	15–59	[55, 56]
9	Fe_2O_3/Al_2O_3	alkali metal carbonates	300–350	1	[57]
10	$Rh_6(CO)_{16}$, $Ru_3(CO)_{12}$	phenanthroline, substituted phenanthrolines, bipyridine, TMEDA	165	30	[58, 59]
11	$Co_2(CO)_8/[Rh(1,5\text{-hexadiene})Cl]_2$	$NaOH/(C_{12}H_{25})Me_3N^+Cl^-$	25	1	[60]
12	Ru and Os carbonyl complexes	KOH, HCl, HBr, HBF_4, CH_3COOH, CF_3COOH	120	69	[61]
13	Co carbonyl complexes	$NaOH/(C_{16}H_{33})Me_3N^+Br^-$	25	1	[62]
14	$(\eta^4\text{-}Ph_4C_4C{=}O)Ru(CO)_3$	Na_2CO_3, $NaHCO_2$, CH_3COOH, CF_3COOH	105	34	[63]
15	Rh carbonyl complexes/amines and diamines	NaOH	25	1	[64]
16	Rh and Ru carbonyl complexes/phosphines and bis-phosphines	NaOH	25–50	1	[65]
17	$Ru_3(CO)_{12}$	alkyl amines	150–180	20	[66–68]
18	$Ru_3(CO)_{12}$/*N*,*N*′-diaryl-diiminoacenaphthene ligands	–	150–180	30	[69]
19	S, CS_2, H_2S, COS/ V_2O_5, NH_4VO_3	NaOH, NH_4OH, $NaOCH_3$, Et_3N	70–150	120–140	[70]
20	$RhCl_3{\cdot}3\,H_2O$ on PVP[a]	–	100	1	[71]
21	$Ru_3(CO)_{12}/\alpha,\alpha$-dimethylbis(2-benzothiazolyl)methane	–	150–200	10–50	[72]
22	$PdCl_2$	$NaOH/(3\text{-}C_6H_4SO_3^-Na^+)_3P$ (TPPTS), BINAS (see Figure 2)	100	120	[73]
23	Pd, $PdCl_2$/Fe, Fe_2O_3/I_2	pyridine	150–180	25–90	[74]
24	K^+, Cs^+, $(PPh_3)_2N^+\,[Rh(CO)_4]^-$	–	200	40–81	[75]

Entry	Metal catalyst	Additives	T [°C]	P_{co} [bar]	Ref.
25	[Rh(nbd)(ppy)]ClO_4[a]	KOH	130	1	[76]
26	Se	pyridine, Et_3N	180–200	4	[77]
27	$[Rh(CO)_2(amine)_2]PF_6$, $[Ir(cod)(amine)_2]PF_6$	pyridine, substituted pyridines	60–150	0.5–30	[78,79]
28	$[Rh(CO)_2(amine)_2]PF_6$, $[Ir(cod)(amine)_2]PF_6$, $[Rh(cod)(amine)_2]PF_6$, $Rh_2(CO)_4Cl_2$ on PVP		70–130	0.5–2	[80–83]
29	$Rh_6(CO)_{16}$/dimethylaminoethylated hydroxypropyl-chitosan		80	10	[84]
30	$Ru_3(CO)_9(PEO\text{-}DPPSA)_3$[a]	–	100–140	20–50	[85]
31	$RhCl_3{\cdot}3\ H_2O$	alkyl amines, 2-picoline, TMEDA	100	1	[86]
32	Se	NaOAc, Na_2CO_3, NaOH, Et_3N, DBU	85–160	1–10	[87]
33	$CuCl_2{\cdot}2\ H_2O$ on PVP	–	100–150	7–27	[88]
34	$Au/Fe(OH)_x$	–	100–120	5–15	[89]
35	Au/TiO_2	–	25	5	[90]
36	Ag, Au, Pd, Rh, Pt on hydrotalcite	–	150	9	[91]
37	Ru/MgF_2	–	175	20	[92]
38	dendrimer-encapsulated $[Rh_5(CO)_{15}]^-$	–	80	10	[93]
39	Co_3O_4/N-doped graphene	–	125	30	[94]
40	$PdCl_2(py)_2/Fe/I_2$	pyridine, substituted pyridines	100–180	40	[95]

[a] PVP=poly(4-vinylpyridine); ppy=polypyridine chelating ligand; PEO-DPPSA=poly(ethylene oxide)-substituted 4-(diphenylphosphino) benzenesulfonamide.

Table 2:

Reaction conditions for the reduction of carbonyls.

Entry	Metal catalyst	Additives	T[°C]	P_{co} [bar]	Substrates	Ref.
1	$RhCl_3 \cdot 3H_2O$	Et_3N	200	51	aliphatic aldehydes	[126]
2	Fe, Ru, Rh carbonyl complexes	KOH	125	55	aromatic aldehydes, acetophenone	[37a]
3	$Fe_3(CO)_{12}$	Et_3N	100	100	acetone	[127]
4	$RhH_2(O_2COH)[P(i\text{Pr})_3]_2$	–	150	15	benzaldehyde, acetophenone	[128]
5	$Rh_6(CO)_{16}$	TMPDA[a]	30–80	5–20	aliphatic and aromatic aldehydes, ketones	[129]
6	$Rh_6(CO)_{16}$/dimethylaminoethylated hydroxypropyl-chitosan	–	80	10	benzaldehyde	[84]
7	Knölker's catalyst	K_2CO_3	100	10	aliphatic and aromatic aldehydes	[130]
8	Knölker's catalyst	Na_2CO_3	120	in situ release	aromatic aldehydes	[131]

[a] *N,N,N′,N′*-tetramethyl-1,3-propanediamine.

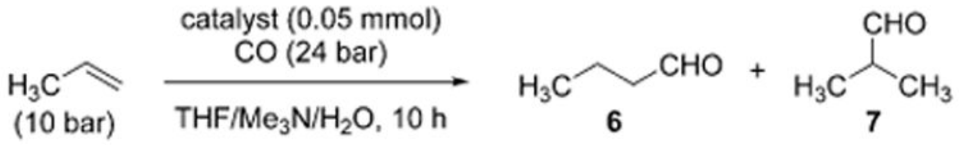
Table 3:

Deoxygenation reactions using the CO/H_2O couple.

Reaction	Metal catalyst	Ref.
Hydroxylamine to amine 	$Rh_6(CO)_{16}$	[52, 99]
Amine *N*-oxide to amine 	$Rh_6(CO)_{16}$ Au/TiO_2 [Ru(cod)py_4]$(BPh_4)_2$	[52, 99] [143] [145]
α-Hydroxycarboxylic acid to carboxylic acid 	Pd/C, $PdCl_2(PPh_3)_2$	[146]
Sulfoxide to sulfide 	Au/TiO_2	[143]

Table 4:

Performance of metal carbonyls in the Reppe-type hydroformylation reaction.



Entry	Metal catalyst	*T* [°C]	TON*[a]*	6:7 ratio
1	$Fe(CO)_5$	110	5.2	1:1
2	$Ru_3(CO)_{12}$	100	47	11.5:1
3	$H_4Ru_4(CO)_{12}$	100	79	11:1
4	$Os_3(CO)_{12}$	180	13	1.9:1
5	$Rh_6(CO)_{16}$	125	300	1.4:1
6	$Ir_4(CO)_{12}$	125	250	1.8:1
7	$(Bu_4N)[Pt_3(CO)_6]_5$	125	0.5	1.9:1

[a] Turnover number (TON)=[mmol(**6**)+mmol(**7**)]/mmol(catalyst)

Table 5:

Reaction conditions for the hydroformylation reaction.

Entry	Metal catalyst	Additives	*T* [°C]	P_{co} [bar]	Ref.
1	$Rh_2O_3/Fe(CO)_5$	*N*-methylpyrrolidine	100–200	203	[158]
2	Fe, Ru, Os, Rh, Ir, Pt carbonyl complexes	Me_3N	100–180	24	[19]
3	$Ru_3(CO)_{12}$, $H_4Ru_4(CO)_{12}$, $Rh_6(CO)_{16}$	KOH	135–150	55	[153]
4	$Co_2(CO)_8$/dppe, other phosphines	none, Et_3N	135–195	12–150	[159]
5	$RhH_2(O_2COH)[P(i\text{Pr})_3]_2$	–	115	15	[128]
6	$Rh_6(CO)_{16}$	aliphatic amines and diamines, pyridine, substituted pyridines	80	5	[137]
7	$Rh_2(CO)_3(dppm)_2$	LiCl, *p*-TsOH	90	0.4	[160]
8	$Fe(CO)_5$	NaOH, Et_3N	110–140	10–27	[161]
9	$Rh_2(St\text{Bu})_2(CO)_2(TPPTS)_2$, $[Rh(cod)(TPPTS)_2](ClO_4)$, $RhH(CO)(TPPTS)_3$ [a]	–	80	8	[162]
10	$K[Ru(EDTA\text{-}H)Cl]\cdot 2H_2O$	–	110–130	10–40	[163]
11	$RhCl_3\cdot 3\ H_2O$ on PVP[a]	–	85–120	0.3–1.7	[164]
12	$[Rh(cod)(amine)_2]PF_6$, $[Rh(CO)_2(amine)_2]PF_6$ on PVP	–	100–140	10–56	[165]
13	$[Ru(OCOEt)(CO)_2]_n$	EtCOOH/EtCOONa	140	18–88	[166]
14	$[Rh_2(\mu\text{-}S_2CBn_2)(cod)_2]$	–	80	1.3–22	[167]

[a] TPPTS=$(3\text{-}C_6H_4SO_3^-Na^+)_3P$, PVP=poly(4-vinylpyridine).