CARBON MONOXIDE-DRIVEN REDUCTIVE ORGANIC TRANSFORMATIONS AND PRECIOUS METALS RECYCLING

BY

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DISSESTATION

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Abstract

Herein we present the efforts made toward employing the homogeneously-catalyzed Water-Gas Shift Reaction (WGSR) to drive essential reductive chemical transformations, and selectively extract rhodium from solid waste. The generation of rhodium hydride from the reaction of rhodium carbonyl with water has been achieved at temperatures as low as room temperature when the reaction was performed in a solution of simple tertiary amines in polar solvents. We investigated the mechanism by which this reaction proceeds and studied the effect of the reaction parameters on the ability of rhodium to deliver its hydride to different reducible functional groups e.g. activated alkenes, aldehydes, and ketones.

We demonstrated the ability of the WGSR to drive the reductive alkylation of several classes of activated methylene compounds at room temperature. Under catalysis by rhodium trichloride (2–3 mol %), carbon monoxide (10 bar), water (2–50 equiv), and tertiary methyl /ethyl amines (2.5–7 equiv), the scope has been successfully expanded to cover a wide range of alkylating agents, including aliphatic and aromatic aldehydes, as well as cyclic ketones, in moderate to high yields. This method is comparable to, and for certain aspects, surpasses the established reductive alkylation protocols. The reductive amination of aldehydes has been demonstrated to be feasible under the same conditions with the exception of furfurals which undergo a newly-identified, reductive Piancatelli rearrangement to yield 2-enoneamines.

A novel Pd/Rh dual-metallic cooperative catalytic process has been developed to effect the reductive carbonylation of aryl halides in moderate to good yield. In this reaction, water is the hydride source, and CO serves both as the carbonyl source and the terminal reductant through the water–gas shift reaction. The catalytic generation of the Rh hydride allows for the selective formation of highly hindered aryl aldehydes that are inaccessible through previously reported reductive carbonylation protocols. Moreover, aldehydes with deuterated formyl groups can be efficiently and selectively synthesized using D₂O as a cost-effective deuterium source without the need for presynthesizing the aldehyde. Addition of an electrophile e.g. allyl acetate to the reaction resulted in the formation of aryl-vinyl ketones through the WGSR-driven reductive carbonylative coupling.

We developed a mild and selective method for rhodium recovery that relies on the use of carbon monoxide to extract rhodium nanoparticles on various supports in polar solvents. Unlike the traditional recycling technologies, this method operates at low temperature and does not
require strong acids. Reductive alkylation CO-induced leaching is complimentary to leaching by acids in terms of selectivity toward rhodium versus other precious metals and results in metal recovery in the form of reduced metallic clusters. The method performs best on freshly reduced surfaces and can be promoted by the addition of tertiary amines. Besides CO gas, formic acid can also be used as a leachant by decomposition to produce CO by Rh catalysis. The concept of the CO-induced leaching could be applied to the extraction of rhodium from catalytic convertors and nuclear waste or utilized to modify rhodium nanoparticle size and composition.

**Key words:** Water-Gas Shift, rhodium carbonyl hydride, reductive carbonylation, alkylation, amination, rhodium recycling.
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Chapter 1: The water-gas shift and its applications in organic synthesis

1.1. Introduction

The reaction of water with carbon monoxide to produce hydrogen and carbon dioxide was first discovered by the Italian physicist Felice Fontana in the late 1700s and later called the Water-Gas Shift Reaction (WGSR). The WGSR remained underutilized until the early 1900s when the need for large quantities of pure hydrogen emerged as a consequence of the development of the Haber-Bosch technology for ammonia synthesis, an essential technology for fertilizers manufacture and other commodity chemicals.¹ The growth of world population and the increasing demand for ammonia attracted research efforts aiming for more efficient WGSR.

The feed to WGSR process is a mixture of water and carbon monoxide in the gas phase (Syn gas); often mixed with hydrogen produced from methane steam reforming, coal gasification, or biomass pyrolysis. The WGSR is utilized to adjust the hydrogen to carbon monoxide ratio to fit the feed requirements for the downstream processes. For instance, the CO/H₂ ratio must be very low (<1 %) for ammonia synthesis since CO deactivates the catalyst.²

The WGSR is a moderately exothermic, equilibrium-limited reaction, and higher CO conversion can theoretically be achieved at lower temperature, Figure 1.1. However, all catalysts require high temperature to be reactive i.e. the reaction is thermodynamically favored at low temperature but kinetically favored at high temperature.

**Figure 1.1.** Equilibrium conversion of CO in the WGSR at different temperatures.³
Owing to the thermodynamic limitation of the WGSR, the lowest CO/H\textsubscript{2} ratio that can be achieved with iron - chromium mixed oxide catalyst is 2 to 4%. To achieve lower CO/H\textsubscript{2} ratio for ammonia synthesis, the reaction is often performed in two adiabatic reactors in series.\textsuperscript{4} The High Temperature Shift (HTS) reactor operates in the temperature range of 310 – 450 °C and affects the shift using Fe-Cr mixed oxide catalyst. The Low Temperature Shift (LTS) operates at 210 - 250 °C and utilizes a mixture of Zn-Cu-Cr oxides as a catalyst to allow for a CO/H\textsubscript{2} ratio as low as 1%. Pressure, on the other hand, does not have a significant impact on the equimolar reaction when performed in the vapor phase and thus it is often kept constant. Much lower ratios (< 10 ppm)\textsuperscript{5} are needed for modern applications such as fuel cells, where CO acts as a strong poison for the Proton Exchange Membrane (PEM) catalysts. Extensive research is carried out to formulate more reactive catalysts at lower temperatures.\textsuperscript{6}

The mechanism by which the WGSR proceeds is still under debate and is believed to vary based on the reaction conditions. At temperature higher than 350 °C, a catalyst redox mechanism is proposed in which the catalyst surface is oxidized by the dissociative adsorption of the hydroxide to form a surface oxygen atom. The oxidation is followed by a catalyst reduction by CO to form CO\textsubscript{2}. An alternative mechanism is proposed for the low temperature reaction in which CO is directly oxidized by the hydroxide ion to form a carboxyl or formate intermediates that decomposes on the surface to form CO\textsubscript{2}. In both mechanisms, hydrogen is formed by the reductive elimination of surface metal hydrides.\textsuperscript{7}

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 the WGSR and organic chemistry.\textsuperscript{8} One of the earliest examples of engaging the WGSR in organic transformation is the Reppe modification on olefin hydroformylation. In this reaction, hydrogen was replaced by water as the source of hydride to produce aldehydes and alcohols under carbon monoxide using Fe catalyst.\textsuperscript{9} The reducing power provided by the CO/H\textsubscript{2}O couple has been further exploited in the synthesis of fine chemicals, mainly in hydrogenation-type reactions (hydrogenation of alkynes, nitro groups, aldehydes and epoxides, Scheme 1.1a to d).\textsuperscript{10} This approach was further developed to affect the C-C reductive coupling of allyl acetates with aldehydes to form allyl alcohols, Scheme 1.1e.
When coupled with organic reactions, the reaction is performed under different conditions from those illustrated for hydrogen production above. For instance, the WGSR-driven organic transformations are commonly carried out with homogeneous catalyst at much lower temperatures than 150 °C. Moreover, in this kind of transformations, water reacts in the form of liquid solutions instead of vapor which not only changes the reaction mechanism but also the thermodynamics, Table 1.1.\textsuperscript{11} When compared to the traditional, vapor phase WGSR, the liquid phase WGSR-driven organic transformations exhibit the following differences:

1- In liquid phase, the overall reaction becomes slightly endothermic and is accompanied by a significant gain in entropy.

2- The reaction becomes favored by high CO pressure to overcome mass transport of gas to liquid.
3- Molecular hydrogen is not produced, instead, the formed metal hydride is used to transfer the hydride to an acceptor (substrate) followed by the regeneration of the metal hydride. In an alternative manifestation of the WGSR, the reductive power of CO/H$_2$O pair is utilized to reduce the metal catalyst that is used to affect an oxidation step.

Table 1.1. Thermodynamic parameters of the WGSR with vapor and liquid water reactants.

<table>
<thead>
<tr>
<th>parameter</th>
<th>vaporized water$^a$</th>
<th>liquid water$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\Delta G^\circ$ 298 (kcal)</td>
<td>-6.82</td>
<td>-4.76</td>
</tr>
<tr>
<td>$\Delta H^\circ$ 298 (kcal)</td>
<td>-9.84</td>
<td>+0.68</td>
</tr>
<tr>
<td>$\Delta S^\circ$ 298 (cal/deg)</td>
<td>-10.1</td>
<td>+18.3</td>
</tr>
</tbody>
</table>

A generally accepted mechanism for the catalytic formation of homogeneous metal hydrides is through the nucleophilic attack of a hydroxide ion on the metal carbonyl catalyst (i) to form hydroxycarbonyl intermediate (ii).$^6$ Figure 1.2. The hydroxycarbonyl intermediate rearranges to form metal formate (or carboxylate) that under goes beta hydride elimination (or decarboxylation) to form the metal hydride (iii). The step following the formation of the metal hydride depends on the nature of the hydride acceptor. For example, reducible substrates capable of coordinating to the metal center under carbon monoxide undergo hydrometalation followed by protonation (vi, and vii). In absence of a hydride acceptor, the metal hydride can be protonated to form a metal dihydride (ix) followed by the reductive elimination of molecular hydrogen.

Our group is interested in expanding the range of applicability of the WGSR to the catalysis of fundamental reductive coupling reactions. One of the simplest approaches to engage the WGSR in a reductive C-C bond formation relies on the well-established capacity of CO/H$_2$O to act as a H$_2$ surrogate or catalyst reductant, Figure 1.3. In the first approach, an independent C-X bond forming event (where X can be C or N) leads to a functional group that can be reduced (hydrogenated) by CO/H$_2$O. The metal catalyst for the WGSR is not involved in the formation of the C-X bond, but only in the generation of a metal-hydride species that will reduce the substrate. The outcome is an overall reductive, tandem transformation that combines two steps in one, therefore enhancing step, and redox economy.$^{12}$ In the later approach, a catalyst, either the same as the WGSR catalyst or a different metal, affects the desired chemical transformation and
becomes oxidized $M^+$ to $M^{x+2}$. To reduce the active catalyst back to its initial oxidation state $M^{x+2}$ to $M^+$, the WGSR provides the reductive equivalent through the formation of carbon dioxide and two protons.

**Figure 1.2.** Proposed mechanism for the homogeneous WGSR.

To render the WGSR-driven organic transformations feasible, the reaction needs to proceed at mild conditions that allow for the selective reduction to occur while other reactive functional groups remain intact, and thus, thorough conditions optimization need to be performed. In this study, the development of novel reductive transformation using the WGSR is illustrated as following:

1- The Rh-catalyzed reductive alkylation of nitrile carbon acids (Chapter 2),$^{13}$ and ketones (Chapter 5) at room temperature

2- The Pd-Rh cooperative catalyst for the reductive carbonylation of aryl halides (Chapter
3) The selective extraction of Rh nanoparticles with CO and water under mild, non-acidic conditions (Chapter 4)

4- The Rh-catalyzed hydrogenation of ketones at room temperature and mechanistic investigation of the WGSR-driven reductions (Chapter 6)

5- The Rh-catalyzed reductive amination and the Ru-catalyzed reductive aminomethylation (Chapter 7)

Figure 1.3. Concepts of the WGSR-driven reductive transformations.
1.2. References


(13) Denmark, S. E., Ibrahim, M. Y. S., Ambrosi, A. ACS Catalysis 2017 7 (1), 613-630


(15) Ibrahim, M. Y. S., Denmark, S. E. J. Mater. Chem. A (in peer review)
Chapter 2: Alkylation of nitrile carbon acids by the water-gas shift-driven reductive Knoevenagel condensation

2.1. Introduction

One of the proposed approaches to engage the WGSR in a reductive C-C bond formation relies on the well-established capacity of CO/H₂O to act as a H₂ surrogate (Figure 2.1). In this approach, an independent C-X bond forming event (where X can be C or N) leads to a functional group that can be reduced (hydrogenated) by CO/H₂O. The metal catalyst for the WGSR is not involved in the formation of the C-X bond, but only in the generation of a metal-hydride species that will reduce the substrate. The outcome is an overall reductive, tandem transformation that combines two steps in one, therefore enhancing step- and redox economy.¹

![Figure 2.1. WGSR in C-X bond forming reactions.](image)

Tandem, WGSR-based approaches have been described for reductive amination,² a C-N bond forming process that entails formation of an imine and its reduction by CO/H₂O. As early as 1978, Watanabe et al. employed WGSR conditions to carry out the methylation or benzylation of amines with aldehydes.³ More recently, the scope and applicability of the reductive amination reaction under WGSR conditions have been significantly expanded by the independent contributions of List, Chusov, Chung and coworkers.⁴

A similar strategy has been adopted in the formation of C-C bonds via tandem aldol condensation/WGSR-mediated alkene reduction. In this context, Watanabe et al. reported the methylation of ketones and methylpyridines with formaldehyde.⁵ In addition, expanding on their studies of reductive amination, Chusov et al. disclosed two protocols for the reductive alkylation of active methylene compounds (reductive Knoevenagel condensation, Figure 2.2).
Figure 2.2. Reductive Knoevenagel alkylation under WGSR conditions.

The transformation was achieved using either homogenous (Rh2(OAc)4) or heterogeneous (Rh/C) catalysis, and allowed for the successful alkylation of methyl cyanoacetate with aldehydes and ketones. However, the reported protocols are plagued by a number of drawbacks. First, the reaction requires impractically high temperatures (110-160 °C) and pressures of CO (50-90 bar). Second, the forcing conditions cause unwanted side reactions, such as transesterification, hydrolysis and decarboxylation of esters (Figure 2.2c). Third, the protocol seems to be only applicable to cyanoacetates as the Knoevenagel nucleophiles.

The reductive variant of the Knoevenagel condensation represents an alternative to the direct alkylation of active methylene compounds with alkyl halides. This traditional method suffers from the need for a (super)stoichiometric amount of base (usually inorganic), as well as the occurrence of over alkylation and O-alkylation. Key benefits of a reductive alkylation approach...
include the smooth C-monoalkylation, the greater availability of aldehydes and ketones compared to halides, their lower cost (§4/mol for benzaldehyde, §38/mol for benzyl bromide, for example)\(^8\) and toxicity. Moreover, the use of WGSR conditions is more mass-efficient than regular alkylation reactions (CO\(_2\) vs. M\(^+\)Br\(^-\) as the byproducts), and it allows for a chemoselective reduction of the intermediate alkene that is compatible with a variety of other reduction-susceptible functional groups. Yet, the protocols developed by Chusov et al. are far from being synthetically useful because of the harshness of the reaction conditions. The identification of milder reaction conditions and the expansion of the substrate scope are essential for the further development of this strategic WGSR-driven, C-C bond forming reaction.

2.2. Background

With over 120 years’ worth of history and applications in synthetic endeavors, the Knoevenagel condensation reaction represents an indispensable tool in organic synthesis.\(^9\) The reaction entails the addition of an active methylene compound to an aldehyde or ketone followed by the elimination of water (Scheme 2.1a). The addition step requires bases such as amines, or inorganic basic salts including ammonium salts or potassium fluoride in organic solvents. Amino acids such as L-proline, glycine, β-alanine and L-tyrosine have also been employed. The pK\(_a\) of the active methylene

![Scheme 2.1. Knoevenagel condensation and reductive Knoevenagel alkylation](image)

compound must be sufficiently low to allow for deprotonation by a weak base. Thus, cyclic and acyclic 1,3-dicarbonyl compounds (and their equivalents) are a privileged class of substrates in Knoevenagel condensations, although reactions with heteroatom-, aryl-, or nitro-stabilized enol equivalents are not uncommon.

Because of its operational simplicity and expedited access to α,β-unsaturated motifs, the
Knoevenagel condensation has found multiple applications in organic synthesis, including in industrial settings.\textsuperscript{10} One of its key features is the possibility to engage the resulting alkene in tandem processes, such as Michael, Diels-Alder, or sigmatropic reactions.\textsuperscript{9} In this context, the reductive variant of the Knoevenagel reaction, in which the alkene is hydrogenated immediately following the condensation (Scheme 2.1b), has also received significant attention. For example, the synthesis of the top-selling anti-diabetic drug pioglitazone (4, Scheme 2.2) involves the Knoevenagel condensation of 2,4-thiazolidinedione (1) with aldehyde 2. The resulting Knoevenagel adduct 3 affords pioglitazone after a standard hydrogenation over Pd/C.\textsuperscript{11}

**Scheme 2.2.** Synthesis of 4 by the hydrogen-driven, two step reductive condensation

Reductive Knoevenagel protocols of this kind, consisting of the reduction of a pre-formed Knoevenagel adduct in a separate step, are numerous. In addition to the widespread use of H\textsubscript{2}, several other hydrogen sources have been employed in the reduction step, including sodium borohydride,\textsuperscript{12} borane,\textsuperscript{13} formic acid/triethylamine,\textsuperscript{14} formate,\textsuperscript{15} the Hantzsch ester,\textsuperscript{16} 2-phenylbenzimidazoline,\textsuperscript{17} and 2-phenylbenzothiazoline.\textsuperscript{18} However, the need for a two-step process is impractical and limits the step-economy.

Consequently, efforts have been made to combine the condensation and reduction steps into a tandem (one-pot) process, using mutually compatible reagents and reaction conditions. Tandem protocols have been developed with several reducing agents (Scheme 2.3): H\textsubscript{2},\textsuperscript{19} formic acid/triethylamine,\textsuperscript{20} the Hantzsch ester (5),\textsuperscript{21} 2-phenylbenzimidazoline,\textsuperscript{22} and, of course, the CO/H\textsubscript{2}O-based systems discussed above (Figure 2.2).\textsuperscript{4d,6} Both aldehydes and ketones can be engaged as the electrophiles.
Although these methods are efficient from a step-economy standpoint, the use of reducing agents other than the simple H₂, H₂O/CO, or HCOOH/Et₃N is highly wasteful and atom-uneconomic. However, the range of applicability of H₂ is limited because of its incompatibility with functional groups such as alkenes, alkynes, carbonyls, halides, nitro groups, and S-bearing functionalities. On the other hand, CO/H₂O and HCOOH/Et₃N have fewer compatibility issues, but are still unpractical because of the harsh conditions needed, or the long incubation time for the condensation to take place, respectively. Therefore, it is not surprising that, for applications of the reductive Knoevenagel condensation with sensitive substrates in a total synthesis context, the use of the mild (yet wasteful) Hantzsch ester has been preferred (Scheme 2.4).²³
An alternative to the use of external reducing agents is represented by the hydrogen-transfer technology.\textsuperscript{24} In methods relying on hydrogen-transfer, the electrophile (aldehyde) is replaced by a primary alcohol, which acts both as the reactant and the source of reducing equivalents. A suitable metal catalyst allows for the \textit{in situ} oxidation of the alcohol to the carbonyl, as well as the reduction of the alkene after the Knoevenagel condensation has taken place (hence the term hydrogen-transfer or hydrogen-borrowing). Although known since 1955,\textsuperscript{25} the hydrogen-transfer alkylation of active methylene compounds has been considerably developed only in the last decade. Recent reports have described protocols for the alkylation of several classes of active methylene precursors, including arylacetonitriles,\textsuperscript{26} barbituric acids,\textsuperscript{27} cyano acetates,\textsuperscript{28} oxindoles,\textsuperscript{29} 1,3-diketones,\textsuperscript{30} keto nitriles,\textsuperscript{31} and malonates\textsuperscript{32}, using Group 8 and 9 transition metal catalysts (Scheme 2.5a-e). The alkylation of unactivated ketones has also been reported (Scheme 2.5f).\textsuperscript{33}

Despite the benefit of their catalytic nature, hydrogen-transfer alkylation protocols are still limited by the need for high temperatures (which, in conjunction with basic conditions, may cause transesterification or decarboxylation of esters),\textsuperscript{28,32} and by the fact that only primary alcohols (mostly benzylic) are compatible. Therefore, the reductive alkylation with ketone electrophiles (from secondary alcohols) cannot be achieved under these conditions.

2.3. Research Objectives

Within the context of our overarching goal to expand the applications of the WGSR in organic synthesis, the present investigation intended to provide a robust and general protocol for the reductive Knoevenagel alkylation using CO/H\textsubscript{2}O as the reducing agent. The development of our synthetic method involved the following steps:

(a) identification of milder and more practical reaction conditions than previously reported;
(b) application of the optimized reaction conditions to a wide range of electrophiles and nucleophiles, thus demonstrating the generality and versatility of the approach;
(c) clarification of the observed reactivity trends through a mechanistic proposal, which may guide further optimization.
Scheme 2.5. Alkylation by transfer hydrogenation

2.4. Results

The alkylation of active methylene compounds was attempted using different aldehydes and ketones at room temperature under carbon monoxide atmosphere. To help both condensation and WGSR to proceed, basic reaction conditions and additional water were applied, aiming at achieving appreciable yields in reasonable length of time. Detailed optimization of each of the process parameters was performed on a selected reductive alkylation case, and then the optimized conditions was extended to other substrates.

The reductive alkylation of ethyl cyanoacetate (6a) with benzaldehyde (7a) to produce ethyl 2-cyano-3-phenylpropionate (8aa) via 9aa was investigated as a model reaction for the proposed
WGSR-assisted, C-C bond formation. Ruthenium, iron, cobalt, manganese, iridium, and rhodium are among the transition metals complexes known to effectively catalyze the WGSR$^{34}$ and hence their carbonyl complexes were tested as catalysts under carbon monoxide atmosphere in presence of water (Table 2.1). Only rhodium was found to be active for the reductive alkylation at room temperature (entries 1-6). In addition to Rh$_4$(CO)$_{12}$, other sources of rhodium including RhCl$_3$·3H$_2$O, [Rh(COD)Cl]$_2$, Rh$_2$(OAc)$_4$, and Rh nanoparticles supported on titanium oxide (Rh/TiO$_2$) were all effective catalysts (entries 7-10).

Table 2.1. Transition Metals Reductive Alkylation Reactivity.

<table>
<thead>
<tr>
<th>entry</th>
<th>catalyst</th>
<th>yield (%)$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ru$<em>3$(CO)$</em>{12}$</td>
<td>&lt;1</td>
</tr>
<tr>
<td>2</td>
<td>Fe$_2$(CO)$_9$</td>
<td>&lt;1</td>
</tr>
<tr>
<td>3</td>
<td>Co$_2$(CO)$_8$</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>Mn$<em>2$(CO)$</em>{10}$</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>[Ir(cod)Cl]$_2$</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>Rh$<em>4$(CO)$</em>{12}$</td>
<td>98</td>
</tr>
<tr>
<td>7</td>
<td>[Rh(COD)Cl]$_2$</td>
<td>95</td>
</tr>
<tr>
<td>8</td>
<td>Rh$_2$(OAc)$_4$</td>
<td>96</td>
</tr>
<tr>
<td>9</td>
<td>RhCl$_3$·3H$_2$O</td>
<td>97</td>
</tr>
<tr>
<td>10</td>
<td>Rh/TiO$_2$</td>
<td>98</td>
</tr>
</tbody>
</table>

$^a$ Measured by GC with an internal standard.

Supported transition metal nanoparticles are preferred to their homogeneous analogs due to their ease of separation and reuse. However, upon testing the reusability of Rh/TiO$_2$, it was found out that excessive leaching of rhodium occurred and hence the heterogeneous catalyst could not be used (see Supporting Information). Among the other active catalysts, RhCl$_3$·3H$_2$O is the most common and inexpensive source of soluble rhodium and thus it was used for the optimization of conditions and investigation of scope.

The catalytic activity can potentially be limited by the catalyst solubility in the reaction medium. In this case, only a small fraction of the catalyst would be actively participating in the reaction. To test for this limitation, the RhCl$_3$ loading was increased from 1 to 3 mol % and the
product yield was measured after 12 h. The product yield increased as the catalyst loading was increased, indicating that there is no solubility limitation on the catalyst concentration in the specified range of metal loading (Table 2.2).

**Table 2.2. Effect of Catalyst Loading on Product Yield.**

<table>
<thead>
<tr>
<th>entry</th>
<th>Rh mole (%)</th>
<th>yield (%)a</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>12</td>
</tr>
<tr>
<td>2</td>
<td>1.5</td>
<td>24</td>
</tr>
<tr>
<td>3</td>
<td>2</td>
<td>67</td>
</tr>
<tr>
<td>4</td>
<td>3</td>
<td>96</td>
</tr>
</tbody>
</table>

a Measured by GC with an internal standard.

The reductive alkylation was attempted in a number of solvents to test the effect of solvent properties on both condensation and reduction (Figure 2.3). Best results were obtained when acetonitrile was used as a solvent followed by butyronitrile, DMF, DMSO, and then 1,4-dioxane. No product was formed when protic solvents such as methanol, ethanol, 2-propanol, or water were used. Less polar solvents such as THF, triethylamine, and toluene were found not to be suitable for this reaction either. The Knoevenagel condensation step proceeded to completion in all the tested solvents except in methanol, water, and toluene. Complete conversion of the aldehyde to the dimethyl acetal and of the ethyl cyanoacetate to the methyl cyanoacetate occurred when methanol was used. Water limits the condensation by shifting the thermodynamic equilibrium towards the starting material and thus, condensation did not proceed to completion in water, whereas toluene is non-polar and does not favor the enolization of the cyano ester for condensation to proceed.

Water, carbon monoxide, and Rh catalyst all need to be soluble in the solvent effect reduction. The incompatibility of alcohols as solvents cannot be explained by their limited ability to dissolve water or carbon monoxide, moreover, when RhCl₃ was replaced by Rh₄(CO)₁₂, a more soluble form of catalyst, reduction still did not proceed in alcohols indicating that they negatively affect the turnover of the catalytic cycle leading to reduction.
Figure 2.3. Effect of solvent on product yield (measured by GC with an internal standard).

Since the CO/H$_2$O couple is hypothesized to be the source of reducing equivalents, the CO pressure dependence of product yield was examined from 0 to 25 bar while keeping the water loading constant (Figure 2.4). A control experiment clearly established that no reaction takes place in the absence of carbon monoxide and increasing carbon monoxide pressure was found to have a positive impact on the desired product yield up to 10 bar. Further increase in carbon monoxide pressure resulted in an inverse response of the product yield.
The effect of water concentration on the reduction step was studied on the pre-formed Knoevenagel condensation product 9aa to eliminate the effect of water produced from the condensation step. Reduction does not proceed in the absence of water and the rate of reduction was found to be dependent on the water concentration. Increasing the amount of water beyond 3 equiv had a negative effect on the yield of the desired product because of an undesired hydrolysis and decarboxylation of 8aa to 10aa (Figure 2.5).

**Figure 2.4.** Effect of CO pressure on product yield (measured by GC with an internal standard).

**Figure 2.5.** Effect of water on product yield (measured by GC with an internal standard).
Tertiary amines with different pKa and structure were tested for the reduction of the Knoevenagel adduct 9aa to 8aa to study the effect of amine properties on reduction rate (Table 2.3). Aliphatic amines were the most suitable for reduction and higher reduction rate was observed as the amine alkyl chain became shorter (entries 7-9).

**Table 2.3.** Effect of Base Properties on Product Yield.

<table>
<thead>
<tr>
<th>entry</th>
<th>base</th>
<th>pKa&lt;sub&gt;MeCN&lt;/sub&gt;</th>
<th>pKa&lt;sub&gt;THF&lt;/sub&gt;</th>
<th>consumption (9aa&lt;sup&gt;d&lt;/sup&gt;)</th>
<th>yield (8aa&lt;sup&gt;d&lt;/sup&gt;)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(DMA)</td>
<td>11.43&lt;sup&gt;a&lt;/sup&gt;</td>
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<td>&lt;5</td>
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</tr>
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<td></td>
<td>12.53&lt;sup&gt;a&lt;/sup&gt;</td>
<td>7.4</td>
<td>&lt;5</td>
<td>&lt;1</td>
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<td></td>
<td>14.23&lt;sup&gt;a&lt;/sup&gt;</td>
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<td>&lt;5</td>
<td>&lt;1</td>
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<td>14.98&lt;sup&gt;a&lt;/sup&gt;</td>
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<td>&lt;5</td>
<td>&lt;1</td>
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<tr>
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<td>(4-DMAP)</td>
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<td>&lt;5</td>
<td>&lt;1</td>
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<td>(DABCO)</td>
<td>18.29&lt;sup&gt;b&lt;/sup&gt;</td>
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<td>73</td>
<td>60</td>
</tr>
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<td>7</td>
<td></td>
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<td>60</td>
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<td>8</td>
<td></td>
<td>18.09&lt;sup&gt;b&lt;/sup&gt;</td>
<td>--</td>
<td>45</td>
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<td>9</td>
<td></td>
<td>18.46&lt;sup&gt;a&lt;/sup&gt;</td>
<td>14.1</td>
<td>100</td>
<td>97</td>
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<td>(PMPS)</td>
<td>18.62&lt;sup&gt;b&lt;/sup&gt;</td>
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<td>5</td>
</tr>
<tr>
<td>12</td>
<td>(DBU)</td>
<td>24.33&lt;sup&gt;a&lt;/sup&gt;</td>
<td>18</td>
<td>73</td>
<td>7</td>
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<td>13</td>
<td>(MTBD)</td>
<td>25.44&lt;sup&gt;a&lt;/sup&gt;</td>
<td>18.6</td>
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</tr>
</tbody>
</table>

<sup>a</sup> pKa values reported by Kaljurand et al.<sup>35</sup>; <sup>b</sup> pKa values reported by Sigma-Aldrich<sup>36</sup>; <sup>c</sup> pKa values reported by Garrido et al.<sup>37</sup>; <sup>d</sup> Measured by GC with an internal standard.
With the exception of 1,4 diazabicyclo[2.2.2.][octane (DABCO), reduction did not proceed in amines that are less basic than triethylamine (entries 1-6), whereas more basic amines were found to inhibit reduction and catalyze the addition of the reduction product to the alkene leading to the unproductive consumption of the reactant (entries 11-13). Slow reductions were also observed when the highly hindered 1,2,2,6,6-pentamethylypiperidine (PMP) and DMAP were used despite having basicities similar to triethylamine (entries 5 and 10).

In addition to base properties, effect of base loading on reduction rate was also studied using triethylamine as a model base. Superstoichiometric amount of triethylamine (2 to 4 equivalent) were needed to drive reduction to completion while higher loading of amine did not affect the product yield. (entry 1 to 8, Table 2.4). It is worth mentioning here that only 0.1 equiv of triethylamine was enough to drive condensation to completion in 30 min which indicates that the superstoichiometric loading of the amine is required for the reduction step to proceed.

**Table 2.4. Effect of Base Loading on Product Yield.**

<table>
<thead>
<tr>
<th>entry</th>
<th>Et$_3$N (equiv)</th>
<th>yield (%)$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0</td>
<td>0$^b$</td>
</tr>
<tr>
<td>2</td>
<td>0.1</td>
<td>&lt;1$^c$</td>
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<tr>
<td>3</td>
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<td>8</td>
<td>7</td>
<td>98</td>
</tr>
<tr>
<td>9</td>
<td>10</td>
<td>95</td>
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</tbody>
</table>

$^a$ yield measured by GC with an internal standard; $^b$ no condensation occurs; $^c$ complete condensation

With the optimized conditions in hand, the substrate scope with respect to the nucleophile and the electrophile was evaluated. Initially, ethyl cyanoacetate was combined with a number of aliphatic and aromatic aldehydes on a 2.0 mmol scale (Table 2.5). During the exploration of the aldehyde scope, it was observed that the condensation was rapid relative to the reduction and that
the rate of the reduction (and therefore the product yield) was highly dependent on the electronic properties of the aldehyde. In general, aliphatic and electron-rich aromatic aldehydes reacted faster than the electron-poor ones. Indeed, with slow-reacting aldehydes, significant amounts of alkene 9 were detected in the reaction mixtures. To account for the different reactivity of the electrophiles and facilitate the reduction of 9, small adjustments of the optimized conditions had to be made.38

Table 2.5. Reductive Alkylation of Ethyl Cyanoacetate: Aldehyde Scope.

<table>
<thead>
<tr>
<th>entry</th>
<th>aldehyde</th>
<th>RhCl3·3H2O (mol %)</th>
<th>H2O (equiv)</th>
<th>time (h)</th>
<th>product</th>
<th>yield (%)</th>
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<td>24</td>
<td>8aa</td>
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<td>24</td>
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<td>7c</td>
<td>2</td>
<td>3</td>
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<td>8ac</td>
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<td>5</td>
<td>7e</td>
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<td>24</td>
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<td>73</td>
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<tr>
<td>6</td>
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<td>18</td>
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<td>2</td>
<td>18</td>
<td>8ah</td>
<td>87</td>
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<tr>
<td>9</td>
<td>7i</td>
<td>2</td>
<td>2</td>
<td>18</td>
<td>8ai</td>
<td>90</td>
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</tbody>
</table>
Table 2.5. Con’t. Reductive Alkylation of Ethyl Cyanoacetate: Aldehyde Scope.

<table>
<thead>
<tr>
<th>entry</th>
<th>aldehyde</th>
<th>RhCl$_3$·3H$_2$O (mol %)</th>
<th>H$_2$O (equiv)</th>
<th>time (h)</th>
<th>product</th>
<th>yield (%)$^a$</th>
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</tr>
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</tr>
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<td>2</td>
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<td>2</td>
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<td><img src="8av.png" alt="image" /></td>
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</table>
Table 2.5. Con’t. Reductive Alkylation of Ethyl Cyanoacetate: Aldehyde Scope.

<table>
<thead>
<tr>
<th>entry</th>
<th>aldehyde</th>
<th>RhCl₃·3H₂O (mol %)</th>
<th>H₂O (equiv)</th>
<th>time (h)</th>
<th>product</th>
<th>yield (%)</th>
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</thead>
<tbody>
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<td><img src="image" alt="8aw" /></td>
<td>0^d</td>
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<td>3</td>
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<td><img src="image" alt="8ax" /></td>
<td>0^d</td>
</tr>
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<td>25^f</td>
<td><img src="image" alt="7y" /></td>
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<td>2</td>
<td>18</td>
<td><img src="image" alt="8au" /></td>
<td>15^d</td>
</tr>
</tbody>
</table>

^a Yield of isolated, purified product; ^b 1 M in CH₃CN; ^c The reaction afforded 9ap' as the main product; ^d Determined by ¹H NMR spectroscopic analysis; ^e The reaction afforded 9ax' as the main product; ^f The reaction afforded 8au in addition to cis- and trans- isomers of the mono- and dienoates.

Thus, benzaldehyde and other nearly electron-neutral aromatic aldehydes were efficiently converted when the reactions were conducted with H₂O (3.0 equiv) for 24 h (entries 1-5). Ortho-substituted benzaldehydes (methyl, fluoro) were good substrates. A meta-vinyl substituent was not reduced over the course of the reaction; however, the product 8ad rapidly polymerized after isolation. The Lewis-basic methylthio substituent in 7e did not significantly inhibit the reaction, nor did it undergo hydrodesulfurization.

Reductive alkylation of electron-rich aromatic aldehydes was achieved with lower H₂O loading (2.0 equiv) and shorter reaction time (18 h, entries 6-9). 4-Methoxy, 4-allyloxy, 4-dimethylamino, and 2,4,6-trimethoxybenzaldehyde all afforded the desired products in high yield. The allyl group in 7h did not undergo competitive reduction or deallylation. The same reaction conditions could also be applied to a number of heteroaromatic aldehydes (entries 10-12), which worked efficiently regardless of their π-rich (7j, 7k) or π-deficient (7l) character.

On the contrary, electron-poor aromatic aldehydes and 2-naphthaldehyde performed poorly when exposed to the same conditions as benzaldehyde. To facilitate the reduction of the corresponding adducts 9, the water loading and the reaction time were increased (5.0 equiv, 36 h, entries 13-15). Under those conditions, decarboxylation of the ester moiety became competitive, accounting for the lower isolated yields for 7n and 7o. Remarkably, the 4-bromo substituent in
remained intact. However, the nitro group in 7p underwent fast reduction to the corresponding aniline, such that only traces of product 8ap were observed (entry 16). The reaction afforded alkene 9ap' primarily, which did not undergo further reduction. The reluctance of 9ap' toward rhodium-catalyzed hydrogenation has already been noted, and might be due to the Lewis-basic character of the amino substituent and its affinity for the rhodium center. On the contrary, the less Lewis-basic dimethylamino group in 7i did not inhibit the reaction.

Aliphatic aldehydes also reacted smoothly under the conditions used for electron-rich aromatic aldehydes (entries 17-20). α-Trisubstituted (7q), α-disubstituted (7r and 7s) and β-branched (7t) aldehydes afforded reductive alkylation products in nearly quantitative yield. The compatibility with 7q is remarkable because the corresponding product 8aq cannot be generated by simple alkylation of a neopentyl halide. With the linear aldehyde 7u (entry 21), self-condensation became competitive and a slightly diminished yield was obtained. Also, reaction of 7u required a higher water loading and longer reaction time compared to other aliphatic aldehydes because of the slower rate of reduction of the intermediate alkene.

The compatibility with alkynyl moieties was also explored (entries 22-23). Trimethylsilylthynyl-substituted benzaldehyde 7v reacted poorly due to the difficulty in reducing the corresponding Knoevenagel adduct 9av. A propargyloxy substituent (7w) inhibited the reaction completely, and only 9aw was observed in the reaction mixture. This observation is in contrast with the smooth reactivity of the similar, allyloxy-substituted benzaldehyde 7h. Although the alkynyl groups themselves did not suffer from reduction under the reaction conditions, these data indicate that alkynes are incompatible because they may act as competitive ligands for the rhodium catalyst. In particular, the terminal alkyne in 7w, in the presence of triethylamine, is prone to form a Rh-acetylide complex.

The Knoevenagel condensation intermediate formed from the reaction of 2-hydroxybenzaldehyde with ethyl cyanoacetate underwent cyclization to form coumarin 9ax', which was not reduced under the reaction conditions (entry 24). Finally, when cinnamaldehyde was used as an alkylation agent, the dienoate on the Knoevenagel intermediate 9ay underwent unselective reduction leading to the formation of a mixture of cis- and trans-, mono- and dienoates, as well as the fully reduced product 8au (entry 25).

The promising results obtained with aldehydes prompted an investigation of ketones as a more challenging class of electrophiles. In general, the reactivity of ketones was limited by their
slower rate of Knoevenagel condensation when compared to aldehydes. Condensation of cyclic ketones was more facile than that of acyclic ones possibly due to the co-planarity effect\textsuperscript{41} and therefore adjustments of H\textsubscript{2}O and Et\textsubscript{3}N loading were needed for each category of ketones.

Cyclic ketones were successfully engaged in the reductive alkylation reaction by increasing the H\textsubscript{2}O and Et\textsubscript{3}N loading to 5.0 and 7.0 equiv, resp. (Table 2.6). However, the isolated yield decreased upon reducing the ring size from 6- to 5- and 4-membered ketones (entries 1-3). This trend reflects the higher propensity of cyclopentanone and cyclobutanone toward enolization and self-condensation,\textsuperscript{42} thus depleting the electrophile. The tetrahydropyran-4-one (7c') alkylation product 8ac' was more prone to decarboxylation than that of cyclohexanone, which lead to lower isolated yield. Alkylation of N-methylpiperdin-4-one (7d') was slower, potentially due to competitive binding of its Lewis-basic site to the Rh catalyst relative to the more sterically hindered triethylamine. The loading of RhCl\textsubscript{3} had to be increased from 2 to 3 mol % for this ketone to achieve complete reduction of the Knoevenagel product.

\textbf{Table 2.6. Reductive Alkylation of Ethyl Cyanoacetate: Cyclic Ketone Scope.}

<table>
<thead>
<tr>
<th>entry</th>
<th>ketone</th>
<th>RhCl\textsubscript{3}·3H\textsubscript{2}O (mol %)</th>
<th>product</th>
<th>yield (%)\textsuperscript{a}</th>
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</thead>
<tbody>
<tr>
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<td>7z</td>
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<td>8az</td>
<td>93</td>
</tr>
<tr>
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<td>8aa'</td>
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<td>3</td>
<td>7b'</td>
<td>2</td>
<td>8ab'</td>
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<tr>
<td>4</td>
<td>7c'</td>
<td>2</td>
<td>8ac'</td>
<td>77</td>
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<td>5</td>
<td>7d'</td>
<td>3</td>
<td>8ad'</td>
<td>81</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Yield of isolated, purified product.
Condensation of acetone \((7e')\) and 3-pentanone \((7f')\) with ethyl cyanoacetate \((6a)\) was found to proceed in triethylamine but not in acetonitrile. Reductive alkylation of ethyl cyanoacetate was attempted using these two ketones in triethylamine as a solvent and reaction time was extended to 72 h to allow enough time for the slow condensation (Table 2.7, entries 1-2). More than 50% loss in yield was observed due to the competing condensation of the ketone with the Knoevenagel product and with itself under the basic reaction conditions. Extension of this protocol to other ketones such as 2,4-dimethyl-3-pentanone \((7g')\) and benzophenone \((7h')\) resulted in no condensation (entries 3-4).

**Table 2.7.** Reductive Alkylation of Ethyl Cyanoacetate: Acyclic Ketone Scope.

<table>
<thead>
<tr>
<th>entry</th>
<th>ketone</th>
<th>product</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>7e'</td>
<td>8ae'</td>
<td>47(^a)</td>
</tr>
<tr>
<td>2</td>
<td>7f'</td>
<td>8af'</td>
<td>18(^b)</td>
</tr>
<tr>
<td>3</td>
<td>7g'</td>
<td>8ag'</td>
<td>0(^b)</td>
</tr>
<tr>
<td>4</td>
<td>7h'</td>
<td>8ah'</td>
<td>0(^b)</td>
</tr>
</tbody>
</table>

\(^a\) Yield of isolated, purified product; \(^b\) Determined by \(^1\)H NMR spectroscopic analysis.

The final dimension of substrate scope of the reductive Knoevenagel reaction involved the investigation of other active methylene compounds. Not surprisingly, this task turned out to be particularly challenging, because of the different behavior of other carbon acids compared to \(6a\).

The one-pot, tandem, condensation-reduction strategy was extended to benzoylacetonitrile \((6b)\), cyanoacetamide \((6c)\), and 2-pyridylacetonitrile \((6d)\) (Table 2.8). Condensation of \(6b\) and \(6c\) with anisaldehyde (entries 1-2) was slower compared to ethyl cyanoacetate and hence the
amount of triethylamine was increased to accelerate the condensation. Decomposition from hydrolysis was less problematic, such that the water content could be increased to accelerate reduction of the condensation product. The rate of condensation of 6d with benzaldehyde was significantly slower owing to its lower carbon acidity (entry 3). Reduction was also slower in this case. Thus, the amount of water was increased by tenfold and the reaction was run for 72 h to allow complete reduction of the condensation product. The yield loss resulted from the competitive reduction of the aldehyde to the corresponding alcohol, a side reaction that is only observed in case of slow condensation.

Table 2.8. Scope of Nucleophile in One-Step Reductive Alkylation.

<table>
<thead>
<tr>
<th>entry</th>
<th>nucleophile</th>
<th>electrophile</th>
<th>RhCl₃·H₂O (mol %)</th>
<th>Et₃N (equiv)</th>
<th>H₂O (equiv)</th>
<th>CH₃CN (M)</th>
<th>product</th>
<th>yield (%)&lt;sup&gt;a&lt;/sup&gt;</th>
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<tr>
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<td>7f</td>
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<td>87</td>
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</tbody>
</table>

<sup>a</sup> Yield of isolated, purified product; <sup>b</sup> Run for 72 h; <sup>c</sup> Determined by <sup>1</sup>H NMR spectroscopic analysis.

Alkylation of the strongly acidic malononitrile (6e) and N,N-dimethylbarbituric acid (6f) (entries 4-5) afforded complex reaction mixtures because of the tendency of the alkylated
product to undergo 1,4-addition to Knoevenagel adducts 9 under basic conditions. Lowering the basicity of the medium by replacing triethylamine with weaker bases negatively affected reduction rate and did not shutdown the product-intermediate side reaction. 3-Pyridylacetonitrile (6g) and benzyl nitrile (6f) are expected to be less acidic compared to 2-pyridylacetonitrile and thus, their condensation with benzaldehyde had to be carried out in a separate pre-condensation step with 1,5 Diazabicyclonon-5-ene DBN (0.05 mol %) in neat solution for 6 h prior to the addition of H₂O, CO, Rh catalyst, and solvent (Table 2.9, entry 1-2). This two-step, one-pot process does not involve any intermediate separation or migration from room temperature operation and thus, does not negatively affect the method efficiency.

Similar approach was applied to alkylate diethyl malonate (6i) and ethyl benzoylacetae (6j) with aldehyde 7a using L-proline (0.1 mol %) as a condensation catalyst in H₂O/Et₃N solvent for 24 h (entry 3-4). The amount of benzaldehyde had to be increased to 2 (equiv) to approach complete reduction while DBN could not be used as it catalyzed undesired reactions in this case.

**Table 2.9. Scope of Nucleophile in Two-Step Reductive Alkylation.**

<table>
<thead>
<tr>
<th>entry</th>
<th>nucleophile</th>
<th>electrophile (equiv)</th>
<th>step 1 (conditions)</th>
<th>total H₂O (equiv)</th>
<th>product</th>
<th>yield (%)&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NC&lt;sub&gt;N&lt;/sub&gt; 6g</td>
<td>1.05</td>
<td>DBN (0.05 equiv), 6 h</td>
<td>50</td>
<td>NC&lt;sub&gt;N&lt;/sub&gt; 8ga</td>
<td>78</td>
</tr>
<tr>
<td>2</td>
<td>NC&lt;sub&gt;N&lt;/sub&gt; 6h</td>
<td>1.05</td>
<td>DBN (0.05 equiv), 6 h</td>
<td>50</td>
<td>NC&lt;sub&gt;N&lt;/sub&gt; 8ha</td>
<td>63</td>
</tr>
<tr>
<td>3</td>
<td>EIOOC&lt;sub&gt;COOEI&lt;/sub&gt; 6i</td>
<td>2</td>
<td>L-proline (0.1 equiv), Et₃N (1.0 equiv), H₂O (5 equiv), 24 h</td>
<td>5&lt;sup&gt;b&lt;/sup&gt;</td>
<td>EIOOC&lt;sub&gt;COOEI&lt;/sub&gt; 8ia</td>
<td>70</td>
</tr>
<tr>
<td>4</td>
<td>COOEI 6j</td>
<td>2</td>
<td>L-proline (0.1 equiv), Et₃N (1.0 equiv), H₂O (5 equiv), 24 h</td>
<td>5&lt;sup&gt;b&lt;/sup&gt;</td>
<td>COOEI 8ja</td>
<td>33&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup> Yield of isolated, purified product; <sup>b</sup> Step 2 was run for 48 h; <sup>c</sup> Determined by ¹H NMR spectroscopic analysis.

Control experiments have demonstrated that CO is essential for the reduction to proceed
It is reasonable to propose that CO undergoes WGSR to produce a Rh hydride species which reduces the condensation product. However, another possibility is that triethylamine may act as a hydride source through a Rh-catalyzed, β-hydride abstraction/hydrolysis mechanism. Under this hypothesis, carbon monoxide could be needed to stabilize the low-valent Rh carbonyl clusters that act as catalyst for hydride formation from the amine.

The rate acceleration caused by triethylamine (compared to base-free conditions, or to the use of other bases, Section 4.2.5) deserved further investigation. In addition to being a potential hydride source, triethylamine may be implicated in several other crucial steps along the reaction pathway. Triethylamine could: (1) catalyze the Knoevenagel condensation; (2) act as a reducing agent for Rh(III) to a catalytically active, low-valent Rh species; (3) promote the WGSR by a base-catalyzed mechanism (generating hydroxide ions in the presence of water); (4) act as a ligand for Rh, to help solubilize the Rh catalyst and disrupt the polynuclear Rh-CO clusters that are formed under CO atmosphere. Consequently, several experiments were designed and executed to elucidate the reduction pathway and the role of the amine.

A deuteration experiment was performed to ascertain the involvement of CO/H₂O as the source of reducing equivalents. Thus, the pre-formed condensation adduct 9af was exposed to modified reaction conditions using Rh₄(CO)₁₂ and D₂O (Scheme 2.6). The choice of the starting material and the Rh catalyst was dictated by the need to remove potential H₂O sources (the condensation forms one equivalent of H₂O, and RhCl₃ is supplied as a trihydrate complex). Under these conditions, 92% deuterium incorporation was measured at C(3) by mass spectrometry. The incomplete incorporation might be due to the adventitious water in acetonitrile and/or CO. No deuterium incorporation was observed at C(2), presumably because of the fast D/H exchange upon exposure to moisture or silica gel.

**Scheme 2.6.** Deuterium incorporation experiment

![Scheme 2.6](image)

Control experiments have shown that 0.1 equiv of triethylamine is enough to drive the
Knoevenagel condensation of the ethyl cyanoacetate with aldehydes, however, higher triethylamine loading was necessary for reduction of the Knoevenagel product to proceed (Table 2.5). If a tertiary amine acts as a hydrogen source, the resulting iminium ion should be hydrolyzed to the corresponding secondary amine and aldehyde (diethylamine and acetaldehyde in the case of triethylamine). Because acetaldehyde and diethylamine are volatile and more difficult to detect, triethylamine was replaced with tributylamine, a base with similar pK\textsubscript{a} and bulk in acetonitrile (Scheme 2.7). The reduction of 9aa was slower with tributylamine likely because of its poor solubility in acetonitrile. Thus, the reaction time and water content had to be increased to achieve complete reduction. Under these conditions, no trace of butyraldehyde, dibutylamine, butylamine, or butyraldehyde self-condensation products was observed by GC analysis. These observations confirm that the amine does not act as a reducing agent, either for the hydrogenation of 9aa, or for the reduction of Rh(III) to a lower oxidation state.

**Scheme 2.7.** Base decomposition in the WGSR-driven reductive alkylation

Earlier studies showed that amines enhance the WGSR reactivity of Rh complexes by acting as ligands, which could explain why a highly hindered amine such as PMP exhibits poor activity compared to the less hindered triethylamine (Table 2.10, entries 1 and 2). However, when a small quantity of triethylamine (0.05 equiv) was added to a reaction medium containing 2.45 equiv of PMP, a tenfold increase in product yield was observed (entry 3). Since triethylamine and PMP have similar pK\textsubscript{a}s, the basicity of the medium (i.e., concentration of hydroxide ions) is expected to be similar for both bases, meaning that the WGSR is taking place at similar rates. Consequently, the increase in reduction rate observed in entry 3 must arise from the capacity of triethylamine to act as a ligand. However, in a separate control experiment, the addition of 0.1 equiv of triethylamine to a neutral reaction medium did not show any increase in the product yield (entry 4).

Similarly, if the amine is too strongly coordinating to the rhodium center, inhibition of the WGSR is observed. For example DMAP and triethylamine have similar pK\textsubscript{a}s but the former is
unable to promote the reduction of 9aa (Table 2.10, entry 5). The inhibitory effect of DMAP is manifest even in the presence of a 25-fold excess of triethylamine (c.f. entries 1 and 6). On the basis of these observations, it appears that triethylamine is uniquely able to promote reduction of 9aa by serving both as a ligand and as a source of hydroxide ions. A substoichiometric amount (0.1 to 0.3 equiv) of triethylamine is needed to coordinate the Rh catalyst, whereas the additional quantity (2.5 equivalent total) is needed to provide the basic medium.

**Table 2.10.** Effect of Amine Coordination-Ability and Basicity of the Medium on Reduction Rate.

| pK_BH⁺ (MeCN) | Et₃N (equiv) | PMP (equiv) | 4-DMAP (equiv) | Yield (%)  
|--------------|-------------|-------------|---------------|------------
| entry 1      | 2.5         | 0           | 0             | 97         |
| 2            | 0           | 2.5         | 0             | 4          |
| 3            | 0.05        | 2.45        | 0             | 45         |
| 4            | 0.1         | 0           | 0             | <1         |
| 5            | 0           | 0           | 2.5           | <1         |
| 6            | 2.5         | 0           | 0.1           | 67         |

*a* Measured by GC with an internal standard.

The reactivity of Rh precursors with different oxidation states and nuclearity was compared at the 6-h time point (Table 2.11). Prior to carbon monoxide introduction, the reaction medium was stirred for two hours to ensure complete dissolution of the catalyst. The Rh₄(CO)₁₂ cluster was found to be the most active form, followed by RhCl₃·3H₂O and [Rh(COD)Cl]₂, whereas the Rh₂(OAc)₄ was the least active. The high activity in the case of the low-valent Rh₄(CO)₁₂ (entry 1) suggests that a catalyst pre-reduction step is involved in all the other cases (entries 2-4). There is also an induction time associated with breaking the dimers, as indicated by the low reactivity of the dimeric [Rh(COD)Cl]₂ and Rh₂(OAc)₄ complexes compared to the monomeric RhCl₃·3H₂O.
Table 2.11. Reductive Alkylation Reactivity of Different Rh Catalyst Precursors

<table>
<thead>
<tr>
<th>entry</th>
<th>catalyst</th>
<th>Rh nuclearity</th>
<th>Rh oxid. state</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Rh₄(CO)₁₂</td>
<td>4</td>
<td>0</td>
<td>85</td>
</tr>
<tr>
<td>2</td>
<td>[Rh(COD)Cl]₂</td>
<td>2</td>
<td>1</td>
<td>53</td>
</tr>
<tr>
<td>3</td>
<td>Rh₂(OAc)₄</td>
<td>2</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>4</td>
<td>RhCl₃.xH₂O</td>
<td>1</td>
<td>3</td>
<td>66</td>
</tr>
</tbody>
</table>

a Measured by GC with an internal standard.

2.5. Discussion

Reductive alkylation of alkyl cyanoacetate 6a with different aldehydes has shown that the reduction of the alkene intermediate is significantly slower than the condensation step and that it requires strong base (pKa>18) to proceed at appreciable rate. Expanding the scope of the activated methylene compounds has shown that the method performance highly depends on the activated methylene acidity as reported by Bordwell et al.43 Figure 2.6.

Compounds with similar methylene acidity to ethyl cyanoacetate (pKa ≈ 12-14 in DMSO) were successfully alkylated in one step using triethylamine at high yields. This includes benzoylacetonitrile (6b), cyanoacetamide (6c), and possibly 2-coumaranone as expected based on its methylene acidity. Contrary, alkylation of strongly-acidic activated methylene compounds (pKa < 12 in DMSO) such as malonitrile (6e), and N, N dimethylbarbituric acid (6f) gave low yield due to the competing Michael addition of the product to the condensation intermediate, an undesired reaction catalyzed by triethylamine. Replacing triethylamine with a weaker base to suppress the undesired reaction was found to shut down the reduction and thus, this category of activated methylene compounds was determined to be incompatible with the proposed method.

Reductive alkylation of slightly less acidic activated methylene compounds (pKa ≈ 14-18 in DMSO) was found to be limited by their condensation rate rather than the intermediate reduction. Condensation of compounds such as diethyl malonate (6i) and ethyl benzoylacetate (6j) required the addition of DBN, piperidine, or L-proline to proceed. DBN was found to catalyze undesired addition to the alkene intermediate whereas piperidine underwent reductive amination with the aldehyde under the reaction conditions. Consequently, condensation was
performed using L-proline in a separate step followed by reduction under WGSR conditions all in one pot.

Weakly acidic compounds (pKa > 18 in DMSO) and their condensation intermediates were found not to be susceptible to the undesired Michael addition and thus, their reductive alkylation was performed using DBN as a co-catalyst either in a single step such as in the case of 2-pyridylacetonitrile (6d) or in two steps for the slower condensation cases such as 3-pyridylacetonitrile (6g) and benzyl nitrile (6h) to minimize the aldehyde reduction to the alcohol.

**Figure 2.6.** Reductive Alkylation Performance of Different Activated Methylene Compounds.
The involvement of the WGSR, in which the CO/H$_2$O system serves as the hydride source, and not triethylamine, was clearly established on the basis of absence of amine oxidation products and deuterium incorporation when D$_2$O was used. Control experiments also clarified that the role of the base is threefold: (1) catalyst for the Knoevenagel condensation; (2) base for the WGSR; and (3) ligand for Rh.

The quest for optimum reaction conditions and the exploration of the substrate scope generated a wealth of mechanistic information that helped to formulate a plausible catalytic cycle (Figure 2.7) and revise a previous mechanistic proposal.

![Proposed catalytic cycle](image-url)

**Figure 2.7.** Proposed catalytic cycle.
Over the course of their studies of the Rh-catalyzed reductive Knoevenagel condensation, Chusov et al. proposed a catalytic cycle that involves Rh insertion into the C-OH bond of an intermediate β-hydroxy ester (11). The occurrence of the WGSR was not directly invoked, but the proposed mechanism clearly shows intermediates (Rh-hydroxycarbonyls, Rh-hydrides) that would be expected for a WGSR-based process. Intermediates such as 11 are fleeting, and prone to dehydrate to form a Knoevenagel adduct (9). Indeed, our studies indicated that 9 rapidly accumulated in the reaction mixtures and was kinetically competent. Therefore, it is necessary to reformulate the mechanistic picture of the reductive Knoevenagel condensation as follows.

The catalytically active, low-valent Rh-carbonyl complex i (generated by WGSR-mediated reduction of the precursor RhCl₃) undergoes nucleophilic addition of hydroxide (from triethylamine and water) to a CO ligand. The resulting Rh-hydroxycarbonyl complex ii decarboxylates to form Rh-hydride iii. These steps are in agreement with those proposed for the WGSR under basic conditions. The basicity of the amine must be sufficient to generate a suitable concentration of hydroxide ions to attack species i and form species ii. The inhibitory effect of alcohols when used as solvents could also be attributed to the competing formation of inactive alkoxy carbonyl complexes [RhLₙ(CO)ₙ₋₁(COOR)]⁻ instead of species ii. The inability of carbonyl complexes of Fe, Co, and Mn to catalyze the WGSR at room temperature might arise from the lower propensity of these species to from the required metal hydroxycarbonyl complexes.

In the next step, loss of a CO ligand from iii opens a coordination site (iv) that enables binding of substrate 9. The need for ligand dissociation prior to olefin coordination can be kinetically relevant at high CO pressures, which explains the inhibitory effect of CO on reduction at pressures higher than 10 bar. Moreover, the strong inhibitory effect of Lewis-basic functional groups, such as primary anilines and terminal alkynes, reinforces the importance of coordinative unsaturation to enable olefin binding. From v, migratory insertion of the olefin and protonation of the anionic Rh complex vi affords vii. Reductive elimination generates the product 8 and the coordinatively unsaturated complex viii, which can reenter the catalytic cycle upon CO coordination.

The exploration of the aldehyde substrate scope led to the puzzling observation that aromatic aldehydes bearing electron-donating groups reacted faster than those bearing electron-withdrawing groups. At a first glance, this observation is difficult to fit in the proposed
mechanistic picture. Reasonably, an electron-poor arene should lower the LUMO of 9 and thus: (1) facilitate the coordination of 9 to the anionic complex iv (a metal-to-ligand interaction); and (2) promote hydride delivery (migratory insertion) to the electron-deficient π-system. These arguments are in agreement with Hammett studies performed on the hydrogenation and hydride reduction of styrene derivatives.\textsuperscript{48} However, 9 already possesses a low-lying LUMO because of the strong conjugating effects of the ester and nitrile groups. Therefore, further lowering of the LUMO energy (and consequent acceleration) by an electron-poor aryl substituent is expected to be minimal.

Alternatively, the accelerating capacity of electron-rich arenes could be explained as a push-pull effect,\textsuperscript{49} whereby the electron-donating substituent enhances the polarization of the alkene and lowers its bond order as represented by resonance structures 9' and 9'' (Scheme 2.8). The resulting weakening of the double bond would account for a more facile hydride delivery in the formation of vi, and explain the observed rates, if formation of vi were turnover-limiting. A similar manifestation of the push-pull effect has been documented in the Ni-catalyzed hydrogenation of styrene derivatives, for which the application of the Yukawa-Tsuno correlation furnished negative ρ values.\textsuperscript{50}

\textbf{Scheme 2.8.} Polarization of activated alkenes

\begin{center}
\begin{tikzpicture}
\node[below] at (0,0) {9};
\node[below] at (1.5,0) {9'};
\node[below] at (3,0) {9''};
\node[below] at (4.5,0) {9'''};
\node[below] at (6,0) {9'''};
\node[below] at (7.5,0) {9'''};
\node[below] at (9,0) {9'''};
\node[below] at (10.5,0) {9'''};
\node[below] at (12,0) {9'''};
\node[below] at (13.5,0) {9'''};
\node[below] at (15,0) {9'''};
\node[below] at (16.5,0) {9'''};
\node[below] at (18,0) {9'''};
\node[below] at (19.5,0) {9'''};
\node[below] at (21,0) {9'''};
\node[below] at (22.5,0) {9'''};
\node[below] at (24,0) {9'''};
\node[below] at (25.5,0) {9'''};
\node[below] at (27,0) {9'''};
\node[below] at (28.5,0) {9'''};
\node[below] at (30,0) {9'''};
\end{tikzpicture}
\end{center}

The proposal that step v to vi is turnover limiting, and slow in the case of electron-poor aldehydes, is also consistent with the need for higher water loadings for such substrates. When hydride delivery is slow, olefin coordination to Rh might be reversible. Thus, the Rh-hydride intermediate iii can participate in a traditional WGSR process, which consumes water unproductively by forming dihydrogen through complex ix.

The investigation of the rhodium-catalyzed, WGSR-driven, reductive Knoevenagel condensation has identified triethylamine as a key component to allow for the reaction to proceed smoothly at room temperature. This is in sharp contrast with the base-free conditions developed by Chusov \textit{et al.}, which require temperatures in the range of 110-160 °C.\textsuperscript{4d,6}

The mild conditions and the use of CO as the reducing agent brought about several
improvements compared to traditional alkylation methods, and other reductive Knoevenagel condensation protocols. In particular, the following improvements were achieved:

- use of an inexpensive, non-wasteful reducing agent, amenable to scale-up;
- the tandem, one-pot nature of the process, which does not require isolation of the intermediate alkene;
- suppression of dialkylation and O-alkylation, common issues when using alkyl halides;
- suppression of decarboxylation, which occurs with methods that require high temperature;
- compatibility with functional groups that are not tolerated when using H₂ (unactivated alkenes, allyl ethers, halides, thioethers);
- compatibility with electrophiles that are prone to self-condensation

The ability to expand the scope of this work to include cyclic ketones affords a more economic route for the formation of important pharmaceutical intermediates. For example, reductive alkylation of ethyl cyanoacetate with tetrahydropryan-2-one yields an intermediate (8ac') that can be transformed to tachykinin antagonist substances (14) with potential application as treatment for anxiety, depression, dementia and other types of central nervous system disorders in addition to inflammatory diseases such as arthritis, and asthma (Scheme 2.9).51

**Scheme 2.9.** Synthesis of 14 by traditional vs. WGSR-driven methods

In comparison with the alkylation method of tosylate 13 employed in the original preparation, the present method has the advantages of starting from a less expensive alkylation agent, lower purification and separation cost, and higher yield of the desired intermediate. In addition,
The reductive alkylation of ethyl cyanoacetate with \(N\)-alkylpiperdin-2-one yields an intermediate (15) that can be converted to substituted indenes (16), a hypotensive agents (Scheme 2.10).\(^{52}\)

**Scheme 2.10.** Alkylation with piperdinone to yield pharmaceutical intermediates

Yet, some limitations of the reductive Knoevenagel condensation under WGSR conditions also became apparent. First of all, the use of carbon monoxide, though desirable for its low cost and waste impact, poses severe safety concerns because of its toxicity and flammability. CO can certainly be handled safely by means of specialized techniques and equipment, but these handling restrictions limit its use in research laboratories.

Moreover, the following aspects also detract from the widespread application of our method:

- Difficulty to optimize conditions for some classes of ketones that do not undergo condensation easily, and for active methylene precursors that are prone to conjugate addition;
- Incompatibility of nitro groups, primary anilines, and alkynes;
- The use of an expensive rhodium catalyst in high molar amount (2-3 mol%).

**2.6. Conclusion**

The reductive power of the WGSR has been successfully harnessed to drive the alkylation of activated methylene compounds with carbonyl compounds at room temperature using rhodium trichloride catalyst. The proposed protocol was proven to be applicable for wide range of alkylating agents including aliphatic and aromatic aldehydes as well as cyclic ketones. The method showed high tolerance towards halides, thioethers, allyl ethers and other functional groups that can be challenging for alternative reduction methods.

Optimization studies have elucidated that the reaction proceeds through Knoevenagel condensation followed by reduction of the alkene and that water is the source of hydrogen in reduction. The optimum amount of water varies from 2 to 50 equivalent depending on the alkene intermediate rate of reduction and the final product vulnerability to hydrolysis.
The necessity of triethylamine was determined to originate from the need for a base to generate hydroxide ions to drive the WGSR catalytic cycle besides its role as a metal ligand and a condensation catalyst. The reductive alkylation of the less acidic activated methylene compounds was rendered possible by increasing the amount of triethylamine or adding a stronger base to adjust the reaction medium basicity.
2.7. References


(8) Prices from Sigma-Aldrich.


(38) Adjustments were also needed to compensate for the more sluggish reactivity observed on the 2-mmol scale, likely due to the change of vessel type and stirring efficiency.


(51) Fox, D. N. A.; Mathias, J. P.; Tommasini, I. EP patent 0962457 A1, **1999**.

(52) Paragamian, V. US patent 3644372, **1972**.

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Chapter 3: Water-gas shift-driven reductive carbonylation of aryl halides

3.1. Introduction

Aromatic aldehydes are ubiquitous building blocks in fine chemicals and pharmaceuticals owing to their versatile reactivity.\(^1\) Industrial production of benzaldehydes is traditionally carried out from toluenes by oxidative chlorination (the Etard Reaction) or from aryl halides with \(N,N\)-dialkylformamides using lithium reagents or magnesium metal (the Bouveault Reaction), or from benzenes with POCl\(_3\) and \(N,N\)-dialkylformamides (the Vilsmeier Reaction).\(^2\) In view of the multiple steps involved and the associated production of large quantities of waste, research efforts have been directed to find superior routes. The reductive carbonylation of aryl halides using CO as a carbonyl source has emerged in the last decade as a more atom-economical and less wasteful alternative.\(^3\)

In the reductive carbonylation approach, phosphine-ligated Pd catalysts are employed to form the Pd aroyl through oxidative addition into the aryl-halogen bond followed by the migratory insertion of CO. To provide the formyl hydrogen and complete the catalytic cycle, external reductants have been applied including tin hydrides,\(^4\) metal formates,\(^5\) hydrogen,\(^3\) and more recently silanes,\(^6\) and water with stoichiometric iron carbonyl\(^7\) (Scheme 3.1a-d). Despite being successful in producing non-hindered aryl aldehydes, the synthesis of hindered aryl aldehydes by reductive carbonylation remains a challenge because of the competition from the more rapid reductive dehalogenation pathway. Attempts to overcome this problem by evaluating different ligands, performing the reaction with slow addition of tin hydride, or testing different silanes were not very successful.\(^3,4,6\)

Besides the vital role of non-deuterated aryl aldehydes in synthesis, aldehydes incorporating deuterium at the formyl position are often needed for mechanistic investigations and metabolic studies.\(^8\) Selectively labeled aldehydes of this sort are traditionally produced from the reduction of either the corresponding ester using LiAlD\(_4\) followed by oxidation,\(^9\) or the corresponding amide with deuterated Schwartz’s reagent (obtained from LiAlD\(_4\)).\(^10\) More recently, alternatives have been proposed to overcome the cost and drawbacks associated with LiAlD\(_4\) through the H/D exchange with the pre-synthesized aldehyde using D\(_2\) gas and Ir catalysis\(^11\) or D\(_2\)O and Ru catalysis (Scheme 3.1e-g).\(^12\)
Scheme 3.1. Established methods to produce aryl aldehydes and their deuterated analogues.

Previous work

**Beller (2012, ref. 3g)**

\[
\begin{align*}
&\text{Me} & & \text{Me} & & \text{Me} & & \text{Me} \\
&\text{Me} & & \text{Me} & & \text{Me} & & \text{Me} \\
&\text{Br} & & \text{Br} & & \text{Br} & & \text{Br} \\
&\text{CO}/\text{H}_2 (5 \text{ bar}) & & \text{toluene (1 M)} & & 100 ^\circ \text{C}, 20 \text{ h}
\end{align*}
\]

\[\text{Pd(OAc)}_2 (0.5 \text{ mol %}) \quad \text{phosphinite ligand (1.5 mol %)} \quad \text{TMEDA (0.75 equiv)}\]

**Liu (2016, ref. 6b)**

\[
\begin{align*}
&\text{Me} & & \text{Me} & & \text{Me} & & \text{Me} \\
&\text{Me} & & \text{Me} & & \text{Me} & & \text{Me} \\
&\text{Br} & & \text{Br} & & \text{Br} & & \text{Br} \\
&\text{CO}_2 (10 \text{ bar}) & & \text{DMF (1 M)} & & 100 ^\circ \text{C}, 20 \text{ h}
\end{align*}
\]

\[\text{[Pd(dppp)Cl]}_2 (2 \text{ mol %}) \quad \text{PMHS (2.5 equiv)} \quad \text{DBU (1.5 equiv)}\]

**Barnard (2007, ref. 6c)**

\[
\begin{align*}
&\text{Me} & & \text{Me} & & \text{Me} & & \text{Me} \\
&\text{Me} & & \text{Me} & & \text{Me} & & \text{Me} \\
&\text{I} & & \text{I} & & \text{I} & & \text{I} \\
&\text{CO (3 bar)} & & \text{DMF (1 M)} & & 60 ^\circ \text{C}, 20 \text{ h}
\end{align*}
\]

\[\text{Pd} \text{Cl}_2 (4 \text{ mol %}) \quad \text{Et}_3 \text{SH (2 equiv)} \quad \text{Na}_2 \text{CO}_3 (1 \text{ equiv})\]

**Khashayar (2015, ref. 7)**

\[
\begin{align*}
&\text{Me} & & \text{Me} & & \text{Me} & & \text{Me} \\
&\text{Me} & & \text{Me} & & \text{Me} & & \text{Me} \\
&\text{I} & & \text{I} & & \text{I} & & \text{I} \\
&\text{H}_2\text{O}:\text{DMF} 1.3\% \nu (0.33 \text{ M}) & & \text{Ar, 110 ^\circ C, 3.5 h}
\end{align*}
\]

\[\text{PdCl}_2 (3.5 \text{ mol %}) \quad \text{Fe}(\text{CO})_5 (1.1 \text{ equiv}) \quad \text{Et}_3 \text{N (3.0 equiv)}\]

**duerated aldehydes**

**Georg (2007, ref. 10)**

\[
\begin{align*}
&\text{Me} & & \text{Me} & & \text{Me} & & \text{Me} \\
&\text{Me} & & \text{Me} & & \text{Me} & & \text{Me} \\
&\text{O} & & \text{O} & & \text{O} & & \text{O} \\
&\text{OR} & & \text{OR} & & \text{OR} & & \text{OR} \\
&\text{1. LiAlD}_4 & & \text{2. oxidation}
\end{align*}
\]

**Madsen (2015, ref. 9)**

\[
\begin{align*}
&\text{Me} & & \text{Me} & & \text{Me} & & \text{Me} \\
&\text{Me} & & \text{Me} & & \text{Me} & & \text{Me} \\
&\text{O} & & \text{O} & & \text{O} & & \text{O} \\
&\text{NR}_2 & & \text{NR}_2 & & \text{NR}_2 & & \text{NR}_2 \\
&\text{Cp}_2 \text{ZrCl}_2
\end{align*}
\]

**Tuttle (2017, ref. 11), Newman (2017, ref. 12)**

\[
\begin{align*}
&\text{Me} & & \text{Me} & & \text{Me} & & \text{Me} \\
&\text{Me} & & \text{Me} & & \text{Me} & & \text{Me} \\
&\text{O} & & \text{O} & & \text{O} & & \text{O} \\
&\text{H} & & \text{H} & & \text{H} & & \text{H} \\
&\text{Ir cat. acetone d}_5 \text{ or D}_2 & & \text{Ru cat. D}_2 \text{O}
\end{align*}
\]

This work

\[
\begin{align*}
&\text{Me} & & \text{Me} & & \text{Me} & & \text{Me} \\
&\text{Me} & & \text{Me} & & \text{Me} & & \text{Me} \\
&\text{O} & & \text{O} & & \text{O} & & \text{O} \\
&\text{H/D} & & \text{H/D} & & \text{H/D} & & \text{H/D} \\
&\text{Pd + Rh cat. CO, H(D)D}_2 \text{O} & & \text{DMF, 65 - 95 ^\circ C}
\end{align*}
\]

TMEDA: \(N,N,N',N'-\text{Tetramethylethlenediamine}\), dpp; 1,3-Bis(diphenylphosphino)propane, PMHS: Polymethylhydrosiloxane, DBU: 1,8-Diazabicyclo(5.4.0)undec-7-ene.

3.2. Background

Despite the ability of water to serve as a hydride source under CO atmosphere through the Water-Gas Shift Reaction (WGSR),\(^{13}\) it has not been used to affect the reductive carbonylation of aryl halides. This approach remains more challenging than the Reppe modification of the Rh-catalyzed olefin hydroformylation, (which utilizes water as a hydride source),\(^{14}\) for the following reasons: (1) the poor catalytic reactivity of palladium in the WGSR, (2) the intervention of the undesired reactions known to occur in an aqueous environment including protio-dehalogenation and hydroxy-carbonylation to benzoic acids,\(^{15}\) and (3) over reduction of the aldehyde to the corresponding alcohol.
In this study we show that the dual metallic, Pd-Rh catalytic system ligated with 4,4’-dimethoxy-2,2’-bipyridine works cooperatively to drive the reductive carbonylation of aryl halides using water as a hydride source and carbon monoxide as a carbonyl source and a terminal reductant (Scheme 3.1h). This protocol can produce 2,6-disubstituted aldehydes and their deuterated analogues with high D incorporation efficiently. The D-labeled aldehydes obtained by this method can be engaged in subsequent WGSR-driven reductive transformations to incorporate more deuterium atoms in alkylated and aminated products using D$_2$O.

3.3. Research Objectives

The purpose of this project was to use CO as both the carbonyl source and the terminal reductant in driving the reductive carbonylation of aryl halides to form aryl aldehydes and their deuterated analogues. The following ideas are applied:

1-The use of two metals, one from group 10 to affect the oxidative addition to the aryl-halide bond and the other from group 8 or 9 to perform the WGSR
2-Screen different ligands to promote the oxidative addition step without inhibiting the WGSR
3-The use the catalytically generated group 8 or 9 metal hydrides to selectively produce the 2,6-disubstituted aldehydes without excessive dehalogenation
4-Replace water with D$_2$O and examine the selectivity of the process for producing D-formyl aldehydes with high D incorporation

3.4. Results

From initial screening, orienting experiments employed 2,6-dimethyliodobenzene 1a together with PdCl$_2$ as the catalyst under CO pressure in presence of 2 equivalents of water, 2 equivalents of tetramethylethylenediamine (TMEDA), 0.1 equivalent 4,4’-dimethoxy-2,2’-bipyridine (4,4’-diMeObpy) as the ligand in dimethylformamide at 85 °C (Table 3.1).

No reaction occurred in absence of a co-catalyst confirming the inability of palladium complexes to generate the reducing species from water (entry 1) and thus, other transition metal catalysts known to affect the WGSR were added as co-catalysts. Ruthenium and cobalt carbonyls were not suitable for this reaction as indicated by the low conversion of 1a (entries 2, 3). High conversion was obtained using Fe$_2$(CO)$_9$, however with low selectivity for the desired aldehyde 1b compared to the undesired deiodination to 1c and overreduction to the alcohol (entry 4). Gratifyingly, a high yield of 1b was obtained when [RhCO$_2$Cl]$_2$ was used with only 2% 1c observed at complete conversion of 1a (entry 5). Replacing the costly and less stable
[Rh(CO)₂Cl]₂ complex with [Rh(COD)₂Cl]₂ also lead to complete conversion of 1a (entry 6). Replacing 4,4'-diMeObpy with other 2,2'-bipyridine ligands resulted in a decrease in reactivity and selectivity, with the following order of selectivity: 4,4'-diMeO > 4,4'-di-t-Bu > 4,4'-diMe > 4,4'-diH > 4,4'-dicarboxy (entries 7 – 10).

A significant drop in the yield of 1b was observed with the more sterically hindered 6,6'-dimethyl-2,2'-bipyridine (entry 11) and the rigid 1,10-phenanthroline ligands (entry 12). Triphenylphosphine severely inhibited the system indicating that phosphine ligands are not

### Table 3.1. Optimization of Reductive Carbonylation.

<table>
<thead>
<tr>
<th>entry</th>
<th>co-catalyst</th>
<th>ligand</th>
<th>1a consumed (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>1b yield (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>1c yield (%)&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>--</td>
<td>4,4'-diMeObpy</td>
<td>4</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>Ru₃(CO)₁₂   (3 mol %)</td>
<td>4,4'-diMeObpy</td>
<td>8</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>3</td>
<td>Co₂(CO)₈    (3 mol %)</td>
<td>4,4'-diMeObpy</td>
<td>5</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>Fe₂(CO)₉    (3 mol %)</td>
<td>4,4'-diMeObpy</td>
<td>74&lt;sup&gt;b&lt;/sup&gt;</td>
<td>36</td>
<td>12</td>
</tr>
<tr>
<td>5</td>
<td>[Rh(CO)₂Cl]₂ (1.5 mol %)</td>
<td>4,4'-diMeObpy</td>
<td>97</td>
<td>93</td>
<td>2</td>
</tr>
<tr>
<td>6</td>
<td>[Rh(COD)Cl]₂ (1.0 mol %)</td>
<td>4,4'-diMeObpy</td>
<td>98</td>
<td>87</td>
<td>4</td>
</tr>
<tr>
<td>7</td>
<td>[Rh(COD)Cl]₂ (1.0 mol %)</td>
<td>4,4'-di-t-Bubpy</td>
<td>96</td>
<td>79</td>
<td>5</td>
</tr>
<tr>
<td>8</td>
<td>[Rh(COD)Cl]₂ (1.0 mol %)</td>
<td>4,4'-diMeObpy</td>
<td>97</td>
<td>74</td>
<td>17</td>
</tr>
<tr>
<td>9</td>
<td>[Rh(COD)Cl]₂ (1.0 mol %)</td>
<td>bpy</td>
<td>79</td>
<td>63</td>
<td>9</td>
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<tr>
<td>10</td>
<td>[Rh(COD)Cl]₂ (1.0 mol %)</td>
<td>4,4'-dicarboxybpy</td>
<td>75</td>
<td>58</td>
<td>14</td>
</tr>
<tr>
<td>11</td>
<td>[Rh(COD)Cl]₂ (1.0 mol %)</td>
<td>6,6'-diMeObpy</td>
<td>62</td>
<td>32</td>
<td>24</td>
</tr>
<tr>
<td>12</td>
<td>[Rh(COD)Cl]₂ (1.0 mol %)</td>
<td>1,10-phenanthroline</td>
<td>14</td>
<td>5</td>
<td>7</td>
</tr>
<tr>
<td>13</td>
<td>[Rh(COD)Cl]₂ (1.0 mol %)</td>
<td>PPh₃</td>
<td>5</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>14&lt;sup&gt;c&lt;/sup&gt;</td>
<td>[Rh(COD)Cl]₂ (1.0 mol %)</td>
<td>4,4'-diMeObpy</td>
<td>81</td>
<td>76</td>
<td>4</td>
</tr>
<tr>
<td>15&lt;sup&gt;d&lt;/sup&gt;</td>
<td>[Rh(COD)Cl]₂ (1.0 mol %)</td>
<td>4,4'-diMeObpy</td>
<td>72</td>
<td>59</td>
<td>10</td>
</tr>
<tr>
<td>16&lt;sup&gt;e&lt;/sup&gt;</td>
<td>[Rh(COD)Cl]₂ (1.0 mol %)</td>
<td>4,4'-diMeObpy</td>
<td>19</td>
<td>13</td>
<td>5</td>
</tr>
<tr>
<td>17&lt;sup&gt;f&lt;/sup&gt;</td>
<td>[Rh(COD)Cl]₂ (1.0 mol %)</td>
<td>4,4'-diMeObpy</td>
<td>4</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>18</td>
<td>[Rh(COD)Cl]₂ (1.0 mol %)</td>
<td>--</td>
<td>70</td>
<td>12</td>
<td>42</td>
</tr>
</tbody>
</table>

<sup>a</sup> measured by GC with an internal standard. <sup>b</sup> benzylic alcohol also detected. <sup>c</sup> solvent: acetonitrile. <sup>d</sup> solvent: DMSO. <sup>e</sup> solvent: dioxygen. <sup>f</sup> solvent: toluene. 4,4'-diMeObpy; 4,4'-dimethoxy-2,2'-bipyrindine, COD: 1,5-cyclooctadiene.

A significant drop in the yield of 1b was observed with the more sterically hindered 6,6'-dimethyl-2,2'-bipyridine (entry 11) and the rigid 1,10-phenanthroline ligands (entry 12). Triphenylphosphine severely inhibited the system indicating that phosphine ligands are not
compatible with the WGSR-driven reductive carbonylation (entry 13). The reaction was found to proceed in the polar solvents e.g. acetonitrile and dimethyl sulfoxide, with higher efficiency than that observed in the less polar ones, i.e. dioxane and toluene (entry 14 - 17). Attempting the reaction in dimethylformamide in absence of a ligand led to a drastic decrease in 1b (entry 18). No enhancement in yield was observed when the Rh(I) dimers tested in Table 3.1 were replaced by other Rh co-catalysts including Rh(0), Rh(II), and Rh (III) precursors (see Supporting Information Table S4). Additionally, removing palladium from the process led to no conversion of 1a confirming that the process requires both metals to proceed. Moreover, replacing PdCl₂ with other catalysts was not as effective (Table S5).

The effect of Pd and Rh loading on the reductive carbonylation of 1a was studied by varying the loading of each metal while keeping the concentration of all other reagents the same. Increasing the Pd loading above 0.25 mol % did not lead to an increase in the formation of 1b; reaction time shortened to 8 h to observe this trend (Figure 3.1a). On the other hand, increasing Rh loading steadily increased the formation of 1b up to 1 mol % (Figure 3.1b).

To further understand the effect of CO and water on the process, reductive carbonylation of 1a was studied with different amounts of water under (Figure S4) and under different CO pressures (Figure 8.5). The water content survey showed that the addition of more than 2 equivalents was deleterious to both the conversion of 1a and the yield of 1b in favor of the formation of 1c. No conversion was observed in absence of CO (reaction performed under nitrogen atmosphere) but almost complete conversion of 1a was achieved under 5 bar CO with slightly lower yield of 1b than that achieved at 10 bar. Increasing the CO pressure beyond 10 bar did not lead to a significant change in the yield of products. Lowering the mount of TMEDA below 2 equivalents led to a decrease in both the overall conversion and the yield of the 1b (Figure 8.6) and thus, the TMEDA loading was kept at 2 equivalents. Varying the concentration of 1a while keeping the absolute concentration of all the other reagents and the CO pressure constant showed that the amounts of 1b and 1c formed are independent of the concentration of 1a i.e. zeroth order in substrate (Figure 8.7). Replacing water with deuterium oxide lead to a decrease in the overall consumption of 1a and a decrease in the ratio of 1b to 1c (Table S7).
Figure 3.1. Effect of Pd (a) and Rh (b) on reductive carbonylation of 1a (measured by GC with internal standard).

With the optimized conditions in hand, reductive carbonylation of aryl iodides with different electronic and steric properties was performed on a 2.0 mmol scale (Figure 3.2). Water was
replaced with D\textsubscript{2}O to test for the extent and selectivity of D incorporation in the formyl position as well as the overall efficiency of the reductive carbonylation. D\textsubscript{2}O loading was kept at 2 equivalents to avoid slowing down the reaction by addition of more D\textsubscript{2}O (Figure 8.4) or attenuating the extent of D incorporation by loading less.

Electron rich benzaldehydes 2b to 5b were obtained in good yield and high D incorporation at 85 ℃. Electron deficient aldehydes such as 6b to 9b were found to be more prone to deiodination, and thus, the reaction temperature was reduced to 65 ℃ and the Pd content was increased from 0.3 to 0.6 mole% while keeping the D\textsubscript{2}O loading at 2 equivalents. Under these conditions, good yields and high D incorporation were achieved without excessive dehalogenation. The highly electron-deficient aldehydes 10b to 13b were obtained in moderate yield and high D incorporation as well. No D incorporation was observed in the arenes of either the electron rich or poor aldehydes as indicated by \textsuperscript{1}H NMR spectroscopic analysis. Having the trifluoromethyl group in the ortho positions slowed down the reaction considerably, and thus the reaction had to be performed with 0.6 mol % Pd, and the temperature was raised to 95 ℃ 12b.

The H/D exchange on the methyl group of 4-formylacetophenone 13b resulted in a significant drop in the D incorporation in the formyl position, and thus, the D\textsubscript{2}O loading had to be increased to 16 equivalent to achieve 90% D. Complete conversion could be achieved for the hindered 2,6-dimethyl- (14b) and 2,6-diethylbenzaldehyde 15b at 85 ℃, however, formation of the more hindered 2,6-diisopropylbenzaldehyde 16a required increasing the temperature to 95 ℃ to achieve complete conversion. In these three cases, high D incorporation was achieved with no detectable D incorporation in the alkyl groups in the ortho position.

Interestingly, lower yields of the less hindered 2- and 3-tolualdehyde 17b and 18b were obtained when compared to the 2,6-dimethylbenzaldehyde 14b owing to the increased production of the dimethyl-benzophenones and the deuteriotoluenes. The synthesis of 2-biphenylcarboxyaldehyde required the addition of 8 equivalents of D\textsubscript{2}O to compensate for the H/D exchange found to occur at the C(2’) position through a Pd catalyzed C-H insertion 19b and 19c. The increase in D\textsubscript{2}O loading from 2 to 8 equivalents was also necessary to achieve high D incorporation into the formyl position in 1-naphthaldehyde 20b owing to the H/D exchange in the C(8) position. D-Formyl heterocyclic aldehydes were also synthesized including aldehydes of
Conditions: (a) 0.3 mol % PdCl$_2$, 2 equiv D$_2$O, 85 °C; (b) 0.6 mol % PdCl$_2$, 2 equiv D$_2$O, 65 °C; (c) 0.6 mol % PdCl$_2$, 2 equiv D$_2$O, 95 °C; (d) 0.6 mol % PdCl$_2$, 16 equiv D$_2$O, 85 °C; (e) 0.3 mol % PdCl$_2$, 8 equiv D$_2$O, 85 °C.

Figure 3.2. Scope of aryl iodides
quinoline 21b, and protected and unprotected indoles 22b and 23b. Submitting α-iodostyrene to the standard conditions with 6 mol % Pd and 65 °C lead to the formation of the vinyl acid and divinyl ketone but no aldehyde was formed.

The deuterium-labeled 4-anisaldehyde 2b was submitted to subsequent, WGSR-driven, reduction, reductive alkylation, and reductive amination in parallel reactions to obtain double deuterated products (Scheme 3.2). 4-Methoxybenzyl alcohol 1d was obtained in 92% yield and 98% D₂-incorporation using 30 equivalents of D₂O at 75 °C with 2 mol % RhCl₃ catalyst. It should be noted that the Rh-catalyzed, WGSR-driven reduction of the aldehyde to the alcohol does not occur under the reductive carbonylation conditions illustrated in this study as the addition of 4,4'-diMeObpy or TMEDA completely inhibited the reaction (Table S8).

**Scheme 3.2.** Double deuterated products from D-formyl aldehydes using D₂O and WGSR.%D calculated from NMR, number in parenthesis is %D calculated by Mass Spec.

The WGSR-driven reductive alkylation of activated methylene compounds can be performed at room temperature as reported earlier from these laboratories,¹⁶ however, higher temperature was required to produce the deuterated product 2d owing to the kinetic isotope effect. The conditions for reductive alkylation can be applied to provide amines selectively deuterated at the
alpha position even with electron-rich benzylic amines 3d which are challenging to synthesize with radical-based H/D exchange methods.\textsuperscript{17}

To examine the extent of H/D exchange at positions prone to C-H activation, 1-naphthaldehyde was submitted to reductive carbonylation conditions with 8 equivalents of D\textsubscript{2}O. No D incorporation was observed in the aldehyde formyl position indicating that aldehyde C-H activation does not occur. Moreover, the C-H activation observed in the C(8) position in the reductive carbonylation of 1-naphthyl iodide occurs only on the Pd aroyl intermediate but not the final product. Additionally, the C-H bonds in TMEDA are not activated with the Pd-Rh cooperative catalyst in this case. Slight H/D exchange was observed at the C(6) and C(6’) positions on 4,4’-diMeObpy.

**Scheme 3.3.** D/H exchange control experiment.

The cooperative effect of Pd and Rh is evident as indicated by the need for both metals to achieve the desired conversion. The oxidative addition to the aryl iodide bond is exclusively performed by Pd, in fact, in absence of Rh, a significant conversion of the non-hindered, electron deficient iodides to the corresponding benzenes and benzoic acids occurs through proto-dehalogenation of the Pd-aryl intermediate and hydroxylative carbonylation, respectively. These two undesired pathways appear to be suppressed in the presence of rhodium especially in the case of the more hindered, 2,6-disubstituted iodides. The ability of Rh to suppress the acid formation may be attributed to the Rh-catalyzed conversion of the hydroxide ions to formate ions under CO atmosphere.\textsuperscript{18}

Formate ions can potentially act as a hydride shuttle to affect the reductive carbonylation. According to this hypothesis, the role of Rh is solely to provide the formate ions that can react with the palladium catalyst to form a palladium hydride species and allow reductive elimination
to take place on the Pd center.\textsuperscript{5} Elimination of the Rh catalyst and water from the reaction and adding 2 equivalents of sodium formate did not result in measurable conversion thus, invalidating this hypothesis (Scheme 3.4).

**Scheme 3.4.** Metal formate as a hydride source for reductive carbonylation.

![Scheme 3.4](image)

Alternatively, molecular hydrogen could be generated from the reaction of water and CO under catalysis by Rh followed by oxidative addition of hydrogen on the Pd center to form a hydride. To test for this hypothesis, a two-chamber experiment was performed under CO atmosphere with water, base, Rh, and ligand in one chamber (hydrogen production chamber) and the aryl iodide, base, Pd, and ligand in the other chamber (carbonylation chamber), Figure 8.8. The two chambers were connected to allow for the hydrogen produced from chamber 1 to transfer to chamber 2. No reaction occurred in this experiment indicating that the WGSR-driven reductive carbonylation does not proceed through the formation of molecular hydrogen as an intermediate.

**3.5. Discussion**

Eliminating the possibility of formate ions and molecular hydrogen as hydride shuttles between the two metals lead us to the proposal of direct reduction of the palladium aryl with a rhodium hydride as the predominant mechanism by which these two metals cooperate to affect the desired transformation (Figure 3.3). The formation of a rhodium hydride under basic WGSR conditions has been proposed earlier\textsuperscript{12,15,16} and is believed to proceed through the nucleophilic attack of the hydroxide ion on the metal carbonyl to form a metal formate that undergoes \(\beta\)-hydride elimination on the Rh center to form carbon dioxide and a rhodium hydride. In the proposed mechanism, TMEDA is required to neutralize the acidity of the hydrogen iodide byproduct and maintain the concentration of the hydroxide/formate ions throughout the reaction which explains the need for two equivalents of the dibasic amine to achieve complete conversion.
The dependence of the conversion on the Rh loading suggests that the rate limiting step in the palladium catalytic cycle is the hydride transfer which is also in agreement with the kinetic isotope effect observed in this process. The rate of hydride transfer can be limited by the probability of the interaction between the two catalytic species; the Rh hydride and the Pd aroyl. However, the product yield was found to be independent of the Pd concentration beyond low Pd loading and thus, hydride transfer does not seem to be the limiting step and that the process is likely limited by the formation of the Rh hydride. The inhibitory effect of water at higher loadings indicates that the hydroxide attack is not the rate limiting, and thus we propose the β-
hydride elimination of the rhodium carboxylate is the rate determining step which agrees with earlier investigation on the WGSR catalyzed by (polypyridine) rhodium complexes,\textsuperscript{19} and the observed kinetic isotope effect.

3.6. Conclusion

In summary, combining the catalytic generation of a rhodium hydride through the WGSR with the Pd-catalyzed carbonylation of haloarenes allows for the use of water as a hydride source to selectively produce highly hindered and deuterated aryl aldehydes. The process employs CO as a carbonyl source as well as a terminal reductant and produces stoichiometric amount of CO\textsubscript{2} as a byproduct. Efficient D incorporation in the formyl position is achieved with only 2 equivalents of D\textsubscript{2}O except in cases where H/D exchange occurs in other positions of the aldehyde. Better yields are obtained when the aryl halide is highly hindered or electron rich. The cooperative interaction of the two transition metals will be further exploited in future studies.
3.7. References


Chapter 4: Selective extraction of supported Rh nanoparticles under mild, non-acidic conditions with carbon monoxide

4.1. Introduction

Owing to their unique catalytic properties, supported Rh nanoparticles (NPs) are widely used as catalysts for carbon monoxide oxidation, selective hydrogenation, formylation, carbon dioxide methanation, and Fisher Tropsch synthesis. Notably, more than 80% of Rh production goes to catalytic converters, which are devices used to treat gaseous emissions from internal combustion engines. In a typical catalytic converter, Rh is often paired with Pd, Pt or both and deposited in the form of nanoparticles on a large surface area metal oxide layer that is contained in a refractory honeycomb structure. The continuing growth of the automotive industry and the stricter regulations on emission levels are expected to increase the need for catalytic converters to the point that the limited Rh supplies will not be able to meet the world demand. Although Rh is generated as a byproduct in nuclear reactors, currently, no method allows for the selective and safe extraction from nuclear waste because of contamination by highly radioactive Ru isotopes.

Several recycling methods have been introduced to extract precious metals from used catalytic converters, however, these methods typically involve melting the catalytic convertor at T > 1500 °C with collector metals such as copper, magnesium, or iron to form alloys with the precious metals that can be separated from the slag containing the ceramic support. Alternatively, a number of hydrometallurgical methods have been proposed based on digesting the spent catalyst in aqua regia or other strong oxidizing acids. Elevated temperatures are required because of strong resistance of Rh to acids. In view of the harsh conditions and the corrosive chemicals needed in established methods, the leaching process is often costly, energy demanding, and not environmentally friendly. The severe leaching conditions also result in destruction of the support material and necessitate further purification of the extracted metals.

4.2. Background

The need to replace the current recycling methods with more environmentally friendly and sustainable processes is growing in response to the rising public awareness and governmental regulations regarding Earth resources. For this purpose, more elegant methods have been invented for precious metal recovery including dry chlorination of Rh with chlorine gas at 500 °C, digestion in basic cyanide solutions at >100 °C, and more recently, induced
surface potential alteration through repetitive cycles of oxidation and reduction with ozone and carbon monoxide for Pt recycling.\textsuperscript{19}

4.3. Research Objectives

In this disclosure, we aim to demonstrate the ability of carbon monoxide to induce the leaching of Rh NPs in a mild and non-corrosive process and achieve the selective removal of Rh from supports containing other metals. The leaching efficiency is examined on NPs of different oxidation states and on different supports.

4.4. Results

A series of supported Rh NPs were synthesized and submitted to different leaching conditions with CO (See SI Section 2). Alumina-supported, metallic Rh(0) NPs in the size range of 1 to 2 nm (\textit{RhA-red}) was dispersed in different solvents and exposed to CO gas at 20 bar. Less than 10 % leaching of Rh was observed in dry, non-polar solvents (hexane, toluene, triethylamine, and methyl \textit{tert}-butyl ether) as indicated by the rhodium content analysis of the alumina support before and after the experiment (Figure 4.1). Improved leaching was observed in solvents with dipole moments higher than 1.6 D and reached a maximum in acetonitrile.

Addition of water to the leaching solvents led to a noticeable increase in the leaching efficiency (Figure 4.1). The salutary effect of water was more prominent in the less polar solvents that form biphasic mixtures with water. Contrariwise, the acetonitrile-water solution remained homogeneous after saturation with CO and resulted in high leaching (78%) which could be further enhanced by the addition of triethylamine (89% leaching was achieved in acetonitrile/water/triethylamine).

The post-leaching supernatants were pale violet after venting the CO and slowly turned into green upon exposure to air. To examine the effect of water on the nature of the leached Rh species, light absorbance of the post leaching solutions was measured in dry and wet acetonitrile. The similarity in light absorbance in dry and wet acetonitrile suggests that the addition of water does not alter the form at which Rh is extracted (Figure 8.12a). To further understand the nature of the Rh extracted species, the alumina support was filtered and the solvent was removed from the filtrate under reduced pressure leaving a Rh-rich brown residue that is soluble in dry acetonitrile. Interestingly, the Uv-vis spectrum of the redissolved Rh species matches with that reported for suspended metallic Rh NP (Figure 8.12b).\textsuperscript{20}
Infrared (IR) spectra taken on the Rh residue directly after solvent removal showed one major peak in the Rh carbonyl stretching region (2100 to 1600 cm$^{-1}$) at 2024 cm$^{-1}$ with two shoulders at 2070 cm$^{-1}$ and 1970 cm$^{-1}$ and a broad peak at 1843 cm$^{-1}$ (Figure 4.2a). Exposure of the residue to air led to attenuation of the peak at 2024 cm$^{-1}$ relative to the peaks at 2070 cm$^{-1}$ and 1970 cm$^{-1}$ (Figure 4.2b). The IR fingerprint of the residue suggests that the neutral Rh carbonyl clusters Rh$_6$(CO)$_{16}$ or Rh$_4$(CO)$_{12}$ are not formed as indicated by the absence of the characteristic strong peaks at 1800 cm$^{-1}$ and 2100 cm$^{-1}$ of these two species, respectively.$^{21,22}$ Additionally, Rh is not extracted in the form of cationic Rh(I) carbonyl species as indicated by the mismatch between the measured IR bands and those reported for [Rh(CO)$_2$]$^+$ surface species or the ligand-stabilized Rh(CO)$_2$(MeCN)$^+$ and Rh(CO)$_2$(Et$_3$N)$^+$ species at 2090, 2020 and 2090 to 2002 cm$^{-1}$ respectively.$^{23}$

The fingerprint of the post-leaching residue resembles that reported for the double cluster anion [Rh$_{12}$(CO)$_{(30-34)}$]$^{2-}$ that contains two [Rh$_6$(CO)$_{16}$] units linked by a Rh-Rh bond and two bridging carbonyls (2055, 2010, 1840 cm$^{-1}$).$^{24}$ Additionally, the anionic [Rh$_6$(CO)$_{15}$]$^{2-}$ species (2045, 1980, 1960 cm$^{-1}$) appear to be present in equilibrium with the double cluster [Rh$_{12}$(CO)$_{30-34}$]$^{2-}$ as indicated by the shoulder peak at 1970 cm$^{-1}$.$^{25}$ Upon air exposure, the residue is
transformed to the hydride cluster \([\text{Rh}_6(\text{CO})_{15} \text{H}_x]^{(x=1,2)}\) that exhibit peaks at 2060 and 2020 cm\(^{-1}\).\textsuperscript{25,26} Mass spectroscopy analysis of the post leaching solution shows that Rh is extracted in the form of polynuclear clusters containing 4 to 10 Rh atoms/cluster and around 3 CO/Rh atom in average (Figure 8.13). Heating the Rh carbonyl clusters under hydrogen atmosphere at 200 °C lead to the formation of metallic powder (93.18 wt% Rh) that does not exhibit any IR bands (Figure 4.2c). Additionally, TEM images of the residue collected after solvent removal showed the formation of metallic NPs in the range of 1 to 3 nm (Figure 4.2d).

![Figure 4.2](image-url)  
Figure 4.2. IR spectra of the post-leaching residue from sample RhA-red (a) after filtration and solvent removal, (b) exposure to air for 10 min, (c) heat treatment at 200 °C under high vacuum, (d) TEM imaging of Rh NPs in post leaching residue.
Figure 4.2. Con’t. IR spectra of the post-leaching residue from sample RhA-red (a) after filtration and solvent removal, (b) exposure to air for 10 min, (c) heat treatment at 200 °C under high vacuum, (d) TEM imaging of Rh NPs in post leaching residue.
NPs of different oxidation states were tested to evaluate the effect the oxidation state on leaching efficiency. A highly oxidized sample (RhA-oxid500) mainly consisting of Rh(I) & (III) species as indicated by XPS (Figure 8.11b) was compared to the reduced sample (RhA-aged1). Despite having similar NP size, no measurable leaching of (RhA-oxid500) was observed below 15 bar CO pressure (Figure 4.3). As CO pressure was increased, leaching began gradually with only 7% leaching obtained at 25 bar. Apart from the drop in the leaching efficiency with the oxidized sample, no leaching of either samples occurred in absence of CO, and the introduction of CO at pressures as low as 1 barg was enough to leach 30% of the reduced and stored under air for one month sample (RhA-aged1). This leaching efficiency was increased as leaching was performed under higher CO pressure and reached a maximum of 55% at 15 barg. Beyond this value, no impact on leaching was observed.

As indicated by XPS, the storage of the reduced sample RhA-red under ambient air caused the oxidation of Rh(0) to Rh(I) and (III) (Figure 8.11C) which lead to the observed drop in the maximum leaching efficiency of sample (RhA-aged1) to 55% compared to the 89% achieved on the same sample before storage.

![Figure 4.3](image-url)

**Figure 4.3.** Effect of CO pressure on leaching of Rh from the pre-reduced and aged (RhA-aged1) sample and the pre-oxidized (RhA-oxid500) in acetonitrile/water/triethylamine solution after 24 h at 25 °C.
Raising the leaching temperature from 25 to 70 to 100 °C increased the leaching efficiency of the highly oxidized (RhA-oxd500) sample from 7 to 11 and 33% respectively (Figure 4.4) signifying that leaching of Rh from the highly oxidized sample is inefficient even at elevated temperatures. Notably, the sample (RhA-oxd350) which was oxidized at lower temperature than (RhA-oxd500) showed more efficient leaching (46% at 70 °C, or 4 times higher than (RhA-oxd500) ). Additionally, pre-reduction of the highly oxidized sample (RhA-oxd500) directly before leaching, lead to a 12-fold increase in the leaching efficiency (RhA-oxd/red vs. RhA-oxd500) (Figure 4.4).

**Figure 4.4.** Effect of temperature on the leaching efficiency of samples pretreated under different conditions. Left: oxidized samples, right: reduced samples

Furthermore, when submitted to leaching under the same conditions, the sample aged under air for 3 months, RhA-aged3, exhibited significantly less leaching (34% only, Figure 4.4) when compared to the sample aged for only 1 month RhA-aged1 (55%, Figure 4.3) indicating the
continuation in the decay of the leaching efficiency upon samples prolonged storage in air. Nevertheless, the leaching efficiency could be partially recovered by increasing the leaching temperature from 25 to 70 °C (34 to 77%). More importantly, resubmitting sample RhA-aged3 to prereduction directly before leaching (sample RhA-aged/red) lead to an increase in the efficiency from 34 to 74%.

A more densely-loaded commercial sample of Rh NPs supported on alumina (RhA-comm) that contains 4.31 wt% Rh was exposed to the standard leaching conditions at 20 barg CO and 70 °C for 24 hours. This experiment resulted in 50% leaching and thus, leaching was extended for another 48 hour (72 hour total) to achieve 86% leaching. A third leaching stage at room temperature for 24 hour was added to obtain an overall leaching efficiency of 94% as indicated by the final Rh content of 0.24 wt % Rh. The Rh NPs size distribution was measured for the partially extracted sample containing 50% of the original loading and compared to that of the original (RhA-comm) sample. The average particle size was reduced due to leaching from 2.7 to 1.6 nm and the particle size distribution was much narrower (standard deviation drop from 0.75 to 0.4) (Figure 4.5).

![Figure 4.5](image)

**Figure 4.5.** Effect of CO leaching on nanoparticle size distribution from (RhA-comm) sample.

Apart from the reduction in the average NPs size and narrowing the size distribution, a decrease in the ratio of the oxidized Rh(I) and (III) species from 21 and 5% to 9 and 3% respectively after leaching was observed (Figure 4.6).
Figure 4.6. XPS Spectra of commercial Rh NP on alumina RhA-comm (oxidation state distribution from curve fitting) (a) before leaching: 74% Rh(0), 21% Rh(I), 5% Rh(III). (b) after leaching under standard conditions at 70 °C for 72 h followed by another 24 h at 25 °C: 88% Rh(0), 9% Rh(I), 3% Rh(III).

To test the effect of other precious metals on leaching, a mixture of Rh, Pd, Pt, and Ru NPs all supported on alumina was prepared by mixing equal amounts of each individual metal supported NP. The resulting solid mixture was homogenized by grinding and then the sample was reduced under a flow of hydrogen at 500 °C. The leaching experiment of the powder mixture was performed under the standard conditions (20 bar CO, 25 °C, and 24 h) with and without triethylamine. High leaching selectivity for Rh was achieved in absence of triethylamine wherein leaching of Pd and Pt was negligible and leaching of Ru was less than 10% (Figure 4.7a). Addition of triethylamine promoted the leaching of Pd to a minor extent but not Rh, Ru, or Pt.

To examine the impact of temperature and pressure on the leaching selectivity for Rh relative to the other metals, the same powder mixture was submitted to leaching at 70 °C under variable CO pressures. No leaching of any of the metals occurred in absence of CO at 70 °C (Figure 4.7b). As the CO pressure increased, a rapid increase in the leaching of Rh, Ru and Pd was observed until it leveled off at 7 and 1 barg for Rh and Pd, respectively. Leaching of Ru increased monotonically with CO pressure across the studied range of pressures.
Figure 4.7. (a) Selective leaching of Rh in presence of Pd, Pt, and Ru with and without triethylamine at 20 barg CO and 25 °C. (b) Effect of CO pressure on leaching of Rh, Pd, Pt, and Ru from a mixture of the four metals in acetonitrile/water/triethylamine 5:1:1 v:v:v mixture at 70 °C.

As an alternative to CO gas as a leachant, surrogates that react in presence of Rh to produce CO were also tested. Leaching of the sample stored under ambient air for 1 month (RhA-aged) was attempted in acetonitrile/water/triethylamine 5:1:1 solution with the addition of either formic acid, formaldehyde, or carbon dioxide/hydrogen gas mixture in individual experiments. The formic acid and formaldehyde leaching experiments were carried out in a sealed tube at 70 °C for 24 h followed by another 12 h at room temperature before opening the tube. As indicated by the metal content analysis, 80% of the Rh NPs leached with formic acid and less than 10% leached with formaldehyde and carbon dioxide/hydrogen mixture (Table 4.1, entry 1-3). To examine whether the substantial leaching with formic acid is ascribed to its acidity...
or its ability to produce CO, the same experiment was run with acetic acid and no leaching was observed. Moreover, suppressing the medium acidity by the addition of super stoichiometric amount of triethylamine did not affect the leaching of Rh with formic acid (Table 4.1, entry 4.5).

Table 4.1. Leaching of Rh nanoparticles with CO surrogates

<table>
<thead>
<tr>
<th>additive</th>
<th>% leaching</th>
</tr>
</thead>
<tbody>
<tr>
<td>H₂O (0.4 mL)</td>
<td>9</td>
</tr>
<tr>
<td>Et₃N (0.4 mL)</td>
<td>0</td>
</tr>
<tr>
<td>H₂ (7 bar) + CO₂ (14 bar)</td>
<td>9</td>
</tr>
<tr>
<td>HCOOH (1 ml)</td>
<td>80</td>
</tr>
<tr>
<td>CH₃COOH (1 ml)</td>
<td>0</td>
</tr>
<tr>
<td>HCOOH (1 ml) + Et₃N(2 ml)</td>
<td>80</td>
</tr>
<tr>
<td>--</td>
<td>0</td>
</tr>
</tbody>
</table>

4.5. Discussion

The small size of the CO molecule and its strong affinity to bind to Rh atoms make it an excellent leachant for the metal from porous supports. The best leaching efficiency was observed on a freshly reduced Rh sample in an acetonitrile/triethylamine/water mixture. Even though both acetonitrile and triethylamine are known to form stable complexes with Rh,²³ no leaching was observed when freshly reduced Rh NP were exposed to a mixture of these two potential leaching agents in absence of CO even at temperature as high as 70 °C. The rate of Rh leaching was found to be dependent on CO pressure as it increased from ambient to 15 barg at 25 °C and from ambient to 7 bar at 70 °C (Figures 4.3 and 4.7). The equilibrium concentration of CO in dry acetonitrile increases linearly with CO pressure in the range of the studied pressures.²⁷ Thus, the asymptotic behavior of the extent of leaching to further increases in CO pressure beyond these two values cannot be attributed to solvent saturation. Alternatively, the insensitivity of the rate of leaching upon increases in CO pressure could be attributed to the limited rate of the mass transport of CO to the nanoparticle or the diffusion of the formed metal carbonyls through the pores of the support.

Disintegration of Rh NPs by the adsorption of CO gas has been observed by EXAFS and
IR measurements in earlier studies. The so-called “breathing rafts” phenomenon is attributed to the formation of the surface mobile, geminal dicarbonyl Rh(I) species from metallic Rh(0) clusters through the oxidation by the hydroxide ions present on the surface of the support:

\[
\text{Rh}(0)/\text{Al}_2\text{O}_3 + 2 \text{ CO} + \text{OH}_a \rightarrow \text{O-Rh(I)(CO)}_2/\text{Al}_2\text{O}_3 + 0.5 \text{H}_2 \quad \text{eq. 1}
\]

This reaction is thought to be thermodynamically driven by the large difference in energy between the Rh-CO strong bond (163 kJ/mol) and the weaker Rh-Rh bond (111 kJ/mol). The breathing rafts effect is reversible as indicated by the reformation of metallic Rh(0) clusters upon venting CO and thus the application of this phenomenon was limited to explaining Rh reactivity under vapor phase reactions involving CO.

The mechanism by which the CO-induced leaching of Rh taking place in acetonitrile in this work is less well understood. For example, the unique ability of acetonitrile to promote the leaching cannot solely be attributed to the high solubility of CO in this solvent (0.0053 mol CO/mol acetonitrile at 25 °C and 13 bar). In fact, CO equilibrium concentration in acetonitrile is 5 times less than that of ethyl acetate and 8 to 9 times less than that of alkanes and ethers. However, these solvents were inferior to acetonitrile in terms of leaching efficiency. Instead, the high polarity of acetonitrile (D=3.92) and the violet color of the post-leaching solution that turns to green upon air exposure suggest that acetonitrile is essential to stabilize the anionic Rh carbonyl species; \([\text{Rh}_{12}(\text{CO})_{30}]^{2-}\) (violet), and \([\text{Rh}_6(\text{CO})_{15}]^{2-}\) (dark green), from the rapid redeposition on the support upon venting CO.

In the breathing rafts phenomenon, the formation of Rh(I)(CO)\(_2\) species was found to be limited by the abundance of surface hydroxide ions. In the liquid phase CO-induced leaching, OH ions are continuously replenished by the added water which explains the increase in the leaching efficiency from 41 to 78 % when water was added to acetonitrile (Figure 4.1). Albeit the ability of hydroxide ions to readily form by the dissociative adsorption on metal oxide surfaces, addition of tertiary amines was found to catalyze the leaching potentially by maximizing the OH concentration. Addition of secondary amine such as piperidine or dibasic amines such as tetramethyl ethylenediamine was found to suppress the leaching (Table 8.10 and 8.14) potentially because of the formation of surface stable metal complexes with these additives. On the other hand, inorganic ions commonly present in water including sodium hydroxide, hydrochloric acid, and sodium chloride did not have a significant impact on the leaching efficiency (Table 8.11).
Apart from the mechanism of leaching of Rh(0) metallic NPs with CO, oxidation of the NP lead to a drastic drop in leaching efficiency (Figure 4.3). Oxidation by air at temperature as high as 500 °C did not lead to a significant change in the average nanoparticle size (1.8 vs. 1.5 nm) and thus, the drop in leaching cannot be attributed to nanoparticles agglomeration. The content of the oxidized Rh(I) and Rh(III) species was 75% in the oxidized sample versus 8% only in the freshly reduced sample (Figure 8.11) which can explain the difference in the resistance towards leaching by CO in these two cases. Although ca. 25% of metallic Rh(0) is present in the oxidized sample, the leaching efficiency remained low at 7%. The inability to extract the Rh(0) in presence of the oxidized Rh(I and III) species can be explained by the structure of the oxidized Rh NPs as a Rh(0) core entrapped in a Rh(I) and Rh(III) shell which makes the metallic Rh(0) species inaccessible for CO to bind. The induction of leaching of the oxidized sample \textit{RhA-oxd500} at high CO pressure (Figure 4.3) and at high leaching temperature (Figure 4.4) is probably resulting from the ability of CO to act as a reductant for Rh(I) and Rh(III) through the following reactions: \[\text{Rh}_2\text{O}_5/\text{Al}_2\text{O}_3 + 2 \text{CO} \rightarrow \text{Rh}_2\text{O}/\text{Al}_2\text{O}_3 + 2 \text{CO}_2 \] (eq. 2) \[\text{Rh}_2\text{O}/\text{Al}_2\text{O}_3 + 2 \text{CO} \rightarrow 2 \text{Rh}/\text{Al}_2\text{O}_3 + 2 \text{CO}_2 \] (eq. 3)

As the Rh(III) shell is reduced to Rh(I) and Rh(0) the NP becomes prone to leaching by CO. The rate of Rh reduction by CO in acetonitrile/water solution appears to be much slower than that of the leaching of Rh(0) and also to be dependent on the CO pressure along the entire range of the studied pressures (Figure 4.3).

The commercial sample \textit{RhA-comm} tested in this study had 10 times more Rh than the synthesized samples and thus it required longer time to achieve appreciable levels of leaching by CO. The longer time needed for leaching can be attributed to the larger average particle size (2.7 nm) and the broader size distribution (0.75 standard deviation). Moreover, spent heterogeneous Rh catalysts are often transferred and stored under atmospheric air for long time and thus the surface of this kind of nanoparticles is often in the form of Rh(I) and Rh(III). Despite these challenges, higher than 90% leaching was achieved on the commercial sample when tested as received after 4 days of leaching. Upon examining the NP size distribution of a partially leached sample containing half of the original Rh content of the pristine sample, the average particle size was brought down from 2.7 to 1.6 nm and the particle size distribution was much narrower as indicated by their standard deviation (0.4 versus 0.75). Besides recycling of metals from spent
catalysts, CO-induced leaching can be exploited as a scalable method to narrow the nanoparticle size distribution and enhance their catalytic selectivity.\textsuperscript{39}

The ability to extract Rh was extended to nanoparticles supported on titanium oxide (See SI Section 5.5) and non-oxide supports as demonstrated in the case of the carbon supported \textit{RhC-comm} sample (See SI Section 6.6). Owing to the mild conditions applied in the CO-induced leaching, destruction of the support is unlikely and thus, recovery of both the metal and the support is possible. The ability to recover the support is economically attractive when highly engineered supports are used such as carbon nanotubes and other nano-shaped structures.\textsuperscript{40-42}

Leaching of alumina-supported Pd, and Pt NPs was found to be much less favorable when compared to Rh (Figure 4.7). This selectivity can be attributed to the lower stability of the carbonyls of Pt and Pd compared to Rh. Moreover, the calculated difference in the gas phase free energy between the metal cluster and the isolated surface carbonyl monomer is much less for Pd and Pt.\textsuperscript{43} Even in the case of the freshly reduced mixture of the un-alloyed nanoparticles, the CO-induced leaching remained highly selective toward Rh indicating the minimal effect of the formed homogeneous Rh carbonyl clusters on catalyzing the leaching of other metals (Figure 4.7a). Addition of triethylamine was found to slightly promote the leaching of Pd, nevertheless, the mechanism of the base-mediated leaching of Pd NPs under CO is probably different from that of Rh and for the purpose of this study, it can be concluded that elimination of the tertiary amine from the leaching medium enhances the selectivity of leaching Rh versus Pd.

Although Rh extraction from the radioactive nuclear waste is beyond the scope of this study, the ability to selectively extract Rh but not Ru is advantageous in this endeavor.\textsuperscript{6} Additionally, the ability to extract Rh in the form of polynuclear clusters could be further exploited to isolate the heavier clusters that are rich in the heavier isotopes by mass centrifugation and bring the radioactivity of the extracted metal to safe levels.

CO-surrogates can be used as an attractive alternative for applications wherein handling high pressure CO gas is troublesome. The success of this process relies on the ability of formic acid to decompose in presence of Rh catalyst to produce CO. In this process, the rate of leaching is expected to be highly dependent on the ability of the Rh catalyst to form CO in situ. The unique ability of formic acid to achieve high leaching of Rh from a partially oxidized sample can be attributed to the rapid decomposition of the acid to CO and H\textsubscript{2}O under mild conditions.\textsuperscript{44-46}
4.6. Conclusion

An efficient and selective method for extraction of rhodium from different supports using CO in polar solvents had been described. Higher than 90% leaching can be achieved on freshly reduced samples with high selectivity for rhodium in presence of other precious metals. This method produces the metal in the form of highly reduced, polynuclear clusters. Beyond extraction of rhodium from spent catalysts under mild conditions, the reported method has potential applications in extracting rhodium from inaccessible sources and tailoring the size and composition of supported NP to enhance their specific reactivity. In addition to CO, formic acid can also be used as a leachant under mild conditions.
4.7. References


Chapter 5: Alkylation of ketones and dicarbonyl compounds by the water-gas shift-driven reductive condensation

5.1. Introduction

The Water-Gas Shift Reaction (WGSR)-driven, reductive alkylation of nitrile carbon acids was realized at room temperature with rhodium catalyst in basic aqueous solution of acetonitrile as described in Chapter 2. Owing to its mild conditions, the reaction shows high tolerance toward numerous functional groups including aryl halides and styrenes. However, the scope of the carbon acids that can be alkylated using this reaction was limited to acid nitriles. This limitation arises from the slow condensation of the less-acidic carbons (pKa > 15 in DMSO) and the slow reduction of alkene intermediates. The reaction conditions can be modified to allow for the reductive alkylation of additional classes of substrates besides the nitriles shown in Chapter 2 to include ketones, diketones, ketoesters, and diesters. Dihydrochalcones are illustrative of the products that can be synthesized by this method and has wide scope of applications in medicinal chemistry, Scheme 5.1.

Scheme 5.1. Dihydrochalcones in food and medicinal chemistry

ref. 1
Phloretin
Glucose absorption inhibitor
Bacterial growth inhibitor

ref. 2
2',4'-dihydroxy-4-methoxy-3'-pren-yl-dihydrochalcone
Platelet aggregation inhibitor

ref. 3
Dargilazone
Treatment for type 2 diabetes

ref. 4
Bipinnatone B
Treatment of malaria

ref. 5
Neohesperidin
Artificial sweetener

ref. 6
Uvaretin
Antitumor agent

ref. 7
(-)-colchicine (Gout treatment)
5.2. Background

The use of the WGSR to produce dihydrochalcones has not been reported previously, and the only prior example related to this process is the homologation of acetophenone with formaldehyde reported by Watanabe at 180 °C and 71 bar CO. Despite the severe conditions used, only 10% yield of the desired propiophenone was achieved. Traditionally, ketones C-alkylation is performed using alkyl halides and a base, however, alkyl halides are more expensive than the aldehyde analogue (benzyl bromide: 38$/mol, benzaldehyde: 4$/mol) and the yield often suffers from side reactions i.e. double C-alkylation and O-alkylation, Scheme 5.2a.

Scheme 5.2. Different methods for ketone alkylation

a. Direct alkylation

\[
\begin{align*}
R'\text{C} = \text{Me} + R'\text{-CH}_2\text{X} & \xrightarrow{\text{base}} R'\text{C} = \text{R} \quad \text{(mono alkylation)} \\
X = & \text{I, Br, Cl}
\end{align*}
\]

b. Traditional reductive alkylation

\[
\begin{align*}
R'\text{C} = \text{Me} + R'\text{-CHO} & \xrightarrow{\text{base}} R'\text{C} = \text{R} \\
& \xrightarrow{\text{H}_2, \text{Pd/C or NaBH}_4, \text{solvent 1, solvent 2}} R'\text{C} = \text{R}
\end{align*}
\]

c. Hydrogen borrowing alkylation

\[
\begin{align*}
R'\text{C} = \text{Me} + R'\text{-CH}_2\text{OH} & \xrightarrow{\text{catalyst, base, heat}} R'\text{C} = \text{R} \\
& \text{limited to primary alcohols, super stoichiometric alkylation}
\end{align*}
\]

d. WGSR reductive alkylation

\[
\begin{align*}
R'\text{C} = \text{Me} + R'\text{-CHO} & \xrightarrow{\text{catalyst, CO, H}_2\text{O, low temp.}} R'\text{C} = \text{R} \\
& \text{one pot, mild conditions, deuterated products}
\end{align*}
\]

Alternatively, several methods have been developed for ketones alkylation through transfer hydrogenation (Scheme 5.2c) using Ir, Co, Mn, and Fe catalysts, Scheme 5.3. In these methods, the alcohol reactant serves both as the alkylation agent and the hydrogen source, and thus, high temperature and superstoichiometric amounts are need. Moreover, strong bases are often needed to affect the reaction. The harsh conditions of the alkylation by transfer hydrogenation make it not compatible with other reducible functional groups and limit the reaction scope.
5.3. Research Objectives

The compatibility of the Claisen-Schmidt condensation with the Rh-catalyzed WGSR will be studied and the following items will be investigated:

1- How to catalyze the Claisen-Schmidt condensation without inhibiting the WGSR
2- Compare the alkylation effectiveness of the simultaneous condensation-reduction protocol with the two-step, one-pot condensation followed by reduction
3- Explore the scope of the identified conditions in alkylating dicarbonyl, ketoesters, and diesters.

5.4. Results

Traditionally, the Claisen-Schmidt condensation is carried out with inorganic bases (alkali metal hydroxides or alkoxides).\textsuperscript{10} The compatibility of KOH with the WGSR-driven reduction of chalcone was studied to examine the possibility of performing both reactions simultaneously. As shown in Figure 5.1, KOH inhibits the reduction underlining the need to find alternative condensation catalysts to allow for the WGSR-driven, reduction to proceed.

In the first step, the condensation of aldehydes with acetophenone was attempted in neat conditions at room temperature using different organic bases. Owing to the relatively low acidity of acetophenone (pKa > 25 in DMSO, see Section 5, Chapter 2), the condensation occurs only in presence of stronger amidine or guanidine bases (1,8-Diazabicyclo(5.4.0)undec-7-ene (DBU), 1,5 Diazabicyclo[4.3.0]non-5-ene (DBN), 7-methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene (MTBD)) but not in triethylamine or piperidine, Table 5.1. The highest condensation yield was observed
with MTBD and thus, MTBD was selected as the condensation catalyst for subsequent optimizations. Besides the desired dihydrochalcone 2aa\textsuperscript{'} product, the chalcone intermediate and the benzyl alcohol, resulting from the hydrogenation of the unreacted 1a\textsuperscript{'} , were also observed as by-products of the alkylation. Hydrogenation of 1a to the phenethyl alcohol was observed with piperidine and at a low rate.

**Figure 5.1.** Effect of KOH on the WGSR-driven reduction of chalcone
Table 5.1. Effectiveness of Different Organic Bases in the Reductive Alkylation of Acetophenone

<table>
<thead>
<tr>
<th>entry</th>
<th>Base (i)</th>
<th>consumption (%) 1a&lt;sup&gt;a&lt;/sup&gt;</th>
<th>yield (%) 2aa&lt;sup&gt;a&lt;/sup&gt;</th>
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</table>

The scope of the MTBD-catalyzed Claisen-Schmidt condensation was examined with different ketones and aldehydes in neat solvent, Table 5.2. The standard conditions were effective for the condensation of aryl and heteroaryl aldehydes with acetophenone (entry 1, and 2) and other electron deficient, acidic ketones (entry 3, and 4). Condensation of α, β unsaturated ketones with aryl aldehydes was much slower (entry 5). The condensation of α, β unsaturated aldehydes with aryl ketones proceeds but unselectively due to the self-condensation of the aldehyde (entry 7). When used as electrophiles, alkyl ketones did not undergo condensation with acetophenone (entry 7, 8).
Despite the efficient condensation of methyl-aryl ketones with aldehydes using MTBD as illustrated in Table 2, the condensation of propiophenone was not possible (Table 5.3, entry 1, and 2). Alternatively, tosic anhydride was used in a stoichiometric amount in neat conditions to drive this condensation. About 50% condensation was achieved after 18 h at room temperature (entry 3, and 4). Interestingly, the WGSR-driven reduction of the alkene intermediate was not inhibited by the addition of the tosic anhydride (or the tosic acid formed as the condensation by-product). However, the overall formation of the alkylated product was slow and only 14% yield was obtained after 24 h under the WGSR conditions indicating that the hydrogenation of the tri-substituted

<table>
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<th>b</th>
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<th>product</th>
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<td>5</td>
<td></td>
<td></td>
<td>25</td>
<td><img src="attachment.png" alt="Product 5" /></td>
</tr>
<tr>
<td>6</td>
<td></td>
<td></td>
<td>87</td>
<td><img src="attachment.png" alt="Product 6" /> + 4 isomers</td>
</tr>
<tr>
<td>7</td>
<td></td>
<td></td>
<td>22</td>
<td><img src="attachment.png" alt="Product 7" /> + b self-cond. products</td>
</tr>
<tr>
<td>8</td>
<td></td>
<td></td>
<td>0</td>
<td>--</td>
</tr>
<tr>
<td>9</td>
<td></td>
<td></td>
<td>0</td>
<td>--</td>
</tr>
</tbody>
</table>
alkene is much slower than that of the di-substituted alkene. Additional dimethylethylamine base to neutralize the acidity did not increase the yield of the desired product.

**Table 5.3.** Reductive Alkylation of Propiophenone under WGSR Conditions

<table>
<thead>
<tr>
<th>entry</th>
<th>cat.</th>
<th>EtNMe₂</th>
<th>Alkene (%)</th>
<th>Alkane (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>MTBD (0.1 equiv)</td>
<td>4</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>MTBD (0.1 equiv)</td>
<td>6</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>Tosyl anh. (1 equiv)</td>
<td>4*</td>
<td>41</td>
<td>14</td>
</tr>
<tr>
<td>4</td>
<td>Tosyl anh. (1 equiv)</td>
<td>6*</td>
<td>41</td>
<td>8</td>
</tr>
</tbody>
</table>

*base added before water

Unlike MTBD, tosic anhydride was also successful in driving the more difficult condensation of cyclohexanone with acetophenone at room temperature, however, cyclohexanone self-condensation was also observed as a by-product, Scheme 5.4.

**Scheme 5.4.** Tosis anhydride-driven Claisen Schmidt condensation of acetophenone with cyclohexanone at room temperature

With the positive tosic anhydride -driven condensation results in hand, the effect of tosic acid (formed from the hydrolysis of the anhydride) was studied on the rate of chalcone reduction. A super stoichiometric amount of the tertiary amine was added to neutralize the tosic acid and maintain the concentration of the hydroxide ions needed to drive the WGSR (see Chapter 2 and 6). As shown in Figure 5.2, addition of up to 1.5 equivalents of tosic acid was not harmful to the rate of reduction. In fact, a beneficial effect on the reduction (98 vs 92% yield) was observed by
the addition of 0.5 equivalent of the acid. Addition of more than 1.5 equivalents had an inhibitory effect on the reduction possibly by suppressing the medium basicity. Under the basic WGSR conditions, the tosylate group is expected to exist as trialkylamonium tosylate. The observed positive effect of the acid addition likely arises from the ability of the tosylate ions to facilitate the reduction of the Rh(III) precursor (chloride - tosylate exchanging) or ligating the Rh active species.

![Chemical reaction](image)

**Figure 5.2.** Effect of tosic acid on the WGSR-driven reduction of chalcone

To further understand the accelerating effect of tosic acid, the reduction was carried out with two different catalyst precursors; the Rh(III) chloride and the Rh(0) Rh₄(CO)₁₂. As shown in Table 5.4, the beneficial effect can be seen with Rh(III) but not Rh(0). These results suggest that the beneficial effect of tosic acid arises from the ability of the tosylates to facilitate the reduction of Rh(III) chloride to the lower valence Rh active species.
Table 5.4. Effect of Tosic acid on the WGSR-driven Reduction by Rh(III) and Rh(0) Catalysts

<table>
<thead>
<tr>
<th>entry</th>
<th>catalyst</th>
<th>additive</th>
<th>consumption (%) 1aa’</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>RhCl₃</td>
<td>--</td>
<td>33</td>
</tr>
<tr>
<td>2</td>
<td>RhCl₃</td>
<td>TsOH</td>
<td>46</td>
</tr>
<tr>
<td>3</td>
<td>Rh₄(CO)₁₂</td>
<td>--</td>
<td>40</td>
</tr>
<tr>
<td>4</td>
<td>Rh₄(CO)₁₂</td>
<td>TsOH</td>
<td>38</td>
</tr>
</tbody>
</table>

The effect of the tertiary amine loading on the reduction of chalcone was investigated in absence of tosic acid to elucidate the optimum basicity for the reduction, Figure 5.3. No reduction was observed in absence of amine and as more dimethylethylamine was added, the yield of the dihydrochalcone increased until it reached a maximum between 2.5 and 5 equivalents. Beyond that loading, the yield decreased probably because of the dilution of the reactive species by increasing the overall reaction medium or suppressing the medium polarity.

Besides the amine loading, the structure of the tertiary amine had a significant impact on the chalcone rate of reduction. As shown in Table 5.5, the shorter the alkyl chains of the amine are, the faster the reduction becomes (entry 1 and 2). Moreover, the less bulky, cyclic amines result in higher reduction rate (entry 3, and 4) except for the cyclic, dibasic 1,4-diazabicyclo[2.2.2]octane DABCO which is significantly less efficient than triethylamine at the same base loading (entry 7). Additionally, significant inhibition was observed when the acyclic, dibasic \(N,N,N',N'\) tetramethylethyllenediamine TMEDA was used (entry 5) potentially due to the formation of a stable, 5-membered, cyclic species with Rh. The acyclic, dibasic \(N,N,N',N'\) tetramethylpropylenediamine TMPDA was also less effective in promoting reduction when compared to dimethylethylamine but more effective than TMEDA (entry 6). The yield difference between TMEDA and TMPDA indicates that the distance between the two nitrogen atoms affects the reactivity. The correlation between the structure of the base and the rate of reduction implies that the accessibility of the N atom in the amine affects the rate of reduction potentially due to the
need for the N atom to coordinate to the Rh catalyst to affect the reduction (see Chapter 5, Section 5).

![Chemical structure and reaction scheme]

**Figure 5.3.** Effect of amine loading on the WGSR-driven reduction of chalcone

**Table 5.5.** Effect of Amine Structure on the Rate of Chalcone Reduction

<table>
<thead>
<tr>
<th>entry</th>
<th>amine</th>
<th>conversion (%) 2aa’</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td>53</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>88</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>66</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>73</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td>&lt;5</td>
</tr>
<tr>
<td>6</td>
<td></td>
<td>35</td>
</tr>
<tr>
<td>7</td>
<td></td>
<td>37</td>
</tr>
</tbody>
</table>
One possible explanation for the inhibitory effect of amines with longer alkyl chains is that these amines are less polar, and thus, reduce the medium polarity. To test for this hypothesis, the solvent composition was changed from acetonitrile (dipole moment 3.92) to 1,4-dioxane (dipole moment 0.45, see Chapter 2) in parallel reduction experiments, Figure 5.4. The rate of reduction was not slowed down by substituting up to 50% of the acetonitrile volume by 1,4-dioxane. This result suggests that the effect of medium polarity is not that significant on the rate of reduction and that the inhibitory effect observed when increasing the amount (Figure 5.3) or the chain length (Table 5.5) of the tertiary amine is not originating from the accompanied depression in the medium polarity.

![Chemical reaction image]

**Figure 5.4.** Effect of solvent composition on the WGSR-driven reduction of chalcone

The effect of water and CO pressure on the reduction of chalcone was studied to maximize the rate of reduction. As shown in Figure 5.5, additional water up to 50 equivalents had a positive effect on the yield. The asymptotic behavior of the yield with the amount of water is originating from the dilution of the reactive species by the excess water or the suppression in the concentration of the soluble CO in the reaction medium (CO is less soluble in more moist solvents).\(^{11}\) CO pressure also has a positive effect on the rate of reduction as shown in Figure 5.6. The optimum pressure when 25 equivalents of water are used is between 5 and 7 bar which is lower than the
optimum pressure measured for the reduction of the Knoevenagel adduct of ethylcyanoacetate with benzaldehyde shown in Figure 2.4.

**Figure 5.5.** Effect of water loading on the WGSR-driven reduction of chalcone

**Figure 5.6.** Effect of CO pressure on the WGSR-driven reduction of chalcone
Excellent yield and selectivity was achieved for the reductive alkylation of ethylcyanoacetate with benzaldehyde at the standard conditions illustrated in Chapter 2 (model reaction). The slow condensation of the less activated methylene compounds can potentially be catalyzed by the addition of secondary amines, amino acids, stronger bases than triethylamine, or protic solvents. In this experiment, the effect of a secondary amine (piperidine), stronger base (DBU, pK$_b$ = 25 in MeCN), and protic solvent (EtOH) on the model reaction was studied.

Addition of 0.5 equivalent of DBU was found to drastically inhibit the reduction of the alkene intermediate in the model reaction (entry 1, Table 5.6). Similarly, replacing the tertiary amine (triethylamine) with a secondary amine (piperidine) was found to completely inhibit the reduction (entry 2). Moreover, addition of 0.5 equivalent of piperidine to a reaction containing 2.5 equivalent triethylamine also slowed down the reduction (entry 3).

**Table 5.6. Effect of Condensation Additives on the Reductive Alkylation of Ethylcyanoacetate**

<table>
<thead>
<tr>
<th>Solvent (v/v)</th>
<th>Et$_3$N eq.</th>
<th>additive</th>
<th>1c cons. (%)</th>
<th>Conv. (%) GC</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>MeCN</td>
<td>2.5</td>
<td>DBU (0.1 equiv)</td>
<td>65</td>
</tr>
<tr>
<td>2</td>
<td>MeCN</td>
<td>0</td>
<td>piperidine (2.5 equiv)</td>
<td>79</td>
</tr>
<tr>
<td>3</td>
<td>MeCN</td>
<td>2.5</td>
<td>piperidine (0.5 equiv)</td>
<td>100</td>
</tr>
<tr>
<td>4</td>
<td>MeCN</td>
<td>2.5</td>
<td>MTBD (0.1 equiv)</td>
<td>100</td>
</tr>
<tr>
<td>5</td>
<td>MeCN</td>
<td>2.5</td>
<td>L-proline (0.1 equiv)</td>
<td>100</td>
</tr>
<tr>
<td>6</td>
<td>MeCN</td>
<td>2.5</td>
<td>NH$_4$OAc (0.1 equiv)</td>
<td>100</td>
</tr>
<tr>
<td>7</td>
<td>MeCN/EtOH (9:1)</td>
<td>2.5</td>
<td>piperidine (0.5 equiv)</td>
<td>100</td>
</tr>
<tr>
<td>8</td>
<td>MeCN/EtOH (7:3)</td>
<td>2.5</td>
<td>piperidine (0.5 equiv)</td>
<td>100</td>
</tr>
<tr>
<td>9</td>
<td>MeCN/EtOH (1:1)</td>
<td>2.5</td>
<td>piperidine (0.5 equiv)</td>
<td>100</td>
</tr>
<tr>
<td>10</td>
<td>MeCN/EtOH (3:7)</td>
<td>2.5</td>
<td>piperidine (0.5 equiv)</td>
<td>100</td>
</tr>
<tr>
<td>11</td>
<td>MeCN/EtOH (1:9)</td>
<td>2.5</td>
<td>piperidine (0.5 equiv)</td>
<td>100</td>
</tr>
</tbody>
</table>

The inhibitory effect of the strong, more hindered base; MTBD was found to be less than that of the less hindered DBU despite having similar pK$_b$ in MeCN (entry 4). Addition of the amino acid L-proline was found to have a minor inhibitory effect on the reduction (entry 5). A gradual decrease in the yield of the reduced product (4) was also observed as the solvent composition was...
gradually changed from absolute acetonitrile to acetonitrile: ethanol (1:9 v:v) in parallel experiments (entry 7 to 11).

Except for cyano esters, the condensation of esters including keto esters, diesters, and nitro esters does not proceed with triethylamine at room temperature (entries 1, 5, 10, and 15 respectively, Table 5.7). The condensation of benzoyl ester slowly proceeded with 0.1 equivalent DBU at 40 °C (entry 1 to 4). Contrarily, the condensation of diethyl malonate was only observed with piperidine but not DBU (entry 5 to 9). Comparable conversion of methylacetoacetate was observed with DBU and piperidine (entry 11 and 12). However, the addition of 0.1 equivalent ammonium acetate or L-proline was more effective for this condensation (entry 13 and 14).

**Table 5.7. Effect of Additives on the Condensation of Activated Acid-esters**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base</th>
<th>Temp. (°C)</th>
<th>Condensation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Et₃N (2.5 equiv)</td>
<td>25</td>
<td>X</td>
</tr>
<tr>
<td>2</td>
<td>Et₃N (10 equiv)</td>
<td>25</td>
<td>X</td>
</tr>
<tr>
<td>3</td>
<td>DBU (0.1 equiv)</td>
<td>25</td>
<td>X</td>
</tr>
<tr>
<td>4</td>
<td>DBU (0.1 equiv)</td>
<td>40</td>
<td>✓ (10%)</td>
</tr>
<tr>
<td>5</td>
<td>Et₃N (2.5 equiv)</td>
<td>25</td>
<td>X</td>
</tr>
<tr>
<td>6</td>
<td>Et₃N (10 equiv)</td>
<td>25</td>
<td>X</td>
</tr>
<tr>
<td>7</td>
<td>DBU (0.1 equiv)</td>
<td>25</td>
<td>X</td>
</tr>
<tr>
<td>8</td>
<td>piperidine (0.1 equiv)</td>
<td>25</td>
<td>✓ (25%)</td>
</tr>
<tr>
<td>9</td>
<td>DBU (0.1 equiv)</td>
<td>40</td>
<td>X</td>
</tr>
<tr>
<td>10</td>
<td>Et₃N (2.5 equiv)</td>
<td>25</td>
<td>X</td>
</tr>
<tr>
<td>11</td>
<td>DBU (0.3 equiv)</td>
<td>25</td>
<td>✓ (48%)</td>
</tr>
<tr>
<td>12</td>
<td>piperidine (0.3 equiv)</td>
<td>25</td>
<td>✓ (51%)</td>
</tr>
<tr>
<td>13</td>
<td>NH₄OAC (0.1 equiv)</td>
<td>25</td>
<td>✓ (62%)</td>
</tr>
<tr>
<td>14</td>
<td>L-proline (0.1 equiv)</td>
<td>25</td>
<td>✓ (70%)</td>
</tr>
<tr>
<td>15</td>
<td>Et₃N (2.5 equiv)</td>
<td>25</td>
<td>X</td>
</tr>
</tbody>
</table>

With the results from Table 5.6 and 5.7 in hand, the reductive condensation of methylacetoacetate was attempted under the standard conditions with piperidine and L-proline as condensation catalysts. The yield of the desired product remained less than 70% after 30 h with piperidine. The yield loss is attributed to the more rapid reductive amination of benzaldehyde with
piperidine, Scheme 5.5a. No reductive amination was observed when L-proline was used as a catalyst instead of piperidine. However, the condensation and reduction turned out to be relatively slow and about 30% of the aldehyde was reduced to the benzyl alcohol, Scheme 5.5b.

**Scheme 5.5.** Reductive alkylation of methylacetoacetate with piperidine and L-proline

\[
\begin{align*}
\text{(a)} & \quad \text{MeCOOEt} + \text{PhCHO} & \xrightarrow{\text{RhCl}_3 (2 \text{ mol \%}), \text{Et}_3 \text{N} (2.5 \text{ equiv}), \text{H}_2 \text{O} (3.0 \text{ equiv}), \text{piperidine} (0.3 \text{ equiv})} & \xrightarrow{\text{CO} (10 \text{ bar})} & \text{MeCOOEt} + \text{N}\text{N} \\
10a & (0.4 \text{ mmol}) & 1a' & (1.05 \text{ equiv}) & 70\% & 25\% \\
\text{(b)} & \quad \text{MeCOOEt} + \text{PhCHO} & \xrightarrow{\text{RhCl}_3 (2 \text{ mol \%}), \text{Et}_3 \text{N} (2.5 \text{ equiv}), \text{H}_2 \text{O} (3.0 \text{ equiv}), \text{L-proline} (0.1 \text{ equiv})} & \xrightarrow{\text{CO} (10 \text{ bar})} & \text{MeCOOEt} + \text{MeCOOEt} + \text{OH} \\
10a & (0.4 \text{ mmol}) & 1a' & (1.05 \text{ equiv}) & 50\% & 20\% & 30\%
\end{align*}
\]

**5.5. Discussion**

The Claisen-Schmidt condensation of ketones with aldehydes is traditionally catalyzed by strong inorganic bases such as KOH. However, KOH inhibits the Rh-catalyzed reduction by the WGSR (Figure 5.1). This inhibitory effect likely arises from the ability of the strong \( K^+ \) cation to stabilize the inactive anionic \([\text{Rh}_{12}(\text{CO})_{30}]^{2-}\) clusters.\(^{12}\)

Base screen for the room temperature condensation of acetophenone with different aldehydes showed that MTBD is the most efficient catalyst as it does not inhibit the Rh-catalyzed WGSR (Table 5.1). Both MTBD and DBU have high pK\(_a\) in acetonitrile (24-25)\(^{13}\) and also strongly bind to the Rh catalyst and inhibit the reduction. The more sterically hindered MTBD appears to be more suitable for the reduction than DBU due to its hindered binding to Rh. Tosic anhydride was identified as another condensation reagent that can be used to drive the more difficult condensations such as the condensation of aldehyde with propiophenone or the condensation of cyclohexanone with acetophenone.

The condensation is fastest when performed in neat conditions without solvent or water, and thus, condensation had to be performed in a separate step prior to the WGSR. Under neat conditions, the produced chalcones are often precipitated in the form of solid powder at room temperature. It is recommended to increase the temperature of this step above room temperature for more efficient condensation while keeping the reduction step at room temperature. The tosic acid, produced as a condensation by-product, does not inhibit the WGSR (Figure 5.2).
The WGSR-driven reduction of activated alkenes was found to proceed at its highest rate in acetonitrile. However, some of the less polar chalcones are not readily soluble in acetonitrile at room temperature, especially when high water loading is used. To overcome this problem, the less polar, 1:1 acetonitrile:1-4 dioxane solvent was demonstrated to be an equally effective solvent for reduction that is capable of dissolving most of the chalcones intermediates. Besides solvent composition, the use of the less hindered, dimethylethylamine base and high water loading were identified as the two key components to achieve high reduction rate at room temperature.

The optimum CO pressure for chalcone reduction is between 5 and 7 bar in acetonitrile. Beyond this value, the reduction is slower as the binding of chalcone to the Rh catalyst becomes less favored under high CO pressure. The optimum value of CO pressure is expected to be dependent on the solvent composition (acetonitrile:1,4-dioxane ratio, and water loading). Further optimization is needed to elucidate the optimum pressure with different solvent compositions. Moreover, the optimum CO pressure appears to be dependent on the ability of the alkene to bind to Rh under CO, and thus, the inhibitory effect of CO can be observed at lower pressure for the less activated alkenes, Scheme 5.6. For example, the reduction of the highly polarized Knoevenagel adduct of ethylcyanoacetate was slowed down at CO pressure > 11 bar (Figure 2.4). However, the less polarized adduct of acetophenone suffered inhibition at 7 bar only (Figure 5.6). As a consequence of the inhibition by CO at high pressure, the reduction of the much less polarized adduct formed from the condensation of propiophenone with benzaldehyde (Table 5.3) is expected to be inhibited at lower CO pressure.

Besides its effect on the reaction kinetics, CO pressure has a strong effect on the initial reduction of the catalyst precursor. This effect is observed when starting from precursors with high oxidation state i.e. Rh(III) chloride and at pressures less than 3 bar, see Figure 6.10. The reducibility of the Rh precursor depends on the counter anion of the Rh(III) cation, for example, the addition of 0.1 tosic acid was found to have a beneficial effect on the reduction, Table 5.4. This can be explained by the difference in energy of the catalyst reduction intermediates under the WGSR, Scheme 5.7.
Scheme 5.6. Competitive binding of CO and activated alkene to Rh hydride

Scheme 5.7. Proposed mechanism for the WGSR-driven reduction of Rh(III) to Rh(I)

The difference in energy between the migratory insertion of CO into a Rh-Cl bond to form Rh-(CO)-Cl acid chloride and the migratory insertion into Rh-OTs bond to form Rh-(CO)-OTs according to mechanism A, Scheme 5.6 can explain the accelerating effect of tosic acid. Alternatively, the abstraction of the tosylate with the trialkylammonium ions can be more facile than the abstraction of the more stable chloride ion, mechanism B. Computational analysis is needed to validate these hypotheses.

The mild conditions of the MTBD-catalyzed condensation-reduction allow for the selective alkylation of acetophenones without dialkylation or O-alkylation which are common side reactions with traditional alkylation methods. The two-step, one-pot alkylation approach allows for the efficient utilization of the alkylating agent (1.01 equivalent of the aldehyde) and avoids the unproductive reduction of the aldehydes to alcohols. The mild hydricity of the Rh hydride and the low temperature allow for the reductive alkylation to selectively proceed in presence of sensitive...
functional groups that are not compatible with the transfer hydrogenation-driven alkylation protocols often carried out under harsh conditions.\textsuperscript{9}

5.6. Conclusion

The reductive alkylation of acetophenones was realized through a two-step, one-pot process that employs MTBD as a condensation catalyst and Rh to drive the alkene reduction by the WGSR. The rate of reduction is at highest when dimethylethylamine and water are added in super stoichiometric amount and the reaction is performed under 5 to 7 bar. Equimolar amount of the alkylating agent is used and thus, the unproductive alcohol formation or double alkylation does not occur. Moreover, no ketone reduction or deoxygenation occurs during the reduction step. Higher temperature ($\simeq 50^\circ\text{C}$) and further CO pressure optimization are needed to expand the scope of this reaction to electron rich and less polar ketones.
5.7. References


(5) Foguet R., Cistero A., Borrego F. US patent US5300309A


(10) Mak, K. K. W.; Chan, W.-F.; Lung, K.-Y.; Lam, W.-Y.; Ng, W.-C.; Lee, S.-F. J. Chem Educ. 2007, 84 (11), 1819.


Chapter 6: Mechanistic investigation of the water-gas shift-driven hydrogenation of carbonyl groups, and activated alkenes

6.1. Introduction

Reduction of aryl ketones is widely practiced as a cost-effective method to produce secondary alcohols in industry.¹ Stoichiometric reductants such as NaBH₄, LiAlH₄ and silanes are often used in the classical reduction processes. The production of these metal hydrides is carried out in energy-intense, multistep processes. For example, NaBH₄ is produced from the reaction of molten sodium with high pressure hydrogen, followed by the reaction of sodium hydride with trimethyl borate,² Scheme 6.1. The high energy consumption and the waste associated with the production and usage of the stoichiometric metal hydrides imposes an economic and environmental burden on the manufacture of fine chemicals and pharmaceuticals. On the other hand, deuterated analogues of the traditionally used reductants (i.e. LiAlD₄) needed to produce deuterated alcohols are often not commercially available or affordable.

Scheme 6.1. Reduction of ketones with NaBH₄ vs. the WGSR

\[
\begin{align*}
\text{CO} + \text{H}_2\text{O}_{(l)} &\xrightarrow{\text{FeCrMgO}_x, 350 - 500 \degree C} \text{CO}_2 + \text{H}_2 \\
\text{Na}_{(l)} + \frac{1}{2}\text{H}_2 &\xrightarrow{250 - 350 \degree C} \text{NaH} \\
4\text{NaH} + \text{B(OCH}_3)_3 &\xrightarrow{225 - 275 \degree C} \text{NaBH}_4 + 3\text{NaOCH}_3 \\
\text{NaBH}_4 + \text{RCR}' &\xrightarrow{\text{H}_2\text{O}, 25 \degree C} \text{RCHR}' + \text{BH}_3 + \text{NaOH} \\
\text{CO} + \text{H}_2\text{O}_{(l)} + \text{RCR}' &\xrightarrow{\text{WGSR}} \text{RCHR}' + \text{CO}_2
\end{align*}
\]

Because of the drawbacks associated with stoichiometric reductants, catalytic reduction of ketones by transition metal hydrides is a more attractive alternative. Ruthenium hydrides, catalytically generated from molecular hydrogen or from the transfer hydrogenation with isopropanol, have been proven to be highly effective for ketone reductions as demonstrated by
Noyori and co-workers in the mid 1990s.\(^3\) High productivity S/C > 10000 was achieved with the 2-aminomethylpyridine AMPY–ligated diphosphine ruthenium catalysts in presence of strong alkali metal alkoxides at temperatures higher than 80 °C. The Ru AMPY catalysts were modified by introducing diverse phosphine ligands by Baratta and co-workers and commercialized by Johnson Matthey for the selective reduction of diverse substrates, Scheme 6.2.\(^4\) Other metal complexes including Re, Mn,\(^5\) Fe,\(^6\) and Ir\(^7\) were also tested for ketone reduction. However, Ru remains the catalyst of choice owing to its high reactivity.

**Scheme 6.2.** Commercial catalysts for ketone reduction by transfer hydrogenation

Despite the high reactivity of the Ru AMPY catalysts, the relatively high temperature (> 80 °C) and the strong bases required to activate the catalyst can harm the product selectivity, especially with alcohols bearing other reducible substituents.\(^8\) Moreover, protocols that employ phosphine-free catalysis and water as a reaction solvent are attractive from the environmental point of view, and thus, research efforts are being directed to find better hydrogenation technologies.\(^7\)

### 6.2. Background

Homogeneous catalysis of the Water Gas-Shift Reaction WGSR has been reported in basic, neutral, and acidic conditions at temperature above 100 °C using transition metals carbonyls.\(^9\) Several mechanisms were proposed for hydrogen production depending on catalyst active species, medium pH, and reaction conditions. For example, Rh\(_6(CO)_{16}\) drives the WGSR in basic medium using organic\(^{10}\) or inorganic base.\(^{11}\) On the other hand, in-situ generated [RhI\(_2(CO)_{2}\)]\(^-\) catalyzes the reaction in acidic medium.\(^{12}\) The undesired hydrogen production is more thermodynamically feasible in presence of strong acids and hence only basic media catalysis was considered for the current study.
Thermodynamic hydricity is the free energy required to heterolytically cleave M-H bond to generate a hydride ion. It is a parameter used to describe the ability of metal hydrides to transfer hydrogen to reducible molecules as the “acceptor”. Owing to their wide applications in organic synthesis; hydricities have been measured/determined and compiled to help predict their ability to transfer hydrides to diverse acceptors. As a convention, the lower the hydricity value, the more hydridic “stronger” the metal hydride is, i.e. it is capable of transferring its hydride to less activated substrates.

Several factors affect hydricity including solvent, and ligand. For example, the hydricity calculated in water is significantly lower than that measured in acetonitrile (31 vs. 62 kcal/mol for [Ir(Cp*)(bpy)H]+). The difference in the calculated values arises from the ability of the solvent to act as a ligand and occupy the open coordination site following the cleavage of the M-H bond. Ligand structure also has a drastic effect on the hydricity (Rh(dppb)2H vs. Rh(dmpe)2H; 34.0 vs 26.6 kcal/mol in MeCN), from the previous example it can be concluded that hydricity decreases with lowering ligand donicity or increasing its basicity.9

The generation of metal hydrides from molecular hydrogen proceeds through oxidative addition to the H-H bond to form metal dihydride. Interestingly, metal dihydrides were found to be less hydridic compared to their mono-hydride analogues (i.e. [Rh(depe)2(H2)]+ vs. Rh(depe)2H, 51.9 kcal/mol vs. 28.3). The formation of the mono hydride from the dihydride often proceeds through deprotonation which requires strong base to occur (pKa >33 for Rh(dmpe)2H).9

The hydricity required to transfer a hydride to a carbon center can be arranged to follow this order aldehydes > ketones > epoxides as indicated by the rate of their reduction using stoichiometric amounts of [W(CO)5H]+ (hydricity = 40 kcal/mol in MeCN). Following the hydride delivery step, the reaction requires an acid to protonate the substrate. For the more difficult substrates e.g. acetophenone, stronger acids were necessary which led to the unproductive loss of the metal hydride through hydrogen evolution reaction.

*The ability of the Water-Gas Shift Reaction WGSR to produce the mono-hydride species directly without going through the less hydridic dihydrides can potentially be employed to drive hydride transfer processes without the need for strong bases to deprotonate the dihydride.*

The WGSR employs water as a hydride source and has been shown to involve the catalytic generation of Rh mono hydrides at temperatures as low as room temperature (see Chapter 2 and 5). The main obstacle in using the WGSR to reduce ketones, especially aryl ketones, is the need
for low hydricity to enable the ketone reduction. While the hydricity can be lowered by ligating the metal with electron donating ligands (i.e. phosphine or diamine ligands),\textsuperscript{13} these ligands have been found to inhibit the regeneration of the Rh hydride under the WGSR conditions (Chapter 2, and 3).

Attempts to overcome this barrier by increasing the reaction temperature have been reported by Tamon,\textsuperscript{14} and Kaneda\textsuperscript{15} with limited success for the reduction of acetophenone using Rh catalysis, Scheme 6.3. In the study by Tamon and co-workers, the reduction of acetophenone is carried out in THF with a diisopropylphosphine Rh dihydride catalyst. Under these conditions, less than 70\% yield of the desired alcohol is obtained at 150 °C after 20 h. A more developed approach is reported by Kaneda and co-worker in which Rh\textsubscript{6}(CO)\textsubscript{16} is used as a catalyst in presence of tetramethylpropanediamine (TMPDA) base in 2-ethoxyethanol solvent. No reduction of acetophenone was observed at 80 °C under these conditions. However, moderate yields (20-50\%) for the reduction of linear and cyclic alkyl ketones are reported.

6.3. Research Objective

The purpose of this project is to affect the reduction of aryl ketones with the WGSR under mild conditions and compare the mechanism by which ketone reduction occurs to the mechanism by which activated alkene reduction occurs. The following concepts are used to guide the reaction optimization:

1- The use of monobasic tertiary amines with short alkyl chain length (i.e. trimethylamine or dimethylethylamine) to promote the reduction
2- The hydricity of metal hydride is lower in water and protic solvents
3- The use of low valent Rh precursor (i.e. Rh(0) and Rh(I) can overcome the initial catalyst reduction barrier
4- Rely on CO as the main ligand to stabilize the Rh active species, avoid the use of phosphine or bidentate nitrogen ligands to avoid inhibition
5- Explore asymmetric reduction by adding chiral N-binding ligands.
6.4. Results

The rhodium-catalyzed reduction of different aldehydes and ketones with the WGSR was tested in acetonitrile, Table 6.1. The reduction of alkyl as well as aryl aldehydes was found to proceed effectively at room temperature (entry 1 to 7). The reduction of the α, β unsaturated aldehydes (i.e. \(E\)-cinnamaldehyde, 2-undecenal, 3-methylbut-2-enal, and \(E\)-2-methylbut-2-enal) resulted in the reduction of the carbonyl as well as the activated olefin (entry 3 to 6). Noticeably, the reduction of the activated olefin in the 2-undecenal was more rapid than that of the olefin in the more stabilized \(E\)-cinnamaldehyde (entry 3 and 4).
Table 6.1. Reducibility of Carbonyl Compounds under the Rhodium-catalyzed WGSR Conditions.

![Chemical structure](image)

<table>
<thead>
<tr>
<th>entry</th>
<th>a</th>
<th>consumption (%) a*</th>
<th>main product (≥50% product total peak area)</th>
<th>other products (&lt;50% product total peak area)</th>
</tr>
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<tbody>
<tr>
<td>1</td>
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</tr>
<tr>
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<td><img src="image" alt="Structure" /></td>
<td>33</td>
<td><img src="image" alt="Structure" /></td>
<td>--</td>
</tr>
</tbody>
</table>

*a* measured by GC-MS versus mesitylene internal standard

The reduction of the substituted aldehyde 3-methylbut-2-enal was much slower than that of the isomer substituted at the 2 position which showed similar rate to that of the non-substituted 2-undecenal (entry 5 and 6). The difference in the rate of reduction of the two methyl butenal isomers can be attributed to the need of the β carbon to coordinate to the Rh catalyst for the reduction to
proceed. The methyl substituent at the β position hinders the olefin coordination and slows down the reaction. The reduction of styrenyl aldehyde was found to proceed selectively towards the benzyl alcohol with minimal reduction of the styrene (entry 7). Unlike the aldehyde carbonyl group and their conjugated olefins, no reduction of the ketone carbonyl group or its conjugated alkene was observed under the test conditions (entry 8 to 14) with the exception of the activated olefins in 2-cyclohexenone and chalcone.

To test the effect of the electronic properties of aryl aldehydes on the reducibility of the carbonyl moiety, the conversion of substituted benzaldehydes was tested in acetonitrile at room temperature, Figure 6.1. The consumption of the electron deficient aldehydes i.e. 4-cyanobenzaldehyde, and 4-bromobenzaldehyde was found to be more rapid than that of the electron rich 4-methyl and 4-methoxybenzaldehydes.

![Diagram of aldehyde reduction](image)

**Figure 6.1.** Effect of benzaldehyde electronic properties on carbonyl reducibility under the WGSR conditions (consumption measured by GC with an internal standard).

The reducibility of acetophenone was tested under the WGSR conditions with Rh(I) [RhCODCl]₂ dimer and dimethylethylamine DMEA base in different solvents other than
acetonitrile, Table 6.2. No reduction was observed in acetonitrile (entry 1) which is in agreement with the result obtained with RhCl₃ catalyst and triethylamine base (entry 8, Table 6.1). Other solvents including n-propanol, 2-propanol, n-butanol, and tetrahydrofuran were also not suitable for this reaction (entry 2 to 5). Interestingly, reduction proceeded in highly polar protic solvents including ethanol, methanol, water and 2-ethoxyethanol (entry 6 to 9). The highest reactivity was observed in methanol followed by 2-ethoxyethanol and water (biphasic medium). Interestingly, the addition of small quantity of acetonitrile to methanol (1:10 v MeCN/MeOH) resulted in complete inhibition of the reduction (entry 10).

<table>
<thead>
<tr>
<th>entry</th>
<th>solvent</th>
<th>conversion (%) 2x</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>MeCN</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>n-propanol</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>2-propanol</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>n-butanol</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>THF</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>ethanol</td>
<td>&lt;5</td>
</tr>
<tr>
<td>7</td>
<td>water (biphasic)</td>
<td>26</td>
</tr>
<tr>
<td>8</td>
<td>2-ethoxyethanol</td>
<td>22</td>
</tr>
<tr>
<td>9</td>
<td>MeOH</td>
<td>65</td>
</tr>
<tr>
<td>10</td>
<td>MeOH:MeCN (10:1) v</td>
<td>0</td>
</tr>
<tr>
<td>11</td>
<td>MeCN</td>
<td>0*</td>
</tr>
<tr>
<td>12</td>
<td>MeOH:1,4-dioxane (1:1) v</td>
<td>26</td>
</tr>
<tr>
<td>13</td>
<td>CH₂Cl₂:MeOH (1:1) v</td>
<td>&lt;5</td>
</tr>
<tr>
<td>14</td>
<td>toluene:MeOH (1:1) v</td>
<td>&lt;5</td>
</tr>
</tbody>
</table>

*reaction at 65 ºC

Table 6.2. Reducibility of Acetophenone under the WGSR in Different Solvents

Moreover, attempting to perform the reduction in acetonitrile at 65 ºC failed to achieve any reactivity indicating that acetonitrile is not suitable for the WGSR-driven reduction of
acetophenone. Other solvent mixtures of methanol with 1,4-dioxane, dichloromethane, and toluene were tested and all found to be less effective than methanol only.

To examine the effect of water to methanol ratio on the rate of reduction, the reduction of acetophenone was performed in methanol at different water loadings in parallel experiments. No measurable reduction was observed with less than 5 equivalents of water after 12 h, Figure 6.2. As the water loading increased from 5 to 40 equivalents, a monotonic increase in the alcohol yield was obtained. The highest yield (85%) was obtained at 40 equivalents of water which is equivalent to 4:1 water/MeOH solvent mixture.

![Figure 6.2](image)

**Figure 6.2.** Effect of water loading on acetophenone reduction under the WGSR (measured by GC with an internal standard).

The reduction of acetophenone with [RhCODCl]₂ in methanol/water mixture was tested with different bases in parallel experiments, Table 6.3. No reduction was observed with KOH (same behavior was observed with alkene reduction in acetonitrile (Figure 5.1). Tertiary amines with pK_BH in the rage of 17 to 19 in MeCN were found to catalyze the reduction and the less hindered, monobasic dimethylethylamine gave the highest yield followed by triethylamine. Interestingly, the dibasic tetramethyldiethyleneamine (TMEDA) did not inhibit the reduction in this case unlike the
alkene reduction in acetonitrile (Table 5.5). The stronger 7-methyl-1,5,7-triazabicyclo(4.4.0)dec-5-ene (MTBD, pK_BH 25.4 in MeCN) completely inhibited the reduction.

The reducibility of alkyl ketones was tested under the newly identified, rhodium-catalyzed WGSR conditions (System B). Rapid reduction of cyclohexanone and methyl cyclopropyl ketone was observed at room temperature, Scheme 6.4. The reduction of the α, β unsaturated E-pent-3-en-2-one was much slower than the non-conjugated alkyl ketones owing to the presence of the easier to reduce activated olefin.

Table 6.3. Reducibility of Acetophenone under the WGSR with Different Bases.

<table>
<thead>
<tr>
<th>entry</th>
<th>base</th>
<th>conversion (%) 2x</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>Et_3N (2.5 equiv)</td>
<td>29</td>
</tr>
<tr>
<td>3</td>
<td>TMEDA (2.5 equiv)</td>
<td>25</td>
</tr>
<tr>
<td>4</td>
<td>KOH (1 equiv)</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>EtNMe_2 (2.5 equiv)</td>
<td>65</td>
</tr>
<tr>
<td>6</td>
<td>MTBD (1 equiv)</td>
<td>0</td>
</tr>
</tbody>
</table>

Three substituted acetophenones were also tested under the WGSR conditions at 65 °C in water to test for the effect of ketone electronic properties on the rate of reduction, Scheme 6.5. High yield and selectivity was obtained for the electron deficient 4-iodoacetophenone and 4-cyanoacetophenone. No dehalogenation or nitrile reduction was observed under the reaction conditions. Contrarily, the electron rich 4-dimethylaminoacetophenone was not hydrogenated under the same conditions.
Scheme 6.4. Alkyl ketone reduction under System B Conditions

\[
\begin{align*}
\text{[Rh(COD)Cl]_2 (5 mol\% Rh)} & \quad \text{EtNMe}_2 (2.5 \text{ equiv}) \\ 
\text{H}_2\text{O} (20 \text{ equiv}) \\
\text{MeOH (1 M), 25 °C, 12 h} \\
\text{CO (28 bar)}
\end{align*}
\]

0.4 mmole

\[
\begin{align*}
\text{0.4 mmole} \\
\text{CO (28 bar)} \\
\text{MeOH (1 M), 25 °C, 12 h} \\
\text{>95% yield}
\end{align*}
\]

\[
\begin{align*}
\text{[Rh(COD)Cl]_2 (5 mol\% Rh)} & \quad \text{EtNMe}_2 (2.5 \text{ equiv}) \\ 
\text{H}_2\text{O} (25 \text{ equiv}) \\
\text{MeOH (1 M), 25 °C, 12 h} \\
\text{CO (20 bar)}
\end{align*}
\]

0.4 mmole

\[
\begin{align*}
\text{0.4 mmole} \\
\text{CO (20 bar)} \\
\text{MeOH (1 M), 25 °C, 12 h} \\
\text{80% yield}
\end{align*}
\]

\[
\begin{align*}
\text{[Rh(COD)Cl]_2 (5 mol\% Rh)} & \quad \text{EtNMe}_2 (2.5 \text{ equiv}) \\ 
\text{H}_2\text{O} (25 \text{ equiv}) \\
\text{MeOH (1 M), 25 °C, 12 h} \\
\text{CO (28 bar)}
\end{align*}
\]

0.4 mmole

\[
\begin{align*}
\text{0.4 mmole} \\
\text{CO (28 bar)} \\
\text{MeOH (1 M), 25 °C, 12 h} \\
\text{15% yield} \\
\text{85% yield}
\end{align*}
\]

Scheme 6.5. Aryl ketones reduction under System B conditions

\[
\begin{align*}
\text{[Rh(COD)Cl]_2 (2.5 mol \text{ % Rh})} & \quad \text{EtNMe}_2 (2.5 \text{ equiv}) \\ 
\text{H}_2\text{O} (1 \text{ M), 65 °C, 8 h} \\
\text{CO (20 bar)}
\end{align*}
\]

0.4 mmole

\[
\begin{align*}
\text{0.4 mmole} \\
\text{CO (20 bar)} \\
\text{H}_2\text{O (1 M), 65 °C, 8 h} \\
\text{>95 % yield}
\end{align*}
\]

\[
\begin{align*}
\text{[Rh(COD)Cl]_2 (2.5 mol \text{ % Rh})} & \quad \text{EtNMe}_2 (2.5 \text{ equiv}) \\ 
\text{H}_2\text{O (1 M), 65 °C, 8 h} \\
\text{CO (20 bar)}
\end{align*}
\]

0.4 mmole

\[
\begin{align*}
\text{0.4 mmole} \\
\text{CO (20 bar)} \\
\text{H}_2\text{O (1 M), 65 °C, 8 h} \\
\text{>95 % yield}
\end{align*}
\]

\[
\begin{align*}
\text{[Rh(COD)Cl]_2 (2.5 mol \text{ % Rh})} & \quad \text{EtNMe}_2 (2.5 \text{ equiv}) \\ 
\text{H}_2\text{O (1 M), 65 °C, 8 h} \\
\text{CO (20 bar)}
\end{align*}
\]

0.4 mmole

\[
\begin{align*}
\text{0.4 mmole} \\
\text{CO (20 bar)} \\
\text{H}_2\text{O (1 M), 65 °C, 8 h} \\
\text{0 %}
\end{align*}
\]

To test for the ability of System B to selectively form α deuterated secondary alcohols, water was replaced with D₂O in proto, and deuterio methanol, Figure 6.3. The mass spectrum of the product alcohol indicates the incorporation of 3 deuterium atoms on average. The deuterium
incorporation in the product appears to occur but unselectively owing to the H/D exchange on the acidic α methyl group.

Figure 6.3. D incorporation in System B reduction of acetophenone.

The kinetic behavior of the Rh-catalyzed, WGS-driven reduction of activated olefin in acetonitrile (System A) was studied and compared to the kinetic behavior of the WGS-driven ketone reduction in methanol (System B). To measure the order on catalyst loading for System A, the reduction of chalcone to dihydrochalcone was studied with different catalyst loading in parallel experiments and the initial rate was calculated from the yield of the product formed during the first
3 to 6 hours (keeping conversion < 40 %). The measured order for catalyst loading was 1.055 and 0.9988 after 3 and 6 hours respectively, Table 6.4.

**Table 6.4.** Order in Catalyst in the WGSR-driven Reduction of Chalcone (system A).

<table>
<thead>
<tr>
<th>entry</th>
<th>RhCl₃ equiv</th>
<th>3 h</th>
<th>6 h</th>
<th>9 h</th>
<th>24 h</th>
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<tbody>
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<td>96.48312</td>
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<td>2</td>
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<td>28.05083</td>
<td>42.84511</td>
<td>56.15827</td>
<td>95.44615</td>
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<tr>
<td>3</td>
<td>2</td>
<td>21.52234*</td>
<td>37.09069</td>
<td>49.17973</td>
<td>78.09843</td>
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<td>4</td>
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<td>5</td>
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<td>42.83599</td>
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<td>1</td>
<td>11.59526</td>
<td>20.98688</td>
<td>28.48687</td>
<td>49.86325</td>
</tr>
</tbody>
</table>

*bad points, excluded from fitting

$r = \text{mmole product/min, } [\text{Rh}] = \text{mole Rh/L MeCN}$
The order in catalyst was also measured for the hydrogenation of acetophenone in methanol (System B) by running reduction experiments with variable loadings of [RhCODCl]$_2$ dimer in parallel. The measured order in this case was 1.001 as well, Figure 6.4.

**Figure 6.4.** Order in catalyst in the WGSR-driven reduction of acetophenone (system B). (measured by GC with an internal standard). Conv 6 to 56%, \( r = \) mmole product/min, \([\text{Rh}] = \) mole Rh/L MeOH

The order in catalyst concentration was also measured with the low valent, Rh$_4$(CO)$_{12}$ tetramer and compared to that measured with Rh(III)Cl$_3$, Figure 6.5. For both catalysts, first order dependence was observed indicating that catalyst fragmentation is not kinetically relevant in the case of Rh carbonyl. The molar reactivity of both catalyst precursors were comparable indicating that there is no advantage in starting from the low valence tetramer and that catalyst dimerization oligomerization does not play a positive role in the reaction.
Previous kinetics studies for WGSR-driven aldehyde reduction using Rh$_6$(CO)$_{12}$ and inorganic base at 120 °C showed that the molar catalyst activity decreases at increasing catalyst concentration because of catalyst oligomerization.$^{16}$ In the present case, the catalyst oligomerization was not observed as the use of an organic base (ethyldimethylamine) can potentially facilitate catalyst fragmentation. To test this hypothesis, initial rates were measured at varying Rh carbonyl concentration at two different amine concentrations (0.3 equiv and 2.5 equiv w.r.t. chalcone). The measured order in catalyst concentration decreased from 1 to 0.6 as the amine loading was cut down from 2.5 equivalents to 0.3 equivalents, Figure 6.6. Moreover, in the low amine concentration experiment, the molar catalyst activity went down with increasing catalyst concentration indicating catalyst oligomerization at high concentration.

**Figure 6.5.** Order in catalyst in the WGSR-driven reduction of chalcone (system A). (measured by GC with an internal standard). $r =$ mmole product/min, [Rh] = mole Rh/L MeCN

\[
y = 1.0712x - 1.4324 \\
R^2 = 0.99
\]

\[
y = 1.005x - 1.6948 \\
R^2 = 0.984
\]
Figure 6.6. Order of catalyst on the WGSR-driven reduction of chalcone (system A) at different dimethylethylamine loading. (measured by GC with an internal standard). \( r = \text{mmole product/min, } [\text{Rh}] = \text{mole Rh/L MeCN} \)

To test for the effect of substrate concentration on the rate of hydrogenation, parallel experiments were done with variable substrate concentration; chalcone (System A), and acetophenone (System B). The variable chalcone concentration experiment was repeated three times under 3.5, 7, and 14 bar CO pressure, for 6, 4 and 3 h respectively, Figure 6.7. Interestingly, a fractional order in chalcone concentration was measured in the three experiments. The order was found to increase at increasing CO pressure but it did not reach an integer at the highest pressure (0.85 at 14 bar). The fractional order could be attributed to either the unproductive, competitive binding of chalcone to the Rh center through the carbonyl, alkene, or both moieties or to the suppression of CO solubility at increasing chalcone concentration (lower medium polarity). In
either scenario, the inhibitory effect of the substrate appears to be mitigated by increasing the CO pressure.

![Chemical reaction diagram]

**Figure 6.7.** Order in chalcone concentration in the WGSR-driven reduction of chalcone (system A). (measured by GC with an internal standard). $r = \text{mmole product/min, } [1\text{aa'}] = \text{mole 1aa'}/L\ \text{MeCN, } r \propto [1\text{aa'}]^n$

Same approach was applied to measure the order in acetophenone concentration in System B. Since System B requires high CO pressure to be operable, the acetophenone loading was varied from 0.05 to 0.8 mmole while keeping CO pressure at 28 bar. Interestingly, a fractional order (0.49) was still measured despite the high CO pressure, Figure 6.8. Similar to the fractional order measured in System A, it can be attributed to either the competitive binding of acetophenone to the Rh catalyst or the drop in medium polarity at increasing acetophenone concentration.

The effect of carbonyl binding on the rate of reduction of activated olefins was studied by measuring the rate of chalcone at variable concentration of acetophenone under System A conditions. The inhibitory effect of the unproductive binding of the ketone carbonyl was found to be negligible (slope < 0.1) indicating that this inhibitory effect is not relevant, Figure 6.9.
Figure 6.8. Order in acetophenone concentration in the WGSR-driven reduction of acetophenone (system B). (measured by GC with an internal standard). Conv. 80 to 22%, \( r = \text{mmole product/min} \), \([1X]=\text{mole 1X/L MeOH}\).

The order in CO pressure was measured for System A and System B at constant concentration of catalyst, substrate, water, and amine. The experiment was repeated twice for System A, once with Rh(III) chloride, and then with Rh(0) carbonyl. The order in both cases was around 0.5 in the range of 3 to 10 bar, Figure 6.10. Below 3 bar CO, a drastic decrease in the rate of reduction was observed at pressure lower than 3 bar with RhCl\(_3\). The drop in reactivity at the lower pressure region with Rh(III) chloride is attributed to the slow initial reduction of the highly oxidized catalyst precursor to the low valence active species at low CO pressure (Scheme 5.7). The similar molar reactivity of Rh(III) chloride monomer and Rh(0) carbonyl tetramer at CO pressure > 3 bar indicates that the effect of CO on the fragmentation of the carbonyl cluster is negligible under the studied conditions. The independence of cluster fragmentation on CO pressure is in agreement with the orders measured in catalyst concentration (1 and 0.6 with 2.5 and 0.3 equivalents of amine respectively) as catalyst fragmentation is facilitated by the tertiary amine not CO in this case.
Figure 6.9. Effect of acetophenone concentration on the reduction of chalcone under System A conditions (measured by GC with an internal standard), \( r = \text{mmole/min} \)

\[
y = -0.0737x - 3.3045 \\
R^2 = 0.2731
\]

\[
y = 0.5245x - 4.0821 \\
R^2 = 0.9844
\]

Figure 6.10. Order in CO pressure in the WGSR-driven reduction of chalcone (system A). (measured by GC with an internal standard). \( r = \text{mmole product/min} \).
The order in CO pressure in System B was also determined in the range of 3 to 20 bar to be a fraction around 0.5 similar to that measured for System A, Figure 6.11. The fractional order measured for both systems can be attributed to the need for a loss of a carbonyl ligand from the Rh hydride to open a coordination site for the substrate to coordinate to the Rh hydride and allow for the hydride transfer to occur, see Figure 2.6 and Scheme 5.6.

![Chemical Reaction](image)

**Figure 6.11.** Order of CO pressure in the WGSR-driven reduction of acetophenone (system B). (measured by GC with an internal standard). \( r = \text{mmole product/min.} \)

The order in amine concentration was measured for System A and System B while keeping the water concentration constant. The amine loading was varied from 0.5 to 2 equiv and the reaction was allowed to occur for 6 hours. An additional point with amine loading of 0.1 equivalents was measured after 21 hours to allow for the formation of a measurable quantity of product at this low amine loading. The order in amine loading was 1.15, Figure 6.12. An additional experiment was performed with 5 equivalents of amine and the value of \( \log (r) \) was measured to be -3.32. This
value is comparable to that measured with 2 equivalents of amine (-3.38) indicating that increasing the base loading beyond 2 equivalents has negligible effect on the rate.

![Chemical reaction diagram]

Figure 6.12. Order of dimethylethylamine concentration in the WGSR-driven reduction of chalcone (system A). (measured by GC with an internal standard). \( r = \text{mmole product/min.} \)

It should be noted here that amine plays multiple roles in this reaction as it provides the hydroxide ions necessary for the hydride to form, and facilitates the Rh cluster fragmentation as indicated above. Additional role of the high amine loading is to neutralize the acidity arising from the formation of CO$_2$ side product. To test for the effect of the acidity (arising from CO$_2$ formation) on the rate of reduction in System A, the rate was measured at different CO$_2$ pressures keeping the partial pressure of CO constant at 7 bar. The experiment was done with two different amine loadings; 2.5 and 5 equivalents, Figure 6.13. No change in the rate of reduction was observed up to 3 bar CO$_2$ pressure, beyond this value, a decrease in the rate of reduction was observed. The decrease in the rate with CO$_2$ was found to be more drastic at lower amine loading confirming the effectiveness of the tertiary amine in neutralizing the CO$_2$ acidity.
Figure 6.13. Effect of CO₂ pressure on the WGSR-driven reduction of chalcone (system A). (measured by GC with an internal standard).

The effect of base loading on System B was measured in the range of 0.5 to 3 equivalents. The measured order was found to change from first order below 1 equivalent to zero order above this value, Figure 6.14. This inversion behavior from first to zero order was observed in both Systems A and B at 2, and 1 base equivalent respectively. The difference in the inversion point between the two systems can be attributed to the solvent used in each system. The saturation with hydroxide ions can be reached in methanol at lower base loading than that at which saturation is reached in acetonitrile. At higher than the saturation value, addition of more amine does not lead to the formation of more hydroxide ions, instead, it dilutes the reaction medium and decreases the medium polarity.

The order in water concentration was measured in System A by varying water loadings from 2 to 25 equivalents with respect to chalcone, Figure 6.15. Interestingly, the measured order was found to be 0.3 which is contradictory to that observed for System B above (second order for System B, Figure 6.2). The difference in the order in water loading between the two systems suggests a difference in the mechanism by which the reduction of activated alkene and ketone occurs.
Figure 6.14. Order in dimethylethylamine concentration in the WGSR-driven reduction of acetophenone (system B). (measured by GC with an internal standard). \( r = \) mmole product/min.

Figure 6.15. Order of water concentration in the WGSR-driven reduction of chalcone (system A). (measured by GC with an internal standard). \( r = \) mmole product/min.
To further understand the role of water in both systems, the reduction was performed with deuterium oxide instead of water, Table 6.5. The yield of dihydrochalcone dropped from 34 to 13% indicating a kinetic isotope effect (KIE) $k_D/k_H = 0.38$. Interestingly, the $k_D/k_H$ for System B was found to be much higher = 0.87. Since System B is performed in methanol, the deuterium experiment was repeated in methanol-$d_4$ and no change in the yield was observed from the yield measured in proto-methanol (KIE = 0.84). The KIE measured for System A indicates that the rate determining step involves a hydride formation or delivery which is in agreement with the proposed mechanism for System A in Chapter 2. The KIE is less noticeable for System B suggesting that the rate determining step maybe different from that in System A. It should be noticed here that H/D exchange occurs in the alpha methyl position in acetophenone which can be the reason for the high KIE measured for System B as well.

**Table 6.5.** Kinetic Isotope Effect in the WGSR-driven Reduction in System A and System B.

<table>
<thead>
<tr>
<th>entry</th>
<th>$H(D)_2O$</th>
<th>$2aa^\prime$ (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H$_2$O</td>
<td>34</td>
</tr>
<tr>
<td>2</td>
<td>D$_2$O</td>
<td>13</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>entry</th>
<th>$H(D)_2O$ equiv</th>
<th>2X (%)</th>
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<tbody>
<tr>
<td>1</td>
<td>H$_2$O</td>
<td>52</td>
</tr>
<tr>
<td>2</td>
<td>D$_2$O</td>
<td>45</td>
</tr>
<tr>
<td>3</td>
<td>D$_2$O 25 in CD$_3$OD</td>
<td>44</td>
</tr>
</tbody>
</table>
The ability of System A to produce molecular hydrogen was studied by measuring the water content of the reaction medium before and after the reaction in absence of a hydride acceptor (chalcone) and, Table 6.6. The experiment was repeated three times to confirm the result and no water consumption was observed indicating that there is no hydrogen evolution under system A conditions. The inability of System A to produce molecular hydrogen potentially arises from the weak acidity of the protonated tertiary amine that renders it incapable of protonating the Rh hydride to form Rh dihydride. Alternatively, the reductive elimination of molecular hydrogen from the Rh dihydride can be energetically un-favored at room temperature.

**Table 6.6.** Water Consumption by Hydrogen Evolution Reaction under System A Conditions in Absence of a Hydride Acceptor.

<table>
<thead>
<tr>
<th>entry</th>
<th>#</th>
<th>H₂O content (g/l) by (KF)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before reaction</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>204.3</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>186.9</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>185</td>
<td></td>
</tr>
<tr>
<td>After reaction</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>209.3</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>200.7</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>201.5</td>
<td></td>
</tr>
<tr>
<td>Dry CH₃CN</td>
<td></td>
<td>0.09</td>
</tr>
</tbody>
</table>

To affect the WGSR-driven asymmetric hydrogenation of acetophenone, different ligands were incorporated in System B, Table 6.7. Alkyl diamine ligands completely inhibited the reduction. Cinchonidine does not inhibit the reduction but does not lead to any significant enantioselection. Chiral, tertiary and secondary alkyl amines as well as amino alcohols did not enhance enantioselection either. Failure to affect an enantioselective, WGSR-driven reduction may arise from the strong binding of CO to the metal center that does not allow other ligands to bind to the metal at the hydride delivery step. Moreover, the strong binding ligands may inhibit the catalytic formation of the metal hydride.
**Table 6.7. Ligand Screen for the WGSR-driven Ketone Asymmetric Reduction**

![Chemical Structure](image)

<table>
<thead>
<tr>
<th>entry</th>
<th>L</th>
<th>solvent</th>
<th>2X (%)</th>
<th>e.r.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image" alt="Ligand 1" /></td>
<td>0.2 mL</td>
<td>0</td>
<td>--</td>
</tr>
<tr>
<td>2</td>
<td><img src="image" alt="Ligand 2" /></td>
<td>0.3 mL</td>
<td>26</td>
<td>50:50</td>
</tr>
<tr>
<td>3</td>
<td><img src="image" alt="Ligand 3" /></td>
<td>0.4 mL</td>
<td>20</td>
<td>49:51</td>
</tr>
<tr>
<td>4</td>
<td><img src="image" alt="Ligand 4" /></td>
<td>L. tartarate 0.2 mL</td>
<td>0</td>
<td>--</td>
</tr>
<tr>
<td>5</td>
<td><img src="image" alt="Ligand 5" /></td>
<td>0.2 mL</td>
<td>16</td>
<td>50:50</td>
</tr>
<tr>
<td>6</td>
<td><img src="image" alt="Ligand 6" /></td>
<td>0.8 mL</td>
<td>4</td>
<td>47:53</td>
</tr>
<tr>
<td>7</td>
<td><img src="image" alt="Ligand 7" /></td>
<td>0.2 mL</td>
<td>4</td>
<td>50:50</td>
</tr>
<tr>
<td>8</td>
<td><img src="image" alt="Ligand 8" /></td>
<td>0.2 mL</td>
<td>40</td>
<td>50:50</td>
</tr>
</tbody>
</table>
6.5. Discussion

The WGSR is a more sustainable and atom economical alternative for hydrogenation processes than the traditionally used stoichiometric reductants. The reducibility of activated alkenes and carbonyl groups under the WGSR is solvent dependent. The reduction of aldehydes and alkenes conjugated to aldehydes is facile in acetonitrile at room temperature (System A). However, the reduction of ketones and conjugated alkenes to ketones is not possible at room temperature in acetonitrile or other organic solvents except methanol (System B). The use of the less hindered, more polar dimethylethylamine and high water loading (> 20 equivalents) drastically enhance the reducibility of ketones at room temperature. For the first time, complete reduction of alkyl ketones was achieved at room temperature with 25 equivalents of water, and 85% reduction of acetophenone was achieved with 40 equivalents of water. Selective reduction of 4-iodoacetophenone, and 4-cyanoacetophenone to the corresponding alcohols was achieved in water without dehalogenation or nitrile reduction.

Both systems A and B displayed a first order dependence on Rh catalyst precursors. The constant molar reactivity at increasing catalyst loading indicates that catalyst oligomerization does not occur when high amine loading is applied (2.5 equivalents dimethylethylamine). Moreover, the order in catalyst was found to be first order when Rh(0) as well as Rh(III) catalyst precursors were used indicating that the reaction is not limited by the catalyst initial reduction or Rh cluster fragmentation.

Fractional order was measured in substrate concentration for both systems. Ideally, a first order dependence should be measured based on the proposed mechanism in Chapter 2. The observed fractional order indicates an inhibitory effect by the substrate. This inhibitory effect likely arises from the unproductive binding of the substrate to the Rh catalyst prior to the hydride formation, Scheme 6.6. The measured order was found to increase with higher CO pressure indicating that the inhibitory effect of the unproductive binding can be overcome by increasing the CO pressure.

A fractional order was also measured for CO pressure in both systems. Similar order was measured for Rh(III) chloride monomer, and Rh(0) carbonyl tetramer indicating that the molar reactivity is not dependent on the precursor nuclearity or oxidation state at pressure higher 3 bar. Below this value, a drop in reactivity was observed with Rh(III) when compared to Rh(0) indicating that the catalyst initial reduction is kinetically limiting at such low pressure (Scheme 5.7).
Tertiary amines are needed to generate hydroxide or formate ions (eq. 1, and 2) that lead to the formation of metal hydride. The order in dimethylethylamine concertation in both systems go from first to zero order indicating system saturation at 2 and 1 equivalent for System A and B respectively. The order on water concentration was found to be 0.3 and 2 for System A and B respectively which could be attributed to the difference in the mode of rhodium carbonyl activation in both systems. This is in agreement with the difference in KIE measured for both systems 0.38 and 0.87 for System A and System B respectively.
Four different mechanisms have been proposed for the activation of carbonyl clusters through nucleophilic attack of \( \text{OH}^- \), \( \text{HCO}_2^- \), \( \text{H}_2\text{O} \), or \( \text{NR}_3 \) depending on cluster electronic properties and medium basicity. The degree of metal to ligand electron density back donation by the metal center to the coordinated carbonyl determines the ease of the cluster activation. High electron density at the metal center such as in the case of negatively charged clusters or clusters containing strong electron donating ligands are thought to be more difficult to activate and can only be activated by the attack of strong nucleophiles such as \( \text{OH}^- \) ions to form anionic metallocarboxylic acids (eq. 3). On the other hand, electron deficient metal centers such as that found in positively charged clusters or high oxidation state metals are prone to attack by weaker nucleophiles such as \( \text{H}_2\text{O} \) to from the metallocarboxylic acid (eq. 4).\(^{17}\)

In basic solution, dissolved CO can react with \( \text{OH}^- \) ions to generate formate ions (eq. 2) that can bind to coordinatively unsaturated carbonyl clusters to form metalloformate species (eq. 5).\(^{13}\) A fourth possible route for cluster activation in presence of amines is through the direct attack of the amine on the carbonyl ligand to form zwitterionic metallocarboxamide species (eq. 6).\(^{18}\) The ability of amine to attack the carbonyl ligand depends on the positive charge strength on the carbonyl carbon and hence, a correlation between the carbonyl stretching force constant and its suitability toward attack by amine was drawn.\(^{19}\)

\[
\begin{align*}
\text{Et}_3\text{N} + \text{H}_2\text{O} & \rightleftharpoons \text{Et}_3\text{NH}^+ + \text{OH}^- & \text{eq. 1} \\
\text{CO} + \text{OH}^- & \rightleftharpoons \text{HCO}_2^- & \text{eq. 2}
\end{align*}
\]

\[
\begin{align*}
\text{M}_x\text{(CO)}_y + \text{OH}^- & \rightleftharpoons \text{M}_x\text{(CO)}_{y-1}\text{(CO}_2\text{H})^- & \text{eq. 3} \\
\text{M}_x\text{(CO)}_y^+ + \text{H}_2\text{O} & \rightleftharpoons \text{M}_x\text{(CO)}_{y-1}\text{(CO}_2\text{H}) + \text{H}^+ & \text{eq. 4} \\
\text{M}_x\text{(CO)}_{y-1} + \text{HCO}_2^- & \rightleftharpoons \text{M}_x\text{(CO)}_{y-1}\text{(OCOH)}^- & \text{eq. 5} \\
\text{M}_x\text{(CO)}_y + \text{NR}_3 & \rightleftharpoons \text{M}_x\text{(CO)}_{y-1}\text{(O}C\text{NR}_3) & \text{eq. 6}
\end{align*}
\]
The dependence of the rate of reduction on the amine structure (Table 5.5) suggests that the direct attack of the amine is potentially the predominant pathway in System A (eq. 6). An alternative explanation for the need for amine is that the amine itself serves as a ligand; however, the first order dependence on amine concentration along with the need for super-stoichiometric amount of amine (100 equiv w.r.t metal) suggests that the ligand effect is much less important in this case. The lack of reactivity observed when the amine is replaced with inorganic base e.g. KOH (Figure 5.1) suggests that the nucleophilic attack by OH\(^-\) or HCO\(_2\)\(^-\) is not operable in System A.

Experimentally, an increase in reduction rate was observed as the tertiary amine alkyl chain length become shorter EtNMe\(_2\) > Et\(_3\)N > EtNi-Pr\(_2\) > n-Bu\(_3\)N >> PMP. This steric hindrance could be manifested in the amine attack on the bulky metal carbonyl. In fact, similar trend is reported for the rate of reaction of amines with the carbonyls of Mn and Re.\(^{20}\) In addition, aromatic amines were not able to form carboxamides which could explain the inability of 4-dimethylaminopyridine (DMAP) to drive the reduction despite having similar basicity to Et\(_3\)N in System A (Table 2.3).

Reduction rate order in water was less than 0.3. The actual order could be zero and the slight increase in reduction rate with water loading could be attributed to catalyst initial reduction rate or the decrease in metal hydricity at increasing H\(_2\)O/MeCN ratio. Water is involved in the metal hydride formation either through the pre-equilibrium with base to form hydroxide ions or the hydrolysis of metallocarboxamide. In either mechanism the formation of metal hydride appears to be zero order in water.

The loss of carbon dioxide follows the activation of the carbonyl clusters. Metallocarboxylic acid or metalloformate species can undergo decarboxylation reaction to form CO\(_2\) and the metal hydride (eq. 7, and 8).\(^{13}\)

$$
\begin{align*}
\text{M}_x(\text{CO})_{y-1}(\text{CO}_2\text{H})^- & \underset{\text{or}}{\rightleftharpoons} \text{HM}_x(\text{CO})_{y-1}^- + \text{CO}_2 & \text{eq. 7} \\
\text{M}_x(\text{CO})_{y-1}(\text{OCOH})^+ & \end{align*}
$$

$$
\begin{align*}
\text{O} & \text{H} \text{O} & \text{O} \\
\text{(CO)}_{y-1}\text{M}_x\text{C–NR}_3 & \rightleftharpoons \text{H}_2\text{O} & \text{HM}_x(\text{CO})_{y-1}^- + \text{CO}_2\cdot\text{R}_3\text{NH}^+ & \text{eq. 8} \\
\end{align*}
$$

Carbon dioxide is the only by-product in WGSR-driven reductive transformation and its accumulation during the course of the reaction slows down the reduction rate. Absorbed CO\(_2\) in the reaction medium can drive the medium basicity down by formation of the bicarbonate (eq. 9).\(^{21}\)
Carbon dioxide showed an inhibitory effect at pressures higher than 3 bar in System A, below this pressure, the base loading was in excess to maintain the medium basicity. Based on the used pressure cell volume, the amount of CO$_2$ produced at complete reduction of chalcone is equivalent to 1 bar of CO$_2$ and hence the effect of CO$_2$ on the measured reduction rates is negligible.

6.6. Conclusion

For the first time, the WGSR-driven reduction of alkyl and aryl ketones was achieved at room temperature using [Rh(COD)Cl]$_2$ dimer in methanol. The use of dimethylethylamine base and high water loading is essential to maximize reactivity. The kinetics of the WGSR-driven reduction of activated alkenes in acetonitrile (System A) and aryl ketones in methanol (System B) were studied. Both systems are first order in catalyst, and exhibit fractional order in substrate and CO due to the competitive binding of substrate and CO to the Rh reactive species. The order of dimethylethylamine was found to be initially first order that reverts to zero order as it reaches saturation in both systems. The order in water concentration and the KIE values measured with D$_2$O were different in mode of Rh carbonyl activation in the two systems.
6.7. References


Chapter 7: Formation of C-N bonds by the water-gas shift-driven reductive amination, aminomethylation, and reductive Piancatelli reaction

7.1. Introduction

The formation of C-N bonds through reductive amination is widely practiced in medicinal chemistry and constitutes about 20% of all the heteroatom alkylations in drug synthesis, Scheme 7.1.¹ Reductive amination proceeds through amine condensation of the amine with an aldehyde or ketone to from an imine (or iminium ion in the case of secondary amines) followed by reduction to yield the amine. When compared N alkylation with alkyl halides, reductive amination offers more control over the selectivity of the product and helps overcome the undesired overalkylation. The need for external reductant to effect the reduction of the imine (or iminium ions) intermediates harms the overall atom economy, especially when stoichiometric reductants are used such alkali metal hydrides (Scheme 6.1).²

Scheme 7.1. Examples of commercial drugs containing C-N bonds

Substituting stoichiometric reductants with molecular hydrogen and palladium catalyst and eliminates the problems associated with the use of the stoichiometric reductants. However, the selective reduction of the imine intermediate in presence of other reducible groups can be challenging because of the low hydricity of the formed palladium hydride.³ Moreover, the solvent requirements for the condensation step is often different from that needed for the hydrogenation by molecular hydrogen due to the difference in polarity.

7.2. Background

The use of Water Gas-Shift Reaction (WGSR) in driving reductive amination is an attractive alternative to molecular hydrogen and alkali metal hydrides. High atom efficiency and low environmental impact can be achieved by utilizing water as a hydride source and producing carbon dioxide as the sole by-product. The idea of using CO to drive reductive amination was proposed
by List and Chusov using rhodium acetate catalyst. In their proposed mechanism, the C-N bond formation does not involve the WGSR, instead, CO directly deoxygenates the formed hemiaminal intermediate. On the basis of the prosed mechanism, no water was added to the reaction and thus, high temperature (120 to 140 °C) was required to effect the reaction, Scheme 7.2. Further development of this strategy was carried out by Chusov and co-workers using iridium catalyst, which exhibits tolerance to reducible groups such as aryl and alkyl chlorides but harsh conditions are still required (150 °C).

**Scheme 7.2.** CO-driven reductive amination without external water

In Chapters 2, 5, and 6 of this study, it was shown that the WGSR-driven reduction of activated alkenes, aldehydes, and ketones can be achieved at room temperature by performing the reaction in excess water and super-stoichiometric amount of non-hindered tertiary amines. Extending these conditions to the reductive amination would allow for effective and selective C-N bond formation. However, the compatibility of the WGSR with the reductive amination is unknown. For example, the hydricity of the formed rhodium hydride is not known to be low enough to allow for the hydride delivery to the formed imine (or iminium ion) intermediate. Moreover, aldehyde hydrogenation with the WGSR in presence of an excess of water is facile and thus, the rate of aldehyde hydrogenation needs to be minimized relative to the aldehyde condensation with the amine to minimize the yield loss.

**7.3. Research Objectives**

The purpose of this project is to extend the WGSR-driven reduction process illustrated in Chapter 2 and 5 to affect reductive amination. The following items will be investigated:

1. The effect of WGSR parameters on the yield of the amines
2. The ability to affect the reductive aminomethylation of olefins through the WGSR-driven, tandem hydroformylation - reductive amination reactions.
3. The formation of α-enaminone through the WGSR-driven reductive Piancatelli rearrangement of 2-furyliminium ions.

7.4. Results

The reductive amination of benzaldehyde with piperidine (1.05 equivalent) to form N-benzylpiperidine was attempted under 10 bar CO in acetonitrile with RhCl₃, water, and triethylamine, Table 7.1. Less than 10% consumption of benzaldehyde was observed with 1 mol% RhCl₃ (entry 1 to 5) and thus, the catalyst loading was increased to 2 mol%. With 2.5 equivalents triethylamine and 15 equivalents water, 38% of the benzaldehyde was consumed and the only identified product was the desired N-benzylpiperidine with no benzyl alcohol formation, entry 6.

**Table 7.1. Effect of WGSR Conditions on the Reductive Amination of Benzaldehyde.**

<table>
<thead>
<tr>
<th>entry</th>
<th>RhCl₃ mol%</th>
<th>Et₃N equiv</th>
<th>H₂O equiv</th>
<th>time h</th>
<th>consumption (%) 1a</th>
<th>identified productb</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>0</td>
<td>15</td>
<td>4</td>
<td>&lt;5</td>
<td>1ab</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>1</td>
<td>15</td>
<td>4</td>
<td>&lt;5</td>
<td>1ab</td>
</tr>
<tr>
<td>3</td>
<td>1</td>
<td>1</td>
<td>35</td>
<td>4</td>
<td>&lt;5</td>
<td>1ab</td>
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</tr>
<tr>
<td>9</td>
<td>2</td>
<td>2.5</td>
<td>5</td>
<td>9</td>
<td>80</td>
<td>1ab</td>
</tr>
<tr>
<td>10</td>
<td>2</td>
<td>2.5</td>
<td>5</td>
<td>9</td>
<td>58*</td>
<td>1ab</td>
</tr>
</tbody>
</table>

a Determined by GC. b Determined by GC-MS. *0.5 M in CH₃CN

Increasing reaction time from 4 to 9 hours increased the benzaldehyde consumption from 38% to 100% (entry 7) and decreasing the water content from 15 to 10 and 5 equivalents decreased the benzaldehyde consumption from 100 to 98 and 80% respectively indicating that the reaction is limited by water loading (entry 8 and 9). Increasing the overall concentration by decreasing the
solvent volume from 0.5 to 0.25 mL resulted in a decrease in the benzaldehyde consumption from 80 to 58%.

To examine the scope of the identified WGSR-driven reductive amination at room temperature, the amination of different carbonyl compounds with piperidine was carried out, Table 7.2. The reaction time was kept at 10 h and the catalyst loading at 2 mol %. The reaction was compatible with alkyl as well as aryl aldehydes with no measurable aldehydes self-condensation side reaction (entry 1). Multiple products were observed with the α, β unsaturated aldehyde due to the reduction of the conjugated double bond and aldehyde self-coupling (entry 2). Slow reaction was observed with acetone, cyclohexanone, and acetophenone (entry 3 to 5) indicating that the reductive amination of ketones is significantly slower than that of aldehydes.

Table 7.2. WGSR-driven Reductive Amination of Carbonyl Compounds

<table>
<thead>
<tr>
<th>entry</th>
<th>b</th>
<th>a</th>
<th>time (h)</th>
<th>consumption (%) a</th>
<th>identified productb</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td></td>
<td>10</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td></td>
<td></td>
<td>10</td>
<td>71</td>
<td>multiple products</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td></td>
<td>10</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td></td>
<td></td>
<td>10</td>
<td>21</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td></td>
<td></td>
<td>10</td>
<td>&lt;5</td>
<td>none</td>
</tr>
</tbody>
</table>

a determined by GC. b determined by GC-MS.

The WGSR-driven reductive amination of different amines was carried out with benzaldehyde at room temperature for 18 h, Table 7.3. The reductive amination with the more hindered 2-methylpiperidine was significantly slower than that of piperidine (entry 1). Owing to the slow reductive amination in this case, measurable quantity of the benzyl alcohol was formed.
Table 7.3. WGSR-driven Reductive Amination of Benzaldehyde with Different Amines.

<table>
<thead>
<tr>
<th>entry</th>
<th>b</th>
<th>a</th>
<th>Time h</th>
<th>consumption (%) a</th>
<th>Identified product b</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td>1</td>
<td>18</td>
<td>36</td>
<td>[Chemical structure]</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>1</td>
<td>18</td>
<td>0</td>
<td>[Chemical structure]</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>1</td>
<td>18</td>
<td>100</td>
<td>[Chemical structure]</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>1</td>
<td>18</td>
<td>100</td>
<td>[Chemical structure]</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td>1</td>
<td>18</td>
<td>0*</td>
<td>[Chemical structure]</td>
</tr>
<tr>
<td>6</td>
<td></td>
<td>1</td>
<td>18</td>
<td>0</td>
<td>none</td>
</tr>
<tr>
<td>7</td>
<td></td>
<td>1</td>
<td>18</td>
<td>65*</td>
<td>[Chemical structure]</td>
</tr>
<tr>
<td>8</td>
<td></td>
<td>1</td>
<td>18</td>
<td>17</td>
<td>[Chemical structure]</td>
</tr>
</tbody>
</table>

a determined by GC. b determined by GC-MS. * complete consumption of a to benzyl alcohol

The 2,2,6,6-tetramethylpiperidine was found to be inactive in the reductive amination and only benzyl alcohol was observed in this case. Complete consumption of pyrrolidine and piperazine was observed with excellent selectivity to the desired N-benzylpyrrolidine (entry 3) and N, N’-dibenzylpiperazine (entry 4). The reductive amination with anilines was not observed under the standard conditions probably because of the low formation of the iminium ion with the much less basic aromatic amines (entry 5).

Moreover, the reductive amination of the amino acid L-proline does not proceed under the reaction conditions (entry 6). Interestingly, in presence of L-proline, reduction seems to be completely inhibited as indicated by deactivated reduction of benzaldehyde to benzyl alcohol. The reaction of the hindered acyclic alkylamine, diisopropylamine was found to proceed but at relatively slower rate (entry 7). The less basic cyclic amine, morpholine was also found to be much
slower in reductive amination than piperidine due to the slower formation of the iminium ion or the facile hydrolysis of the less stable iminium ion.

Two products of the same mass were observed when 2-furfural 2a was aminated with piperidine under the WGSR conditions. The experiment was done on 2 mmole scale and the two products were isolated and identified as the methylfurylamine 1S and 2-(piperidin-1-yl)cyclopent-2-en-1-one 2S., Scheme 7.3. The molar ratio of 1S to 2S was 1:0.56 and no reduction of the 2-furfural to 2-furyl alcohol was observed. When 5-methyl-2-furfural 3a was aminated with piperidine under the same conditions, one product was observed, the methylfurylamine 3S.

Scheme 7.3. Reductive amination of 2-furfurals under the WGSR conditions.

The effect of the WGSR parameters on the ratio of 1S to 2S was studied to maximize the yield of 2S. Incomplete consumption of 2a was observed with less than 10 equivalents of water after 18 hours, Figure 7.1a. The ratio of 2S/1S increased with increasing the water loading from 1.5 to 10 equivalents and decreased beyond this value, Figure 7.1b.
Figure 7.1. (a) Effect of water loading on the consumption of 2a in the reductive amination reaction. (b) Effect of water loading on the ratio of 2S to 1S.

The reductive amination of 2a with 1b was performed with different loadings of triethylamine in parallel experiments. Figure 7.2a. The consumption of 2a increased as the triethylamine loading was increased from zero to 2 equivalents. Beyond 2 equivalents, the consumption of 2a decreased with increasing triethylamine due to dilution. The ratio of 2S to 1S was at highest in absence of triethylamine and decreased from 1.6 to 0.4 when 0.5 equivalent was added. Figure 7.2b. Increasing the triethylamine from 0.5 to 2 equivalents increased the ratio of 2S to 1S from 0.4 to 0.6. Beyond this value, the increase in triethylamine lead to a decrease in the ratio between the two isomers.
Figure 7.2. (a) effect of triethylamine loading on the consumption of 2a in the reductive amination reaction. (b) effect of triethylamine loading on the ratio of 2S to 1S.

The effect of CO pressure was also studied on the reductive amination of 2a using 10 equivalents of water and 3 equivalents of triethylamine. It should be noted here that the equivalents of 2a to 1b was reduced from 1.05 to 0.95 in this experiment (2a is the limiting reactant and 1b in excess). Incomplete consumption of 2a was observed at pressure less than 100 psi (7 bar), Figure 7.3a. The ratio of 2S to 1S remained zero for CO pressures up to 50 psi (3.5 bar) and increased with increasing CO pressure until it reached a maximum at 120 psi (8 bar), Figure 7.3b. A side
reaction occurred at pressure less than 60 psi that lead to the consumption of 2a and the formation of other product than 1S, 2S, or the furyl alcohol (potentially polymerization products).

Figure 7.3. (a) effect of CO pressure on the consumption of 2a in the reductive amination reaction. (b) effect of CO pressure on the ratio of 2S to 1S.

To overcome the issues associated with the rapid carbonyl reduction relative to the desired reductive amination shown in some cases in Table 7.2 and 7.3, the formation of aldehyde from olefin was attempted under the WGSR conditions through hydroformylation. The reductive aminomethylation of allylbenzene with piperidine was attempted with RhCl₃ catalyst at 85 °C in different solvents, Table 7.4. The temperature was increased and the water loading was cut down to 4 equivalents to facilitate the formation of the iminium ions and minimize its hydrolysis. No
consumption of the allyl benzene was observed in DMF and DMSO (entry 1 and 2). However, higher than 80% consumption was observed in acetonitrile and 2-ethoxyethanol (entry 3 and 4). No aldehyde or alcohol was observed in the latter two cases indicating the rapid condensation and reduction of the iminium ion. Two isomers of the amino methylated products were observed (linear and branched) arising from the carbonylation of the terminal or the internal carbon of the olefin.

**Table 7.4.** WGSR-driven Reductive Aminomethylation of Allylbenzene in Different Solvents.

<table>
<thead>
<tr>
<th>entry</th>
<th>solvent</th>
<th>allyl consumption%</th>
<th>b/l ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>DMF</td>
<td>&lt; 5</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>DMSO</td>
<td>&lt; 5</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>2-ethoxyethanol</td>
<td>80</td>
<td>0.69</td>
</tr>
<tr>
<td>4</td>
<td>MeCN</td>
<td>89</td>
<td>0.78</td>
</tr>
</tbody>
</table>

The WGSR-driven reductive aminomethylation was performed in presence of different ligands to maximize the ratio of one isomer to the other. The reaction was performed at 75 °C in acetonitrile, Table 7.5. The branched to linear ratio was 0.86 without ligand. This value is slightly higher than the 0.78 observed at 85 °C, Table 7.4, entry 1 indicating that the branched product is more favored at lower temperature. The ratio increased to 2.1 and the overall consumption decreased from 57 to 17% when 2,2’-bipyridyl was used in a ratio of 2:1 ligand/Rh, entry 2. Complete inhibition was observed when triphenylphosphine and 4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene (Xantphos) was used (entry 3 and 4). Ethylene-dinitrilo-tetraacetic acid (EDTA) was found to slightly decrease the b/l ratio to 0.78 (entry 5). The dibasic $N,N,N',N'$-tetramethylethlenediamine (TMEDA) was used as a base instead of triethylamine and found to slightly slow down the reaction but not have a significant impact on the b/l ratio (entry 6).
Table 7.5. Ligand Effect on the I/b Ratio of the WGSR-driven Reductive Aminomethylation.

<table>
<thead>
<tr>
<th>entry</th>
<th>ligand</th>
<th>allyl consumption%</th>
<th>b/l ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-</td>
<td>57</td>
<td>0.86</td>
</tr>
<tr>
<td>2</td>
<td>bpy (6 mol %)</td>
<td>17</td>
<td>2.1</td>
</tr>
<tr>
<td>3</td>
<td>Pph3 (6 mol %)</td>
<td>&lt; 5</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>Xantphos (3 mol %)</td>
<td>&lt; 5</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>EDTA (10 mol %)</td>
<td>51</td>
<td>0.78</td>
</tr>
<tr>
<td>6</td>
<td>TMEDA (200 mol %)*</td>
<td>41</td>
<td>0.93</td>
</tr>
</tbody>
</table>

*no Et3N in this run

To test the selectivity of other catalysts to one isomer over the other, the reaction was performed at 80 °C in acetonitrile, Table 7.6. High selectivity for the linear product was observed with the trinuclear ruthenium carbonyl (entry 2). Contrarily, no reactivity was observed with iridium and cobalt carbonyls (entries 3 and 4). When Ru3(CO)12 was used as a catalyst, isomerization of the allylbenzene to β-methylstyrene was observed but to a small extend (< 10% yield). Amine carbonylation to amide or hydroamination of the olefin were not observed.

Table 7.6. WGSR-driven Reductive Aminomethylation of Allylbenzene with Different Catalysts.

<table>
<thead>
<tr>
<th>entry</th>
<th>cat</th>
<th>allyl consumption%</th>
<th>b/l ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>RhCl3 (3 mol Rh %)</td>
<td>99</td>
<td>0.82</td>
</tr>
<tr>
<td>2</td>
<td>Ru3(CO)12 (6 mol Ru %)</td>
<td>83</td>
<td>0.04*</td>
</tr>
<tr>
<td>3</td>
<td>Ir3(CO)12 (3 mol Ir %)</td>
<td>&lt;5</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>Co3(CO)8 (6 mol Co %)</td>
<td>&lt;5</td>
<td>-</td>
</tr>
</tbody>
</table>

*isomerization product of allyl benzene was detected as well <10%
7.5. Discussion

For the first time, the CO-driven reductive amination was realized at room temperature. This goal was achieved by performing the reaction in acetonitrile with Rh catalyst in presence of super stoichiometric amounts of water and tertiary amines. With 2 mol % catalyst, the reaction time had to be extended beyond 4 hours to realize reactivity. This lag time can be attributed to the relatively slow reduction of Rh(III) precursors (Scheme 5.7). The WGSR-driven reductive amination is a self-sufficient reaction in terms of hydride source since the water needed for reduction is generated from the condensation step. However, a positive effect was observed with higher water loading on the reduction kinetics, and thus the water loading was increased up to 20 equivalents.

Despite the high basicity of the reaction medium arising from the formation of the tertiary amine product, the addition of triethylamine was necessary to catalyze the condensation reaction. Complete amination of aryl and alkyl aldehydes was achieved with 2.5 equivalents triethylamine in 10 hours. Amination of ketones, on the other hand, was found to be much slower potentially due to the slow formation of the iminium ion. This problem could be overcome by performing the reaction in presence of a stronger base than triethylamine (MTBD or DBN, Table 5.1).

The reducibility of the formed iminium ion was also found to be highly affected by steric hindrance and basicity of the aminating agent. For example, only 38% yield of the desired amine was obtained when benzaldehyde was aminated with 2-methyl piperidine under the same conditions that allow for complete amination of the same substrate with piperidine. Additionally, slower amination was observed when benzaldehyde was aminated with the less basic morpholine. Under these slow amination conditions, the unproductive reduction of the aldehyde to the alcohol harms the product yield. Water content needs to be optimized for the slower condensation cases to accelerate this step and push equilibrium toward the formation of the iminium ion, Scheme 7.4.

α-enaminones are useful building blocks that can be synthesized from the reaction of ketones with O-benzoylhydroxylamines at moderate yields. Despite being more economical and green starting materials, furfurals have not been used to produce α-enaminones before because of the the lack of enabling technologies for this transformation. The reductive amination of 2-furfural with piperidine under the WGSR conditions resulted in the formation of two isomers; the methylfurylpiperidine which is the expected product and the 2-(piperidin-1-yl)cyclopent-2-en-1-one formed from the newly identified reductive Piancatelli rearrangement.
Scheme 7.4. Effect of water loading on the formation and consumption of iminium ions.

Traditional, non-reductive Piancatelli rearrangement of the iminium furyl ions are known to yield the dibasic 4,5-diamine-enone, Scheme 7.5. As opposed to the traditional reaction, performing the reaction under the proposed WGSR conditions intercepts the rearrangement with the metal hydride and allows for the formation of the monobasic, 2-aminocyclopentenone.

Scheme 7.5. Formation of 4,5-diamine-enone through the Piancatelli rearrangement.

The proposed mechanism for the formation of the 2-aminocyclopentenone involves the nucleophilic attack of water (hydroxide ion) on the C5 position of the iminium ion (i), followed by ring opening (ii), Scheme 7.6. The formed enedione undergoes a condensation reaction to form the 5-hydroxycyclopent-2-enone (iii). The product undergoes an olefin reduction driven by the WGSR to form the hydroxyl ketone (iv) which dehydrates to form the 2-aminoenone (v).

This mechanism is in agreement with the observed inhibition of the rearrangement when 5-methylfurfural was used. Moreover, the beneficial effect on the ratio of 2S to 1S with increasing water content from 1.5 to 10 equivalents indicates that water has a positive impact on the rate of the rearrangement which is manifested in the nucleophilic attack on the C5 carbon. The effect of triethylamine loading on the 2S to 1S ratio is less understood. While adding more triethylamine
can catalyze the nucleophilic attack by the hydroxide ions on the iminium ion, it is also known to catalyze the WGSR and the direct reduction of the iminium ion (vi). The low 2S to 1S ratio at low CO pressures could be attributed to the slow reduction of the hydroxylenone relative to the more reactive iminium ion (assuming that the substrate binding to Rh hydride is rate determining for both pathways, see Scheme 5.6).

**Scheme 7.6. WGSR-driven Piancatelli rearrangement.**

The WGSR-driven reductive aminomethylation proceeds by the hydroformylation of olefins to aldehydes followed by the reductive amination of the aldehyde. In this mechanism, the role of the WGSR is manifested in both the hydroformylation and the reduction of the iminium ion. Theoretically, one water equivalent is required for every amine molecule formed. The water loading was kept between 4 and 5 equivalent to accelerate the hydroformylation without allowing for excessive alcohol formation. In presence of 1.1 equivalent amine, no aldehyde or alcohol was observed indicating the rapid condensation under the reaction conditions. The hydroformylation was found to proceed only in acetonitrile and 2-ethoxyethanol but not DMF or DMSO potentially because of the strong binding of solvent to the Rh catalyst in the later cases which inhibits the olefins from coordinating.

The main drawback of the proposed WGSR-driven aminomethylation is the control over the branched to linear product ratio. Although 2,2’-bipyridyl showed some control over this ratio, it also exhibited strong inhibiting effect. Interestingly, when the Rh catalyst was replaced by the more economic Ru carbonyl, high selectivity towards the normal product was observed. Similar selectivity was observed by Beller and co-workers when the same catalyst was used for the hydrogen-driven reductive aminomethylation at 130 °C and 60 bar (CO/H₂) pressure. When
compared to the work by Beller and co-workers, the WGSR-driven aminomethylation reported in the current study has the advantage of performing the reaction at lower temperature (80 °C) and lower pressure (20 bar CO) without the need for hydrogen or phosphine ligands, Scheme 7.7.

Scheme 7.7. Hydrogen vs. water-driven aminomethylation of allylbenzene.

### 7.6. Conclusion

The formation of C-N bonds was accomplished through the WGSR-driven reductive amination, reductive Piancatelli rearrangement, and reductive aminomethylation. In the reductive amination reaction, the steric hindrance and the stability of the iminium ion drastically affect the product yield. Room temperature conditions work best when aldehydes are aminated with non-hindered alkylamines. Further optimization in terms of water loading, auxiliary base structure (dimethylethylamine for example), and reaction temperature may accelerate the slower aminations e.g. amination with hindered amines, arylamines, or morpholine. On the other hand, the stronger metal hydride formed in methanol (System B in Chapter 6) and the use of stronger bases such as MTBD (see Chapter 5) could be employed to affect the more difficult reductive amination of ketones.

The reductive amination of 2-furfural resulted in the formation of 2-aminoenone through the newly-identified reductive Piancatelli rearrangement. Further optimization and additives need to be performed/employed to maximize the ratio of the 2-aminoenone to the furylamine.

The WGSR-driven reductive aminomethylation of olefins was accomplished at T > 70 °C with Rh and Ru catalysts. Non-ligated, trinuclear ruthenium carbonyl drives the reductive aminomethylation of olefins with high selectivity for the linear product. When compared to the
aminomethylation driven by synthesis gas, the WGSR-driven aminomethylation is efficient at lower temperature and pressure and does not need phosphine ligands.

7.7. References

Chapter 8: Experimental section

8.1. General experimental

All reactions were performed in glass vials under an atmosphere of carbon monoxide, unless noted otherwise. Glass vials were put in a stainless steel, bolted-closure autoclave with a removable top section fitted with an inlet and outlet needle valves and a pressure gauge.

Figure 8.1. Pressure autoclave setup used for reductive alkylation.
Reaction solvent acetonitrile (Aldrich, HPLC grade) was distilled over CaH\textsubscript{2} and further dried over 4 Å molecular sieves. Reaction solvent tetrahydrofuran (Fisher, HPLC grade) was dried by percolation through two columns packed with neutral alumina under a positive pressure of argon. Reaction solvent toluene (Fisher, ACS grade) was dried by percolation through a column packed with neutral alumina and a column packed with Q5 reactant, a supported copper catalyst for scavenging oxygen, under a positive pressure of argon. Reaction solvent dioxane (Macron, ACS grade) was distilled over sodium and further dried over 4 Å molecular sieves. Reaction solvent methanol (Optima, HPLC grade) was distilled over magnesium and further dried over 3 Å molecular sieves. Reaction solvent ethanol (Decon, 200 proof) was distilled over magnesium and further dried over 4 Å molecular sieves. Reaction solvents N,N dimethylformamide (Fisher, ACS grade), and dimethyl sulfoxide (Fisher, ACS grade) were dried by percolation through two columns packed with Linde type 4 Å molecular sieves under a positive pressure of argon and further dried over 4 Å molecular sieves. Reaction solvents 2-ethoxyethanol (Aldrich, ACS grade), Butyronitrile (Aldrich, >99%), and 2-propanol (Fisher, ACS grade) were dried over 4 Å molecular sieves. Solvents for filtration and chromatography were certified ACS grade.

\textsuperscript{1}H and \textsuperscript{13}C NMR spectra were recorded on Varian Unity 500, Varian VXR 500, Varian Unity Inova 500 NB, or Bruker Avance III HD 500 spectrometers (500 MHz, \textsuperscript{1}H; 126 MHz, \textsuperscript{13}C). Spectra are referenced to residual chloroform (\(\delta\) 7.26 ppm, \textsuperscript{1}H; \(\delta\) 77.0 ppm, \textsuperscript{13}C), CFCl\textsubscript{3} (10% in CDCl\textsubscript{3}) as an external reference for \textsuperscript{19}F NMR (\(\delta\) 0.00 ppm \textsuperscript{19}F). Chemical shifts are reported in ppm, multiplicities are indicated by s (singlet), d (doublet), t (triplet), q (quartet), p (pentet), h (hextet), sept (septet), m (multiplet) and br (broad). Coupling constants, \(J\), are reported in Hertz. All assignments are corroborated by \textsuperscript{13}C APT and/or 2D experiments (COSY, HSQC).

Elemental analyses were performed by the University of Illinois Microanalytical Service Laboratory, or by Robertson Microlit Laboratories. Mass Spectrometry was performed by the University of Illinois Mass Spectrometer Center. Electron Impact (EI) spectra were recorded on a Waters 70-VSE spectrometer. Electrospray Ionization (ESI) spectra were recorded on Waters Q-TOF Ultima or Waters Synapt G2-Si spectrometers. Data are reported in the form of \(m/z\). Infrared spectra (IR) were recorded on a Perkin Elmer Spectrum Two ATR spectrometer using neat sample. Peaks are reported in cm\textsuperscript{-1} with indicated relative intensities: s (strong, 67-100%); m (medium, 34-66%), w (weak, 0-33%). Kugelrohr distillations were performed on a Büchi GKR-
50 Kugelrohr and boiling points correspond to uncorrected air bath temperatures (ABT). Melting points were obtained in a vacuum-sealed capillary tube using a Thomas Hoover melting point apparatus and are corrected. Analytical thin-layer chromatography was performed on Merck silica gel plates with QF-254 indicator. Visualization was accomplished with UV (254). Column chromatography was performed using 230-400 mesh silica gel purchased from Silicycle.

Analytical gas chromatography (GC) was performed using a Hewlett Packard 5890 Series II Gas Chromatograph fitted with a flame ionization detector (H2 carrier gas, 1 mL/min) Injections were made on a Hewlett-Packard HP-1 (30 meter) capillary column. The injector temperature was 250 °C, the detector temperature was 300 °C, with a split ratio of 100:1. Retention times (tR) and integrated ratios were obtained using Agilent Chemstation Software.

Hydrocinnamaldehyde (Alfa), pyridine (Fisher), triethylamine (Fisher), N,N,N’N’-Tetramethylethene-1,2-diamine (Sigma), benzaldehyde (Aldrich), furfural (Alfa), 4-(trifluoromethyl)benzaldehyde (Oakwood), isobutyraldehyde (Aldrich), isovaleraldehyde (Aldrich) were distilled prior to use. RhCl3 hydrate, [RhCODCl]2 hydrate, RuCl3 hydrate were purchased from Pressure and used as received. H2PtCl6 hydrate was purchased from Aldrich and used as received. Aluminum oxide, gamma pahse, 20 nm powder was purchased from Alfa Aesar. Titanium oxide P 25 was purchased from Acros and used as received. All metal-carbonyl complexes were purchased from Strem, stored and handled in a drybox, and used as received. D2O (99.7%) was purchased from Sigma. All other reagents and solvents were purchased from Aldrich, Fisher, Oakwood, or Strem and used as received.

8.2. Experimental section for chapter 2

Literature Preparations

The following compounds were prepared according to published procedures: 9aa, 9af, 7h, 7v, 7w.
General Procedure I: Catalyst Screening and Conditions Optimization: Reaction of Ethyl Cyanoacetate with Benzaldehyde (Tables 2.1 and 2.2, Figures 2.3 and 2.4)

The catalyst was added to a 4-mL glass vial, followed by solvent, ethyl cyanoacetate 6a, benzaldehyde 7a, deionized water, triethylamine, and mesitylene as internal standard. A stir bar was added, and the vial was placed in an autoclave. The autoclave was pressurized with CO and vented three times, and then pressurized to the specified pressure. The mixture was stirred at room temperature for the indicated time. After venting and purging the autoclave with nitrogen, the vial was removed. An aliquot was taken and diluted in EtOAc before being passed through a short silica column and injected into a HP-1 GC column (25 m, 0.2 mm ID, 0.33 μm thickness).

The column oven temperature program was as follows: 100 °C for 3 minutes, 100 °C to 260 °C at 20 °C /min, then 260 °C for 1 minute.

GC response factors were established by the following equation using mesitylene as the internal standard:

\[ \text{Response Factor} = \frac{(\text{mmols of compound})}{(\text{area of compound})} \times \frac{(\text{area of mesitylene})}{(\text{mmol of mesitylene})} \]

Three samples containing a known amount of the desired compound and mesitylene were prepared and dissolved in EtOAc. A small portion of each sample was diluted further to 1 mL. An aliquot of each sample was injected into GC in triplicates. The average of 9 response factors was used to monitor reductive alkylation reactions.

<table>
<thead>
<tr>
<th>Table 8.1. GC calibration factors.</th>
</tr>
</thead>
<tbody>
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<td>compound</td>
</tr>
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<td>6a</td>
</tr>
<tr>
<td>7a</td>
</tr>
<tr>
<td>8aa</td>
</tr>
<tr>
<td>9aa</td>
</tr>
<tr>
<td>10aa</td>
</tr>
<tr>
<td>mesitylene</td>
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</tbody>
</table>
General Procedure II: Water and Base Optimization: Reduction of 9aa (Tables 2.3, 2.4, 2.10, 2.11, Figure 2.5, Scheme 2.7)

RhCl₃•3H₂O (2.1 mg) was added to a 4-mL glass vial, followed by acetonitrile (0.8 mL), ethyl-2-cyano-3-phenylacrylate 9aa, deionized water, base, and mesitylene as internal standard. A stir bar was added, and the vial was placed in an autoclave. The autoclave was pressurized with CO and vented three times, and then pressurized to 10 bar. The reaction was stirred at room temperature for the indicated time. After venting and purging the autoclave with nitrogen, the vial was removed. An aliquot was taken and diluted in EtOAc before being passed on a short silica column and injected to a GC. The analysis and calibration factors used are described above.

General Procedure III: Rh/TiO₂ Synthesis and Recycle (Table 2.1, entry 2.10)

One gram TiO₂ (P25, Acros) was washed with 300 mL deionized water (18.2 MΩ·cm) and dried at 100 °C in static air. Rhodium chloride solution was prepared by dissolving 51 mg of RhCl₃•3H₂O in 50 mL deionized water and the pH of the solution was adjusted to 11 by adding sat. aq. NH₄OH solution. The dried TiO₂ was dispersed in the solution and stirred for 24 h at room temperature. The slurry was centrifuged and the recovered solid was washed with deionized water three times and then dried under vacuum at 60 °C overnight. The dried catalyst was reduced under flowing hydrogen at 100 °C for 30 min and cooled down to room temperature before exposure to air.

The Rh/TiO₂ catalyst used for reductive alkylation was recovered from the reaction mixture by centrifugation (10000 rpm) and was washed with acetonitrile (1 mL) before being resued for the next reaction cycle. The yield of 8aa was 98% for the first reaction cycle versus 6% for the second.
Figure 8.2. Recycle-ability of Rh supported nanoparticles catalyst.

General Procedure IV: Reaction of Ethyl Cyanoacetate with Aldehydes (Table 2.5)

RhCl₃•3H₂O was added to a 40-mL glass vial, followed by acetonitrile, ethyl cyanoacetate 6a, the aldehyde 7, deionized water, and triethylamine. A stir bar was added, and the vial was placed in an autoclave. The autoclave was pressurized with CO and vented three times, and then pressurized to 10 bar. The reaction was stirred at room temperature for the indicated time. After venting and purging the autoclave with nitrogen, the vial was removed. The volatiles were removed by rotary evaporation (25-30 °C, 15 mmHg), then the residue was dissolved in CH₂Cl₂, and was loaded on silica gel (1 g). The crude mixture was purified by silica gel column chromatography (2.5 x 20-25 cm), followed by distillation or recrystallization.
Ethyl 2-Cyano-3-phenylpropanoate (8aa)

Following General Procedure IV, RhCl₃·3H₂O (10.5 mg, 0.04 mmol, 2 mol %), CH₃CN (4.0 mL), ethyl cyanoacetate (0.213 mL, 2.0 mmol), benzaldehyde (0.214 mL, 2.1 mmol, 1.05 equiv), H₂O (0.108 mL, 6.0 mmol, 3.0 equiv), and Et₃N (0.70 mL, 5.0 mmol, 2.5 equiv) were sequentially added to a 40-mL vial which was then placed in an autoclave and pressurized. The reaction was stirred at room temperature for 24 h followed by standard workup. Purification by silica gel column chromatography (pentane/Et₂O 80:20), followed by Kugelrohr distillation, afforded 8aa (363 mg, 89%) as a colorless oil. The spectral data matched those previously reported in the literature.⁶

Data for 8aa:

bp: 192 °C (ABT, 0.5 mmHg)

¹H NMR: (500 MHz, CDCl₃)

δ 7.38 – 7.26 (m, 5 H, C(aryl)H), 4.24 (q, J = 7.1 Hz, 2 H, C(4)H₂), 3.72 (dd, J = 8.4, 5.8 Hz, 1 H, C(2)H), 3.28 (dd, J = 13.8, 5.8 Hz, 1 H, C(6)H), 3.20 (dd, J = 13.8, 8.4 Hz, 1 H, C(6)H’), 1.27 (t, J = 7.1 Hz, 3 H, C(5)H₃)

¹³C NMR: (126 MHz, CDCl₃)

δ 165.5 C(3), 135.4 C(7), 129.0, 128.8, 127.7 C(10), 116.0 C(1), 62.8 C(4), 39.6 C(2), 35.9 C(6), 13.9 C(5)

HRMS: (EI)

m/z: [M]⁺ Calcd for C₁₂H₁₃NO₂: 203.0946; Found: 203.0950

TLC: Rf 0.21 (pentane/Et₂O, 80:20) [silica gel, UV, iodine]

Ethyl 2-Cyano-3-(2-tolyl)propanoate (8ab)
Following General Procedure IV, RhCl\(_3\)·3H\(_2\)O (10.5 mg, 0.04 mmol, 2 mol %), CH\(_3\)CN (4.0 mL), ethyl cyanoacetate (0.213 mL, 2.0 mmol), o-tolualdehyde (0.243 mL, 2.1 mmol, 1.05 equiv), H\(_2\)O (0.108 mL, 6.0 mmol, 3.0 equiv), and Et\(_3\)N (0.70 mL, 5.0 mmol, 2.5 equiv) were sequentially added to a 40-mL which was then placed in an autoclave and pressurized. The reaction was stirred at room temperature for 24 h followed by standard workup. Purification by silica gel column chromatography (pentane/Et\(_2\)O, 85:15), followed by Kugelrohr distillation, afforded 8ab (383 mg, 88%) as a colorless oil.

Data for 8ab:

- **bp:** 209 °C (ABT, 0.5 mmHg)
- **\(^1\)H NMR:** (500 MHz, CDCl\(_3\))
  \[\delta 7.24 - 7.16 (m, 4 H, C(aryl)H), 4.31 - 4.22 (m, 2 H, C(4)H\(_2\)), 3.67 (dd, \(J = 9.4, 6.0 \) Hz, 1 H, C(2)H), 3.34 (dd, \(J = 14.1, 6.0 \) Hz, 1 H, C(6)H), 3.19 (dd, \(J = 14.1, 9.4 \) Hz, 1 H, C(6)H\(^\prime\)), 2.37 (s, 3 H, C(13)H\(_3\)), 1.29 (t, \(J = 7.2 \) Hz, 3 H, C(5)H\(_3\))
- **\(^{13}\)C NMR:** (126 MHz, CDCl\(_3\))
  \[\delta 165.7 \text{ C(3)}, 136.2 \text{ C(7)}, 133.6 \text{ C(8)}, 130.8, 129.6, 127.8, 126.4, 116.2 \text{ C(1)}, 62.9 \text{ C(4)}, 38.4 \text{ C(2)}, 33.1 \text{ C(6)}, 19.2 \text{ C(13)}, 13.9 \text{ C(5)}
- **IR:** (neat)
  \[2983 \text{ (w)}, 2250 \text{ (w)}, 1741 \text{ (s)}, 1455 \text{ (w)}, 1370 \text{ (w)}, 1259 \text{ (m)}, 1200 \text{ (m)}, 1160 \text{ (m)}, 1027 \text{ (m)}, 860 \text{ (w)}, 753 \text{ (s)}
- **HRMS:** (EI)
  \[m/z: [M]^+ \text{ Calcd for C}_{13}\text{H}_{15}\text{NO}_2: 217.1103; \text{ Found: 217.1103}
- **TLC:** \(R_f\) 0.30 (pentane/Et\(_2\)O, 80:20) [silica gel, UV, iodine]

**Analysis:**

- Calcd: C, 71.87; H, 6.96; N, 6.45
- Found: C, 71.95; H, 6.95; N, 6.57
Ethyl 2-Cyano-3-(2-fluorophenyl)propanoate (8ac)

Following General Procedure IV, RhCl₃·3H₂O (10.5 mg, 0.04 mmol, 2 mol %), CH₃CN (4.0 mL), ethyl cyanoacetate (0.213 mL, 2.0 mmol), 2-fluorobenzaldehyde (0.221 mL, 2.1 mmol, 1.05 equiv), H₂O (0.108 mL, 6.0 mmol, 3.0 equiv), and Et₃N (0.70 mL, 5.0 mmol, 2.5 equiv) were sequentially added to a 40-mL vial which was then placed in an autoclave and pressurized. The reaction was stirred at room temperature for 24 h followed by standard workup. Purification by silica gel column chromatography (pentane/Et₂O, 85:15), followed by Kugelrohr distillation, afforded 8ac (407 mg, 92%) as a colorless oil. The spectral data matched those previously reported in the literature.⁷

Data for 8ac:

bp: 188 °C (ABT, 0.5 mmHg)

¹H NMR: (500 MHz, CDCl₃)
δ 7.34 – 7.27 (m, 2 H, C(10)H, C(12)H), 7.13 (td, J = 7.5, 1.1 Hz, 1 H, C(11)H), 7.10 – 7.04 (m, 1 H, C(9)H), 4.28 – 4.21 (m, 2 H, C(4)H₂), 3.81 (dd, J = 8.8, 6.4 Hz, 1 H, C(2)H), 3.38 (dd, J = 14.0, 6.4 Hz, 1 H, C(6)H), 3.19 (dd, J = 13.9, 8.8 Hz, 1 H, C(6)H’), 1.28 (t, J = 7.2 Hz, 3 H, C(5)H₃)

¹³C NMR: (126 MHz, CDCl₃)
δ 165.2 C(3), 161.0 (d, J = 246.4 Hz, C(8)), 131.4 (d, J = 3.9 Hz, C(12)), 129.7 (d, J = 8.2 Hz, C(10)), 124.4 (d, J = 3.6 Hz, C(11)), 122.3 (d, J = 15.2 Hz, C(7)), 115.8 C(1), 115.5 (d, J = 21.6 Hz, C(9)), 62.9 C(4), 37.9 (d, J = 1.6 Hz, C(2)), 29.5 (d, J = 2.4 Hz, C(6)), 13.81 C(5)

¹⁹F NMR: (470 MHz, CDCl₃)
δ -118.2

HRMS: (EI)
m/z [M]⁺ Calcd for C₁₂H₁₂FNO₂: 221.0852; Found: 221.0851

TLC: Rf 0.29 (pentane/Et₂O, 80:20) [silica gel, UV, iodine]
Ethyl 2-Cyano-3-(3-vinylphenyl)propanoate (8ad)

Following General Procedure IV, RhCl$_3$·3H$_2$O (10.5 mg, 0.04 mmol, 2 mol %), CH$_3$CN (4.0 mL), ethyl cyanoacetate (0.213 mL, 2.0 mmol), 3-vinylbenzaldehyde (0.267 mL, 2.1 mmol, 1.05 equiv), H$_2$O (0.108 mL, 6.0 mmol, 3.0 equiv), and Et$_3$N (0.70 mL, 5.0 mmol, 2.5 equiv) were sequentially added to a 40-mL vial which was then placed in an autoclave and pressurized. The reaction was stirred at room temperature for 24 h followed by standard workup. Purification by silica gel column chromatography (pentane/Et$_2$O, 80:20) afforded 8ad (423 mg, 92%) as a pale yellow oil. 8ad underwent polymerization over the course of a few hours at room temperature.

**Data for 8ad:**

$^1$H NMR: (500 MHz, CDCl$_3$)
\[\delta 7.38 - 7.28 \text{ (m, 3 H, C}(8)\text{H, C}(10)\text{H, C}(11)\text{H)}, 7.17 \text{ (d, } J = 7.3 \text{ Hz, 1 H, C}(12)\text{H}), 6.70 \text{ (dd, } J = 17.6, 10.9 \text{ Hz, 1 H, C}(13)\text{H}), 5.76 \text{ (d, } J = 17.6 \text{ Hz, 1 H, C}(14)\text{H}_{\text{trans}}), 5.27 \text{ (d, } J = 10.9 \text{ Hz, 1 H, C}(14)\text{H}_{\text{cis}}), 4.24 \text{ (q, } J = 7.1 \text{ Hz, 2 H, C}(4)\text{H}_2), 3.73 \text{ (dd, } J = 8.4, 5.9 \text{ Hz, 1 H, C}(2)\text{H}), 3.27 \text{ (dd, } J = 13.8, 5.8 \text{ Hz, 1 H, C}(6)\text{H}), 3.19 \text{ (dd, } J = 13.8, 8.4 \text{ Hz, 1 H, C}(6)\text{H}'), 1.26 \text{ (t, } J = 7.1 \text{ Hz, 3 H, C}(5)\text{H}_3)\]

$^{13}$C NMR: (126 MHz, CDCl$_3$)
\[\delta 165.5 \text{ C}(3), 138.1 \text{ C}(9), 136.3 \text{ C}(13), 135.5 \text{ C}(7), 129.0 \text{ C}(11), 128.4 \text{ C}(12), 126.8 \text{ C}(8), 125.6 \text{ C}(10), 116.1 \text{ C}(1), 114.5 \text{ C}(14), 62.9 \text{ C}(4), 39.6 \text{ C}(2), 35.6 \text{ C}(6), 13.9 \text{ C}(5)\]

HRMS: (EI)
\[m/z: [M]^+ \text{ Calcd for C}_{14}\text{H}_{15}\text{NO}_2: 229.1103; \text{ Found: 229.1113}\]

TLC: \(R_f 0.31\) (pentane/Et$_2$O, 80:20) [silica gel, UV, iodine]
Ethyl 2-Cyano-3-(4-(methylthio)phenyl)propanoate (8ae)

Following General Procedure IV, RhCl$_3$·3H$_2$O (10.5 mg, 0.04 mmol, 2 mol %), CH$_3$CN (4.0 mL), ethyl cyanoacetate (0.213 mL, 2.0 mmol), 4-(methylthio)benzaldehyde (0.279 mL, 2.1 mmol, 1.05 equiv), H$_2$O (0.108 mL, 6.0 mmol, 3.0 equiv), and Et$_3$N (0.70 mL, 5.0 mmol, 2.5 equiv) were sequentially added to a 40-mL vial. which was then placed in an autoclave and pressurized. The reaction was stirred at room temperature for 24 h followed by standard workup. Purification by silica gel column chromatography (pentane/Et$_2$O, 80:20), followed by Kugelrohr distillation, afforded 8ae (365 mg, 73%) as a yellow oil.

Data for 8ae:

bp: 244 °C (ABT, 0.5 mmHg)

$^1$H NMR: (500 MHz, CDCl$_3$)

δ 7.22 (d, J = 8.6 Hz, 2 H, C(9)H), 7.19 (d, J = 8.5 Hz, 2 H, C(8)H), 4.24 (q, J = 7.1 Hz, 2 H, C(4)H)$_2$, 3.69 (dd, J = 8.3, 5.8 Hz, 1 H, C(2)H), 3.23 (dd, J = 13.9, 5.8 Hz, 1 H, C(6)H), 3.15 (dd, J = 13.9, 8.3 Hz, 1 H, C(6)H’), 2.47 (s, 3 H, C(11)H$_3$), 1.28 (t, J = 7.1 Hz, 3 H, C(5)H$_3$)

$^{13}$C NMR: (126 MHz, CDCl$_3$)

δ 165.4 C(3), 138.1 C(10), 131.9 C(7), 129.4 C(8), 126.8 C(9), 116.0 C(1), 62.9 C(4), 39.6 C(2), 35.1 C(6), 15.6 C(11), 13.9 C(5)

IR: (neat)

2983 (w), 2923 (w), 2250 (w), 1739 (s), 1601 (w), 1495 (m), 1441 (w), 1369 (w), 1257 (m), 1193 (m), 1094 (m), 1025 (m), 856 (w), 830 (w), 804 (m)

HRMS: (EI)

m/z: [M]$^+$ Calcd for C$_{13}$H$_{15}$NO$_2$S: 249.0823; Found: 249.0826

TLC: $R_f$ 0.16 (pentane/Et$_2$O, 80:20) [silica gel, UV, iodine]

Analysis: C$_{13}$H$_{15}$NO$_2$S

Calcd: C, 62.63; H, 6.06; N, 5.62

Found: C, 62.53; H, 5.99; N, 5.58
Ethyl 2-Cyano-3-(4-methoxyphenyl)propanoate (8af)

Following General Procedure IV, RhCl$_3$·3H$_2$O (10.5 mg, 0.04 mmol, 2 mol %), CH$_3$CN (4.0 mL), ethyl cyanoacetate (0.213 mL, 2.0 mmol), p-anisaldehyde (0.256 mL, 2.1 mmol, 1.05 equiv), H$_2$O (0.072 mL, 4.0 mmol, 2.0 equiv), and Et$_3$N (0.70 mL, 5.0 mmol, 2.5 equiv) were sequentially added to a 40-mL vial which was then placed in an autoclave and pressurized. The reaction was stirred at room temperature for 18 h followed by standard workup. Purification by silica gel column chromatography (pentane/Et$_2$O, 70:30), followed by Kugelrohr distillation, afforded 8af (433 mg, 93%) as a colorless oil. The spectral data matched those previously reported in the literature.$^7$

Data for 8af:
- bp: 210 °C (ABT, 0.5 mmHg)
- $^1$H NMR: (500 MHz, CDCl$_3$)
  \[ \delta 7.19 \text{ (d, } J = 8.6 \text{ Hz, } 2 \text{ H, C(8)H), 6.87 \text{ (d, } J = 8.6 \text{ Hz, } 2 \text{ H, C(9)H), 4.24 \text{ (q, } J = 7.1 \text{ Hz, } 2 \text{ H, C(4)H2), 3.80 \text{ (s, } 3 \text{ H, C(11)H3), 3.68 \text{ (dd, } J = 8.3, 5.8 \text{ Hz, } 1 \text{ H, C(2)H), 3.22 \text{ (dd, } J = 13.9, 5.8 \text{ Hz, } 1 \text{ H, C(6)H), 3.15 \text{ (dd, } J = 13.9, 8.3 \text{ Hz, } 1 \text{ H, C(6)H'), 1.28 \text{ (t, } J = 7.1 \text{ Hz, } 3 \text{ H, C(5)H3))} \]
- $^{13}$C NMR: (126 MHz, CDCl$_3$)
  \[ \delta 165.5 \text{ C(3), 159.1 C(10), 130.1 C(8), 127.2 C(7), 116.2 C(1), 114.2 C(9), 62.8 C(4), 55.2 C(11), 39.9 C(2), 35.0 C(6), 13.9 C(5)} \]
- HRMS: (EI)
  \[ m/z: [M]^+ \text{ Calcd for C}_{13}H_{15}NO_3: 233.1052; \text{ Found: } 233.1056 \]
- TLC: \[ R_f \text{ 0.15 (pentane/Et}_2\text{O, 80:20) [silica gel, UV, iodine]} \]
Ethyl 2-Cyano-3-(2,4,6-trimethoxyphenyl)propanoate (8ag)

Following General Procedure IV, RhCl$_3$·3H$_2$O (10.5 mg, 0.04 mmol, 2 mol %), CH$_3$CN (4.0 mL), ethyl cyanoacetate (0.213 mL, 2.0 mmol), 2,4,6-trimethoxybenzaldehyde (412 mg, 2.1 mmol, 1.05 equiv), H$_2$O (0.072 mL, 4.0 mmol, 2.0 equiv), and Et$_3$N (0.70 mL, 5.0 mmol, 2.5 equiv) were sequentially added to a 40-mL vial which was then placed in an autoclave and pressurized. The reaction was stirred at room temperature for 18 h followed by standard workup. Purification by silica gel column chromatography (pentane/Et$_2$O, 1:1), followed by recrystallization (hexane/acetone 90:10), afforded 8ag (535 mg, 91%) as a white, crystalline solid.

Data for 8ag:

<table>
<thead>
<tr>
<th>Property</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>mp</td>
<td>81-82 °C (hexane/acetone, 90:10)</td>
</tr>
<tr>
<td>$^1$H NMR</td>
<td>δ 6.12 (s, 2 H, C(9)H), 4.23 (q, J = 7.1 Hz, 2 H, C(4)H$_2$), 3.89 – 3.75 (m, 10H, C(2)H, C(11)H$_3$, C(12)H$_3$), 3.29 (dd, J = 13.3, 9.2 Hz, 1 H, C(6)H), 3.19 (dd, J = 13.4, 6.8 Hz, 1 H, C(6)H$'$), 1.30 (t, J = 7.1 Hz, 3 H, C(5)H$_3$)</td>
</tr>
<tr>
<td>$^{13}$C NMR</td>
<td>δ 166.4 C(3), 160.7 C(10), 159.1 C(8), 116.8 C(1), 104.2 C(7), 90.4 C(9), 62.4 C(4), 55.6 C(11), 55.3 C(12), 37.1 C(2), 23.6 C(6), 13.9 C(5)</td>
</tr>
<tr>
<td>IR</td>
<td>3004 (w), 2948 (w), 2836 (w), 2252 (w), 1732 (s), 1597 (s), 1501 (m), 1469 (m), 1459 (m), 1420 (m), 1370 (w), 1343 (w), 1272 (m), 1194 (s), 1147 (s), 1120 (s), 1056 (m), 1038 (m), 995 (w), 946 (m), 820 (s), 809 (s)</td>
</tr>
<tr>
<td>HRMS</td>
<td>(EI) m/z: [M]$^+$ Calcd for C$<em>{15}$H$</em>{19}$NO$_5$: 293.1263; Found: 293.1269</td>
</tr>
<tr>
<td>TLC</td>
<td>$R_f$ 0.08 (pentane/Et$_2$O, 80:20) [silica gel, UV, iodine]</td>
</tr>
<tr>
<td>Analysis</td>
<td>C$<em>{15}$H$</em>{19}$NO$_5$</td>
</tr>
<tr>
<td></td>
<td>Calcd: C, 61.42; H, 6.53; N, 4.78</td>
</tr>
</tbody>
</table>
Found:  C, 61.30;  H, 6.58;  N, 4.79

Ethyl 3-(4-(Allyloxy)phenyl)-2-cyanopropanoate (8ah)

Following General Procedure IV, RhCl₃·3H₂O (10.5 mg, 0.04 mmol, 2 mol %), CH₃CN (4.0 mL), ethyl cyanoacetate (0.213 mL, 2.0 mmol), 4-allyloxybenzaldehyde (0.322 mL, 2.1 mmol, 1.05 equiv), H₂O (0.072 mL, 4.0 mmol, 2.0 equiv), and Et₃N (0.70 mL, 5.0 mmol, 2.5 equiv) were sequentially added to a 40-mL vial which was then placed in an autoclave and pressurized. The reaction was stirred at room temperature for 18 h followed by standard workup. Purification by silica gel column chromatography (pentane/Et₂O, 80:20) afforded 8ah (450 mg, 87%) as a colorless oil.

Data for 8ah:

**¹H NMR:** (500 MHz, CDCl₃)
\[ \delta 7.18 \text{ (d, } J = 8.5 \text{ Hz, } 2 \text{ H, C(8)H)} , 6.88 \text{ (d, } J = 8.6 \text{ Hz, } 2 \text{ H, C(9)H)} , 6.05 \text{ (ddt, } J = 16.9, 10.3, 5.2 \text{ Hz, } 1 \text{ H, C(12)H)} , 5.41 \text{ (ddd, } J = 17.3, 2.9, 1.4 \text{ Hz, } 1 \text{ H, C(13)H}_\text{trans}) , 5.29 \text{ (ddd, } J = 10.5, 2.3, 1.2 \text{ Hz, } 1 \text{ H, C(13)H}_\text{cis}) , 4.52 \text{ (dt, } J = 5.3, 1.3 \text{ Hz, } 2 \text{ H, C(11)H}_2) , 4.23 \text{ (q, } J = 7.1 \text{ Hz, } 2 \text{ H, C(4)H}_2) , 3.67 \text{ (dd, } J = 8.2, 5.8 \text{ Hz, } 1 \text{ H, C(2)H}) , 3.21 \text{ (dd, } J = 13.9, 5.8 \text{ Hz, } 1 \text{ H, C(6)H}) , 3.14 \text{ (dd, } J = 13.9, 8.3 \text{ Hz, } 1 \text{ H, C(6)H'}) , 1.27 \text{ (t, } J = 7.2 \text{ Hz, } 3 \text{ H, C(5)H}_3) \]

**¹³C NMR:** (126 MHz, CDCl₃)
\[ \delta 165.5 \text{ C(3)} , 158.1 \text{ C(10)} , 133.1 \text{ C(12)} , 130.1 \text{ C(8)} , 127.4 \text{ C(7)} , 117.6 \text{ C(13)} , 116.2 \text{ C(1)} , 114.9 \text{ C(9)} , 68.7 \text{ C(11)} , 62.8 \text{ C(4)} , 39.9 \text{ C(2)} , 34.9 \text{ C(6)} , 13.9 \text{ C(5)} \]

**IR:** (neat)
2984 (w), 2924 (w), 2868 (w), 2254 (w), 1888 (w), 1725 (s), 1612 (w), 1511 (s), 1443 (w), 1430 (w), 1371 (m), 1345 (w), 1298 (m), 1247 (s), 1216 (s), 1180 (s), 1111 (m), 1022 (s), 997 (m), 943 (s), 744 (m), 646 (m)

**HRMS:** (EI)
\[ m/z: [M]^{+} \text{ Calcd for C}_{15}H_{17}NO_{3}: 259.1208; \text{ Found: } 259.1197 \]
TLC: \( R_f 0.19 \) (pentane/Et\(_2\)O, 80:20) [silica gel, UV, iodine]

Analysis: \( \text{C}_{15}\text{H}_{17}\text{NO}_3 \)
Calcd: C, 69.48; H, 6.61; N, 5.40
Found: C, 69.36; H, 6.49; N, 5.55

Ethyl 2-Cyano-3-(4-(dimethylamino)phenyl)propanoate (8ai)

Following General Procedure IV, RhCl\(_3\)·3H\(_2\)O (10.5 mg, 0.04 mmol, 2 mol %), CH\(_3\)CN (4.0 mL), ethyl cyanoacetate (0.213 mL, 2.0 mmol), 4-dimethylaminobenzaldehyde (313 mg, 2.1 mmol, 1.05 equiv), H\(_2\)O (0.072 mL, 4.0 mmol, 2.0 equiv), and Et\(_3\)N (0.70 mL, 5.0 mmol, 2.5 equiv) were sequentially added to a 40-mL vial which was then placed in an autoclave and pressurized. The reaction was stirred at room temperature for 18 h followed by standard workup. Purification by silica gel column chromatography (pentane/Et\(_2\)O, 70:30), followed by Kugelrohr distillation, afforded 8ai (445 mg, 90%) as a yellow oil.

Data for 8ai:

bp: 220 °C (ABT, 0.5 mmHg)

\(^1\text{H NMR:}\) (500 MHz, CDCl\(_3\))
\[ \delta 7.13 \text{ (d, } J = 8.7 \text{ Hz, } 2 \text{ H, C(8)H)} , 6.69 \text{ (d, } J = 8.7 \text{ Hz, } 2 \text{ H, C(9)H)} , 4.23 \text{ (q, } J = 7.1 \text{ Hz, } 2 \text{ H, C(4)H)}_2 , 3.65 \text{ (dd, } J = 8.3 \text{, } 5.8 \text{ Hz, } 1 \text{ H, C(2)H)} , 3.18 \text{ (dd, } J = 13.9 \text{, } 5.8 \text{ Hz, } 1 \text{ H, C(6)H)} , 3.11 \text{ (dd, } J = 13.9 \text{, } 8.3 \text{ Hz, } 1 \text{ H, C(6)H'}) , 2.94 \text{ (s, } 6 \text{ H, C(11)H)}_3 , 1.28 \text{ (t, } J = 7.1 \text{ Hz, } 3 \text{ H, C(5)H)}_3 \]

\(^{13}\text{C NMR:}\) (126 MHz, CDCl\(_3\))
\[ \delta 165.7 \text{ C(3), } 150.0 \text{ C(10), } 129.7 \text{ C(8), } 122.7 \text{ C(7), } 116.4 \text{ C(1), } 112.6 \text{ C(9), } 62.7 \text{ C(4), } 40.5 \text{ C(11), } 40.1 \text{ C(2), } 35.1 \text{ C(6), } 13.9 \text{ C(5)} \]

IR: (neat)
2983 (w), 2936 (w), 2804 (w), 2249 (w), 1739 (s), 1614 (s), 1522 (s), 1477 (w), 1444 (m), 1342 (m), 1257 (m), 1193 (s), 1162 (s), 1026 (m), 946 (m), 856 (w), 804 (m)
**HRMS:**  (EI)

\[ m/z \, [M]^+ \text{ Calcd for } C_{14}H_{18}N_2O_2: \ 246.1368; \text{ Found: } 246.1365 \]

**TLC:**  \( R_f 0.13 \) (pentane/Et\(_2\)O, 80:20) [silica gel, UV, iodine]

**Analysis:**  
\[
C_{14}H_{18}N_2O_2
\]
Calcd:  C, 68.27;  H, 7.37;  N, 11.37  
Found:  C, 68.11;  H, 7.07;  N, 11.47

Ethyl 2-Cyano-3-(furan-2-yl)propanoate (8aj)

Following General Procedure IV, RhCl\(_3\)·3H\(_2\)O (10.5 mg, 0.04 mmol, 2 mol %), CH\(_3\)CN (4.0 mL), ethyl cyanoacetate (0.213 mL, 2.0 mmol), furfural (0.174 mL, 2.1 mmol, 1.05 equiv), H\(_2\)O (0.072 mL, 4.0 mmol, 2.0 equiv), and Et\(_3\)N (0.70 mL, 5.0 mmol, 2.5 equiv) were sequentially added to a 40-mL vial which was then placed in an autoclave and pressurized. The reaction was stirred at room temperature for 18 h followed by standard workup. Purification by silica gel column chromatography (pentane/Et\(_2\)O, 80:20), followed by Kugelrohr distillation, afforded 8aj (313 mg, 81%) as a pale yellow oil. The spectral data matched those previously reported in the literature.

**Data for 8aj:**

- **bp:**  188 °C (ABT, 0.5 mmHg)
- **\(^1\)H NMR:**  (500 MHz, CDCl\(_3\))

\[
\begin{align*}
\delta & \ 7.37 \text{ – } 7.35 \text{ (m, 1 H, C(10)H)}, \ 6.33 \text{ (dd, } J = 3.0, 2.0 \text{ Hz, 1 H, C(9)H)}, \ 6.25 \text{ (d, } J = 3.2 \text{ Hz, 1 H, C(8)H}), \ 4.27 \text{ (q, } J = 7.1 \text{ Hz, 2 H, C(4)H}_2), \ 3.82 \text{ (dd, } J = 7.9, 6.1 \text{ Hz, 1 H, C(2)H}), \ 3.33 \text{ (dd, } J = 15.1, 6.1 \text{ Hz, 1 H, C(6)H)}, \ 3.27 \text{ (dd, } J = 15.1, 8.0 \text{ Hz, 1 H, C(6)H'}), \ 1.31 \text{ (t, } J = 7.1 \text{ Hz, 3 H, C(5)H}_3)
\end{align*}
\]

- **\(^{13}\)C NMR:**  (126 MHz, CDCl\(_3\))

\[
\begin{align*}
\delta & \ 165.1 \text{ C(3)}, \ 148.8 \text{ C(7), 142.5 C(10), 115.8 C(1), 110.5 C(9), 108.3 C(8), 63.0 C(4), 37.0 C(2), 28.5 C(6), 13.9 C(5)
\end{align*}
\]

**HRMS:**  (EI)
Ethyl 2-Cyano-3-(thiophen-2-yl)propanoate (8ak)

Following General Procedure IV, RhCl₃·3H₂O (10.5 mg, 0.04 mmol, 2 mol %), CH₃CN (4.0 mL), ethyl cyanoacetate (0.213 mL, 2.0 mmol), 2-thiophenecarboxaldehyde (0.196 mL, 2.1 mmol, 1.05 equiv), H₂O (0.072 mL, 4.0 mmol, 2.0 equiv), and Et₃N (0.70 mL, 5.0 mmol, 2.5 equiv) were sequentially added to a 40-mL vial which was then placed in an autoclave and pressurized. The reaction was stirred at room temperature for 18 h followed by standard workup. Purification by silica gel column chromatography (pentane/Et₂O, 80:20), followed by Kugelrohr distillation, afforded 8ak (397 mg, 95%) as a pale yellow oil. The spectral data matched those previously reported in the literature.

Data for 8ak:

bp: 185 °C (ABT, 0.5 mmHg)

¹H NMR: (500 MHz, CDCl₃)

δ: 7.23 (dd, J = 5.1, 1.1 Hz, 1 H, C(10)H), 7.01 (d, J = 2.8 Hz, 1 H, C(8)H), 6.97 (dd, J = 5.0, 3.5 Hz, 1 H, C(9)H), 4.27 (q, J = 7.2 Hz, 2 H, C(4)H₂), 3.76 (dd, J = 7.5, 6.0 Hz, 1 H, C(2)H), 3.54 – 3.42 (m, 2 H, C(6)H₂), 1.30 (t, J = 7.1 Hz, 3 H, C(5)H₃)

¹³C NMR: (126 MHz, CDCl₃)

δ: 165.0 C(3), 136.6 C(7), 127.3 C(8), 127.2 C(9), 125.3 C(10), 115.9 C(1), 63.1 C(4), 39.9 C(2), 29.9 C(6), 13.9 C(5)

HRMS: (EI)

m/z: [M]+ Calcd for C₁₀H₁₁NO₃S: 209.0511; Found: 209.0512

TLC: Rf 0.23 (pentane/Et₂O, 80:20) [silica gel, UV, iodine]
Ethyl 2-Cyano-3-(pyridin-3-yl)propanoate (8al)

Following General Procedure IV, RhCl\(_3\)·3H\(_2\)O (10.5 mg, 0.04 mmol, 2 mol %), CH\(_3\)CN (4.0 mL), ethyl cyanoacetate (0.213 mL, 2.0 mmol), 3-pyridinecarboxaldehyde (0.197 mL, 2.1 mmol, 1.05 equiv), H\(_2\)O (0.072 mL, 4.0 mmol, 2.0 equiv), and Et\(_3\)N (0.70 mL, 5.0 mmol, 2.5 equiv) were sequentially added to a 40-mL vial which was then placed in an autoclave and pressurized. The reaction was stirred at room temperature for 18 h followed by standard workup. Purification by silica gel column chromatography (CH\(_2\)Cl\(_2\)/Et\(_2\)O, 80:20), followed by Kugelrohr distillation, afforded 8al (356 mg, 87%) as a pale yellow oil.

Data for 8al:

bp: 205 °C (ABT, 0.5 mmHg)

\(^1\)H NMR: (500 MHz, CDCl\(_3\))
\[\delta 8.55 (dd, J = 4.8, 1.6 Hz, 1 H, C(9)H), 8.52 (d, J = 2.1 Hz, 1 H, C(8)H), 7.65 (dt, J = 7.9, 1.9 Hz, 1 H, C(11)H), 7.28 (dd, J = 7.8, 4.8 Hz, 1 H, C(10)H), 4.24 (q, J = 7.1 Hz, 2 H, C(4)H\(_2\)), 3.75 (dd, J = 8.0, 5.9 Hz, 1 H, C(2)H), 3.27 (dd, J = 14.1, 5.9 Hz, 1 H, C(6)H), 3.21 (dd, J = 14.1, 8.0 Hz, 1 H, C(6)H\(^+\)), 1.26 (t, J = 7.2 Hz, 3 H, C(5)H\(_3\))\]

\(^{13}\)C NMR: (126 MHz, CDCl\(_3\))
\[\delta 164.9 \text{ C(3)}, 150.2 \text{ C(8), 149.2 C(9), 136.6 C(11), 130.8 C(7), 123.5 C(10), 115.6 C(1), 63.1 C(4), 39.0 C(2), 32.6 C(6), 13.8 C(5)}\]

IR: (neat)
2985 (w), 2940 (w), 2251 (w), 1738 (s), 1576 (w), 1480 (w), 1426 (m), 1370 (w), 1252 (m), 1205 (m), 1106 (w), 1028 (s), 857 (w), 796 (w), 713 (s)

HRMS: (El)
\[m/z: [\text{M}]^+ \text{ Calcd for C}_{11}\text{H}_{12}\text{N}_2\text{O}_2: 204.0899; \text{ Found: 204.0907}}\]

TLC: 
\[R_f 0.19 \text{ (CH}_2\text{Cl}_2/\text{Et}_2\text{O, 80:20}) \text{ [silica gel, UV, iodine]}\]
Calcd:  C, 64.69;  H, 5.92;  N, 13.72  
Found:  C, 64.96;  H, 6.13;  N, 13.49

Ethyl 3-(4-Bromophenyl)-2-cyanopropanoate (8am)  

Following General Procedure IV, RhCl₃·3H₂O (15.8 mg, 0.06 mmol, 3 mol %), CH₃CN (4.0 mL), ethyl cyanoacetate (0.213 mL, 2.0 mmol), 4-bromobenzaldehyde (389 mg, 2.1 mmol, 1.05 equiv), H₂O (0.180 mL, 10.0 mmol, 5.0 equiv), and Et₃N (0.70 mL, 5.0 mmol, 2.5 equiv) were sequentially added to a 40-mL vial which was then placed in an autoclave and pressurized. The reaction was stirred at room temperature for 36 h followed by standard workup. Purification by silica gel column chromatography (pentane/Et₂O, 75:25), followed by Kugelrohr distillation, afforded 8am (461 mg, 82%) as a white solid. The spectral data matched those previously reported in the literature.⁷

**Data for 8am:**

bp:  234 °C (ABT, 0.5 mmHg)  
mp:  39-40 °C  

**¹H NMR:**  
δ 7.47 (d, J = 8.4 Hz, 2 H, C(9)H), 7.16 (d, J = 8.4 Hz, 2 H, C(8)H), 4.24 (q, J = 7.1 Hz, 2 H, C(4)H₂), 3.70 (dd, J = 8.2, 5.8 Hz, 1 H, C(2)H), 3.23 (dd, J = 13.9, 5.8 Hz, 1 H, C(6)H), 3.16 (dd, J = 13.9, 8.2 Hz, 1 H, C(6)H’), 1.28 (t, J = 7.1 Hz, 3 H, C(5)H₃)

**¹³C NMR:**  
δ 165.2 C(3), 134.2 C(7), 132.0 C(9), 130.8 C(8), 121.9 C(10), 115.8 C(1), 63.1 C(4), 39.3 C(2), 35.0 C(6), 13.9 C(5)

**HRMS:**  
(EI)  
m/z: [M]+ Calcd for C₁₂H₁₂BrNO₂: 281.0051; Found: 281.0050

**TLC:**  
Rf 0.20 (pentane/Et₂O, 80:20) [silica gel, UV, iodine]
Ethyl 2-Cyano-3-(4-(trifluoromethyl)phenyl)propanoate (8an)

Following General Procedure IV, \( \text{RhCl}_3 \cdot 3\text{H}_2\text{O} \) (15.8 mg, 0.06 mmol, 3 mol %), \( \text{CH}_3\text{CN} \) (4.0 mL), ethyl cyanoacetate (0.213 mL, 2.0 mmol), 4-(trifluoromethyl)benzaldehyde (0.287 mL, 2.1 mmol, 1.05 equiv), \( \text{H}_2\text{O} \) (0.180 mL, 10.0 mmol, 5.0 equiv), and \( \text{Et}_3\text{N} \) (0.70 mL, 5.0 mmol, 2.5 equiv) were sequentially added to a 40-mL vial which was then placed in an autoclave and pressurized. The reaction was stirred at room temperature for 36 h followed by standard workup. Purification by silica gel column chromatography (pentane/Et\(_2\)O, 70:30), followed by Kugelrohr distillation and recrystallization (pentane), afforded 8an (294 mg, 54%) as a white, crystalline solid.

Data for 8an:

bp: 203 °C (ABT, 0.5 mmHg)
mp: 33-34 °C (pentane)

\(^1\text{H NMR:}\) (500 MHz, CDCl\(_3\))
\[ \delta 7.61 (d, J = 8.1 \text{ Hz}, 2 \text{ H}, \text{C(9)H}), 7.41 (d, J = 8.1 \text{ Hz}, 2 \text{ H}, \text{C(8)H}), 4.25 (q, J = 7.1 \text{ Hz}, 2 \text{ H}, \text{C(4)H}_2), 3.75 (dd, J = 8.3, 5.8 \text{ Hz}, 1 \text{ H}, \text{C(2)H}), 3.33 (dd, J = 13.9, 5.8 \text{ Hz}, 1 \text{ H}, \text{C(6)H}), 3.26 (dd, J = 13.9, 8.3 \text{ Hz}, 1 \text{ H}, \text{C(6)H'}), 1.28 (t, J = 7.2 \text{ Hz}, 3 \text{ H}, \text{C(5)H}_3) \]

\(^{13}\text{C NMR:}\) (126 MHz, CDCl\(_3\))
\[ \delta 165.1 \text{ C(3)}, 139.3 \text{ C(7)}, 130.2 (q, J = 32.6 \text{ Hz}, \text{C(10)}), 129.5 \text{ C(8)}, 125.8 (q, J = 3.7 \text{ Hz}, \text{C(9)}), 123.9 (q, J = 272.0 \text{ Hz}, \text{C(11)}), 115.7 \text{ C(1)}, 63.2 \text{ C(4)}, 39.1 \text{ C(2)}, 35.2 \text{ C(6)}, 13.9 \text{ C(5)} \]

\(^{19}\text{F NMR:}\) (470 MHz, CDCl\(_3\))
\[ \delta -63.07 \]

IR: (neat)
2988 (w), 2251 (w), 1742 (m), 1619 (w), 1447 (w), 1421 (w), 1322 (s) 1263 (m), 1161 (m), 1109 (s), 1066 (s), 1019 (m), 855 (w), 819 (w) 734 (w)

HRMS: (EI)
m/z: [M]+ Calcd for C₁₃H₁₂F₃NO₂: 271.0820; Found: 271.0821

**TLC:**  
R<sub>f</sub> 0.17 (pentane/Et₂O, 80:20) [silica gel, UV, iodine]

**Analysis:**  
C₁₃H₁₂F₃NO₂  
Calcd: C, 57.57; H, 4.46; N, 5.16  
Found: C, 57.70; H, 4.44; N, 5.40

Ethyl 2-Cyano-3-(naphthalen-2-yl)propanoate (8ao)

![Chemical Structure of 8ao]

Following General Procedure IV, RhCl₃·3H₂O (15.8 mg, 0.06 mmol, 3 mol %), CH₃CN (2.0 mL), ethyl cyanoacetate (0.213 mL, 2.0 mmol), 2-naphthaldehyde (328 mg, 2.1 mmol, 1.05 equiv), H₂O (0.180 mL, 10.0 mmol, 5.0 equiv), and Et₃N (0.70 mL, 5.0 mmol, 2.5 equiv) were sequentially added to a 40-mL vial which was then placed in an autoclave and pressurized. The reaction was stirred at room temperature for 36 h followed by standard workup. Purification by silica gel column chromatography (pentane/Et₂O, 70:30), followed by Kugelrohr distillation, afforded 8ao (349 mg, 69%) as a white solid.

**Data for 8ao:**

- **bp:** 251 °C (ABT, 0.5 mmHg)
- **mp:** 42-43 °C
- **¹H NMR:** (500 MHz, CDCl₃)  
  δ 7.86 – 7.79 (m, 3 H, C(9)H, C(11)H, C(14)H), 7.75 (s, 1 H, C(16)H), 7.53 – 7.46 (m, 2 H, C(12), C(13)), 7.39 (dd, J = 8.4, 1.8 Hz, 1 H, C(8)), 4.24 (qd, J = 7.1, 0.5 Hz, 2 H, C(4)H₂), 3.82 (dd, J = 8.4, 5.9 Hz, 1 H, C(2)H), 3.45 (dd, J = 13.9, 5.8 Hz, 1 H, C(6)H), 3.37 (dd, J = 13.9, 8.4 Hz, 1 H, C(6)H’), 1.25 (t, J = 7.2 Hz, 3 H, C(5)H₃)
- **¹³C NMR:** (126 MHz, CDCl₃)  
  δ 165.4 C(3), 133.3 C(7), 132.7, 132.6, 128.6 C(9), 128.0 C(16), 127.7, 127.6, 126.6 C(8), 126.3, 126.1, 116.1 C(1), 62.9 C(4), 39.5 C(2), 35.8 C(6), 13.8 C(5)

**IR:** (neat)
3051 (w), 2984 (w), 2938 (w), 2906 (w), 2250 (w), 1731 (s), 1600 (w), 1507 (w),
1463 (w), 1368 (w), 1245 (s), 1095 (w), 1028 (m), 903 (m), 852 (m), 821 (m),
803 (m), 749 (s)

**HRMS:**
(El)
m/z: [M]+ Calcd for C\textsubscript{16}H\textsubscript{15}NO\textsubscript{2}: 253.1103; Found: 253.1096

**TLC:**
R\textsubscript{f} 0.17 (pentane/Et\textsubscript{2}O, 80:20) [silica gel, UV, iodine]

**Analysis:**
C\textsubscript{16}H\textsubscript{15}NO\textsubscript{2}
Calcd: C, 75.87; H, 5.97; N, 5.53
Found: C, 75.86; H, 5.91; N, 5.54

Ethyl 2-Cyano-4,4-dimethylpentanoate (8aq)

Following General Procedure IV, RhCl\textsubscript{3}·3H\textsubscript{2}O (10.5 mg, 0.04 mmol, 2 mol %), CH\textsubscript{3}CN (4.0 mL), ethyl cyanoacetate (0.213 mL, 2.0 mmol), pivaldehyde (0.228 mL, 2.1 mmol, 1.05 equiv), H\textsubscript{2}O (0.072 mL, 4.0 mmol, 2.0 equiv), and Et\textsubscript{3}N (0.70 mL, 5.0 mmol, 2.5 equiv) were sequentially added to a 40-mL vial which was then placed in an autoclave and pressurized. The reaction was stirred at room temperature for 18 h followed by standard workup. Purification by silica gel column chromatography (pentane/Et\textsubscript{2}O, 90:10), followed by Kugelrohr distillation, afforded 8aq (329 mg, 90%) as a colorless oil.

**Data for 8aq:**
bp: 130 °C (ABT, 0.5 mmHg)

**\textsuperscript{1}H NMR:**
(500 MHz, CDCl\textsubscript{3})
δ 4.26 (q, J = 7.2 Hz, 2 H, C(4)H\textsubscript{2}), 3.42 (dd, J = 8.6, 4.6 Hz, 1 H, C(2)H), 1.95 (dd, J = 14.2, 4.6 Hz, 1 H, C(6)H), 1.89 (dd, J = 14.2, 8.6 Hz, 1 H, C(6)H\textsuperscript{'}), 1.32 (t, J = 7.2 Hz, 3 H, C(5)H\textsubscript{3}), 1.00 (s, 9H, C(8)H\textsubscript{3})

**\textsuperscript{13}C NMR:**
(126 MHz, CDCl\textsubscript{3})
δ 166.8 C(3), 117.7 C(1), 62.8 C(4), 43.2 C(6), 33.6 C(2), 30.7 C(7), 28.9 C(8), 13.9 C(5)
IR: (neat)
2960 (w), 2249 (w), 1743 (s), 1477 (w), 1369 (m), 1244 (m), 1195 (m), 1028 (m), 916 (w), 856 (w)

HRMS: (EI)
m/z: [MH]+ Calcd for C_{10}H_{17}NO_{2}: 184.1338; Found: 184.1338

TLC: R_f 0.48 (pentane/Et_{2}O, 80:20) [silica gel, iodine]

Analysis: C_{10}H_{17}NO_{2}
Calcd: C, 65.54; H, 9.35; N, 7.64
Found: C, 65.75; H, 9.33; N, 7.79

Ethyl 2-Cyano-3-cyclohexylpropanoate (8ar)

Following General Procedure IV, RhCl_3·3H_2O (10.5 mg, 0.04 mmol, 2 mol %), CH_3CN (4.0 mL), ethyl cyanoacetate (0.213 mL, 2.0 mmol), cyclohexanecarboxaldehyde (0.254 mL, 2.1 mmol, 1.05 equiv), H_2O (0.072 mL, 4.0 mmol, 2.0 equiv), and Et_3N (0.70 mL, 5.0 mmol, 2.5 equiv) were sequentially added to a 40-mL vial which was then placed in an autoclave and pressurized. The reaction was stirred at room temperature for 18 h followed by standard workup. Purification by silica gel column chromatography (pentane/Et_{2}O, 90:10), followed by Kugelrohr distillation, afforded 8ar (404 mg, 97%) as a colorless oil.

Data for 8ar:

bp: 158 °C (ABT, 0.5 mmHg)

^1H NMR: (500 MHz, CDCl_3)
δ 4.25 (q, J = 7.1 Hz, 2 H, C(4)H_2), 3.54 (dd, J = 9.4, 6.2 Hz, 1 H, C(2)H), 1.89 – 1.77 (m, 2 H, C(6)H_2), 1.77 – 1.63 (m, 5 H, C(8-12)H_{eq}), 1.57 – 1.47 (m, 1 H, C(7)H), 1.31 (t, J = 7.1 Hz, 3 H, C(5)H_3), 1.29 – 1.20 (m, 2 H, C(9)H_{ax}, C(11)H_{ax}), 1.19 – 1.09 (m, 1 H, C(10)H_{ax}), 1.02 – 0.84 (m, 2 H, C(8)H_{ax}, C(12)H_{ax})

^13C NMR: (126 MHz, CDCl_3)
δ 166.5 C(3), 116.7 C(1), 62.7 C(4), 37.0 C(6), 35.3 C(2), 35.2 C(7), 33.0 C(12),
31.9 C(8), 26.1 C(10), 25.8 C(9), 25.7 C(11), 13.9 C(5)

IR: (neat)
2984 (w), 2924 (m), 2852 (w), 2249 (w), 1742 (s), 1449 (m), 1321 (w), 1247 (m), 1188 (m), 1096 (w), 1023 (m), 855 (w)

HRMS: (EI)

m/z: [M-H]+ Calcd for C₁₂H₁₈NO₂: 208.1338; Found: 208.1340

TLC: R_f 0.52 (pentane/Et₂O, 80:20) [silica gel, iodine]

Analysis: C₁₂H₁₉NO₂
Calcd: C, 68.87; H, 9.15; N, 6.69
Found: C, 69.15; H, 9.00; N, 6.88

Ethyl 2-Cyano-4-methylpentanoate (8as)

Following General Procedure IV, RhCl₃·3H₂O (10.5 mg, 0.04 mmol, 2 mol %), CH₃CN (4.0 mL), ethyl cyanoacetate (0.213 mL, 2.0 mmol), isobutyraldehyde (0.192 mL, 2.1 mmol, 1.05 equiv), H₂O (0.072 mL, 4.0 mmol, 2.0 equiv), and Et₃N (0.70 mL, 5.0 mmol, 2.5 equiv) were sequentially added to a 40-mL vial which was then placed in an autoclave and pressurized. The reaction was stirred at room temperature for 18 h followed by standard workup. Purification by silica gel column chromatography (pentane/Et₂O, 90:10), followed by Kugelrohr distillation, afforded 8as (307 mg, 91%) as a colorless oil.

Data for 8as:

bp: 121 °C (ABT, 0.5 mmHg)

¹H NMR: (500 MHz, CDCl₃)
δ 4.26 (q, J = 7.1 Hz, 2 H, C(4)H₂), 3.51 (dd, J = 9.3, 5.9 Hz, 1 H, C(2)H), 1.91 –
1.81 (m, 2 H, C(6)H, C(7)H), 1.81 – 1.74 (m, 1 H, C(6)H’), 1.32 (t, J = 7.1 Hz, 3
H, C(5)H₃), 0.99 (d, J = 6.3 Hz, 3 H, C(8)H₃), 0.96 (d, J = 6.4 Hz, 3 H, C(9)H₃)

¹³C NMR: (126 MHz, CDCl₃)
δ 166.4 C(3), 116.6 C(1), 62.7 C(4), 38.3 C(6), 35.9 C(2), 26.0 C(7), 22.4 C(8),
21.2 C(9), 13.9 C(5)

IR: (neat)
2962 (w), 2875 (w), 2249 (w), 1742 (s), 1470 (w), 1390 (w), 1370 (w), 1265 (m),
1244 (m), 1185 (m), 1113 (w), 1023 (m), 927 (w), 857 (w)

HRMS: (EI)
m/z: [M]+ Calcd for C₉H₁₅NO₂: 169.1103; Found: 169.1106

TLC: Rₛ 0.36 (pentane/Et₂O, 80:20) [silica gel, iodine]

Analysis: C₉H₁₅NO₂
Calcd: C, 63.88; H, 8.93; N, 8.28
Found: C, 63.89; H, 9.17; N, 8.39

Ethyl 2-Cyano-5-methylhexanoate (8at)

Following General Procedure IV, RhCl₃·3H₂O (10.5 mg, 0.04 mmol, 2 mol %), CH₃CN (4.0
mL), ethyl cyanoacetate (0.213 mL, 2.0 mmol), isovaleraldehyde (0.230 mL, 2.1 mmol, 1.05
equiv), H₂O (0.072 mL, 4.0 mmol, 2.0 equiv), and Et₃N (0.70 mL, 5.0 mmol, 2.5 equiv) were
sequentially added to a 40-mL vial which was then placed in an autoclave and pressurized. The
reaction was stirred at room temperature for 18 h followed by standard workup. Purification by
silica gel column chromatography (pentane/Et₂O, 90:10), followed by Kugelrohr distillation,
afforded 8at (347 mg, 95%) as a colorless oil. The spectral data matched those previously
reported in the literature.⁷

Data for 8at:
bp: 138 °C (ABT, 0.5 mmHg)
¹H NMR: (500 MHz, CDCl₃)
δ 4.26 (q, J = 7.1 Hz, 2 H, C(4)H₂), 3.46 (dd, J = 7.6, 6.4 Hz, 1 H, C(2)H), 2.03 –
1.86 (m, 2 H, C(6)H₂), 1.66 – 1.55 (m, 1 H, C(8)H), 1.42 – 1.35 (m, 2 H,
C(7)H₂), 1.32 (t, J = 7.1 Hz, 3 H, C(5)H₃), 0.92 (d, J = 6.6 Hz, 3 H, C(9)H₃),
0.91 (d, $J = 6.6$ Hz, 3 H, C(10)H$_3$)

$^{13}$C NMR: (126 MHz, CDCl$_3$)

$\delta$ 166.2 C(3), 116.6 C(1), 62.7 C(4), 37.7 C(2), 35.6 C(7), 27.8 C(6), 27.5 C(8), 22.3 C(9), 22.1 C(10), 14.0 C(5)

HRMS: (ESI)

$m/z$: [MH]$^+$ Calcd for C$_{10}$H$_{18}$NO$_2$: 184.1338; Found: 184.1339

TLC: $R_f$ 0.37 (pentane/Et$_2$O, 80:20) [silica gel, iodine]

Ethyl 2-Cyano-5-phenylpentanoate (8au)

Following General Procedure IV, RhCl$_3$·3H$_2$O (10.5 mg, 0.04 mmol, 2 mol %), CH$_3$CN (4.0 mL), ethyl cyanoacetate (0.213 mL, 2.0 mmol), hydrocinnamaldehyde (0.277 mL, 2.1 mmol, 1.05 equiv), H$_2$O (0.108 mL, 6.0 mmol, 3.0 equiv), and Et$_3$N (0.70 mL, 5.0 mmol, 2.5 equiv) were sequentially added to a 40-mL vial which was then placed in an autoclave and pressurized. The reaction was stirred at room temperature for 24 h followed by standard workup. Purification by silica gel column chromatography (pentane/Et$_2$O, 80:20), followed by Kugelrohr distillation, afforded 8au (329 mg, 71%) as a colorless oil. The spectral data matched those previously reported in the literature.$^7$

Data for 8au:

bp: 211 °C (ABT, 0.5 mmHg)

$^1$H NMR: (500 MHz, CDCl$_3$)

$\delta$ 7.30 (t, $J = 7.5$ Hz, 2 H, C(11)H), 7.21 (t, $J = 7.4$ Hz, 1 H, C(12)H), 7.18 (d, $J = 7.4$ Hz, 2 H, C(10)H), 4.25 (q, $J = 7.1$ Hz, 2 H, C(4)H$_2$), 3.48 (t, $J = 6.8$ Hz, 1 H, C(2)H), 2.69 (t, $J = 7.5$ Hz, 2 H, C(8)H$_2$), 2.01 – 1.94 (m, 2 H, C(6)H$_2$), 1.90 – 1.79 (m, 2 H, C(7)H$_2$), 1.31 (t, $J = 7.1$ Hz, 3 H, C(5)H$_3$)

$^{13}$C NMR: (126 MHz, CDCl$_3$)
δ 166.0 C(3), 140.8 C(9), 128.5 C(11), 128.3 C(10), 126.2 C(12), 116.4 C(1),
62.8 C(4), 37.4 C(2), 34.9 C(8), 29.2 C(6), 28.3 C(7), 14.0 C(5)

HRMS: (EI)
m/z: [M]+ Calcd for C_{14}H_{17}NO_2: 231.1259; Found: 231.1267

TLC: R_f 0.28 (pentane/Et_2O, 80:20) [silica gel, UV, iodine]

Table 2.5, entry 16

Following General Procedure IV, RhCl_3·3H_2O (15.8 mg, 0.06 mmol, 3 mol %), CH_3CN (4.0 mL), ethyl cyanoacetate (0.213 mL, 2.0 mmol), 4-nitrobenzaldehyde (317 mg, 2.1 mmol, 1.05 equiv), H_2O (0.180 mL, 10.0 mmol, 5.0 equiv), and Et_3N (0.70 mL, 5.0 mmol, 2.5 equiv) were sequentially added to a 40-mL vial which was then placed in an autoclave and pressurized. The reaction was stirred at room temperature for 36 h followed by standard workup. Analysis of the reaction mixture by GC-MS showed only trace amounts of 8ap, and 9ap as the major product.

Table 2.5, entry 22

Following General Procedure IV, RhCl_3·3H_2O (15.8 mg, 0.06 mmol, 3 mol %), CH_3CN (4.0 mL), ethyl cyanoacetate (0.213 mL, 2.0 mmol), 4-(2-trimethylsilylethynyl)benzaldehyde (425 mg, 2.1 mmol, 1.05 equiv), H_2O (0.180 mL, 10.0 mmol, 5.0 equiv), and Et_3N (0.70 mL, 5.0 mmol, 2.5 equiv) were sequentially added to a 40-mL vial which was then placed in an autoclave and pressurized. The reaction was stirred at room temperature for 24 h followed by standard workup. The conversion to 8av was determined to be 19% by analysis of the crude reaction mixture by ^1H NMR (based on mesitylene (0.096 mL, 0.5 mmol) as the standard), with 9av being the major component of the mixture.

Table 2.5, entry 23

Following General Procedure IV, RhCl_3·3H_2O (10.5 mg, 0.04 mmol, 2 mol %), CH_3CN (4.0 mL), ethyl cyanoacetate (0.213 mL, 2.0 mmol), 4-prop-2-ynoxybenzaldehyde (336 mg, 2.1 mmol, 1.05 equiv), H_2O (0.072 mL, 4.0 mmol, 2.0 equiv), and Et_3N (0.70 mL, 5.0 mmol, 2.5 equiv) were sequentially added to a 40-mL vial which was then placed in an autoclave and pressurized. The reaction was stirred at room temperature for 18 h followed by standard workup.
Analysis of the reaction mixture by GC-MS and $^1$H NMR showed no 8aw, and 9aw as the major product.

Table 2.5, entry 24

Following General Procedure IV, RhCl$_3$·3H$_2$O (15.8 mg, 0.06 mmol, 3 mol %), CH$_3$CN (4.0 mL), ethyl cyanoacetate (0.213 mL, 2.0 mmol), 2-hydroxybenzaldehyde (223.6 mL, 2.1 mmol, 1.05 equiv), H$_2$O (0.108 mL, 6.0 mmol, 3.0 equiv), and Et$_3$N (0.70 mL, 5.0 mmol, 2.5 equiv) were sequentially added to a 40-mL vial which was then placed in an autoclave and pressurized. The reaction was stirred at room temperature for 18 h followed by standard workup. Analysis of the reaction mixture by GC-MS and $^1$H NMR (based on mesitylene (0.096 mL, 0.5 mmol) as the standard) showed 9ax' as the major component of the mixture.

Table 2.5, entry 25

Following General Procedure IV, RhCl$_3$·3H$_2$O (15.8 mg, 0.06 mmol, 3 mol %), CH$_3$CN (4.0 mL), ethyl cyanoacetate (0.213 mL, 2.0 mmol), 2-hydroxybenzaldehyde (223.6 mL, 2.1 mmol, 1.05 equiv), H$_2$O (0.072 mL, 4.0 mmol, 2.0 equiv), and Et$_3$N (0.70 mL, 5.0 mmol, 2.5 equiv) were sequentially added to a 40-mL vial which was then placed in an autoclave and pressurized. The reaction was stirred at room temperature for 18 h followed by standard workup. Analysis of the reaction mixture by GC-MS and $^1$H NMR (based on mesitylene (0.096 mL, 0.5 mmol) as the standard) showed a mixture of cis- and trans- isomers of the mono- and dienoates with 15% yield of 8au.

General Procedure V: Reaction of Ethyl Cyanoacetate with Cyclic Ketones (Table 2.6)

![Chemical Reaction Diagram]

RhCl$_3$·3H$_2$O was added to a 40-mL glass vial, followed by acetonitrile, ethyl cyanoacetate 6a, the ketone 7, deionized water, and triethylamine. A stir bar was added, and the vial was placed in an autoclave. The autoclave was pressurized with CO and vented three times, and then pressurized to 10 bar. The reaction was stirred at room temperature for the indicated time. After
venting and purging the autoclave with nitrogen, the vial was removed. The volatiles were removed by rotary evaporation (25-30 °C, 15 mmHg), the residue was dissolved in CH₂Cl₂, and loaded on silica gel (1 g). The crude mixture was purified by silica gel column chromatography (2.5 x 20-25 cm), followed by distillation.

**Ethyl 2-Cyano-2-cyclohexylacetate (8az)**

Following General Procedure V, RhCl₃·3H₂O (10.5 mg, 0.04 mmol, 2 mol %), CH₃CN (1.0 mL), ethyl cyanoacetate (0.213 mL, 2.0 mmol), cyclohexanone (0.217 mL, 2.1 mmol, 1.05 equiv), H₂O (0.180 mL, 10.0 mmol, 5.0 equiv), and Et₃N (1.95 mL, 14.0 mmol, 7.0 equiv) were sequentially added to a 40-mL vial which was then placed in an autoclave and pressurized. The reaction was stirred at room temperature for 30 h followed by standard workup. Purification by silica gel column chromatography (pentane/Et₂O, 95:5), followed by Kugelrohr distillation, afforded 8az (364 mg, 93%) as a colorless oil. The spectral data matched those previously reported in the literature.⁸

**Data for 8az:**

bp: 178 °C (ABT, 0.5 mmHg)

**¹H NMR:** (500 MHz, CDCl₃)

δ 4.28 – 4.23 (m, 2 H, C(4)H₂), 3.36 (d, J = 5.7 Hz, 1 H, C(2)H), 2.10 – 1.96 (m, 1 H, C(6)H), 1.86 – 1.64 (m, 5 H, C(7-11)H(eq)), 1.31 (t, J = 7.1 Hz, 3 H, C(5)H₃), 1.29 – 1.10 (m, 5 H, C(7-11)H(ax))

**¹³C NMR:** (126 MHz, CDCl₃)

δ 165.8 C(3), 115.7 C(1), 62.5 C(4), 44.5 C(2), 38.8 C(6), 31.0, 29.3, 25.7, 25.5, 25.4, 14.0 C(5)

**HRMS:** (ESI)

m/z: [MH]⁺ Calcd for C₁₁H₁₈NO₂: 196.1338; Found: 196.1332

**TLC:** Rf 0.48 (pentane/Et₂O, 80:20) [silica gel, iodine]
Ethyl 2-Cyano-2-cyclopentylacetate (8aa’)

Following General Procedure V, RhCl₃·3H₂O (10.5 mg, 0.04 mmol, 2 mol %), CH₃CN (1.0 mL), ethyl cyanoacetate (0.213 mL, 2.0 mmol), cyclopentanone (0.186 mL, 2.1 mmol, 1.05 equiv), H₂O (0.180 mL, 10.0 mmol, 5.0 equiv), and Et₃N (1.95 mL, 14.0 mmol, 7.0 equiv) were sequentially added to a 40-mL vial which was then placed in an autoclave and pressurized. The reaction was stirred at room temperature for 30 h followed by standard workup. Purification by silica gel column chromatography (pentane/Et₂O, 85:15), followed by Kugelrohr distillation, afforded 8aa’ (285 mg, 79%) as a colorless oil.

**Data for 8aa’:**

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<th>Value</th>
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</thead>
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<td>(500 MHz, CDCl₃)</td>
</tr>
<tr>
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<tr>
<td><strong>¹³C NMR:</strong></td>
<td>(126 MHz, CDCl₃)</td>
</tr>
<tr>
<td>δ 166.1 C(3), 116.0 C(1), 62.5 C(4), 42.5 C(2), 40.1 C(6), 30.7 C(7), 29.7 C(10), 25.0 C(8), 24.9 C(9), 14.0 C(5)</td>
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<td>(neat)</td>
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<tr>
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<td></td>
</tr>
<tr>
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<td>(ESI)</td>
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<td>C₁₀H₁₅NO₂</td>
</tr>
<tr>
<td>Calcd: C, 66.27; H, 8.34; N, 7.73</td>
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<td>Found: C, 65.94; H, 8.25; N, 7.60</td>
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Ethyl 2-Cyano-2-cyclobutylacetate (8ab')

Following General Procedure V, RhCl₃·3H₂O (10.5 mg, 0.04 mmol, 2 mol %), CH₃CN (1.0 mL), ethyl cyanoacetate (0.213 mL, 2.0 mmol), cyclobutanone (0.149 mL, 2.1 mmol, 1.05 equiv), H₂O (0.180 mL, 10.0 mmol, 5.0 equiv), and Et₃N (1.95 mL, 14.0 mmol, 7.0 equiv) were sequentially added to a 40-mL vial which was then placed in an autoclave and pressurized. The reaction was stirred at room temperature for 30 h followed by standard workup. Purification by silica gel column chromatography (pentane/Et₂O, 90:10), followed by Kugelrohr distillation, afforded 8ab' (157 mg, 47%) as a colorless oil. The spectral data matched those previously reported in the literature.⁹

Data for 8ab':

bp: 95 °C (ABT, 0.5 mmHg)

¹H NMR: (500 MHz, CDCl₃)
δ 4.22 (q, J = 7.1 Hz, 2 H, C(4)H₂), 3.49 (d, J = 7.3 Hz, 1 H, C(2)H), 2.91 (h, J = 8.1 Hz, 1 H, C(6)H), 2.20 – 2.10 (m, 2 H, C(7)H, C(9)H), 2.08 – 1.82 (m, 4 H, C(7)H', C(8)H₂, C(9)H'), 1.29 (t, J = 7.1 Hz, 3 H, C(5)H₃)

¹³C NMR: (126 MHz, CDCl₃)
δ 165.4 C(3), 115.6 C(1), 62.5 C(4), 43.1 C(2), 35.1 C(6), 26.5 C(7), 25.8 C(9), 17.7 C(8), 14.0 C(5)

HRMS: (ESI) m/z: [MH]⁺ Calcd for C₉H₁₄NO₂: 168.1025; Found: 168.1019

TLC: Rf 0.42 (pentane/Et₂O, 80:20) [silica gel, iodine]

Ethyl 2-Cyano-2-(tetrahydro-2 H-pyran-4-yl)acetate (8ac')
Following General Procedure V, RhCl$_3$·3H$_2$O (10.5 mg, 0.04 mmol, 2 mol %), CH$_3$CN (1.0 mL), ethyl cyanoacetate (0.213 mL, 2.0 mmol), tetrahydro-pyran-4-one (0.194 mL, 2.1 mmol, 1.05 equiv), H$_2$O (0.180 mL, 10.0 mmol, 5.0 equiv), and Et$_3$N (1.95 mL, 14.0 mmol, 7.0 equiv) were sequentially added to a 40-mL vial which was then placed in an autoclave and pressurized. The reaction was stirred at room temperature for 30 h followed by standard workup. Purification by silica gel column chromatography (pentane/Et$_2$O, 70:30), followed by Kugelrohr distillation, afforded 8ac’ (304 mg, 77%) as a colorless oil that slowly solidified at room temperature.

Data for 8ac’:

bp: 185 °C (ABT, 0.5 mmHg)
mp: 39-40 °C

$^1$H NMR: (500 MHz, CDCl$_3$)
δ 4.32 – 4.23 (m, 2 H, C(4)H$_2$), 4.07 – 3.98 (m, 2 H, C(8)H$_{eq}$, C(9)H$_{eq}$), 3.45 – 3.37 (m, 3 H, C(2)H, C(8)H$_{ax}$, C(9)H$_{ax}$), 2.35 – 2.21 (m, 1 H, C(6)H), 1.75 – 1.67 (m, 1 H, C(7)H$_2$), 1.67 – 1.57 (m, 2 H, C(10)H$_2$), 1.36 – 1.28 (t, $J = 7.2$ Hz, 3 H, C(5)H$_3$)

$^{13}$C NMR: (126 MHz, CDCl$_3$)
δ 165.2 C(3), 115.1 C(1), 67.19 C(8), 67.16 C(9), 62.9 C(4), 43.8 C(2), 36.1 C(6), 30.6 C(7), 29.4 C(10), 14.1 C(5)

IR: (neat)
2934 (w), 2920 (m), 2856 (m), 2246 (w), 1737 (s), 1468 (m), 1446 (m), 1371 (m), 1305 (m), 1246 (s), 1208 (s), 1090 (s), 1022 (s), 1010 (s), 986 (s), 855 (s), 770 (m)

HRMS: (EI)
m/z: [M]$^+$ Calcd for C$_{10}$H$_{15}$NO$_3$: 197.1052; Found: 197.1055

TLC: $R_f$ 0.28 (pentane/Et$_2$O, 70:30) [silica gel, iodine]

Analysis:
C$_{10}$H$_{15}$NO$_3$
Calcd: C, 60.90; H, 7.67; N, 7.10
Found: C, 60.86; H, 7.53; N, 7.04
Ethyl 2-Cyano-2-(1-methylpiperidin-4-yl)acetate (8ad’)

Following General Procedure V, RhCl$_3$·3H$_2$O (15.8 mg, 0.06 mmol, 3 mol %), CH$_3$CN (1.0 mL), ethyl cyanoacetate (0.213 mL, 2.0 mmol), N-methyl-4-piperdinone (0.246 mL, 2.1 mmol, 1.05 equiv), H$_2$O (0.180 mL, 10.0 mmol, 5.0 equiv), and Et$_3$N (1.95 mL, 14.0 mmol, 7.0 equiv) were sequentially added to a 40-mL vial which was then placed in an autoclave and pressurized. The reaction was stirred at room temperature for 30 h followed by standard workup. Purification by silica gel column chromatography (EtOAc/MeOH/NH$_4$OH, 90:9:1), followed by Kugelrohr distillation, afforded 8ad’ (352 mg, 89%) as a clear, colorless oil which rapidly discolored in air.

Data for 8ad’:

bp: 135 °C (ABT, 0.5 mmHg)

$^1$H NMR: (500 MHz, CDCl$_3$)

$\delta$ 4.24 – 4.15 (m, 2 H, C(4)H$_2$), 3.30 (d, J = 6.6 Hz, 1 H, C(2)H), 2.88 – 2.78 (m, 2 H, C(8)H$_{eq}$, C(9)H$_{eq}$), 2.19 (s, 3 H, C(11)H$_3$), 1.98 – 1.83 (m, 3 H, C(6)H, C(8)H$_{ax}$, C(9)H$_{ax}$), 1.77 – 1.69 (m, 1 H, C(7)H$_{eq}$), 1.67 – 1.59 (m, 1 H, C(10)H$_{eq}$), 1.57 – 1.45 (m, 2 H, C(7)H$_{ax}$, C(10)H$_{ax}$), 1.25 (t, J = 7.1 Hz, 3 H, C(5)H$_3$)

$^{13}$C NMR: (126 MHz, CDCl$_3$)

$\delta$ 165.5 C(3), 115.3 C(1), 62.7 C(4), 55.1 C(8), 55.0 C(9), 46.1 C(11), 43.6 C(2), 36.7 C(6), 30.2 C(10), 29.1 C(7), 14.0 C(5)

IR: (neat)

2939 (w), 2849 (w), 2785 (w), 2686 (w), 2249 (w), 1739 (s), 1466 (w), 1448 (m), 1380 (w), 1369 (w), 1280 (m), 1250 (m), 1197 (m), 1179 (m), 1139 (m), 1093 (w), 1066 (w), 1028 (m), 985 (w), 853 (w), 765 (w)

HRMS: (EI)

$m/z$: [M]$^+$ Calcd for C$_{11}$H$_{18}$N$_2$O$_2$: 210.1364; Found: 210.1368

TLC: R$_f$ 0.45 (EtOAc/MeOH/NH$_4$OH, 90:9:1) [silica gel, iodine]

Analysis: C$_{11}$H$_{18}$N$_2$O$_2$
Calcd:  C, 62.83;  H, 8.63;  N, 13.32
Found:  C, 62.40;  H, 8.40;  N, 13.27

General Procedure VI: Reaction of Ethyl Cyanoacetate with Acyclic Ketones (Table 2.7)

\[
\text{RhCl}_3 \cdot 3\text{H}_2\text{O} \quad \text{7} \quad \text{RhCl}_3 \cdot 3\text{H}_2\text{O} \quad \text{8}
\]

RhCl₃·3H₂O was added to a 40-mL glass vial, followed by triethylamine, ethyl cyanoacetate 6a, the ketone 7, and deionized water. A stir bar was added, and the vial was placed in an autoclave. The autoclave was pressurized with CO and vented three times, and then pressurized to 10 bar. The reaction was stirred at room temperature for the indicated time. After venting and purging the autoclave with nitrogen, the vial was removed. The volatiles were removed by rotary evaporation (25-30 °C, 15 mmHg), the residue was dissolved in CH₂Cl₂, and loaded on silica gel (1 g). The crude mixture was purified by silica gel column chromatography (2.5 x 20-25 cm), followed by distillation.

Ethyl 2-Cyano-3-methylbutanoate (8ae')

Following General Procedure VI, RhCl₃·3H₂O (10.5 mg, 0.04 mmol, 2 mol %), triethylamine (2.0 mL), ethyl cyanoacetate (0.213 mL, 2.0 mmol), acetone (0.154 mL, 2.1 mmol, 1.05 equiv), and H₂O (0.180 mL, 10.0 mmol, 5.0 equiv) were sequentially added to a 40-mL vial which was then placed in an autoclave and pressurized. The reaction was stirred at room temperature for 72 h followed by standard workup. Purification by silica gel column chromatography (pentane/Et₂O, 90:10), followed by Kugelrohr distillation, afforded 8ae' (146 mg, 47%) as a colorless oil. The spectral data matched those previously reported in the literature.⁶

Data for 8ae':

bp:  93 °C (ABT, 0.5 mmHg)

¹H NMR:  (500 MHz, CDCl₃)
δ 4.30 – 4.22 (m, 2 H, C(4)H$_2$), 3.38 (d, $J = 5.4$ Hz, 1 H, C(2)H), 2.46 – 2.35 (m, 1 H, C(6)H), 1.31 (t, $J = 7.2$ Hz, 3 H, C(5)H$_3$), 1.12 (d, $J = 6.9$ Hz, 3 H, C(7)H$_3$), 1.09 (d, $J = 6.8$ Hz, 3 H, C(8)H$_3$)

$^{13}$C NMR: (126 MHz, CDCl$_3$)
δ 165.9 C(3), 115.5 C(1), 62.6 C(4), 45.3 C(2), 30.0 C(6), 20.7 C(7), 18.8 C(8), 14.0 C(5)

HRMS: (EI)
m/z: [M]$^+$ Calcd for C$_8$H$_{13}$NO$_2$: 155.0944; Found: 155.0946

TLC: $R_f$ 0.19 (pentane/Et$_2$O, 90:10) [silica gel, iodine]

Table 2.7, entry 2
Following General Procedure VI, RhCl$_3$·3H$_2$O (10.5 mg, 0.04 mmol, 2 mol %), Et$_3$N (2.0 mL), ethyl cyanoacetate (0.213 mL, 2.0 mmol), 3-pentanone (0.222 mL, 2.1 mmol, 1.05 equiv), and H$_2$O (0.180 mL, 10.0 mmol, 5.0 equiv) were sequentially added to a 40-mL vial which was then placed in an autoclave and pressurized. The reaction was stirred at room temperature for 72 h followed by standard workup. Analysis of the reaction mixture by GC-MS and $^1$H NMR (based on mesitylene as the standard) showed no product formation.

Table 2.7, entry 3
Following General Procedure VI, RhCl$_3$·3H$_2$O (10.5 mg, 0.04 mmol, 2 mol %), Et$_3$N (2.0 mL), ethyl cyanoacetate (0.213 mL, 2.0 mmol), 2,4-dimethyl-3-pentanone (0.297 mL, 2.1 mmol, 1.05 equiv), and H$_2$O (0.180 mL, 10.0 mmol, 5.0 equiv) were sequentially added to a 40-mL vial which was then placed in an autoclave and pressurized. The reaction was stirred at room temperature for 72 h followed by standard workup. Analysis of the reaction mixture by GC-MS and $^1$H NMR (based on mesitylene (0.096 mL, 0.5 mmol) as the standard) showed no product formation.

Table 2.7, entry 4
Following General Procedure VI, RhCl$_3$·3H$_2$O (10.5 mg, 0.04 mmol, 2 mol %), Et$_3$N (2.0 mL), ethyl cyanoacetate (0.213 mL, 2.0 mmol), benzophenone (383 mg, 2.1 mmol, 1.05 equiv), and H$_2$O (0.180 mL, 10.0 mmol, 5.0 equiv) were sequentially added to a 40-mL vial which was
then placed in an autoclave and pressurized. The reaction was stirred at room temperature for 72 h followed by standard workup. Analysis of the reaction mixture by GC-MS and $^1$H NMR (based on mesitylene (0.096 mL, 0.5 mmol) as the standard) showed no product formation.

**General Procedure VII: Reaction of Other Active Methylene Compounds with Aldehydes in One Step (Table 2.8)**

RhCl$_3$·3H$_2$O was added to a 40-mL glass vial, followed by acetonitrile, the active methylene compound 6, the aldehyde 7, deionized water, and triethylamine. A stir bar was added, and the vial was placed in an autoclave. The autoclave was pressurized with CO and vented three times, and then pressurized to 10 bar. The reaction was stirred at room temperature for the indicated time. After venting and purging the autoclave with nitrogen, the vial was removed. The volatiles were removed by rotary evaporation (25-30 °C, 15 mmHg), the residue was dissolved in CH$_2$Cl$_2$, and loaded on silica gel (1 g). The crude mixture was purified by silica gel column chromatography (2.5 x 20-25 cm), followed by distillation or recrystallization.

**2-(4-Methoxybenzyl)-3-oxo-3-phenylpropanenitrile (8bf)**

Following General Procedure VII, RhCl$_3$·3H$_2$O (15.8 mg, 0.06 mmol, 3 mol %), CH$_3$CN (3.0 mL), benzylocetonitrile (290 mg, 2.0 mmol), $p$-anisaldehyde (0.256 mL, 2.1 mmol, 1.05 equiv), H$_2$O (0.180 mL, 10.0 mmol, 5.0 equiv), and Et$_3$N (1.12 mL, 8.0 mmol, 4.0 equiv) were sequentially added to a 40-mL vial which was then placed in an autoclave and pressurized. The reaction was stirred at room temperature for 24 h followed by standard workup. Purification by silica gel column chromatography (pentane/Et$_2$O, 75:25 to 50:50), followed by Kugelrohr distillation, afforded 8bf (463 mg, 87%) as a yellow oil.
Data for 8bf:

bp: 256 °C (ABT, 0.5 mmHg)

\(^1\)H NMR: (500 MHz, CDCl\(_3\))
\[\delta \text{ } 7.95 (dd, J = 8.4, 1.2 \text{ Hz}, 2 \text{ H, C(5)H}), 7.65 (t, J = 7.4 \text{ Hz}, 1 \text{ H, C(7)H}), 7.51 (t, J = 7.8 \text{ Hz}, 2 \text{ H, C(6)H}), 7.20 (d, J = 8.7 \text{ Hz}, 2 \text{ H, C(10)H}), 6.86 (d, J = 8.7 \text{ Hz}, 2 \text{ H, C(11)H}), 4.51 (dd, J = 8.8, 5.8 \text{ Hz}, 1 \text{ H, C(2)H}), 3.78 (s, 3 \text{ H, C(13)H}_3), 3.30 (dd, J = 14.1, 5.8 \text{ Hz}, 1 \text{ H, C(8)H}), 3.19 (dd, J = 14.1, 8.8 \text{ Hz}, 1 \text{ H, C(8)H'}\) 

\(^13\)C NMR: (126 MHz, CDCl\(_3\))
\[\delta \text{ } 190.2 \text{ C(3), 159.0 C(12), 134.5 C(7), 134.0 C(4), 130.1 C(10), 129.1 C(6), 128.7 C(5), 127.8 C(9), 117.0 C(1), 114.2 C(11), 55.2 C(13), 42.1 C(2), 34.8 C(8)\]

IR: (neat)
3003 (w), 2935 (w), 2836 (w), 2249 (w), 1688 (m), 1611 (m), 1596 (m), 1582 (m), 1512 (s), 1448 (m), 1301 (m), 1246 (s), 1178 (s), 1110 (w), 1030 (m), 949 (w), 874 (w), 810 (m), 744 (m), 690 (s)

HRMS: (EI)
\[m/\text{z}: \text{[M]}^+ \text{ Calcd for C}_{17}\text{H}_{15}\text{NO}_2: 265.1103; \text{Found: 265.1111}\]

TLC: \(R_f\) 0.16 (pentane/Et\(_2\)O, 70:30) [silica gel, UV, iodine]

Analysis: C\(_{17}\)H\(_{15}\)NO\(_2\)
Calcd: C, 76.96; H, 5.70; N, 5.28
Found: C, 76.63; H, 5.61; N, 5.23

2-Cyano-3-(4-methoxyphenyl)propanamide (8cf)

Following General Procedure VII, RhCl\(_3\)·3H\(_2\)O (10.5 mg, 0.04 mmol, 2 mol %), CH\(_3\)CN (4.0 mL), 2-cyanoacetamide (168, 2.0 mmol), \(p\)-anisaldehyde (0.256 mL, 2.1 mmol, 1.05 equiv), H\(_2\)O (0.180 mL, 10.0 mmol, 5.0 equiv), and Et\(_3\)N (1.12 mL, 8.0 mmol, 4.0 equiv) were sequentially added to a 40-mL vial which was then placed in an autoclave and pressurized. The reaction was
stirred at room temperature for 24 h followed by standard workup. After evaporation of the volatiles (25-30 °C, 15 mmHg), the residue was suspended in Et₂O and filtered. The solid residue was redissolved in acetone and filtered through a silica plug eluting with acetone. The filtrate was concentrated to provide an off-white solid. Recrystallization (EtOH, abs.) afforded 8cf (344 mg, 84%) as a white, crystalline solid.

**Data for 8cf:**

**mp:** 170-171 °C (EtOH)

**¹H NMR:** (500 MHz, d₆-acetone)
δ 7.26 (d, J = 8.6 Hz, 2 H, C(6)H), 7.20 (br s, 1 H, NH), 6.88 (d, J = 8.7 Hz, 2 H, C(7)H), 6.78 (br s, 1 H, NH), 3.86 (dd, J = 8.5, 6.6 Hz, 1 H, C(2)H), 3.78 (s, 3 H, C(9)H₃), 3.20 (dd, J = 13.8, 6.6 Hz, 1 H, C(4)H), 3.08 (dd, J = 13.8, 8.5 Hz, 1 H, C(4)H’)

**¹³C NMR:** (126 MHz, d₆-acetone)
δ 167.2 C(3), 159.9 C(8), 131.1 C(6), 129.7 C(5), 118.8 C(1) 114.7 C(7), 55.5 C(9), 41.0 C(2), 35.9 C(4)

**IR:** (neat)
3397 (m), 3321 (w), 3274 (w), 3210 (w), 3042 (w), 2942 (w), 2843 (w), 2252 (w), 1669 (s), 1611 (m), 1584 (w), 1514 (s), 1455 (w), 1406 (m), 1325 (w), 1304 (m), 1240 (s), 1173 (m), 1119 (w), 1027 (s), 895 (w), 825 (s), 815 (m), 736 (w)

**HRMS:** (EI)
m/z: [M]⁺ Calcd for C₁₁H₁₂N₂O₂: 204.0899; Found: 204.0899

**Analysis:** C₁₁H₁₂N₂O₂
Calcd:  C, 64.69;  H, 5.92;  N, 13.72
Found:  C, 64.39;  H, 5.93;  N, 13.61

3-Phenyl-2-(pyridin-2-yl)propanenitrile (8da)
Following General Procedure VII, RhCl₃·3H₂O (15.8 mg, 0.06 mmol, 3 mol %), CH₃CN (1.0 mL), 2-pyridylacetonitrile (0.223 mL, 2.0 mmol), benzaldehyde (0.214 mL, 2.1 mmol, 1.05 equiv), H₂O (1.80 mL, 100.0 mmol, 50.0 equiv), and Et₃N (0.70 mL, 5.0 mmol, 2.5 equiv) were sequentially added to a 40-mL vial which was then placed in an autoclave and pressurized. The reaction was stirred at room temperature for 72 h followed by standard workup. Purification by silica gel column chromatography (CH₂Cl₂/EtOAc, 80:20), followed by recrystallization (hexane/Et₂O 90:10), afforded 8da (283 mg, 68%) as a white, crystalline solid. The spectral data matched those previously reported in the literature.¹⁰

Data for 8da:

- **mp:** 62-64 °C (hexane/Et₂O, 90:10)
- **¹H NMR:** (500 MHz, CDCl₃)
  \[ \delta 8.64 \text{ (d, } J = 4.6 \text{ Hz, } 1 \text{ H, C(7)H}), 7.67 \text{ (td, } J = 7.7, 1.5 \text{ Hz, } 1 \text{ H, C(5)H}), 7.32 - 7.26 \text{ (m, } 5 \text{ H, C(4)H, C(6)H, C(11)H, C(12)H}), 7.17 \text{ (d, } J = 6.7 \text{ Hz, } 2 \text{ H, C(10)H}), 4.21 \text{ (dd, } J = 8.6, 5.9 \text{ Hz, } 1 \text{ H, C(2)H}), 3.37 \text{ (dd, } J = 13.6, 5.8 \text{ Hz, } 1 \text{ H, C(8)H}), 3.26 \text{ (dd, } J = 13.6, 8.7 \text{ Hz, } 1 \text{ H, C(8)H'}) \]
- **¹³C NMR:** (126 MHz, CDCl₃)
  \[ \delta 154.5 \text{ C(3), 150.0 C(7), 137.2 C(5), 136.2 C(9), 129.2 C(10), 128.6 C(11), 127.4, 123.1, 122.2, 119.6 C(1), 42.0 C(2), 40.0 C(8) \]
- **HRMS:** (ESI)
  \[ m/z: [MH]^+ \text{ Calcd for } C_{14}H_{13}N_2: 209.1079; \text{ Found: 209.1086} \]
- **TLC:** \( R_f 0.50 \text{ (CH₂Cl₂/Et₂O, 80:20) [silica gel, UV, iodine] } \)

Table 2.8, entry 4

Following General Procedure VII, RhCl₃·3H₂O (15.8 mg, 0.06 mmol, 3 mol %), CH₃CN (4.0 mL), malononitrile (132 mg, 2.0 mmol), benzaldehyde (0.214 mL, 2.1 mmol, 1.05 equiv), H₂O (0.900 mL, 25.0 mmol, 25.0 equiv), and Et₃N (0.70 mL, 5.0 mmol, 2.5 equiv) were sequentially added to a 40-mL vial which was then placed in an autoclave and pressurized. The reaction was stirred at room temperature for 72 h followed by standard workup. The conversion to 8ea was determined to be 54% by analysis of the crude reaction mixture by ¹H NMR (based on mesitylene (0.096 mL, 0.5 mmol) as the standard).
Table 2.8, entry 5

Following General Procedure VII, RhCl₃·3H₂O (15.8 mg, 0.06 mmol, 3 mol %), CH₃CN (4.0 mL), N, N dimethylbarbituric acid (312 mg, 2.0 mmol), benzaldehyde (0.214 mL, 2.1 mmol, 1.05 equiv), H₂O (0.900 mL, 25.0 mmol, 25.0 equiv), and Et₃N (0.70 mL, 5.0 mmol, 2.5 equiv) were sequentially added to a 40-mL vial which was then placed in an autoclave and pressurized. The reaction was stirred at room temperature for 24 h followed by standard workup. The conversion to 8fa was determined to be 23% by analysis of the crude reaction mixture by ¹H NMR (based on mesitylene (0.096 mL, 0.5 mmol) as the standard).

General Procedure VIII: Reaction of Other Active Methylene Compounds with Benzaldehyde in Two Steps (Table 2.9)

1,5-Diazabicyclo[4.3.0]non-5-ene (DBN) or L-proline was added to a 40-mL glass vial, followed by the active methylene compound 6, benzaldehyde 7a, deionized water, and triethylamine, and the reaction mixture was stirred using a stir bar for the specified length of time. RhCl₃·3H₂O was added to the glass vial, followed by acetonitrile, additional deionized water, and triethylamine. The vial was placed in an autoclave. The autoclave was pressurized with CO and vented three times, and then pressurized to 10 bar. The reaction was stirred at room temperature for the indicated time. After venting and purging the autoclave with nitrogen, the vial was removed. The volatiles were removed by rotary evaporation (25-30 °C, 15 mmHg), the residue was dissolved in CH₂Cl₂, and loaded on silica gel (1 g). The crude mixture was purified by silica gel column chromatography (2.5 x 20-25 cm), followed by distillation or recrystallization.
3-Phenyl-2-(pyridin-3-yl)propanenitrile (8ga)

Following General Procedure VIII, 3-pyridylacetonitrile (0.212 mL, 2.0 mmol), benzaldehyde (0.214 mL, 2.1 mmol, 1.05 equiv), and DBN (0.012 mL, 0.1 mmol, 0.05 equiv) were sequentially added to a 40-mL vial and the reaction was stirred at room temperature for 6 h under air. RhCl$_3$·3H$_2$O (15.8 mg, 0.06 mmol, 3 mol %), CH$_3$CN (1.0 mL), H$_2$O (1.80 mL, 100.0 mmol, 50.0 equiv), and Et$_3$N (0.70 mL, 5.0 mmol, 2.5 equiv) were added to the vial and the vial was transferred to an autoclave where the reaction was stirred at room temperature for 72 h under CO followed by standard workup. Purification by silica gel column chromatography (CH$_2$Cl$_2$/EtOAc, 90:10), followed by recrystallization (hexane/benzene, 90:10), afforded 8ga (325 mg, 78%) as a white, crystalline solid. The spectral data matched those previously reported in the literature.$^{10}$

**Data for 8ga:**

- mp: 60-61 °C (hexane/benzene, 90:10)
- $^1$H NMR: (500 MHz, CDCl$_3$)  
  \[ \delta 8.58 \text{ (dd, } J = 4.8, 1.4 \text{ Hz, } 1 \text{ H, C(6)H}), 8.46 \text{ (d, } J = 2.1 \text{ Hz, } 1 \text{ H, C(7)H}), 7.61 – 7.55 \text{ (m, } 1 \text{ H, C(4)H}), 7.34 – 7.27 \text{ (m, } 4 \text{ H, C(5)H, C(11)H, C(12)H}), 7.10 \text{ (dd, } J = 7.4, 1.6 \text{ Hz, } 2 \text{ H, C(10)H}), 4.11 – 4.01 \text{ (m, } 1 \text{ H, C(2)H}), 3.23 \text{ (dd, } J = 13.6, 7.9 \text{ Hz, } 1 \text{ H, C(8)H}), 3.14 \text{ (dd, } J = 13.6, 6.7 \text{ Hz, } 1 \text{ H, C(8)H}) \]
- $^{13}$C NMR: (126 MHz, CDCl$_3$)  
  \[ \delta 149.6 \text{ C(6), 148.8 C(7), 135.2 C(9), 134.9 C(4), 130.9 C(3), 129.1 C(10), 128.7 C(11), 127.6 C(12), 123.6 C(5), 119.3 C(1), 41.7 C(8), 37.1 C(2) } \]
- HRMS: ESI  
  \[ m/z: [MH]^+ \text{ Calcd for C}_{14}H_{13}N_2: 209.1079; \text{ Found: 209.1081 } \]
- TLC: \( R_f 0.21 \) (CH$_2$Cl$_2$/EtOAc, 90:10) [silica gel, UV, iodine]
2,3-Diphenylpropanenitrile (8ha)

Following General Procedure VIII, phenylacetonitrile (0.231 mL, 2.0 mmol), benzaldehyde (0.214 mL, 2.1 mmol, 1.05 equiv), and DBN (0.012 mL, 0.1 mmol, 0.05 equiv) were sequentially added to a 40-mL vial and the reaction was stirred at room temperature for 6 h under air. RhCl$_3$·3H$_2$O (15.8 mg, 0.06 mmol, 3 mol %), CH$_3$CN (1.0 mL), H$_2$O (1.80 mL, 100.0 mmol, 50.0 equiv), and Et$_3$N (0.70 mL, 5.0 mmol, 2.5 equiv) were added to the vial and the vial was transferred to an autoclave where the reaction was stirred at room temperature for 72 h under CO followed by standard workup. Purification by silica gel column chromatography (pentane/CH$_2$Cl$_2$ 70:30), followed by recrystallization (pentane/CH$_2$Cl$_2$, 95:5), afforded 8ha (261 mg, 63%) as a white, crystalline solid. The spectral data matched those previously reported in the literature.$^{10}$

Data for 8ha:

**mp:** 56-57 °C (pentane/CH$_2$Cl$_2$, 95:5)

**$^1$H NMR:** (500 MHz, CDCl$_3$)

δ 7.39 – 7.25 (m, 8H), 7.17 – 7.12 (m, 2 H), 4.00 (dd, $J = 8.4$, 6.4 Hz, 1 H, C(2)H), 3.20 (dd, $J = 13.6$, 8.4 Hz, 1 H, C(7)H), 3.14 (dd, $J = 13.6$, 6.4 Hz, 1 H, C(7)H’)

**$^{13}$C NMR:** (126 MHz, CDCl$_3$)

δ 136.3, 135.2, 129.2, 129.0, 128.6, 128.9, 127.5, 127.4, 120.4 C(1), 42.2 C(7), 39.8 C(2)

**HRMS:** (EI)

$m/z$: [M]$^+$ Calcd for C$_{15}$H$_{13}$N: 207.1048; Found: 207.1055

**TLC:** $R_f$ 0.21 (pentane/CH$_2$Cl$_2$ 70:30) [silica gel, UV, iodine]
Diethyl 2-Benzylmalonate (8ia)

Following General Procedure VIII, diethyl malonate (0.304 mL, 2.0 mmol), benzaldehyde (0.408 mL, 4 mmol, 2 equiv), L-proline (23 mg, 0.2 mmol, 0.1 equiv), H₂O (0.180 mL, 10.0 mmol, 5.0 equiv), and Et₃N (0.28 mL, 2.0 mmol, 1 equiv) were sequentially added to a 40-mL vial and the reaction was stirred at room temperature for 24 h under air. RhCl₃·3H₂O (15.8 mg, 0.06 mmol, 3 mol %), CH₃CN (1.0 mL), and additional Et₃N (0.42 mL, 3.0 mmol, 1.5 equiv) were added to the vial and the vial was transferred to an autoclave where the reaction was stirred at room temperature for 48 h under CO followed by standard workup. Purification by silica gel column chromatography (pentane/Et₂O, 90:10), followed by Kugelrohr distillation, afforded 8ia (353 mg, 70%) as a colorless oil. The spectral data matched those previously reported in the literature.¹¹

**Data for 8ia:**

- **bp:** 168 °C (ABT, 0.5 mmHg)
- **¹H NMR:** (500 MHz, CDCl₃)
  - δ 7.30 – 7.24 (m, 2 H, C(8)H), 7.24 – 7.18 (m, 3 H, C(7)H, C(9)H), 4.23 – 4.09 (m, 4 H, C(2)H₂), 3.65 (t, J = 7.9 Hz, 1 H, C(4)H), 3.22 (d, J = 7.9 Hz, 2 H, C(5)H₂), 1.20 (t, J = 7.2 Hz, 6H, C(1)H₃)
- **¹³C NMR:** (126 MHz, CDCl₃)
  - δ 168.9 C(3), 137.9 C(6), 128.9 C(8), 128.5 C(7), 126.7 C(9), 61.4 C(2), 53.9 C(4), 34.7 C(5), 14.0 C(1)
- **HRMS:** (EI)
  - m/z: [M]+ Calcd for C₁₄H₁₈O₄: 250.1205; Found: 250.1199
- **TLC:** Rf 0.38 (pentane/Et₂O, 80:20) [silica gel, UV, iodine]
Table 2.9, entry 4

Following General Procedure VIII, ethyl benzoacetate (0.346 mL, 2.0 mmol), benzaldehyde (0.407 mL, 4.0 mmol, 2.0 equiv), H₂O (0.180 mL, 10.0 mmol, 5.0 equiv), and Et₃N (0.280 mL, 2.0 mmol, 1.0 equiv) were sequentially added to a 40-mL vial and stirred under air for 24 h. RhCl₃·3H₂O (15.8 mg, 0.06 mmol, 3 mol %), CH₃CN (1.0 mL), and additional Et₃N (0.420 mL, 3.0 mmol, 1.5 equiv) were added and the reaction was stirred at room temperature for 48 h under CO followed by standard workup. The conversion to 8ja was determined to be 33% by analysis of the crude reaction mixture by ¹H NMR (based on mesitylene (0.096 mL, 0.5 mmol) as the standard).

Deuterium Incorporation Experiment (Scheme 6)

In the glove box, Rh₄(CO)₁₂ (3.7 mg, 0.005 mmol, 1.25 mol %) was added to a 10-mL glass vial. The vial was sealed and removed from the glove box. Acetonitrile (0.8 mL), the pre-formed Knoevenagel condensation adduct 9af (93 mg, 0.4 mmol), D₂O (0.108 mL, 6.0 mmol, 15.0 equiv), and triethylamine (0.139 mL, 1.0 mmol, 2.5 equiv) were sequentially added to the vial. A stir bar was added, and the vial was placed in an autoclave. The autoclave was pressurized with CO and vented three times, and then pressurized to 10 bar. The reaction was stirred at room temperature for 24 h. After venting and purging the autoclave with nitrogen, the vial was removed. The volatiles were removed by rotary evaporation (25-30 °C, 15 mmHg), the residue was dissolved in CH₂Cl₂, and filtered through a silica plug (eluting with CH₂Cl₂). Deuterium incorporation at C(3) was determined to be 92% by mass spectrometry analysis (ESI) of the filtrate.¹²,¹³

<table>
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<tr>
<td>% average</td>
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</table>
Figure 8.3. Mass-spec signal of 8af(D).
8.3. Experimental section for chapter 3

The following compounds were prepared according to published procedures: 4-iodo-\(N,N\)-dimethylaniline \(5a\),\(^{14}\) 2,6-diethylldiodobenzene \(15a\),\(^{15}\) 2,6-diisopropyldiodobenzene \(16a\),\(^{16}\) and tert-butyl 5-iodo-1H-indole-1-carboxylate \(22a\).\(^{17}\)

General Procedure I: Catalyst Screening and Conditions Optimization: Reductive Carbonylation of 2,6-Dimethyliodobenzene (Table 3.1)

A DMF stock solution containing PdCl\(_2\) (0.3 mmol/L) and 4,4‘dimethoxy-2,2’bipyridyl \(L\) (0.1 mol/L) was prepared by heating at 50 °C for 1 h. The co-catalyst – 0.008 mmol or 1.9 mg of \([\text{RhCODCl}]_2\) - was added to a 4-mL glass vial, followed by 0.4 mL of the DMF stock solution, 0.4 mmol or 57.7 μL of 2,6-dimethyliodobenzene \(1a\), 14.4 μL of deionized water, 120 μL of TMEDA (base), and 20 μL of mesitylene as internal standard. A stir bar was added, and the vial was placed in an autoclave. The autoclave was pressurized with CO and vented three times, and then pressurized to the specified pressure. The mixture was stirred at 85 °C for 18 h. After venting and purging the autoclave with nitrogen, the vial was removed. An aliquot was taken and diluted in ethylether before being passed through a short silica column and injected into a HP-1701 GC column (25 m, 0.2 mm ID, 0.33 μm thickness). The column oven temperature program was as follows: 100 °C for 10 minutes, 100 °C to 200 °C at 10 °C /min, 200 °C to 260 °C at 20 °C /min, then 260 °C for 5 minutes.

GC response factors were established by the following equation using mesitylene as the internal standard:

\[
\text{Response Factor} = \frac{\text{area of compound}}{\text{area of mesitylene}} \times \frac{(\text{mmols of compound})}{(\text{mmol of mesitylene})}.
\]

Three samples containing a known amount of the desired compound and mesitylene were
prepared and dissolved in ethylether. A small portion of each sample was diluted further to 1 mL. An aliquot of each sample was injected into GC in triplicates. The average of 9 response factors was used to monitor reductive carbonylation reactions Table 8.3.

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<th>compound</th>
<th>response factor</th>
<th>( t_k ) (min)</th>
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<td>1a</td>
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<td>12.19</td>
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<tr>
<td>1b</td>
<td>1.95</td>
<td>11.21</td>
</tr>
<tr>
<td>1c</td>
<td>1.67</td>
<td>3.34</td>
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<tr>
<td>mesitylene</td>
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</table>

**Table 8.3. GC calibration factors.**

**General Procedure II: Screen of Different Rh Co-Catalyst Precursors.**

A DMF stock solution containing PdCl\(_2\) (3 mmol/L) and 4,4’dimethoxy-2,2’bipyridyl (0.1 mol/L) was prepared by heating at 50 °C for 1 h. The rhodium co-catalyst was added to a 4-mL glass vial, followed by 0.4 mL of the DMF stock solution, 0.4 mmol or 57.7 \( \mu \)L of 2,6-dimethyliodobenzene 1a, 14.4 \( \mu \)L of deionized water, 120 \( \mu \)L of TMEDA (base), and 20 \( \mu \)L of mesitylene as internal standard. A stir bar was added, and the vial was placed in an autoclave. The autoclave was pressurized with CO and vented three times, and then pressurized to the specified pressure. The mixture was stirred at 85 °C for 18h. After venting and purging the autoclave with nitrogen, the vial was removed. An aliquot was taken and diluted in ethylether before being passed through a short silica column and injected into a GC. The analysis and calibration factors used are described above. The effectiveness of different Rh precursors is shown in Table 8.4.
Table 8.4. Screen of different Rh co-catalysts sources

<table>
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<th>entry</th>
<th>co-catalyst</th>
<th>1b consumption (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>1a yield (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>1c yield (%)&lt;sup&gt;a&lt;/sup&gt;</th>
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<td>4</td>
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<tr>
<td>2</td>
<td>Rh&lt;sub&gt;2&lt;/sub&gt;(OAc)&lt;sub&gt;4&lt;/sub&gt; (1.5 mol %)</td>
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<td>10</td>
</tr>
<tr>
<td>3</td>
<td>Rh&lt;sub&gt;4&lt;/sub&gt;(CO)&lt;sub&gt;12&lt;/sub&gt; (0.75 mol %)</td>
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<td>74</td>
<td>6</td>
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<tr>
<td>4</td>
<td>Rh/C (5 wt%, 20 mg)</td>
<td>12</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>5</td>
<td>RhCOD(MeCN)&lt;sub&gt;2&lt;/sub&gt;BF&lt;sub&gt;4&lt;/sub&gt; (3 mol %)</td>
<td>97</td>
<td>redo</td>
<td>redo</td>
</tr>
<tr>
<td>6</td>
<td>Rh(PPh&lt;sub&gt;3&lt;/sub&gt;)&lt;sub&gt;3&lt;/sub&gt;Cl</td>
<td>redo</td>
<td>redo</td>
<td>redo</td>
</tr>
</tbody>
</table>

General Procedure III: Screen of Different Pd Catalyst Precursors

DMF stock solutions containing different Pd precursors (3 mmol/L each) and 4,4’-dimethoxy-2,2’-bipyridyl (0.1 mol/L) were prepared by heating at 50 °C for 1 h. The co-catalyst – 0.008 mmol or 1.9 mg of [RhCODCl]<sub>2</sub> - was added to a 4-mL glass vial, followed by 0.4 mL of the DMF stock solution containing the Pd catalyst to be tested, 0.4 mmol or 57.7 µL of 2,6-dimethyliodobenzene 1a, 14.4 µL of deionized water, 120 µL of TMEDA (base), and 20 µL of mesitylene as internal standard. A stir bar was added, and the vial was placed in an autoclave. The autoclave was pressurized with CO and vented three times, and then pressurized to the specified pressure. The mixture was stirred at 85 °C for 18h. After venting and purging the autoclave with nitrogen, the vial was removed. An aliquot was taken and diluted in ethylether before being passed through a short silica column and injected into a GC. The analysis and calibration factors used are described above. The effectiveness of different Pd precursors is shown in Table 8.5.
Table 8.5. Screen of different Pd catalysts sources

<table>
<thead>
<tr>
<th>entry</th>
<th>Pd cat.</th>
<th>1b consumption (%)</th>
<th>1a yield (%)</th>
<th>1c yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>--</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>Pd(PPh₃)₄ (0.3 mol %)</td>
<td>97</td>
<td>89</td>
<td>3</td>
</tr>
<tr>
<td>3</td>
<td>Pd PEPPSI-iPr (0.3 mol %) + KOH (100 mol %)</td>
<td>67</td>
<td>11</td>
<td>45</td>
</tr>
<tr>
<td>4</td>
<td>Pd(OAc)₂ (0.3 mol %)</td>
<td>66</td>
<td>54</td>
<td>7</td>
</tr>
<tr>
<td>5</td>
<td>PdCl₂ (0.3 mol %)</td>
<td>98</td>
<td>87</td>
<td>4</td>
</tr>
<tr>
<td>6</td>
<td>Pd(acac)₂ (0.3 mol %)</td>
<td>99</td>
<td>81</td>
<td>5</td>
</tr>
<tr>
<td>7</td>
<td>Pd/Al₂O₃ (5wt%) 30 mg</td>
<td>99</td>
<td>86</td>
<td>3</td>
</tr>
<tr>
<td>8</td>
<td>Pd(NO₃)₂</td>
<td>7</td>
<td>3</td>
<td>1</td>
</tr>
</tbody>
</table>

General Procedure IV: Effect of Pd Loading (Figure 3.1a)

A DMF stock solution containing PdCl₂ (3 mmol/L) and 4,4’-dimethoxy-2,2’-bipyridyl (0.1 mol/L) was prepared by heating at 50 °C for 1 h. The co-catalyst – 0.008 mmol or 1.9 mg of [RhCODCl]₂ - was added to a 4-mL glass vial, followed by different quantities of the DMF stock solution containing the Pd catalyst were added to each vial and the total volume of DMF solvent was adjusted to 0.4 mL by adding blank DMF. Additional 4,4’-dimethoxy-2,2’-bipyridyl was added to each vial to bring the total mass of the ligand to 8.5 mg (0.1 equiv) in each vial. 0.4 mmol or 57.7 μL of 2,6-dimethylidobenzene 1a was added to each vial followed by 14.4 μL of deionized water, 120 μL of TMEDA (base), and 20 μL of mesitylene as internal standard. A stir bar was added, and the vials were placed in an autoclave. The autoclave was pressurized with CO and vented three times, and then pressurized to the specified pressure. The mixture was stirred at 85 °C for 8h. After venting and purging the autoclave with nitrogen, the vials were removed. An aliquot was taken and diluted in ethylether before being passed through a short silica column and injected into a GC. The analysis and calibration factors used are described above.
General Procedure V: Effect of Rh Loading (Figure 3.1b)

A DMF stock solution containing PdCl$_2$ (3 mmol/L) and 4,4’-dimethoxy-2,2’bipyridyl (0.1 mol/L) was prepared by heating at 50 °C for 1 h. Different amounts of the co-catalyst [RhCODCl]$_2$ were added to a 4-mL glass vial, followed by 0.4 mL of the DMF stock solution containing the Pd catalyst to each vial. 0.4 mmol or 57.7 µL of 2,6-dimethyliodobenzene 1a was added to each vial followed by 14.4 µL of deionized water, 120 µL of TMEDA (base), and 20 µL of mesitylene as internal standard. A stir bar was added, and the vials were placed in an autoclave. The autoclave was pressurized with CO and vented three times, and then pressurized to the specified pressure. The mixture was stirred at 85 °C for 18 h. After venting and purging the autoclave with nitrogen, the vials were removed. An aliquot was taken and diluted in ethylether before being passed through a short silica column and injected into a GC. The analysis and calibration factors used are described above.

General Procedure VI: Effect of Water Loading

A DMF stock solution containing PdCl$_2$ (3 mmol/L) and 4,4’-dimethoxy-2,2’bipyridyl (0.1 mol/L) was prepared by heating at 50 °C for 1 h. To 4 mL glass vials, 0.008 mmol or 1.9 mg of [RhCODCl]$_2$ of the co-catalyst was added followed by 0.4 mL of the DMF stock solution, and 0.4 mmol or 57.7 µL of 2,6-dimethyliodobenzene 1a. Different amounts of deionized water were added to the vials followed by 120 µL of TMEDA, and 20 µL of mesitylene as internal standard. A stir bar was added, and the vials were placed in an autoclave. The autoclave was pressurized with CO and vented three times, and then pressurized to 15 bar. The mixture was stirred at 85 °C for 18 h. After venting and purging the autoclave with nitrogen, the vial was removed. An aliquot was taken and diluted in ethylether before being passed through a short silica column and injected into a GC. The analysis and calibration factors used are described above. The effect of water loading is shown in Figure 8.4.
General Procedure VII: Effect of CO Pressure

A DMF stock solution containing PdCl\(_2\) (3 mmol/L) and 4,4’dimethoxy-2,2’bipyridyl (0.1 mol/L) was prepared by heating at 50 °C for 1 h. To 4 mL glass vials, 0.008 mmol or 1.9 mg of [RhCODCl\(_2\)] of the co-catalyst was added followed by 0.4 mL of the DMF stock solution, and 0.4 mmol or 57.7 µL of 2,6-dimethylidobenzene 1a, 14.4 µL or 2 equiv of deionized water were added to the vials followed by 120 ul TMEDA, and 20 ul mesitylene as internal standard. A stir bar was added, and the vials was placed in a multicell pressure control autoclave. The autoclave was pressurized with CO and vented three times, and then each cell was pressurized to the desired pressure. The mixture was stirred at 85 °C for 18 h. After venting and purging the autoclave with nitrogen, the vial was removed. An aliquot was taken and diluted in ethylether before being passed through a short silica column and injected into a GC. The analysis and calibration factors used are described above. The effect of CO pressure is shown in Figure 8.5.
Figure 8.5. Effect of CO pressure on the reductive carbonylation of 1a

General Procedure VIII: Screen of Different Bases and Optimization of TMEDA Loading

DMF stock solutions containing PdCl$_2$ (3 mmol/L each) and 4,4’dimethoxy-2,2’bipyridyl (0.1 mol/L) were prepared by heating at 50 °C for 1 h. The co-catalyst – 0.008 mmol or 1.9 mg of [RhCODCl]$_2$ - was added to a 4-mL glass vial, followed by 0.4 mL of the DMF stock solution, 0.4 mmol or 93.7 mg 4-methoxyiodobenzene 1g, 14.4 uL deionized water, 4 equiv of the tested monobasic bases (or 2 equiv of the dibasic bases), and 20 μL of mesitylene as internal standard. A stir bar was added, and the vial was placed in an autoclave. The autoclave was pressurized with CO and vented three times, and then pressurized to the specified pressure. The mixture was stirred at 85 °C for 18h. After venting and purging the autoclave with nitrogen, the vial was removed. An aliquot was taken and diluted in ethylether before being passed through a short silica column and injected into a GC. The analysis and calibration factors used are described above. The effect of base is shown in Table 8.6.
Table 8.6. Screen of different bases for the reductive carbonylation of 4-iodoanisole

<table>
<thead>
<tr>
<th>entry</th>
<th>base</th>
<th>1g consump. (%)</th>
<th>2g yield. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td>96</td>
<td>20</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>90</td>
<td>22</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>97</td>
<td>23</td>
</tr>
<tr>
<td>4</td>
<td>TMEDA</td>
<td>94.3</td>
<td>81</td>
</tr>
<tr>
<td>5</td>
<td>Et₃N</td>
<td>65</td>
<td>48</td>
</tr>
<tr>
<td>6</td>
<td>EtNMe₂</td>
<td>50</td>
<td>43</td>
</tr>
<tr>
<td>7</td>
<td>N,N dimethylaniline</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>9</td>
<td>pyridine</td>
<td>9</td>
<td>0</td>
</tr>
<tr>
<td>10</td>
<td>K₂CO₃ (1 equiv)</td>
<td>87</td>
<td>12</td>
</tr>
<tr>
<td>11</td>
<td>N-Methylmorpholine</td>
<td>12</td>
<td>7</td>
</tr>
<tr>
<td>12</td>
<td>KOH (1 equiv)</td>
<td>93</td>
<td>69</td>
</tr>
</tbody>
</table>

To investigate the amount of TMEDA needed for the reaction, the co-catalyst – 0.008 mmol or 1.9 mg of [RhCODCl]₂ - was added to a 4-mL glass vial, followed by 0.4 mL of the PdCl₂ DMF stock solution, 0.4 mmol or 57.7 μL of 2,6-dimethyliodobenzene 1a, 14.4 μL of deionized water, different quantities of TMEDA, and 20 μL of mesitylene as internal standard. A stir bar was added, and the vials were placed in an autoclave. The autoclave was pressurized with CO and vented three times, and then pressurized to the specified pressure. The mixture was stirred at 85 °C for 18 h. After venting and purging the autoclave with nitrogen, the vials were removed. An aliquot was taken and diluted in ethylether before being passed through a short silica column and injected into a GC. The analysis and calibration factors used are described above. The effect of TMEDA loading is shown in Figure 8.6.
General Procedure IX: Effect Aryl Iodide Concentration

A DMF stock solution containing PdCl₂ (3 mmol/L) and 4,4’-dimethoxy-2,2’-bipyridyl (0.1 mol/L) was prepared by heating at 50 °C for 1 h. To 4 mL glass vials, 0.008 mmol or 1.9 mg of [RhCODCl]₂ of the co-catalyst was added followed by 0.4 mL of the DMF stock solution, and different amounts of 2,6-dimethyliodobenzene 1a, 14.4 μL of or 2 equiv of deionized water were added to the vials followed by 120 μL of TMEDA, and 20 μL of mesitylene as internal standard. A stir bar was added, and the vials were placed in a pressure autoclave. The autoclave was pressurized with CO and vented three times, and then pressurized to 15 bar. The mixture was stirred at 85 °C for 18 h. After venting and purging the autoclave with nitrogen, the vial was removed. An aliquot was taken and diluted in ethylether before being passed through a short silica column and injected into a GC. The analysis and calibration factors used are described above. The effect of the loading of (1a) is shown in Figure 8.7.
General Procedure X: H/D Isotope Effect

A DMF stock solution containing PdCl₂ (3 mmol/L) and 4,4’dimethoxy-2,2’bipyridyl (0.1 mol/L) was prepared by heating at 50 °C for 1 h. To 4 mL glass vials, 0.008 mmol or 1.9 mg of [RhCODCl]₂ of the co-catalyst was added followed by 0.4 mL of the DMF stock solution, 0.4 mmol or 57.7 µL of 2,6-dimethyliodobenzene 1a, 120 µL of TMEDA, and 20 µL of mesitylene as internal standard. To one vial, 14.4 µL of DI water was added and to another vial, 14.4 µL of D₂O (99.9%) was added. A stir bar was added, and the vials was placed in a pressure autoclave. The autoclave was pressurized with CO and vented three times, and then pressurized to 15 bar. The mixture was stirred at 85 °C for 18 h. After venting and purging the autoclave with nitrogen, the vial was removed. An aliquot was taken and diluted in ethylether before being passed through a short silica column and injected into a GC. The analysis and calibration factors used are described above. The effect of H/D switch is shown in Table 8.7.

**Figure 8.7.** Effect of 1a concentration on the rate of reductive carbonylation.
Table 8.7. Effect of replacing H₂O with D₂O on reductive carbonylation of 1a

<table>
<thead>
<tr>
<th>entry</th>
<th>reductant</th>
<th>1a consumption (%)*</th>
<th>1b yield (%)*</th>
<th>1c yield (%)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H₂O</td>
<td>87</td>
<td>79</td>
<td>6</td>
</tr>
<tr>
<td>2</td>
<td>D₂O</td>
<td>48</td>
<td>35</td>
<td>9</td>
</tr>
</tbody>
</table>

* measured by GC with an internal standard

General Procedure XI: Reductive Carbonylation of Aryl Iodides

DMF stock solutions containing PdCl₂ and 4,4′dimethoxy-2,2′bipyridyl (0.1 mol/L) were prepared by heating at 50 °C for 1 h. The co-catalyst – 0.02 mmol or 9.86 mg of [RhCODCl]₂ - was dissolved in 2 mL of the DMF stock solution in a 20-mL glass vial, and 2 mmol of the aryl iodide a, D₂O, and 600 µL of TMEDA were added sequentially. A stir bar was added, and the vial was placed in an autoclave. The autoclave was pressurized with CO and vented three times, and then pressurized to the specified pressure. The mixture was stirred at the identified reaction temperature for 24 h. After venting and purging the autoclave with nitrogen, the vial was removed. The reaction mixture was diluted in diethyl ether (30 mL) and extracted with 1:1 brine/water mixture (3 X 30 mL) and the organic layer was dried by MgSO₄. The volatiles were removed by rotary evaporation (25-30 °C, 15 mmHg), then the residue was dissolved in ether, and was loaded on silica gel (1 g). The crude mixture was purified by silica gel column chromatography (2.5 x 20-25 cm). Deuterium incorporation was calculated by ¹H NMR and by comparison of the signals ratios of the aldehyde mass M and M+1 for the deuterated and nondeuterated compound as measured by EI-MS.

For mono deuterated compounds:

\[
\% D = \frac{I_D(M+1) - (I_D(M) \times [I_S(M+1)/I_S(M)])}{I_D(M+1)}
\]

\% D = % deuterium incorporation

\(I_D(M) = \text{EI-MS intensity of deuterated compound at mass } M\)

\(I_S(M) = \text{EI-MS intensity of non-deuterated compound at mass } M\)
4-Methoxybenzaldehyde-formyl-d$_1$ (2b)

Following General Procedure XI, 0.02 mmol or 9.86 mg of [RhCODCl]$_2$ was dissolved in 2 mL of the DMF stock solutions containing PdCl$_2$ (3 mmol/L) and 4,4′dimethoxy-2,2′bipyridyl (0.1 mol/L), followed 2 mmol or 0.468 g 4-methoxyiodobenzene (2a), 72 μL of D$_2$O, and 600 μL of TMEDA. The reaction was carried out at 85 °C for 24 h under 25 bar CO pressure followed by standard workup. Purification by silica gel column chromatography (pentane/Et$_2$O 80:20) afforded 2b (227 mg, 83%) as a colorless oil. The spectral data matched those previously reported.$^{18}$

Data for 2b:

$^1$H NMR: (500 MHz, Chloroform-d)

9.89 (s, 0.01 H, C(6)H), 7.85 (d, $J = 8.9$ Hz, 2 H, C(1)H), 7.01 (d, $J = 8.9$ Hz, 1 H, C(2)H), 3.89 (s, 3H, C(4)H$_3$).

D incorporation by $^1$H NMR: 99%

$^{13}$C NMR: (126 MHz, Chloroform-d)

192.83 – 187.96 (m) C(6), 164.61 C(3), 131.98 C(1), 130.93 – 128.33 (m) C(5), 114.32 C(2), 55.60 C(4).

HRMS: (ESI)

$m/z$: [M+1]$^+$ Calcd for C$_8$H$_7$DO$_2$: 138.0665; Found: 138.0670

D incorporation by EI-MS:

<table>
<thead>
<tr>
<th></th>
<th>136</th>
<th>137</th>
</tr>
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<tbody>
<tr>
<td>non-D</td>
<td></td>
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</tr>
<tr>
<td>non-D intensity</td>
<td>3.57E+06</td>
<td>3.45E+05</td>
</tr>
<tr>
<td>non D ratio</td>
<td>1</td>
<td>9.68E-02</td>
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<tr>
<td>D</td>
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<td></td>
</tr>
<tr>
<td>enriched intensity</td>
<td>102416</td>
<td>709952</td>
</tr>
<tr>
<td>contribution of non-D intensity due to D</td>
<td>102416</td>
<td>9911.76</td>
</tr>
</tbody>
</table>

%enrichment 98.60388
IR: (neat)
3334 (w), 3075 (w), 3010 (w), 2967 (w), 2937 (w), 2842 (w), 2582 (w), 2105 (w), 2057 (w), 1919 (w), 1671 (s), 1595 (s), 1577 (s), 1510 (s), 1460 (w), 1443 (w), 1422 (m), 1379 (w), 1318 (m), 1305 (w), 1236 (s), 1182 (w), 1161 (s), 1109 (w), 1024 (m), 956 (w), 876 (w), 814 (s), 748 (w), 737 (w), 710 (w), 642 (w), 632 (w), 605 (m), 594 (m), 515 (w).

TLC: $R_f$ 0.12 (pentane/Et$_2$O, 90:10) [silica gel, UV]

4-Methylthiobenzaldehyde-formyl-d$_{1}$ (3b)

Following General Procedure XI, 0.02 mmol or 9.86 mg of [RhCODCl]$_2$ was dissolved in 2 mL of the DMF stock solutions containing PdCl$_2$ (3 mmol/L) and 4,4’dimethoxy-2,2’bipyridyl (0.1 mol/L), followed 2 mmol or 0.490 g 4-methylthiiodobenzene (3a), 72 µL of D$_2$O, and 600 µL of TMEDA. The reaction was carried out at 85 °C for 24 h under 25 bar CO pressure followed by standard workup. Purification by silica gel column chromatography (pentane/Et$_2$O 80:20) afforded (3b) (242 mg, 79%) as a colorless oil. The spectral data matched those previously reported.$^5$

Data for 3b:

$^1$H NMR: (500 MHz, Chloroform-d)
$\delta$ 9.92 (s, 0.01 H, C(6)H), 7.78 (d, $J = 8.6$ Hz, 2 H, C(1)H), 7.33 (d, $J = 8.6$ Hz, 2 H, C(2)H), 2.54 (s, 3 H, C(4)H$_3$).

D incorporation by $^1$H NMR: 99%

$^{13}$C NMR: (126 MHz, Chloroform-d)
$\delta$ 193.54 – 187.17 (m) C(6), 147.90 C(3), 133.91 – 131.71 (m) C(5), 129.99 C(1), 125.20 C(2), 14.71 C(4).

HRMS: (El)
$m/z$: [M]$^+$ Calcd for C$_8$H$_7$DOS: 153.03595; Found: 153.03587
D incorporation by EI-MS:

<table>
<thead>
<tr>
<th></th>
<th>152</th>
<th>153</th>
</tr>
</thead>
<tbody>
<tr>
<td>non-D</td>
<td>non-D intensity</td>
<td>905216</td>
</tr>
<tr>
<td></td>
<td>non D ratio</td>
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<tr>
<td></td>
<td></td>
<td>1.52E-01</td>
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<tr>
<td>D</td>
<td>enriched intensity</td>
<td>2647</td>
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<tr>
<td></td>
<td>contribution of non-D</td>
<td>2647</td>
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<tr>
<td></td>
<td>intensity due to D</td>
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<tr>
<td></td>
<td>%enrichment</td>
<td>98.7487</td>
</tr>
</tbody>
</table>

IR: (neat)

3332 (w), 3178 (w), 3055 (w), 2988 (w), 2922 (w), 2835 (w), 2599 (w), 2566 (w), 2103 (w), 2059 (w), 2044 (w), 1920 (w), 1751 (w), 1678 (s), 1665 (s), 1588 (s), 1558 (s), 1490 (w), 1435 (w), 1401 (m), 1324 (w), 1306 (w), 1281 (w), 1230 (s), 1173 (m), 1120 (w), 1092 (s), 1041 (w), 1010 (w), 968 (w), 953 (w), 876 (w), 795 (s), 726 (w), 700 (w), 681 (m), 628 (w), 540 (w), 532 (w), 482 (m).

TLC: \( R_f 0.19 \) (pentane/Et\(_2\)O, 90:10) [silica gel, UV]

3-Methoxybenzaldehdye-formyl-\( d_1 \) (4b)

Following General Procedure XI, 0.02 mmol or 9.86 mg of [RhCODCl\(_2\)] was dissolved in 2 mL of the DMF stock solutions containing \( \text{PdCl}_2 \) (3 mmol/L) and \( 4,4' \text{dimethoxy-2,2'bipyridyl} \) (0.1 mol/L), followed 2 mmol or 0.468 g 3-methoxyiodobenzene \( 4\text{a} \), 72 \( \mu\)L of D\(_2\)O, and 600 \( \mu\)L of TMEDA. The reaction was carried out at 85 °C for 24 h under 25 bar CO pressure followed by standard workup. Purification by silica gel column chromatography (pentane/Et\(_2\)O 90:10) afforded \( 4\text{b} \) (221 mg, 64%) as a colorless oil. The spectral data matched those previously reported in the literature.\(^5\)

Data for \( 2\text{b} \):

\(^1\)H NMR: (500 MHz, Chloroform-\( d\))

9.98 (s, 0.02 H, C(8)H), 7.50 – 7.42 (m, 2 H, C(5)H, C(6)H), 7.41 – 7.38 (m, 1 H,
C(1)H, 7.18 (dt, J = 6.9, 2.5 Hz, 1 H, C(4)H), 3.87 (s, 3 H, C(3)H₃).

D incorporation by ¹H NMR: 98%

¹³C NMR: (126 MHz, Chloroform-d)

193.14 – 189.45 (m) C(8), 160.17 C(2), 139.10 – 135.01 (m) C(7), 130.04 C(5), 123.57 C(6), 121.57 C(4), 112.01 C(1), 55.5 C(3).

HRMS: (EI)
m/z: [M]+ Calcd for C₈H₇DO₂: 137.05871; Found: 137.0581

D incorporation by EI-MS:

<table>
<thead>
<tr>
<th></th>
<th>136</th>
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<tbody>
<tr>
<td>non-D</td>
<td>1673728</td>
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<tr>
<td>non-D ratio</td>
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<td>8.99E-02</td>
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<tr>
<td>D enriched intensity</td>
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<td>contribution of non-D</td>
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<td>intensity due to D</td>
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<td>763432.8</td>
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<tr>
<td>%enrichment</td>
<td></td>
<td>98.61638</td>
</tr>
</tbody>
</table>

IR: (neat)

3349 (w), 3068 (w), 3007 (w), 2943 (w), 2838 (w), 2593 (w), 2189 (w), 2109 (w), 2059 (w), 1676 (s), 1651 (w), 1596 (m), 1584 (m), 1486 (m), 1465 (m), 1455 (m), 1431 (m), 1329 (w), 1287 (m), 1263 (s), 1196 (m), 1169 (m), 1154 (m), 1081 (w), 1034 (m), 993 (w), 907 (w), 882 (w), 844 (w), 781 (m), 749 (w), 732 (w), 723 (m), 682 (m), 639 (w), 551 (w).

TLC: Rf 0.26 (pentane/Et₂O, 90:10) [silica gel, UV]

4-N,N-Dimethylaminobenzaldehyde-formyl-d₁ (5b)

Following General Procedure XI, 0.02 mmol or 9.86 mg of [RhCODCl]₂ was dissolved in 2 mL of the DMF stock solutions containing PdCl₂ (3 mmol/L) and 4,4’dimethoxy-2,2’bipyridyl
(0.1 mol/L), followed 2 mmol or 0.493 g 4-iodo-\textit{N},\textit{N}-dimethylaniline 5a, 72 μL of D$_2$O, and 600 μL of TMEDA. The reaction was carried out at 85 °C for 24 h under 25 bar CO pressure followed by standard workup. Purification by silica gel column chromatography (pentane/Et$_2$O 70:30) afforded 5b (126 mg, 42%) as a white solid. The spectral data matched those previously reported in the literature.$^{19}$

**Data for 5b:**

$^1$H NMR: (500 MHz, Chloroform-\textit{d})

9.74 (s, 0.02 H, C(6)H), 7.74 (d, $J$ = 8.9 Hz, 2 H, C(1)H), 6.70 (d, $J$ = 9.0 Hz, 2 H, C(2)H), 3.09 (s, 6 H, C(4)H$_3$).

D incorporation by $^1$H NMR: 98%

$^{13}$C NMR: (126 MHz, Chloroform-\textit{d})

191.65 – 187.56 (m) C(6), 154.32 C(3), 132.00 C(1), 125.03 C(5), 110.98 C(2), 40.14 C(4).

HRMS: (EI) $m/z$: [M]$^+$ Calcd for C$_9$H$_{10}$DNO: 150.09093; Found: 150.09034

D incorporation by EI-MS:

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IR: (neat)

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TLC: $R_f$ 0.06 (pentane/Et$_2$O, 90:10) [silica gel, UV]
4-Chlorobenzaldehyde-formyl-\textit{d}_1 (6b)

Following General Procedure XI, 0.02 mmol or 9.86 mg of [RhCODCl]_2 was dissolved in 2 mL of the DMF stock solutions containing PdCl₂ (6 mmol/L) and 4,4’dimethoxy-2,2’bipyridyl (0.1 mol/L), followed 2 mmol or 0.476 g 4-chloro-iodobenzene 6a, 72 μL of D₂O, and 600 μL of TMEDA. The reaction was carried out at 65 °C for 24 h under 25 bar CO pressure followed by standard workup. Purification by silica gel column chromatography (pentane/Et₂O, 90:10) afforded 6b (180 mg, 64%) as a white solid. The spectral data matched those previously reported in the literature.\(^5\)

Data for 6b:

\[^1\text{H} \text{NMR:} \quad (500 \text{ MHz, Chloroform-d})\]

9.98 (s, 0.03 H, C(5)H), 7.83 (d, \(J = 8.5 \text{ Hz})\), 2 H, C(1)H), 7.52 (d, \(J = 8.6 \text{ Hz})\), 2 H C(2)H).

D incorporation by \[^1\text{H} \text{NMR:} \quad 97\%

\[^{13}\text{C} \text{NMR:} \quad (126 \text{ MHz, Chloroform-d})\]

193.14 – 187.56 (m) C (5), 140.97 C(3), 135.80 – 133.20 (m) C(4), 130.90 C(1), 129.47 C(2).

HRMS: \quad (EI)

\(m/z: [M]^+\) Calcd for C₇H₄DCIO: 141.0092; Found: 141.0089

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1368 (w), 1321 (w), 1285 (m), 1221 (s), 1176 (w), 1155 (s), 1110 (w),
1090 (s), 1077 (s), 1046 (m), 1010 (m), 974 (w), 966 (w), 883 (m), 838 (w), 823
(m), 798 (s), 774 (m), 736 (w), 691 (m), 628 (w), 539 (s), 478 (m).

TLC: Rf 0.31 (pentane/Et₂O, 90:10) [silica gel, UV]

4-Bromobenzaldehyde- formyl-d₅ (7b)

Following General Procedure XI, 0.02 mmol or 9.86 mg of [RhCODCl]₂ was dissolved in 2
mL of the DMF stock solutions containing PdCl₂ (6 mmol/L) and 4,4’dimethoxy-2,2’bipyridyl
(0.1 mol/L), followed 2 mmol or 0.564 g 4-bromo-iodobenzene 7a, 72 μL of D₂O, and 600 μL of
TMEDA. The reaction was carried out at 65 °C for 24 h under 25 bar CO pressure followed by
standard workup. Purification by silica gel column chromatography (pentane/Et₂O 90:10)
afforded 7b (203 mg, 55%) as a white solid. The spectral data matched those previously reported
in the literature.⁶

Data for 7b:

¹H NMR: (500 MHz, Chloroform-d)
9.98 (s, 0.05 H, C(5)H), 7.75 (d, J = 8.5 Hz, 2 H, C(2)H), 7.69 (d, J = 8.5 Hz, 2 H,
C(1)H).

D incorporation by ¹H NMR: 95%

¹³C NMR: (126 MHz, Chloroform-d)
191.65 – 189.45 (m) C(5), 136.50 – 133.91 (m) C(4), 132.45 C(2), 130.96 C(1),
129.79 C(3).

HRMS: (EI)
m/z: [M]+ Calcd for C₇H₄DBrO: 185.9665; Found: 185.9666
D incorporation by EI-MS:

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IR: (neat)
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TLC: $R_f$ 0.27 (pentane/Et$_2$O, 90:10) [silica gel, UV]

4-Fluorobenzaldehyde- formyl-$d_1$ (8b)

Following General Procedure XI, 0.02 mmol or 9.86 mg of [RhCODCl]$_2$ was dissolved in 2 mL of the DMF stock solutions containing PdCl$_2$ (6 mmol/L) and 4,4’dimethoxy-2,2’bipyridyl (0.1 mol/L), followed 2 mmol or 0.444 g 4-fluoro-iodobenzene 8a, 72 µL of D$_2$O, and 600 µL of TMEDA. The reaction was carried out at 65 °C for 24 h under 25 bar CO pressure followed by standard workup. Purification by silica gel column chromatography (pentane/Et$_2$O 90:10) afforded 8b (153 mg, 61%) as a colorless liquid. The spectral data matched those previously reported in the literature.$^{20}$

Data for 8b:

$^1$H NMR: (500 MHz, Chloroform-$d$)
9.97 (s, 0.04 H, C(5)H), 8.06 – 7.77 (m, 2 H, C(1)H), 7.22 (t, J = 8.5 Hz, 2 H,
C(1)H.

**D incorporation by $^1$H NMR: 96%**

**$^{13}$C NMR: (126 MHz, Chloroform-$d$)**

$^{13}$C NMR: 192.35 – 188.95 (m) C(5), 166.54 (d, $J = 256.8$ Hz) C(3), 132.89 C(4), 132.23 (d, $J = 9.7$ Hz) C(1), 116.37 (d, $J = 22.3$ Hz) C(2).

**$^{19}$F NMR: (470 MHz, Chloroform-$d$)**

$^\delta$ -102.16 – -103.94 (m) C(3).

**HRMS: (EI)**

$m/z$: [M]$^+$ Calcd for $C_7H_4DFO$: 125.0387; Found: 125.0391

**D incorporation by EI-MS:**

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**IR: (neat)**

3354 (w), 3076 (w), 2618 (w), 2444 (w), 2252 (w), 2112 (w), 2059 (w), 1972 (w), 1923 (w), 1680 (s), 1595 (s), 1506 (m), 1412 (w), 1296 (w), 1229 (s), 1150 (m), 1095 (w), 1041 (w), 1011 (w), 957 (w), 882 (m), 847 (w), 812 (s), 749 (w), 699 (w), 635 (w), 596 (m), 505 (m).

**TLC:** $R_f$ 0.29 (pentane/Et$_2$O, 90:10) [silica gel, UV]

**4-Trifluoromethylbenzaldehyde- formyl-$d_1$ (9b)**

![4-Trifluoromethylbenzaldehyde- formyl-$d_1$ (9b)](image)

Following General Procedure XI, 0.02 mmol or 9.86 mg of [RhCODCl]$_2$ was dissolved in 2 mL of the DMF stock solutions containing PdCl$_2$ (6 mmol/L) and 4,4’dimethoxy-2,2’bipyridyl.
(0.1 mol/L), followed 2 mmol or 0.544 g 4-trifluoromethyl-iodobenzene 9a, 72 μL of D₂O, and 600 μL of TMEDA. The reaction was carried out at 65 °C for 24 h under 25 bar CO pressure followed by standard workup. Purification by silica gel column chromatography (pentane/Et₂O 95:5) afforded 9b (174 mg, 42%) as a colorless liquid. The spectral data matched those previously reported. 5

Data for 9b:

^1H NMR: (500 MHz, Chloroform-d)

10.11 (s, 0.03 H, C (6)H), 8.18 – 7.94 (m, 2 H, C(1)H), 7.82 (d, J = 8.0 Hz, 2 H C(2)H).

D incorporation by ^1H NMR: 97%

^13C NMR: (126 MHz, Chloroform-d)

192.83 – 188.66 (m) C(6), 138.57 C(5), 135.64 (d, J = 32.7 Hz) C(3), 129.90 C(1), 126.12 (q, J = 3.8 Hz) C(2), 123.42 (d, J = 272.9 Hz) C(4).

^19F NMR: (471 MHz, Chloroform-d)

δ -63.17 C(4).

HRMS: (EI) m/z: [M]^+ Calcd for C₈H₄DF₃O: 175.03553; Found: 175.03489

D incorporation by EI-MS:

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IR: (neat)

3073 (w), 2956 (w), 2924 (w), 2854 (w), 1725 (w), 1674 (m), 1617 (w), 1584 (w), 1511 (w), 1462 (w), 1411 (w), 1365 (w), 1322 (s), 1294 (w), 1215 (w), 1173 (m), 1129 (s), 1067 (s), 1038 (w), 1016 (w), 965 (w), 931 (w), 893 (w), 857 (w), 784 (w), 767 (w), 756 (w), 712 (w), 699 (w), 672 (w), 629 (w), 591 (w), 509 (w), 489 (w).

TLC:  Rf 0.62 (pentane/Et₂O, 90:10) [silica gel, UV]

209
Methyl 4-Formylbenzoate- formyl-\textit{d}_1(10b)

Following General Procedure XI, 0.02 mmol or 9.86 mg of [RhCODCl]$_2$ was dissolved in 2 mL of the DMF stock solutions containing PdCl$_2$ (6 mmol/L) and 4,4’dimethoxy-2,2’bipyridyl (0.1 mol/L), followed 2 mmol or 0.524 g 4-methylbenzoate-iodobenzene 10a, 72 μL of D$_2$O, and 600 μL of TMEDA. The reaction was carried out at 65 °C for 24 h under 25 bar CO pressure followed by standard workup. Purification by silica gel column chromatography (pentane/Et$_2$O 75:25) afforded 10b (211 mg, 64%) as a white solid. The spectral data matched those previously reported in the literature.\textsuperscript{21}

**Data for 10b:**

\textsuperscript{1}H NMR: (500 MHz, Chloroform-\textit{d})

10.11 (s, 0.11 H, C(7)H), 8.23 – 8.16 (m, 2 H, C(1)H), 7.96 (d, \(J = 8.6 \) Hz, 2 H, C(2)H), 3.97 (s, 3H, C(5)H$_3$).

\textit{D} incorporation by \textsuperscript{1}H NMR: 89%  

\textsuperscript{13}C NMR: (126 MHz, Chloroform-\textit{d})

191.35 (d, \(J = 66.1 \) Hz) C(7), 166.06 C(4), 139.10 C(6), 135.11 C(3), 130.20 C(2), 129.51 C(1), 52.59 C(5).

HRMS: (EI)

\(m/z: [M]^+\) Calcd for C$_9$H$_7$DO$_3$: 165.0536; Found: 165.05379

\textit{D} incorporation by EI-MS:

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IR: (neat)

3424 (w), 3327 (w), 2962 (w), 2927 (w), 2853 (w), 2436 (w), 2160 (w), 2126 (w),
2073 (w), 1956 (w), 1721 (s), 1689 (m), 1669 (s), 1611 (w), 1575 (m), 1502 (w),
1436 (m), 1407 (m), 1381 (w), 1277 (s), 1218 (s), 1198 (m), 1170 (m), 1105 (s),
1048 (m), 1011 (m), 955 (m), 898 (m), 858 (w), 850 (w), 834 (m), 809 (m), 788
(s), 746 (s), 684 (m), 674 (m), 628 (w), 533 (m), 514 (w), 463 (m).

TLC: Rf 0.13 (pentane/Et₂O, 90:10) [silica gel, UV]

4-Cyanobenzaldehyde- formyl-d₁ (11b)

Following General Procedure XI, 0.02 mmol or 9.86 mg of [RhCODCl]₂ was dissolved in 2
mL of the DMF stock solutions containing PdCl₂ (6 mmol/L) and 4,4’dimethoxy-2,2’bipyridyl
(0.1 mol/L), followed 2 mmol or 0.458 g 4-cyano-iodobenzene 11a, 72 µL of D₂O, and 600 µL
of TMEDA. The reaction was carried out at 65 °C for 24 h under 25 bar CO pressure followed by
standard workup. Purification by silica gel column chromatography (pentane/Et₂O 70:30)
afforded 11b (84 mg, 32%) as a white solid. The spectral data matched those previously reported
in the literature.⁶

Data for 11b:

₁H NMR: (500 MHz, Chloroform-d)

10.09 (s, 0.02 H, C(6)H), 7.99 (d, J = 8.5 Hz, 2 H, C(2)H), 7.84 (d, J = 8.5 Hz, 2
H, C(1)H).

D incorporation by ¹H NMR: 98%

¹³C NMR: (126 MHz, Chloroform-d)

192.83 – 187.96 (m) C(6), 138.87 – 138.14 (m) C(5), 132.90 C(2), 129.87 C(1),
117.70 C(3), 117.62 C(4).

HRMS: (EI)

m/z: [M]+ Calcd for C₈H₄DNO: 132.04329; Found: 132.04339
D incorporation by EI-MS:

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IR: (neat)
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TLC: \( R_f 0.07 \) (pentane/Et\(_2\)O, 90:10) [silica gel, UV]

**2-Trifluoromethylbenzaldehyde- formyl-d\(_1\) (12b)**

![Structure of 2-Trifluoromethylbenzaldehyde- formyl-d\(_1\) (12b)](structure.png)

Following General Procedure XI, 0.02 mmol or 9.86 mg of \([\text{RhCODCl}]_2\) was dissolved in 2 mL of the DMF stock solutions containing \(\text{PdCl}_2\) (6 mmol/L) and 4,4’-dimethoxy-2,2’-bipyridyl (0.1 mol/L), followed 2 mmol or 0.544 g 2-trifluoromethyl-iodobenzene \(12a\), 72 \(\mu\)L of D\(_2\)O, and 600 \(\mu\)L of TMEDA. The reaction was carried out at 95 °C for 24 h under 25 bar CO pressure followed by standard workup. Purification by silica gel column chromatography (pentane/Et\(_2\)O 95:5) afforded \(12b\) (168 mg, 48%) as a colorless liquid. The spectral data matched those previously reported in the literature.\(^8\)

Data for \(12b\):

\(^1\)H NMR: (500 MHz, Chloroform-\(d\))
10.40 (d, \(J = 2.0\) Hz, 0.13 H, C(8)H), 8.20 – 8.04 (m, 1 H, C(1)H), 7.79 (dd, \(J =\) 212
5.2, 3.8 Hz, 1 H, C(4)H), 7.74 – 7.66 (m, 2 H, C(2)H, C(3)H).

D incorporation by $^1$H NMR: 87%

$^{13}$C NMR: (126 MHz, Chloroform-$d$)

$^{1}$H NMR: (376 MHz, Chloroform-$d$)

δ -55.97 C(6).

HRMS: (EI)

$m/z$: [M]$^+$ Calcd for C$_8$H$_4$DF$_3$O: 175.03505; Found: 175.03553

D incorporation by EI-MS:

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IR: (neat)

2926 (w), 2163 (w), 1704 (w), 1686 (m), 1601 (m), 1583 (w), 1313 (s), 1275 (s), 1210 (m), 1175 (s), 1120 (s), 1072 (s), 1032 (s), 969 (w), 802 (m), 768 (s), 725 (m), 668 (m), 639 (m), 594 (w), 581 (w).

TLC: $R_f$ 0.63 (pentane/Et$_2$O, 90:10) [silica gel, UV]

4-Acetylbenzaldehyde- formyl-$d_1$ (13b)

Following General Procedure XI, 0.02 mmol or 9.86 mg of [RhCODCl]$_2$ was dissolved in 2 mL of the DMF stock solutions containing PdCl$_2$ (6 mmol/L) and 4,4’dimethoxy-2,2’bipyridyl

213
(0.1 mol/L), followed 2 mmol or 0.492 g 4-acetyl-iodobenzene 13a, 576 μL of D₂O, and 600 μL of TMEDA. The reaction was carried out at 85 °C for 24 h under 25 bar CO pressure followed by standard workup. Purification by silica gel column chromatography (pentane/Et₂O, 70:30) afforded 13b (185 mg, 61%) as a white solid. The spectral data matched those previously reported in the literature.⁸

Data for 13b:

**¹H NMR:** (500 MHz, Chloroform-d)
10.11 (s, 0.16 H, C(7)H), 8.10 (d, J = 8.3 Hz, 2 H, C(2)H), 7.98 (dd, J = 8.5, 1.4 Hz, 2 H, C(1)H), 2.67 (s, 0.32 H, C(5)H₃).

**D incorporation by ¹H NMR:** 84%

**¹³C NMR:** (126 MHz, Chloroform-d)
198.41 – 195.81 (m) C(4), 191.66 C(7), 141.18 C(3), 139.03 C(6), 129.86 C(1), 128.84 C(2), 28.80 – 24.72 (m) C(5).

**HRMS:** (EI)

\[ m/z : \text{[M]}^+ \text{ Calcd for C}_9\text{H}_7\text{DO}_2: 152.07803; \text{Found: } 152.07754 \]

**D incorporation by EI-MS:**

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**IR:**
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**TLC:** \( R_f 0.06 \) (pentane/Et₂O, 90:10) [silica gel, UV]
2.6-Dimethylbenzaldehyde-\textit{formyl-}\textit{d}_1 (14b)

Following General Procedure XI, 0.02 mmol or 9.86 mg of [RhCODCl]_2 was dissolved in 2 mL of the DMF stock solutions containing PdCl\textsubscript{2} (3 mmol/L) and 4,4′-dimethoxy-2,2′-bipyridyl (0.1 mol/L), followed 2 mmol or 0.464 g 2,6 dimethyliodobenzene 1a, 72 μL of D\textsubscript{2}O, and 600 μL of TMEDA. The reaction was carried out at 85 °C for 24 h under 25 bar CO pressure followed by standard workup. Purification by silica gel column chromatography (pentane/Et\textsubscript{2}O 95:5) afforded 14b (224 mg, 83%) as a colorless oil. The spectral data matched those previously reported in the literature.\textsuperscript{22}

Data for 14b:

\textbf{\textsuperscript{1}H NMR:} (500 MHz, Chloroform-\textit{d})

10.63 (s, 0.14 H, C(6)H), 7.32 (t, J = 7.6 Hz, 1 H, C(4)H), 7.09 (d, J = 7.6 Hz, 2 H, C(3)H), 2.61 (s, 6 H, C(2)H\textsubscript{3}).

\textbf{D incorporation by \textsuperscript{1}H NMR:} 86%

\textbf{\textsuperscript{13}C NMR:} (126 MHz, Chloroform-\textit{d})

196.13 – 190.94 (m) C(6), 141.18 C(1), 132.98 (d, J = 2.2 Hz) C(4, 5), 129.70 C(3), 20.50 C(2).

\textbf{HRMS:} (EI)

\textit{m/z:} [M]\textsuperscript{+} Calcd for C\textsubscript{9}H\textsubscript{9}DO: 135.0795; Found: 135.08011

\textbf{D incorporation by EI-MS:}

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215
IR: (neat)  
3331 (w), 3065 (w), 3024 (w), 2965 (w), 2766 (w), 2160 (w), 2125 (w), 2104 (w), 2076 (w), 1950 (w), 1731 (w), 1592 (m), 1576 (w), 1466 (m), 1439 (w), 1418 (w), 1381 (m), 1286 (w), 1253 (w), 1211 (m), 1191 (w), 1169 (w), 1121 (w), 1099 (w), 1074 (w), 1056 (w), 1033 (w), 999 (w), 926 (w), 867 (w), 824 (w), 804 (w), 774 (s), 707 (w), 688 (m), 586 (w), 526 (w), 472 (w).

TLC:  
$R_f$ 0.46 (pentane/Et$_2$O, 90:10) [silica gel, UV]

2,6-Diethylbenzaldehyde- formyl-$d_1$ (15b)

Following General Procedure XI, 0.02 mmol or 9.86 mg of [RhCODCl]$_2$ was dissolved in 2 mL of the DMF stock solutions containing PdCl$_2$ (3 mmol/L) and 4,4’-dimethoxy-2,2’bipyridyl (0.1 mol/L), followed 2 mmol or 0.52 g 2,6 diethyliodobenzene 15a, 72 µL of D$_2$O, and 600 µL of TMEDA. The reaction was carried out at 85 °C for 24 h under 25 bar CO pressure followed by standard workup. Purification by silica gel column chromatography (pentane/Et$_2$O 95:5) afforded 15b (257 mg, 79%) as a colorless oil. The spectral data matched those previously reported in the literature.$^{23}$

Data for 15b:

$^1$H NMR: (500 MHz, Chloroform-$d$)  
10.60 (s, 0.05 H, C(7)H), 7.38 (t, $J = 7.6$ Hz, 1 H, C(5)H), 7.12 (d, $J = 7.6$ Hz, 2 H, C(4)H), 2.97 (q, $J = 7.5$ Hz, 4 H, C(2)H)$_2$, 1.25 (t, $J = 7.5$ Hz, 6 H, C(3)H$_3$).

D incorporation by $^1$H NMR: 95%

$^{13}$C NMR: (126 MHz, Chloroform-$d$)  

HRMS: (EI)  
m/z: [M]$^+$ Calcd for C$^{13}$H$_{13}$DO: 163.11075; Found: 163.11078
D incorporation by EI-MS:

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IR: (neat)
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TLC: \( R_f 0.57 \) (pentane/Et\(_2\)O, 90:10) [silica gel, UV]

2,6-Diisopropylbenzaldehyde- formyl-\( d_7 \) (16b)

Following General Procedure XI, 0.02 mmol or 9.86 mg of \([\text{RhCODCl}]_2\) was dissolved in 2 mL of the DMF stock solutions containing \( \text{PdCl}_2 \) (6 mmol/L) and 4,4’-dimethoxy-2,2’bipyridyl (0.1 mol/L), followed 2 mmol or 0.576 g 2,6-diisopropylidobenzene 16a, 72 \( \mu \)L of \( \text{D}_2\)O, and 600 \( \mu \)L of TMEDA. The reaction was carried out at 95 °C for 24 h under 25 bar CO pressure followed by standard workup. Purification by silica gel column chromatography (pentane/Et\(_2\)O 98:2) afforded 16b (218 mg, 57%) as a colorless oil.

Data for 16b:

\(^1\text{H NMR:} \) (500 MHz, Chloroform-\( d \))

10.71 (s, 0.1 H, C(7)H), 7.44 (t, \( J = 7.8 \) Hz, 1 H, C(5)H), 7.27 – 7.25 (m, 2 H,
C(4)H, 3.52 (p, J = 6.8 Hz, 2 H, C(2)H), 1.27 (d, J = 6.8 Hz, 12 H, C(3)H₃).

D incorporation by ¹H NMR: 90%

¹³C NMR: (126 MHz, Chloroform-d)
195.50 C(7), 149.95 C(1), 132.99 C(6), 132.59 C(5), 123.68 C(4), 29.06 C(2),
24.38 C(3).

HRMS: (EI)
m/z: [M]+ Calcd for C₁₃H₁₇OD: 191.14189; Found: 191.14205

D incorporation by EI-MS:

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D enriched intensity

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%enrichement

98.1

IR: (neat)
3067 (w), 2964 (m), 2929 (w), 2870 (w), 2115 (w), 2061 (w), 1678 (s), 1592 (m), 1577 (w), 1461 (m), 1385 (w), 1363 (w), 1300 (w), 1274 (w), 1251 (w), 1234 (w), 1197 (m), 1183 (m), 1145 (w), 1106 (w), 1057 (m), 1037 (w), 939 (w), 925 (w), 904 (w), 882 (w), 867 (w), 829 (w), 799 (s), 764 (w), 741 (m), 709 (w), 684 (m), 637 (w), 615 (w), 558 (w), 487 (w).

TLC: Rf 0.62 (pentane/Et₂O, 90:10) [silica gel, UV]

Analysis: C₁₃H₁₇DO (measured by TCD, corrected for mass change due to D incorporation)
Calcd: C, 81.63; H, 9.49
Found: C, 81.41; H, 9.31
2-Methylbenzaldehyde-\textit{formyl-}$d_1$ (17b)

Following General Procedure XI, 0.02 mmol or 9.86 mg of [RhCODCl]$_2$ was dissolved in 2 mL of the DMF stock solutions containing PdCl$_2$ (3 mmol/L) and 4,4’dimethoxy-2,2’bipyridyl (0.1 mol/L), followed 2 mmol or 0.436 g 2-methyliodobenzene 17a, 72 µL of D$_2$O, and 600 µL of TMEDA. The reaction was carried out at 85 °C for 24 h under 25 bar CO pressure followed by standard workup. Purification by silica gel column chromatography (pentane/Et$_2$O 95:5) afforded 17b (165 mg, 68%) as a colorless oil. The spectral data matched those previously reported in the literature.\textsuperscript{8}

Data for 17b:

\textsuperscript{1}H NMR: (500 MHz, Chloroform-$d$)

10.28 (s, 0.05 H, C(8)H), 7.81 (dd, $J = 7.6, 1.4$ Hz, 1 H, C(6)H), 7.48 (td, $J = 7.5, 1.4$ Hz, 1 H, C(5)H), 7.39 – 7.34 (m, 1 H, C(4)H), 7.27 (d, $J = 6.8$ Hz, 1 H, C(3)H), 2.68 (s, 3 H, C(2)H$_3$).

D incorporation by \textsuperscript{1}H NMR: 95%

\textsuperscript{13}C NMR: (126 MHz, Chloroform-$d$)

δ 194.32 – 189.45 (m) C(8), 140.64 C(1), 133.66 C(4,7), δ 131.88 (d, $J = 27.8$ Hz) C(3,6), 126.33 C(5), 19.58 C(2).

HRMS: (EI)

\textit{m/z}: [M]$^+$ Calcd for C$_8$H$_7$DO: 121.0638; Found: 121.064

D incorporation by EI-MS:

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(neat)
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1667 (s), 1574 (m), 1488 (w), 1457 (w), 1381 (w), 1297 (w), 1284 (m), 1258 (w), 1215 (s), 1178 (w), 1160 (w), 1120 (w), 1076 (w), 1054 (w), 1036 (w), 958 (w), 925 (w), 883 (w), 861 (w), 846 (m), 815 (w), 769 (m),
745 (s), 721 (m), 657 (m), 631 (m), 537 (w), 496 (w), 486 (w), 464 (w).

TLC:  \( R_f 0.44 \) (pentane/Et\(_2\)O, 90:20) [silica gel, UV]

3-Methylbenzaldehyde- formyl-\( \text{d}_1 \) (18b)

![Diagram of 3-Methylbenzaldehyde- formyl-\( \text{d}_1 \) (18b)]

Following General Procedure XI, 0.02 mmol or 9.86 mg of [RhCODCl]\(_2\) was dissolved in 2 mL of the DMF stock solutions containing PdCl\(_2\) (3 mmol/L) and 4,4’-dimethoxy-2,2’-bipyridyl (0.1 mol/L), followed 2 mmol or 0.436 g 2-methyliodobenzene 18a, 72 \( \mu \)L of D\(_2\)O, and 600 \( \mu \)L of TMEDA. The reaction was carried out at 85 °C for 24 h under 25 bar CO pressure followed by standard workup. Purification by silica gel column chromatography (pentane/Et\(_2\)O 95:5) afforded 18b (172 mg, 71%) as a colorless oil. The spectral data matched those previously reported.\

Data for 18b:

\(^1\text{H NMR:}\) (500 MHz, Chloroform-\( d \))
9.99 (s, 0.02 H, C(8)H), 7.75 – 7.63 (m, 2 H, C(1)H, C(6)H), 7.51 – 7.37 (m, 2 H, C(4)H, C(5)H), 2.44 (s, 3 H, C(3)H\(_3\)).

\( \text{D incorporation by } ^1\text{H NMR:} \) 98%

\(^{13}\text{C NMR:}\) (126 MHz, Chloroform-\( d \))
193.93 – 189.45 (m) C(8), 138.92 C(2), 136.75 – 136.20 (m) C(7), 135.29 C(4),
130.01 C(1), 128.88 C(5), 127.22 C(6), 21.21 C(3).

HRMS:  
(EI)
\( m/z: [\text{M}]^+ \) Calcd for C\(_8\)H\(_7\)DO: 121.0638; Found: 121.06415
D incorporation by EI-MS:

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IR: (neat)
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1605 (w), 1587 (m), 1485 (w), 1456 (w), 1427 (w), 1381 (w), 1309 (w), 1295
(w), 1257 (m), 1168 (w), 1156 (m), 1088 (w), 1046 (w), 1004 (w), 932 (w), 910
(w), 891 (w), 774 (m), 753 (m), 726 (w), 684 (m), 647 (w), 520 (w), 496 (w).

TLC: \( R_f 0.43 \) (pentane/Et\(_2\)O, 90:10) [silica gel, UV]

2-Phenylbenzaldehyde- formyl-\( d_\) \( \text{I9b} \)

Following General Procedure XI, 0.02 mmol or 9.86 mg of [RhCODCl]\(_2\) was dissolved in 2
mL of the DMF stock solutions containing PdCl\(_2\) (3 mmol/L) and 4,4′dimethoxy-2,2′bipyridyl
(0.1 mol/L), followed 2 mmol or 0.560 g 2-iodo-1,1′-biphenyl \( \text{I9a} \), 72 \( \mu \)L of D\(_2\)O, and 600 \( \mu \)L of
TMEDA. The reaction was carried out at 85 °C for 24 h under 25 bar CO pressure followed by
standard workup. Purification by silica gel column chromatography (pentane/Et\(_2\)O 90:10)
afforded \( \text{I9b} \) (267 mg, 73%) as a colorless oil. The spectral data matched those previously
reported.\(^8\)

Data for \( \text{I9b} \):

\(^1\)H NMR: (500 MHz, Chloroform-\( d \))
10.07 – 9.94 (m, 0.24 H, C(11)H), 8.10 – 8.00 (m, 1 H, C(4)H), 7.65 (td, \( J = 7.5 \),
1.4 Hz, 1 H, C(1)H), 7.53 – 7.43 (m, 5 H, C(2)H, C(3)H, C(9)H, C(8)H), 7.39 (dd, 
J = 7.9, 1.6 Hz, 1.47 H, C(7)H).

D incorporation by $^1$H NMR: 76%

$^{13}$C NMR: (126 MHz, Chloroform- $d$)

193.17 – 191.25 (m) C(11), 145.99 C(10), 137.76 C(6), 133.57 C(3), 130.76 C(5), 
130.10 C(8), 128.44 C(1), 128.33 C(2), 128.12 C(7), 127.78 C(9), 127.57 C(4).

HRMS: (EI)

$m/z$: [M]$^+$ Calcd for C$_{13}$H$_9$DO: 183.23; Found: 184.0871

D incorporation by EI-MS: For double deuterated compounds: 

$$D = 1 - \frac{I_D(M) X (I_S(M+2))}{I_D(M+2) X (I_S(M+1))}$$

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IR: (neat)

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1596 (m), 1562 (w), 1497 (w), 1473 (w), 1452 (w), 1433 (w), 1392 (w), 1298 (w), 
1271 (w), 1250 (m), 1208 (m), 1160 (w), 1112 (w), 1075 (w), 1055 (w), 1032 (w), 
1008 (w), 963 (w), 919 (w), 885 (w), 866 (w), 846 (w), 827 (w), 798 (w), 777 
(m), 742 (s), 702 (s), 633 (s), 615 (w), 606 (m), 551 (w), 530 (w).

TLC: $R_f$ 0.33 (pentane/Et$_2$O, 90:10) [silica gel, UV]
2-Phenylbenzaldehyde-\textit{formyl}-\textit{d}_1 (19c)

Following General Procedure XI, 0.02 mmol or 9.86 mg of [RhCODCl]$_2$ was dissolved in 2 mL of the DMF stock solutions containing PdCl$_2$ (3 mmol/L) and 4,4’-dimethoxy-2,2’-bipyridyl (0.1 mol/L), followed 2 mmol or 0.560 g 2-iodo-1,1’-biphenyl 19a, 288 \mu L of D$_2$O, and 600 \mu L of TMEDA. The reaction was carried out at 85 °C for 24 h under 25 bar CO pressure followed by standard workup. Purification by silica gel column chromatography (pentane/Et$_2$O 90:10) afforded 19c (245 mg, 67%) as a colorless oil. The spectral data matched those previously reported.$^8$

Data for 19c:

\textbf{\textsuperscript{1}H NMR:} (500 MHz, Chloroform-\textit{d})

10.07 – 9.94 (m, 0.03 H, C(11)H), 8.10 – 8.00 (m, 1 H, C(4)H), 7.65 (td, \textit{J} = 7.5, 1.4 Hz, 1 H, C(1)H), 7.53 – 7.43 (m, 5 H, C(2)H, C(3)H, C(9)H, C(8)H), 7.39 (dd, \textit{J} = 7.9, 1.6 Hz, 1.31 H, C(7)H).

\textbf{D incorporation by} \textsuperscript{1}H NMR: 97%

\textbf{\textsuperscript{13}C NMR:} (126 MHz, Chloroform-\textit{d})

193.17 – 191.25 (m) C(11), 145.99 C(10), 137.76 C(6), 133.57 C(3), 130.76 C(5), 130.10 C(8), 128.44 C(1), 128.33 C(2), 128.12 C(7), 127.78 C(9), 127.57 C(4).

\textbf{HRMS:} (EI)

\textit{m/z}: [M]$^+$ Calcd for C$_{13}$H$_9$DO: 183.23; Found: 184.0871
D incorporation by EI-MS: For double deuterated compounds: 
\[
\% D = 1 - \frac{I_D(M) \times I_S(M+2)}{I_D(M+2) \times I_S(M+1)}
\]

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IR: (neat)
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TLC: 
Rf 0.33 (pentane/Et₂O, 90:10) [silica gel, UV]

1-Naphthaldehyde-\textit{formyl-}d₁ (20b)

Following General Procedure XI, 0.02 mmol or 9.86 mg of [RhCODCl]₂ was dissolved in 2 mL of the DMF stock solutions containing PdCl₂ (3 mmol/L) and 4,4’dimethoxy-2,2’bipyridyl (0.1 mol/L), followed 2 mmol or 0.508 g 1-iodonaphthalene 20a, 288 µL of D₂O, and 600 µL of TMEDA. The reaction was carried out at 85 °C for 24 h under 25 bar CO pressure followed by standard workup. Purification by silica gel column chromatography (pentane/Et₂O 90:10) afforded 20b (242 mg, 77%) as a colorless oil. The spectral data matched those previously reported. \(^8\)
Data for 20b:

**1H NMR:** (500 MHz, Chloroform-d)

10.41 (s, 0.07 H, C(11)H), 9.35 – 9.21 (m, 0.32 H, C(8)), 8.11 (dd, J = 8.2, 1.0 Hz, 1 H, C(3)H), 8.00 (dd, J = 7.0, 1.3 Hz, 1 H, C(1)H), 7.93 (dd, J = 8.2, 1.1 Hz, 1 H, C(5)H), 7.70 (dt, J = 6.7, 4.5, 1.4 Hz, 1 H, C(7)H), 7.62 (ddd, J = 16.9, 8.2, 7.0 Hz, 2 H, C(2)H, C(6)H).

**D incorporation by 1H NMR:** 93%

**13C NMR:** (126 MHz, Chloroform-d)

δ 194.33 – 191.91 (m) C(11), 136.62 (d, J = 2.4 Hz) C(1), 135.31 C(3), 133.74 C(4), 131.35 C(10), 130.53 (d, J = 12.2 Hz) C(9), 129.08 C(7), 128.96 C(5), 128.47 C(6), 126.98 C(2), 124.89 (d, J = 1.9 Hz) C(8).

**HRMS:** (EI)

m/z: [M]+ Calcd for C_{11}H_{7}DO: 157.06; Found: 158.0179

**D incorporation by EI-MS:** For double deuterated compounds: \( \% D = 1 - \left( \frac{I_D (M) \times I_S (M+2)}{I_D (M+2) \times I_S (M+1)} \right) \)

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**IR:** (neat)

3050 (w), 2117 (w), 2069 (w), 2052 (w), 1669 (s), 1618 (w), 1591 (w), 1569 (m), 1500 (m), 1455 (w), 1436 (w), 1370 (w), 1346 (w), 1270 (w), 1246 (m), 1225 (m), 1202 (m), 1144 (w), 1099 (m), 1087 (w), 1069 (w), 1056 (w), 1024 (w), 1012 (w), 980 (w), 907 (w), 875 (w), 834 (m), 822 (m), 798 (m), 770 (s), 740 (w), 692 (m), 675 (w), 641 (m), 616 (w), 544 (w), 516 (w), 506 (w).

**TLC:** \( R_f 0.34 \) (pentane/Et2O, 00:10) [silica gel, UV]
Quinoline-5-carbaldehyde-\textit{formyl-}\textit{d}_{1} (21b)

Following General Procedure XI, 0.02 mmol or 9.86 mg of [RhCODCl]$_2$ was dissolved in 2 mL of the DMF stock solutions containing PdCl$_2$ (3 mmol/L) and 4,4’dimethoxy-2,2’bipyridyl (0.1 mol/L), followed 2 mmol or 0.510 g 6-iodoquinoline 21a, 72 µL of D$_2$O, and 600 µL of TMEDA. The reaction was carried out at 85 °C for 24 h under 25 bar CO pressure followed by standard workup. Purification by silica gel column chromatography (pentane/Et$_2$O 75:25) afforded 21b (164 mg, 52%) as a white solid. The spectral data matched those previously reported.$^{24}$

Data for 21b:

$^1$H NMR: (500 MHz, Chloroform-\textit{d})
10.20 (s, 0.01 H, C(10)H), 9.05 (dd, $J = 4.2, 1.7$ Hz, 1 H, C(4)H), 8.43 – 8.30 (m, 2 H, C(6)H, C(8)H), 8.26 – 8.15 (m, 2 H, C(1)H, C(2)H), 7.52 (dd, $J = 8.3, 4.2$ Hz, 1 H, C(5)H).

D incorporation by $^1$H NMR: 99%

$^{13}$C NMR (126 MHz, Chloroform-\textit{d})
191.98–189.88 (m) C(10), 153.13 C(4), 150.94 C(3), 137.44 C(6), 134.52–134.00 (m) C(9), 133.59 C(8), 130.86 C(7), 127.72 C(2), 126.74 C(1), 122.22 C(5).

HRMS: (EI)
m/z: [M]$^+$ Calcd for C$_{10}$H$_6$DNO: 158.05909; Found: 158.05904

D incorporation by EI-MS:

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226
IR:  (neat)
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2091 (w), 1950 (w), 1689 (m), 1668 (s), 1622 (s), 1593 (m), 1575 (s), 1530 (w),
1501 (m), 1459 (m), 1429 (s), 1383 (m), 1350 (m), 1323 (s), 1256 (m), 1236 (s),
1215 (s), 1162 (s), 1112 (s), 1051 (w), 1035 (w), 952 (w), 885 (w), 863 (w),
824 (s), 801 (m), 770 (s), 742 (s), 623 (m), 608 (m), 475 (m).

TLC:  Rf 0.01 (pentane/Et2O, 90:10) [silica gel, UV]

t-Butyl 5-Formyl-1H-indole-1-carboxylate- formyl-δ1 (22b)

Following General Procedure XI, 0.02 mmol or 9.86 mg of [RhCODCl]2 was dissolved in 2
mL of the DMF stock solutions containing PdCl2 (3 mmol/L) and 4,4’dimethoxy-2,2’bipyridyl
(0.1 mol/L), followed 2 mmol or 0.686 g tert-butyl 5-ido-1H-indole-1-carboxylate 22a, 72 μL
of D2O, and 600 μL of TMEDA. The reaction was carried out at 85 °C for 24 h under 25 bar CO
pressure followed by standard workup. Purification by silica gel column chromatography
(pentane/Et2O 75:25) afforded 22b (305 mg, 62%) as a white solid. The spectral data matched
those previously reported.11

Data for 22b:

1H NMR:  (500 MHz, Chloroform-d)
10.07 (s, 0.05 H, C(11)H), 8.29 (d, J = 8.6 Hz, 1 H, C(9)H), 8.10 (d, J = 1.2 Hz, 1
H, C(2)H), 7.86 (dd, J = 8.6, 1.6 Hz, 1 H, C(7)H), 7.69 (d, J = 3.7 Hz, 1 H, C(1)H),
6.75 – 6.62 (m, 1 H, C(8)H), 1.69 (s, 9 H, C(6)H3).

D incorporation by 1H NMR; 95%

13C NMR:  (126 MHz, Chloroform-d)
δ 193.93 – 190.16 (m) C(11), 149.25 C(4), 138.77 C(3), 131.64 C(10), 130.69
C(9), 127.71 C(7), 125.19 C(9), 124.23 C(1), 115.62 C(2), 107.84 C(8), 84.68
C(5), 28.15 C(6).
HRMS: (EI)

\[ m/z: [M]^+ \text{ Calcd for C}_{14}H_{14}DNO_3: 246.11148; \text{ Found: 246.11147} \]

D incorporation by EI-MS:

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IR: (neat)

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1536 (w), 1469 (m), 1440 (w), 1385 (m), 1371 (m), 1351 (s), 1335 (s), 1317 (s),
1302 (m), 1285 (m), 1259 (m), 1220 (s), 1192 (m), 1155 (s), 1128 (m), 1084 (m),
1041 (w), 1023 (m), 958 (w), 941 (w), 913 (w), 850 (w), 807 (m), 765 (m), 727
(m), 684 (w), 646 (w), 623 (w), 599 (w), 524 (w), 489 (w), 454 (w).

TLC: \( R_f 0.17 \) (pentane/Et\(_2\)O, 90:10) [silica gel, UV]

1H-Indole-5-carbaldehyde-\( \alpha-d_1 \) (23b)

Following General Procedure XI, 0.02 mmol or 9.86 mg of [RhCODCl]\(_2\) was dissolved in 2
mL of the DMF stock solutions containing PdCl\(_2\) (3 mmol/L) and 4,4′dimethoxy-2,2′bipyridyl
(0.1 mol/L), followed 2 mmol or 0.486 g 5-iodo-1H-indole 23a, 72 \( \mu \)L of D\(_2\)O, and 600 \( \mu \)L of
TMEDA. The reaction was carried out at 85 °C for 24 h under 25 bar CO pressure followed by
standard workup. Purification by silica gel column chromatography (pentane/Et\(_2\)O 70:30)
afforded 23b (160 mg, 55%) as a white solid. The spectral data matched those previously
reported.\(^{25}\)
Data for 23b:

**¹H NMR:** (500 MHz, Chloroform-**d**)

10.04 (s, 0.48 H, C(9)H), 8.55 (s, 1 H, N(H)), 8.19 (s, 1 H, C(7)H), 7.79 (d, J = 8.5 Hz, 1 H, C(1)H), 7.49 (d, J = 8.5 Hz, 1 H, C(2)H), 7.32 (d, J = 2.1 Hz, 1 H, C(4)H), 6.72 (ddd, J = 3.0, 2.0, 0.9 Hz, 0.37 H, C(5)H)

D incorporation by ¹H NMR: 52%

**¹³C NMR:** (126 MHz, Chloroform-**d**)

192.57 C(9), 139.29 C(3), 129.85 C(8), 127.68 (d, J = 10.2 Hz) C(6), 126.26 C(4), 125.93 (d, J = 11.1 Hz) C(7), 122.34 (C1), 111.68 C(2), 104.54 C(5).

**HRMS:**

EI

$m/z$: [M]⁺ Calcd for C₉H₆DNO: 146.17; Found: 147.0669

D incorporation by EI-MS: For double deuterated compounds:

\[
\%D = 1 - \frac{I_D(M) X (I_S(M+2))}{I_D(M+2) X (I_S(M+1))}
\]

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non-D intensity

| non-D ratio | 1.0   | 0.2    | 0.0 | 0.0 |

D enriched intensity

| 214848.0   | 169088.0 | 106936.0 | 12068.0 |

%enrichment

| 84.3 | 100.0 |

%average

| 92.1 |

**IR:** (neat)

3060 (w), 3027 (w), 2964 (w), 2923 (w), 2851 (w), 2148 (w), 2120 (w), 2055 (w), 1670 (s), 1596 (m), 1562 (w), 1497 (w), 1473 (w), 1452 (w), 1434 (w), 1392 (w), 1298 (w), 1253 (m), 1245 (m), 1208 (m), 1179 (w), 1160 (w), 1111 (w), 1075 (w), 1030 (w), 1008 (m), 964 (w), 919 (w), 884 (w), 866 (w), 846 (w), 797 (m), 777 (s), 752 (s), 743 (s), 702 (s), 632 (s), 606 (m), 549 (w), 529 (w).

**TLC:** \(R_f 0.1\) (pentane/Et₂O, 90:10) [silica gel, UV]
Procedure XII: Double Deuterated (4-Methoxyphenyl)methan-d$_3$-ol from 4-Methoxybenzaldehyde-$\alpha$-d$_1$ (2b) Using D$_2$O and WGSR.

![Chemical Structure]

RhCl$_3$ catalyst – 0.02 mmol or 10.52 mg was dissolved in 2 mL of the MeCN solvent in a 20-mL glass vial, and 2 mmol (242.8 µL) of p-methoxybenzaldehyde-$\alpha$-d$_1$ (2b), 30 equiv D$_2$O (1080 µL), and 2 equiv triethylamine (560 µL) were added sequentially. A stir bar was added, and the vial was placed in an autoclave. The autoclave was pressurized with CO and vented three times, and then pressurized to 20 bar. The mixture was stirred at 75 °C for 24 h. After venting and purging the autoclave with nitrogen, the vial was removed. The reaction mixture was diluted in diethyl ether (30 mL) and extracted with 1:1 brine/water mixture (3 X 30 mL) and the organic layer was dried by MgSO$_4$. The volatiles were removed by rotary evaporation (25-30 °C, 15 mmHg), then the residue was dissolved in ether, and was loaded on silica gel (1 g). The crude mixture was purified by silica gel column chromatography (2.5 x 20-25 cm) using (80:20 pentane/Et$_2$O). The isolated mass of 1d was 258 mg or 92% yield as a colorless oil. The spectral data matched those previously reported in the literature.$^{26}$ Deuterium incorporation was calculated by $^1$H NMR and by comparison of the signals ratios of the aldehyde mass M and M+1 for the deuterated and nondeuterated compound as measured by EI-MS.

Data for 1d:

$^1$H NMR: (500 MHz, Chloroform-d)

7.29 (d, J = 8.7 Hz, 2 H, C(1)H), 6.89 (d, J = 8.7 Hz, 2 H, C(2)H), 4.59 (s, 0.06 H, C(6)H$_2$), 3.81 (s, 3 H, C(4)H$_3$), 1.71 (s, 1 H, O(H))

D incorporation by $^1$H NMR: 97%

$^{13}$C NMR: (126 MHz, Chloroform-d)

159.22 C(3), 133.03 C(5), 128.68 C(1), 113.96 C(2), 67.22 – 62.34 (m) C(6), 55.31 C(4).

HRMS: (EI)

$m/z$: [M]$^+$ Calcd for C$_8$H$_8$O$_2$D: 140.08053; Found: 140.08063
D incorporation by EI-MS: For double deuterated compounds:  
\[
\% D = 1 - \frac{I_D(M) \times I_S(M+2)}{I_D(M+2) \times I_S(M+1)}
\]

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IR: (neat)  
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TLC: \( R_f 0.6 \) (pentane/Et\(_2\)O, 90:10) [silica gel, UV]

Procedure XIII: Double Deuterated 2-Benzoyl-3-(4-Methoxyphenyl)propanenitrile-3,3-\( d_2 \) from 4-Methoxybenzaldehyde-\( \alpha - d_1 \) (2b) Using D\(_2\)O and WGSR.

RhCl\(_3\) catalyst – 0.02 mmol or 10.52 mg was dissolved in 2 mL of the MeCN solvent in a 20-mL glass vial, and 2.02 mmol (245.2 µL) of 4-methoxybenzaldehyde-\( \alpha - d_1 \) (2b), 2.0 mmol 3-oxo-3-phenylpropanenitrile (290 mg), 30 equiv D\(_2\)O (1080 µL), and 2 equiv triethylamine (560 µL) were added sequentially. A stir bar was added, and the vial was placed in an autoclave. The autoclave was pressurized with CO and vented three times, and then pressurized to 20 bar. The mixture was stirred at 65 °C for 24 h. After venting and purging the autoclave with nitrogen, the vial was removed. The reaction mixture was diluted in diethyl ether (30 mL) and extracted with
1:1 brine/water mixture (3 X 30 mL) and the organic layer was dried by MgSO₄. The volatiles were removed by rotary evaporation (25-30 °C, 15 mmHg), then the residue was dissolved in ether, and was loaded on silica gel (1 g) using (pentane/Et₂O, 70:30). The crude mixture was purified by silica gel column chromatography (2.5 x 20-25 cm). The isolated mass of 2d was 475 mg or 89% yield as a white solid. The spectral data matched those previously reported in the literature. Deuterium incorporation was calculated by ¹H NMR and by comparison of the signals ratios of the aldehyde mass M and M+1 for the deuterated and nondeuterated compound as measured by EI-MS.

Data for 2d:

¹H NMR: (500 MHz, Chloroform-d)

7.95 (dd, J = 8.4, 1.1 Hz, 2 H, C(11)H), 7.69 – 7.60 (m, 1 H, C(13)H), 7.56 – 7.46 (m, 2 H, C(12)H), 7.20 (d, J = 8.7 Hz, 2 H, C(1)H), 6.86 (d, J = 8.7 Hz, 2 H, C(2)H), 4.48 (s, 1 H, C(8)H), 3.79 (s, 3 H, C(4)H₃), 3.24 (dd, J = 51.0, 7.2 Hz, 0.31 H, C(6)H₂).

D incorporation by ¹H NMR: 85%

¹³C NMR: (126 MHz, Chloroform-d)

190.16 C(9), 159.09 C(3), 134.53 C(10), 134.14 C(13), 130.12 C(5), 129.13 C(11), 128.80 C(12), 127.80 (d, J = 5.7 Hz) C(1), 117.06 C(7), 114.33 C(2), 55.28 C(4), 42.06 (d, J = 8.7 Hz) C(8), 36.26 – 32.18 (m) C(6).

HRMS: (EI)

m/z: [M]+ Calcd for C₁₇H₁₃D₂NO₂: 267.12260; Found: 267.12283

D incorporation by EI-MS: For double deuterated compounds: % D = 1- \(\frac{I_D(M)X(I_5(M+2))}{I_D(M+2)X(I_5(M+1))}\)

<table>
<thead>
<tr>
<th></th>
<th>M</th>
<th>M+1</th>
<th>M+2</th>
<th>M+3</th>
</tr>
</thead>
<tbody>
<tr>
<td>non-D</td>
<td>265</td>
<td>266</td>
<td>267</td>
<td>268</td>
</tr>
<tr>
<td>non-D intensity</td>
<td>37808.0</td>
<td>8987.0</td>
<td>1025.0</td>
<td>272.0</td>
</tr>
<tr>
<td>non D ratio</td>
<td>1.0</td>
<td>0.2</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>D</td>
<td>enriched intensity</td>
<td>362.0</td>
<td>6992.0</td>
<td>48056.0</td>
</tr>
<tr>
<td>%enrichment</td>
<td>99.9</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>%average</td>
<td>99.9</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
IR: (neat)
3063 (w), 3033 (w), 3005 (w), 2958 (w), 2935 (w), 2909 (w), 2837 (w), 2247 (w),
1892 (w), 1691 (s), 1611 (m), 1596 (m), 1581 (w), 1513 (s), 1464 (w), 1449 (m),
1418 (w), 1332 (w), 1297 (m), 1246 (s), 1206 (w), 1179 (m), 1112 (w), 1030 (m),
1002 (w), 966 (w), 948 (w), 906 (w), 860 (w), 812 (m), 775 (w), 745 (w), 722
(w), 692 (m), 670 (w), 634 (w), 617 (w), 583 (w), 560 (w), 517 (w).

TLC: \( R_f 0.07 \) (pentane/Et\(_2\)O, 90:10) [silica gel, UV]

Procedure XIV: Double Deuterated 1-((4-Methoxyphenyl)methyl-d\(_2\))piperidine from 4-Methoxybenzaldehyde-\(\alpha\)-d\(_1\) (2b) Using D\(_2\)O and WGSR.

\[
\begin{array}{c}
\begin{tikzpicture}
\node (1) at (0,0) {1};
\node (2) at (0.5,0.5) {2};
\node (3) at (1.25,0.5) {3};
\node (4) at (2.25,0) {4};
\node (5) at (2.75,0.5) {5};
\node (6) at (3.25,0.5) {6};
\node (7) at (3.75,0) {7};
\node (8) at (4.25,0) {8};
\node (D) at (1.75,1) {D};
\node (N) at (2.75,1) {N};
\end{tikzpicture}
\end{array}
\]

RhCl\(_3\) catalyst – 0.02 mmol or 10.52 mg was dissolved in 2 mL of the MeCN solvent in a 20-
ml glass vial, and 2.02 mmol (245.2 \(\mu\)L) of \(p\)-methoxybenzaldehyde-\(\alpha\)-d\(_1\) (2b), 2.0 mmol
piperidine (198 \(\mu\)L), 15 equiv D\(_2\)O (540 \(\mu\)L), and 2 equiv. triethylamine (560 \(\mu\)L) were added
sequentially. A stir bar was added, and the vial was placed in an autoclave. The autoclave was
pressurized with CO and vented three times, and then pressurized to 10 bar. The mixture was
stirred at 55 °C for 24 h. After venting and purging the autoclave with nitrogen, the vial was
removed. The reaction mixture was diluted in diethyl ether (30 mL) and extracted with 1:1
brine/water mixture (3X30 mL) and the organic layer was dried by MgSO\(_4\). The volatiles were
removed by rotary evaporation (25-30 °C, 15 mmHg), then the residue was dissolved in ether,
and was loaded on silica gel (1 g) using (70:30 pentane/Et\(_2\)O). The crude mixture was purified by
silica gel column chromatography (2.5 x 20-25 cm). The isolated mass of 3d was 377 mg or 91%
yield as a yellow oil. The spectral data matched those previously reported in the literature.\(^{28}\)
Deuterium incorporation was calculated by \(^1\)H NMR and by comparison of the signals ratios of
the aldehyde mass M and M+1 for the deuterated and nondeuterated compound as measured by
EI-MS.
Data for 3d:

\(^1\text{H} \text{NMR:} \quad (500 \text{ MHz, Chloroform}-d)\)

7.22 (d, \(J = 8.6 \text{ Hz, 2 H, C(1)H}\)), 6.85 (d, \(J = 8.6 \text{ Hz, 2 H, C(2)H}\)), 3.80 (s, 3 H, C(4)H\(_3\)), 3.38 (t, \(J = 1.8 \text{ Hz, 0.15 H, C(6)H}_2\)), 2.42 – 2.29 (m, 4 H, C(7)H\(_2\)), 1.56 (p, \(J = 5.6 \text{ Hz, 4 H, C(8)H}_2\)), 1.46 – 1.33 (m, 1 H, C(9)H).

\(\text{D incorporation by } ^1\text{H NMR:} \quad 93\%\)

\(^{13}\text{C} \text{NMR:} \quad (126 \text{ MHz, Chloroform}-d)\)

158.55 C(3), 130.51 C(1), 130.39 C(5), 113.43 C(2), 65.02 – 61.64 (m) C(6), 55.24 C(7), 54.29 C(4), 26.02 C(8), 24.45 C(9).

HRMS: (EI)

\(m/z: [M]^+ \text{ Calcd for } \text{C}_{13}\text{H}_{17}\text{D}_2\text{NO: 207.15972; Found: 207.15922}\)

\(\text{D incorporation by EI-MS: For double deuterated compounds: } \% D = 1-\left(\frac{I_D(M) \times (I_S(M+2))}{I_D(M+2) \times (I_S(M+1))}\right)\)

\begin{tabular}{|c|c|c|c|}
\hline
& M & M+1 & M+2 & M+3 \\
\hline
non-D intensity & 591744 & 835072 & 136384 & 22192 \\
non D ratio & 1 & 1.41E+00 & 2.30E-01 & 0.037502704 \\
D enriched intensity & 122632 & 1370432 & 305216 & 44560 \\
\hline
%enrichment & 93.438 & 92.6864009 & 93.0622 & 93.0622 \\
\hline
\end{tabular}

IR: (neat)

2931 (m), 2852 (w), 2834 (w), 2783 (w), 2742 (w), 2700 (w), 2671 (w), 2034 (w), 1612 (m), 1583 (w), 1510 (s), 1464 (w), 1453 (w), 1441 (m), 1415 (w), 1384 (w), 1298 (m), 1271 (w), 1242 (s), 1179 (m), 1170 (m), 1154 (m), 1122 (m), 1103 (m), 1064 (w), 1032 (s), 1010 (w), 974 (w), 928 (w), 899 (w), 858 (w), 842 (m), 799 (m), 767 (m), 736 (w), 695 (w), 616 (w), 582 (w), 547 (w), 512 (w).

TLC: \(R_f 0.05\) (pentane/Et\(_2\)O, 90:10) [silica gel, UV]
Procedure XV: Effect of Additives on the WGSR-Driven Reduction of 4-Methoxybenzaldehyde to 4-Methoxybenzyl alcohol

RhCl₃ catalyst – 0.008 mmol or 2.1 mg was dissolved in 0.4 mL MeCN solvent in a 4-mL glass vial, and 0.4 mmol (48.5 μL) of 4-methoxybenzaldehyde, 5 equiv H₂O (36 μL), and 2 equiv triethylamine (112 μL) were added sequentially. To separate vials, the same reagents were added and different additives were added as following to each vial: 8.6 mg 4,4’-diMeObpy or 0.1 equiv; 2.7 mg Pd(OAc)₂ or 3 mol %; 4.9 mg benzoic acid or 0.1 equiv; 44.8 μL iodobenzene or 1 equiv; 120 μL TMEDA or 2 equiv. A stir bar was added to each vial, and the vials were placed in an autoclave. The autoclave was pressurized with CO and vented three times, and then pressurized to 14 bar. The mixture was stirred at 80 °C for 4 h. After venting and purging the autoclave with nitrogen, the vials were removed. An aliquot was taken and diluted in ethylether before being passed through a short silica column and injected into a GC for composition analysis. The effect of additives on the WGSR-driven reduction of aldehydes is shown in Table 8.8.

Table 8.8. Effect of additives on aldehyde reduction under Rh-catalyzed WGS conditions

<table>
<thead>
<tr>
<th>entry</th>
<th>additive</th>
<th>alcohol yield. (%) by GC</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td>36.8</td>
</tr>
<tr>
<td>2</td>
<td>4,4’diMeObpy (0.1 equiv)</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>Pd(OAc)₂ (3 mol %)</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>benzoic acid (0.1 equiv)</td>
<td>37.4</td>
</tr>
<tr>
<td>5</td>
<td>iodobenzene (1 equiv)</td>
<td>41.2</td>
</tr>
<tr>
<td>6</td>
<td>TMEDA (2 equiv)</td>
<td>5</td>
</tr>
</tbody>
</table>
Procedure XVI: Mechanistic Investigation - H/D Exchange Experiment

DMF stock solutions containing PdCl₂ (3 mmol/L each) and 4,4’dimethoxy-2,2’bipyridyl (0.1 mol/L) were prepared by heating at 50 °C for 1 h. The co-catalyst – 0.008 mmol or 1.97 mg of [RhCODCl]₂ - was added to a 4-mL glass vial, followed by 0.4 mL of the DMF stock solution, 0.4 mmol or 0.102 g 1-iodonapthalene 20a, 57.6 µL of D₂O, and 120 µL of TMEDA. A stir bar was added, and the vial was placed in an autoclave. The autoclave was pressurized with CO and vented three times, and then pressurized to the specified pressure. The mixture was stirred at 85 °C for 24 h. After venting and purging the autoclave with nitrogen, the vial was removed. An aliquot was taken and diluted in ethylether before being passed through a short cilite column and injected into a GC-MS. Deuterium incorporation was calculated by comparison of the signals ratios of the compound mass M and M+1 for the deuterated and nondeuterated compound as measured by EI-MS.

D incorporation by EI-MS:

<table>
<thead>
<tr>
<th>1-naphthaldehyde:</th>
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<th>157.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>non-D</td>
<td></td>
<td></td>
</tr>
<tr>
<td>non-D intensity</td>
<td>939712.0</td>
<td>108320.0</td>
</tr>
<tr>
<td>non-D ratio</td>
<td>1.0</td>
<td>0.1</td>
</tr>
<tr>
<td>D</td>
<td></td>
<td></td>
</tr>
<tr>
<td>enriched intensity</td>
<td>632000.0</td>
<td>76224.0</td>
</tr>
<tr>
<td>contribution of non-D</td>
<td>632000.0</td>
<td>72850.2</td>
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<tr>
<td>intensity due to D</td>
<td>0.0</td>
<td>3373.8</td>
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<tr>
<td>%enrichment</td>
<td></td>
<td>4.4</td>
</tr>
</tbody>
</table>
4,4’diMeObpy:

<table>
<thead>
<tr>
<th></th>
<th>216.0</th>
<th>217.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>non-D</td>
<td></td>
<td></td>
</tr>
<tr>
<td>non-D intensity</td>
<td>15933.000</td>
<td>1423.000</td>
</tr>
<tr>
<td>non D ratio</td>
<td>1.0</td>
<td>0.1</td>
</tr>
<tr>
<td>D</td>
<td></td>
<td></td>
</tr>
<tr>
<td>enriched intensity</td>
<td>14442.000</td>
<td>1495.000</td>
</tr>
<tr>
<td>contribution of non-D</td>
<td>14442.0</td>
<td>1289.8</td>
</tr>
<tr>
<td>intensity due to D</td>
<td>0.0</td>
<td>205.2</td>
</tr>
<tr>
<td>%enrichment</td>
<td></td>
<td>13.7</td>
</tr>
<tr>
<td>%average</td>
<td></td>
<td>13.7</td>
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</tbody>
</table>

TMEDA:

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<tr>
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<th>116.0</th>
<th>117.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>non-D</td>
<td></td>
<td></td>
</tr>
<tr>
<td>non-D intensity</td>
<td>22512.000</td>
<td>1458.0</td>
</tr>
<tr>
<td>non D ratio</td>
<td>1.0</td>
<td>0.1</td>
</tr>
<tr>
<td>D</td>
<td></td>
<td></td>
</tr>
<tr>
<td>enriched intensity</td>
<td>59064.0</td>
<td>3889.0</td>
</tr>
<tr>
<td>contribution of non-D</td>
<td>59064.0</td>
<td>3825.3</td>
</tr>
<tr>
<td>intensity due to D</td>
<td>0.0</td>
<td>63.7</td>
</tr>
<tr>
<td>%enrichment</td>
<td></td>
<td>1.6</td>
</tr>
</tbody>
</table>

Procedure XVII: Mechanistic investigation - Sodium Formate as a Hydride Source

![Diagram](attachment:image.png)

DMF stock solutions containing PdCl\(_2\) (3 mmol/L each) and 4,4’dimethoxy-2,2’bipyridyl (0.1 mol/L) were prepared by heating at 50 ºC for 1 h. To a 4-mL glass vial, 0.4 mL of the DMF stock solution was added followed by 0.4 mmol or 57.7 µL of 2,6-dimethyliodobenzene 1a, 54.4 mg sodium formate (2 equiv), and 120 µL of TMEDA (2 equiv). A stir bar was added, and the vial was placed in an autoclave. The autoclave was pressurized with CO and vented three times, and then pressurized to 15 bar. The mixture was stirred at 85 ºC for 24 h. After venting and purging the autoclave with nitrogen, the vial was removed. An aliquot was taken and diluted in diethyl ether before being passed through a short Celite column and injected into a GC. The analysis and calibration factors used are described above.
Procedure XVIII: Mechanistic Investigation - Two-Chamber Experiment

DMF stock solutions containing PdCl$_2$ (3 mmol/L each) and 4,4’dimethoxy-2,2’bipyridyl (0.1 mol/L) were prepared by heating at 50 °C for 1 h. To a 2-mL glass tube, 0.4 mL of the DMF stock solution was added followed by 0.4 mmol or 57.7 uL 2,6-dimethyliodobenzene Ia, and 120 μL of TMEDA (2 equiv). A stir bar was added, and the vial was placed in an autoclave. In another 2-mL glass tube, 1.97 mg of [RhCODCl]$_2$ was dissolved in 0.4 mL DMF solution containing 4,4’dimethoxy-2,2’bipyridyl (0.1 mol/L). 57.6 ul or 8 equiv of DI water was added to the second tube and 120 μL of TMEDA (2 equiv). The two tubes were put inside the same autoclave Figure 5S. The autoclave was pressurized with CO and vented three times, and then pressurized to 14 bar. The mixture was stirred at 85 °C for 18 h. After venting and purging the autoclave with nitrogen, the vial was removed. An aliquot was taken and diluted in ethylether before being passed through a short Celite column and injected into a GC. The analysis and calibration factors used are described above.

**Figure 8.8.** Dual-chamber, hydrogen driven, reductive carbonylation with separate WGSR chamber
8.4. Experimental section for chapter 4

Synthesis of Supported Nanoparticles

(Samples: RhA-red, RhA-oxid500, RhA-oxid350, RhA-oxid/red, RhA-aged1, RhA-aged3, RhA-aged/red)

A solution of the Rh(III) precursor was prepared by dissolving 64.5 mg RhCl₃·3H₂O in 250 mL deionized DI water in a 500 mL round-bottomed flask and the pH was adjusted to 10 using NH₄OH solution (0.2 mL). Five grams of Al₂O₃ powder was added and the pH was readjusted to 10. The slurry was stirred at room temperature for 24 h before stirring was stopped and the slurry was allowed to settle for 1 h. The solid residue was separated by centrifugation and decanting the supernatant then was dried under vacuum (15 mmHg) at room temperature overnight.

Three grams of the dried Rh/Al₂O₃ powder was reduced under hydrogen flowing at 20 mL/min in a tube furnace. The furnace temperature was raised at a rate of 2 °C/min and held at 500 °C for 4 h then cooled to room temperature. The hydrogen flow was gradually reduced to zero to avoid reheating the sample due to rapid oxidation upon exposure to air. Two grams of the reduced sample was stored under argon atmosphere (RhA-red) and 0.5 g of the reduced sample was stored under air for 1 month (RhA-aged1) and 3 months (RhA-aged3). A 100 mg portion of the (RhA-aged3) sample was submitted to a second reduction cycle by hydrogen as described above and stored under argon (RhA-aged/red).

One gram of the dried Rh/Al₂O₃ powder was calcined under dry air flowing at 20 mL/min in a tube furnace. The furnace temperature was raised at a rate of 2 °C/min and held at 500 °C for 4 h then cooled to room temperature and stored under air (RhA-oxid500). A 250 mg portion of sample RhA-oxid500 was submitted to reduction by hydrogen at 500 °C as described above and stored under argon (RhA-oxid/red). Another 500 mg portion of the dried Rh/Al₂O₃ powder was calcined under air at 350 °C the same way as described above and stored under air (RhA-oxid350).

RhNP on TiO₂ (RhT)

A solution of the Rh(III) precursor was prepared by dissolving 25.8 mg RhCl₃·3H₂O in 50 mL DI water in a 100 mL round-bottomed flask and the pH was adjusted to 10 by addition of a solution of NH₄OH (0.01 mL). One gram of TiO₂ (P-25) powder was added and the pH was
readjusted to 10. The slurry was stirred at room temperature for 24 h before stirring was stopped and the slurry was decanted for 1 h. The solid residue was separated by centrifugation and decantation of the supernatant then was dried under vacuum (15 mmHg) at room temperature overnight.

A 500 mg portion of the dried Rh/TiO\(_2\) powder was reduced under hydrogen flowing at 20 mL/min in a tube furnace. The furnace temperature was raised at a rate of 2 °C/min and held at 350 °C for 4 h then cooled to room temperature. The hydrogen flow was gradually reduced to zero to avoid reheating the sample due to rapid oxidation upon exposure to air the stored under argon. Another 500 mg portion of the dried Rh/TiO\(_2\) was calcined under dry air flowing at 20 mL/min in a tube furnace. The furnace temperature was raised at a rate of 2 °C/min and held at 350 °C for 4 h then cooled to room temperature and stored under air.

PtNP on Al\(_2\)O\(_3\) (PtA)

A solution of the Pt(IV) precursor was prepared by dissolving 13.3 mg H\(_2\)PtCl\(_6\).3H\(_2\)O in 1 mL DI water in a one-dram vial. The solution was added dropwise to one gram of Al\(_2\)O\(_3\) powder with continuous stirring of the powder. The resulting paste was aged at room temperature for 24 h then dried under vacuum (15 mmHg) at room temperature overnight.

The dried Pt/Al\(_2\)O\(_3\) powder was calcined under dry air flowing at 20 mL/min in a tube furnace. The furnace temperature was raised at a rate of 2 °C/min and held at 500 °C for 4 h then cooled to room temperature. The calcined sample was reduced under hydrogen at 500 °C following the same procedure described above and stored under air (PtA)

RuNP on Al\(_2\)O\(_3\) (RuA)

A solution of the Ru(III) precursor was prepared by dissolving 12.9 mg RuCl\(_3\).3H\(_2\)O in 50 mL DI water in a 100 mL round-bottomed flask and the pH was adjusted to 10 by addition of NH\(_4\)OH solution (0.01 mL). One gram Al\(_2\)O\(_3\) (P-25) powder was added and the slurry was stirred at room temperature for 24 h before stirring was stopped and the slurry was allowed to settle for 1 h. The solid residue was separated by centrifugation and decantation of the supernatant then was dried under vacuum (15 mmHg) at room temperature overnight.

The dried Ru/Al\(_2\)O\(_3\) powder was reduced under hydrogen flowing at 20 mL/min in a tube furnace. The furnace temperature was raised at a rate of 2 °C/min and held at 650 °C for 4 h then cooled to room temperature. The hydrogen flow was gradually reduced and the sample was stored under argon atmosphere (RuA)
Commercial Rh and PdNP ($\text{RhA-comm}$, $\text{RhC-comm}$, $\text{PdA-Comm}$)

One gram of the densely loaded, commercial samples of Rh NPs supported on alumina ($\text{RhA-comm}$) and carbon ($\text{RhC-comm}$) in addition to Pd NPs on alumina ($\text{PdA-comm}$) were prewashed in 20 mL solution of acetonitrile/water/triethylamine 1/0.2/0.2 v at 70 °C for 24 h in sealed 20 mL vials then filtered and dried under vacuum (15 mmHg) overnight.

Characterization of NP

The metal content of the samples was measured using Inductively Coupled Plasma-Optical Emission Spectroscopy (ICP-OES, PerkinElmer 2000DV). X-ray Photoelectron Spectroscopy (XPS) was measured by Kratos Axis Ultra XPS with Mg, Al dual anode X-ray source on samples under UHV. The Rh peaks were deconvoluted using three-component analysis for Rh(0), (I) and (III) at ca. 307, 309, 310 (eV) respectively. The nanoparticle size was measured using Transmission Electron Microscopy (TEM, JEOL 2010-LaB$_6$, 200 kV, bright field mode, single tilt holder). Prior to TEM imaging, 10 mg of each sample was ground and sonicated in methanol then dispersed on “holey carbon” Cu grids. The diameter of 200 particles was measured and the algebraic mean was determined as the average particle size $D$ in nm.

Table 8.9. Nanoparticles pretreatment conditions, size, and support metal content

<table>
<thead>
<tr>
<th>sample</th>
<th>Pretreatment conditions</th>
<th>wt %</th>
<th>$D_{\text{avg}}$ nm</th>
</tr>
</thead>
<tbody>
<tr>
<td>RhA-red</td>
<td>$H_2$ at 500 °C</td>
<td>0.47</td>
<td>1.47</td>
</tr>
<tr>
<td>RhA-aged1</td>
<td>RhA-red, 1 month storage in air</td>
<td>0.47</td>
<td>nd</td>
</tr>
<tr>
<td>RhA-aged3</td>
<td>RhA-red, 3 month storage in air</td>
<td>0.47</td>
<td>nd</td>
</tr>
<tr>
<td>RhA-aged/red</td>
<td>RhA-aged3, $H_2$ at 500 °C</td>
<td>0.47</td>
<td>nd</td>
</tr>
<tr>
<td>RhA-oxid500</td>
<td>air at 500 °C</td>
<td>0.47</td>
<td>1.76</td>
</tr>
<tr>
<td>RhA-oxid350</td>
<td>air at 350 °C</td>
<td>0.47</td>
<td>nd</td>
</tr>
<tr>
<td>RhA-oxid/red500</td>
<td>RhA-oxid500, $H_2$ at 500 °C</td>
<td>0.47</td>
<td>nd</td>
</tr>
<tr>
<td>RhT</td>
<td>$H_2$ at 350 °C</td>
<td>0.84</td>
<td>&lt;1</td>
</tr>
<tr>
<td>RhA-comm</td>
<td>As recieved</td>
<td>4.31</td>
<td>2.66</td>
</tr>
<tr>
<td>RhC-comm</td>
<td>MeCN/$H_2$O/Et$_3$N wash at 70 °C</td>
<td>2.53</td>
<td>1.69</td>
</tr>
<tr>
<td>PdA-comm</td>
<td>$H_2$ at 500 °C</td>
<td>4.83</td>
<td>1.21</td>
</tr>
<tr>
<td>PtA</td>
<td>$H_2$ at 500 °C</td>
<td>0.44</td>
<td>1.63</td>
</tr>
<tr>
<td>RuA</td>
<td>$H_2$ at 650 °C</td>
<td>0.48</td>
<td>1.34</td>
</tr>
</tbody>
</table>
Figure 8.9. Rh NP size distribution by TEM (a) RhA-red. (b) RhA-oxd500. (c) RhA-comm. (d) RhT. (e) RhC-comm.
Figure 8.10. Pd, Pt, and Ru metals NP size distribution by TEM (a) PdA-comm. (b) PtA. (c) RuA.

Figure 8.11. XPS Spectra of synthesized Rh NP on alumina (oxidation state distribution from curve fitting) (a) RhA-red: 92% Rh(0), 8% Rh(III). (b) RhA-aged3: 83% Rh(0), 11% Rh(I), 6% Rh(III). (c) RhA-oxid500: 26% Rh(0), 29% Rh(I), 45% Rh(III).
Leaching Experiment

Standard leaching experiments were performed by immersing 30 mg of the supported NP sample in a solution containing 2 ml acetonitrile, 0.4 ml triethylamine, and 0.4 ml deionized water in a glass vial with a stir bar. The vial was placed in a stainless-steel, bolted-closure pressure autoclave with a removable top that is fitted with an inlet and outlet needle valves and a pressure gauge. The autoclave was purged with CO three times and then pressurized to the desired CO pressure. The autoclave temperature and stir rate were controlled by a stir plate for 24 h then was cooled to room temperature and depressurized. Under the standard leaching conditions, the solution color remains yellow that turns to dark green upon air exposure. The leaching slurry was filtered under atmospheric air and the residue was rinsed three times with diethyl ether 3X10 ml then dried and sent for metal content measurement by ICP-OES. The leaching efficiency was determined as following:

\[ \% \text{leaching} = \frac{(\text{metal wt\% before leaching} - \text{metal wt\% after leaching}) \times 100}{\text{metal wt\% before leaching}} \]

Characterization of Post Leaching Solution

Post leaching characterization was done on solutions and residue resulting from leaching RhA-red sample at 25 °C for 24 h under 25 barg. Infrared spectra (IR) were recorded on a Perkin Elmer Spectrum Two ATR spectrometer using neat sample. Uv-vis spectra were recorded on a Cary 60 Spectrometer using quartz cuvettes after baseline correction with pure solution of the same composition of the sample. The post leaching spectra were collected after allowing the slurry to settle down for 2 h before CO depressurizing. An aliquot was taken from the CO-saturated clear solution and transferred to the cuvette under atmospheric air directly after depressurizing CO.
Effect of water and triethylamine addition on leaching of RhA-red sample in acetonitrile

Leaching of 30 mg of RhA-red sample was performed by immersing 30 mg of the sample in a solution containing 2 ml acetonitrile and 0.2 ml of water, and/or 0.2 ml of triethylamine as indicated in Figure 4S. The post-leaching supernatants were pale violet after venting the CO and slowly turned into green upon exposure to air. UV-vis spectra taken directly after venting CO showed three main peaks at 387, 334, and 277 nm when leaching was performed in dry as well as wet acetonitrile (Figure 4Sa). The spectrum of the acetonitrile/water/triethylamine solution showed a diminished absorbance at 387 and enhanced absorbance at 279 nm when compared to the spectra from the amine-free solutions. The similar absorbance features of dry as well as wet acetonitrile indicates the formation of the same Rh species in both cases. The different absorbance in the triethylamine-containing solution indicates the coordination of the amine with the Rh species. Upon filtration and solvent removal under vacuum, a brown residue was formed that is soluble in triethylamine/water mixture, and insoluble in polar solvents. The UV-vis spectra taken after removal of solvent and re-dissolving the residue in dry acetonitrile were featureless and exhibited an increasing absorbance at the lower wavelength (Figure 4Sb). The monotonically increasing absorbance at decreasing light wavelength in the re-dissolved residue is characteristic of the formation of metallic Rh NP.²⁰

![Figure 8.12](image)

**Figure 8.12.** (a) UV-vis absorbance of the post leaching solution of sample RhA-red. in dry acetonitrile, acetonitrile/water, 5:1 v:v, and acetonitrile/water/triethylamine 5:1:1 v:v:v after 24 h under 20 barg CO pressure at 25 °C (b) UV-vis absorbance after solvent removal under vacuum and re-dissolving of the residues from the three experiments in dry acetonitrile.
Leaching in acetonitrile/water/triethylamine 5:1:1 was repeated on 2 g scale of RhA-red sample for 36 h. The post leaching slurry was filtered and rinsed with deionized water. The filtrate was evacuated under reduced pressure to remove the solvent and the residue was redissolved in acetone and transferred to a glass boat for hydrogen treatment in a tube furnace. The hydrogen treatment was performed with hydrogen flow at 200 °C for 2 h and the resulting powder was analyzed by ICP-OES which indicated 93.12% Rh content.

Effect of amine addition on leaching of RhA-red sample in dry acetonitrile

Leaching of 30 mg of RhA-red sample was performed by immersing 30 mg of the sample in a solution containing 2 ml acetonitrile and 0.4 ml of either triethylamine or piperdine. The CO pressure was set to 20 barg and the leaching was allowed to occur for 24 h at room temperature.

Table 8.10. Effect of amine on leaching of RhA-red sample in dry MeCN

<table>
<thead>
<tr>
<th>base</th>
<th>% leaching</th>
</tr>
</thead>
<tbody>
<tr>
<td>--</td>
<td>41</td>
</tr>
<tr>
<td>triethylamine</td>
<td>56</td>
</tr>
<tr>
<td>piperdine</td>
<td>21</td>
</tr>
</tbody>
</table>

Mass Spec. characterization of soluble extracted Rh species

Leaching of 30 mg of RhA-red sample was performed by immersing 30 mg of the sample in a solution containing 2 ml acetonitrile and 0.4 ml triethylamine to form a slurry. The CO pressure was set to 20 barg and the leaching was allowed to occur by stirring the slurry for 24 h at room temperature. The stirring was stopped and the slurry was allowed to settle down for 3 hours before venting the pressure vessel. Once CO was vented, a sample was taken from the top clear solvent phase and injected to Waters Q-TOF Ultima Mass Spectrometry Electrospray Ionization (MS-ESI) instrument. Data are reported in the form of m/z, Figure 5Sa. The observed mass spectrum indicated the formation of a series of rhodium carbonyl clusters with m/z in the range of 700 to 1850. Based on the calculated mass for rhodium carbonyl clusters containing 2 to
5 CO atoms/Rh atom, the nuclearity of the observed clusters was estimated to be between 4 to 10 Rh atoms per cluster, Figure 5Sb. The average atomic ratio CO/Rh in the clusters is estimated to be around 3 based on comparison of the observed masses and those calculated for clusters of different CO/Rh ratios, Figure 8.13.

Figure 8.13. (a) MS-ESI of the post leaching solution of sample RhA-red. in acetonitrile/water/triethylamine 5:1:1 v:v:v after 24 h under 20 barg CO pressure at 25 °C. (b) assignment of the observed masses to Rh carbonyl clusters with the nearest calculated mass. (c) estimation of the average CO/Rh atomic ratio in the formed clusters by comparing the observed masses (red triangles) to the masses calculated for CO/Rh = 1, 2, 3, 4.
Effect of inorganic additives on the leaching of RhA-red sample in MeCN/Et₃N/H₂O mixture at 25 °C.

Leaching of 30 mg of RhA-red sample was performed by immersing 30 mg of the sample in a solution containing 2 ml acetonitrile, 0.4 ml water, and 0.4 ml of triethylamine with 10 mg of either NaCl, or NaOH, or 0.01 ml HCl ACS grade solution. The CO pressure was set to 20 barg and the leaching was allowed to occur for 24 h at room temperature. Slight increase in leaching was observed by the addition of NaOH and NaCl and slight decrease in leaching occurred when HCl was added (Table 8.11).

**Table 8.11.** Effect of inorganic additives on the leaching of RhA-red sample in MeCN/Et₃N/H₂O mixture at 25 °C.

<table>
<thead>
<tr>
<th>additive</th>
<th>% leaching</th>
</tr>
</thead>
<tbody>
<tr>
<td>--</td>
<td>89</td>
</tr>
<tr>
<td>NaCl (10 mg)</td>
<td>93</td>
</tr>
<tr>
<td>NaOH (10 mg)</td>
<td>90</td>
</tr>
<tr>
<td>HCl (0.01 ml)</td>
<td>83</td>
</tr>
</tbody>
</table>

Leaching of Rh NP supported on titanium oxide

Predominantly-anatase, P-25 titanium oxide-supported Rh NPs RhT samples also leach in CO-saturated acetonitrile. As was found with the alumina-supported samples, prereduction enhanced the leaching efficiency and the addition of water and a tertiary amine improved leaching efficicncy. Greater than 90% leaching was achieved on the freshly reduced RhT sample in a CO-saturated solution containing acetonitrile, water, and amine at room temperature (Table 8.12).
Table 8.12. Leaching of $RhT$ sample at 25 °C

<table>
<thead>
<tr>
<th>pretreatment</th>
<th>leaching conditions</th>
<th>% leaching</th>
</tr>
</thead>
<tbody>
<tr>
<td>gas</td>
<td>$X_{ml}$ $Y_{ml}$</td>
<td></td>
</tr>
<tr>
<td>Air</td>
<td>0 0 42</td>
<td></td>
</tr>
<tr>
<td>Hydrogen</td>
<td>0 0 56</td>
<td></td>
</tr>
<tr>
<td>Air</td>
<td>0.2 0.2 78</td>
<td></td>
</tr>
<tr>
<td>Hydrogen</td>
<td>0.2 0.2 93</td>
<td></td>
</tr>
</tbody>
</table>

Leaching of Rh NP supported on activated carbon

The standard leaching conditions at 20 barg CO pressure and 70 °C were also effective in extraction of Rh from a commercial, carbon supported sample $RhC$-$comm$ and the Rh content was measured before and after CO leaching for 24 h at 2.53 and 0.67 wt % respectively, i.e. 74% leaching.

Leaching of non-mixed Pd, Pt, and Ru NPs on alumina at room temperature

Commercial Pd NPs $PdA$-$comm$ sample and synthesized Pt and Ru NPs, $PtA$, and $RuA$ all supported on alumina were reduced under hydrogen flow and submitted to the standard leaching conditions at 20 barg CO and room temperature with and without the addition of triethylamine to the acetonitrile/water, 5:1 v:v solution. No observable leaching of any of the three metals was detected without triethylamine, however, the addition of triethylamine caused slight leaching of Pd, and Ru at 15% and 7% respectively (Table 8.13).
Effect of additives on the leaching of a mixture of Rh, Pd, Pt, and Ru NP in DMF at 80 °C.

A mixture of nanoparticles of Rh, Pd, Pt, and Ru all supported on alumina was prepared by mixing equal amounts of each individual metal. The resulting powder mixture was homogenized by further grinding and then the sample was reduced under a flow of hydrogen at 500 °C before the leaching experiment to minimize the effect of surface re-oxidation under ambient air. The leaching experiment of the solid mixture was performed at 80 °C in dimethylformamide solution of water and triethylamine 5:1:1 v. The CO pressure was set to 25 barg and the leaching was allowed to go for 40 h to test the leachability of Pd, Pt, and Ru under more forcing conditions. Additives were added to individual experiments as following; 10 mg bipyridyl as an auxiliary ligand, 0.4 ml of phenyl iodide as a source of halogen ions, and 0.4 ml of tetraethylene diamine TMEDA as an auxiliary ligand.

Addition of phenyl iodide was found to increase the leaching of Pd and Pt indicating the effectiveness of the CO-inducned leaching of these two metals in presence of a source of halogen (Table 8.14). TMEDA was found to drastically inhibit leaching of Rh potentially due to the formation of surface stable complex or hindering the formation of the soluble polynuclear carbonyl clusters. Bipyridyl did not have a significant impact on the leaching efficiency or selectivity.
Table 8.14. Effect of additives on the leaching of Rh, Pd, Pt, and Ru NP in DMF at 80 °C.

<table>
<thead>
<tr>
<th>additive</th>
<th>% leaching</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rh</td>
</tr>
<tr>
<td>--</td>
<td>77</td>
</tr>
<tr>
<td>bipyridyl (10 mg)</td>
<td>80</td>
</tr>
<tr>
<td>Phenyl iodide (0.4 ml)</td>
<td>90</td>
</tr>
<tr>
<td>tetramethylethylene diamine (0.4 ml)*</td>
<td>20</td>
</tr>
</tbody>
</table>

*no triethylamine added
8.5. Experimental section for chapter 5

General Procedure 1: Effect of KOH on the WGSR-driven reduction of chalcone (Figure 5.1)

The RhCl₃ catalyst (3 mol % or 3.2 mg) was added to a 4-mL glass vial, followed by 0.4 mL solvent (acetonitrile unless mentioned otherwise), 83 mg chalcone 1aa', 0.18 mL deionized water, 0.14 mL triethylamine, and mesitylene as internal standard. Different amounts of KOH were added to different vials as following: 2.10 mg (0.1 equiv), 6.70 mg (0.3 equiv), 11.20 mg (0.5 equiv), 22.40 mg (1.0 equiv). A stir bar was added, and the vial was placed in an autoclave. The autoclave was pressurized with CO and vented three times, and then pressurized to 10 bar. The mixture was stirred at room temperature for the indicated time. After venting and purging the autoclave with nitrogen, the vial was removed. An aliquot was taken and diluted in EtOAc before being passed through a short silica column and injected into a HP-1 GC column (25 m, 0.2 mm ID, 0.33 μm thickness). The column oven temperature program was as follows: 100 °C for 3 minutes, 100 °C to 260 °C at 20 °C /min, then 260 °C for 1 minute.

GC response factors were established by the following equation using mesitylene as the internal standard:

\[
\text{Response Factor} = \frac{\text{(mmols of compound)}}{\text{(area of compound)}} \times \frac{\text{(area of mesitylene)}}{\text{(mmol of mesitylene)}}
\]

Three samples containing a known amount of the desired compound and mesitylene were prepared and dissolved in EtOAc. A small portion of each sample was diluted further to 1 mL. An aliquot of each sample was injected into GC in triplicates. The average of 9 response factors was used to monitor the reaction.

General Procedure 2: Effectiveness of different amines on the WGSR-driven reductive Claisen-Schmidt (Table 5.1)

To six different 4-mL glass vials, 0.0466 mL acetophenone was added followed by 0.043 mL benzaldehyde (1.05 equiv) and 0.1 equiv. of the following bases in different vials in parallel; DBN, DBU, MTBD, TBD, triethylamine, and piperidine. A stir bar was added and the reaction was stirred at room temperature for 24 h under air. 0.4 mL acetonitrile was added to each vial followed by 0.120 mL water, 0.056 mL triethylamine, and 2.12 mg RhCl₃. Mesitylene was added as internal standard and the vials were placed in an autoclave. The autoclave was pressurized with CO and vented three times, and then pressurized to 10 bar. The mixture was stirred at room temperature for 48 h. After venting and purging the autoclave with nitrogen, the vial was
removed. An aliquot was taken and diluted in EtOAc before being passed through a short silica
column and injected into GC for quantification.

**General Procedure 3: Effectiveness of different amines on the WGSR-driven reductive Claisen-
Schmidt (Table 5.2)**

To nine different 4-mL glass vials, 2 mmole of the following ketones were added: acetophenone (vials 1, 2, 6, 7, 8, and 9), 4-acylpyridine (vial 3), 4-cyanoacetophenone (vial 4), and 2-acylcyclohexene (vial 5). To the same vials, 2.1 mmole of the following carbonyl compounds were added: benzaldehyde (vial 1, 3, 4, and 5), 2-furfural (vial 2), E-cinnamaldehyde (vial 6), 3-methylbutenal (vial 7), acetone (vial 8), and cyclohexanone (vial 9). 1 equivalent, or 0.2 mmole, of MTBD was added to each vial along with mesitylene internal standard and a stir bar. The reaction was allowed to proceed for 24 h at room temperature under air. The reaction
was diluted with ethylacetate (5 mL) and an aliquot was taken and passed through a short silica
column and injected into GC for quantification.

**General Procedure 4: Effectiveness of MTBD and tosyllic anhydride on the WGSR-driven
reductive Claisen-Schmidt of propiophenone (Table 5.3)**

To four different 4-mL glass vials, 0.133 mL propiophenone was added followed by 0.107
mL benzaldehyde (1.05 equiv.). To vials 1 and 2, 0.1 mmole MTBD was added and to vials 3,
and 4 1 mmole tosyllic anhydride was added. A stir bar was added and the reaction was stirred at
room temperature for 18 h under air. 1.0 mL acetonitrile was added to each vial followed by
0.450 mL water, and 5.3 mg RhCl₃. To vials 1 and 3, 0.433 mL dimethylethylamine and to vials
2 and 4, 0.649 mL of dimethylethylamine was added. Mesitylene was added as internal standard
and the vials were placed in an autoclave. The autoclave was pressurized with CO and vented
three times, and then pressurized to 710 bar. The mixture was stirred at room temperature for 24
h. After venting and purging the autoclave with nitrogen, the vial was removed. An aliquot was
taken and diluted in EtOAc before being passed through a short silica column and injected into
GC for quantification.

**General Procedure 5: Effect of tosylic acid on the WGSR-driven reduction of chalcone (Figure
5.2, Table 5.4)**

The RhCl₃ catalyst (2 mol % or 2.1 mg) or Rh₄(CO)₁₂ (2 mol % Rh or 1.5 mg) was added to
a 4-mL glass vial, followed by 0.4 mL solvent (acetonitrile unless mentioned otherwise), 83 mg
General Procedure 6: Effect of different dimethylethylamine loadings on the WGS-driven reduction of chalcone (Figure 5.3)

The RhCl₃ catalyst (2 mol % or 2.1 mg) was added to a 4-mL glass vial, followed by 0.4 mL solvent (acetonitrile unless mentioned otherwise), 83 mg chalcone 1aa', 0.18 mL deionized water, and mesitylene as internal standard. Different amounts of dimethylethylamine were added to different vials as following: 21.6 mL (0.5 equiv), 43.3 mL (1.0 equiv), 108 mL (2.5 equiv), 216.3 mL (5.0 equiv), 302.8 mL (7.0 equiv), 432.3 mL (10.0 equiv), 865.1 mL (20.0 equiv). A stir bar was added, and the vial was placed in an autoclave. The autoclave was pressurized with CO and vented three times, and then pressurized to 7 bar. The mixture was stirred at room temperature for the indicated time. After venting and purging the autoclave with nitrogen, the vial was removed. An aliquot was taken and diluted in EtOAc before being passed through a short silica column and injected into GC for quantification.

General Procedure 7: Effect of different amines on the WGS-driven reduction of chalcone (Table 5.5)

The RhCl₃ catalyst (2 mol % or 2.1 mg) was added to a 4-mL glass vial, followed by 0.4 mL solvent (acetonitrile), 83 mg chalcone 1aa', 0.18 mL deionized water, and mesitylene as internal standard. 2.5 equivalents of triethylamine, dimethylethylamine, N-methyl pyrrolidine, and N-methyl piperidine. 1.25 equivalent’s were added of the following amines; N,N,N',N'-tetramethylethylene diamine, N,N,N',N'-tetramethylpropylenediamine, and 1,4-diazabicyclo[2.2.2]octane were added to different vials. A stir bar was added, and the vial was placed in an autoclave. The autoclave was pressurized with CO and vented three times, and then pressurized to 7 bar. The mixture was stirred at room temperature for the indicated time. After...
venting and purging the autoclave with nitrogen, the vial was removed. An aliquot was taken and diluted in EtOAc before being passed through a short silica column and injected into GC for quantification.

General Procedure 8: Effect of solvent composition on the WGSR-driven reduction of chalcone (Figure 5.4)

The RhCl₃ catalyst (2 mol % or 2.1 mg) was added to a 4-mL glass vial, followed by 83 mg chalcone 1aa’, 0.108 mL dimethylethylamine, 0.18 mL deionized water, and mesitylene as internal standard. 0.4 mL of solvent (different 1, 4-dioxane/acetonitrile volume composition was used as following: 0:100, 10:90, 25:75, 50:50, 75:25, 100:0) was added to each vial. A stir bar was added, and the vial was placed in an autoclave. The autoclave was pressurized with CO and vented three times, and then pressurized to 7 bar. The mixture was stirred at room temperature for the indicated time. After venting and purging the autoclave with nitrogen, the vial was removed. An aliquot was taken and diluted in EtOAc before being passed through a short silica column and injected into GC for quantification.

General Procedure 9: Effect of water loading on the WGSR-driven reduction of chalcone (Figure 5.5)

The RhCl₃ catalyst (2 mol % or 2.1 mg) was added to a 4-mL glass vial, followed by 0.4 mL solvent (acetonitrile), 83 mg chalcone 1aa’, 0.108 mL dimethylethylamine, and mesitylene as internal standard. The following amounts of water were added to different vials as following: 0.036 mL (5 equiv), 0.072 mL (10 equiv), 0.108 mL (15 equiv), 0.180 mL (25 equiv), 0.252 mL (35 equiv), 0.360 mL (50 equiv). A stir bar was added, and the vial was placed in an autoclave. The autoclave was pressurized with CO and vented three times, and then pressurized to 7 bar. The mixture was stirred at room temperature for the indicated time. After venting and purging the autoclave with nitrogen, the vial was removed. An aliquot was taken and diluted in EtOAc before being passed through a short silica column and injected into GC for quantification.

General Procedure 10: Effect of CO pressure on the WGSR-driven reduction of chalcone (Figure 5.6)

The RhCl₃ catalyst (2 mol % or 2.1 mg) was added to a 4-mL glass vial, followed by 0.4 mL solvent (acetonitrile), 83 mg chalcone 1aa’, 0.108 mL dimethylethylamine, 0.18 mL deionized water, and mesitylene as internal standard. A stir bar was added, and the vial was placed in an
autoclave. The autoclave was pressurized with CO and vented three times, and then pressurized to different CO pressures. The mixture was stirred at room temperature for the indicated time. After venting and purging the autoclave with nitrogen, the vial was removed. An aliquot was taken and diluted in EtOAc before being passed through a short silica column and injected into GC for quantification.

General Procedure 11: Effect of different amines on the WGSR-driven reductive alkylation of ethylcyanoacetate (Table 5.6)

The RhCl₃ catalyst (1.52 mol % or 1.5 mg) was added to a 4-mL glass vial, followed by 1.0 mL solvent (acetonitrile for vial 1 to 6). For vials 7 to 11, the following solvent composition was added in 1.0 mL in order: MeCN/EtOH (9:1), MeCN/EtOH (7:3), MeCN/EtOH (1:1), MeCN/EtOH (3:7), MeCN/EtOH (1:9). ethylcyanoacetate 0.0425 mL or 0.4 mmole, 0.043 mL benzaldehyde or 1.05 equivalent, and 0.015 mL deionized water (2 equiv), and mesitylene as internal standard were added to each vial. triethylamine (2.5 equivalents) was added to vials 1, and 3 to 11. 0.1 equivalent of DBU was added to vial 1, 2.5 equivalent of piperidine was added to vial 2, 0.5 equivalent of piperidine was added to vial 3, 0.1 equivalent of MTBD was added to vial 4, 0.1 equivalent L-proline was added to vial 5, 0.1 equivalent of ammonium acetate was added to vial 6. To vials 7 to 11, 0.5 equivalents of piperidine were added to each vial. A stir bar was added, and the vial was placed in an autoclave. The autoclave was pressurized with CO and vented three times, and then pressurized to 10 bar. The mixture was stirred at room temperature for 14 h. After venting and purging the autoclave with nitrogen, the vial was removed. An aliquot was taken and diluted in EtOAc before being passed through a short silica column and injected into GC for quantification.

General Procedure 12: Effect of different amines on the condensation of different esters (Table 5.7)

To fifteen different vials, acetonitrile (0.8 mL) was added and to one vial, 0.8 mL ethanol was added followed by 0.043 mL benzaldehyde (or 1.05 equivalent), and mesitylene as internal standard to each vial. To vials 1 to 4, 0.4 mmole ethyl benzoyletacetate was added, to vials 5 to 9, 0.4 mmole diethylmalonate was added, to vials 10 to 15, 0.4 mmole methylacetoacetate was added, to vial 16, 0.4 mmole of nitroethylacetate was added. To vials 1, 5, 10, and 16, 2.5 equivalents of triethylamine were added. To vials 2 and 6, 10 equivalents of triethylamine was added. To vials 3, 4, 7, and 9, 0.1 equivalents of DBU was added. To vials 8, 12, and 13, 0.3
piperidine was added. To vial 14, 0.1 equivalent of ammonium acetate was added. To vial 15, 0.1 equivalent of L-proline was added. A stir bar was added, and the reaction was allowed to occur for 18 h under air at room temperature. An aliquot was taken and diluted in EtOAc before being passed through a short silica column and injected into GC for quantification.

General Procedure 13: Effect of piperidine and L-proline on the reductive alkylation of ethylacetooacetate (Scheme 5.5)

The RhCl₃ catalyst (2 mol % or 2.1 mg) was added to a 4-mL glass vial, followed by 0.8 mL solvent (acetonitrile), 0.0432 mL ethylacetooacetate, and 0.043 ml benzaldehyde (or 1.05 equivalents). To vials were prepared with the same composition. To the vials, 0.140 mL triethylamine, 0.022 mL water, and mesitylene as internal standard were added. To vial 1, 0.3 equivalents was added and to vial 2, 0.1 equivalent of L-proline was added. A stir bar was added, and the vial was placed in an autoclave. The autoclave was pressurized with CO and vented three times, and then pressurized to 10 bar. The mixture was stirred at room temperature for 30 h. After venting and purging the autoclave with nitrogen, the vial was removed. An aliquot was taken and diluted in EtOAc before being passed through a short silica column and injected into GC for quantification.

General Procedure 14: Reductive alkylation of diketones with and without L-proline

The reductive alkylation of diketones including acetylacetone and dimerdone was carried out with and without L-proline. In a 4- mL glass vial, 40 mg, or 0.4 mmol acetylacetone was added followed by 1.05 equiv benzaldehyde or 44.5 mg. 1 mL acetonitrile was added followed by 1.6 mg RhCl₃ catalyst or 1.5 mol %. 2.5 equiv triethylamine was added (0.140 mL) and 5 equiv water (0.036 mL). 20 ul mesitylene was added as internal standard. In the L-proline experiment, 0.3 equiv or 13.8 mg L-proline was added. A stir bar was added, and the vial was placed in an autoclave. The autoclave was pressurized with CO and vented three times, and then pressurized to 150 psi (10 bar). The mixture was stirred at room temperature for 24 h. After venting and purging the autoclave with nitrogen, the vial was removed. An aliquot was taken and diluted in EtOAc before being passed through a short silica column and injected into GC for quantification.

For the alkylation of dimerdone, 56 mg dimerdone was added in a 4- mL glass vial followed by 1.05 equiv benzaldehyde or 44.5 mg. 1 mL acetonitrile was added followed by 1.6 mg RhCl₃ catalyst or 1.5 mol %. 2.5 equiv triethylamine was added (0.140 mL) and 5 equiv water (0.036 mL). 20 ul mesitylene was added as internal standard. In the L-proline experiment, 0.3 equiv or
13.8 mg l-proline was added. A stir bar was added, and the vial was placed in an autoclave. The autoclave was pressurized with CO and vented three times, and then pressurized to 150 psi (10 bar). The mixture was stirred at room temperature for 24 h. After venting and purging the autoclave with nitrogen, the vial was removed. An aliquot was taken and diluted in EtOAc before being passed through a short silica column and injected into GC for quantification.

For both substrates, the alkylation was found to be extremely slow under the standard conditions. Addition of L-proline was found to be advantageous in the reductive alkylation of these two compounds, however, incomplete consumption was achieved.

General Procedure 15: Reductive alkylation of Thiazolidinodiones

Thiazolidinodiones (glitazones) are useful substrates for the treatment of type 2 diabetes that could potentially be synthesized by the reductive alkylation. The Knoevenagel condensation of thiazolidinodione was found to require piperidine catalyst in ethanol solvent but not acetonitrile. The reductive alkylation of 2,4-Thiazolidinodionewas carried out in two steps, condensation, then reduction. In a 4- mL glass vial, 46.8 mg, or 0.4 mmol 2,4-Thiazolidinodionewas was added
followed by 1.05 equiv benzaldehyde or 44.5 mg. 1 mL ethanol was added followed by 17 mg or 0.3 equiv piperidine as a condensation catalyst and the reaction was stirred at room temperature for 24 h. Solvent was removed under high vac. (15 mmHg) and the condensation product was dissolved in 1 mL acetonitrile followed by 1.6 mg RhCl₃ catalyst or 1.5 mol %. 2.5 equiv triethylamine was added (0.140 mL) and 2 equiv water (0.014 mL). 20 ul mesitylene was added as internal standard. A stir bar was added, and the vial was placed in an autoclave. The autoclave was pressurized with CO and vented three times, and then pressurized to 150 psi (10 bar). The mixture was stirred at room temperature for 24 h. After venting and purging the autoclave with nitrogen, the vial was removed. An aliquot was taken and diluted in EtOAc before being passed through a short silica column and injected into GC for quantification. No reduction was observed and the condensation product was the only observed product.

Addition of thiazolidinedione to the reductive alkylation of ethylcyanoacetate (model reaction, General procedure 11) was also found to inhibit the reduction indicating that the incompatibility of the Rh catalyst with the sulfur containing compound.
8.6. Experimental section for chapter 6

General Procedure I: Reducibility of different carbonyl compounds under WGSR conditions in acetonitrile (Table 6.1)

The RhCl₃ catalyst (2 mol % or 2.1 mg) was added to a 4-mL glass vial, followed by 0.4 mL acetonitrile, 0.144 mL deionized water (20 equiv), 0.139 mL triethylamine (2.5 equiv), and mesitylene as internal standard. The carbonyl compounds were added to the vials at 0.4 mmol as following: benzaldehyde: 42.2 mg, hydrocinnamaldehyde: 53.8 mg, cinnamaldehyde: 51.8 mg, undecanal: 68 mg, 3-methylbutenal: 33.6 mg, 2-methylbutenal: 33.6 mg, 3-vinylbenzaldehyde: 52.8 mg, aceto phenone: 48 mg, 2-hexanone: 40 mg, cyclohexenone: 36.2 mg, cyclohexanone: 38.2 mg, 4-methyl-2-pentene: 38.2 mg, 3-penten-2-one: 33.6 mg, chalcone: 84 mg. A stir bar was added, and the vial was placed in an autoclave. The autoclave was pressurized with CO and vented three times, and then pressurized to 10 bar. The mixture was stirred at room temperature for 18 h. After venting and purging the autoclave with nitrogen, the vial was removed. An aliquot was taken and diluted in EtOAc before being passed through a short silica column and injected into a HP-1 GC column (25 m, 0.2 mm ID, 0.33 μm thickness). The column oven temperature program was as follows: 100 °C for 3 minutes, 100 °C to 260 °C at 20 °C/min, then 260 °C for 1 minute.

GC response factors were established by the following equation using mesitylene as the internal standard:

\[
\text{Response Factor} = \frac{\text{(mmols of compound)}}{\text{(area of compound)}} \times \frac{\text{(area of mesitylene)}}{\text{(mmol of mesitylene)}}
\]

Three samples containing a known amount of the desired compound and mesitylene were prepared and dissolved in EtOAc. A small portion of each sample was diluted further to 1 mL. An aliquot of each sample was injected into GC in triplicates. The average of 9 response factors was used to monitor the reaction.

General Procedure 2: Reducibility of substituted benzaldehydes under WGSR conditions in acetonitrile (Figure 6.1)

The RhCl₃ catalyst (2 mol % or 2.1 mg) was added to a 4-mL glass vial, followed by 0.4 mL acetonitrile, 0.144 mL deionized water (20 equiv), 0.139 mL triethylamine (2.5 equiv), and mesitylene as internal standard. The carbonyl compounds were added to the vials at 0.4 mmol as following: benzaldehyde: 42.2 mg, 4-cyanobenzaldehyde: 52.4 mg, 4-bromobenzaldehyde: 74
mg, 4-methylbenzaldehyde: 48 mg, 4-methoxybenzaldehyde: 54.4 mg. A stir bar was added, and the vial was placed in an autoclave. The autoclave was pressurized with CO and vented three times, and then pressurized to 10 bar. The mixture was stirred at room temperature for 18 h. After venting and purging the autoclave with nitrogen, the vial was removed. An aliquot was taken and diluted in EtOAc before being passed through a short silica column and injected into a GC-MS for product identification/quantification.

General Procedure 3: Reducibility of acetophenone under WGSR conditions in different solvents (Table 6.2)

The [RhCODCl]_2 catalyst (2.5 mol % or 5.3 mg) was added to a 4-mL glass vial, followed by 48 mg acetophenone 1X and 0.4 mL solvent as following: vial 1: acetonitrile, vial 2: n-propanol, vial 3: 2-propanol, vial 4: n-butanol, vial 5: THF, vial 6: ethanol, vial 7: water, vial 8: 2-ethoxyethanol, vial 9: methanol, vial 10: Methanol/acetonitrile 10:1 v, vial 11: acetonitrile, vial 12: methanol/1,4-dioxane 1:1 v, vial 13: methanol/dichloromethane 1:1 v, vial 14 methanol/toluene 1:1 v. To each vial, 0.180 mL deionized water (25 equiv), 0.108 mL dimethylethylamine (2.5 equiv), and 20 ul mesitylene as internal standard were added. A stir bar was added, and the vial was placed in an autoclave. The autoclave was pressurized with CO and vented three times, and then pressurized to 25 bar. The mixture was stirred at room temperature for 18 h. After venting and purging the autoclave with nitrogen, the vial was removed. An aliquot was taken and diluted in EtOAc before being passed through a short silica column and injected into a GC-MS for product identification/quantification.

General Procedure 4: Effect of water loading on the reducibility of acetophenone under WGSR conditions (Figure 6.2)

The [RhCODCl]_2 catalyst (2.5 mol % or 5.3 mg) was added to a 4-mL glass vial, followed by 0.4 mL methanol and 48 mg acetophenone 1X. To each vial 0.108 mL dimethylethylamine (2.5 equiv), and 20 ul mesitylene as internal standard were added. Water was added as following: vial 1: none, vial 2: 0.022 mL (3 equiv), vial 3: 0.036 mL (5 equiv), vial 4: 0.072 mL (10 equiv), vial 6: 0.108 mL (15 equiv), vial 7: 0.180 mL (25 equiv), and vial 8: 0.288 mL (40 equiv). A stir bar was added, and the vial was placed in an autoclave. The autoclave was pressurized with CO and vented three times, and then pressurized to 28 bar. The mixture was stirred at room temperature for 12 h. After venting and purging the autoclave with nitrogen, the vial was
removed. An aliquot was taken and diluted in EtOAc before being passed through a short silica column and injected into a GC-MS for product identification/quantification.

**General Procedure 5: Effect of base on the reducibility of acetophenone under WGSR conditions (Table 6.3)**

The \([\text{RhCODCl}]_2\) catalyst (2.5 mol % or 5.3 mg) was added to a 4-mL glass vial, followed by 0.4 mL methanol and 48 mg acetophenone \(1\text{X}\). To each vial, 0.180 mL (25 equiv) water and 20 ul mesitylene as internal standard were added. The following bases were added to the vials as following: vial 1: none, vial 2: triethylamine 0.139 mL (2.5 equiv), vial 3: TMEDA 0.150 mL (2.5 equiv), vial 4: KOH 22.4 mg (1 equiv), vial 5: DMEA 0.108 mL (2.5 equiv), MTBD 61.2 mg (1 equiv). A stir bar was added, and the vial was placed in an autoclave. The autoclave was pressurized with CO and vented three times, and then pressurized to 25 bar. The mixture was stirred at room temperature for 24 h. After venting and purging the autoclave with nitrogen, the vial was removed. An aliquot was taken and diluted in EtOAc before being passed through a short silica column and injected into a GC-MS for product identification/quantification.

**General Procedure 6: Reduction of alkyl ketones under WGSR conditions (Scheme 6.4)**

The \([\text{RhCODCl}]_2\) catalyst (2.5 mol % or 5.3 mg) was added to a 4-mL glass vial, followed by 0.4 mL methanol. To each vial, 0.180 mL (25 equiv) water and 0.108 mL DMEA (2.5 equiv) were added followed by 20 ul mesitylene as internal standard. The following ketones were added at 0.4 mmol as following: vial 1: cyclohexanone 38.2 mg, methylcyclopropyl ketone 33.6 mg, 3-pentene 33.6 mg. A stir bar was added, and the vial was placed in an autoclave. The autoclave was pressurized with CO and vented three times, and then pressurized to 28 bar. The mixture was stirred at room temperature for 12 h. After venting and purging the autoclave with nitrogen, the vial was removed. An aliquot was taken and diluted in EtOAc before being passed through a short silica column and injected into a GC-MS for product identification/quantification.

**General Procedure 7: Reduction of aryl ketones under WGSR conditions (Scheme 6.5)**

The \([\text{RhCODCl}]_2\) catalyst (1.25 mol % or 2.6 mg) was added to a 4-mL glass vial, followed by 0.4 mL water. To each vial, 0.180 mL DMEA (2.5 equiv) was added followed by 20 ul mesitylene as internal standard. The following ketones were added at 0.4 mmol as following: vial 1: 4-iodoacetophenone 98.4 mg, vial 2: 4-cyanoacetophenone 58 mg, vial 3: 4-dimethylaminoacetophenone 65.2 mg. A stir bar was added, and the vial was placed in an
autoclave. The autoclave was pressurized with CO and vented three times, and then pressurized to 20 bar. The mixture was stirred at 65 °C for 8 h. After venting and purging the autoclave with nitrogen, the vial was removed. An aliquot was taken and diluted in EtOAc before being passed through a short silica column and injected into a GC-MS for product identification/quantification.

General Procedure 8: Reductive deuteration of acetophenone under WGSR conditions (Figure 6.3)

The [RhCODCl]₂ catalyst (2.5 mol % or 5.3 mg) was added to a 4-mL glass vial, followed by 48 mg acetophenone 1X, and 0.4 mL methanol (methanol-d₄). To each vial, 0.180 mL (25 equiv) water (D₂O) and 0.108 mL DMEA (2.5 equiv) were added followed by 20 ul mesitylene as internal standard. The following ketones were added at 0.4 mmol as following: vial 1: cyclohexanone 38.2 mg, methylcyclopropyl ketone 33.6 mg, 3-pentneone 33.6 mg. A stir bar was added, and the vial was placed in an autoclave. The autoclave was pressurized with CO and vented three times, and then pressurized to 28 bar. The mixture was stirred at room temperature for 12 h. After venting and purging the autoclave with nitrogen, the vial was removed. An aliquot was taken and diluted in EtOAc before being passed through a short silica column and injected into a GC-MS for product identification/quantification.

General Procedure 9: Order in catalyst in the WGSR-driven reduction of chalcone in acetonitrile (Table 6.4)

The RhCl₃ catalyst (X mol % or Y mg) was added to a 4-mL glass vial, followed by 83 mg chalcone 1aa', and 0.4 mL acetonitrile. To each vial, 0.180 mL (25 equiv) water and 0.108 mL DMEA (2.5 equiv) were added followed by 20 ul mesitylene as internal standard. A stir bar was added, and the vial was placed in an autoclave. The autoclave was pressurized with CO and vented three times, and then pressurized to 7 bar. The mixture was stirred at room temperature for 3 h. After venting and purging the autoclave with nitrogen, the vial was removed. An aliquot was taken and diluted in EtOAc before being passed through a short silica column and injected into a GC-MS for product identification/quantification. The remaining catalyst medium in vial was placed in the autoclave. The autoclave was pressurized with CO and vented three times, and then pressurized to 7 bar. The mixture was stirred at room temperature for another 3 h. After
venting and purging the autoclave with nitrogen, the vial was removed. Another aliquot was taken and diluted in EtOAc before being passed through a short silica column and injected into a GC-MS for product identification/quantification.

**Table 8.15.** Conversion at different catalyst loading.

<table>
<thead>
<tr>
<th>mol % Rh X</th>
<th>mg RhCl₂ Y</th>
<th>Rh conc. Mol/L</th>
<th>conv. (3 h)</th>
<th>conv. (6 h)</th>
</tr>
</thead>
<tbody>
<tr>
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<td>28.08474</td>
<td>45.01571</td>
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<tr>
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<td>28.05083</td>
<td>42.84511</td>
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<tr>
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<td>0.02</td>
<td>21.52234</td>
<td>37.09069</td>
</tr>
<tr>
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<td>1.862</td>
<td>0.0175</td>
<td>21.43469</td>
<td>35.29192</td>
</tr>
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<td>1.5</td>
<td>1.596</td>
<td>0.015</td>
<td>19.43631</td>
<td>31.09089</td>
</tr>
<tr>
<td>1.25</td>
<td>1.33</td>
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<td>15.48769</td>
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<td>1.064</td>
<td>0.01</td>
<td>11.59526</td>
<td>20.98688</td>
</tr>
</tbody>
</table>

General Procedure 10: Order in catalyst in the WGSR-driven reduction of acetophenone in methanol (Figure 6.4)

The [RhCODCl]₂ catalyst (X mol % or Y mg) was added to a 4-mL glass vial, followed by 48 mg acetophenone 1X, and 0.4 mL methanol. To each vial, 0.180 mL (25 equiv) water and 0.108 mL DMEA (2.5 equiv) were added followed by 20 µl mesitylene as internal standard. A stir bar was added, and the vial was placed in an autoclave. The autoclave was pressurized with CO and vented three times, and then pressurized to 28 bar. The mixture was stirred at room temperature for 12 h. After venting and purging the autoclave with nitrogen, the vial was removed. An aliquot was taken and diluted in EtOAc before being passed through a short silica column and injected into a GC-MS for product identification/quantification.

**Table 8.16.** Conversion at different catalyst loading.

<table>
<thead>
<tr>
<th>mol % Rh X</th>
<th>mg [RhCODCl]₂ Y</th>
<th>Rh conc. Mol/L</th>
<th>conv. (12 h)</th>
</tr>
</thead>
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<tr>
<td>0.5</td>
<td>0.522</td>
<td>0.014286</td>
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<tr>
<td>2</td>
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<td>0.057143</td>
<td>17.49344</td>
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<td>4</td>
<td>4.176</td>
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</tr>
<tr>
<td>5</td>
<td>5.22</td>
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<td>15.23911</td>
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<tr>
<td>6</td>
<td>6.264</td>
<td>0.171429</td>
<td>14.36776</td>
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</table>
**General Procedure 11: Order in Rh\textsubscript{4}(CO)\textsubscript{12} catalyst in the WGSR-driven reduction of chalcone in acetonitrile (Figure 6.5)**

The Rh\textsubscript{4}(CO)\textsubscript{12} catalyst (X mol % or Y mg) was added to a 4-mL glass vial, followed by 83 mg chalcone 1aa’, and 0.4 mL acetonitrile. To each vial, 0.180 mL (25 equiv) water and 0.108 mL DMEA (2.5 equiv) were added followed by 20 ul mesitylene as internal standard. A stir bar was added, and the vial was placed in an autoclave. The autoclave was pressurized with CO and vented three times, and then pressurized to 7 bar. The mixture was stirred at room temperature for 3 h. After venting and purging the autoclave with nitrogen, the vial was removed. An aliquot was taken and diluted in EtOAc before being passed through a short silica column and injected into a GC-MS for product identification/quantification.

**Table 8.17. Conversion at different catalyst loading.**

<table>
<thead>
<tr>
<th>mol % Rh X</th>
<th>mg Rh\textsubscript{4}(CO)\textsubscript{12} Y</th>
<th>Rh conc. Mol/L</th>
<th>conv. (3 h)</th>
</tr>
</thead>
<tbody>
<tr>
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<tr>
<td>1.25</td>
<td>0.93375</td>
<td>0.0125</td>
<td>10.99717</td>
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<tr>
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<td>14.20855</td>
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<tr>
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<td>0.0175</td>
<td>16.10514</td>
</tr>
<tr>
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<td>17.27197</td>
</tr>
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<td>0.0225</td>
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<tr>
<td>2.5</td>
<td>1.8675</td>
<td>0.025</td>
<td>19.18462</td>
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**General Procedure 12: Order in Rh\textsubscript{4}(CO)\textsubscript{12} catalyst in the WGSR-driven reduction of chalcone in acetonitrile with 0.3 equiv DMEA (Figure 6.6)**

The Rh\textsubscript{4}(CO)\textsubscript{12} catalyst (X mol % or Y mg) was added to a 4-mL glass vial, followed by 83 mg chalcone 1aa’, and 0.4 mL acetonitrile. To each vial, 0.180 mL (25 equiv) water and 0.013 mL DMEA (0.3 equiv) were added followed by 20 ul mesitylene as internal standard. A stir bar was added, and the vial was placed in an autoclave. The autoclave was pressurized with CO and vented three times, and then pressurized to 7 bar. The mixture was stirred at room temperature for 17 h. After venting and purging the autoclave with nitrogen, the vial was removed. An aliquot was taken and diluted in EtOAc before being passed through a short silica column and injected into a GC-MS for product identification/quantification.
Table 8.18. Conversion at different catalyst loading.

<table>
<thead>
<tr>
<th>mol % Rh X</th>
<th>mg Rh(<em>2)(CO)(</em>{12}) Y</th>
<th>Rh conc. Mol/L</th>
<th>conv. (17 h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.25</td>
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<td>1.494</td>
<td>0.02</td>
<td>28.85345</td>
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<td>2.5</td>
<td>1.8675</td>
<td>0.025</td>
<td>33.23742</td>
</tr>
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</table>

General Procedure 13: Order in chalcone in the WGSR-driven reduction of chalcone in acetonitrile (Figure 6.7)

The RhCl\(_3\) 0.008 mmol or 2.12 mg was added to a 4-mL glass vial, followed by X amount of chalcone 1aa' as shown in the table below and 0.8 mL acetonitrile. To each vial, 0.09 mL (5 mmol) water and 0.108 mL DMEA (1 mmol) were added followed by 20 ul mesitylene as internal standard. A stir bar was added, and the vial was placed in an autoclave. The autoclave was pressurized with CO and vented three times, and then pressurized to 3.5 bar. The mixture was stirred at room temperature for 6 h. After venting and purging the autoclave with nitrogen, the vial was removed. An aliquot was taken and diluted in EtOAc before being passed through a short silica column and injected into a GC-MS for product identification/quantification.

Table 8.19. Conversion at different chalcone loading.

<table>
<thead>
<tr>
<th>3.5 bar CO</th>
<th>mmole 1aa'</th>
<th>mg 1aa' X</th>
<th>1aa' conc. Mol/L</th>
<th>conv. (6 h)</th>
</tr>
</thead>
<tbody>
<tr>
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</tr>
<tr>
<td>0.30625</td>
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</tr>
<tr>
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<td>0.213462</td>
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<tr>
<td>0.1</td>
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</table>

The RhCl\(_3\) 0.008 mmol or 2.12 mg was added to a 4-mL glass vial, followed by X amount of chalcone 1aa' as shown in the table below and 0.8 mL acetonitrile. To each vial, 0.09 mL (5 mmol) water and 0.108 mL DMEA (1 mmol) were added followed by 20 ul mesitylene as internal standard. A stir bar was added, and the vial was placed in an autoclave. The autoclave
was pressurized with CO and vented three times, and then pressurized to 7 bar. The mixture was stirred at room temperature for 4 h. After venting and purging the autoclave with nitrogen, the vial was removed. An aliquot was taken and diluted in EtOAc before being passed through a short silica column and injected into a GC-MS for product identification/quantification.

**Table 8.20.** Conversion at different chalcone loading.

<table>
<thead>
<tr>
<th>mmmole Iaa'</th>
<th>mg Iaa' X</th>
<th>Iaa' conc. Mol/L</th>
<th>conv. (4 h)</th>
</tr>
</thead>
<tbody>
<tr>
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<td>0.480769</td>
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The RhCl₃ 0.008 mmol or 2.12 mg was added to a 4-mL glass vial, followed by X amount of chalcone Iaa' as shown in the table below and 0.8 mL acetonitrile. To each vial, 0.09 mL (5 mmol) water and 0.108 mL DMEA (1 mmol) were added followed by 20 ul mesitylene as internal standard. A stir bar was added, and the vial was placed in an autoclave. The autoclave was pressurized with CO and vented three times, and then pressurized to 14 bar. The mixture was stirred at room temperature for 63 h. After venting and purging the autoclave with nitrogen, the vial was removed. An aliquot was taken and diluted in EtOAc before being passed through a short silica column and injected into a GC-MS for product identification/quantification.

**Table 8.21.** Conversion at different chalcone loading.

<table>
<thead>
<tr>
<th>mmmole Iaa'</th>
<th>mg Iaa' X</th>
<th>Iaa' conc. Mol/L</th>
<th>conv. (3 h)</th>
</tr>
</thead>
<tbody>
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<td>0.384615</td>
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<td>0.480769</td>
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</tr>
<tr>
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</tbody>
</table>
General Procedure 14: Order in acetophenone in the WGSR-driven reduction of acetophenone in methanol (Figure 6.8)

0.01 mmol or 2.7 mg of the \([\text{RhCODCl}_2]\) catalyst was added to a 4-mL glass vial, followed by X amount of acetophenone \(1X\) as shown in the table below and 0.2 mL methanol. To each vial, 0.090 mL (5 mmol) water and 0.054 mL DMEA (0.5 mmol) were added followed by 20 ul mesitylene as internal standard. A stir bar was added, and the vial was placed in an autoclave. The autoclave was pressurized with CO and vented three times, and then pressurized to 28 bar. The mixture was stirred at room temperature for 12 h. After venting and purging the autoclave with nitrogen, the vial was removed. An aliquot was taken and diluted in EtOAc before being passed through a short silica column and injected into a GC-MS for product identification/quantification.

<table>
<thead>
<tr>
<th>mmole (1X)</th>
<th>mg (1X)</th>
<th>(1X) conc. Mol/L</th>
<th>conv. (12 h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.05</td>
<td>6</td>
<td>0.142857</td>
<td>80.28939</td>
</tr>
<tr>
<td>0.1</td>
<td>12</td>
<td>0.285714</td>
<td>69.43145</td>
</tr>
<tr>
<td>0.2</td>
<td>24</td>
<td>0.571429</td>
<td>49.88427</td>
</tr>
<tr>
<td>0.4</td>
<td>48</td>
<td>1.142857</td>
<td>30.26747</td>
</tr>
<tr>
<td>0.6</td>
<td>72</td>
<td>1.714286</td>
<td>24.06557</td>
</tr>
<tr>
<td>0.8</td>
<td>96</td>
<td>2.285714</td>
<td>21.60481</td>
</tr>
</tbody>
</table>

Table 8.22. Conversion at different acetophenone loading.

General Procedure 15: Effect of acetophenone on the WGSR-driven reduction of chalcone in acetonitrile (Figure 6.9)

The \(\text{RhCl}_3\) catalyst (2 mol % or 2.12 mg) was added to a 4-mL glass vial, followed by 83 mg chalcone \(1\alpha'\), and 0.4 mL acetonitrile. To each vial, 0.180 mL (25 equiv) water and 0.108 mL DMEA (2.5 equiv) were added followed by 20 ul mesitylene as internal standard. X amount of acetophenone was added to the vials as shown in the table below. A stir bar was added, and the vial was placed in an autoclave. The autoclave was pressurized with CO and vented three times, and then pressurized to 7 bar. The mixture was stirred at room temperature for 3 h. After venting and purging the autoclave with nitrogen, the vial was removed. An aliquot was taken and diluted in EtOAc before being passed through a short silica column and injected into a GC-MS for product identification/quantification.
Table 8.23. Conversion at different acetophenone loading.

<table>
<thead>
<tr>
<th>mmole IX</th>
<th>mg IX X</th>
<th>IX conc. Mol/L</th>
<th>conv. (3 h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>0</td>
<td>26.3243</td>
</tr>
<tr>
<td>0.04</td>
<td>4.8</td>
<td>0.1</td>
<td>24.1551</td>
</tr>
<tr>
<td>0.08</td>
<td>9.6</td>
<td>0.2</td>
<td>28.01551</td>
</tr>
<tr>
<td>0.12</td>
<td>14.4</td>
<td>0.3</td>
<td>21.56149</td>
</tr>
<tr>
<td>0.16</td>
<td>19.2</td>
<td>0.4</td>
<td>23.22008</td>
</tr>
<tr>
<td>0.2</td>
<td>24</td>
<td>0.5</td>
<td>23.64961</td>
</tr>
<tr>
<td>0.24</td>
<td>28.8</td>
<td>0.6</td>
<td>25.50131</td>
</tr>
</tbody>
</table>

General Procedure 16: Effect of CO pressure on the WGSR-driven reduction of chalcone in acetonitrile (Figure 6.10)

The RhCl₃ catalyst (2 mol % or 2.12 mg) was added to a 4-mL glass vial, followed by 83 mg chalcone 1aa’, and 0.4 mL acetonitrile. To each vial, 0.180 mL (25 equiv) water and 0.108 mL DMEA (2.5 equiv) were added followed by 20 ul mesitylene as internal standard. X amount of acetophenone was added to the vials as shown in the table below. A stir bar was added, and the vial was placed in a multi-well autoclave. The autoclave was pressurized with CO and vented three times, and then each well was pressurized to the pressure below. The mixture was stirred at room temperature for 6 h. After venting and purging the autoclave with nitrogen, the vial was removed. An aliquot was taken and diluted in EtOAc before being passed through a short silica column and injected into a GC-MS for product identification/quantification.

Table 8.24. Conversion at different CO pressure.

<table>
<thead>
<tr>
<th>CO P bar</th>
<th>Conv.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.360544</td>
<td>1.540946937</td>
</tr>
<tr>
<td>2.721088</td>
<td>20.89296636</td>
</tr>
<tr>
<td>4.081633</td>
<td>23.67452135</td>
</tr>
<tr>
<td>5.442177</td>
<td>26.29606496</td>
</tr>
<tr>
<td>7.482993</td>
<td>26.70799752</td>
</tr>
<tr>
<td>8.843537</td>
<td>28.91259547</td>
</tr>
</tbody>
</table>

The Rh₄(CO)₁₂ catalyst (2 mol % or 1.5 mg) was added to a 4-mL glass vial, followed by 83 mg chalcone 1aa’, and 0.4 mL acetonitrile. To each vial, 0.180 mL (25 equiv) water and 0.108 mL DMEA (2.5 equiv) were added followed by 20 ul mesitylene as internal standard. X amount
of acetophenone was added to the vials as shown in the table below. A stir bar was added, and the vial was placed in a multi-well autoclave. The autoclave was pressurized with CO and vented three times, and then each well was pressurized to the pressure below. The mixture was stirred at room temperature for 6 h. After venting and purging the autoclave with nitrogen, the vial was removed. An aliquot was taken and diluted in EtOAc before being passed through a short silica column and injected into a GC-MS for product identification/quantification.

**Table 8.25.** Conversion at different CO pressure.

<table>
<thead>
<tr>
<th>CO P bar</th>
<th>Conv.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.360544</td>
<td>8.43149411</td>
</tr>
<tr>
<td>2.721088</td>
<td>15.50358355</td>
</tr>
<tr>
<td>4.081633</td>
<td>18.77756774</td>
</tr>
<tr>
<td>5.442177</td>
<td>19.38288233</td>
</tr>
<tr>
<td>7.482993</td>
<td>21.80311651</td>
</tr>
<tr>
<td>8.843537</td>
<td>8.43149411</td>
</tr>
</tbody>
</table>

**General Procedure 17: Effect of CO pressure on the WGSR-driven reduction of acetophenone in methanol (Figure 6.11)**

The [RhCODCl]₂ catalyst (2.5 mol % or 5.3 mg) was added to a 4-mL glass vial, followed by 48 mg acetophenone 1X, and 0.4 mL methanol. To each vial, 0.180 mL (25 equiv) water and 0.108 mL DMEA (2.5 equiv) were added followed by 20 ul mesitylene as internal standard. A stir bar was added, and the vial was placed in a multi-well autoclave. The autoclave was pressurized with CO and vented three times, and then each well was pressurized to the pressure below. The mixture was stirred at room temperature for 12 h. An aliquot was taken and diluted in EtOAc before being passed through a short silica column and injected into a GC-MS for product identification/quantification.

**Table 8.26.** Conversion at different CO pressure.

<table>
<thead>
<tr>
<th>CO P bar</th>
<th>Conv.</th>
</tr>
</thead>
<tbody>
<tr>
<td>20.40816</td>
<td>62.88668</td>
</tr>
<tr>
<td>13.60544</td>
<td>58.39659</td>
</tr>
<tr>
<td>10.20408</td>
<td>49.17072</td>
</tr>
<tr>
<td>6.802721</td>
<td>40.19194</td>
</tr>
<tr>
<td>3.401361</td>
<td>33.66951</td>
</tr>
<tr>
<td>20.40816</td>
<td>62.88668</td>
</tr>
</tbody>
</table>
General Procedure 18: Order in DMEA base in the WGSR-driven reduction of chalcone in acetonitrile (Figure 6.12)

The RhCl₃ catalyst (2 mol % or 2.1 mg) was added to a 4-mL glass vial, followed by 83 mg chalcone 1aa', and 0.4 mL acetonitrile. To each vial, 0.180 mL (25 equiv) water and the amounts shown below of DMEA were added followed by 20 ul mesitylene as internal standard. A stir bar was added, and the vial was placed in a multi-well autoclave. The autoclave was pressurized with CO and vented three times, and then each well was pressurized to 7 bar. The mixture was stirred at room temperature for the specified time below. After venting and purging the autoclave with nitrogen, the vial was removed. An aliquot was taken and diluted in EtOAc before being passed through a short silica column and injected into a GC-MS for product identification/quantification.

Table 8.27. Conversion at different DMEA loading.

<table>
<thead>
<tr>
<th>DMEA mmol</th>
<th>DMEA mL</th>
<th>DMEA conc mol/L</th>
<th>Time h</th>
<th>conv.</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.04</td>
<td>0.004171</td>
<td>0.098928</td>
<td>21</td>
<td>5.583756</td>
</tr>
<tr>
<td>0.2</td>
<td>0.020857</td>
<td>0.474303</td>
<td>6</td>
<td>12.52085</td>
</tr>
<tr>
<td>0.4</td>
<td>0.041714</td>
<td>0.902238</td>
<td>6</td>
<td>23.86749</td>
</tr>
<tr>
<td>0.6</td>
<td>0.062571</td>
<td>1.290286</td>
<td>6</td>
<td>32.74665</td>
</tr>
<tr>
<td>0.8</td>
<td>0.083429</td>
<td>1.643776</td>
<td>6</td>
<td>37.83657</td>
</tr>
<tr>
<td>2</td>
<td>0.216296</td>
<td>3.24301</td>
<td>6</td>
<td>43.40519</td>
</tr>
</tbody>
</table>

General Procedure 19: Effect of CO₂ on the WGSR-driven reduction of chalcone in acetonitrile (Figure 6.13)

The RhCl₃ catalyst (4 mol % or 4.2 mg) was added to a 4-mL glass vial, followed by 83 mg chalcone 1aa', and 0.8 mL acetonitrile. To each vial, 0.180 mL (25 equiv) water and (2.5 and 5 equiv, or 0.108 mL and 0.216 mL) of DMEA were added followed by 20 ul mesitylene as internal standard. A stir bar was added, and the vial was placed in a multi-well autoclave. The autoclave was pressurized with CO and vented three times, and then each well was pressurized to 7 bar CO then further pressurized with CO₂ as shown below. The mixture was stirred at room temperature for 6 h. After venting and purging the autoclave with nitrogen, the vial was removed. An aliquot was taken and diluted in EtOAc before being passed through a short silica column and injected into a GC-MS for product identification/quantification.
**Table 8.28.** Conversion at different DMEA loading.

<table>
<thead>
<tr>
<th>DMEA mmol</th>
<th>DMEA mL</th>
<th>DMEA conc mol/L</th>
<th>conv.</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.6</td>
<td>0.062571</td>
<td>1.69067</td>
<td>49.16136</td>
</tr>
<tr>
<td>0.5</td>
<td>0.052143</td>
<td>1.453175</td>
<td>52.50917</td>
</tr>
<tr>
<td>0.4</td>
<td>0.041714</td>
<td>1.200267</td>
<td>49.71433</td>
</tr>
<tr>
<td>0.3</td>
<td>0.031286</td>
<td>0.930393</td>
<td>47.63121</td>
</tr>
<tr>
<td>0.2</td>
<td>0.020857</td>
<td>0.641787</td>
<td>42.23024</td>
</tr>
<tr>
<td>0.1</td>
<td>0.010429</td>
<td>0.33243</td>
<td>22.28798</td>
</tr>
</tbody>
</table>

General Procedure 20: Order in DMEA base in the WGSR-driven reduction of acetophenone in methanol (Figure 6.14)

The $[\text{RhCODCl}]_2$ catalyst (2.5 mol % or 2.6 mg) was added to a 4-mL glass vial, followed by 24 mg acetophenone $1\text{X}$, and 0.2 mL methanol. To each vial, 0.090 mL (25 equiv) water and different amounts of TMEDA were added as shown below followed by 20 ul mesitylene as internal standard. A stir bar was added, and the vial was placed in a multi-well autoclave. The autoclave was pressurized with CO and vented three times, and then each well was pressurized to 28. The mixture was stirred at room temperature for 12 h. After venting and purging the autoclave with nitrogen, the vial was removed. An aliquot was taken and diluted in EtOAc before being passed through a short silica column and injected into a GC-MS for product identification/quantification.
**General Procedure 21: Order in water in the WGSR-driven reduction of chalcone in acetonitrile (Figure 6.15)**

The RhCl₃ catalyst (4 mol % or 4.2 mg) was added to a 4-mL glass vial, followed by 41.5 mg chalcone 1aa', and 0.8 mL acetonitrile. To each vial, 5 equiv, or 0.108 mL DMEA were added followed by 20 µL mesitylene as internal standard. Water was added in the amounts shown below. A stir bar was added, and the vial was placed in a multi-well autoclave. The autoclave was pressurized with CO and vented three times, and then each well was pressurized to 7 bar CO. The mixture was stirred at room temperature for 3 h. After venting and purging the autoclave with nitrogen, the vial was removed. An aliquot was taken and diluted in EtOAc before being passed through a short silica column and injected into a GC-MS for product identification/quantification.

**Table 8.30. Conversion at different water loading.**

<table>
<thead>
<tr>
<th>water mmol</th>
<th>water mL</th>
<th>water conc mol/L</th>
<th>conv.</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>0.18</td>
<td>17.24138</td>
<td>11.46135</td>
</tr>
<tr>
<td>7.2</td>
<td>0.1296</td>
<td>13.59517</td>
<td>12.08181</td>
</tr>
<tr>
<td>5.2</td>
<td>0.0936</td>
<td>10.53485</td>
<td>12.76114</td>
</tr>
<tr>
<td>3.2</td>
<td>0.0576</td>
<td>6.993007</td>
<td>14.78846</td>
</tr>
<tr>
<td>2.4</td>
<td>0.0432</td>
<td>5.415162</td>
<td>17.08176</td>
</tr>
<tr>
<td>1.6</td>
<td>0.0288</td>
<td>3.731343</td>
<td>19.9923</td>
</tr>
<tr>
<td>1.2</td>
<td>0.0216</td>
<td>2.8463</td>
<td>19.61753</td>
</tr>
</tbody>
</table>

**General Procedure 22: KIE by D₂O in the WGSR-driven reduction of chalcone in acetonitrile and acetophenone in methanol (Table 6.5)**

The RhCl₃ catalyst (2 mol % or 2.1 mg) was added to a 4-mL glass vial, followed by 83 mg chalcone 1aa', and 0.4 mL acetonitrile. To each vial, 2.5 equiv or 0.108 mL DMEA, and 25 equiv or 0.180 mL water (or D₂O) were added followed by 20 µL mesitylene as internal standard. A stir bar was added, and the vial was placed in a multi-well autoclave. The autoclave was pressurized with CO and vented three times, and then each well was pressurized to 7 bar CO. The mixture was stirred at room temperature for 3 h. After venting and purging the autoclave with nitrogen, the vial was removed. An aliquot was taken and diluted in EtOAc before being
passed through a short silica column and injected into a GC-MS for product identification/quantification.

The [RhCODCl]₂ catalyst (2.5 mol % or 5.3 mg) was added to a 4-mL glass vial, followed by 48 mg acetonophenone 1X, and 0.4 mL methanol (or methanol-d₄). To each vial, 0.180 mL (25 equiv) water (or D₂O) and 2.5 equiv DMEA or 0.108 mL followed by 20 ul mesitylene as internal standard. A stir bar was added, and the vial was placed in a multi-well autoclave. The autoclave was pressurized with CO and vented three times, and then each well was pressurized to 28 bar. The mixture was stirred at room temperature for 12 h. After venting and purging the autoclave with nitrogen, the vial was removed. An aliquot was taken and diluted in EtOAc before being passed through a short silica column and injected into a GC-MS for product identification/quantification.

**General Procedure 23: Water consumption by hydrogen evolution through the WGSR in acetonitrile (Table 6.6)**

The RhCl₃ catalyst (0.1 mol % or 2.66 mg) was added to a 4-mL glass vial, followed by 0.4 mL acetonitrile, 0.1 equiv or 0.043 mL DMEA, 10 mmol or 0.180 mL water (or D₂O), and 20 ul mesitylene as internal standard. A stir bar was added, and the vial was placed in a multi-well autoclave. The autoclave was pressurized with CO and vented three times, and then each well was pressurized to 10 bar CO. The mixture was stirred at room temperature for 24 h. After venting and purging the autoclave with nitrogen, the vial was removed. An aliquot was taken and injected into Karl-Fisher moisture detector.

**General Procedure 23: Asymmetric WGSR-driven reduction of acetonophenone in methanol (Table 6.7)**

The [RhCODCl]₂ catalyst (2.5 mol % or 2.6 mg) was added to a 4-mL glass vial, followed by 24 mg acetonophenone 1X, and 0.2 to 0.8 mL methanol/1,4-dioxane solvent 1:1 v. To each vial, 0.090 mL (25 equiv) water and 0.108 mL (2.5 equiv) TMEDA were added as shown below followed by 20 ul mesitylene as internal standard. The chiral ligands were added as 1 equiv w.r.t. 1X. A stir bar was added, and the vial was placed in a multi-well autoclave. The autoclave was pressurized with CO and vented three times, and then each well was pressurized to 28. The mixture was stirred at room temperature for 12 h. After venting and purging the autoclave with nitrogen, the vial was removed. An aliquot was taken and diluted in EtOAc before being passed through a short silica column and injected into a Cyclosil-B chiral GC for product quantification.
Table 8.31. added amounts of different ligands.

<table>
<thead>
<tr>
<th>Ligand</th>
<th>amount (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1R,2R)-N1,N2-dimethyl-1,2-diphenylethane-1,2-diamine</td>
<td>96</td>
</tr>
<tr>
<td>N2,N2'-dimethyl-[1,1'-binaphthalene]-2,2'-diamine</td>
<td>124.8</td>
</tr>
<tr>
<td>4-isopropyl-4,5-dihydro-3H-dinaphtha[2,1-c:1',2'-e]azepine</td>
<td>134.8</td>
</tr>
<tr>
<td>(2R)-2,2'-bipiperidine</td>
<td>67.2</td>
</tr>
<tr>
<td>(R)-bis((R)-1-phenylethyl)amine</td>
<td>90</td>
</tr>
<tr>
<td>cinchonidine</td>
<td>118</td>
</tr>
<tr>
<td>(2S,4R)-2,4-diphenyloxazolidine</td>
<td>90</td>
</tr>
<tr>
<td>(R)-(1-methylpyrrolidin-2-yl)methanol</td>
<td>46</td>
</tr>
</tbody>
</table>

8.7. Experimental section for chapter 7

General Procedure I: Reductive amination of benzaldehyde with piperidine (Table 7.1)

The RhCl₃ catalyst (1 mol %, 1.3 mg, or 2 mol %, 2.7 mg) was added to a 4-mL glass vial for each entry in the table, followed by 0.5 mL acetonitrile, 53 mg or 0.5 mmole benzaldehyde 1a, and 44.6 mg or 1.05 equivalent piperidine 1b. Deionized water was added in variable amounts as following (15 equiv or 0.135 mL, 35 equiv or 0.315 mL, 10 equiv or 0.090 mL, 5 equiv or 0.045 mL). Triethylamine was added in variable amounts as following (1 equiv or 0.070 mL, 2.5 equiv or 0.174 mL). 20 ul Mesitylene was added as internal standard and a stir bar was added. The vial was placed in an autoclave. The autoclave was pressurized with CO and vented three times, and then pressurized to 10 bar. The mixture was stirred at room temperature for the indicated time. After venting and purging the autoclave with nitrogen, the vial was removed. An aliquot was taken and diluted in EtOAc before being passed through a short silica column and injected into a GC-MS for product identification.

General Procedure 2: Reductive amination of carbonyl compounds with piperidine (Table 7.2)

The RhCl₃ catalyst (2 mol %, 2.7 mg) was added to a 4-mL glass vial for each entry in the table, followed by 0.5 mL acetonitrile, and 0.5 mmole of the carbonyl compound a as following (3-methylbutanal, 43 mg, 3-methylbutenal, 42 mg, acetone, 29 mg, cyclohexanone, 49 mg, acetoephone, 60 mg). Piperidine 1b was added to each vial as 44.6 mg or 1.05 equivalent. Deionized water was added at 20 equiv or 0.18 mL. Triethylamine was added 2.5 equiv or 0.174 mL. 20 ul Mesitylene was added as internal standard and a stir bar was added. The vial was placed in an autoclave. The autoclave was pressurized with CO and vented three times, and then
pressurized to 10 bar. The mixture was stirred at room temperature for 10 h. After venting and purging the autoclave with nitrogen, the vial was removed. An aliquot was taken and diluted in EtOAc before being passed through a short silica column and injected into a GC-MS for product identification.

**General Procedure 3: Reductive amination of benzaldehyde with different amines (Table 7.3)**

The RhCl₃ catalyst (2 mol %, 2.7 mg) was added to a 4-mL glass vial for each entry in the table, followed by 0.5 mL acetonitrile, 53 mg or 0.5 mmole benzaldehyde 1a was added. Amines b were added at 1.05 equiv as following (2-methylpiperidine, 52 mg, 2,2,6,6-tetramethylpiperidine, 74 mg, pyrrolidine, 37 mg, piperazine, 45 mg, N-methylaniline, 56 mg, l-proline, 60 mg, diisopropylamine, 53 mg, morpholine, 46 mg). Deionized water was added at 20 equiv or 0.18 mL. Triethylamine was added 2.5 equiv or 0.174 mL. 20 ul Mesitylene was added as internal standard and a stir bar was added. The vial was placed in an autoclave. The autoclave was pressurized with CO and vented three times, and then pressurized to 10 bar. The mixture was stirred at room temperature for 18 h. After venting and purging the autoclave with nitrogen, the vial was removed. An aliquot was taken and diluted in EtOAc before being passed through a short silica column and injected into a GC-MS for product identification.

**General Procedure 4: Reductive amination of 2-furfurals with piperidine (Scheme 7.3)**

The RhCl₃ catalyst (1 mol %, 5.3 mg) was added to a 20-mL glass vial, followed by 2 mL acetonitrile, Piperidine 1b was added at 2 mmol or 170 mg followed by 201 mg or 1.05 equiv furfural 2a in one vial and 231 mg of 5-methylfurfural 3a in another. Deionized water was added at 20 equiv or 0.72 mL. Triethylamine was added 2.5 equiv or 0.695 mL. 80 ul Mesitylene was added as internal standard and a stir bar was added. The vial was placed in an autoclave. The autoclave was pressurized with CO and vented three times, and then pressurized to 15 bar. The mixture was stirred at room temperature for 18 h. After venting and purging the autoclave with nitrogen, the vial was removed. The reaction was extracted with diethyl ether and washed with brine three times. An aliquot was taken and injected into a GC-MS for product identification. The extracted organic phase was purified by column chromatography using silica as a stationary phase and pentane/diethyl ether 3/1 v as an eluent for the reaction with 2a.

**General Procedure 5: Effect of water loading on the reductive amination of 2-furfural with piperidine (Figure 7.1)**

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The RhCl₃ catalyst (1 mol %, 1.06 mg) was added to a 4-mL glass vial for each entry in the figure, followed by 0.4 mL acetonitrile, Piperidine 1b was added at 0.4 mmol or 34 mg followed by 40.3 mg or 1.05 equiv furfural 2a. Deionized water was added at variable loadings as following (1.5 equiv or 0.011 mL, 4 equiv or 0.029 mL, 10 equiv or 0.072 mL, 20 equiv or 0.144 mL, 40 equiv or 0.288 mL, 60 equiv or 0.432 mL). Triethylamine was added 2.5 equiv or 0.139 mL. 20 ul Mesitylene was added as internal standard and a stir bar was added. The vial was placed in an autoclave. The autoclave was pressurized with CO and vented three times, and then pressurized to 15 bar. The mixture was stirred at room temperature for 18 h. After venting and purging the autoclave with nitrogen, the vial was removed. An aliquot was taken and diluted in EtOAc before being passed through a short silica column and injected into a GC-MS for product quantification.

General Procedure 6: Effect of triethylamine loading on the reductive amination of 2-furfural with piperidine (Figure 7.2)

The RhCl₃ catalyst (1 mol %, 1.06 mg) was added to a 4-mL glass vial for each entry in the figure, followed by 0.4 mL acetonitrile, Piperidine 1b was added at 0.4 mmol or 34 mg followed by 40.3 mg or 1.05 equiv furfural 2a. Deionized water was added at 20 equiv or 0.144 mL. Triethylamine was added at variable loadings as following (zero equiv, 0.5 equiv or 0.028 mL, 1 equiv or 0.056 mL, 2 equiv or 0.111 mL, 3 equiv or 0.167 mL, 5 equiv or 0.278 mL, 10 equiv or 0.556 mL). 20 ul Mesitylene was added as internal standard and a stir bar was added. The vial was placed in an autoclave. The autoclave was pressurized with CO and vented three times, and then pressurized to 15 bar. The mixture was stirred at room temperature for 18 h. After venting and purging the autoclave with nitrogen, the vial was removed. An aliquot was taken and diluted in EtOAc before being passed through a short silica column and injected into a GC-MS for product quantification.

General Procedure 7: Effect of CO pressure on the reductive amination of 2-furfural with piperidine (Figure 7.3)

The RhCl₃ catalyst (1 mol %, 1.06 mg) was added to a 4-mL glass vial for each entry in the figure, followed by 0.4 mL acetonitrile, Piperidine 1b was added at 0.4 mmol or 34 mg followed by 36.5 mg or 0.95 equiv furfural 2a. Deionized water was added at 10 equiv or 0.072 mL. Triethylamine was added 3 equiv or 0.167 mL. 20 ul Mesitylene was added as internal standard and a stir bar was added. The vial was placed in a multi-well autoclave. The autoclave was
pressurized with CO and vented three times, and then each well pressurized to the following pressures: 20, 40, 60, 80, 100, 120, 150, and 200 psi. The mixture was stirred at room temperature for 18 h. After venting and purging the autoclave with nitrogen, the vial was removed. An aliquot was taken and diluted in EtOAc before being passed through a short silica column and injected into a GC-MS for product quantification.

General Procedure 8: Aminomethylation of allylbenzene with piperidine in different solvents (Table 7.4)

The RhCl₃ catalyst (3 mol %, 3.2 mg) was added to a 4-mL glass vial for each entry in the table, followed by 0.4 mL solvent as following (DMF, DMSO, 2-ethoxyethanol, acetonitrile). Piperidine 1b was added at 0.44 mmol or 37.4 mg followed by 47.2 mg or 0.4 mmol allylbenzene 1c. Deionized water was added at 4 equiv or 0.029 mL. Triethylamine was added at 2 equiv or 0.111 mL. 20 ul Mesitylene was added as internal standard and a stir bar was added. The vial was placed in an autoclave. The autoclave was pressurized with CO and vented three times, and then pressurized to 20 bar. The mixture was stirred at 85 ºC for 18 h. After venting and purging the autoclave with nitrogen, the vial was removed. An aliquot was taken and diluted in EtOAc before being passed through a short silica column and injected into a GC-MS for product quantification.

General Procedure 9: Effect of ligand on the aminomethylation of allylbenzene with piperidine (Table 7.5)

The RhCl₃ catalyst or 3 mol %, 3.2 mg) was added to a 4-mL glass vial for each entry in the table, followed by 0.4 mL acetonitrile. Piperidine 1b was added at 0.44 mmol or 37.4 mg followed by 47.2 mg or 0.4 mmol allylbenzene 1c. Deionized water was added at 4 equiv or 0.029 mL. Triethylamine was added at 2 equiv or 0.111 mL to vials 1 to 5, none in vial 6. The following additives were added to the vials: vial one: none, vial 2: 3.7 mg bipyridine, vial 3: 6.2 mg triphenylphosphine, vial 4: 6.9 mg Xantphos, vial 5: 11.7 mg EDTA, vial 6: 0.120 mL TMEDA. 20 ul Mesitylene was added as internal standard and a stir bar was added. The vial was placed in an autoclave. The autoclave was pressurized with CO and vented three times, and then pressurized to 20 bar. The mixture was stirred at 75 ºC for 18 h. After venting and purging the autoclave with nitrogen, the vial was removed. An aliquot was taken and diluted in EtOAc before being passed through a short silica column and injected into a GC-MS for product quantification.
General Procedure 10: Aminomethylation of allylbenzene with piperidine using different catalysts (Table 7.6)

In separate 4-mL glass vials, the following amounts of catalysts were added: RhCl₃ (3 mol %, 3.2 mg), Ru₃(CO)₁₂ (6 mol % Ru, 5.1 mg), Ir₄(CO)₁₂ (3 mol % Ir, 3.3 mg), Co₂(CO)₈ (6 mol % Co, 4.1 mg). To each vial, 0.4 mL acetonitrile was added followed by 0.44 mmol or 37.4 mg piperidine 1b and 47.2 mg or 0.4 mmol allylbenzene 1c. Deionized water was added at 5 equiv or 0.036 mL. Triethylamine was added at 2 equiv or 0.111 mL. 20 μL Mesitylene was added as internal standard and a stir bar was added. The vial was placed in an autoclave. The autoclave was pressurized with CO and vented three times, and then pressurized to 20 bar. The mixture was stirred at 80 °C for 36 h. After venting and purging the autoclave with nitrogen, the vial was removed. An aliquot was taken and diluted in EtOAc before being passed through a short silica column and injected into a GC-MS for product quantification.
NC\_COOEt

8ac
NC\text{\textunderscore}COOEt

8am
$\text{NC} \! \text{COOEt}$

8am
NC\_\text{COOEt}

8an

\[
\begin{align*}
\text{peak 1:} & \quad 2.01 \text{ppm} \\
\text{peak 2:} & \quad 2.02 \text{ppm} \\
\text{peak 3:} & \quad 4.26 \text{ppm} \\
\text{peak 4:} & \quad 3.76 \text{ppm} \\
\text{peak 5:} & \quad 3.32 \text{ppm} \\
\text{peak 6:} & \quad 3.35 \text{ppm} \\
\end{align*}
\]
NC\_COOEt

8ar
NC\_\text{COOEt} 8ac'
$\text{NC} - \text{COOEt}$

$8\text{ad}'$
8.8. References

(12) Deuterium incorporation was determined as described in Olsen, M. T.; Barton, B. E.; Rauchfuss, T. B. Inorg. Chem. 2009, 48, 7507-7509.
(13) Previous control experiments had shown that, under similar reaction conditions, 9af is completely reduced to 8af(D), and no deuterium incorporation is observed at C(2) (as determined by 1H NMR analysis).


Appendix A: Water-gas shift-driven deoxygenation of amides, phosphine oxides, and deoxygenative cyclization of 2-nitroimines

A.1. Introduction

Deoxygenation reactions are essential transformations in organic synthesis, pharmaceutical industry, and biomass conversion.\(^1\) Deoxygenation of common oxygenated moieties such as nitro, amides, sulfoxides, and phosphine oxides are often carried out with stoichiometric reductants such as metal hydrides or silanes which require high energy to be manufactured and generate significant amount of waste when used.\(^2\)

Scheme A.1. Silane -driven deoxygenation reactions

The reductive power of carbon monoxide has been successfully employed to affect few examples of the deoxygenation reactions including nitro deoxygenation to anilines, aryl nitro deoxygenative cyclization, hydroxylamines deoxygenation to amines, and sulfoxide deoxygenation to sulfides.\(^3\) One the other hand, the deoxygenation of amides to amines and phosphine oxides to phosphines have not been realized by the WGSR.
WGSR is a more attractive alternative to drive the common deoxygenation reactions. The availability of carbon monoxide and the ease of separation and disposal of carbon dioxide by-product enhance the process atom economy and environmental impact. Phosphine oxides, for example, are generated as byproducts from a number of organic transformations such as the Wittig, Mitsunobo, and Appel reactions. O’Brien et al. proposed the use of silanes to deoxygenate 3-methyl-1-phenylphospholane-1-oxide under Wittig reaction at 100 °C.\textsuperscript{4}

![Proposed catalytic cycle for the WGSR-driven Wittig olefination with catalytic phosphine oxide.](image)

**Figure A.1.** Proposed catalytic cycle for the WGSR-driven Wittig olefination with catalytic phosphine oxide.

Performing the Wittig olefination under WGSR conditions would allow for the use of catalytic amount of phosphine oxide that can be generated under the reaction conditions, Figure 1. Numerous challenges are involved in this approach; for example, the Rh-catalyzed WGSR illustrated in Chapter 2, and 7 was found to be inhibited by the addition of phosphine ligands. Moreover, the aldehyde can be easily hydrogenated under the WGSR before it undergoes the Wittig reaction.

Besides serving as a more economic and environmentally benign alternative for amide deoxygenation, the use of the WGSR to affect this reaction would allow for the production of doubly deuterated alpha amines in one step If water is replaced with D\textsubscript{2}O. Alpha deuterated amines are useful for mechanistic and metabolism studies, Chapter 7.
A.2. Results

In this Appendix we study the effect of water addition on the CO-driven, deoxygenative cyclization of 2-nitroimine compounds and investigate the ability to deoxygenate amides and phosphine oxides under WGSR. The following items will be studied:

1- The effect of CO pressure on the deoxygenation of amides and nitro compounds
2- The effect of water addition on the 2-nitroimine cyclization product identity
3- The reactivity of different catalysts in the deoxygenation of phosphine oxides

The deoxygenation of N-(p-tolyl)acetamide was attempted under CO pressure with [RhCODCl]_2 catalyst and tetramethylethylenediamine (TMEDA) base at 85 °C for 24 h, Table A.1. No deoxygenation was observed in polar solvents i.e. acetonitrile, DMF, and DMSO. Less than 10% deoxygenation was observed in the less polar solvents i.e. mesitylene, and 1, 4-dioxane. High solvent evaporation occurred with mesitylene due to the large autoclave volume with respect to the reaction volume. The reaction was repeated in 1.4-dioxane/mesitylene mixture at 1:1 volumetric ratio. Interestingly, the deoxygenation was found to be inhibited at increasing CO pressure, Figure A.2.

Table A.1. Deoxygenation of N-(p-tolyl)acetamide under WGSR Conditions in Different Solvents

<table>
<thead>
<tr>
<th>entry</th>
<th>solvent</th>
<th>1A</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>MeCN</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>Mesitylene*</td>
<td>7%</td>
</tr>
<tr>
<td>3</td>
<td>DMF</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>DMSO</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>dioxane</td>
<td>5%</td>
</tr>
</tbody>
</table>

*solvent evaporated
The (dry) deoxygenation of (E)-1-(2-nitrophenyl)-N-phenylmethanimine with gold nanoparticles under CO was attempted in dry solvents and no water was added. No deoxygenation was observed in all the tested solvents after 24 h reaction at 75 °C, Table A.2. High CO pressure was found to inhibit the deoxygenation of amides likely due to the inhibited binding of amide to Rh at high CO pressure (Scheme 6, Chapter 5). The effect of CO pressure on the deoxygenation of nitrobenzene was also studied. Contrarily, high CO pressure was found to enhance the reductive deoxygenation of nitrobenzene to aniline in presence of water, Figure A.3. In the low-pressure experiments, nitrosobenzene was identified as the main intermediate.
Table A.2. Dry Deoxygenation of (E)-1-(2-nitrophenyl)-N-phenylmethanimine with CO

![Scheme](image)

<table>
<thead>
<tr>
<th>entry</th>
<th>solvent</th>
<th>1N</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>MeCN</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>DMF</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>Dioxane</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>Mesitylene</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>Ethoxyethanol</td>
<td>0</td>
</tr>
</tbody>
</table>

Figure A.3. Deoxygenation of nitrobenzene under different CO pressures

The deoxygenation of (E)-1-(2-nitrophenyl)-N-phenylmethanimine was attempted under WGSR conditions using supported gold nanoparticles catalyst. Unlike the dry deoxygenation described in Table 2, high rate of deoxygenation was observed at temperature as low as 60 °C when water was added, Table 3. However, the major cyclized product formed is benzo[c]isoxazole 5S not 2-phenyl-2H-indazole. When gold nanoparticle catalyst was replaced with RhCl₃ and dimethylethylamine (2 equiv), the only observed product was 7S indicating that cyclization does not occur with homogeneous Rh catalyst under wet deoxygenation conditions.
Table A.3. Deoxygenation of (E)-1-(2-nitrophenyl)-N-phenylmethanimine under WGSR Conditions

![Chemical structure](image)

<table>
<thead>
<tr>
<th>entry</th>
<th>Water (equiv)</th>
<th>Consumption of 3S</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>15</td>
<td>95</td>
</tr>
<tr>
<td>2</td>
<td>5</td>
<td>65</td>
</tr>
<tr>
<td>3</td>
<td>1</td>
<td>55</td>
</tr>
</tbody>
</table>

The identified WGSR conditions to reduce acetophenone in Chapter 6 were applied for the deoxygenation of triphenylphosphine oxide. No deoxygenation was observed in all the tested solvents, Table 4. The deoxygenation of triphenylphosphine oxide was attempted under high CO pressure (40 bar) and water loading (20 equivalents). RhCl₃ catalyst was used as a catalyst and a mixture of benzonitrile and tetramethylpropylenediamine TMPDA was used as a solvent. No deoxygenation was observed after 18 h at 100 °C, Table 5.

Table A.4. Deoxygenation of Triphenylphosphine Oxide with CO in Different Solvents

![Chemical structure](image)

<table>
<thead>
<tr>
<th>entry</th>
<th>solvent</th>
<th>product</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2-ethoxyethanol</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>TMEDA</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>piperidine</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>MeCN/TMEDA</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>MeCN/piperidine</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>MeOH/dioxane</td>
<td>0</td>
</tr>
</tbody>
</table>

Addition of Lewis acids including the chlorides of Cu, Sc, and Ce to activate the phosphine oxides did not accelerate the deoxygenation. Addition of tosic acid did not catalyst the
deoxygenation either. Supported metallic nanoparticles were tested as catalyst for the deoxygenation of triphenylphosphine oxide. Supported nanoparticles of Ru, Pd, Cu, Ni, Rh, and Ir on aluminum oxide support did not catalyze the reaction, Table 6. Trace amount of triphenylphosphine were formed when RuO$_2$ was used as a catalyst.

Harsher conditions are needed in terms of temperature to allow for this deoxygenation to occur. Moreover, the effect of CO pressure on this reaction remains unknown. Another approach to facilitate this reaction is to modify the alkyl (or aryl) groups on the phosphine oxide to activate the P=O bond. 1-(4-methoxyphenyl)phospholane oxide is proposed as a better substrate to study this reaction.

Table A.5. Deoxygenation of Triphenylphosphine Oxide with Different Additives

<table>
<thead>
<tr>
<th>entry</th>
<th>additive</th>
<th>2a (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>--</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>CuCl$_2$</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>ScCl$_3$</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>TsOH</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>CeCl$_3$</td>
<td>0</td>
</tr>
</tbody>
</table>

In summary, we have shown that the reducibility of amides is possible under WGSR with homogeneous Rh catalyst in low polarity solvent and low CO pressure. Small Au nanoparticles (3-5 nm) supported on TiO$_2$ were synthesized using urea deposition method and used as a catalyst for the deoxygenative cyclization of 2-nitroimine. The target product 2-phenyl-2H-indazole was not observed and benzo[c]isoxazole 5S was the main reductive cyclization product instead. The formation of 5S from 3S has been reported before using super-stoichiometric amounts of indium or zinc reductants, $^5$ Scheme 2. And thus, performing this reaction with WGSR is a better alternative in terms of atom economy.
Table A.6. Deoxygenation of Triphenylphosphine Oxide with CO using Heterogeneous Catalysts

![Chemical structure](image)

<table>
<thead>
<tr>
<th>entry</th>
<th>catalyst</th>
<th>2a (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ru/Al₂O₃</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>Pd/Al₂O₃</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>Cu/Al₂O₃</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>Ni/Al₂O₃</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>Rh/Al₂O₃</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>Ir/TiO₂</td>
<td>0</td>
</tr>
<tr>
<td>7</td>
<td>RuO₂</td>
<td>trace</td>
</tr>
</tbody>
</table>

Scheme A.2. Deoxygenative cyclization with superstoichiometric metal reductants

![Chemical structures](image)
A.3. References


Appendix B: Water-gas shift-driven reductive carbonylative coupling of aryl halides with allyl electrophiles to form vinyl ketones

B.1. Introduction

The ability of the WGSR to drive the reduction of Pd(II) to Pd(0) was demonstrated to be able to drive the reductive carbonylative coupling of aryl halides with allyl acetates to yield aryl vinyl ketones. This method can potentially serve as an alternative to the current, wasteful, multistep methods for synthesizing aryl vinyl ketones from aryl halides through Grignard reaction with the unsaturated aldehyde followed by oxidation with stoichiometric metal oxide.1

B.2. Results

When the Rh/Pd cooperative catalyst described in Chapter 3 was used to affect the reaction in presence of 2 equivalents of allyl acetate, the aryl vinyl ketone and the aryl alkyl ketone were formed in the amount of 10-15% yield, Scheme 1a. When Rh was eliminated from the reaction, only two products were observed, the benzoic acid and the aryl vinyl ketones, Scheme 1b.

Scheme B.1. Pd/Rh vs. Pd-catalyzed reductive carbonylative coupling

The coupling occurred in highly polar solvents only and complete recovery of the aryl halide was obtained in non-polar solvents, Table 1. Additionally, the selectivity to ketone was found to vary with the addition of phosphine ligands; complete inhibition of the coupling was observed with Xantphos, Table 2. The effect of CO pressure was studied, and the reaction was
found to be inhibited by CO pressure higher than 300 psi, Figure 1. The ketone selectivity was at lowest at 200 psi.

**Table B.1.** Pd-catalyzed Reductive Carbonylative Coupling in Different Solvents

\[
\begin{align*}
\text{MeO} & + \text{MeO} & \text{CO} & \rightarrow \text{MeO} & \text{MeO} & \text{MeO} & \text{MeO} \\
\end{align*}
\]

Table B.1. Pd-catalyzed Reductive Carbonylative Coupling in Different Solvents

<table>
<thead>
<tr>
<th>solvent</th>
<th>iodoanisole consumption%</th>
<th>vinyl ketone selectivity%</th>
</tr>
</thead>
<tbody>
<tr>
<td>dioxane</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>DMF</td>
<td>55</td>
<td>25</td>
</tr>
<tr>
<td>MeCN</td>
<td>48</td>
<td>37</td>
</tr>
<tr>
<td>DMSO</td>
<td>92</td>
<td>44</td>
</tr>
<tr>
<td>PhCl</td>
<td>0</td>
<td>-</td>
</tr>
</tbody>
</table>

**Table B.2.** Effect of P ligands on the Pd-catalyzed Reductive Carbonylative Coupling

\[
\begin{align*}
\text{MeO} & + \text{MeO} & \text{CO} & \rightarrow \text{MeO} & \text{MeO} & \text{MeO} & \text{MeO} \\
\end{align*}
\]

Table B.2. Effect of P ligands on the Pd-catalyzed Reductive Carbonylative Coupling

<table>
<thead>
<tr>
<th>ligand</th>
<th>iodoanisole consumption%</th>
<th>vinyl ketone selectivity%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Xantphos</td>
<td>92</td>
<td>&lt;5</td>
</tr>
<tr>
<td>PCy3</td>
<td>23</td>
<td>55</td>
</tr>
<tr>
<td>dpppentane</td>
<td>55</td>
<td>57</td>
</tr>
<tr>
<td>--</td>
<td>55</td>
<td>43</td>
</tr>
</tbody>
</table>
Figure B.1. Effect of CO pressure on the Pd-catalyzed Reductive Carbonylative Coupling.

Diverse organic and inorganic bases were tested and TMEDA was found to be the most suitable likely because of its ability to ligate Pd in addition to raising the medium basicity.
Table B.3. Effect of base structure on the Pd-catalyzed Reductive Carbonylative Coupling

<table>
<thead>
<tr>
<th>base</th>
<th>iodoanisole consumption%</th>
<th>vinyl ketone selectivity%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1,2,2,6,6 pentamethylpiperidine (2 equiv)</td>
<td>100</td>
<td>3</td>
</tr>
<tr>
<td>Et3N (3 equiv)</td>
<td>100</td>
<td>5</td>
</tr>
<tr>
<td>KOH (2 equiv)</td>
<td>100</td>
<td>7</td>
</tr>
<tr>
<td>K2CO3 (2 equiv)</td>
<td>100</td>
<td>10</td>
</tr>
<tr>
<td>N-Memorpholine (4 equiv)</td>
<td>63</td>
<td>4</td>
</tr>
<tr>
<td>TMEDA (1 equiv)</td>
<td>71</td>
<td>24</td>
</tr>
<tr>
<td>TMEDA (2 equiv)</td>
<td>76</td>
<td>22</td>
</tr>
</tbody>
</table>

Figure B.2. Effect of Pd precursor on the Pd-catalyzed Reductive Carbonylative Coupling.
Figure B.3. Effect of catalyst loading on the Pd-catalyzed Reductive Carbonylative Coupling.
Figure B.4. Effect of co-catalysts on the Pd-catalyzed Reductive Carbonylative Coupling.

Figure B.5. Effect of ligands on the Pd-catalyzed Reductive Carbonylative Coupling.
Figure B.6. Proposed mechanism for the Pd-catalyzed Reductive Carbonylative Coupling.

B.3. References