METHODS FOR THE RAPID SCREENING OF HETEROGENOUS CATALYSTS IN BOTH ANALYTICAL AND PREPARATIVE CONTEXTS

William Louis Hutcherson

Follow this and additional works at: https://digitalcommons.memphis.edu/etd

Recommended Citation

This Dissertation is brought to you for free and open access by University of Memphis Digital Commons. It has been accepted for inclusion in Electronic Theses and Dissertations by an authorized administrator of University of Memphis Digital Commons. For more information, please contact khggerty@memphis.edu.
METHODS FOR THE RAPID SCREENING OF HETEROGENOUS CATALYSTS
IN BOTH ANALYTICAL AND PREPARATIVE CONTEXTS

by
William L. Hutcherson III

A Dissertation
Submitted in Partial Fulfillment of the
Requirements for the Degree of
Doctor of Philosophy

Major: Chemistry

The University of Memphis
December 2023
Acknowledgements

First, I would like to thank my research advisor, Dr. Charles Garner, for his guidance. I truly appreciate all the time you have invested.

I would like to thank my committee members: Dr. Brewster, Dr. Brown, Dr. Zhao, and Dr. Fujiwara.

Thanks to all of the members of my group for helping me along my time here.

Thanks to Bre Von Dollen for sticking it out with me for so long and for helping me though my purification using the radial chromatotron.

Thanks to Mark Wilson for working with me on the project and putting in a lot of work in getting the flow reactor half to work wonderfully.

Thanks to Forough Rahim for the help in investigating how MOFs may work when using this kind of study.

Thanks to Jared Kaiser for working with me to get through all of the hundreds of GC reactions when I was first coming into this project.

Thanks to Emily Zhao for working with me to make and run some of our most recent work.

Thanks to my parents Billy and Mary for supporting me and letting me grow into the person I am today.
Abstract

The discovery of new catalysts and reactions is an important field in chemical synthesis. Typical catalyst screening methods require two steps: reaction and analysis. In this work, both of these steps have been successfully combined using a gas chromatograph (GC) with an inlet injection port liner that has been intentionally “contaminated” with a catalyst. This allows the instrument to perform as a microreactor while continuing to function as an incredibly powerful tool for identification of reaction components. It was observed that GC retention times were highly reproducible even for compounds formed directly in the inlet. This method has the potential to rapidly screen a large number of substrates and catalysts. Newly-discovered reactions can therefore be studied preparatively through the unique use of a packed-column GC equipped with a nondestructive detector as a fixed bed flow reactor. The products of any given reaction can then be collected for further identification as necessary. Further work was conducted to apply these reactions from these specific conditions and transition them to solution-phase reactions.
Table of contents

List of Figures .................................................................................................................. vi
List of Tables ................................................................................................................... vii
List of Abbreviations ........................................................................................................ viii
I. Reaction Gas Chromatography Background ............................................................... 9
II. Practical Considerations of In-inlet Reactions ............................................................ 15
   Packing of Inlet Liners ............................................................................................... 15
   Effects of Supported Catalyst on Inlet Flow/Pressure ............................................... 16
   Choice of Solid Support ............................................................................................. 17
   Catalysts Chosen ........................................................................................................ 18
III. Qualitative Observation of In-inlet Reactions ............................................................ 40
   Substrates Chosen ...................................................................................................... 40
   Silver (I) Perchlorate Products ................................................................................ 42
   Cobalt (II) chloride .................................................................................................... 44
   Cobalt (II) Perchlorate .............................................................................................. 50
   Copper (II) Chloride .................................................................................................. 50
   Copper (II) Perchlorate .............................................................................................. 52
   Iridium (III) Chloride ............................................................................................... 56
   Manganese (II) Chloride ........................................................................................... 60
   Manganese (II) Perchlorate ...................................................................................... 62
   Nickel (II) Chloride .................................................................................................... 63
   Nickel (II) Perchlorate .............................................................................................. 64
   Palladium (II) Chloride ............................................................................................. 66
   Rhodium (III) Chloride ............................................................................................. 67
   Ruthenium (III) Chloride .......................................................................................... 69
   MOF Chemistry ........................................................................................................ 71
IV. Quantitative Results of In-inlet Reactions ................................................................. 75
   First Attempt at Product Isolation .............................................................................. 75
   Packing Columns with Catalyst ................................................................................ 76
   Acceptable Particle Sizes .......................................................................................... 77
   Collecting Products ................................................................................................... 77
   Determining Which Isomer of Xylene was Created in the Sulcatone/RhCl₃ Reaction ....... 77
   Quantification of GC Inlet Reactions ........................................................................ 78
   Attempts at Measuring Turnover Numbers ............................................................... 80
Vial Reactions ........................................................................................................................................... 82
Ampule Reactions ....................................................................................................................................... 83

V. Experimental ........................................................................................................................................... 85
General ...................................................................................................................................................... 85
Solid Support DE ....................................................................................................................................... 86
General IPRA Catalyst Preparation ...................................................................................................... 86
General Injection Solutions .................................................................................................................. 87
Silylation of Inlet Liners .......................................................................................................................... 87
Synthesis of IPO ........................................................................................................................................ 87
Synthesis of 4,4-dimethyl-6-heptyn-2-one (6H2O) ............................................................................... 88
Synthesis of 4,4-dimethyl-6-heptyn-2-ol (6H2OA) ................................................................................ 88
Synthesis of myrcene epoxide .............................................................................................................. 89
Synthesis of Cyclooctadiene Epoxide and Diepoxide ....................................................................... 89
Removal of water from Rhodium Chloride .......................................................................................... 90
Reference list .......................................................................................................................................... 92
List of Figures

Figure 1: Catalyst packed glass inlet liner ................................................................. 15
Figure 2: trans-4-tert-Butyl-1-phenylcyclohexanol dehydration .................................. 18
Figure 3: Transition metal catalysts initially chosen .................................................... 19
Figure 4: Celite solid support TGA ........................................................................... 20
Figure 5: Silver nitrate and perchlorate TGA ............................................................... 22
Figure 6: Cobalt chloride and perchlorate TGA ........................................................... 24
Figure 7: Copper chloride and perchlorate TGA ......................................................... 26
Figure 8: Manganese chloride and perchlorate TGA .................................................... 28
Figure 9: Sodium perchlorate and palladium chloride TGA ......................................... 30
Figure 10: Nickel chloride and perchlorate TGA ......................................................... 32
Figure 11: Rhodium and ruthenium trichloride TGA ................................................... 34
Figure 12: Vanadium pentoxide TGA ......................................................................... 35
Figure 13: Example of measuring peak asymmetry of a fronting peak ......................... 37
Figure 14: Substrates chosen for IPRA ....................................................................... 42
Figure 15: Cyclization product of 6H2OA ................................................................... 43
Figure 16: Chromatogram of 6H2OA inlet reaction through silver perchlorate .......... 43
Figure 17: 6H2OA reactant mass spectrum through silver perchlorate ....................... 44
Figure 18: 6H2OA product mass spectrum .................................................................. 44
Figure 19: Reaction of IPO to 2,4,4-trimethylcyclopentanone ..................................... 45
Figure 20: Chromatogram of isophorone oxide inlet reaction through cobalt chloride ... 45
Figure 21: IPO product mass spectra through cobalt chloride .................................. 46
Figure 22: Reaction of citral to cymene ...................................................................... 47
Figure 23: Chromatogram of citral injected through cobalt chloride ......................... 47
Figure 24: Citral product, cymene, mass spectra through cobalt chloride ................. 47
Figure 25: 6H2OA/CoCl2 chromatogram .................................................................. 48
Figure 26: Reaction of β-ionone to α-ionene ............................................................... 48
Figure 27: β-ionone/CoCl2 product α-ionene chromatogram ..................................... 49
Figure 28: β-ionone/CoCl2 product α-ionene mass spectra ....................................... 49
Figure 29: β-ionone starting material mass spectrum .................................................. 50
Figure 30: Sulcatone/ CuCl2 chromatogram ............................................................. 51
Figure 31: Sulcatone chlorination with copper chloride ................................................ 51
Figure 32: Citral/CuCl2 chromatogram ................................................................... 52
Figure 33: Citral/ CuCl2 chlorinated Mass spectrum .................................................... 52
Figure 34: Potential product of DCKA monochlorination ........................................... 53
Figure 35: DCKA/Cu(ClO4)2 chromatogram .............................................................. 53
Figure 36: DCKA/ Cu(ClO4)2 chlorinated product ..................................................... 54
Figure 37: Geraniol reaction giving a cymene .............................................................. 54
Figure 38: Geraniol/Co(ClO4)2 chromatogram ............................................................ 55
Figure 39: Geraniol/Cu(ClO4)2 cymene product mass spectrum ................................... 55
Figure 40: Sulcatone reaction to xylene ...................................................................... 56
Figure 41: Sulcatone/IrCl3 chromatogram ............................................................... 56
Figure 42: Sulcatone/IrCl3 xylene product mass spectrum ......................................... 57
Figure 43: 3-carene formation of cymene ................................................................. 57
Figure 44: 3-carene/ IrCl3 Chromatogram .......................................................... 58
Figure 45: 3-carene/ IrCl3 cymene product mass spectrum .................................. 58
Figure 46: Linalool reaction to form cymene .......................................................... 59
Figure 47: Linalool/IrCl3 Chromatogram .............................................................. 59
Figure 48: Linalool/ IrCl3 cymene Product ............................................................ 59
Figure 49: 6H2OA/MnCl2 chromatogram ............................................................... 61
Figure 50: 3-carene/ MnCl2 chromatogram ........................................................... 61
Figure 51: 3-carene/ MnCl2 cymene product mass spectrum .................................. 62
Figure 52: 6H2OA cyclization product manganese perchlorate ............................. 62
Figure 53: Sulcatone/NiCl2 chromatogram ............................................................ 63
Figure 54: Citral/NiCl2 Chromatogram ................................................................. 64
Figure 55: Sulcatone/ Ni(ClO4)2 chromatogram ..................................................... 64
Figure 56: Myrcene forming a cymene ................................................................. 65
Figure 57: Myrcene/ Ni(ClO4)2 chromatogram ..................................................... 65
Figure 58: Citral/ Ni(ClO4)2 Chromatogram .......................................................... 66
Figure 59: Sulcatone/ PdCl3 chromatogram .......................................................... 67
Figure 60: 6H2OA/PdCl3 chromatogram ............................................................... 67
Figure 61: Sulcatone/ RhCl3 chromatogram .......................................................... 68
Figure 62: Myrcene/RhCl3 chromatogram ............................................................ 68
Figure 63: Citral/ RhCl3 chromatogram ................................................................. 69
Figure 64: Sulcatone/RuCl3 chromatogram ........................................................... 70
Figure 65: Myrcene/RuCl3 chromatogram ............................................................ 70
Figure 66: Citral/ RuCl3 chromatogram ................................................................. 71
Figure 67: Structures of MOF components used with sulfonated-nano-cellulose ....... 72
Figure 68: Reaction of DCKA with ZIF-8, showing best GC-MS database matching structures ........................................................... 73
Figure 69: Chromatogram from DCKA passing through s-cello-ZIF-8 ...................... 73
Figure 70: Mass spectrum of major product from passage of DCKA through s-cello-ZIF-8 ........................................................... 74
Figure 71: Packed column GC used as a fixed-bed flow reactor .............................. 76
Figure 72: Sulcatone formation of xylene mechanism .......................................... 78
Figure 73: First injection used to determine catalytic activity ................................. 81
Figure 74: 250th Injection used to determine catalytic activity .............................. 82

List of Tables

Table 1: Retention time comparison using IPRA ..................................................... 38
Table 2: Width at half height comparison using IPRA .......................................... 39
Table 3: Peak asymmetry comparison using IPRA .............................................. 39
Table 4: Multiple temperature product quantification .......................................... 80
Table 5: Ampule reaction completion for a. 6H2OA for 4 hrs b. 3-carene varied time .. 84
List of Abbreviations

6H2O: 4,4-dimethyl-6-heptyn-2-one
6H2OA: 4,4-dimethyl-6-heptyn-2-ol
DE: Diatomaceous earth
GCCR: Gas Chromatography Column Reactor
IPO: Isophorone oxide
IPRA: Injection Port Reaction and Analysis
MI: Molecular ion
TGA: Thermal Gravimetric Analysis
I. Reaction Gas Chromatography Background

Importance of Catalysts

Catalyst discovery is a fundamental part of the chemical exploration process. Developing the ability to produce novel and/or valuable materials in a fashion that is both easier and more inexpensive than previously possible is something that many synthetic laboratories strive toward. In general, new catalysts are designed based on previous successful reactions, this design based on the metal, the type of ligands and the types of organic substrates involved. Successfully improving performance, even with some degree of precedent, is still trial-and-error. This means that previous experience and intuition alone are not always enough for catalyst discovery. Another approach to catalyst discovery is to find reactions by serendipity, that is, unintentionally. This is prone to even more trial-and-error, but if reasonably high throughput techniques are available, this approach is both feasible and likely to identify new and unexpected reactions. One example of this approach comes from the Macmillian research group at Princeton University. They used a robotic reaction set-up and sampling techniques to rapidly evaluate approximately 1000 metal and/or light-promoted reactions. The reactants were selected to avoid any known reactions. Through this process they discovered a new C-H arylation of amines that holds promise for a simpler production of certain pharmaceuticals. This level of automation, however, requires expensive instrumentation that not all labs readily have access to. An approach to serendipitous discovery that used instrumentation already common in typical synthesis labs could greatly benefit the synthesis endeavour. A method that combined the synthesis with the analysis would increase the speed with which new reactant combinations could be evaluated. One solution to this is to use a gas chromatograph (GC) injection port as a microreactor, with the usual chromatography and detection as the analysis. By intentionally "contaminating" a
typical GC injection port inlet liner with various potential reactants or catalysts, the
instrument easily becomes a convenient screening device. This single-step reaction/analysis
process is designated as Injection Port Reaction and Analysis (IPRA).

**Advantages of GC Inlets as Reactors**

Within the limitations of this approach (discussed below), there are several
advantages in using a GC inlet as a micro-fixed-bed reactor. (a) The GC inlet lends itself
readily to being a reactor, having built-in temperature, flow and (often) pressure controls.
Newer GC systems are interfaced to a computer that can digitally control both the flow and
pressure, though in older GCs these settings are done manually. In particular, the ability to
easily and digitally control the inlet temperature between ambient and 400 °C is convenient.
(b) Because the glass injection port liner is easily changed, loading of the inlet with potential
catalysts is easily done, and easily reversed. Thus, this screening method does not require a
dedicated instrument. With a simple change in inlet liners, a single GC would be able to
perform both catalyst analysis and everyday GC work. (c) Given capillary GC’s large
number of theoretical plates, the instrument is able to separate nearly all components,
including reaction products. The addition of a mass spectrometry detector (MS) further
allows for identification of many products. Therefore, nearly all products can be expected to
resolve from starting material, and in most cases be identified. (d) This catalyst screening
method is amenable to reliable autosampler technology, allowing automated data collection
for several dozen organic substrates overnight. (e) Possibly the greatest advantage of this
approach is how widely available it makes catalyst research. Most organic research labs
already have the required GC instrumentation, and even undergraduate programs typically
have at least one operational GC-MS. Given that a dedicated instrument is not necessary, this
would enable many laboratories to rapidly screen appropriate materials for catalytic activity.
Purpose

One goal of the Garner group is to evaluate and develop this IPRA method into one that can be implemented by any laboratory for batch screening of catalysts and substrates. To that end, the method must be applicable to analyze various substrates and catalysts. The use of this method should also be simple enough that the only knowledge of GC needed is the ability to interpret the resulting chromatograms. The ability to vary the injection port temperature will also allow this general screening method to be used to determine optimum temperatures for the observed reactions. Reactions discovered in this type of study can then be attempted preparatively, either in a fixed-bed reactor or in solution. The ability to isolate macroscopic amounts of the products is critical for further analyses by, for example, NMR to determine structures that are not in the GC-MS database, or in the case of aromatic isomers such as ortho, meta, and para, which cannot reliably be determined through simple database matching.

Limitations and Possible Problems of Catalyst Screening by IPRA

The IPRA method does have some potential limitations. (1) The catalyst must be non-volatile, otherwise it will no longer be entirely contained in the inlet liner and would likely damage the capillary column and shorten catalyst lifetime. (2) The residence time in the inlet is approximately 2 seconds, therefore only rapid reactions can be studied using this technique.

There are also some more practical considerations: (a) Will the introduction of solid material into the injection port restrict the flow rate of the carrier gas? (b) Would the catalyst packing cause a degradation in the chromatography? In particular, how would the retention
time, width at half height, and peak asymmetry be affected? (c) Would the technique tend to degrade the capillary column, and limit its lifetime?

**Studies in Injection Port Chemistry thus far**

Reports of reactions in GC inlets are less common than traditional bed reactors. These can occur either as intentional and unintentional processes. Reports of unintentional processes include such examples as the heated inlet resulting the conversion of methanol solvent to formaldehyde followed by condensations with amines;\(^2\) dimerization of isoprene;\(^3\) hydrolysis and alcoholsysis of siloxanes from septum particles;\(^4\) epoxide formation from chlorohydrins;\(^5,6\) methyl transfer reactions in methamphetamine analyses;\(^7\) decarbamylation of arylureas;\(^8,9\) artifacts following diazomethane derivatization;\(^10\) loss of unsaturated FAME components from base-catalyzed reactions;\(^11\) decarboxylation of cannabolinic acids;\(^12\) and intramolecular reactions of phenidate analogs.\(^13\)

In the case of the intentional reactions, the most typical reactions are derivatizations, that is, conversion of polar (usually OH) groups that tend to cause tailing or even decomposition to less polar functionalities with better chromatographic behaviour. In a process called IPD, injection-port derivatization, the analytes and a derivatization agent would be co-injected to generate the desired product. These types of derivatizations by co-injection have been reviewed in 2013.\(^14,15\) More recent examples include the silylation of glycosylated polyphenols;\(^16\) acetylation of parabens;\(^17\) the silylation of sunscreen components;\(^18,19\) the silylation of phytoestrogens;\(^20\) and silylation of cocaine and three metabolites.\(^21\) One example that involves derivatization through sequential injection of analytes and a derivatizing reagent has also been reported.\(^9\)
Of those reports of in-inlet reactions, some described reactions that were promoted or catalysed by the packing of solids into the inlet liner. These include an extensive study of 28 solids screened as inlet additives to promote silylation reactions;\textsuperscript{22} an inlet packed with granular sodium borohydride to convert organostannyl chlorides to hydrides;\textsuperscript{23} inlets packed with zeolites to measure acid site density using amine injections;\textsuperscript{24} inlets packed with Pd or Pt catalysts for doing hydrodechlorinations of PCBs and related materials using hydrogen carrier gas;\textsuperscript{25} and the use of strongly acidic or basic inlet packings to convert fatty acid salts or amine salts, resp., into their neutral, chromatographable forms.\textsuperscript{26} In addition, several alcohol dehydrations are notable: catalyzed by CoSO$_4$ on γ-alumina;\textsuperscript{27} on zirconium and aluminum silicates.\textsuperscript{28} A GC inlet was used to do catalytic cracking of alkanes.\textsuperscript{29} Another GC inlet reaction comes through the methylation of phenoxy acids and phenolic herbicides.\textsuperscript{29} Additionally, there was one report of a reaction within a capillary column\textsuperscript{30} rather than in the inlet. There is a 2008 review of the use of GC in high-throughput screening in offline, online, and integrated modes was reported.\textsuperscript{31}

Another type of in-GC reactions uses a separate reactor installed somewhere along the carrier gas flow. There are a number of these types of reactors that are commercially available. The main problems are that they must be installed directly onto the GC, rendering the instrument unusable for day-to-day sample analysis, and that they allow for only one type of reactivity. For example, a post-column reactor (Polyarc\textsuperscript{®}) that converts all organics to CO$_2$ then to CH$_4$ has been described\textsuperscript{32} as a way to avoid the need for response factors in quantification. Another example is of a group that used a coiled stainless-steel wire inside of a modified syringe needle that is attached to the modified injection port of a GC for the purpose of thermochemolysis.\textsuperscript{33}
The routine use of a GC inlet as a reactor has not been reported to date. The goal of this work is to establish the viability of such an application, and to determine the critical parameters for successful operation.
II. Practical Considerations of In-inlet Reactions

Packing of Inlet Liners

In IPRA, the inlet of the GC and GC-MS is under constant pressure during operation. If there is a pressure drop across the inlet due to packing of a catalyst, this will influence the carrier gas linear velocity and result in changes to the retention time of all analytes in the resulting chromatogram. One question is to what extent would solids packed into the inlet liner restrict flow of the carrier gas. In our approach, the "gooseneck" type inlet liners were chosen to allow the catalyst packing to be entirely below the point of injection, i.e., needle insertion depth. The liners were packed with catalyst between two plugs of deactivated glass wool, as shown in Figure 1.

![Diagram of Catalyst packed glass inlet liner](image)

*Figure 1: Catalyst packed glass inlet liner*
Effects of Supported Catalyst on Inlet Flow/Pressure

Two important factors will be considered here. What might be termed "compression", how much force applied to the top glass wool plug, was found to be significant at this stage. If the packing materials were over-compressed then the flow began to diminish. In cases where the top glass wool plug was lightly compressed, there were no observed flow issues on a diatomaceous earth (DE) scaffold. The other important factor is particle size. Our standard method involved dissolving the catalyst in dry methanol, adding an amount of solid support such that a given loading (e.g., by weight) would be achieved upon rotary evaporation. In one case, the catalyst used was found to be insoluble in methanol. In an attempt to use this material, the support and catalyst were ground together in a mortar and pestle to insure through mixing. This fine powder, after packing, resulted in severely reduced flow through the inlet. On an instrument with electronic pressure control, this resulted in wildly fluctuating pressures. The problem was due to the support being too fine, and afterwards we powdered only the catalyst before dispersing it on the support, which worked well. The need to disperse powdered catalysts on the support was uncommon, but in the cases where it was used, the packing performed similarly to the solution-coated packings. In general, we sieved the coated support to a 100-325 mesh range, and this worked well in IPRA studies.

Something else tested was the need for a support at all. Using a pure transition metal chloride, cobalt (II) chloride, that had been sieved to a 100-325 mesh range resulted in initial runs that proceeded as normal, but the material had a tendency to turn to powder, especially at the higher inlet temperatures (250-300 °C).

Another set of catalysts were metal organic frameworks (MOFs) that were prepared in the presence of sulfonated nano cellulose fibers. In the case of these fluffy, low-density MOF composites, while the pressure did not get so unstable that the run was terminated, it was
much more apparent that the overpacking can readily occur. In these cases, the degree of "compression" was critical to getting an unimpeded carrier gas flow.

In efforts to scale up our reactions to produce enough product to do analysis, we used a "packed column GC" where the column (1/4" x 1-4') was filled with supported catalyst to mimic a fixed bed flow reactor in a we technique refer to as gas chromatography column reactor (GCCR). GCCR was done at higher pressures than the IPRA studies, typically with a flow of 25 mL/min through a 1- or 4-ft stainless steel column that had been packed with catalyst coated onto unsieved DE support that contained about 25% material finer than 325 mesh. As column length increased, the carrier gas flow rate dropped to the point that the maximum flow through the 4 ft column was 18 mL/min (at 50 psi He carrier). To contend with this problem, the packing material was sieved to a mesh range of 100-325. This diminished the flow issues that were apparent on the longer columns.

**Choice of Solid Support**

The first task was to identify an inert support for the potential catalysts. Important factors are inertness, surface area, and particle size. Common supports in catalysis work are typically oxides, though carbon-based supports are being developed. As a probe for inertness, we chose *trans-4-tert*-butyl-1-phenylcyclohexanol (1, Figure 2), which is known to survive clean injection ports but dehydrates very easily when exposed to contaminants (Figure 1), particularly acidic ones. We prepared silylated versions (heated with HMDS) of diatomaceous earth (DE), silica gel (40-63 μm), alumina and Florisil. Of these, the DE gave the least dehydration (40%), with the others all giving complete dehydration. However, one commercial form of silylated DE, Restek's DiatoSorb®-WHP, gave no dehydration, and this was used as the support for all of the IPRA work. A range of particle sizes have been reportedly used in GC injection ports, from 250-1000 μm (< 35 mesh), to 100 μm (150 mesh). Finer particles (> 500 mesh) have been used when coated onto
more granular supports. We found that the particle-size range of the as-received DiatoSorb® (80/100 mesh) gave no flow-related issues. In the course of evaluation the other supports, we found that 100/325 mesh DE prepared and sieved ourselves gave no flow problems, but this was used only in the GCCR experiments where the cost of DiatoSorb® would be prohibitive. As mentioned above, if the support was powdered (> 325 mesh) using a mortar and pestle, the flow was unduly restricted as evidenced by pronounced pressure instability on systems with electronic pressure control.

![Figure 2: trans-4-tert-Butyl-1-phenylcyclohexanol dehydration](image)

**Catalysts Chosen**

The catalysts chosen to be screened were selected for their low volatility and solubility in methanol rather than any particular expected reactivity. We chose a number of transition metal chlorides and perchlorates. In general, we found that hydrates were more soluble than anhydrous forms. Solution coating was done by dissolving the catalyst into a solvent (nearly always methanol) to which the DiatoSorb® support was added, in quantities such that the final solid would have a particular percent metal (irrespective of ligands) by weight, usually 5%. Rotary evaporation was used to evenly coat the catalyst onto the scaffold. Based on boiling points, some transition metal catalysts were immediately ruled out based on the potential for the catalyst to sublime onto the column. Here we found that thermal gravimetric analysis (TGA) was very useful in determining stability of the potential catalysts, and whether our standard inlet operating temperatures (250-300 °C) were safe for the capillary column. The TGA instrument only required a few milligrams of material (metal...
complex with no support) and measured the weight to the nearest microgram in the range of room temperature to 400 °C. Before use in the GC or GC-MS, the "contaminated" liners were conditioned using the inlet of another GC with only a short section of capillary tubing attached to the inlet, using a slow flow of nitrogen at temperatures where the catalyst was stable, as judged by TGA, or 250 °C, whichever was lowest. Loss of water or methanol did not disqualify any catalyst candidate. Using this insight, the gas exiting the conditioning GC was tested for the release of acid at the outlet of the capillary attached to the inlet using moist pH paper. It was found that several hydrates (NiCl₂, RuCl₃, RhCl₃) would release acid during heating. This modified our conditioning method to continue heating until acid stops exiting the carrier gas. Additionally, the thermal stability of the chosen catalysts was drawn into question.

<p>| | | | | | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>V</td>
<td>Cr</td>
<td>Mn</td>
<td>Fe</td>
<td>Co</td>
<td>Ni</td>
<td>Cu</td>
<td></td>
</tr>
<tr>
<td>V₂O₅</td>
<td>CrCl₃*</td>
<td>MnCl₂</td>
<td>FeCl₂</td>
<td>CoCl₂</td>
<td>NiCl₂</td>
<td>CuCl₂</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mn(CIO₄)₂*</td>
<td>Fe(CIO₄)₃*</td>
<td>Co(CIO₄)₂*</td>
<td>Ni(CIO₄)₂*</td>
<td>Cu(CIO₄)₂*</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>RuCl₃*</td>
<td>RhCl₃*</td>
<td>PdCl₂</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Coated as hydrate

Figure 3: Transition metal catalysts initially chosen

 Thermal Gravimetric Analysis of Transition Metal Catalysts

Using the TGA, a small amount of each pure catalyst (no support) was brought to an upper temperature (400 °C) equal to the highest we could possibly use in the IPRA technique. Using aluminium pans, the material to be tested was taken from room temperature to 400°C at a ramp of 10°C per minute. During operation the instrument was under a flow of
nitrogen. In addition, the support was analysed to identify any thermal instability it might possess. In some of the TGA data, an instrumental issue (bent sample holder wire) resulted in an increase in the amount of noise relative to a typical TGA run. This can be seen for acid-washed, oven-dried DE in Figure 4. While the data looks noisy, there is practically no weight loss during the entire run. This indicated that the support was not the source of any degradation in the inlet.

![TGA graph](image)

**Figure 4: Celite solid support TGA**

Both of the silver catalysts (AgNO₃, AgClO₄) behaved well on TGA. There was some worry that light may lead to a degradation of these to silver metal. To prevent this, the samples were stored in containers that were covered in foil when not in use. This was not something that proved to be a problem in the IPRA study. Thermally, both of these compounds were treated as stable, as there was no real weight loss. Silver nitrate lost less
than 1 percent of its weight. The silver perchlorate preformed a bit worse, with a loss of 8 percent. This is attributed to a loss of water rather than any degradation of the catalyst. A loss of the single perchlorate would result in a loss of over half of the mass.
Figure 5: Silver nitrate and perchlorate TGA
The TGA for cobalt (II) chloride and cobalt (II) perchlorate are shown in Figure 6. The cobalt chloride was anhydrous, but just during the time required to load the pan it changed from blue to pink, indicating the presence of some of the dihydrate. CoCl₂ can exist as a few different hydrates, but the pink form is the dihydrate. This material lost 15% of its weight by 170 °C, with no further loss all the way to 400 °C. In addition, no loss of HCl was observed at the column outlet during conditioning. A loss of one water would be a loss of 11 percent and a loss of 2 hydrates would be a 22 percent loss. Based on this TGA, it can reliably be inferred that cobalt chloride absorbs between one and two molecules of water while being loaded into the pan, and this water is removed relatively easily by heating.

Cobalt perchlorate was used as the hexahydrate. If all the water were to be lost during heating, then it would exhibit a loss of 30 percent. The TGA has 2 steps at the start giving a loss of 20% indicating that at least some hydrate can be removed with heating. However, as it approaches the general operating temperature of 250°C the material exhibits a loss of nearly 80 percent, which corresponds to only cobalt (II) oxide remaining. This demonstrates a pronounced instability, and indicates a potential to damage the GC column or even the detector. There could be some merit to using cobalt perchlorate below 200 °C, but for any general use it was removed from our consideration. The chloride still remains as a usable catalyst.
Figure 6: Cobalt chloride and perchlorate TGA
The TGA data for copper (II) chloride and copper (II) perchlorate are shown in Figure 7. Copper chloride is anhydrous, but it will become a dihydrate if exposed to the air for some time. If heating were to only remove the water, that would result in the loss of 20 percent. While copper chloride visually exhibits less than the loss of two water molecules, a loss of HCl would be similar to a loss of both hydrates in weight. Copper perchlorate instead exists as a hexahydrate. If it was to lose all of its hydrates, there would be a loss of 30 percent. There is, however, no clean break between losing water and further decomposition, and an extensive loss of weight (~ 70%) is observed. This indicates that using copper perchlorate in the IPRA technique would risk damaging the column or instrument. Using this data set and the knowledge we gained from observed chlorination in IPRA studies (discussed below) led to the discontinuing of the use of both the chloride and perchlorate of copper during typical IPRA screening.
Figure 7: Copper chloride and perchlorate TGA
In the case of manganese (II) chloride and manganese(II) perchlorate, the thermal behaviour was similar to that of the corresponding cobalt compounds. For the chloride, there was only about an 8 percent loss by 190 °C, and complete stability thereafter. Although this material was purchased as "anhydrous", there was likely some addition of water during the weighing process. The anhydrous material is composed of half chlorine and half manganese by weight. A loss of one chloride would result in a weight change of 25 percent. The small loss we observe must then be attributed to water. The perchlorate, however, underwent extensive decomposition, leaving only 20 percent of the original mass by 240 °C. This perchlorate was a hexahydrate. Losing all of the attached hydrates would incur a loss of only 27 percent. This could be consistent with the weight loss below 240 °C. The loss of 80 percent suggests the formation of the metal oxide. It should be noted that while cobalt, copper and manganese perchlorates are clearly too thermally unstable for our use, silver perchlorate appears to be significantly more stable, and probably usable at 200 °C or below.
Figure 8: Manganese chloride and perchlorate TGA
The thermal analysis of sodium perchlorate was done to observe the inherent thermal stability of the perchlorate anion in the absence of transition metals. According to the bottle, this perchlorate is anhydrous. This was consistent with the TGA data, in which the material had no weight loss above 50 °C, and the 2.7% loss up to that point is attributed to easily-removed water acquired during weighing. This indicates very good thermal stability.

Sodium perchlorate can be purchased as the mono hydrate. If it lost that one water, then it would lose 12 percent. This indicates the material began to gain water as it was weighed, but will lose that water again upon heating.

Palladium chloride exhibited virtually no weight loss. This likely means the material does not rapidly gain water and will likely lose it again upon the addition of heat. This is indicative of good behaviour in IPRA studies.
Figure 9: Sodium perchlorate and palladium chloride TGA
The next materials were the perchlorate and chloride of nickel. The chloride is labelled as anhydrous, but it is likely that the material will absorb at least some water. The material is yellow, the colour of the anhydrous material. The hexahydrate is green. The di-, tetra- and hexa-hydrates of the chloride are known. In the case of our work, the anhydrous material apparently absorbed some water during weighing, and this was lost during heating as shown by the loss of 13 percent by 250 °C. Acid was not regularly observed exiting the conditioning GC during IPRA studies. This material is still useful for IPRA studies. The perchlorate, however, is not nearly as stable. It is a hexahydrate, and a loss of water would result in a loss of 27 percent. There was no clean break in the weight loss curve, suggesting continual decomposition. Remarkably, weight loss was complete by 330 °C, resulting in an empty TGA pan at the end of the analysis. Nickel perchlorate is clearly unusable in the IPRA technique.
Figure 10: Nickel chloride and perchlorate TGA
The thermal analysis of rhodium (III) chloride was done next. This material was labelled as a "hydrate", but sources vary between one and three water molecules of hydration. This material was a light red when coated and a light grey after conditioning at 250°C. The injection port outlet in which this was conditioned was tested using moist pH paper and was found to be strongly acidic. Initially it was believed that the grey product could be a chloro-oxide, however there appear to be no known chloro-oxos of rhodium, so it was decided that the likely product is rhodium oxide. This material continued to be used with IPRA, however it must be conditioned until it stops producing acid. Some attempt to render the chloride anhydrous before conditioning was made, discussed below.

Ruthenium chloride behaved very much like the corresponding rhodium compound, releasing HCl during conditioning, but it did not undergo a color change. Ruthenium chloride is thought of generally as a trihydrate. A loss of three water molecules would result in a 20 percent weight change, thus it is likely that it could also undergo a conversion to an oxide similarly to the rhodium. This material was continued to be used with the IPRA technique, after conditioning until acid ceased to be released.
Figure 11: Rhodium and ruthenium trichloride TGA
The vanadium pentoxide resulted in no significant weight loss. The changes in the measurement is likely a result of noise in the instrument rather than any possible loss of the material.

Figure 12: Vanadium pentoxide TGA

Peak Quality

A major question any analytical chemist would have is how badly the quality of the chromatography is affected by contaminates in the inlet of a GC. There are three major changes that can occur in the chromatogram. The first is the retention time. While the use of an MS database provides a powerful means of identification, capillary GC is known for highly reproducible retention times such that authentic material can be used to determine product identity. One major question is whether materials in the inlet would change the retention times significantly. The second measure of peak quality is the width at half height.
of the peaks. If an inlet contaminant results in broadening, this results in a loss of resolution in the chromatogram. In the case of capillary GC, it is the more the sharpness of the peaks, rather than differences in retention times, that resolves nearby analytes. The final measure of peak quality is peak asymmetry. This is mainly a measure of tailing, which is common in aged capillaries with "active (binding) sites". This is measured by dividing the peak into two halves vertically along a line passing through the peak maximum and perpendicular to the baseline. Asymmetry is measured at 10% the height of the peak to the left and right of the dividing line, as in Figure 13. The resulting halves are measured and the right half (later portion) is divided by the left half (earlier portion). If this ratio is less than 1, this is termed "fronting". Fronting occurs when a column is overload by the amount of analyte injected. We typically observe this on our GC-MS. Because the capillary column’s capacity is low on account of the narrow diameter (0.15 mm ID) and phase thickness (0.15 µm), sample concentrations as low as 5 mg/mL can still exhibit fronting on this column. In cases where the ratio is larger than 1 correspond to "tailing". Tailing results from interactions between the analyte and "active sites" in the injection port or (more often) in the column. Active sites are any places where an attractive interaction with the analyte is not rapidly reversible. It is entirely reasonable to anticipate that "contaminating" the inlet would result in such interactions and cause tailing.
In a study of the peak quality, first the retention times (Table 1) of a few hydrocarbon standards, reactants, and products using the IPRA technique through a number of liners were determined. The results can be compared to the values obtained using a clean liner on the same column. The first seven entries are for analytes injected, and the last three are for products formed. Except for the clean liner case, product values are the result of a reaction (R) of one of the substrates directly above. In some cases, a value is not given. If the result is a D ("disappeared") then there was an apparently irreversible adsorption onto the liner resulting in neither a starting material nor product peak in the resultant chromatogram. Conversely, an entry of R means that the starting material reacted, and a product was observed in the chromatogram. In the case of sulcatone, isophorone oxide and 6H2OA, the products were determined to be xylene (meta), cymene (para), and the enol ether derived from an intramolecular addition followed by a rearrangement, respectfully. Finally, in the case an NF ("not found"), this indicates that particular product was not observed. The result of any given substrate is evident by reading from left to right, from clean liner through any of five "contaminated" (10 wt %) by metal liners.
### Table 1: Retention time comparison using IPRA

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Liner</th>
<th>Clean</th>
<th>Diat</th>
<th>AgNO₃</th>
<th>CoCl₂</th>
<th>MnCl₂</th>
<th>RhCl₃</th>
</tr>
</thead>
<tbody>
<tr>
<td>Undecane</td>
<td></td>
<td>6.91</td>
<td>6.91</td>
<td>6.96</td>
<td>6.94</td>
<td>6.92</td>
<td>6.93</td>
</tr>
<tr>
<td>Decane</td>
<td></td>
<td>5.63</td>
<td>5.64</td>
<td>5.68</td>
<td>5.66</td>
<td>5.65</td>
<td>5.66</td>
</tr>
<tr>
<td>Isophorone Oxide</td>
<td></td>
<td>6.93</td>
<td>6.95</td>
<td>D</td>
<td>R</td>
<td>6.95</td>
<td>D</td>
</tr>
<tr>
<td>4,4-dimethyl-hept-6-yn-2-ol (6H₂OA)</td>
<td></td>
<td>5.73</td>
<td>5.74</td>
<td>D</td>
<td>R</td>
<td>5.75</td>
<td>D</td>
</tr>
<tr>
<td>Citral</td>
<td></td>
<td>8.82</td>
<td>8.83</td>
<td>D</td>
<td>R</td>
<td>8.84</td>
<td>D</td>
</tr>
<tr>
<td>6-methyl-5-hepten-2-one (Sulc)</td>
<td></td>
<td>5.40</td>
<td>5.42</td>
<td>D</td>
<td>5.43</td>
<td>5.42</td>
<td>R</td>
</tr>
<tr>
<td>4-nitrotoluene</td>
<td></td>
<td>8.34</td>
<td>8.35</td>
<td>D</td>
<td>8.37</td>
<td>8.36</td>
<td>8.37</td>
</tr>
<tr>
<td>Xylene</td>
<td></td>
<td>3.92</td>
<td>NF</td>
<td>NF</td>
<td>NF</td>
<td>NF</td>
<td>3.93</td>
</tr>
<tr>
<td>Cymene</td>
<td></td>
<td>6.01</td>
<td>NF</td>
<td>NF</td>
<td>6.03</td>
<td>NF</td>
<td>NF</td>
</tr>
<tr>
<td>6H₂OA Cyclization</td>
<td></td>
<td>4.19</td>
<td>NF</td>
<td>NF</td>
<td>4.10</td>
<td>NF</td>
<td>NF</td>
</tr>
</tbody>
</table>

In all cases the retention time, shown in Table 1, is practically no change in the retention times for any of the inlet packings. In the case of all these runs, an autosampler was used. Typically, autosamplers give retention times that are consistent to ± 0.005 min, while manual injections give about 10 times larger variations. In the case of IPRA, the retention time changes slightly at the second decimal place. At most, a deviation of 0.05 minutes (3 seconds) is observed, averaging 0.023 (1.4 seconds). This consistency suggests that retention times could still be used for product identification on a GC with a different detector, such as an FID, through the use of authentic material.

The second aspect of peak quality is value of the width at half height. These figures for the same materials can be seen in Table 2. The value of the width at half height barely changes, by no more than 0.004 minutes, and often not at all. The average change in half-height width is 0.001 minutes. Remarkably, the resolution of the peaks is, in general, virtually unaffected by the IPRA technique.
Finally, the asymmetry values are shown in Table 3. The samples were made to be close to 5 mg/mL in hexane. Nearly all of samples exhibited slight fronting, probably due to the somewhat concentrated samples (5 mg/mL) required to obtain strong enough GC-MS peaks to get reliable database matches. Though any tailing might have been obscured by this slight overloading, the very narrow peak widths in Table 2 (hardly any wider than on a clean liner) suggest that tailing is insignificant, at least with these inlet packings and substrates.

Table 2: Width at half height comparison using IPRA

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Clean</th>
<th>Diat</th>
<th>AgNO3</th>
<th>CoCl2</th>
<th>MnCl2</th>
<th>RhCl3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Undecane</td>
<td>0.018</td>
<td>0.018</td>
<td>0.021</td>
<td>0.019</td>
<td>0.019</td>
<td>0.018</td>
</tr>
<tr>
<td>Decane</td>
<td>0.019</td>
<td>0.018</td>
<td>0.020</td>
<td>0.018</td>
<td>0.018</td>
<td>0.018</td>
</tr>
<tr>
<td>Isophorone Oxide</td>
<td>0.019</td>
<td>0.021</td>
<td>D</td>
<td>R</td>
<td>0.020</td>
<td>D</td>
</tr>
<tr>
<td>4,4-dimethyl-hept-6-yn-2-ol (6H2OA)</td>
<td>0.019</td>
<td>0.020</td>
<td>D</td>
<td>R</td>
<td>0.020</td>
<td>D</td>
</tr>
<tr>
<td>Citral</td>
<td>0.017</td>
<td>0.021</td>
<td>D</td>
<td>R</td>
<td>0.020</td>
<td>D</td>
</tr>
<tr>
<td>6-methyl-5-hepten-2-one (Sulc)</td>
<td>0.018</td>
<td>0.018</td>
<td>D</td>
<td>0.020</td>
<td>0.019</td>
<td>R</td>
</tr>
<tr>
<td>4-nitrotoluene</td>
<td>0.023</td>
<td>0.024</td>
<td>D</td>
<td>0.024</td>
<td>0.025</td>
<td>0.022</td>
</tr>
<tr>
<td>Xylene</td>
<td>0.020</td>
<td>NF</td>
<td>NF</td>
<td>NF</td>
<td>NF</td>
<td>0.017</td>
</tr>
<tr>
<td>Cymene</td>
<td>0.024</td>
<td>NF</td>
<td>NF</td>
<td>0.021</td>
<td>NF</td>
<td>NF</td>
</tr>
<tr>
<td>6H2OA Cyclization</td>
<td>0.017</td>
<td>NF</td>
<td>NF</td>
<td>0.019</td>
<td>NF</td>
<td>NF</td>
</tr>
</tbody>
</table>

Table 3: Peak asymmetry comparison using IPRA

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Clean</th>
<th>Diat</th>
<th>AgNO3</th>
<th>CoCl2</th>
<th>MnCl2</th>
<th>RhCl3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Undecane</td>
<td>0.94</td>
<td>0.93</td>
<td>0.94</td>
<td>0.88</td>
<td>0.83</td>
<td>0.89</td>
</tr>
<tr>
<td>Decane</td>
<td>0.87</td>
<td>0.99</td>
<td>0.97</td>
<td>0.96</td>
<td>0.85</td>
<td>0.71</td>
</tr>
<tr>
<td>Isophorone Oxide</td>
<td>0.88</td>
<td>0.95</td>
<td>D</td>
<td>R</td>
<td>0.93</td>
<td>D</td>
</tr>
<tr>
<td>4,4-dimethyl-hept-6-yn-2-ol (6H2OA)</td>
<td>0.90</td>
<td>0.80</td>
<td>D</td>
<td>R</td>
<td>0.85</td>
<td>D</td>
</tr>
<tr>
<td>Citral</td>
<td>0.96</td>
<td>0.87</td>
<td>D</td>
<td>R</td>
<td>0.85</td>
<td>D</td>
</tr>
<tr>
<td>6-methyl-5-hepten-2-one (Sulc)</td>
<td>1.05</td>
<td>0.85</td>
<td>D</td>
<td>0.99</td>
<td>0.92</td>
<td>R</td>
</tr>
<tr>
<td>4-nitrotoluene</td>
<td>0.89</td>
<td>0.76</td>
<td>D</td>
<td>0.79</td>
<td>0.79</td>
<td>0.84</td>
</tr>
<tr>
<td>Xylene</td>
<td>0.82</td>
<td>NF</td>
<td>NF</td>
<td>NF</td>
<td>NF</td>
<td>1.10</td>
</tr>
<tr>
<td>Cymene</td>
<td>0.85</td>
<td>NF</td>
<td>NF</td>
<td>1.04</td>
<td>NF</td>
<td>NF</td>
</tr>
<tr>
<td>6H2OA Cyclization</td>
<td>0.94</td>
<td>NF</td>
<td>NF</td>
<td>0.93</td>
<td>NF</td>
<td>NF</td>
</tr>
</tbody>
</table>
III. Qualitative Observation of Inlet Reactions

Substrates Chosen

The organic substrates were chosen for this work with three factors in mind. First, they needed to be easily analyzed by GC, which in practice means having at least six carbons and preferably 10-15. This is because capillary GC exhibits much less retention than did the thick stationary phases in packed columns, and small molecules can easily elute too rapidly or require inconveniently low initial temperatures. Second, we anticipated that under IPRA conditions bimolecular reactions would be, in general, unlikely to occur. To favor unimolecular reactions, which would include rearrangements and fragmentations, we sought molecules that contained unsaturation in the form of double bonds and/or small rings. Other structural features that could fit that description would be alcohols, epoxides, and ketones. Finally, we sought compounds that were readily available at low cost. This was not only for reasons of project cost considerations, but also that we might identify processes that would produce more valuable products. Terpenes and terpenoids were a good fit for this, being generally inexpensive and often possessing multiple degrees of unsaturation. Terpenes are defined as (Wikipedia):\textsuperscript{35} “The terpenoids, also known as isoprenoids, are a class of naturally occurring organic chemicals derived from the 5-carbon compound isoprene and its derivatives called terpenes, diterpenes, etc. While sometimes used interchangeably with "terpenes", terpenoids contain additional functional groups, usually containing oxygen. When combined with the hydrocarbon terpenes, terpenoids comprise about 80,000 compounds. They are the largest class of plant secondary metabolites, representing about 60% of known natural products.” Fully 13 of the 25 substrates we studied (3, 6, 8, 9, 14-22) are terpenes or terpenoids.
The catalysts were constructed to by 10% by weight of the catalyst to the DE. A standard run on the GC would include injection port temperatures of 250°C, and a detector temperature of 280°C using helium carrier at 10 psi with a split ratio of 40:1. The column used in this work was a 12m x 0.2 mm HP-5. Products were able to be separated by the GC and identified by the MS. The identification as done through database matching using the NIST20 EI library. For a compound to be called as identified it had to have a fragmentation match percentage of 90% or higher and look similar enough to the starting material the match makes sense. i.e., A compound with no nitrogen cannot match to a nitrogen containing compound even if the “molecular ion” suggests that to be the case. In the cases where this match was low, or the product was not included in the database the reactant structure, molecular ion, and apparent common fragments were used to determine potential formed products in lieu of the ability to perform NMR.
Using the catalysts found to have sufficiently good thermal stability from Figure 3, we observed many reactions. The reaction types most commonly observed include cyclizations, aromatizations, and chlorinations. The results from individual catalysts are given below.

### Silver (I) Perchlorate Products

In the case of 6H2OA, the starting material undergoes a cyclization to the enol ether product shown in Figure 15. This was not in any of the GC-MS databases, and the identity was proven by NMR of a sample isolated by GCCR. This cyclic enol ether is the result of a Markovnikov addition of the OH group across the C-C triple bond, followed by isomerization of the exocyclic double bond to the endocyclic position. The chromatogram shows little to no
remaining starting material. There also appears to be a small peak corresponding to the oxidation product (ketone) of 6H2OA. Being the immediate precursor, this is likely leftover from the synthesis of 6H2OA.

\[ \text{O} \longrightarrow \text{C} \quad \text{H} \]

**Figure 15: Cyclization product of 6H2OA**

The chromatogram and mass spectra of the product and starting material are shown in Figure 17 Figure 18, and Figure 18 respectfully. Both molecules have the same molecular ion of 140 m/z, but the product gives a stronger one. The base peak differs as it is 125 m/z in the product and 87 m/z in the starting material. The MI of the starting material is not present at the lower concentrations used for the IPRA study, but it does appear in more concentrated solutions. This is to be expected, as the MI of alcohols tend to be less abundant. No other tested substrates appeared to react in a appreciably and/or cleanly with silver perchlorate.

**Figure 16: Chromatogram of 6H2OA inlet reaction through silver perchlorate**
Figure 17: 6H2OA reactant mass spectrum through silver perchlorate

Figure 18: 6H2OA product mass spectrum

Cobalt (II) chloride

Isophorone oxide is apparently converted completely into product, shown in Figure 19 as 2,4,4-trimethylcyclopentanone. The chromatogram and mass spectra of the product are shown in Figure 20 and Figure 21 respectfully. In each of these spectra the base peak is 83
m/z. The MI did differ with the starting material showing a 154 m/z and while the product MI had a 126 m/z. The product was identified as 2,4,4-trimethylcyclopentanone.

![Chemical structure of 2,4,4-trimethylcyclopentanone]

**Figure 19: Reaction of IPO to 2,4,4-trimethylcyclopentanone**

![Chromatogram of isophorone oxide inlet reaction through cobalt chloride]

**Figure 20: Chromatogram of isophorone oxide inlet reaction through cobalt chloride**
The next material to react with CoCl$_2$ was citral, which reacts to give a cymene as shown in Figure 22. The citral used in this study was a combination of both E and Z isomers in about a 1:2 ratio, respectively. This aromatization reaction leaves only a small amount of starting material and gives only one of the three possible isomers of cymene. The chromatogram and the mass spectra for the cymene product are shown in Figure 23 and Figure 24. Both spectra have different base peaks and MI. The product also has the inclusion of strong mass ions at 91 and 119, which is indicative of the cymene benzene ring with the loss of either the isopropyl or the methyl groups, respectively. While the database matching can distinguish the product peak belong to one of the cymene isomers, it is unable to determine which of these isomers is present based on the mass spectra alone. It could be possible to use retention time data to inquire about the identities of the product isomers. Still, all cymene isomers have similar retention times with the meta- and para- peaks occurring so closely that the peaks nearly overlap.
Figure 22: Reaction of citral to cymene

Figure 23: Chromatogram of citral injected through cobalt chloride

Figure 24: Citral product, cymene, mass spectra through cobalt chloride
The reaction of 6H2OA with CoCl$_2$ generated the same enol ether product as shown in Figure 15. This is a clean reaction with no starting material and only one product. The chromatogram from the reaction appears in Figure 25. The starting material and product mass spectra is shown in Figure 18 and Figure 18. The resulting ions are the same as described above.

![Figure 25: 6H2OA/CoCl$_2$ chromatogram](image)

The final reaction that cleanly occurred using cobalt chloride is for β-ionone. It is converted, though not completely, into α-ionene. The product peak has a 174 m/z and the reactant has a much higher 193 m/z that is not as intense.

![Figure 26: Reaction of β-ionone to α-ionene](image)
Figure 27: β-ionone/CoCl$_2$ product α-ionene chromatogram

Figure 28: β-ionone/CoCl$_2$ product α-ionene mass spectra
Figure 29: β-ionone starting material mass spectrum

**Cobalt (II) Perchlorate**

We studied cobalt perchlorate before realizing that it had poor thermal stability. In this case, the substrates tested resulted in giving more starting material than products. Beyond that, there was some evidence of unidentifiable chlorination in resulting spectra. These results coupled with the limited thermal stability led to the cobalt perchlorate being discontinued from future IPRA studies.

**Copper (II) Chloride**

The first notable reaction was with sulcatone and was not a clean reaction. The major product could not be identified, but the product peak obviously has multiple chlorines present from the multiple ions 2 mass units apart. It is likely that this particular product is trichlorinated as shown in Figure 31.
Citral also gave a chlorinated peak. This peak as shown in Figure 33 reveals the classic 3:1 m/z ratio of a single chlorination. Again, the starting material has been mostly consumed to give these chlorinated products. This is a reason that the copper chloride reactions were not pursued further at this stage. The major product of this reaction is likely p-chlorotoluene.
The copper perchlorate appeared to have similar problems as the copper chloride. Many of the starting materials reacted but gave either many peaks and/or chlorinated peaks.

Copper (II) Perchlorate
Such is the case of DCKA, dicyclopropyl methanol, which gives a number of peaks, including one for the mono-chlorinated product shown in Figure 36.

![Figure 34: Potential product of DCKA monochlorination](image)

![Figure 35: DCKA/Cu(ClO₄)₂ chromatogram](image)
Figure 36: DCKA/ Cu(ClO₄)₂ chlorinated product

The substrate geraniol, however, did give a relatively clean reaction that generated a single isomer of cymene. The chromatogram and product mass spectrum are shown in Figure 38 and Figure 39. While a fairly clean reaction is shown in the chromatogram in Figure 38 the ease of chlorination in the reaction screening along with a poor thermal stability led the discontining of this perchlorate for IPRA studies.

Figure 37: Geraniol reaction giving a cymene
Figure 38: Geraniol/Co(ClO$_4$)$_2$ chromatogram

Figure 39: Geraniol/Cu(ClO$_4$)$_2$ cymene product mass spectrum
Iridium (III) Chloride

In the iridium IPRA reactions, sulcatone was converted cleanly into a single xylene, probably the meta isomer. This reaction is shown in Figure 40. The chromatogram and product mass spectrum are shown in Figure 41 and Figure 42. In both cases the MI and base peak are different. The product peak also gains typical aromatic markers, such as the strong 91 m/z.

![Figure 40: Sulcatone reaction to xylene](image)

![Figure 41: Sulcatone/IrCl₃ chromatogram](image)
Figure 42: Sulcatone/IrCl₃ xylene product mass spectrum

3-Carene reacted to form two cymene isomers that are nearly overlapping in the chromatogram, indicating meta and para (ortho is well separated from the others). The reaction is shown in Figure 43. This is a clean reaction with no observed starting material. The chromatogram and product mass spectrum are shown in Figure 44 and Figure 45. In both cases the base peak and the MI are different. The MI is close but varies by 2 mass units. That variance and the aromatic markers found in the product mass spectra indicate the conversion to a cymene. It is difficult to differentiate the isomers of cymene using the database matching as the MS are nearly identical.

Figure 43: 3-carene formation of cymene
The final reaction observed for iridium comes from linalool. The linalool produced a single cymene isomer as shown in Figure 46. The results are similar to the 3-carene in that the MI and base peak change, while the product gains aromatic markers. The chromatogram and product mass spectrum are shown in Figure 47 and Figure 48.
Figure 46: Linalool reaction to form cymene

Figure 47: Linalool/IrCl₃ Chromatogram

Figure 48: Linalool/IrCl₃ cymene Product
Manganese (II) Chloride

Reactions using manganese chloride generally exhibited either messy reactions or no reaction with these substrates. There were two cases where a clean reaction occurred. The first was with 6H2OA. It generated the cyclization product before, as in Figure 15. However, it still contained much unreacted starting material, unlike from earlier liners. Another difference is the presence of an additional peak slightly later than the product peak previously mentioned. It is believed that the first peak is the endocyclic compound and the later peak corresponds to the exocyclic precursor.

The second was that of 3-carene. Much like the previous reactions, this also produced two cymenes that are almost overlapping in the chromatogram. There may be some unreacted starting material, but the reaction appears to be otherwise clean. The mass spectra can be seen in Figure 51. Unlike the previous run, the former of the two cymene is the major peak, possibly indicating a different cymene is the major product of this reaction. The GC-MS chromatogram in this case exhibited a lower abundance than usual. This may be due to a lower concentration in the injected solution. This leads to less ions in the mass spectra as seen in Figure 51. The peaks that do show up correspond with the presence of cymene.
Figure 49: 6H2OA/MnCl$_2$ chromatogram

Figure 50: 3-carene/ MnCl$_2$ chromatogram
Manganese (II) Perchlorate

Manganese perchlorate reacted with the substrate 6H2OA to accomplish the same cyclization efficiently. The chromatogram is shown below in Figure 52. The remaining substrates either do not react or react too messily with manganese perchlorate for consideration.
Nickel (II) Chloride

First, sulcatone behaves as it had previously, using almost all of the starting material to cleanly generate a single xylene. The given chromatogram can be seen in Figure 53. A smaller peak appears after the large xylene peak with a MI of 106 m/z. One the GC column being used, only the ortho isomer is separated from the meta and para isomers, so probably the minor peak is ortho xylene.

![Figure 53: Sulcatone/NiCl₂ chromatogram](image)

Citral also produces a single isomer of cymene under these conditions, as in Figure 22. The single isomer is cleanly formed and there is no starting material of either the E or Z citral. The resulting mass spectra can be seen in Figure 54. Like previous spectra, the presence of aromatic markers further indicates the formation of the aromatics.
Nickel (II) Perchlorate

Sulcatone reacted in the exact same way as previously described in the nickel chloride section. The chromatogram can be seen below in Figure 55.

Myrcene gave a single isomer of cymene. Some starting material still remains in the chromatogram. The reaction that occurs is shown in Figure 56.
Figure 56: Myrcene forming a cymene

Under the same conditions citral will give the same product from Figure 22. This reaction occurs cleanly without leaving any starting material. The chromatogram can be seen in Figure 58. The chromatogram only shows one cymene isomer.
Palladium (II) Chloride

Palladium chloride also exhibited a tendency to chlorinate. Sulcatone, for example, chlorinates in these conditions as shown with Figure 59 containing 2 monochlorinated sulcatone products. Thus, while some reactions such as the 6H2OA go forward to some extent, two monochlorinated reactant peaks are also present, as shown below. Such chlorinations are unlikely to be useful processes, since they cannot be catalytic.
Rhodium (III) Chloride

Rhodium chloride caused a number of aromatizations. First, it will aromatize sulcatone into a single xylene. It also aromatizes both myrcene and citral into a single cymene. These chromatograms can be seen in Figure 61, Figure 62, and Figure 63. It should be understood that the actual catalyst is probably rhodium (III) oxide.
Figure 61: Sulcatone/RhCl₃ chromatogram

Figure 62: Myrcene/RhCl₃ chromatogram
Ruthenium (III) Chloride

Ruthenium, while being about 10 times less expensive than rhodium, reacts in a similar manner. Reactions that worked in the IPRA for rhodium chloride generally worked for ruthenium. This includes reactions such as the aromatizations of sulcatone, myrcene and citral. For sulcatone, the product is formed relatively cleanly, but there is more starting material left over than when rhodium was used. The performance of myrcene was on par with the rhodium. Finally, for citral it appears two cymenes are formed. In this case, rhodium is superior to rhodium. Ruthenium, being a cheaper catalyst, would make for more advantageous reactions if they can be made to work on a larger scale. Work will be done to test both of these catalysts specifically to determine if ruthenium is as robust as rhodium in these reactions.

Figure 63: Citral/ RhCl₃ chromatogram
Figure 64: Sulcatone/RuCl₃ chromatogram

Figure 65: Myrcene/RuCl₃ chromatogram
Another avenue of approach was to use metal-organic frameworks (MOFs) as catalysts. Most MOFs employ oxygen or nitrogen ligation of the metal component, and allows the use of many of our current transition metals but without the presence of chloride. The major question in this approach would be how would MOFs perform using the IPRA? An approach to this was to use common MOFs that are already well known. For this multiple MOF-sulfonated nano-cellulose hybrid derivatives from the Professor Li group at the UT Knoxville Department of Forestry, Wildlife and Fisheries were tested using the standard IPRA technique. All MOFs tested had been coated onto sulfonated nanocellulose fibers. These MOFs included ZiF-6, ZiF-67, HKUST-1, UIO-66, and MIL-100. The structures are shown below in Figure 67.

Figure 66: Citral/RuCl₃ chromatogram

MOF Chemistry

Another avenue of approach was to use metal-organic frameworks (MOFs) as catalysts. Most MOFs employ oxygen or nitrogen ligation of the metal component, and allows the use of many of our current transition metals but without the presence of chloride. The major question in this approach would be how would MOFs perform using the IPRA? An approach to this was to use common MOFs that are already well known. For this multiple MOF-sulfonated nano-cellulose hybrid derivatives from the Professor Li group at the UT Knoxville Department of Forestry, Wildlife and Fisheries were tested using the standard IPRA technique. All MOFs tested had been coated onto sulfonated nanocellulose fibers. These MOFs included ZiF-6, ZiF-67, HKUST-1, UIO-66, and MIL-100. The structures are shown below in Figure 67.
Figure 67: Structures of MOF components used with sulfonated-nano-cellulose

In all cases, these-cello-MOF hybrids were fluffy, low density materials prepared by lyophilization. That meant that only about 10 mg could be packed into the liner without overly compressing the material, which was easily crushed. And unlike our normal inlet materials, these cello-MOFs were extremely easy to pack in such a way that did not allow for proper gas flow. TGA showed that these hybrid materials also had a much lower thermal stability, resulting in inlet temperatures being hard limited to 150°C. From this work, it was determined that there was at least one new reaction that occurs between ZiF-8 and DCKA (Figure 68). The reaction appears to be fairly clean (one major product formed), but (remarkably), rather than the usual rearrangement or fragmentations we expected, it formed a significantly larger product. DCKA (at 7.86 min) has a mass of 112 amu, and the major product's (15.97 min) mass is in excess of 165 amu (Figure 69), the odd mass indicating that it must be a fragment ion. The structures giving the best matches (only ~ 74%) are shown in Figure 68, but it should be understood that neither of these can be the actual product because the unknown compound's mass is > 165. Another challenge found from MOF work is that the materials seem to hold onto injected samples more readily than the typical IPRA catalysts,
and in the case of ZIF-containing MOFs, a broad low peak for 2-methylimidazole (8.9-10.4 min) is observed. This results in tailing and nearly all of the chromatograms having a low abundance for both starting material and potential product peaks. This may be possible to fix using higher temperatures, but the thermal stability of these specific materials, at least with the cellulose component, would not allow that.

Figure 68: Reaction of DCKA with ZIF-8, showing best GC-MS database matching structures

Figure 69: Chromatogram from DCKA passing through s-cello-ZIF-8.
Figure 70: Mass spectrum of major product from passage of DCKA through s-cello-ZIF-8.
IV. Quantitative Results of In-inlet Reactions

The identities of products produced from inlet reactions were not always identifiable using the MS database. In order to fully identify these products, a method for the nondestructive preparation of the product had to be developed.

First Attempt at Product Isolation

Sulcatone gave a clean, seemingly quantitative reaction to make xylene using rhodium chloride. For this reason, it was chosen to be used in attempts to scale up the reaction and eventually isolate the product. Our first attempt was to use a GC injection port connected to a 15 cm metal capillary with the split flow set to zero. With a standard rhodium chloride liner at 250 °C, a 5 µL sulcatone injections was made while the capillary outlet was bubbled through an NMR solvent (DMSO-$d_6$). After bubbling for a few minutes, it was submitted to NMR analysis, but only starting material was present. The failure to react was attributed to severely exceeding the capacity of the small amount (~ 40 mg) of catalyst in the inlet liner.

Utilizing a packed-column GC as a fixed-bed reactor

After considering various way to scale up the process, we decided to investigate the use of a simple packed-column GC (Figure 71) as a fixed-bed flow reactor. The columns of the instrument were stainless steel (1/4” x 4’) and could hold roughly 450 times as much catalyst (~ 17 g) as a GC inlet liner (~ 40 mg). The detector was a non-destructive thermal conductivity detector (TCD), allowing for the products to be both detected and collected after reaction. The only modification necessary was the installation of an outlet heater, if not already present, between the detector and the outlet to prevent condensation of the organic compounds. This was accomplished by inserting a soldering iron heating element behind the insulation and against the metal tubes between the detector and outlet. This was connected to
an external power control and brought to 200 °C as closely as possible. One aspect of GCCR that was not studied in this work is the ability to use nearly any conceivable carrier gas, while GC-MS is practically limited to helium, and GC-FID to inert gases or hydrogen carrier. Thus, reactive gases, even pure oxygen, can potentially be used, though the detector might need to be left off with oxidizing gases.

![Packed column GC used as a fixed-bed flow reactor](image)

**Figure 71: Packed column GC used as a fixed-bed flow reactor**

**Packing Columns with Catalyst**

After removing the chromatography packing, the column was filled with catalyst using a 20 cm x 4 cm metal cylinder with 1/4" pipe threads at each end. This "pressurizable powder funnel" was attached to the empty, tared GC column using standard Swagelok fittings. The outlet of the GC column was fitted with a flow restrictor that allowed gas but not
solids to pass. After adding the dried, free-flowing catalyst to the funnel, it was attached to a compressed air inlet. Then 90 psi of compressed air were applied for about 20 seconds while the column was "banged" to help the material to flow through. Once the pressure had dissipated, the column was carefully removed from the funnel and weighed. This process was repeated until constant weight was obtained, and packing could be observed at both ends of the column. Then about 1 cm of packing was removed from each end and replaced with glass wool. Then the column was installed in the instrument and heated under a flow of helium. If the catalyst was one that evolved HCl, the column was heated to 250 °C until the acid ceased to be evolved.

Acceptable Particle Sizes

We found that the GCCR method was more sensitive to particle size than was IPRA, and that we had to sieve out the finer particles (> 325 mesh) in order to achieve a reasonable gas flow (20 mL/min) with an applied helium pressure of 50 psi. The DE we used had roughly 25 weight percent of particles finer than 325 mesh.

Collecting Products

A major consideration in preparative GC is how to efficiently condense the gaseous organic compounds exiting the instrument. Passage through a simple glass tube will condense about 40% of the material, depending on the boiling point. We have found that condensation by bubbling through an organic solvent is much more efficient. With a 6 cm Teflon® tube connected to the outlet, about 70-80% of the product could be condensed by simply bubbling through 1.5 mL of pentane. An NMR solvent like CDCl₃ or DMSO-d₆ could also be used.

Determining Which Isomer of Xylene was Created in the Sulcatone/RhCl₃ Reaction

Using a 4' column with 10% RhCl₃ on DE packing and helium carrier, and with the column, injection port and detector at 250°C, 10-µL portions of sulcatone was injected and
the outlet gas was bubbled through a vial with 0.5 mL of DMSO-$d_6$. It was observed that products would begin to elute very quickly, within 5-10 seconds, suggesting that the column had very little retention. This could have been anticipated, since chromatography is not occurring. The product was then taken to the NMR, where it was determined that sulcatone gave strictly meta-xylene under these conditions. The likely mechanism is shown below.

![Figure 72: Sulcatone formation of xylene mechanism](image)

The product of 6H2OA was also isolated using this method. Using a 4’ column with 10% CoCl$_2$ on DE packing with helium carrier. The column, injection port and detector were kept at 250°C, and 10-µL portions of 6H2OA was injected and the outlet gas was bubbled through a vial with 0.5 mL of DMSO-$d_6$. The product was then taken to the NMR, where the endo-cyclization product was determined to be the correct product.

**Quantification of GC Inlet Reactions**

The next goal was to determine the amount of conversion that occurred in the inlet reaction method. To do that, the internal standard method was the best approach. This consists of including a non-reactive hydrocarbon standard into the substrate samples. First, a sample that includes weighed quantities of the reactant, product and standard were analyzed using a clean inlet liner. The relative peak areas allowed correction factors to be determined.
Using these correction factors, data from analyses using catalyst-bearing liners allowed for calculation of the amounts of reactants and products present. This allows for calculation of GC yields from this data. The inlet temperatures are easily varied, providing information about the optimal reaction temperatures, which could help guide parameter choices with GCCR. The inlet temperatures were varied from 100°C to 300°C. At the lowest temperature the injected sample does not vaporize as cleanly, resulting in peaks that are much broader than typical. However, at an inlet temperature of 150°C, the chromatogram peaks were nearly as sharp as the higher temperature injections.

Initially, these yield studies did not work as intended. Reactions that had previously occurred at a low catalyst content (5% by weight) were no longer giving clean reactions, and in the worst of cases no reactions were observed. For some metals it was also found that some reactants were entirely retained, i. e., disappeared from the chromatogram. This resulted in multiple runs with only the alkane internal standard visible in the chromatograms. The first attempt at fixing this was to use pure catalyst in the injection port, that is, with no DE support. The conditioning seemed to work, with gas flow evident at 300°C. However, upon installation in the GC-MS, the instrument was unable to hold a constant pressure as time went on. We attribute this to a powdering of the material with time, blocking the flow. Next, the catalyst concentration was made to be 80% by weight. A number of the reactions now worked at this higher metal concentration. The GC yields can be seen in Table 4. In the case of the listed reactions, the product yields tend to vary based on both metal and temperature. In the case of a product forming more than one isomer, only the percent yield strongest peak is listed. Two things stand out. First, in many of these, what appears as a quantitative reaction based on the presence of only a peak for product present, the yields are often low. This means that some process that creates either non-volatile or else high-volatility materials is occurring. Second, each process generally has an optimal temperature, usually 150-250
°C. The exception is sulcatone on cobalt chloride, where the product yield increases with inlet temperature.

Table 4: Multiple temperature product quantification

<table>
<thead>
<tr>
<th>Substrate</th>
<th>3-Carene</th>
<th>3-Carene</th>
<th>Citral</th>
<th>Sulcatone</th>
<th>Sulcatone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metal</td>
<td>MnCl₂</td>
<td>RhCl₃</td>
<td>NiCl₂</td>
<td>CoCl₂</td>
<td>NiCl₂</td>
</tr>
<tr>
<td>100°C</td>
<td>10.6%</td>
<td>30.4%</td>
<td>0.00%</td>
<td>0.00%</td>
<td>0.00%</td>
</tr>
<tr>
<td>150°C</td>
<td>14.0%</td>
<td>65.3%</td>
<td>17.1%</td>
<td>21.7%</td>
<td>0.00%</td>
</tr>
<tr>
<td>200°C</td>
<td>3.4%</td>
<td>69.6%</td>
<td>40.0%</td>
<td>40.4%</td>
<td>0.00%</td>
</tr>
<tr>
<td>250°C</td>
<td>0.9%</td>
<td>6.51%</td>
<td>40.0%</td>
<td>34.6%</td>
<td>29.0%</td>
</tr>
<tr>
<td>300°C</td>
<td>1.0%</td>
<td>0.00%</td>
<td>31.2%</td>
<td>89.3%</td>
<td>27.1%</td>
</tr>
</tbody>
</table>

Attempts at Measuring Turnover Numbers

A question not answered in determining the yields of reactions: is the reaction actually catalytic? While the entire injection passes through the catalyst, before any of it reaches the split flow, there is still a large excess of catalyst relative to reactant. Using a typical example of the IPRA studies, as used in the GC yield work, a 5 mg per mL sample will have a concentration of approximately 0.03 M (assumes a MW of 150 amu). A 1 µL injection will contain about $3 \times 10^{-5}$ mmols. Using 5 wt% metal on DE (corresponds to about 10 wt% with ligands included) and a metal MW of 60 amu, there would be about 0.03 mmols of metal present in the liner. Thus, the liner contains about a thousand times more metal than organic substrate being injected. This makes it difficult to determine if the material is catalytic, and if so, what turnover numbers might apply. The amount of catalyst in the liner
was not further decreased in order to ensure the reaction would occur as completely as possible. The lowering of catalyst wt% to something such as 1% or 0.1% was thought to allow too much of the unreacted starting material through. In an attempt to get such information under IPRA conditions, the concentration of the substrate was increased to 20 mg per mL. This reduced the stoichiometric amount to about 250 injections. It was deemed less suitable to reduce the metal concentration or to increase the injection volume. This was studied using the 6H2OA reaction on a 5 wt% cobalt chloride liner previously described. It was found that around 220 injections would exceed the stoichiometric amount of catalyst, so 250 back-to-back autosampler injections were planned to determine if the catalyst would continue to function past that stoichiometric point.

![Figure 73: First injection used to determine catalytic activity](image)

**Figure 73: First injection used to determine catalytic activity**
It was determined that the product did form under these conditions in all injected samples. However, there was an unidentifiable peak of the same mass (140 amu) that appeared only in these analyses. It occurs a few minutes later than the cyclic product and, in many cases, there is a tail connecting the two peaks (suggestive of an equilibrium). It was speculated that the second peak had an exocyclic double bond, a precursor of the major product, due to the similarity of the mass spectra. However, this minor structural difference is not expected to make such a large difference in retention time. Thus, cobalt chloride does seem to be a true catalyst in this reaction. However, using this approach is generally untenable. The initial goal was to keep injecting until the catalyst stopped working; however, even going a little past the stoichiometric point in this experiment took nearly 3 days to complete the runs. It was determined that dedicating the GC-MS to doing this type of work was not desired at this time.

**Vial Reactions**

Another goal was to make progress in moving the reactions observed in the IPRA studies to a more conventional reaction medium. While the GCCR work does a good job at getting enough product for immediate studies, it would be more convenient to make the
products on a larger scale. Some attempts were made to accomplish the reactions in vials. A vial reaction could produce hundreds of milligrams of the product at once. The first work was done using 1-dram vials that were inserted into the top of an oven through holes that were drilled for this purpose. In this work both the cyclization of 6H2OA and the formation of cymene from 3-carene were studied. It was important that the vial's caps were not subjected to the full heat of the reaction, otherwise they would leak. So, we used cardboard spacers to keep the caps above the oven surface. While the caps would still become warm outside of the oven, the seal was not compromised by that increase in temperature. Catalysts without diatomaceous earth support and reactant were placed in the vial together for a day at 140°C. A sample was then analyzed using GC-MS. The reaction, however, contained only starting material. In order to test the reaction at higher temperatures a different set up had to be used. For this a stir bar was added to the vial and the vial was placed in an aluminum bead bath for a day. It was found that reactions would proceed further at higher temperatures, but the heating of the vial seemed inconsistent. In all cases the use of this type of heating resulted largely in starting material. Even reactions that appeared to fully react under IPRA conditions would contain mostly starting material. Ultimately as the temperatures increased the vials caps would not be able to hold in the solvent vapor. A solution to the inconsistent heating/sealing was to use a GC oven as the heating unit. A beaker was used to contain the sample, so the convection oven does not cause the vial to thrash about in the oven. This did not help with the sealing issue, however. The solution best found for that was to seal the reaction into an ampule under vacuum.

**Ampule Reactions**

The reactions consisted of a vacuum-sealed ampule that contained a few hundred milligrams of reactant and 10 mol percent of catalyst. The GC oven was able to provide precise temperatures and even gives a programable temperature ramp up and down in order to
prevent thermal shock from bursting the ampule. In one case where a temperature ramp was not used, an ampule did shatter violently. The contents of the ampule can then be tested using GC-MS to determine whether the reaction had occurred. It was found that these reactions did occur in a similar way to IPRA studies, but in general less cleanly. It is likely that the use of higher temperatures for longer times is what results in the undesired side reactions. Including in one case using 6H2OA and CoCl$_2$ it was found that not only does high temperature not favor the ring formation nearly as cleanly, the catalyst also underwent an irreversible color change from blue to green. Another indication that a reaction is occurring during the 6H2OA study is that the catalyst would dissolve in the starting material but is insoluble in the product. In Table 5 it can be seen that those higher temperatures will eventually kill the reaction. In the case of 3-carene, it was found to form two products that both correspond to a cymene when using RhCl$_3$ that is coated 10% on DE. In the case of 6H2OA, the time for the reactions was a similar 4 hours, but the time was varied with 3-carene.

Table 5: Ampule reaction completion for a. 6H2OA for 4 hrs b. 3-carene varied time

<table>
<thead>
<tr>
<th>Temperature (°C)</th>
<th>Percent of Product</th>
<th>Time (hrs)</th>
<th>Percent of product A</th>
<th>Percent of product B</th>
</tr>
</thead>
<tbody>
<tr>
<td>350</td>
<td>0.05</td>
<td>24</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>300</td>
<td>1</td>
<td>24</td>
<td>6</td>
<td>18</td>
</tr>
<tr>
<td>250</td>
<td>28</td>
<td>36</td>
<td>18</td>
<td>38</td>
</tr>
<tr>
<td>200</td>
<td>73</td>
<td>24</td>
<td>17</td>
<td>51</td>
</tr>
<tr>
<td>150</td>
<td>68</td>
<td>36</td>
<td>25</td>
<td>34</td>
</tr>
</tbody>
</table>

Ampule reactions provide enough product that purification techniques, such as radial chromatography, can be used to isolate pure materials. This is especially useful for products needed in pure form for GC correction factor purposes.
V. Experimental

General

All reactants and reagents not specifically listed were purchased from Sigma-Aldrich, Acros Organics, Fisher, TCI America, Beantown Chemical and other common vendors. Unless otherwise noted these materials were used with no further purification. The gooseneck, single-taper glass inlet liners (6.3 mm OD, 4.0 mm ID, 78.5 mm length) were purchased from Trajan Scientific (#092223). The deactivated glass wool, used in the inlet liners, was bought from Restek. Diatomaceous earth (24 lbs) was purchased from Leslie’s pool supplies. DiatoSorb® (Reztek #25670 100/200 mesh range) was bought and used as received from Restek. Solvents were used as received unless otherwise noted. Hexanes and ethyl acetate were distilled through a three-stage Snyder column to remove any non-volatile materials. Proton NMR spectra were obtained with a JEOL 400 MHz spectrometer, with chemical shifts referenced to internal TMS (where possible) or to residual NMR solvent signals.

Gas chromatography-mass spectrometry was done using a Hewlett-Packard GCD (HP 5890 equipped with a 5972-mass spectrometer). The column used in the early work was a 12 m x 0.2 mm Restek Rti-5ms with a film thickness of 0.33 µm using helium carrier at 10 psi. This was later replaced by a 20 m x 0.15 mm Restek Rxi-5Sil MS with a film thickness of 0.15 µm using helium carrier at 15 psi and a 40:1 split ratio. In both cases, unless otherwise stated, the inlet temperature was 250°C and the detector temperature was 280°C. Packed column work was done using a GOW-MAC 69-350 equipped with a thermal conductivity detector and an after-market outlet heater. The carrier used for the work described here was helium, but could be varied to include hydrogen, nitrous oxide, carbon monoxide, oxygen, and even a 4% ozone/oxygen mixture. The flow rate was adjusted to be 20 mL/min. The
columns lengths were between 1 to 4 ft. The columns were made out of ¼ in stainless steel and were formed to fit the instrument oven from curved metal tubing.

**Solid Support DE**

Pool-grade diatomaceous earth (DE), 250 mL, was added to a 1000 mL Erlenmeyer flask. This material was acid washed using 200 mL of 6 M HCl. This was well-mixed then allowed to stand for 2 hours with the flask covered. The mixture was then filtered through a 600 mL fritted funnel and washed with DI water until the filtrate was no longer acidic. This DE was oven dried until the material remained at a constant weight.

**General IPRA Catalyst Preparation**

Where possible, transition metal catalysts were first dissolved in methanol prior to addition of the DE support. In the rare cases where the solid did not fully dissolve, small amounts of water could be added until dissolution occurred. In the worst cases (V₂O₅), pure water can be used with significant difficulty in removing the solvent by rotary evaporation. The amount of transition metal used varied based on the use. For general qualitative work, the material is 10% by weight of catalyst/support, including any water of hydration. For quantitative work this can go as high as 80% catalyst/support by weight. After the material is dissolved, the support is added to the flask. Solvent was then removed by rotary evaporation, which allows for fairly even coating. The flask is allowed to spin before the vacuum is applied. This helps to break up large clumps of the Celite in the flask, then solvent was removed by rotary evaporation using a dry ice condenser. After this, the material was dried under pump vacuum (< 2 mmHg) until constant weight was achieved. This dry material is then typically sieved to a mesh range of 100 to 325.
**General Injection Solutions**

All substrates were diluted for GC analysis to 5 to 10 mg/mL with either pentane or hexane. Generally, the solutions should skew towards the lower end as the column on the GC-MS will overload (front) easily even at these concentrations with a 40:1 split flow. Authentic product injected through a clean liner was used to determine retention times for each product, reactants, and standards as a second way to be able to determine peak identity, especially in the case of compounds not in the GC-MS database.

**Silylation of Inlet Liners**

First the liners were cleaned using a bath of 1M hydrochloric acid in a covered beaker for at least 8 hours. If the solution was deeply colored, then this process could be repeated. Then the liners were washed with water then methanol and dried. The now activated glass liner must then be placed in another small sealable jar and covered with 10% dimethyldichlorosilane in toluene. It is left in this bath for at least 8 hours before it is removed and washed with toluene then methanol.

**Synthesis of IPO**

Isophorone (0.20 mol) were added to a 500 mL flask with a stir bar. A thermocouple was also used to determine the internal temperature of the flask. Then 0.6 moles of 30% hydrogen peroxide were added to the flask along with 200 mL of methanol. The flask was cooled to between 15 to 20°C using an ice bath. Then 0.10 moles of 6 M NaOH was added dropwise over the course of a few minutes. After the addition was complete the reaction was allowed to stir for 3 hours. The final product was extracted using two 200 mL portions of ether and an equal amount of water. After drying and concentration, the product was isolated by vacuum distillation (bp 70 °C at 5 mmHg).
Synthesis of 4,4-dimethyl-6-heptyn-2-one (6H2O)

Isophorone oxide (7.71 g, 50 mmol) was measured in a tared graduated cylinder, poured into a 100 mL round bottom flask with a stir bar and rinsed in with 30 mL of ethanol. Then p-toluenesulfonylhydrazide (8.76 g, 50.9 mmol, 1.02 equiv) was added, and the flask equipped with a septum-sealed condenser. This mixture was placed under inert atmosphere using two vacuum/N₂ cycles through a 27-gauge needle, then heated in an oil bath. Nitrogen evolution began very early in the heating process, and the heterogeneous mixture was equilibrated at ~ 65 °C in a water bath and was kept at this temperature until the solution began to clear. The flask was refluxed briefly (bath temperature 100-105 °C) then allowed to cool to room temperature. Ethanol was removed by rotary evaporation, during which time a yellow solid might form. This was filtered off and rinsed well with hexanes, then the filtrate was concentrated by rotary evaporation. Kugelrohr (bulb-to-bulb) distillation provided the product (3.4 g, 24 mmol, 49%) as a colorless liquid.

Synthesis of 4,4-dimethyl-6-heptyn-2-ol (6H2OA)

To a 100 mL recovery flask, 4,4-dimethyl-6-heptyn-2-one (6H2O, 8.736 g, 62.3 mmols) along with 36 mL of methanol and a stir bar. The flask was placed in a water bath with stirring and sodium borohydride (600 mg, 15.8 mmols) was added over the course of 5 minutes. TLC was preformed and the solution was allowed to react until the ketone disappeared. The product was then extracted using a saturated sodium chloride solution and two hexane washes in a separatory funnel. The hexane layer was then dried with magnesium sulfate. The dried product was then concentrated using rotary evaporation, then brought to constant weight under aspirator vacuum (~ 35 mmHg) to give 4,4-dimethyl-6-heptyn-2-ol (7.70 g, 55.7 mmols, 89%) as a colorless oil. This was determined to be pure by GC-MS.
Synthesis of myrcene epoxide

To a 1-dram vial myrcene (1.0052 g, 7.7 mmols) was added with a flea stir bar. Then 19.2 mg (1 mol%) of methylrhenium trioxide was added to this vial with 71 µL of pyridine. The vial was placed in a water bath to prevent possible exotherm. Then 1.5 eq (1.135 mL; 30%) of hydrogen peroxide was then added to this vial over the course of a few minutes. The reaction was a pale-yellow color during the reaction. The reaction was allowed to progress for a few days. The reaction was checked for completion using TLC, using 5% ethyl acetate in hexanes. After determining there was no further starting material, the solution was worked up with water and hexanes. The dried hexane phase was removed by rotary evaporation. Purification was done using radial chromatography on a silica plate with a solvent gradient of 5 to 15% ethyl acetate in hexanes. The product was characterized by GC-MS. The MI does not show up, and the base peak is 79 m/z.

Synthesis of Cyclooctadiene Epoxide and Diepoxide

Similar to the synthesis of myrcene epoxide above, 1,5 cyclooctadiene (1.0155 g) was added to a 1-dram vial with a flea stir bar. Then 1 mol% of methylrhenium trioxide (24 mg, 0.093 mmol) was added to this vial with 0.12 equiv (89.8 µL) of pyridine. The vial was placed in a water bath to prevent possible exotherm. Then 1.5 eq (1.43 mL) of 30% hydrogen peroxide was then added to this vial over the course of a few minutes. The reaction was allowed to progress for a few days. The reaction was checked for completion using TLC using 5% ethyl acetate in hexanes. After determining there was no remaining starting material, the solution was worked up with water and hexanes. The hexane was removed by rotary evaporation. Purification was done by using radial chromatography on a silica plate. The solvent gradients were 5, 10, and 15% ethyl acetate in hexanes. The product was characterized using GC-MS. The monoepoxide came out earlier than the diepoxide (8.88
min vs 12.05 min) The mono had a base peak of 41 while the diepoxide had a base peak of 67, though the 67 m/z peak was strong in both mass spectra. The molecular ion was weak for both of these peaks.

**Synthesis of DCPO1, DCPO2, and DCPDE**

Again this synthesis was done like above, dicyclopentadiene (1.0055 g) was added to a 1-dram vial with a flea stir bar. Then 1 mol% of methylrhenium trioxide (19 mg, 0.076 mmol) was added to this vial with 0.12 equiv (89.8 µL) of pyridine. The vial was placed in a water bath to prevent possible exotherm. Then 1.5 eq (1.43 mL) of 30% hydrogen peroxide was then added to this vial over the course of a few minutes. The reaction was allowed to progress for a few days. The reaction was checked for completion using TLC using 5% ethyl acetate in hexanes. After determining there was no remaining starting material, the solution was worked up with water and hexanes. The hexane was removed by rotary evaporation. Purification was done by using radial chromatography on a silica plate. Both of the two monoepoxides and the diepoxide were easily separable. The solvent gradients were 5, 10, and 15% ethyl acetate in hexanes. The product was characterized using GC-MS.

**Removal of water from Rhodium Chloride**

An inlet liner was packed with 5% RhCl₃ on DiatoSorb® making a 10-11 mm column of catalyst (36.7 mg) between two glass wool plugs. This liner was placed in a screw-top tube with a septum cap, and about 100 µL of oxalyl chloride was syringed directly into the inside of the liner, soaking the entire packing. No obvious gas evolution or change of color of the RhCl₃ was noted. The tube was warmed a little, and after approximately 10-15 minutes aspirator vacuum was applied until well after all liquid seemed to be gone. Then the tube was filled with nitrogen and the liner, still the pink-orange-red of the RhCl₃, was placed into the conditioning GC injection port. Gas flow was verified, then checked for acid: very little was observed. Warmed gradually to 105 °C, checking for acid exiting the column: very little acid
was present, quite unlike the normal RhCl₃ conditioning. The color also remained more red. The temperature was raised to 250 °C and held there for 60 minutes, with no acid evolution noted. The liner was cooled and stored in a sealed tube until use.
Reference list


(8) Duplicate of reference 7.


