PREPARATION AND APPLICATION OF CATALYSTS FOR THE STEREOSPECIFIC REDUCTION AND PHOTOOXYGENATION OF OLEFINS IN CONTINUOUS OPERATIONS: A NOVEL METHOD FOR THE PRODUCTION OF ARTEMISININ

Daniel C. Fisher
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PREPARATION AND APPLICATION OF CATALYSTS FOR THE STEREOSELECTIVE REDUCTION AND PHOTOOXYGENATION OF OLEFINS IN CONTINUOUS OPERATIONS: A NOVEL METHOD FOR THE PRODUCTION OF ARTEMISININ

A dissertation submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy at Virginia Commonwealth University

By

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2017
ACKNOWLEDGEMENTS

I would like to express my sincere gratitude to:

My advisor, Dr. Frank Gupton, who has challenged and guided me through this journey, affording me opportunities to collaborate with industrial partners and pursue philanthropic research.

Dr. Katherine Belecki, who served as an invaluable mentor, teaching me the fundamentals of conducting bench chemistry and providing me with the wisdom necessary to overcome obstacles.

Dr. Carlos Costano, for his help on solid surface characterization.

Dr. Daniel DiRocco, Dr. Francois Levesque and Michael Shevlin for their assistance and tutelage during my visits at Merck & Co.

Dr. Melissa Herbage, Dr. Carl Busacca, Dr. Jon Lorenz and Dr. Chris Senanayake for their guidance and support while working with Boehringer – Ingelheim.

My colleagues and lab mates at VCU for their friendship, encouragement and insights throughout our years together in the trenches.

My family and friends, who have inspired and cared for me along the way, especially my mom and dad.

Lastly, I would like to thank my wife, Allison, who has shared her ear, mind and heart as we have walked this circuitous road together, hand-in-hand. She, along with our devoted dogs, Brady and Finley, have consistently reminded me of all that is true, all that is lovely and all that is good. To them, I dedicate this work.
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APIs – active pharmaceutical ingredient
CPM – continuous pharmaceutical manufacturing
PAT – process analytical technology
ITNs – insecticide-treated nets
IRS – indoor residual spraying
RDTs – rapid diagnostic testing
ACTs – artemisinin-based combination therapy
WHO – World Health Organization
QAACT – Quality-Assured ACTs
GDP – gross domestic product
FPP – farnesyl diphosphate
ADS – amorphadiene synthase
Cu(OTf)$_2$ – copper (II) trifluoroethanesulfonate
t-BuOH – tert-butyl alcohol
TsOH – p-toluenesulfonic acid
TFA – trifluoroacetic acid
FDA – Food and Drug Administration
DIPAMP – 1,2-bis((2-methoxyphenyl)(phenyl)phosphaneyl)ethane
DIOP – 2,3-O-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane
BINAP – 2,2’-bis(diphenylphosphanyel)-1,1’-binaphthalene
AIBN – 2,2’-azobis(2-methylpropionitrile)
COD – 1,5-cyclooctadiene
HTE – high throughput experimentation
DPEN – (R,R)-diphenylethylenediamine
CPG – controlled pure glass
PTA – phosphotungstic acid
Me-Duphos – (-)-1,2-Bis[(2R,5R)-2,5-dimethylphospholano]benzene
BIPI – Boehringer – Ingelheim phosphinoimidazoline
DABCO – 1,4-diazabicyclo[2.2.2]octane
TEA or NEt₃ – triethylamine
DMAc – dimethylacetamide
EtOAc – ethyl acetate
DCM – dichloromethane
DMSO – dimethyl sulfoxide
PhMe – toluene
n-PrOH – n-propyl alcohol
BARF – tetrakis(3,5-bis(trifluoromethyl)phenyl)borate
BOC – tert-butylxycarbonyl
CBZ – carboxybenzyl
Ac – acetyl
Cy – cyclohexyl
GO – graphene oxide
BOC₂O – di-tert-butyl dicarbonate
iPrOH – isopropyl alcohol
EDC – N-{3-Dimethylaminopropyl}-N'-ethylcarbodiimide hydrochloride
HOBt – 1-hydroxybenzotriazole hydrate
DIPEA – N,N'-diisopropylethylamine
DCC – N,N'-dicyclohexyld carbodiimide
THF – tetrahydrofuran
SEM/EDX – scanning electron microscope/energy dispersive x-ray spectroscopy
NBD – norbornadiene
XPS – X-ray photoelectron spectroscopy
FTIR – Fourier transform infrared spectroscopy
XRD – X-ray diffraction
ICP-OES – inductively coupled plasma optical emission spectrometry
NMR – nuclear magnetic resonance
DMF – dimethylformamide
MeOH – methanol
HPLC – high pressure liquid chromatography
TON – turnover number
HOSA – hydroxylamine-O-sulfonic acid
GC – gas chromatography
EtOH – ethyl alcohol
TFE – 2,2,2-trifluoroethanol
iPrOAc – isopropyl acetate
MEK – methyl ethyl ketone
MIBK – methyl isobutyl ketone
2-Me-THF – 2-methyltetrahydrofuran
CPME – cyclopentyl methyl ether
DME – 1,2-dimethoxyethane
PhCF₃ – trifluorotoluene
PhCl – chlorobenzene
DCE – 1,2-dichloroethane
CSTR – continuous stirred tank reactor
DOE – design of experiment
STY – space-time-yield
TPP – tetraphenylporphyrin
LED – light emitting diodes
DCA – 9,10-antracenedicarbonitrile
scCO₂ – supercritical carbon dioxide
RB – rose bengal
PFD – perfluorodecaline
AcOH – acetic acid
MeSO₃H – methanesulfonic acid
TCA – trichloroacetic acid
BPR – back pressure regulator
ETFE – ethylene tetrafluoroethylene
HOMO – highest occupied molecular orbital
LUMO – lowest unoccupied molecular orbital
DHAA – dihydroartemisinic acid
Abstract

PREPARATION AND APPLICATION OF CATALYSTS FOR THE STEREOSPECIFIC REDUCTION AND PHOTOOXYGENATION OF OLEFINS IN CONTINUOUS OPERATIONS: A NOVEL METHOD FOR THE PRODUCTION OF ARTEMISININ

A dissertation submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy at Virginia Commonwealth University

By Daniel C. Fisher, Ph.D.
Virginia Commonwealth University, 2017

Advisor: Dr. B. Frank Gupton, Professor of Chemistry, Professor and Chair of Chemical and Life Science Engineering

Over the last two centuries, the discovery and application of catalysts has had a substantial impact on how and what chemicals are produced. Given their broad significance, our group has focused on developing new catalyst systems that are recoverable and reusable, in an attempt to reduce concomitant costs.
Our efforts have centered on constructing a recyclable chiral heterogeneous catalyst capable of effecting asymmetric hydrogenations of olefins with high stereoselectivity. A class of phosphinoimidazoline ligands, developed by researchers at Boehringer-Ingelheim, known as BIPI ligands, have proven efficacious in the asymmetric reduction of alkenes.\textsuperscript{2-6} However, these chiral ligands are homogeneous and coordinated to precious metals, rendering them irrecoverable and expensive. To address these issues, our group has derivatized the BIPI ligand-metal complex and immobilized it to the surface of graphene oxide as well as polystyrene. Their efficacy and recyclability toward the asymmetric hydrogenation of a functionalized olefin have been evaluated.

Another facet of our work has included developing a cost effective synthetic process to artemisinin, the gold standard drug in the treatment of malaria.\textsuperscript{7-9} As a natural product, artemisinin’s worldwide supply remains highly unpredictable, contributing to great price volatility.\textsuperscript{10,11} Combining the benefits of catalysis and the advantages of continuous flow chemistry, our research has sought to develop an economical approach to convert a biosynthetic precursor, artemisinic acid, to artemisinin in three chemical transformations.

High-throughput experimentation allowed us to screen a prodigious number of catalysts and identify those effective in the asymmetric hydrogenation of artemisinic acid to dihydroartemisinic acid, the first step in the transformation. This screening directed us to an inexpensive, heterogeneous ruthenium catalyst. The second step of the process includes the photooxygenation of dihydroartemisinic acid, which involves photochemically generated singlet oxygen. We have evaluated
a commercially available heterogeneous photocatalyst packed in a transparent bed, surrounded by light emitting diodes in the continuous photooxygenation of dihydroartemisinic acid to dihydroartemisinic acid hydroperoxide. The third and final step, an acid induced hock cleavage, initiates an intricate cascading reaction that installs an endoperoxide bridge to deliver artemisinin. Our process afforded a 57% yield from dihydroartemisinic acid to artemisinin.
CHAPTER I
INTRODUCTION

1.1 Catalytic reactions

“Catalysis is the science or technology of influencing the rates of chemical reactions.” Affecting the kinetics of a chemical reaction can seemingly affect the outcome of that reaction, as catalysis can assist in yielding products that would otherwise be inexpedient or uneconomical to generate in their absence.

The word catalysis is rooted in the Greek words *kata*, which means *down*, and *lyein*, which translates to *loosen*. J.J Berzelius first used the term during a 1835 presentation at the Stockholm Academy of Sciences to describe the decomposition of bodies and the formation of new ones as a result of certain forces he described as catalytic.

Catalysts work by offering a chemical reaction a different, more efficient mechanism or pathway to transform reactants to products. They alter the kinetics of a reaction without themselves being expended by the reaction or affecting the reaction equilibrium. As a result, catalysts lower the activation energy ($E_a$) of the reaction or increase the frequency factor ($A$), which are parameters included in the Arrhenius equation (Equation 1), a formula used to describe temperature dependence on reaction rates.

$$k = Ae^{-E_a/RT}$$

*Equation 1. Arrhenius equation*
Since the catalyst is regenerated throughout the reaction, a small amount of catalyst can convert a large quantity of reactant to product. Thus, catalysts can be thought of as "super-stoichiometric." The most common materials used as catalysts include: metals, oxides and sulfides. Catalysts can be assembled to selectively interact with a specific substrate. Substrate specificity can be accomplished by constructing catalysts with different ligands, creating a host of catalysts with a diverse range of geometrical confirmations.

Over the last two centuries, the discovery and application of catalysts has had a substantial impact on how and what chemicals are produced. As certain reactions have become feasible with the aid of catalysts, scientists have discovered new synthetic processes to manufacture a plethora of novel materials. The production and availability of commodity chemicals, polymers, petrochemicals, biofuels and pharmaceuticals have all increased as a result of their use. This, in turn, has had far reaching impacts on our society. Businesses have benefitted from the cost reduction, time savings and decrease in waste generation. Catalysis has also supported more environmentally sound production methods by mitigating energy consumption, waste and the overall carbon-footprint, all while augmenting product yields. Additionally, enantioselective catalysis have rendered optically pure materials more accessible, which has minimized the use of kinetic or chiral resolution steps. For this reason and others, catalysts arguably represent the greatest technological innovation for organic reactions. Accordingly, the significance of catalysis in the scientific community and beyond has been recognized
numerous times through the awarding of Nobel Prizes in Chemistry for work done in this area.

Today, catalysts have become fundamental for the manufacture of essential chemicals.\textsuperscript{15} In 2011, it was estimated that over 90\% of all industrial chemicals were produced catalytically, equating to a market value of approximately 900 billion dollars.\textsuperscript{1,16} “Catalysts unequivocally impact a sizable fraction of any nation’s gross domestic product.”\textsuperscript{1} Consequently, the worldwide demand for catalysts is significant; approximately 850,000 tons were used in 2007 with that number projected to increase by 4\% annually.\textsuperscript{16} As a result, entire industrial companies have emerged to manufacture and sell these value-added chemicals.\textsuperscript{1}

1.1.1 Heterogeneous catalyst systems

As mentioned, catalysts participate in chemical transformations by changing the path of the reaction without themselves being consumed. While in theory this holds true for homogeneous catalysts, homogeneous catalysts exist in the same phase as the reactants, and therefore practically are “consumed” as they are often expended after a reaction due to the challenges associated with separation and recovery. Heterogeneous catalysts, conversely, are catalysts that exist in a different phase from the reactants. These insoluble catalysts, consequently, are much easier to retrieve through simple filtration or centrifugation.\textsuperscript{17} They are also more stable and thus easier to handle.\textsuperscript{18} These inherent properties offer many economic benefits. Transition metal catalysts tend to be expensive.\textsuperscript{19} The increased ease of
recovery more readily facilitates reuse, which ultimately reduces process costs by improving atom economy.

Transition metals also tend to contaminate reaction products. Transition metals also tend to contaminate reaction products. Heterogeneous catalysts can circumvent the high-priced, laborious separation techniques (to remove the toxic residual metals) that are often associated with homogeneous catalyst use. Given the strict governmental regulations that demand very high product purity, particularly in the pharmaceutical industry, the ability to more facilely and adequately separate heavy metal catalysts from the product is of great value.

It is well established that "recovery and reuse of catalysts is crucial in organic synthesis not only form an economical aspect but also from an environmental point of view." As a result of their fundamental properties, heterogeneous catalysts have received significant attention for their economic, environmental and operational advantages. Accordingly, these systems possess a broad range of industrial applications in the manufacture of fine chemicals, such as pharmaceuticals and agrochemicals.

For over two centuries, heterogeneous catalysts have consciously been a part of chemists' proverbial toolboxes. Their incorporation into chemistry dates back as early as 1834 when Michael Faraday experimented with platinum plate to combine gaseous hydrogen and oxygen. Extending well into the nineteenth and twentieth centuries, heterogeneous catalysts facilitated the development of some historical processes. These processes included Fritz Haber’s preparation of ammonia from nitrogen and hydrogen via reduced magnetite, as well as Wilhelm
Normann's conversion of oils, fats and waxes into edible foodstuffs via hydrogenation with nickel powder. Other landmark processes achieved by heterogeneous catalysis include the commencement of catalytic cracking, which converted sizable petroleum molecules to small hydrocarbons in the presence of acid-treated clays and zeolites, as well as Karl Ziegler's and Giulio Natta's discovery and use of titanium-based catalysts to advance polymerization chemistry.\textsuperscript{25}

Within synthetic organic chemistry, the processes that involve heterogeneous catalysis are numerous. These include: acid-base mediated reactions, cross coupling reactions, oxidations, and hydrogenations.\textsuperscript{17} Attracted to heterogeneous catalyst’s ability to reduce waste, remove hydrolytic work-up steps and mitigate safety risks, synthetic organic chemists have sought to replace homogeneous catalysts wherever feasible. For example, in acid-mediated reactions, some corrosive mineral or Lewis acids have been exchanged for solid-acid catalysts like acidic clays, zeolites and sulfonated polysiloxanes. These materials also favor greener approaches to electrophilic aromatic substitution reactions, Friedel-Crafts alkylations and acylations as well as various cyclization and rearrangement reactions. Likewise, solid-base catalysts such as hydrotalcite anionic clays and mesoporous silicas have demonstrated sufficient activity to supplant organic bases in aldol condensation reactions. In oxidation reactions, processes that use molecular oxygen or hydrogen peroxide in combination with a heterogeneous catalyst have in some cases replaced procedures that utilize stoichiometric quantities of an inorganic oxidant like chromium trioxide. Examples of olefin
metathesis, Heck, Suzuki and other related couplings involving heterogeneous catalysts are also prevalent.\textsuperscript{17,26}

Heterogeneous catalysts exist in two principle forms: supported or unsupported. Raney nickel is an example of an unsupported catalyst; the product is formed by removing a portion of aluminum from an aluminum-nickel alloy. Conversely, supported catalysts are comprised of chemically inert, insoluble substances that anchor metalled molecules or electrostatically retain deposited metals or metal-ligand complexes. The most commonly used supports include: carbon, graphite, alumina, polystyrene and inorganic salts. (An elaborate discussion on metal-ligand complexes covalently and noncovalently immobilized onto insoluble supports will be presented in section 2.1.2).

In general, electrostatically supported metal catalysts consist of metal particles that are highly dispersed onto porous materials possessing high surface areas, commonly deposited as nanoparticles. They can exist in their oxidized or reduced form with the oxidation state contingent on the method of catalyst preparation. The particles can merely coat the surface or they can invade the micropores of the support. Systems where the particles remain on the surface are referred to as eggshell, while those that penetrate the cavities are classified as uniform. The surfaces of metal supported catalysts are characterized as random, dynamic structures; the metal clusters interact with the reaction medium, desorbing from the surface and redepositing in other areas on the support.\textsuperscript{27}

In reactions involving these heterogeneous catalysts, the adsorption of chemicals onto the catalyst occurs in two steps: physisorption followed by
chemisorption. In the first stage, physisorption, van der Waals forces of attraction between the substrate and the catalyst surface draws the adsorbate (substrate) into closer proximity to the catalyst surface. In the second stage, chemisorption, chemical bonds are formed between the adsorbate and the catalyst. In some cases, chemical bonds within the adsorbate are later broken as a result of its interaction with the catalyst. Regardless of the transformation at hand, effective metal supported catalysts often demonstrate a combination of: high activity, high selectivity, rapid filtration, facile recoverability and good recyclability. In many instances, the ability to attain these outcomes greatly depends on the metal and the solid support. The metal influences the strength of the adsorption of the reactants and the rate of desorption of the products.  

1.1.1.1 Immobilization of molecules onto solid supports

Driven by the desire to increase process efficiency and lower costs, chemists in the 1960s began envisioning what it may look like to combine the superior stereoselectivity and activity traditionally provided by homogeneous catalysis with heterogeneous catalysis’ ease of handle, separation and reuse. The result: the immobilization of metal-ligand complexes to insoluble supports. Initial work focused on achiral ligands, though research has since extended to chiral ones. (Chapter 2 will focus on the immobilization of chiral ligands for a specific application: asymmetric hydrogenation.) While interest to combine the best of both worlds has fluctuated over the past fifty years, the chemistry behind the
immobilization of homogeneous catalysts onto insoluble supports has advanced to the point that solid phase catalysis is nearly industrially relevant.  

Solid supports used in the formation of these heterogeneous catalysts have tended to be well-defined, inert and mechanically stable, possessing a large surface area with reactive sites to sufficiently attach ligand-metal complexes.  

Several organic polymers and inorganic supports fit this description. Organic polymers utilized for anchoring ligands include dendrimers, polystyrene and polyacrylates. Studies have shown that the reaction rates of polymer bound catalysts are generally higher than those analogous catalysts on inorganic supports.  

In contrast, inorganic supports include amorphous oxides such as alumina, zirconia and silica, inert porous materials with high surface areas. Compared to polymers, the rigid structures of inorganic supports prevent aggregation of the catalysts, are impervious to swelling, and possess enhanced stability when subjected to harsh reaction conditions.  

Silica is a common inorganic support due to thermal and chemical stability, and modification versatility. Silica resists swelling when immersed in solvent, is inflexible and non-compressible, characteristics that render it amenable to continuous flow chemistry. Its inflexibility also provides greater control of ligand loading, resulting in improved site isolation, as compared to polymers.  

Since its inception, three different strategies to immobilize catalysts to heterogeneous supports have been developed. These approaches include: the formation of a covalent bond between support and ligand, noncovalent attachment,
which contain adsorption and ion-pair formation, and entrapment methods (Figure 1). \textsuperscript{18, 30}

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\textbf{Figure 1.} Strategies for immobilizing homogeneous ligands to the surfaces of insoluble supports

Covalent immobilization is a commonly used strategy with a broad scope given that it can be used to anchor ligands to organic polymers and inorganic supports, and that the connection is stable to most solvents.\textsuperscript{18} This method of attachment is achievable either through copolymerization of functionalized ligand with an appropriate monomer or by reacting a functionalized ligand with the reactive site on a preformed solid support such as polymers, inorganic oxides or nanotubes.\textsuperscript{18, 28} Covalently tethering ligands onto functionalized polymers originated from Merrifield’s solid-phase peptide synthesis work in the 1960s.\textsuperscript{28} Since then, various functionalized polymers have been used to anchor ligands in addition to Merrifield’s resin. Some examples include: JandaJEL, TentaGel and other PS-PEG resins. While both strategies are efficacious, the advantage to copolymerization are the diverse polymeric ligand libraries that can easily be
amassed by reacting vinyl-modified ligands with a broad range of suitable monomers, such as styrene or divinylbenzene via radical polymerization. As mentioned, homogeneous ligands have also been attached to inorganic supports. These materials include: zeolites and other mesoporous materials, such as MCM-41 (mobile crystalline material) and carbosil, a nonporous silica. The functionalized ligands, which are usually modified to contain a pendant alkoxy silane group, serving as a spacer, form covalent bonds with the silanol moieties that protrude from the inner walls of the support. Other inorganic supports include crystalline nanoparticles, such as super-paramagnetic magnetite (Fe₃O₄).

ImmobIlizing homogeneous ligands to solid supports via noncovalent interactions represents an alternative approach to heterogenizing catalysts. This method includes attachment by adsorption, ion exchange and entrapment. Adsorption or physisorption is achieved through van der Waals interactions between the support and a metal complex. This strategy is advantageous from a time and cost prospective as it obviates the need to synthetically modify the ligand prior to attachment. Yet, some restrictions on its application exist, as ligand interactions with the surface may be in competition with solvents and ionic substances or the substrates themselves. Because the metal-ligand complexes are weakly adhered to the supports, optimization of reaction conditions and selection of the appropriate solvent are imperative to the functionality of the catalyst. Studies indicate that anchoring the metal-ligand complex to a polar support, like silica, via hydrogen bonding provides the most stability when immobilizing through physical adsorption. Some examples exist that immobilize the catalysts to silica via hydrogen
bonding. Another noncovalent approach to immobilizing metal-ligand complexes to solid supports is through ion exchange. This methodology requires that the ligand and the support contain opposite charges; it then exploits the opposing charges and joins the two together through their electrostatic interactions.

Finally, a lesser-used strategy exists that does not necessitate any favorable interaction between the ligand and the support. Known as entrapment, but commonly referred to as *ship in a bottle*, this method of immobilization is accomplished through the encapsulation of a metal-ligand complex inside the pore of a support. Here, metal-ligand complexes are built up in rigidly defined cavities of porous supports.¹⁸ In order for this approach to be viable though, the support and the metal-ligand complex must be unaffected by the synthetic methods. Moreover, the openings of the pore containing the catalyst must be large enough for the substrate to access the active site of metal-ligand complex as to not reduce mass transport, yet be small enough to avoid leaching of the catalyst. Accordingly, the size of metal complex tends to be parameter under consideration.¹⁸ For these aforementioned reasons, there is a dearth of encapsulated catalysts in the literature.²⁸

Research has shown that reaction mechanisms between homogeneous ligands and those that have been anchored to insoluble supports remain identical.²⁹ Despite this similarity, their use is not always directly transferrable. Heterogeneous metal-ligand complexes come with certain challenges, and additional variables must be taken into account: the length between the ligand and the support, the spacer's flexibility, the type of support used, compatibility with solvent, degree of surface
coverage, accessibility of the active stereogenic center, and catalyst loading.\textsuperscript{18,28} For this reason, a thorough understanding of all of these variables is required to construct and characterize heterogeneous catalysts.\textsuperscript{18}

In general, anchoring ligands to an insoluble support engenders catalysts that are often more intricate than their homogeneous counterparts.\textsuperscript{31} The nature of the solid support and any concomitant interactions with the ligand can often lead to changes in the properties of the catalysts as well as performance variation.\textsuperscript{18, 29} Specifically, the support can restrict access to the catalyst, adversely affecting reaction kinetics, and it can limit the movement of the catalyst, decreasing stereoselectivity.\textsuperscript{28} As a result, “most heterogenized analogs of homogeneous catalysts are less active or lose part of their activity in every recycling cycle.”\textsuperscript{31} As a result, it is often difficult to predict the behavior of immobilized catalysts.\textsuperscript{18}

Metal-ligand complexes are often attached to the surface of a solid support via a tether or spacer. Immobilizing homogeneous catalysts generally necessitates front-end steps to prepare the ligand for attachment.\textsuperscript{28} Considering the challenges of solid supported catalysts once again, the spacer may influence the catalytic activity of the derivatized catalyst, “especially if the tether is attached to the complex close to the active site.”\textsuperscript{31} In examples involving catalytic asymmetric epoxidation, the activity and stereoselectivity of the immobilized Jacobsen's catalyst was compromised due to a deleterious interaction between the tether and the stereodirective substituents of the catalyst.\textsuperscript{32} With regard to asymmetric transformations, studies have provided evidence that the length of the spacer linking the ligand to the support’s surface has an affect on the chiral purity of the
product. Thus, it is widely held that when immobilizing a chiral ligand, the linker connecting the ligand to the support should be as far from the stereogenic center as possible to minimize perturbations to the chiral induction process. Whether chiral or achiral, attaching the ligands to a support in a manner that puts enough distance between them and the support to prevent interaction, known as site isolation, is believed to help the heterogenized catalyst retain the same performance as the unbound species. Studies have shown that effective site isolation can be achieved by using an appropriate catalyst precursor that maintains a tight attachment to the surface and is anchored in low concentrations.

Beyond the influence of the spacer, the affects of the support on the catalyst’s activity should be considered. As mentioned, the support can also be restrictive. In the case of asymmetric catalysis, interactions between the support and the catalyst can prevent the ligand from assuming the requisite configuration to induce chiral selectivity on the substrate. If the attached catalyst becomes trapped in the small pores of the support a reduction in mass transport can occur, slowing down the rate of the reaction. To minimize ligand interaction with the support, the linker should be long and flexible.

Some enhancement to the activity of the bound catalyst as compared to homogeneous counterpart has been observed. This boost in performance can be attributed to site isolation or site cooperation effects. Superior performance in some cases can be explained by the confinement concept. Here, the substrate experiences a favorable interaction with the surface of the support and the directing group on the catalyst that enhances the stereoselectivity of the process beyond what
the free catalyst could afford. This phenomenon has been demonstrated in a few cases.

It is widely held that in order for the benefits of immobilized catalysts to offset their costs they should meet several criteria. Preparation should be straightforward, efficient and widely applicable. The catalyst’s performance should be comparable to the detached catalyst. On the back end of a reaction, separation of the heterogeneous catalyst should be feasible through simple filtration and the amount recovered should exceed 95%. Moreover, leaching of the ligand-metal complex from the support should be almost non-existent, which implies that the metal ligation and other bonds or interactive forces should be sufficiently strong. Finally, the catalyst should also be recyclable without any appreciable loss of activity. If this criteria can be met, then among the many advantages of heterogeneous catalysts is their ability to be easily integrated into continuous processing.

1.2 New technology: continuous flow processing

For hundreds of years, chemical transformations have been conducted in batch reactors, such as round bottom flasks, autoclaves or complementary large-scale vessels. In its most simplistic form, a batch reaction involves a vessel that is charged with reactants, which are then stirred while heat is applied or removed for a period of time deemed sufficient prior to being emptied from the vessel as product (Figure 2).
Figure 2. A general batch reaction schematic

Chemists have spent centuries developing and optimizing synthetic routes to organic molecules within this infrastructure. Now, given the full repertoire of today’s synthetic toolbox, most organic molecules are accessible through this methodology. Thus, the success of, and familiarity with traditional synthetic practices along with established regulatory standards has contributed to batch reactors becoming “mainstays of modern fine chemical and pharmaceutical synthesis.” While other chemical industries, like petrochemical and polymer, have transitioned to manufacturing their materials in continuous operations, the pharmaceutical industry remains one of the last still dominated by batch processing.

Despite the intellectual capital and the financial investments pharmaceutical companies have put toward developing infrastructures that support the batch processing of active pharmaceutical ingredients (APIs), there are incentives to change. The impetus primarily concerns the fiscal bottom-line: it is increasingly difficult for pharmaceutical companies to remain profitable. Conducting syntheses in batch reactors is inherently wasteful; studies estimate that for every 1
kg of API produced, between 25 kg and 100 kg of waste are generated. This methodology is not only uneconomical, but also environmentally burdensome. Increased competition from generics manufactures, higher research and development costs, growing prices of starting materials, and current drug shortages are among a myriad of factors driving a burgeoning pursuit to synthesize APIs in a more efficacious manner.\textsuperscript{37,39,41}

In addition to exploiting the functional advantages of catalysts, pharmaceutical companies are starting to explore ways to improve the efficiency of chemical processing by conducting syntheses, catalytic or otherwise, in continuous flow reactors (Figure 3).\textsuperscript{42} Although chemical engineers have worked with continuous flow reactors for more than a century, research chemists have only recently gained access to this technology as smaller devices have become available.\textsuperscript{43} Continuous pharmaceutical manufacturing (CPM) has the potential to “decrease production costs while improving product quality.”\textsuperscript{41} The cost-saving benefits are possible from early drug development to late stage, large-scale production.\textsuperscript{42}

\textbf{Figure 3.} A general continuous-flow reaction schematic
Within flow reactors, chemical reactions occur in tubes as continuous streams of different reagents are mixed within chemically inert coils or chips, or are passed over packed beds of insoluble substance, through the force generated by peristaltic or syringe pumps, referred to as hydrodynamic flow (Figure 4). The boost in process efficiency comes from the small diameter of the reactor coils or the diminutive size of the channels within the chip reactors, which engender high surface-to-volume ratios. Accordingly, the control over heat exchange, mass transfer and the exposure to ultraviolet/visible radiation are significantly improved, and the formation of “hot spots” or convective dead zones that are common to batch reactors are effectively nonexistent. With increased control of these variables, reactions in flow are shown to be more regio- and chemically selective, yielding purer products.

Figure 4. Continuous plug flow reactor coil (A), microchip reactor (B) and packed bed reactor (C)
To further ensure product quality, continuous flow reactors are easily outfitted with in-line monitoring devices, known as process analytical technology (PAT) such as diode array UV detectors or flow IR equipment. While batch reactors can incorporate PAT in a similar manner, once deleterious by-products or impurities are formed and identified in batch, the entire reaction succumbs to contamination. Conversely, in continuous operations, once an undesired substance is detected, the reaction can be stopped or adjusted to prevent the unprocessed reactants or the already synthesized product from being wasted.

Continuous flow reactors also enable controlled use of hazardous or unstable intermediates. In flow, transient intermediates can be intercepted and elaborated to final products by injecting multiple reagent streams or by rapidly varying the reaction temperature or pressure. In addition to greater thermal management, the small volumes and the containment of substances within these sealed reactors provide safer use of dangerous materials, which may include toxic reagents or flammable solvents. This is significant since “the most time- and atom-efficient routes frequently demand the use of highly reactive, often low-molecular-weight, compounds or of otherwise problematic reaction conditions.” Now, these hazardous materials, traditionally excluded from batch manufacturing and supplanted with more expensive and time intensive procedures, can be utilized in continuous operators to provide a more affordable and direct route to a target molecule.

In terms of process development, an attractive feature inherent to continuous flow technology is its “scalability.” Continuous flow reactors enable
direct transfer from discovery to larger scale production. Instead of scaling up, or changing the reactor dimensions, as done in batch chemistry, the number of continuous reactors run in parallel can be increased, a technique known as “numbering up.” \textsuperscript{37} This aspect ensures greater reliability and reproducibility. Continuous flow chemistry also enables multiple reactions to be run in sequence, which reduces the amount of solvent used in intermediate work up steps and periods of inactivity as reactors are emptied, cleaned and prepared for subsequent reactions.

Over the last decade, advancements in continuous flow chemistry have enabled chemists to conduct nearly all reactions through this methodology. \textsuperscript{43} To date, the literature is replete with examples that showcase the syntheses of natural products, APIs and polymers. Since 2005, which marked the first reported continuous synthesis of a natural product, grossamide, many other biologically significant molecules have been constructed continuously, including: (±)-oxomaritidine, pristane, (−)-perhydrohistrionicotoxin, vitamin D\textsubscript{3}, pauciflorol F, as well as (−)-sedamine and (+)-sedridine. \textsuperscript{45} As mentioned, many APIs have been produced using CPM. In 2005, Schwalbe and co-workers synthesized the antibacterial API ciprofloxacin in a five multistep, semi-continuous micro-reactor system. \textsuperscript{46} Several years later, Tyler McQuade \textit{et al} performed a multistep synthesis of ibuprofen continuously, starting from the commercially available reagents, trifluoromethane sulfonic acid, propionic acid and isobutylbenzene. \textsuperscript{47} In 2015, several members of the Gupton group developed a streamlined, continuous process to the antihypertensive drug, telmisartan through a novel cross-coupling step that
joined two functionalized benzimidazole rings. \(^{48}\) A host of commonly used and popular chemical reactions have also been demonstrated in continuous operations. These include: alkylations, fluorinations, oxidations, deprotections, hydrogenations, photochemical transformations, heterocycle formations, cross-coupling reactions, \(^{49}\) nitrations and polymerizations. \(^{37,50-54}\)

Recently, a team of researchers at Massachusetts Institute of Technology built upon this work and assembled a reconfigurable continuous manufacturing unit capable of producing, purifying and formulating large quantities of APIs from start-to-finish. This system is modifiable, which enables it to conduct a diverse array of chemical reactions that can be integrated to perform multistep syntheses. From the single modular platform equivalent to the size of a refrigerator, this group constructed four biologically distinct pharmaceuticals via four different continuous synthetic routes: diphenhydramine hydrochloride, lidocaine hydrochloride, diazepam, and fluoxetine hydrochloride. Accordingly, this device holds significant potential to generate APIs on-demand, especially to regions of the world currently facing shortages that cannot otherwise support batch-processing infrastructure. \(^{39}\)

Despite the many benefits of CPM, challenges still exist and some chemical transformations remain better suited for batch. Thus, this technology should be viewed as an accompaniment to batch processing, not a complete replacement. \(^{43}\) Continuous flow processing is constrained by solubility issues. Insoluble reactants or the formation of precipitates have a tendency to clog the reactors, rendering them inoperable. Although specialized equipment capable of handling slurries exists, improvements are necessary in this area to render these reactions more
viable.\textsuperscript{43,45} When telescoping steps, the production of unwanted by-products can potentially lead to complications in downstream reactions. Challenges also persist with the incorporation of reactor components, such as pumps, back-pressure regulators and in-line monitors into flow systems.\textsuperscript{43} Moreover, more continuous workup and purification techniques need to be developed for this technology to be fully self-sustainable. Lastly, given the many intricate, moving parts, frequent maintenance and repair of the reactor systems is common, which can lead to periods of inactivity and unproductivity.\textsuperscript{43}

Despite the challenges, the advantages of continuous flow processing have contributed in its application in the synthesis of the antimalarial drug, artemisinin.

1.3 The gold standard of malaria treatment: artemisinin

1.3.1 Malaria

Malaria is an infectious, life-threatening disease caused by five Plasmodium parasitic species, with two, \textit{Plasmodium falciparum} and \textit{Plasmodium vivax}, the most threatening to humans. The disease is transmitted to humans via female \textit{Anopheles} mosquitoes during blood meals (Figure 5). Once the vector injects the parasites into the human host, the microorganisms develop and proliferate, initially in the liver, and then in the red blood cells. As the parasites mature inside the red blood cells, the cells are destroyed, leading to the release of progenies that invade other red blood cells. It is during this blood stage that an infected person becomes symptomatic. It is also the period when, during blood meals, the human hosts transmit the parasites to other female \textit{Anopheles} mosquitoes. After 10 to 18 days,
the parasites are present in the newly inoculated mosquito's salivary glands and are able to infect another human during the next blood meal.⁵⁵

**Figure 5.** The life cycle of parasite, *P. falciparum* within an infected host

On average, symptoms appear a week after the virulent mosquito bite. Patients often present with a combination of: fevers, headaches, nausea and vomiting. Severely infected children stand the risk of developing anemia and respiratory distress. If left untreated for more than 24 hours in adults and children, *P. falciparum* malaria can lead to other serious health complications and potentially death.⁶

Malaria predominates in the tropical and subtropical regions of the world (Figure 6). Most transmissions occur in sub-Saharan Africa, where the lifespan of the native mosquitoes is longer and the frequency of initiating human blood meals is greater. In 2015, 95 countries and territories, mainly in Africa and Southeast Asia reported malaria transmission. That year, an estimated 3.2 billion persons – half the
world’s population – stood at risk of infection, with 214 million cases that resulted in 438,000 deaths. In all areas where incidence is high, children under five years of age are disproportionately vulnerable, accounting for 70% of all malaria deaths. Pregnant women, immunocompromised persons and travellers are among others who are particularly susceptible to infection.\(^8\)

\[\text{Figure 6. Percent of population at-risk for contracting malaria in 2013, by country}\]

Since 2000, tremendous global health efforts have worked to significantly decrease the number of malaria infections and fatalities; a 37% global reduction in malaria incidence, or approximately 663 million new cases, was realized between 2000 and 2015. During that same period, approximately 6.2 million malaria deaths were averted and the death rate for children under 5-years-old was reduced by 65%. These life-saving trends have been the result of improved preventative and responsive measures: increased mosquito control such as, insecticide-treated nets (ITNs) and indoor residual spraying (IRS), accessibility to rapid diagnostic testing
(RDTs), as well as greater availability of drug therapies. In sub-Saharan Africa for example, the percentage of the population that had access to ITNs increased from 2% in 2000 to 56% in 2014. Global sales of RDTs, meanwhile, increased from less than 50 million in 2008 to 314 million by 2014. Moreover, the number of artemisinin-based combination therapy (ACTs) drug courses acquired from manufacturers rose from 11 million in 2005 to 331 million in 2014.8

Despite the substantial progress, however, the burden remains significant. Accordingly, the World Health Organization (WHO) has established the Global Technical Strategy for Malaria 2016-2030 to move the needle even closer towards malaria eradication. The goals for 2030 include: reducing malaria case incidence and fatality rates by at least 90%, eliminating the disease in at least 35 countries and preventing its transmission into countries that are currently malaria-free. To accomplish these aims, annual funding for malaria must increase from its current $2.5 billion level to $8.7 billion by 2030.8

1.3.1.1 The economics of malaria

Nearly a quarter of the 663 million averted malaria incidences since 2001 have been attributed to the increased availability of ACTs.8 Currently, the WHO endorses ACTs, derived from the natural product, artemisinin (1), and combined with partner drugs as the most efficacious medication against the disease.7,9

As of 2012, about 95% of the world's supply of artemisinin (1) came from commercially harvesting the plant, Artemisia Annua (Figure 7).56 China and Vietnam have been among the major cultivators. Since 2013, Sanofi-Aventis has
annually injected a modest amount of the anti-parasitic agent into global markets through an industrial scale biosynthetic production, approximately one-third of the global supply. Currently, there are at most seven WHO pre-qualified suppliers for any one of the Quality-Assured ACTs (QAACT) drug combinations.

While ACTs are considered the most effective anti-malarial treatments, they are more expensive than their predecessor medicines. Consequently, the higher costs have created a significant barrier to access for an infected patient who lives on $1 a day. One ACT course treatment costs between $0.9 – $1.4 per adult and $0.3 – $0.4 per child, compared to approximately $0.10 for treatment with another anti-malarial, such as chloroquine. The relative expense of artemisinin treatments is a result of high production costs that are associated with sourcing the compound from *Artemisia annua*. The cost of the panacea has been limited by several factors inherent to, and external from the plant. On average, a 12 to 18 month maturation period is required before artemisinin (1) can be isolated, and recovery yields are less than 1 weight percent. Additionally, highly variable weather patterns threaten and in some instances decimate annual crops, causing shortages and concomitant price spikes. Yet, in periods of abundance, markets respond with price reductions, discouraging farmers from planting the crop, which then leads to shortages in subsequent years and more price fluctuations. For example, in one year (from 2012 to 2013) the cost of artemisinin (1) oscillated between $300 per kg to $600 per kg. Thus, reliance on the botanical source for this drug has proven highly unviable. Without consistent availability, the price of artemisinin (1) remains volatile and cost prohibitive, especially to those most in need of its use.
Figure 7. An Artemisia Annua commercial farming site in China

The consumer demand for antimalarial medicines, defined as the number of treatments persons would seek to acquire and administer if available, currently stands at an estimated 1.3 billion treatment courses per year with ACTs comprising approximately one-third of this market. In 2015, this translated to 196 metric tons of artemisinin (1) needed. As the population increases in infected areas and a larger consensus embraces ACTs as the most effective malaria treatment, the demand is expected to rise to 1.4 billion treatment courses or 230 metric tons of artemisinin (1) by 2018 (Figure 8). Although it is difficult to calculate the need for antimalarial drugs, which is defined as the number of treatments required to treat symptomatic persons regardless of whether or not those individuals seek treatment, that figure is projected to increase similarly.
Despite the increased number of QA ACTs procured from manufactures since 2005, the amount of QA ACTs ordered is forecasted to peak in 2016 and trend downward, unless the cost of the therapy decreases or more funding becomes available (Figure 9). The fact that the demand for these treatments is predicted to increase over this period while the procurement is anticipated to decline suggests that the recent gains realized in treating this deadly disease may not extend as far in the near future. The current reality is that millions of infected persons do not receive the treatment they need; between half to three-quarters of malarious children in sub-Saharan Africa did not receive an ACT in 2014.
Figure 9. QAACT market: historical and projected growth, 2005 – 2018 in millions

Malaria and poverty are interrelated; the geographical bull’s-eye of highest absolute poverty coincides with the tropical and subtropical regions of the world that most support malaria transmission. The costs of globally treating malaria are high. In 2014, estimated 2.5 billion dollars was spent on treating the disease. Yet, the burden of not treating this infectious disease is even higher. Malaria acts as a major impediment to the societal welfare and economic development of endemic regions, preventing human flourishing. The annual loss of life is often greater than or equal to a half of million persons worldwide. From a microeconomic perspective, the disease affects behaviors such as schooling and household savings. On a macroeconomic level, it influences the human capital in the workforce, trade, tourism and foreign investment. It is estimated that the disease costs the continent
of Africa $12 billion a year in lost productivity. Moreover, a report in 1995 found that the gross domestic product (GDP), adjusted for parity of purchasing power, was 5 times higher for malaria-free countries than for endemic ones. Meanwhile, the burden on the healthcare systems is significant. In endemic countries as much as 40% of public health expenditures go toward fighting malaria; 50% of inpatient admissions to hospitals and 60% of outpatient visits are associated with the parasitic disease. So, while the underequipped infrastructures of the developing world have made it particularly challenging to combat malaria transmission, its prevalence in turn has made it difficult for these countries to gain sustained economic traction, perpetuating the pernicious cycle.

1.3.2 Artemisinin

Artemisinin (1) is an intriguingly complex molecule containing seven stereocenters throughout its tetracyclic core, which includes an endoperoxide bridge (Figure 10). As mentioned, it is a natural product found in the plant *Artemisia annua*. While the plant is native to Asia, it has been naturalized to other parts the world. Historically, extracting 1 from the harvested plant has served as the world’s only source. While its therapeutic properties have been known and used for centuries in traditional Chinese medicine, artemisinin’s (1) benefits were not publicized on a global stage until 1979. Quickly thereafter, the natural product gained worldwide recognition for its anti-malarial properties, and in 2015, Tu Youyou was awarded the Noble Prize for her work on methods of extraction, its structure elucidation and treatment. While the exact mechanism of action remains
elusive, structure-activity relationship studies suggest that the unusual endoperoxide bridge serves as the active part of the molecule.\textsuperscript{9} It is hypothesized that upon reacting with heme and ferrous ions in the blood, the peroxide bond is cleaved, producing free radicals that are capable of deleteriously interacting with target proteins within the parasites.\textsuperscript{63}

The ACT cocktail circumvents the traditional challenges of drug resistance that are often associated with a single drug such as chloroquine\textsuperscript{64}; artemisinin's (1) function is to reduce the main parasite load in the first 3 days of treatment, while the partner drugs, with longer half lives, serve to remove residual parasites beyond those initial days.\textsuperscript{57} Due to artemisinin's (1) low bioavailability, however, several semisynthetic analogues of 1 with modifications to the C-12 position have been developed. These derivatives, artesunate (2), dihydroartemisinin (3) and artemether (4), have much improved $EC_{50}$ values and have supplanted 1 in treating malaria (Figure 10).\textsuperscript{64, 65} The artemisinin derivative – partner drug combinations include: artemether-lumefantrine, artesunate-amodiaquine, artesunate-mefloquine, artesunate-pyronaridine, artemesunate-sulfadoxine pyrimethamine and dihydroartemisinin piperquine.

Figure 10. The natural product and antimalarial artemisinin (1) and its derivatives
1.3.2.1 Synthetic routes to artemisinin

Despite its global attention since 1979, the world’s point of access to 1 has primarily relied on its isolation and purification from the plant. As discussed, this method of acquisition has resulted in unstable and inadequate global supply of 1. With more sustainable sources of 1 needed, much work has been done to develop other access points to the life saving therapy. Several decades of research have resulted in three main routes to the natural product: total synthetic, semi-synthetic and biosynthetic.

Since Tu Youyou’s seminal work, tremendous efforts have focused on the total synthesis of 1. 66-75 The first successful synthesis was reported in 1983. 74 Starting from (−)-isopulegol (5), the pioneering work of Schmid and Hofheinz delivered the anti-malarial drug (1) in 13 steps, through two key intermediates (6 and 7), with a 2.95% overall yield (Scheme 1).

![Scheme 1. Schmid and Hofheinz total synthesis of artemisinin (1)]

As shown in scheme 2, in 2010, Yadav and coworkers disclosed a synthetic sequence that commenced from a different commercially available chiral starting material, (R)-(+)-Citronellal (8), which reduced the number of linear steps before
generating the intermediate (9), furnishing artemisinin (1) in a 5.00% overall yield.

Scheme 2. Yadav et al. total synthesis of artemisinin (1) in 2010

This work was substantially improved upon in 2012, when Cook and coworkers demonstrated a more efficient and economical approach to the natural product (1). The concise total synthesis started with the inexpensive and readily available reagent, cyclohexenone (10). From this achiral precursor, the key intermediate (11) was constructed in four steps. Although structurally analogous to the intermediates fashioned in other processes, this enol olefin species 11 was subjected to singlet oxygen that was not photochemically generated. In this approach, singlet oxygen was evolved in a controlled manner through the decomposition of hydrogen peroxide by ammonium molybdate. The reactive oxygen molecule then reacted with the enol intermediate just the same to introduce the hydroperoxide. Subsequently, the oxidized intermediate underwent an acid-induced cyclization to deliver 1. The final two chemical transformations combined to afford a 42% yield. This process included just 5 steps with an overall
yield of 13.7%. To date, this work represents the most concise total synthesis of 1 (Scheme 3).  

Scheme 3. Cook et al. total synthesis of artemisinin (1)

In combination with the total synthetic approach, simultaneous attention turned toward the semi-synthetic production of artemisinin (1). The isolation of artemisinic acid (12), a naturally occurring precursor of 1, containing the essential carbon backbone and requisite stereochemistry, provided synthetic chemists with an excellent starting point to the anti-malarial agent. In 1989, Acton and Roth published a salient approach to convert 12 to artemisinin (1) in 3 steps (Scheme 4). Their sequence involved a nickel boride reduction of 12 to dihydroartemisinic acid (13). Then, a photochemical transformation catalyzed by the photosensitizer, methylene blue, initiated an ene reaction between 13 and singlet oxygen to deliver the hydroperoxide (14). An acid–induced Hock cleavage and a subsequent cascading condensation furnished 1 in a 30% overall yield. While the work of Acton and Roth was not industrially practical, it was significant for two reasons. First, it suggested that if access to 12 increased, artemisinin (1) would be much more
attainable. Second, it laid the foundation for future biomimetic strategies that would work to bring this route to industrial relevance.

![Scheme 4. Acton and Roth semi-synthesis of artemisinin (1)](image)

At the turn of the 21st century, the Semi-synthetic Artemisinin Project was launched with the intent to develop a viable, alternative route to access an artemisinin precursor. Collaborative efforts between the laboratory of Jay Keasling at the University of California, Berkeley, PATH Drug Solutions (a non-profit pharmaceutical company), and Amyris Inc. with magnanimous funding by the Bill and Melinda Gates Foundation sought after a solution inspired by the botanical production of artemisinin (1). A thorough investigation into the natural pathways guided their work: *Artemisia annua* photosynthetically generates sugars that are converted to acetyl-CoA, which enters the mevalonate biosynthetic pathway to produce farnesyl diphosphate (FPP), a 15-carbon intermediate. A terpene synthase enzyme, amorphadiene synthase (ADS) then converts FPP to amorphadiene, an isoprenoid hydrocarbon. Through oxidative processes, *Artemisia annua* subsequently transforms amorphadiene into either 12 or 13, precursors that contain the essential carbon backbone of artemisinin (1). Despite the natural production of 12 and 13, the biosynthetic production of 12 was pursued because at
the commencement of the work the enzyme responsible for converting amorphadiene to 13 was unknown. With this knowledge the biological processes in hand, the group genetically modified several host organisms. After engineering bacteria and yeast by taking genes from Artemisia annua and inserting them into the microorganisms, the team found that S. cerevisiae could effectively ferment glucose to fabricate 12 at a titre of 25 g L⁻¹. The project, conceived out of the need to sustainably meet the world’s treatment demands resulted in a significant leap forward: the discovery of an efficient biosynthetic process that delivered a molecule that in just two-to-three chemical transformations could be converted into the drug target (1).

Following the landmark biosynthetic manufacture of artemisinic acid (12), Keasling et al. transformed their yeast-sourced 12 to artemisinin (1). First, the team hydrogenated 12 to 13. (This reaction will be described in more detail in Chapter 3.1.1). Next, 13 was esterified to 15 in attempt to reduce the formation of undesired side-products in future transformation (Scheme 5). Aware of the scale up challenges associated with photochemistry, the team then employed an oxygenation procedure that used the same chemistry as the Cook group to generate singlet oxygen, although on a different molecule. In this case, hydroperoxide moiety was installed on to 15 via an ene reaction with singlet oxygen generated from lithium molybdate and hydrogen peroxide. The resulting intermediate (16) was subjected to a solid supported acidic catalyst (sulfonated polystyrene) and copper (II) p-toluenesulfonate, which initiated a Hock fragmentation of the allylic hydroperoxide. This commenced a cascading reaction that involved the installation of the
endoperoxide bridge and concomitant ring closure to deliver artemisinin (1) in 19% overall yield (Scheme 5).\(^{80}\)

![Scheme 5. Keasling et al. semi-synthesis of artemisinin (1)](image)

With a reliable and affordable biosynthetic process established, the race to affordably complete the final chemical conversions intensified. Over the last ten years, many research groups have dedicated their efforts to: the asymmetric reduction of 12 to 13, and the photochemical reaction of 13 to artemisinin (1).\(^{83-86}\) Investigations into these transformations have included various synthetic approaches and manufacturing operations. These strategies will be covered in greater detail in subsequent chapters.
CHAPTER II

THE DEVELOPMENT AND EVALUATION OF NEW GRAPHENE SUPPORTED CATALYSTS FOR USE IN ASYMMETRIC HYDROGENATIONS OF OLEFINS

2.1 Background and prior work

2.1.1 History and explanation of asymmetric hydrogenations

"Chirality is an intrinsic, universal feature of various levels of matter." Most biological functions depend on very specific interactions between molecules. Accordingly, a chiral host molecule may interact differently with two guest molecules that vary only by their three-dimensional conformation. With respect to synthetic drugs, the subtle geometric differences between two enantiomers can have divergent pharmacological activities, resulting in disparate physiological effects. An example that underscores the sensitive relationship between the shapes of molecules and pharmacological action was revealed in the 1960s with the administration of thalidomide to pregnant women. While one enantiomer, \((R)\)-thalidomide, affords the intended anti-nausea effects, the other isomer, \((S)\)-thalidomide, induces fetal deformities. Without this knowledge in hand though, the racemic mixture of the drug was distributed. Tragically, reports indicate that a mother dosed with a single 50 mg tablet had a 50% chance of giving birth to a child with phocomelia, as well as other body malformations.
In 1992, with the thalidomide tragedy as a dark backdrop, the United States Food and Drug Administration (FDA) instituted a guideline requiring that commercialized clinical drugs consist of a single enantiomer. At that time, approximately 90% of synthetic chiral pharmaceuticals were racemic. This mandate, however, made it imperative that the pharmaceutical industry develop processes to synthesize enantiomeric enriched compounds and separate any resulting mixtures into pure stereoisomers.\textsuperscript{87} Since generating racemic mixtures to then only separate and discard one enantiomer later is inherently wasteful and uneconomical, initially synthesizing a drug that yields high enantiomeric excess of the desired isomer is preferred. Thus, in the years following the federal mandate, the quest to discover asymmetric metal catalysts, chiral auxiliaries and biocatalysts that deliver APIs in high enantiomeric excess received significant attention.

Beginning in 1992, 58% of the federally approved drugs contained a chiral center. By 2006, the percentage of chiral drugs increased significantly to 75%. Over that same time period, the quantity of single enantiomer drugs produced by purely synthetic methodologies expanded from 20% to 50%.\textsuperscript{89} Moreover, by 2013, of the top 150 worldwide selling drugs, 54% of the non-biologicals possessed at least one chiral center.\textsuperscript{90} In 2014, 22 of the 29 small molecules approved by the FDA were chiral.\textsuperscript{91} These statistics further emphasize not only the importance molecular chirality plays in biological systems but also the response of the scientific community to the federal laws requiring pharmaceutical manufactures to distribute optically pure clinical drugs.
In recent decades, academic and industrial scientists alike have worked to develop many different asymmetric catalytic transformations to furnish stereogenic centers. Some examples of asymmetric chemocatalysis include: alkylation, cycloaddition, dihydroxlation, epoxidation, hydroformylation, hydrogenation and oxidation. Of these, however, asymmetric hydrogenation is the most established, studied and dependable enantioselective reaction in pharmaceutical manufacturing for its versatility and efficiency.

In general, catalytic hydrogenation is the most widely used synthetic processes to install the elements of hydrogen across carbon-carbon double bonds; its use is extended to carbon-oxygen and carbon-nitrogen double bonds as well (Figure 11). Currently, it is estimated that between 10–20% of all industrial reactions are catalytic hydrogenations. This high percentage can be explained by the nature of the reaction. Hydrogenations proceed cleanly and rapidly, with some exceptions to sterically crowded olefins, and devoid of considerable by-product formation. These reactions are also known for their high chemo-, regio- and enantioselectivities.

**Figure 11.** General asymmetric hydrogenation schematic of: unsaturated carbon-carbon, carbon-oxygen and carbon-nitrogen bonds
In hydrogenations, the surface of certain transition metals, such as platinum, palladium, rhodium, ruthenium, nickel, either adsorbed onto the surface of a solid support or coordinated to a soluble molecular complex, serve as the reactive site. To the metal, molecular hydrogen and the unsaturated moiety of the substrate are adsorbed. Three major intermediates are understood to form during the hydrogenation of an unsaturated species (Figure 12). The first intermediate depicts both atoms of the double bond adsorbed to the metal via π-type bonding through the π-bond (A). Here, the interaction consists of the π and the π* orbitals of the substrate and the acceptor and donor orbitals of the metal catalyst. Following the addition of a hydrogen atom to the adsorbed substrate, a σ-type bond between the other atom (initially a part of the π-bond) and the metal is formed (B). This intermediate species can either react with an adjacent hydrogen atom to deliver the saturated product, which is then desorbed from the metal surface, or the metal can remove an allylic hydrogen atom from the reactant to form the third intermediate (C). This species is comparable to an allylic moiety attached to the surface by π bonds and represents the process of double bond migration. The exchange of hydrogen atoms between the substrate and the metal can result in the formation of an isomerized side-product. 92
In contrast to nonasymmetric hydrogenations, asymmetric hydrogenations possess subtle mechanistic differences; more apparent of course is that the two hydrogen atoms add preferentially to one face of a π–bond as influenced by the chiral ligand-metal complex. It is the unique spatial interaction between the ligated metal and the substrate that dictates the rate at which the oxidative addition of diatomic hydrogen occurs; this process represents the rate determining step of the reaction. Once this dihydride complex is established, the reactant’s π–bond inserts itself into the metal-hydrogen bond, which is then followed by reductive elimination. The time it takes to proceed from the oxidative addition step to reductive elimination can vary based on the geometric orientation of the ligated metal and the substrate, and therefore, one enantiomer predominates over the other. Studies indicate that electronic factors contribute to the relative activities. A highly active catalyst that yields good enantioselectivity is often comprised of structurally well-defined and electron-donating chiral ligands. The stronger the
preference for a specific orientation between the substrate and catalyst, the greater the difference in thermodynamic stabilities and rates of hydrogenation between the two intermediates, and thus the higher optical purity of the resulting saturated product.  

The groundbreaking work of W. Knowles, Kagan, and R. Noyori over 40 years ago provided the chemical community with the first generation of homogeneous chiral ligands designed for asymmetric hydrogenations.  

Knowles replaced the achiral phosphine ligands previously used in Wilkinson catalysts with a chiral monodentate phosphine analogue and later, a much improved C₂-symmetric bidentate phosphine ligand, 1,2-bis((2-methoxyphenyl)(phenyl)phosphaneyl) ethane (DIPAMP). Similarly, Kagan developed and employed the chiral bidentate phosphine ligand, 2,3-O-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino) butane (DIOP). Noyori discovered and demonstrated the utility of 2,2’-bis(diphenylphosphaneyl)-1,1’-binaphthalene (BINAP), a chiral organophosphorous compound that despite lacking a stereogenic center possesses axil chirality due to restricted rotation of the two naphthyl rings. The scientific and broader societal significance of developing and employing chiral catalysts in asymmetric hydrogenation was highlighted in 2001 by awarding the pioneers, W. Knowles and R. Noyori, the Noble Prize in Chemistry for their seminal contributions.

In the 1990s, tremendous research efforts generated many novel ligand systems, for example DuPhos and Josiphos, developed by Burk, and Togni and Spindler, respectively. Today, along with the original phosphine ligands, thousands of chiral ligands are available with a diverse collection of chelating atoms. These
systems include classes of: oxazoline, phosphinooxazoline, phosphinoimadazoline and heterocyclic carbene ligands. Within each class, ligands have been further modified to construct analogues that possess differing structural and electronic properties, resulting in an even larger ligand pool. Due to the limitless combinations of chiral ligands and transition metal species, pharmaceutical companies have invested much in high throughput experimentation (HTE) technology that serves to rapidly evaluate the optimal ligand, metal combination to conduct a particular asymmetric hydrogenation. These recent advancements have increased the industrial chemist’s rapid access to innovative catalyst systems and as a result, expanded their application, and augmented the substrate scope. Although the extent of utility was initially limited, and successful hydrogenations required the substrate to possess a carbonyl moiety for ligand coordination, improvements in chiral ligand systems have rendered it feasible to reduce a broad range of olefins, even unfunctionalized ones with good stereoselectivity. Underscoring its versatility, asymmetric hydrogenations have been demonstrated on various prochiral substrates such as: olefins, ketones, aldehydes and imines.

Asymmetric hydrogenations meet many of the industrial process requirements for safety, throughput, atom-economy, and waste minimization. The cost of hydrogen gas is low. Furthermore, the transformation can be applied to broad range of prochiral API building blocks to introduce stereogenic centers in high yields with exceptionally low catalyst loadings. For the aforementioned reasons, “asymmetric hydrogenation is the most significant asymmetric technology utilized to establish chirality in pharmaceutical products,” and essential to many broader
organic materials of commerce. Accordingly, several drugs launched in the last decade used this asymmetric technology: Tipranavir, Rozerem, Sitagliptin, and Aliskiren.

2.1.2 Prior work: immobilization of ligands to solid supports for asymmetric hydrogenations

As a pioneering catalytic reaction used in many synthetic applications, asymmetric hydrogenation of olefins has received significant attention from the chemical community since its inception. In recent decades, this interest, accelerated by aspirations to improve catalyst recovery and reuse, has motivated chemists to explore attaching these chiral molecular catalysts to the surface of insoluble materials.

In the 1970s and 1980s, work began on grafting catalysts to polymers via Merrifield’s chemistry. (An application of this chemistry will be detailed in Chapter 4.1.6). Other methods of generating polymer-supported catalysts included copolymerization. In one example, Stille et al. reacted a styrene monomer (17), which included a precursor to the chiral diphosphine DIOP ligand (18) with another vinyl monomer to assemble a polymeric catalyst (19) (Scheme 6).
When coordinated to rhodium, this polymer-bound catalyst hydrogenated 2-acetamidoacrylic acid (20) and 2-acetamidocinnamic acid (21) with modest enantiomeric excess, 52-60% and 86% respectively. These results proved comparable to the homogeneous analog, Rh(I)-DIOP, 73% and 81%, respectively (Scheme 7). Despite the similar selectivities, studies indicated that this material was more than five times less reactive and considerably more susceptible to oxidation by air than the unbound counterpart.101

Stille's work later extended to incorporating the same chiral diphosphine ligand into different co-polymers, but did so by varying the type of monomer used in
the co-polymerization process.\textsuperscript{102, 103} The group discovered that simple filtration could be utilized to recover the heterogeneous catalysts. In one example, the cross-linked acrylate-acrylamide catalyst was recovered and recycled without loss in optical purity.\textsuperscript{102}

Additional approaches to tethering these chiral molecules to polymers have also been pursued. One route involved functionalizing the ligands with a reactive group capable of covalently bonding with a functional group proceeding from polystyrene. This method was successfully demonstrated by Bayston \textit{et al}., who derivatized BINAP (22) with a pendant carboxylic acid (23), and then covalently attached it to an aminomethyl derivative of polystyrene via peptide coupling chemistry (Scheme 8).\textsuperscript{19} Complexation to ruthenium delivered the heterogeneous catalyst 24.

\begin{center}
\textbf{Scheme 8.} Bayston \textit{et al.} preparation of a heterogeneous BINAP catalyst (24)
\end{center}
This polymer-supported catalyst, upon metallation with ruthenium, was moderately effective in stereoselectively hydrogenating itaconic acid (25), and 2-acetamidoacrylic acid (20): 56% and 64% e.e., respectively (Scheme 9).

![Scheme 9](image)

**Scheme 9.** Hydrogenation of itaconic acid (25) and 2-acetamidoacrylic acid (20) using heterogeneous Ru(II)-BINAP catalyst (24)

More remarkable however, was this heterogeneous catalyst’s ability to reduce methyl propionylacetate with 97% e.e. This polymeric catalyst was retrievable via filtration. Furthermore, it proved recyclable, although reuse necessitated increased reaction times.\(^{19}\)

Noncovalent attachment of ligands to polymeric solid supports has also been explored. A common route has involved anchoring the ligands to ion-exchange resins via ion-pair immobilization. Several groups have investigated this strategy. In one example, a cationic p-dimethylaminophenylphosphine rhodium catalyst (26) was immobilized onto a sulfonated fluoropolymer ion-exchange resin (27) (Scheme 10).\(^{104}\)
Scheme 10. Hanson and Davis immobilization of a cationic p-dimethylaminophenylphosphine rhodium catalyst (26) onto an ion-exchange resin

The resulting heterogeneous catalyst (28) proved reusable in six recycles (conversions were maintained between 97-98%), the e.e. values across the six successive hydrogenations of methyl α-acetamidocinnamate (29) were lower than the homogeneous analog (73% compared to 98%) and decreased throughout each run (from 73% to 63%) (Scheme 11).
Scheme 11. Hydrogenation of methyl α-acetamidocinnamate (29) using cationic p-dimethylaminophenylphosphine rhodium immobilized onto an ion-exchange resin

The immobilization of chiral ligands onto inorganic supports for use in asymmetric hydrogenations has also been evaluated. In one example, Thomas et al covalently attached cationic rhodium (R,R)-diphenylethylenediamine (DPEN) catalyst to the mesoporous material, MCM-41 (Figure 13).105

Figure 13. Cationic rhodium DPEN bound to mesostructured silica, prepared by Thomas et al.
Remarkably, this heterogeneous catalyst hydrogenated phenylcinnamic acid (30) with higher stereoselectivity than the homogeneous catalyst, 93% e.e. compared to 81%, and was reused twice with negligible loss in optical purity (Scheme 12).

Scheme 12. Hydrogenation of phenylcinnamic acid (30) via heterogenized Rh(I)-DPEN

Other noncovalent approaches to immobilizing chiral ligands to inorganic solid supports have also been investigated. In one example by Wan and Davis, a modified BINAP–Ru complex (31) dissolved in ethylene glycol, was adsorbed onto controlled pure glass (CPG-240) with a pore diameter of 242 Å (Figure 14).
Figure 14. Schematic of derivatized BINAP ligand absorbed to inorganic solid support, prepared by Wan and Davis

This heterogeneous BINAP catalyst afforded 96% e.e. in the hydrogenation of 32 to naproxen (33), similar in value compared to the homogeneous counterpart (Scheme 13).106

Scheme 13. Hydrogenation of naproxen (33) using heterogeneous BINAP catalyst
In another example, Rh(DIPAMP) (34), as seen in figure 15, was anchored to Montmorillonite K (2:1 silica/alumina) through their shared interactions with a heteropoly acid linker, phosphotungstic acid (PTA), which served as the anchoring agent. An advantage of this approach is that it obviates the need to synthetically modify the ligand prior to immobilization. Use of this catalyst toward the asymmetric reduction of methyl 2-acetamidoacrylate (35) was more enantioselective than the homogeneous species, with up to 97% e.e. (Scheme 14). It also proved to be recyclable, without appreciable leaching of the metal or loss in catalytic activity after fifteen uses. Maschmeyer et al. successfully demonstrated the immobilization of a similar rhodium chelated catalyst, (-)-1,2-Bis[(2R,5R)-2,5-dimethylphospholano]benzene (Me-Duphos) (36), as seen in figure 15, to an acidic mesoporous aluminosilicate support via ion exchange chemistry. This material afforded greater than a 98% e.e. and in the asymmetric hydrogenation of 35, a value comparable to the homogeneous analog (Scheme 14).

![Chemical structures of Rh(DIPAMP) and Rh(Me-Duphos)](image)

**Figure 15.** Chemical structures of Rh(DIPAMP) and Rh(Me-Duphos)
Scheme 14. Hydrogenation of methyl 2-acetamidoacrylate (35) using heterogeneous Rh(DIPAMP) and Rh(Me-Duphos) catalysts

2.1.3 The development and use of BIPI ligands

In the 1990s, scientists at the pharmaceutical company, Boehringer–Ingelheim developed a proprietary class of chiral phosphinoimidazoline ligands, referred to as BIPI (Boehringer–Ingelheim phosphinoimidazoline) ligands, for use in asymmetric hydrogenations (Figure 16). The concept and design of the BIPI ligands was conceived out of the phosphinooxazoline ligand motif. Although very useful ligands, phosphinooxazolines are not easily tunable from an electronic standpoint. By contrast, the BIPI ligands were constructed to offer facile electronic modification by exchanging the $R_2$ substituent bound to the nitrogen within the imidazoline ring. The chiral information, the $R_1$ substituents, can easily be adjusted as well. Furthermore, the modular design of the BIPI ligands offered the opportunity to rapidly modify other regions of the ligand, such as the arene backbone or the $R_3$ aliphatic groups bonded to the phosphine moiety, to optimize for performance. Accordingly, this highly tunable system afforded a single ligand structural class.
capable of constructing a plethora of catalysts with varying electronic and steric demands to effect asymmetric hydrogenations on a broad range of substrates.

![Figure 16. General structure of a BIPI ligand](image)

The synthesis of BIPI ligands was designed for an efficient, large-scale production. This objective was realized by scientists at Boehringer – Ingelheim with a facile production of kilogram quantities of BIPI 69. From a synthetic perspective, preparing BIPI ligands has proven less laborious than common routes to assemble highly stereoselective diphosphine ligands, obviating the need for optical resolution of intermediates. BIPI ligands are also derived from a comparatively inexpensive chiral diamine instead of an uneconomical chiral diol, reducing costs of the manufacture.

Scheme 15 depicts a generalized synthetic route to a BIPI ligand. The synthesis begins with condensation of a fluoroimidate (37) with a chiral diamine, diphenylethylenediamine or dialkylphenylethylenediamine. The imidate (37) is generated by a facile reaction between fluorobenzamide and commercially available Meerwein’s salt. Next, the essential carbon-phosphorous bond is formed by a nucelophilic aromatic substitution (S_NAr) on the fluoroimidazoline (38) with a dialkylphosphide borane to deliver 39. Subsequent treatment with a tertiary amine
base such as 1,4-diazabicyclo[2.2.2]octane (DABCO) furnishes the deboronated, trivalent phosphine species (40). The final sequence reacts 40 with an acid chloride or electrophile to functionalize the nitrogen atom and produce the BIPI ligand (41).

Scheme 15. Boehringer-Ingelheim synthetic route to BIPI ligands (BIPI 69)

As shown in scheme 16, initial application studies revealed that electron-rich BIPI ligands containing N-alkyl substituents, for example BIPI 35 and BIPI 36 (Figure 17), delivered 10% conversion in the hydrogenation of the substrate 42 with an enantiomeric excess of less than 10%. Conversely, more electron-deficient ligands possessing N-acyl substituents, like BIPI 39 and BIPI 41, (Figure 17) gave quantitative conversion of 42 to 43, with good enantiomeric excess, 85% and 71%, respectively (scheme 16). These results defied the common “rule” that electron-rich ligands were more proficient at performing asymmetric hydrogenations. Moreover,
this discovery was significant as it not only demonstrated how easily tunable the ligand was, but provided insight into the nature of the system. Many different analogues of BIPI 39 and BIPI 41 were synthesized with slight variations to the amide substituent. It was determined that as long as the nitrogen was acylated and that the amide bore an aliphatic substituent, good stereoselectivity was achieved; this region is described as being very “forgiving.”

Scheme 16. Hydrogenation of 42 using BIPI ligands
Studies highlighted the degree to which changes to the aliphatic group bound to the carbonyl within the $R_2$ substituent could be made without affecting the performance of the BIPI ligand. Despite variations to the ring size or the length of the carbon chain of the aliphatic group, consistently high enantioselectivities in the hydrogenation of olefin 42 were realized (Figure 18).
Conversely, further experimentation elucidated the very sensitive nature of a specific region within BIPI ligand. Variations to the substituents attached to the imidazoline ring, R₁, the chiral backbone of the molecule, exhibited a detrimental effect on enantioselectivity. This is clearly evidenced by the performance of BIPI 43, BIPI 51, BIPI 81 and BIPI 86 in the hydrogenation of 42 (Figure 19). The low chiral purity generated by BIPI 43 and BIPI 86 suggests that mobility of the rings is imperative to achieving high selectivity.
Figure 19. Effect of R₁ substituent optimization in the hydrogenation of 42

Other regions of the BIPI ligand were also sensitive to subtle variations with regards to substituent size. Studies indicated that the size of the R₃ aliphatic substituents bound to the phosphine group significantly impacted the activity of the catalysts. Small modifications to that region had very deleterious consequences toward the hydrogenation of 42. This phenomenon is most clearly substantiated by the performance of BIPI 50 versus BIPI 69, a difference of the phosphine bearing a cyclopentyl group instead of a cyclohexyl group. BIPI 50 failed to convert any of 42 to 43, while BIPI 69 afforded quantitative conversion (Figure 20). Accordingly, this region is considered to be the most “unforgiving” in the ligand.
Another part of the ligand explored was the “arene core.” Studies indicated that in the hydrogenation of olefin 42 the enantiomeric excess generated across a range of ligands possessing different substituents off the arene were rather consistent, although BIPI 153 was vastly superior. These substituents included the installation of a naphthyl core, BIPI 153, biphenyl cores, BIPI 87 and BIPI 88, and a tolyl core, BIPI 157 (Figure 21).
Following the optimization studies toward the asymmetric hydrogenation of olefin 42, several BIPI ligand–transition metal complexes (Figure 22) were screened against unfunctionalized olefins. The summarized asymmetric hydrogenation results of 44 to 45 and 46 to 47 underscore the tremendous versatility of the BIPI ligand scaffold and the benefits realized by adjusting minute facets of the structure (Tables 1 and 2).³
Figure 22. BIPI ligands screened in the asymmetric hydrogenation of 44 and 46

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<th>L* = Ligand</th>
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<tbody>
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<td>BIPI 81</td>
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<td>BIPI 153</td>
<td>100</td>
<td>48</td>
</tr>
<tr>
<td>BIPI 206</td>
<td>100</td>
<td>68</td>
</tr>
<tr>
<td>BIPI 238</td>
<td>100</td>
<td>96</td>
</tr>
</tbody>
</table>

Table 1. BIPI ligand screen in the hydrogenation of 44
A range of different functionalized substrates: ene-ureas, ene-amides, ene-carbamates were screened using BIPI 153. While the BIPI 153 delivered the reduced product of each substrate in very high yield, the enantioselectivity varied as shown in scheme 17.4

![Scheme 17. Hydrogenation of functionalized alkenes with BIPI 153](image)

BIPI 153 was examined on additional unsaturated urea-ester derivatives (48-51) and demonstrated excellent enantioselectivity for each substrate, a greater than 99% e.e. was afforded in each case (Figure 23).6
The research team at Boehringer-Ingelheim also examined how BIPI ligands responded to being complexed to different metals. When complexed to rhodium both BIPI 69 and BIPI 153 exhibited high stereoselectivity in the hydrogenation of an unsaturated urea-ester 42 to render 43 in 95% ee and 99% ee, respectively (Scheme 18). BIPI 153 when complexed to iridium, however, the facial selectivity was reserved to deliver the other isomer of 43 in 79% ee.  

Scheme 18. Hydrogenation of 42 with BIPI 69 and BIPI 153 coordinated to rhodium and iridium
2.1.4 An explanation on the development, chemistry and uses of graphene and graphene oxide

In 2010, Andre Geim and Konstantin Novoselov were awarded the Nobel Prize for their groundbreaking work with graphene. Since then, this two-dimensional sheet of sp\(^2\) - hybridized carbon has been central to much innovative research due to its unique thermal, electronic and mechanical properties.\(^{109}\) Graphene has proven effective as a solid support for metallic nanoparticles in heterogeneous catalysis; particularly in carbon-carbon cross coupling reactions, affording low levels of metal leaching as well as high catalytic activity and recyclability.\(^{26,110,111}\)

Graphene is a monolayer of graphite; a single sheet of carbon atoms in arranged in a continuous hexagonal pattern, much like chicken wire, held together by π-stacking interactions. Through acidic oxidation, graphite can be converted to graphite oxide, a derivatized form of the carbon framework, which contains epoxide and hydroxide groups on the basal plane as well as carboxylic acids along the edges (Figure 24). This process concomitantly converts many of sp\(^2\)-hybridized carbons to sp\(^3\)-hybridized, and in so doing, disrupts many of the van der Waals forces of attraction that keep the sheets proximate to one another. Ultrasonication of graphite oxide has proven to exfoliate this three-dimensional crystalline substance to its monolayer, two-dimensional constituent, graphene oxide (GO).\(^{112}\) This process is described in figure 24.
With its functional groups or "handles", GO has emerged a versatile candidate for the covalent immobilization of various molecules onto its surface. Specifically, GO has served to anchor gold electrode scaffolds for use in nitrogen dioxide gas recognition. It has been utilized to fabricate a robust electrochemical sensor for detection of 4-nonylphenol in the environment as well. Moreover, this oxidized form of graphene has been functionalized with drugs, electrochemiluminescent reagents, and peptides for a variety of meaningful applications. Recently, this carbon scaffold has served to attach ligand–metal complexes for use in catalytic reactions. In one example, an achiral ligand coordinated to Wilkinson catalyst demonstrated enhanced activity towards hydrogenating an unfunctionalized alkane, cyclohexenone, and was recycled up to five times. In another case, a chiral ligand was covalently bound to GO for use in an asymmetric epoxidation of an olefin, exhibiting excellent stereoselectivity and reusability.

Several methods to covalently bond molecules to GO exist; all of which exploit the chemical reactivity of various oxygen functional groups on the surface to serve as anchor points. Numerous immobilizations have been achieved by peptide
coupling chemistry; a reaction between a carboxylic acid group on the edge of GO and a pendant amine moiety on the reactant in the presence of an activating agent, resulting in the formation of an amide bond. Variations to this end have been realized by initially converting the carboxylic acids to acid chlorides, a highly reactive electrophile that reacts with an amine moiety without the need of any additives. Another route to functionalization includes “click” chemistry, a cycloaddition that requires installing either an azide or an alkyne group onto the surface of GO before treating it with the reactant bearing the other moiety. Several other attachment sequences involve alkylation via SN₂ chemistry between chemically installed nucleophilic groups on GO and electrophilic reactants, as well as silylations between the hydroxyl groups on the basal plane of GO and reactants containing alkoxy silane groups.

2.1.5 Significance of work

As evidenced, BIPI ligands are very useful in asymmetric hydrogenations. They have a broad range of application, enabled by their tunability and segmental design. Their highly scalable, facile and economical synthetic sequence supports large-scale production, rendering them valuable on an industrial level. However, these chiral ligands are homogeneous and coordinated to precious metals, rendering them irrecoverable and expensive.

Fortunately, the nature of the “forgiving” N-acyl region has shown, upon certain R₂ substituent modification, not to compromise the catalytic functionality, offering a
reactive site that could serve as a point of attachment to other chemical species. For these aforementioned reasons, BIPI ligands are promising candidates for their immobilization onto solid support systems, particularly GO for its unique physical properties.\(^4\)

The demand for enantio-pure compounds in the life sciences continues to increase,\(^28\) and “among the various methods to selectively produce one single enantiomer of a chiral compound, enantioselective catalysis is arguably the most attractive method.”\(^18\) While chemists have developed a prodigious arsenal of chiral catalysts and procedures to effect asymmetric induction, sophisticated chiral ligands are often more expensive than the already costly concomitant metal. Thus, “catalyst recovery is of paramount importance for the application of enantioselective metal catalysis to large scale processes.”\(^29\) Fully cognizant of the importance, we sought to tether these BIPI ligands to GO to enable their use as heterogeneous catalysts in asymmetric hydrogenations, and in so doing provide an economical and environmentally friendly, chiral catalyst to the chemical community.

### 2.2 Immobilization of BIPI ligand onto GO

#### 2.2.1 Installation of the spacer onto BIPI 69 precursor

Given the numerous literature precedents that use spacers to minimize interactions between ligands and the solid supports to which they are covalently bound,\(^28\) we chose to install a linker onto BIPI 69 in an effort to create some distance between the ligand and the surface of GO. A precursor to BIPI 69 (52) was
selected as the test ligand due to its availability, which was sourced from our collaborators at Boehringer-Ingelheim (Scheme 20). This non-amidated form of BIPI 69 provided a reactive site, a nitrogen atom within the imidazoline ring, to install the spacer; the region of the molecule identified as most “forgiving” and optimal for attachment to solid supports. We elected to use γ-aminobutyric acid (53) as the spacer.

To prevent the spacer from polymerizing in subsequent reactions, the primary amine on 53 was first protected by reacting it with di-tert-butyl dicarbonate (BOC₂O) in a mixture of sodium hydroxide and isopropanol, which delivered 54 in 90% isolated yield (Scheme 19). With the BOC (tert-butyloxy carbonyl)-protected spacer (54) in hand, we then subjected it to peptide coupling chemistry with 52, to afford 55 in a 48% isolated yield. Since deboration tends to occur in the presence of tertiary amines and unprotected phosphines are highly susceptible to oxidation, the solvent used in this reaction (and all future reactions until BIPI complexation with rhodium) was degassed and the reaction was conducted under an inert atmosphere. Acid treatment then quantitatively deprotected 55 to render 56, the amidated BIPI 69 product possessing a four-carbon linker with a reactive amino terminus.

![Scheme 19. BOC-protection of γ-aminobutyric acid (53)](image-url)
2.2.2 Proof of concept: functionalization of GO with 4-bromobenzyl amine

Prior to immobilizing 56 to GO, we functionalized GO with an analogous molecule, p-bromobenzylamine (57) via peptide coupling chemistry with N,N'-dicyclohexylcarbodiimide (DCC) as a proof of concept with conditions acquired from the literature (Scheme 21). The reaction contents were heated to reflux in tetrahydrofuran (THF) for 48 hours. The bromine substituent acted as a diagnostic tag allowing us to determine the extent of immobilization by scanning electron microscope/energy dispersive x-ray spectroscopy (SEM/EDX). SEM/EDX analysis indicated successful attachment: approximately 0.291 mmol of 57/g GO.
2.2.3 Proof of concept: rhodium deposition onto GO

Our collaborators at Boehringer-Ingelheim cautioned us that the peptide coupling conditions we used to attach 56 to GO might be harsh, and that if 56 is complexed to a metal prior to immobilization, leaching could transpire. Considering their advice, we initially elected to attach 56 to GO and then coordinate the heterogenized BIPI 69 ligand to rhodium (Rh) afterward, rather than change the reaction conditions. Interested in whether or not this approach could lead to nonselective coordination between Rh and any unreacted carboxylic acid sites on GO-BIPI 69, we added a Rh precatalyst, Bis(norbornadiene)rhodium(I) tetrafluoroborate, (Rh(nbd))\(_2\)BF\(_4\), to a slurry of GO (Scheme 22). SEM/EDX analysis suggested that Rh coordinated to GO: approximately 0.494 mmol of Rh/g GO. We hypothesized that the carboxylate groups on the edges of GO chelate the Rh serving to anchor it to the surface.

Scheme 21. Immobilization of 57 to the surface of GO

Scheme 22. Rhodium deposition onto GO
2.2.4 Functionalization of GO with BIPI 69 (-Rh): two routes

With a peptide coupling method in hand, yet fully aware of the potential for nonselective Rh coordination, we pursued two paths to prepare the heterogeneous BIPI 69 catalyst.

2.2.4.1 Route I: functionalize GO with BIPI 69, then complex to rhodium

The first route sought to immobilize 56 to GO using the established amide bond forming conditions, followed by complexation to Rh (Scheme 23). The attachment of 56 to GO and subsequent coordination to Rh was monitored by a multitude of techniques: X-ray photoelectron spectroscopy (XPS), X-ray diffraction (XRD), Fourier transform infrared spectroscopy (FTIR), SEM/EDX and inductively coupled plasma optical emission spectrometry (ICP-OES).

Scheme 23. Route I: immobilize 56 to GO, then coordinate to Rh
To examine the compositional changes to the surface of GO, XPS was conducted. After subjecting 56 and GO to the peptide coupling conditions, XPS of GO-BIPI 69 indicated the presence of phosphorous (P) with a weak signal at 132.04 eV and nitrogen (N) with a signal at 399.46 eV (Figure 25, A). This spectrum was similar to the XPS spectrum of 52 (the precursor to 56), which contained the same signals for P 2p and N 1s (Figure 25, B). The P and N atoms served as the diagnostic tags on 56, allowing us to easily monitor the appearance of 56 on the surface of GO. Although the XPS spectrum of pristine GO (Figure 25, C) did contain the N 1s signal, it did not contain the P 2p peak. The emergence of the P 2p signal on XPS spectrum, although not strong, along with the reduction in the O 1s signal relative to the C 1s signal provided evidence for successful immobilization.
Figure 25. XPS spectra of GO-BIPI 69 (A), 52 (B), GO (C) and GO-BIPI 69-Rh (D)
High-resolution XPS revealed significant changes in the binding energies of the carbon atoms associated with the carboxylic acid groups residing on the surface of GO. As seen in figure 26, pristine GO contains a large signal at 286.67 eV, which corresponds to C-O-C and C-OH bonding energies, along with a broad signal at 288.12 eV that represents the COOH peak. Compared to GO, the XPS spectrum of GO-BIPI 69 (Figure 26, B) shows a reduction in these signal intensities and the appearance of a C-N peak while maintaining a consistent C=O peak, indicating the formation of amide bonds between 56 and GO. We also monitored the complexation of GO-BIPI 69 to Rh by XPS, which revealed the same signals associated with GO-BIPI 69, but additionally included the Rh 3p peak (Figure 25, D).

To evaluate the changes to the surface structure of GO through the immobilization process, XRD was employed. XRD analysis was performed on pristine GO, GO-BIPI 69 and GO-BIPI 69-Rh. In theory, exfoliated monolayers of GO are amorphous and therefore no diffractions should be observed. However, a broad
band at diffraction angles $2\theta = 11^\circ$ is present for GO, which is indicative of some of 
GO reaggregation (Figure 27, A). Upon immobilization, the peak of GO-BIPI 69 
showed a slight shift downward to $2\theta = 10^\circ$, suggesting that the interlayer space 
between the GO sheets had increased (Figure 27, B). We hypothesized that the 
increase in distance between the layers was a result of the successful attachment of 
56. XRD analysis of GO-BIPI-Rh continued that downward trend ($2\theta = 9^\circ$), 
indicating that addition of Rh caused further disruption of the GO stacking (Figure 
27, C).

![Figure 27. XRD measurements of GO (A), GO-BIPI 69 (B) and GO-BIPI 69-Rh (C)](image)

FTIR was also used to analyze the attachment of 56 to GO. The FTIR 
spectrum of GO included three signature stretches corresponding to: the hydroxyl 
group (3407.48 cm$^{-1}$) and the carbonyl moiety (1729.17 cm$^{-1}$) of the carboxylic acid, 
as well as the epoxy group (1222.51 cm$^{-1}$), as seen in figure 28. FTIR revealed
that the characteristic cyclic C-H stretching vibrations at 2922 cm\(^{-1}\) and branched C-H stretches at 2853 cm\(^{-1}\), seen on the spectrum of 52 (the precursor to 56), are present on GO following the peptide coupling reaction with 52. Additional diagnostic stretches originating from 52 are prominent on the surface of GO as well: C=N (1529 cm\(^{-1}\)), P–aromatic (1216 cm\(^{-1}\)) and aliphatic (1105 cm\(^{-1}\)). The emergence of these absorption bands was also accompanied by a reduction with respect to the hydroxyl group absorption band. The spectrum of GO-BIPI 69 was nearly identical to GO-BIPI 69-Rh in these regions, which provided further evidence that 52, the precursor to 56, containing numerous aliphatic groups was immobilized to GO. Despite these results, inspection of the carbonyl region was ambiguous as to whether the peptide coupling chemistry successfully converted the carboxylic acids to amides on GO. The carbonyl stretching vibration of a carboxylic acid occurs between 1760 cm\(^{-1}\)–1706 cm\(^{-1}\), while that of an amide carbonyl occurs at a slightly lower range of wavenumbers, between 1694 cm\(^{-1}\)–1640 cm\(^{-1}\). The FTIR data did not conclusively support these literature values.\(^{129}\)
Next, we quantified the extent of 56 immobilization to GO by two different methods: SEM/EDX and ICP-OES. SEM/EDX revealed that approximately 0.431 mmol of 56 was attached to 1 gram of GO. We then conducted an orthogonal experiment to validate these results. To do so, a sample of GO-BIPI 69 was subjected to acid hydrolysis, cleaving the ligand from the solid support. The supernatant containing 56 was then separated from GO and analyzed by ICP-OES. ICP-OES analysis corroborated the initial surface characterization results: approximately 0.419 mmol of 56 was loaded onto 1 g of GO.
To verify these results, we double backed and analyzed the GO material after acid hydrolysis as well as the supernatant following a wash that did not contain acid. We were interested in whether the amide bond was hydrolyzed or if 56 was detected by ICP-OES due to inadequate washing during the preparation of the material. After subjecting the sample of GO-BIPI 69 to acid hydrolysis, the resulting solid material, by SEM/EDX, showed a ligand loading of 0.082 mmol/g GO, which suggested that acid was necessary to cleave the ligand from the support. The presence of some 56, we theorized, was due to insufficient washing after the acid treatment. Given these results, we then analyzed the supernatant after washing the GO-BIPI 69 material in the absence of acid by ICP-OES showed 0.136 mmol 56/g GO.

That ICP-OES revealed a higher amount of 56 after acid hydrolysis (0.419 mmol/g GO) coupled with the fact that the measurement reflected the value ascertained by SEM/EDX of the GO-BIPI 69 not exposed to acid (0.431 mmol/g GO), provided additional evidence that amide bonds had been formed between 56 and GO.

Qualitatively, we looked for evidence of immobilization by placing GO and GO-BIPI 69-Rh in separate vials that contained an immiscible mixture of water and dichloromethane (DCM). We inspected for any phase preference between the two materials. GO, which possesses oxygenated functional groups, is capable of hydrogen bonding with water. The immobilization process however, forms highly aliphatic amide moieties bearing the BIPI 69 ligand, which favor organic solvents. As anticipated, GO was preferentially suspended in the water layer, while the GO-BIPI 69 sample was predominately located in the organic phase (Figure 29).
These results further supported the covalent attachment of the chiral ligand to GO, and were consistent with a published report.\textsuperscript{116}

![Image of suspensions of GO-BIPI 69 and GO in DCM and water]

**Figure 29.** Suspensions of GO-BIPI 69 (left) in DCM and GO (right) in water

### 2.2.4.2 Route II: complex BIPI 69 to rhodium, then immobilize to GO

The second approach sought to coordinate 56 to Rh prior to loading the complex onto the surface of GO (Scheme 24). Cognizant of the potential for nonselective Rh coordination to GO, we deliberately added less than one molar equivalent of Rh to 56 to minimize that undesired outcome. \textsuperscript{31}P nuclear magnetic resonance (NMR) was used to confirm that after addition of Rh, Rh was complexed to P through dative bonding to render 58. This technique was also used to determine that some 56 still bore P in the trivalent oxidation state; a result that suggested no unchelated Rh would be present during the subsequent immobilization process. Once the ligand-metal complex was successfully prepared, the same amide bond forming reaction used in route I was employed here.
SEM/EDX analysis was used to quantify the loading of 58 to the surface of GO. Results indicated that approximately 0.229 mmol of 58 was attached to 1 g of GO, a lower value than the material prepared through route I.

**2.3 Application of GO-BIPI 69 in asymmetric hydrogenation of an olefin**

Given the high reactivity and enantiomeric selectivity that BIPI 69 exhibited toward hydrogenating 42, we selected to use 42 as our model substrate in evaluating the activity of GO-BIPI-69. All hydrogenation reactions were conducted in autoclaves using a HEL-ChemSCAN (Figure 30).
2.3.1 Application of homogeneous derivatized BIPI 69–Rh

BIPI 69, as developed by our collaborators at Boehringer-Ingelheim, contains a cyclohexyl group as a part of the amide moiety. The analogue that we prepared, 58, contains a straight four-carbon chain with a primary amine terminus. Interested in whether this pendant group would alter the catalytic activity or selectivity of the hydrogenation, it was screened against 42 (Scheme 25). The hydrogenation conditions were slightly modified from what was reported in the literature with BIPI 69; the literature precedent achieved full conversion of 42 to 43 in 95% e.e. under 7 bar of H₂, at 30°C for 16 hours in methanol (MeOH).⁴ Comparatively, under 30 bar of H₂, at 65°C for 18 hours in MeOH, our homogenous BIPI 69 derivative 58 afforded complete conversion of 42 to a mixture of the stereoisomers of 43, with 74% enantiomeric excess.
Scheme 25. Hydrogenation of 42; model substrate evaluated in the application of various homogeneous and heterogeneous BIPI 69 catalysts

2.3.2 Application of rhodium deposition onto GO

The GO-Rh material was tested for catalytic activity in the hydrogenation of 42 (Scheme 25). The GO-Rh material demonstrated high reactivity and the ability to be recovered and recycled; not surprisingly, the catalyst afforded no enantiomeric selectivity to the saturated product (Table 3). That this material exhibits high catalytic activity with several recycles, yet does so without any stereoselectivity strongly suggests that the rhodium is in fact coordinated to the functional groups on the surface of GO.
Table 3. Recyclability study in the hydrogenation of 42 with GO-Rh

<table>
<thead>
<tr>
<th>Entry</th>
<th>Recycle</th>
<th>% Conversion</th>
<th>% ee</th>
</tr>
</thead>
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<td></td>
<td>100</td>
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</tr>
<tr>
<td>3</td>
<td>2</td>
<td>25</td>
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*a0.494 mmol Rh/1 gram GO; 29.4 mol% catalyst. b% conversion determined by 1H NMR. c% ee determined by HPLC.*

2.3.3 Application of GO – BIPI 69 – Rh prepared from route I

The GO-BIPI-69-Rh material prepared via route I was used as a catalyst to effect the asymmetric hydrogenation of 42. While the material demonstrated catalytic activity, with the ability to be recovered and recycled, it failed to do so stereoselectively (Table 4). The hydrogenation results were analogous to those produced by the GO-Rh material that did not bear the chiral ligand. Similarities in outcomes led us to conclude that Rh was not complexed to the immobilized BIPI ligand, but mostly likely coordinated to the oxygenated functional groups on GO. We speculated that the decrease in activity (entries 1–4) could be the result of coordinated Rh leaching from GO. We also considered that any Rh that was uncoordinated to GO and acted like a homogeneous catalyst in the hydrogenation experiments. We theorized this was due to inadequate washing during the preparation of GO-BIPI 69-Rh. Both hypotheses were examined.
Table 4. Recyclability study in the hydrogenation of 42 with GO-BIPI 69-Rh (prepared via route I)

<table>
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<th>Entry</th>
<th>Recycle</th>
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*0.413 mmol ligand & 0.348 mmol Rh/1 gram GO; 20.7 mol% catalyst. % conversion determined by $^1$H NMR. % ee determined by HPLC.

To test our hypothesis that Rh was overwhelmingly coordinated to the oxygenated functional groups on GO but had leached over time, we first evaluated the product mixture for Rh following the second reaction. To do this, the GO-BIPI 69-Rh material was centrifuged, and the supernatant was separated from the heterogeneous mass and used in a subsequent hydrogenation with fresh 42 under identical conditions. Surprisingly, use of the supernatant in the hydrogenation showed no conversion of the unsaturated compound, 42. This strongly suggested that no Rh was present in the solution and therefore Rh had not leached off the surface of GO. We conducted an orthogonal test to validate this hypothesis. We analyzed the wash layers after the first reaction and the product mixture after the third and final reaction to ICP-OES. From the ICP-OES analysis, the Rh content in the solutions was 44 ppb and 40 ppb, respectively. The values of Rh in the first
reaction's wash layer and final reaction's product mixture, although low, indicated that steady, minute leaching might be the cause of the decrease in activity.

The next study tested the theory that Rh was present as a result of inadequate washing during the preparation of GO-BIPI 69-Rh. We evaluated the extent of any unbound Rh after the procedural five wash treatments by washing another allotment of unused GO-BIPI 69-Rh and subjecting the supernatant of the sixth wash in the hydrogenation of 42 without any added catalyst. Despite scrupulous measures to completely separate the heterogeneous material from the supernatant, trace amounts were added to the reaction. The supernatant afforded a 14% conversion of 42 to 43. That only 14% of 42 was converted to 43 using the supernatant of the sixth wash, despite the presence of some heterogeneous material, while two uses of the GO-BIPI 69-Rh saw quantitative conversion, suggested that uncoordinated Rh was not present in large enough quantities to effectively catalyze the reaction of 42. Thus, we concluded that the majority of the Rh present in the initial recyclability study was coordinated to the surface of GO and was slowly leaching over subsequent runs.

Since the prior experiment with the homogeneous BIPI 69-Rh complex indicated that the homogeneous catalyst was capable of stereoselectively hydrogenating the substrate 42, we concluded that the lack of stereoselectivity produced by heterogenized catalyst was not due to pertubations of the ligand as a result of derivatizing it with a spacer. Moreover, that the GO-Rh material was able to non-stereoselectively hydrogenate 42 through multiple trials, we concluded that addition of Rh to GO-BIPI 69 may result in nonspecific complexation of the metal.
Thus, we turned our attention to form the ligand-metal complex prior to immobilizing the ligand onto GO.

2.3.4 Application of GO – BIPI 69 – Rh prepared from route II

Given the inability of GO-BIPI 69-Rh prepared via route I to selectivity hydrogenate 42, we turned our attention to evaluating the heterogeneous material assembled through route II. Under identical reaction conditions to previous experiments, the GO-BIPI 69-Rh material that was formed by first pretreating the ligand with Rh converted 42 to 43 with modest stereoselectivity. However, it failed to convert all of 42 to 43 (entry, 1 Table 5). To test the recyclability of this material, we resubjected it to another portion of 42. Conversion results were comparable to the first reaction, but the stereoselectivity of the process decreased (entry 2, Table 5).

We hypothesized that the reactions would proceed to completion if more equivalents of the heterogeneous material were added. Despite increasing the catalyst loading 6 fold, however, a boost in conversion of 42 was not realized. That the material was somewhat catalytically active, favoring the production of one stereoisomer over the other, but unable to fully consume 42 regardless of the high loading, led us to two suppositions. First, we concluded that to obtain any stereoselectivity Rh should be coordinated to the ligand prior to immobilization, and thus route II was superior toward achieving that result. Second, we theorized that the ligand-metal complex was not readily accessible by the substrate due to either
reaggregation of GO or the nature of bulk GO, which could contribute to steric hinderance of the ligand. Thus, we sought to test our hypotheses by attaching 58 to a different solid support, a polystyrene resin.

Table 5. Recyclability study in the hydrogenation of 42 with GO-BIPI 69-Rh (prepared via route II)

<table>
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<th>Entry</th>
<th>Recycle</th>
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<th>% ee</th>
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</tr>
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*0.229 mmol ligand & 0.147 mmol Rh/1 gram GO; 8.75 mol% catalyst. % conversion determined by ¹H NMR. % ee determined by HPLC.

2.4 Immobilization of BIPI 69 ligand onto polystyrene resins

To gain insight into immobilizing a molecule onto a polystyrene resin, we elected to initially use 4-bromobenzyl amine (57) as the proxy ligand. Once reaction conditions were established, we then sought to employ the aforementioned route II approach that was used to immobilize the BIPI 69 ligand-metal complex to GO, to the polystyrene resin.
2.4.1 Proof of concept: functionalization of carboxylic resin with 4-bromobenzyl amine

In attempt to maintain as much consistency between this work and our previous efforts with GO, we elected to use the same peptide coupling conditions to tether 57 to the carboxylic acid polystyrene resin (Scheme 26).

Scheme 26. Immobilization of 57 to polystyrene resin

SEM/EDX analysis was once again employed to monitor the presence of bromine and measure the extent of attachment. Results indicated successful attachment: approximately 0.310 mmol of 57/g resin, analogous to the immobilization of 57 to GO.

2.4.2 Functionalization of carboxylic resin with BIPI 69 ligand

Having successfully anchored 57 to the polystyrene resin, we repeated the same procedure to immobilize the BIPI 69-Rh ligand-metal complex, 58 (Scheme 27). SEM/EDX analyzed indicated successful amide bond formation, approximately 0.308 mmol of 58/g resin.
2.5 Application of BIPI 69-Rh resin in asymmetric hydrogenations of olefins

Since the intention for immobilizing the BIPI 69-Rh ligand metal complex was to validate the hypothesis that GO impeded the hydrogenation of 42, we elected to hydrogenate 42 under identical conditions to evaluate this material's catalytic activity (Scheme 25). Results showed that 58 attached to the polystyrene resin was catalytically active, completely converting 42 to 43. Moreover, it formed 43 with similar enantioselectivity as the free derivatized ligand (entry 1, Table 6). The recyclability of the heterogeneous catalyst was then evaluated. While there was a noticeable reduction in conversion of the unsaturated substrate to product, a more pronounced decrease in the stereoselectivity of the hydrogenation was observed (entry 2, Table 6). A third use of this material continued this trend, a drop in both catalytic activity and the asymmetric induction of 42.

Scheme 27. Immobilization of BIPI 69-Rh complex to polystyrene resin

\[
\text{carboxylic resin} \quad \overset{\text{DCC, DIPEA}}{\longrightarrow} \quad \overset{\text{THF; reflux 48 hrs}}{\text{BIPI 69-Rh resin}}
\]

\[
\text{Scheme 25. Application of BIPI 69-Rh resin in asymmetric hydrogenations of olefins}
\]
Table 6. Recyclability study in the hydrogenation of 42 with BIPI 69-Rh resin

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*0.308 mmol ligand & 0.229 mmol Rh/1 gram GO; 13.67 mol% catalyst. % conversion determined by 1H NMR. % ee determined by HPLC.

The results of the first hydrogenation reaction with BIPI 69-Rh resin strongly supported our hypothesis that GO was inhibiting the catalytic process. The lack of recyclability, however, generated concern that the ligand-metal complex was not covalently bound to the resin. To gather insight into the decreasing catalytic activity and stereoselectivity of the material, we performed SEM/EDX analysis of BIPI 69-Rh resin prior to the first reaction and after the third. Results from this elemental analysis technique revealed that the amount of ligand in the sample remained constant, as indicated by the presence of P, but that the quantity of Rh had decreased by more than 40%. This data indicated that the ligand was bound to the resin, and that the steady loss of activity could be explained by the leaching of the metal. To verify this discovery, we repeated the same experiment with another sample of BIPI 69-Rh resin. The SEM/EDX results were the same. We theorized that Rh leaching could be responsible for the loss of stereoselectivity: Rh, unchelated to
the chiral ligand, would be present to catalyze the hydrogenation of 42 to 43, but would not do so enantioselectively.

2.6 Conclusions

With the immobilization of the BIPI 69 ligand to the surface of GO, we have demonstrated, to the best of our knowledge, the second example of the covalent attachment of chiral ligand-metal complexes to the surface of GO. Moreover, we have developed a procedure that can serve as a template to attach a broad range of other BIPI ligands or other chiral ligands to solid supports like GO or polystyrene resins.

As demonstrated, the GO-BIPI 69-Rh material prepared by attaching the ligand to GO prior to Rh complexation is catalytically active and recyclable, but not stereoselective. Conversely, the GO-BIPI 69-Rh material prepared by pre-coordinating the Rh to the ligand was enantioselective, but not very catalytically active. Given the ability of the derivatized BIPI 69-Rh complex to catalyze the hydrogenation of 42 when covalently anchored to the resin, however, we encourage future work to explore how GO as a solid support impacts asymmetric catalytic hydrogenation. Moreover, a study to evaluate whether a spacer with a longer carbon chain improves the catalytic activity of the ligand supported on GO should be executed.

In examining the lack of recyclability and the leaching of Rh from the heterogenized BIPI 69 ligand (whether bound to GO or the resin), it is plausible that
the phosphine became increasingly oxidized during successive reactions despite being coordinated to the metal. This phenomenon has been documented in the literature: “accidental oxidation is a common problem in synthesis of immobilized phosphine ligands and can be a limitation in catalyst recycling.” In one example, chiral pyrrolidine-containing diphosphines coordinated with Rh(I) and tethered to polymers demonstrated the ability to hydrogenate alkenes such as N-benzoyl dehydrophenylalanine to N-benzoyl phenylalanine in 90% enantiomeric excess. However, the polymeric phosphine was oxidized during dialytic separation techniques that involved large volumes of solvents.

Given this knowledge, we conclude that the issue of phosphine oxidation could be mitigated with greater experimental care, such as sufficiently degassing the solvents or conducting the reaction and isolation steps under an inert atmosphere, like in a glove box. Future work should ensure that the large amounts of solvent used for washing this heterogeneous material, after metal complexation and between reactions, are adequately degassed and that the catalyst is stored in an inert environment.

2.7 Experimental

2.7.1 General remarks

All reactions were conducted under ambient conditions unless otherwise indicated. Hydrogenation reactions were conducted using a HEL ChemSCAN, a parallel high-pressure reaction system. The reagents were purchased from
commercial suppliers including Sigma Aldrich, ChemPep Inc., Inorganic Ventures and Graphene Supermarket, as well as from collaborating chemists at Boehringer-Ingelheim; all were used as received. Surface analysis was executed on a PANalytical X’Pert Pro diffractometer and a Nicolet Nexus 670 FTIR. Elemental analysis was performed on: a ThermoFisher Scientific ESALAB 250 X-ray photoelectron spectrometer using a monochromatic Al KR X-ray, a Zeiss Auriga FIB scanning electron microscope equipped with energy dispersive X-ray detection, and an Varian Vista MPX Axial inductively coupled plasma optical emission spectrometer (ICP-OES). Sonication was carried out using a Cole-Parmer CPX 750 ultrasonicator. The chiral purity of the hydrogenation reactions were monitored using a Waters ACQUITY UPLC M-Class system equipped with a chiral, reverse phase column (Chiralpak AD-H, 4.6 mm X 25 cm, 5 micron particle size) acquired from Daicel. Both \textsuperscript{1}H NMR and \textsuperscript{13}C NMR spectra were obtained on a Varian Mercury 300 MHz or Bruker 600 MHz NMR spectrometer using CDCl\textsubscript{3} or DMSO-d\textsubscript{6} as solvents. NMR data is represented as follows: chemical shift, multiplicity (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, m = multiplet), integration. Mass spectrometry data was acquired on an Advion expression CMS equipped with a TLC plate reader. Purification was carried out on a Biotage Isolera Flash Purification System.
2.7.2 Preparation of GO-BIPI 69–Rh: route 1

4-((tert-butoxycarbonyl)amino)butanoic acid (54)

\[
\text{HO} \quad \text{N} \quad \text{O} \quad \text{C}=\text{O} \\
\text{C} \quad \text{H} \quad \text{C} \quad \text{H} \quad \text{N} \quad \text{O} \quad \text{C}=\text{O}
\]

In a 250 mL round bottom flask, equipped with a magnetic stir bar, a mixture of 100 mL 1M NaOH (aq.)-iPrOH (4:3) was added, followed by γ-amino butyric acid (3.09 g, 30 mmol, 1 eq.) and di-tert butyl dicarbonate (6.55, 30 mmol, 1 eq.). The reaction mixture was then stirred for two hours. At the conclusion of the reaction, the reaction contents were washed with low boiling petroleum ether (2 x 50 mL), acidified with 2 N H₂SO₄ until a pH of 3 was established. Finally, the acidified solution was extracted with CH₂Cl₂ (3 x 20 mL), dried over MgSO₄ and concentrated on a rotary evaporator to yield BOC-γ-amino butyric acid (5.48 g, 90%). ¹H NMR (CDCl₃): \(\delta = 9.87 \text{ (br s, 1H)}, 4.74 \text{ (m, 1H)}, 3.16 \text{ (m, 2H)}, 2.37 \text{ (t, 2H)}, 1.80 \text{ (quint, 2H)}, 1.42 \text{ (s, 9H)} \ \text{ppm.}\) ¹³C NMR (CDCl₃): \(\delta = 177.6, 156.3, 79.3, 39.7, 31.2, 28.3, 25.4 \ \text{ppm.}\) Upon comparison, the spectra collected was identical to that reported in the literature.
**tert-butyl (4-((4S,5S)-2-(2-(dicyclohexylphosphanyl)phenyl)-4,5-diphenyl-4,5-dihydro-1H-imidazol-1-yl)-4-oxobutyl)carbamate (55)**

![Chemical Structure](attachment:image.png)

In a 250 mL three neck round bottom flask, equipped with a stir bar and a direct nitrogen line and septum, 100 mL of anhydrous dimethylformamide (DMF) was charged. The DMF was sparged with gaseous nitrogen for 15 minutes prior to the addition of BIPI 69 (7.46 g, 13.7 mmol, 1 eq.), 4-((tert-butoxycarbonyl)amino)butanoic acid, 54 (3.35 g, 16.5 mmol, 1.2 eq.), 1-hydroxybenzotriazole (HOBt) (2.52 g, 16.5 mmol, 1.2 eq.), N-(3-dimethylaminopropyl)-N’-ethylcarbodiimide hydrochloride (EDC) (3.16 g, 16.5 g mmol, 1.2 eq.), and N,N’-diisopropylethylamine (DIPEA) (7.169 mL, 41.2 mmol, 3 eq.). The reaction mixture was stirred for 19 hours at room temperature (RT). After completion, the reaction contents were then take up in 375 mL of degassed ethyl acetate (EtOAc) and washed with 500 mL of 0.5 N HCl, followed by 500 mL of 0.1 N NaOH. The resulting solution was dried over MgSO₄ and concentrated on a rotary evaporator to yield a crude mixture. ESI-MS, m/z calculated for 55, C₄₂H₅₄N₅O₃P + H⁺: 680.40, was found: 680.39. Purification of the crude product, using a flash chromatography unit equipped with a 50 g KP-Sil SNAP column, eluted via a gradient of 90:10 hexane:EtOAc to 50:50 hexane:EtOAc across 11 column volumes, and observed at 254 and 280 nm, afforded a 48% isolated yield of 55 as a white solid. ^1H NMR (DMSO-d₆): δ = 7.92 (m, 1H) 7.41–7.62 (m, 13H), 6.69 (t, 1H),
5.88 (br s, 2H), 5.15 (d, 1H), 2.70-2.79 (m, 3H), 0.99-2.00 (m, 34H) ppm. $^{13}$C NMR (DMSO-d$_6$): δ = 170.3, 156.1, 130.9, 129.9, 129.2, 128.58, 128.54, 127.9, 126.1, 125.2, 79.3, 39.7, 31.2, 28.3, 25.4, 77.9, 33.6, 33.2, 28.7, 27.1, 26.4, 26.3, 25.9, 24.8 ppm.

4-((4S,5S)-2-(dicyclohexylphosphanyl)phenyl)-4,5-diphenyl-4,5-dihydro-1H-imidazol-1-yl)-4-oxobutan-1-aminium chloride (56)

![Chemical Structure](image)

104 mL of 4M HCl in dioxane was charged to a 250 mL three neck round bottom flask, equipped with a stir bar and a direct nitrogen line and septum. The reaction vessel was submerged in an ice bath and allowed to cool to 0°C and the solvent was sparged with nitrogen for 15 minutes. Then, tert-butyl (4-((4S,5S)-2-(dicyclohexylphosphanyl)phenyl)-4,5-diphenyl-4,5-dihydro-1H-imidazol-1-yl)-4-oxobutyl)carbamate 55 (7.27g, 10.4 mmol, 1 eq.) was added to the round bottom flask. After 10 minutes, the vessel was removed from the ice bath and allowed to warm to room temperature (RT) for 90 minutes. After completion, the reaction contents were then placed on a rotary evaporator with degassed MeOH to remove the HCl/dioxane to yield 56 as an oil (6.54 g, 100%). ESI-MS, $m/z$ calculated for 56, $C_{37}H_{47}N_3OP^+$: 580.35, was found: 580.34.
**GO-(4-bromophenyl)methanamine (57)**

In a 100 mL three neck round bottom flask, equipped with a magnetic stir bar, 0.050 g of GO, (4-bromophenyl)methanamine 57 (0.124 mL, 0.65 mmol, 1 eq.), DCC (0.050 g, 0.024 mmol, 0.37 eq.), and 25 mL THF were added. The reaction mixture was sonicated for 1 hour. Then, the reaction vessel was then removed from the sonicator and heated to reflux for 48 hours. After completion, the reaction contents were placed on a rotary evaporator and heated in an oven at 120°C for five hours. It was then taken up in 10 mL of THF and poured into a 400 mL flask of MeOH. The solid settled to the bottom of the flask and the supernatant was decanted. The solid was filtered over a 3 micron filter, washed with 30 mL of water, followed by a subsequent 30 mL washed with MeOH to deliver 0.032 g of material. SEM/EDX: 0.291 mmol of 57/g GO.

**GO-Rh**

To a 3 neck round bottom flask, equipped with a stir bar, 20 mL of degassed THF, 0.200 g of bis(norbornadiene)rhodium(I) tetrafluoroborate and 0.200 g of GO were charged. The reaction was stirred for 24 hours. The product was placed into a vial, washed with 20 mL of MeOH and centrifuged. The resulting supernatant was decanted, leaving behind the solid GO material in the vial. This process was repeated four more times. The sample was dried under vacuum. SEM/EDX: 0.494 mmol Rh/g GO.
GO–BIPI 69

In a 50 mL three neck round bottom flask, equipped with a magnetic stir bar and a direct nitrogen line and septum, 30 mL THF was added. The THF was sparged with nitrogen for 15 minutes prior to the addition of GO (300 mg) and DCC (1.025 g, 4.97 mmol, 1.02 eq.). The reaction mixture was sonicated for 15 minutes, then 4-((4S,5S)-2-(2-(dicyclohexylphosphanyl)phenyl)-4,5-diphenyl-4,5-dihydro-1H-imidazol-1-yl)-4-oxobutan-1-aminium chloride 56 (3 g, 4.875 mmol, 1 eq.) and the DIPEA (2.54 mL, 14.6 mmol, 3 eq.) were charged to the flask and the contents were further subjected to sonication for 1 hour. The reaction vessel was then removed from the sonicator and heated to reflux for 48 hours. After completion, the reaction contents were suspended in degassed MeOH (200 mL), centrifuged at 4,200 rpm and decanted. This process was repeated four times. Finally, the product was placed in an oven under vacuum to yield 0.401 g. SEM/EDX: 0.389 mmol ligand (56)/g GO.

GO–BIPI 69–Rh

In a 50 mL three neck round bottom flask equipped with a magnetic stir bar and a direct nitrogen line and septum, 30 mL MeOH was added. The MeOH was sparged with nitrogen for 15 minutes. GO–BIPI 69 (100 mg) and bis(norbornadiene)rhodium(I) tetrafluoroborate (100 mg, 0.26 mmol) were charged to the flask and subjected to sonication for three hours. At the conclusion of the reaction, the reaction mixture was suspended in degassed MeOH (50 mL), centrifuged at 4,200 rpm and decanted. This process was repeated four times. Finally, the product was placed in an oven under vacuum. 0.0843 g of the solid
product was recovered. SEM/EDX: 0.413 mmol ligand (56) and 0.348 mmol Rh/g GO.

2.7.3 Preparation of GO-BIPI 69-Rh: route II

4-amino-1-(((4S,5S)-2-(dicyclohexylphosphanyl)phenyl)-4,5-diphenyl-4,5-dihydro-1H-imidazol-1-yl)butan-1-one (59)

\[
\text{NH}_2 \quad \text{N} \quad \text{Ph} \\
\text{P} \quad \text{Cy} \quad \text{Cy}
\]

In a 20 mL scintillation vial, 2,2,2-trifluoro-1-ethan-1-one, 4-((4S,5S)-2-(2-(dicyclohexylphosphanyl)phenyl)-4,5-diphenyl-4,5-dihydro-1H-imidazol-1-yl)-4-oxobutan-1-aminium salt (56) (0.3457 g, 0.510 mmol) and Amberlite IRA-67 free base (1.25 g) were combined in 10 mL of dry, degassed THF and allowed to stir for 10 minutes. After 10 minutes, the supernatant was removed via syringe and pushed through a 0.2-micron syringe filter. The solution was injected directly into the subsequent reaction. This intermediate (59) was not isolated or characterized.
In a 20 mL scintillation vial, 59 and bis(norbornadiene)rhodium(I) tetrafluoroborate (0.163 g, 0.439 mmol, 0.78 eq.) and 4-amino-1-((4S,5S)-2-(2-(dicyclohexylphosphanyl)phenyl)-4,5-diphenyl-4,5-dihydro-1H-imidazol-1-yl)butan-1-one (0.295 g, 0.510 mmol, 1 eq.) were combined in 10 mL of dry, degassed THF and allowed to stir. Immediately, the solution turned red. An aliquot was removed and concentrated on a rotary evaporator.

GO–BIPI 69–Rh

A 3 neck round bottom flask, sparged with argon and equipped with a stir bar, was charged with GO (0.200 g), DCC (0.319 g, 1.55 mmol, 6 eq.) and 20 mL of anhydrous, degassed THF. The mixture was sonicated for 1 hour. After 1 hour, DIPEA (0.202 g, 1.55 mol, 6 eq.) was added, followed by 58 (0.200 g, 0.259 mmol, 1 eq.). The reaction was stirred for 48 hours at 50°C. The product mixture was then poured out into a 50 mL conical vial, and diluted with MeOH to the 50 mL mark. The suspended mixture was centrifuged at 4,200 rpm and the supernatant was decanted. This process was repeated four more times. Finally, the product was placed in an oven under vacuum. SEM/EDX: 0.229 mmol ligand (59) and 0.147 mmol Rh/g GO.
2.7.4 Preparation of BIPI 69–Rh resin

Carboxylic acid resin – (4-bromophenyl)methanamine (57)

In a one neck round bottom flask, DCC (0.619 g, 3.00 mmol, 6 eq.) and 2.0 mmol/g of the carboxylic acid resin (0.250 g, 0.5 mmol, 1 eq.) were combined in 23 mL of degassed THF. The resulting mixture was stirred for 1 hour. Then, (4-bromophenyl)methanamine (57) (0.093 g, 0.5 mmol, 1 eq.) and DIPEA (0.388 g, 3.0 mmol, 6 eq.) were charged to the round bottom flask. The reaction mixture was allowed to stir under reflux for 48 hours. At the conclusion of the reaction, the mixture was suspended in MeOH (50 mL), centrifuged at 4,200 rpm and decanted. This process was repeated four times. Finally, the product was placed in an oven under vacuum. SEM/EDX: 0.304 mmol 57/g of carboxylic resin.

Carboxylic acid resin–BIPI 69–Rh

In a one neck round bottom flask, DCC (0.619 g, 3.00 mmol, 6 eq.) and the carboxylic acid resin (0.250 g, 2.0 mmol/g, 0.5 mmol, 1 eq.) were combined in 23 mL of degassed THF. The resulting mixture was stirred for 1 hour. Then, under a blanket of argon, a 1:1 solution mixture of 58 (0.192 g, 0.25 mmol, 0.5 eq.) and 59 (0.145 g, 0.25 mmol, 0.5 eq.) in 3.65 mL of degassed THF, along with DIPEA (0.389 g, 3.0 mmol, 6 eq.) was charged to the round bottom flask. The reaction mixture was allowed to stir under reflux for 48 hours. At the conclusion of the reaction, the mixture was suspended in degassed MeOH (50 mL), centrifuged at 4,200 rpm and decanted. This process was repeated four times. Finally, the product was placed in
an oven under vacuum. SEM/EDX: 0.308 mmol ligand (59) and 0.229 mmol Rh/g of carboxylic resin.

2.7.5 General batch hydrogenation procedure using the heterogeneous catalysts

In a HEL ChemSCAN 20 mL hastelloy autoclave, methyl 5,5-dimethyl-2-(morpholine-4-carboxamido)hept-2-enoate 42 (0.020 g, 0.0670 mmol), the immobilized BIPI ligand catalyst (mol% for each reaction was included within the respective tables presented in chapter 2.3 and 2.5) and 5 mL of MeOH were combined. The hastelloy autoclave was screwed onto the ChemSCAN unit by hand. The vessel was pressurized with hydrogen gas to 30 bar, vented and pressurized again with hydrogen gas to 30 bar. The reactor was heated to 65°C for 18 hours with overhead agitation. Additional hydrogen gas was injected into the reactor as necessary to maintain a constant pressure. At the conclusion of the reaction, the hydrogen gas was vented from the autoclave and it was allowed to cool to RT. The reaction contents were transferred to a 20 mL scintillation vial, allowing the phases to separate completely. The supernatant was transferred to another scintillation vial by a syringe. The solution was concentrated on a rotary evaporator and the resulting white solid was analyzed by high-pressure liquid chromatography (HPLC) (method is presented below) and ¹H NMR using CDCl₃ as the solvent. Upon comparison, the spectra collected was identical to that reported in the literature.² In the case that the heterogeneous catalyst was subject to further recycles, the catalyst was washed by transferring it into a 50 mL conical vial with 50 mL of MeOH.
The suspended mixture was centrifuged at 4,200 rpm and the supernatant was decanted. The resulting solid catalyst was dried under vacuum.

2.7.5.2 Chiral HPLC method

12 minute run time; chiralpak AD-H, 4.6 mm X 25 cm, 5-micron particle size; isocratic mobile phase, 75:25 n-heptane: n-propanol, flow rate of 1.0 mL/min at 25°C; 5 μL injection volume; elution times of the enantiomers: 3.75 minutes and 4.60 minutes; observed at 210 nm and 254 nm.
CHAPTER III
THE APPLICATION OF A COMMERCIAL Ya AVAILABLE CATALYST FOR THE CONTINUOUS ASYMMETRIC HYDROGENATION OF ARTEMISINIC ACID TO DIHYDROARTEMISINIC ACID

3.1 Background and prior work

With a reliable, economic source of artemisinic acid, (12) made available through the work of Keasling et al. in 2006, significant efforts have since focused on three synthetic steps to convert the anti-malarial precursor to artemisinin, (1). The first of which is a regio- and diastereomeric reduction of the exocyclic methylene group of 12 to install the correct stereochemistry found in 1. To this end, many different processes have been developed and several scaled for industrial production.

3.1.1 Batch hydrogenation with homogeneous achiral catalysts

Collaborative efforts between the laboratory of Jay Keasling at the University of California, Berkeley and Amyris, Inc. worked to screen 50 different catalysts in the hydrogenation of 12 to 13. Their screening yielded a promising candidate, tris-(triphenylphosphine)RhCl, known colloquially as Wilkinson’s catalyst. This homogeneous, achiral catalyst delivered complete consumption of 12, no over-
reduction to tetrahydroartemisinic acid (60) and high diastereomeric ratio in production of 13 (Scheme 28). Optimization rendered 100% conversion of 12 to product, with a 94-to-6 diastereomeric ratio in favor of the desired isomer (R,R)-dihydroartemisinic acid (13) and insignificant amounts of the overreduced 60. As a commercially available catalyst, this material’s performance was also buoyed by its associated cost-savings.⁸⁰

![Scheme 28. Keasling et al. hydrogenation of artemisinic acid (12)](image)

### 3.1.2 Batch hydrogenation with homogeneous chiral catalysts

In 2011, a team of researchers at Sanofi developed a hydrogenation process to convert 12 to 13 with the aid of a homogeneous chiral ligand complexed to ruthenium (Ru). Ruthenium was selected due to its reduced cost and higher turnover number (TON) as compared to rhodium (Rh) and iridium (Ir), two metals that were also examined. The ligand used, 5,5′-Bis(diphenylphosphino)-4,4′-bi-1,3-benzodioxole, commonly referred to as Segphos, is a diphosphine molecule that possesses a dibenzodioxole backbone.⁸³ With this catalyst system, slightly higher stereoselectivity was realized, 95-to-5, notwithstanding lower catalyst loading.
reduced reaction time and decreased temperature and pressure requirements as compared to Wilkinson’s catalyst (Scheme 29). Despite the high diastereometric excess afforded with this process however, the authors mention the high cost and the air sensitivity associated with the ligand as a limitation.\(^{83}\)

\[\text{Scheme 29. Sanofi catalytic hydrogenation of artemisinic acid (12)}\]

3.1.3 Batch diimide reduction

In recent years, several non-catalytic reduction processes have been developed to take 12 to 13. Building upon years of work that demonstrated diimides capable of reducing carbon–carbon double bonds, various research teams sought out diimide to serve as the reductant in this reaction. In 2011, Volker Kraft \textit{et al.} confirmed that diimide was effective in converting 12 to 13. Due to the highly reactive nature of diimide however, the reducing agent was generated \textit{in situ} from a host of precursors. The sources of diimide included: hydroxylamine-O-sulfonic acid (HOSA) and sodium methanolate, hydroxylamine and HOSA, dipotassium azodicarboxylate, and from hydrazine hydrate and hydrogen peroxide. Generating
diimide from hydroxylamine and HOSA afforded 100% conversion of 12 with a 96- to-4 diastereomeric ratio of product (Scheme 30).\textsuperscript{132}

![Scheme 30. Kraft et al. hydrogenation of artemisinic acid (12)](image)

As depicted in scheme 31, subsequent work by Sanofi established an industrial scale process that also used diimide as the reductant, though it was generated from a different source. In this method, diimide was prepared from hydrazine hydrate and synthetic air composed of 5% v/v oxygen. Serving as the oxidant, oxygen was carefully substituted for hydrogen peroxide. The oxygen limit concentration at standard temperature and pressure for isopropanol is less than 9% by volume; above this percentage, the flammable solvent becomes much less safe to handle. Thus, the group of researchers decreased the concentration of oxygen in the solvent by using a prepared mixture of oxygen and nitrogen. In this process, reduction of the α-β unsaturated carboxylic acid was accomplished by bubbling this gaseous mixture into the reaction. After 11 hours, 13 was furnished in 95% yield with very high stereoselectivity favoring the desired diastereomer. Gas
chromatography (GC) analysis revealed that over-reduction to 60 accounted for some of the produce loss. Despite the successful transformation, a pilot plant processing that includes a highly reactive reagent such as hydrazine, a component of rocket fuel, is most likely a high-risk venture.  

Scheme 31. Sanofi non-catalytic hydrogenation of artemisinic acid (12)

3.1.4 Continuous diimide reduction

In 2015, Oliver Kappe et al. built upon Sanofi’s diimide batch process by developing a continuous methodology that involved multi-injections of hydrazine hydrate (Scheme 32). Safety concerns associated with the use of hydrazine on large scales rendered conducting this reaction in continuous-flow operations an attractive option. The small volumes of the reactor channels ensured that any potential fire propagation would be mitigated.

Initial studies mirrored Sanofi’s procedure; a solution of hydrazine hydrate and 12 was passed through the reactor, eventually mixing with oxygen. This set up afforded incomplete conversion of the substrate, however, most likely due to rapid consumption of the reductant. Thus, a multi-injection approach that added fresh
Reagent into the reaction stream at several points was pursued. It was found that by spreading out equimolar amounts of the reagents, what was previously unable to fully consume starting material with a single injection was now capable of doing so with multi-injections. Many different multi-injection arrangements were then investigated, leading to a robust system. A combination of four liquid feeds of hydrazine hydrate (a total of five equivalents) at various points along the reaction pathway afforded nearly complete conversion, a 93% isolated yield of 13, and very high chiral selectivity at 97-to-3; about 2% of the resulting mixture was comprised of the over-reduced product, 60.\textsuperscript{134}

\textbf{Scheme 32.} Kappe \textit{et al.} continuous non-catalytic hydrogenation of 12
3.1.5 The unique geometry of artemisinic acid: no chiral ligand required

With regard to asymmetric induction, “the best-documented and most powerful factor is the steric one...it is virtually always taken for granted that the selectivity is the result of a difference in steric hindrance between the two approaches the reagent may choose.”135 Many theoretical and experimental studies have underscored the close relationship between steric effects and stereoselectivity of chemical processes. Accordingly, steric considerations are fundamental to the design and construction of asymmetric catalysts. In general, a reaction proceeds through the lowest energy transition state when the substrate adopts a conformation that minimizes steric interactions with the other reagent. This pathway leads to the major stereoisomer. Consequently, manipulations of steric bulk on the catalyst can augment the energy differences between the favored and less favored substrate conformations to increase the ratio of the stereoisomers.

Through the many catalytic and non-catalytic processes that have transformed artemisinic acid (12) to dihydroartemisinic acid (13) in the last decade, a discovery that runs against chemical intuition has emerged: 12 does not require a chiral catalyst to stereoselectively reduce its exocyclic double bond. Published examples of achiral catalysts as well as other reducing agents that deliver 12 in high diastereomeric excess suggest that 12 possesses inherent substrate control over its interaction with the reductant. Fortunately, this control favors the desired stereoisomer. Recently reported computational and 2-D NMR studies support the empirical findings and provide insight into the cause.136
That 12 can be stereoselectively reduced without a chiral catalyst is enigmatic. More surprising still is that although 12 does contain four chiral centers throughout the cis-decalene core, the exocyclic methylene group can freely rotate about the C7-C11 single bond, as there is nothing to sterically impede it from doing so (Figure 31). And besides the endocyclic olefin, the molecule possesses no additional functional groups. Therefore, no dominant interaction between the reactive site of interest and the bicyclic core capable of rendering a particular geometrical configuration is anticipated. Without any bias in facial selectivity, the reduction of the α,β-unsaturated carboxylic acid should not deliver any diastereomeric excess. Yet, it does.

Computational and 2-D NMR studies indicate that 12 does adopt a preferred, low-energy conformation. Stabilizing this configuration is the noncovalent interaction between the electron density of the C11-C13 alkene and the proximate vinylic H5C5 bond. As a result of this nonclassical hydrogen bond, a face of the C11=C13 alkene forms a cis orientation to the decalene ring, which effectively blocks it from coming in contact with a reducing agent. This in turn causes the reductant to disproportionate approaches the double bond from the opposite side and deliver the desired (R,R)-diastereomer of 13 in high quantities. Additional studies have that found no interactions between the reductant and the cis-decalene ring are responsible for transferring chirality; stereoselectivity comes from the substrate's three-dimensional geometry dictated by specific intramolecular interactions.\textsuperscript{136}
Figure 31. Artemisinic acid’s (12) intramolecular nonclassical CH-π interaction

3.1.6 Significance of Work

Artemisinin (1) is a vital medication from a global health perspective. To ensure steady worldwide access, especially for those who are most vulnerable, the anti-malarial agent 1 must be manufactured as economically and reliably as possible. Keasling et al has supplied the scientific community with an excellent starting point to 1 in form of artemisinic acid (12). Numerous reports have demonstrated that in three chemical transformations 12 can be elaborated to 1.

Our work sought to improve the economics and safety profile of the first step, the asymmetric hydrogenation of 12 to the desired diastereomer of 13, the biologically relevant stereoisomer. Given the prior research that established that 13 could be delivered enantioselectively without a chiral catalyst, we aimed to identify and employ a selective, low-cost, reusable achiral heterogeneous catalyst for this step. We envisioned that the insoluble catalyst would be used in a continuous hydrogenation regime, residing in a packed bed reactor, which would allow for easy
purification and the opportunity to telescope the product 13 in a multistep process. Accordingly, it was the goal of this project to increase global access of 1 by reducing the costs associated with this key step.

3.2 Screening BIPI ligands for immobilization and use on artemisinic acid

One aspect of this project was to construct a heterogeneous catalyst specifically tailored for the hydrogenation of 12 to 13. Similar to what was covered in Chapter 2, we envisioned fashioning a catalyst by immobilizing a BIPI ligand onto the surface of an insoluble resin or GO. Since the stereoselectivity of the transformation was of great importance, the BIPI ligand anchored to the solid support had to deliver the desired stereoisomer of 13 in high diastereomeric excess.

Before we investigated which BIPI ligand would afford the highest chiral purity in the hydrogenation of 12 to 13, we first screened three different metals with various ligand and solvent combinations to gain insights into their interactions (Table 7). BIPI 69 and BIPI 153, as seen in figure 32 coordinated to rhodium, ruthenium and iridium, were tested in MeOH (entries 1–7). The results proved inconclusive with regard to which metal was superior at delivering 13 with the largest diastereomeric ratio. However, despite complete conversion of starting material with all other catalysts, the preformed Ru–BIPI 69 was not able to fully consume the starting material (entry 3). To test solvent effects, further screens were conducted using BIPI 69 complexed to rhodium (entries 11–13). While toluene (PhMe) and EtOAc afforded very similar results as the reaction conducted in
MeOH, THF failed to convert any 12 to 13. Slight variations to catalyst loading (entries 13 and 14) did not have a significant impact on the conversion or stereoselectivity. A Josiphos ligand, coordinated to both rhodium and ruthenium (entries 8 and 9) served as an additional point of comparison against the BIPI ligands. This diphosphine ligand did not furnish the desired diastereomer of 13 in any higher yields than the BIPI ligands. Use of Wilkinson’s catalyst, which served as a reference point to previously reported work, provided very comparable to published results (entry 10).80

**Table 7. Metal screening in the asymmetric hydrogenation of 12**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Ligand</th>
<th>Solvent</th>
<th>Temp (°C)</th>
<th>% Conversion of 12</th>
<th>DR</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Rh(nbd)BF₄</td>
<td>BIPI69</td>
<td>MeOH</td>
<td>65</td>
<td>100</td>
<td>80:20</td>
</tr>
<tr>
<td>2</td>
<td>Rh(nbd)BF₄</td>
<td>BIPI153</td>
<td>MeOH</td>
<td>65</td>
<td>100</td>
<td>23:77</td>
</tr>
<tr>
<td>3</td>
<td>Ru BIPI69</td>
<td></td>
<td>MeOH</td>
<td>65</td>
<td>22</td>
<td>70:30</td>
</tr>
<tr>
<td>4</td>
<td>Ru BIPI153</td>
<td></td>
<td>MeOH</td>
<td>65</td>
<td>100</td>
<td>56:44</td>
</tr>
<tr>
<td>5</td>
<td>[RuCl₂pcymen]₂</td>
<td>BIPI69</td>
<td>MeOH</td>
<td>65</td>
<td>100</td>
<td>49:51</td>
</tr>
<tr>
<td>6</td>
<td>[RuCl₂pcymen]₂</td>
<td>BIPI153</td>
<td>MeOH</td>
<td>65</td>
<td>100</td>
<td>84:16</td>
</tr>
<tr>
<td>7</td>
<td>Ir BIPI153</td>
<td></td>
<td>MeOH</td>
<td>65</td>
<td>100</td>
<td>68:32</td>
</tr>
<tr>
<td>8</td>
<td>Rh(nbd)BF₄</td>
<td>J212-2</td>
<td>MeOH</td>
<td>25</td>
<td>100</td>
<td>68:32</td>
</tr>
<tr>
<td>9</td>
<td>[RuCl₂pcymen]₂</td>
<td>J212-2</td>
<td>MeOH</td>
<td>25</td>
<td>100</td>
<td>46:54</td>
</tr>
<tr>
<td>10</td>
<td>RhCl(PPh₃)₃</td>
<td>n/a</td>
<td>PhMe</td>
<td>65</td>
<td>100</td>
<td>93:7</td>
</tr>
<tr>
<td>11</td>
<td>Rh(nbd)BF₄</td>
<td>BIPI69</td>
<td>PhMe</td>
<td>65</td>
<td>90</td>
<td>83:17</td>
</tr>
<tr>
<td>12</td>
<td>Rh(nbd)BF₄</td>
<td>BIPI69</td>
<td>THF</td>
<td>65</td>
<td>0</td>
<td>nd</td>
</tr>
<tr>
<td>13</td>
<td>Rh(nbd)BF₄</td>
<td>BIPI69</td>
<td>EtOAc</td>
<td>65</td>
<td>100</td>
<td>79:21</td>
</tr>
<tr>
<td>14</td>
<td>Rh(nbd)BF₄</td>
<td>BIPI69</td>
<td>EtOAc</td>
<td>65</td>
<td>100</td>
<td>77:23</td>
</tr>
</tbody>
</table>

*a All experiments carried out under 24 bar of H₂ with 2 mol% catalyst loading except for entry 14 (0.5 mol%). b Conversions and DR (diastereomeric ratio) determined by HPLC.*
Our next screen explored the relationship between the substituents bound to the phosphinoimidazoline core of BIPI ligands and the reactivity, as well as the diastereoselectivity toward the hydrogenation of 12 to 13 (Table 8). Due to its relative consistency in the initial screen, we elected to perform the hydrogenations with rhodium. These reactions were conducted in MeOH at 65°C and 24 bar of H₂. Consistent with the results from the metal screening studies, BIPI 69 provided enhanced selectivity to the desired diastereomer as compared to BIPI 153 (Table 7, 8). The variation in diastereoselectivity was attributed to the size of the phenyl versus naphthyl substituents bound to the phosphine. In examining the chiral centers of BIPI 69, it was determined that BIPI 69 (R,R) decreased the diastereoselectivity toward the reduction of 12 to 13 as compared to BIPI 69 (S,S). While modification of the amide substituent did not result in an appreciable change in diastereoselectivity, we observed that the substitution patterns of the groups attached to the aryl backbone (R₁) contributed significantly to the diastereomeric ratio of the products; the bulkier aryl substituents afforded the highest diastereoselectivity. Most notably, BIPI 186, containing the meta tert-butyl groups, afforded a 94:6 diastereomeric ratio of 13.
Table 8. BIPI ligand screen in the asymmetric hydrogenation of 12

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ligand</th>
<th>% Conversion of 12&lt;sup&gt;b&lt;/sup&gt;</th>
<th>DR&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>BIPI 69 (SS)</td>
<td>100</td>
<td>83:17</td>
</tr>
<tr>
<td>2</td>
<td>BIPI 153 (SS)</td>
<td>100</td>
<td>23:77</td>
</tr>
<tr>
<td>3</td>
<td>BIPI 69 (RR)</td>
<td>100</td>
<td>60:40</td>
</tr>
<tr>
<td>4</td>
<td>BIPI 61 (RR)</td>
<td>100</td>
<td>76:24</td>
</tr>
<tr>
<td>5</td>
<td>BIPI 65 (RR)</td>
<td>31</td>
<td>nd</td>
</tr>
<tr>
<td>6</td>
<td>BIPI 74 (SS)</td>
<td>64</td>
<td>nd</td>
</tr>
<tr>
<td>7</td>
<td>BIPI 77 (SS)</td>
<td>100</td>
<td>83:17</td>
</tr>
<tr>
<td>8</td>
<td>BIPI 79 (SS)</td>
<td>100</td>
<td>81.5:18.5</td>
</tr>
<tr>
<td>9</td>
<td>BIPI 115 (RR)</td>
<td>100</td>
<td>81:19</td>
</tr>
<tr>
<td>10</td>
<td>BIPI 154 (SS)</td>
<td>100</td>
<td>84:16</td>
</tr>
<tr>
<td>11</td>
<td>BIPI 87 (RR)</td>
<td>100</td>
<td>76:24</td>
</tr>
<tr>
<td>12</td>
<td>BIPI 178 (SS)</td>
<td>21</td>
<td>nd</td>
</tr>
<tr>
<td>13</td>
<td>BIPI 179 (SS)</td>
<td>74</td>
<td>81:18</td>
</tr>
<tr>
<td>14</td>
<td>BIPI 186 (SS)</td>
<td>100</td>
<td>94:6</td>
</tr>
<tr>
<td>15</td>
<td>BIPI 81 (RR)</td>
<td>100</td>
<td>83:17</td>
</tr>
<tr>
<td>16</td>
<td>BIPI 86 (RR)</td>
<td>100</td>
<td>77:23</td>
</tr>
<tr>
<td>17</td>
<td>BIPI 253 (RR)</td>
<td>100</td>
<td>79:21</td>
</tr>
</tbody>
</table>

<sup>a</sup>All experiments carried out under 24 bar of H₂ with 2 mol% catalyst loading of Rh(nbd)₂BF₄ at 65°C in MeOH. <sup>b</sup>Conversions and DR (diastereomeric ratio) determined by HPLC.
Despite the promising stereoselectivity results, the challenges associated with the use and reuse of the solid supported BIPI ligands disclosed in Chapter 2, dissuaded us from pursuing the immobilization of BIPI 186 onto either GO or an insoluble resin for this application.
3.3 **High throughput screen: identifying a homogeneous achiral catalysts**

Another aim of this project was to identify an achiral, homogeneous catalyst capable of effecting the hydrogenation of 12 in high diastereomeric excess. To that end, we partnered with Merck & Co. and inhabited their laboratories to conduct HTE. These reactions were carried out on milligram scale in 96-reactor well plates. Integrated high pressure liquid chromatography (HPLC) analytical methods, computer software and other instrumentation enabled us to screen 192 different metal, ligand and solvent combinations each day to assess nearly a thousand reactions over the period of a week. We examined rhodium; ruthenium; nickel; and cobalt coordinated to a broad range of tridentate triphosphine and amine diphosphine as well as bidentate diphosphine and other oxo-phosphorous ligands. With seemingly innumerable possibilities, HTE afforded us rapid discovery of promising candidates. An abridged selection of the best performing catalysts is presented (Table 9). The results indicate that compared to the ruthenium, nickel and cobalt metals, rhodium converted 12 to 13 in highest amount and diastereomeric excess. However, there were a few exceptions to that trend. Cobalt complexed to bis[(2-diisopropylphosphino)ethyl]amine (entry 1) and bis[(2-diterbuthylphosphino)ethyl]amine (entry 9) afforded near quantitative conversion of 12 to 13 in good stereoselectivity. Similarly, nickel coordinated to bis[(2-diphenylphosphino)ethyl]amine (entry 8) delivered 13 in high conversion with comparable stereoselectivity. From an economic perspective, these first row transition metals offered a competitive advantage to the precious rhodium and ruthenium metals despite their lower stereoselectivity. Accordingly, we subjected
these catalysts for optimization. Other amino diphosphine ligands possessing different size alkyl substituents bound to the phosphorous atoms were investigated. Smaller substituents, such as methyl and ethyl had deleterious effects, as did larger substituents like naphthyl, indicating that there was a narrow range of operability with respect to the size of group bound to the chelating phosphorous atoms. Despite the promising results seen with these commodity metals and achiral ligands, we chose not to further execute optimization studies. Instead, we diverted our attention to findings from HTE with a heterogeneous achiral catalyst (presented in Chapter 3.4) given the benefits of heterogeneous catalysts.
Table 9. Homogeneous achiral catalyst screen in the hydrogenation of 12

<table>
<thead>
<tr>
<th>Entry&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Metal</th>
<th>Ligand</th>
<th>% 13&lt;sup&gt;c&lt;/sup&gt;</th>
<th>% DE&lt;sup&gt;c&lt;/sup&gt;</th>
<th>% 60&lt;sup&gt;c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Co(ClO₄)₂·6H₂O / 2 TMSCH₂Li</td>
<td>(iPr₂PCH₂CH₂)₂NH</td>
<td>100.0</td>
<td>75.4</td>
<td>0.0</td>
</tr>
<tr>
<td>2</td>
<td>Rh(nbd)₂BF₄</td>
<td>HiersoPhos 4</td>
<td>99.6</td>
<td>91.6</td>
<td>0.4</td>
</tr>
<tr>
<td>3</td>
<td>Rh(nbd)₂BF₄</td>
<td>NiXantPhos</td>
<td>99.4</td>
<td>83.3</td>
<td>0.4</td>
</tr>
<tr>
<td>4</td>
<td>Rh(nbd)₂BF₄</td>
<td>XantPhos</td>
<td>99.1</td>
<td>93.0</td>
<td>0.9</td>
</tr>
<tr>
<td>5</td>
<td>Rh(nbd)₂BF₄</td>
<td>Ph₂P(CH₂)₂(2-pyr)</td>
<td>99.0</td>
<td>77.1</td>
<td>0.0</td>
</tr>
<tr>
<td>6</td>
<td>Rh(nbd)₂BF₄</td>
<td>dppe</td>
<td>98.8</td>
<td>86.3</td>
<td>1.2</td>
</tr>
<tr>
<td>7</td>
<td>Rh(nbd)₂BF₄</td>
<td>Ph₂P(CH₂CH₂NH₂)₂</td>
<td>98.3</td>
<td>94.0</td>
<td>1.7</td>
</tr>
<tr>
<td>8</td>
<td>Ni(OAc)₂</td>
<td>Ph₂P(CH₂)₂NH₂</td>
<td>98.2</td>
<td>69.1</td>
<td>0.0</td>
</tr>
<tr>
<td>9&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Co(ClO₄)₂·6H₂O / 2 TMSCH₂Li</td>
<td>(tBu₂PCH₂CH₂)₂NH</td>
<td>98.0</td>
<td>75.3</td>
<td>0.0</td>
</tr>
<tr>
<td>10</td>
<td>Rh(nbd)₂BF₄</td>
<td>Cy-DPEPhos</td>
<td>97.7</td>
<td>79.6</td>
<td>2.3</td>
</tr>
<tr>
<td>11</td>
<td>Rh(nbd)₂BF₄</td>
<td>dppe</td>
<td>97.6</td>
<td>89.7</td>
<td>2.4</td>
</tr>
<tr>
<td>12</td>
<td>Rh(nbd)₂BF₄</td>
<td>4,5-{(iPr₂PCH₂)₂-acridine}</td>
<td>97.6</td>
<td>86.8</td>
<td>2.4</td>
</tr>
<tr>
<td>13</td>
<td>Rh(nbd)₂BF₄</td>
<td>Ph₂P(CH₂)₂NH₂</td>
<td>94.7</td>
<td>81.3</td>
<td>1.6</td>
</tr>
<tr>
<td>14</td>
<td>Rh(nbd)₂BF₄</td>
<td>tBu-Biphep</td>
<td>93.6</td>
<td>78.2</td>
<td>3.6</td>
</tr>
<tr>
<td>15</td>
<td>Rh(nbd)₂BF₄</td>
<td>tBu-XantPhos</td>
<td>92.6</td>
<td>77.8</td>
<td>1.0</td>
</tr>
<tr>
<td>16</td>
<td>Rh(nbd)₂BF₄</td>
<td>2-(tBu₂PCH₂)₆-(Et₂NCH₂)-Py</td>
<td>90.6</td>
<td>79.0</td>
<td>1.8</td>
</tr>
<tr>
<td>17</td>
<td>Rh(nbd)₂BF₄</td>
<td>(Ad₂PCH₂CH₂)₂NH</td>
<td>88.4</td>
<td>77.9</td>
<td>0.4</td>
</tr>
<tr>
<td>18</td>
<td>Rh(nbd)₂BF₄</td>
<td>2-Ph₂PPhOH</td>
<td>83.2</td>
<td>75.3</td>
<td>0.1</td>
</tr>
<tr>
<td>19&lt;sup&gt;b&lt;/sup&gt;</td>
<td>[(cymene)RuCl₂]₂</td>
<td>dtbppe</td>
<td>78.4</td>
<td>85.2</td>
<td>0.1</td>
</tr>
<tr>
<td>20</td>
<td>Rh(nbd)₂BF₄</td>
<td>2,6-(tBu₂PCH₂)₂-Py</td>
<td>41.3</td>
<td>79.9</td>
<td>0.5</td>
</tr>
</tbody>
</table>

<sup>a</sup>All reactions were conducted. <sup>b</sup>included triethylamine as additive. <sup>c</sup>Conversions to 13 and 60 and DE (diastereomeric excess) determined by HPLC equipped with a chiral reverse phase column.

3.4 High throughput screen: identifying a heterogeneous achiral catalysts

The collaborative efforts to efficiently and cost effectively execute the asymmetric hydrogenation of 12 continued with Merck & Co. with a focus on achiral
heterogeneous catalysts. A plethora of different heterogeneous catalysts were screened via HTE. These catalysts varied by metal type, concentration, as well as source. Table 10 is a compilation of the catalysts that provided the best conversion and stereoselectivity to the desired diastereomer of 13. Aware of the highly intricate interactions between catalysts and substrates in asymmetric transformations, and the subtle differences between the solid supports that comprise heterogeneous catalysts, we were methodical in labeling and identifying the catalysts by the information supplied by the vendors. The initial HTE revealed that platinum (Pt) and rhodium catalysts were superior to both the ruthenium and palladium (Pd) ones. However, in an attempt to perform this reaction as economically, yet high yielding as possible, we elected to look further into the ruthenium catalysts (Table 11), particularly the 5% Ru/C catalyst seen in entry 7.

A more expansive screen of ruthenium heterogeneous catalysts revealed that the 5% Ru/C Strem (BASF) 44-4065 ESCAT 4401 (entry 1, Table 11) in MeOH afforded the highest conversion to 13 with moderate stereoselectivity. The same catalyst in a nonpolar solvent, PhMe, generated very little of the desired dihydroartemisinic acid isomer of 13 (entry 6). Given the apparent sensitivity to solvent polarity, 16 different solvents were then investigated for effects on yield and/or chiral purity (Table 12) with the 5% Ru/C Strem (BASF) 44-4065 ESCAT 4401 catalyst. The experiments conducted in alcohols were vastly superior to others, especially nonpolar solvents; ethanol (EtOH) (entry 2) provided the highest conversion to 13 and a diastereomeric excess comparable to the other best performing solvents.
Table 10. Heterogeneous achiral catalyst screen in the hydrogenation of 12

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Vendor/Information</th>
<th>% 13&lt;sup&gt;b&lt;/sup&gt;</th>
<th>% DE&lt;sup&gt;b&lt;/sup&gt;</th>
<th>% 60&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5% Pt_5% Bi/C&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Evonik (degussa), PMPC130487, Nobylst P8077</td>
<td>98.9</td>
<td>56.5</td>
<td>0.8</td>
</tr>
<tr>
<td>2</td>
<td>5% Rh/C</td>
<td>JM - 35, C-12021, C101038-5</td>
<td>97.7</td>
<td>74.9</td>
<td>1.9</td>
</tr>
<tr>
<td>3</td>
<td>5% Rh/C</td>
<td>JM - 34, C-11630, C101023-5</td>
<td>95.9</td>
<td>75.0</td>
<td>1.0</td>
</tr>
<tr>
<td>4</td>
<td>5% Pt_Bi/C</td>
<td>JM - 29, C-11654, B503032-5</td>
<td>95.3</td>
<td>57.1</td>
<td>1.0</td>
</tr>
<tr>
<td>5</td>
<td>5% Rh/C</td>
<td>Evonik (degussa), PMP130489, Nobylst P2086</td>
<td>94.7</td>
<td>72.9</td>
<td>0.0</td>
</tr>
<tr>
<td>6</td>
<td>5% Rh/C</td>
<td>Strem (BASF), 18945700, 45-1875, ESCAT 3401</td>
<td>93.3</td>
<td>79.0</td>
<td>0.0</td>
</tr>
<tr>
<td>7</td>
<td>5% Ru/C&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Strem (BASF) 21589500 44-4065, ESCAT 4401</td>
<td>93.0</td>
<td>71.0</td>
<td>0.0</td>
</tr>
<tr>
<td>8</td>
<td>5% Ru/C&lt;sup&gt;a&lt;/sup&gt;</td>
<td>JM - 38 C-11266 D101002-5</td>
<td>89.4</td>
<td>71.1</td>
<td>0.0</td>
</tr>
<tr>
<td>9</td>
<td>5% Pd_1% Fe/C</td>
<td>Evonik (degussa), 18JLM29, CE 105 R/W</td>
<td>88.7</td>
<td>28.3</td>
<td>1.0</td>
</tr>
<tr>
<td>10</td>
<td>5% Pd_0.5% Fe/C</td>
<td>Evonik (degussa), CC1-2373, CE 105 RC/W</td>
<td>88.4</td>
<td>36.9</td>
<td>1.6</td>
</tr>
<tr>
<td>11</td>
<td>5% Pd/C</td>
<td>Evonik (degussa), PMPC130428, Nobylst P1109</td>
<td>86.1</td>
<td>7.2</td>
<td>4.8</td>
</tr>
<tr>
<td>12</td>
<td>5% Pd_1% Fe/C</td>
<td>JM, C-10079, A113032-5</td>
<td>85.5</td>
<td>25.7</td>
<td>2.4</td>
</tr>
<tr>
<td>13</td>
<td>5% Pd/C</td>
<td>Evonik (degussa), PMPC130429, Nobylst P1126</td>
<td>82.2</td>
<td>10.9</td>
<td>1.2</td>
</tr>
<tr>
<td>14</td>
<td>5% Pd/C</td>
<td>Evonik (degussa), PMPC130426, Nobylst P1064</td>
<td>82.0</td>
<td>34.4</td>
<td>2.1</td>
</tr>
<tr>
<td>15</td>
<td>5% Pd/C</td>
<td>BASF (Engelhard), SE16027, C3663</td>
<td>81.5</td>
<td>44.1</td>
<td>4.0</td>
</tr>
<tr>
<td>16</td>
<td>1% Pt/C</td>
<td>JM, C-12539, 1R163</td>
<td>81.1</td>
<td>64.3</td>
<td>5.8</td>
</tr>
<tr>
<td>17</td>
<td>5% Pd/C</td>
<td>JM, C-8095, A503038-5</td>
<td>80.2</td>
<td>26.4</td>
<td>3.2</td>
</tr>
</tbody>
</table>

<sup>a</sup>Reactions run in MeOH. <sup>b</sup>Conversions to 13 and 60 and DE (diastereomeric excess) determined by HPLC equipped with a chiral reverse phase column.
Table 11. Screen of selected Ru heterogeneous catalyst in hydrogenation of 12

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Vendor/Information</th>
<th>%13&lt;sup&gt;c&lt;/sup&gt;</th>
<th>% DE&lt;sup&gt;c&lt;/sup&gt;</th>
<th>%60&lt;sup&gt;c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5% Ru/C&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Strem (BASF) 21589500 44-4065, ESCAT 4401</td>
<td>93.0</td>
<td>71.0</td>
<td>0.0</td>
</tr>
<tr>
<td>2</td>
<td>5% Ru/C&lt;sup&gt;a&lt;/sup&gt;</td>
<td>JM - 38 C-11266 D101002-5</td>
<td>89.4</td>
<td>71.1</td>
<td>0.0</td>
</tr>
<tr>
<td>3</td>
<td>5% Ru_0.25% Pd/C&lt;sup&gt;a&lt;/sup&gt;</td>
<td>JM - 40 C-12017 G101038 - 5/0.25</td>
<td>60.9</td>
<td>-32.5</td>
<td>11.9</td>
</tr>
<tr>
<td>4</td>
<td>5% Ru/C&lt;sup&gt;a&lt;/sup&gt;</td>
<td>JM - 37 C-12085 D101023-5</td>
<td>54.8</td>
<td>67.8</td>
<td>0.4</td>
</tr>
<tr>
<td>5</td>
<td>5% Ru_0.25% Pd/C&lt;sup&gt;b&lt;/sup&gt;</td>
<td>JM - 40 C-12017 G101038 - 5/0.25</td>
<td>33.0</td>
<td>42.4</td>
<td>0.5</td>
</tr>
<tr>
<td>6</td>
<td>5% Ru/C&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Strem (BASF) 21589500 44-4065, ESCAT 4401</td>
<td>20.5</td>
<td>60.9</td>
<td>0.1</td>
</tr>
<tr>
<td>7</td>
<td>5% Ru/C&lt;sup&gt;b&lt;/sup&gt;</td>
<td>JM - 38 C-11266 D101002-5</td>
<td>6.0</td>
<td>58.9</td>
<td>0.0</td>
</tr>
<tr>
<td>8</td>
<td>5% Ru/C&lt;sup&gt;b&lt;/sup&gt;</td>
<td>JM - 37 C-12085 D101023-5</td>
<td>0.7</td>
<td>N/A</td>
<td>0.0</td>
</tr>
<tr>
<td>9</td>
<td>5% Ru/C&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Engelhard (BASF) 38370 C4021</td>
<td>0.3</td>
<td>N/A</td>
<td>0.0</td>
</tr>
<tr>
<td>10</td>
<td>5% Ru/C&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Engelhard (BASF) 38370 C4021</td>
<td>0.2</td>
<td>N/A</td>
<td>0.0</td>
</tr>
</tbody>
</table>

<sup>a</sup>Reactions run in MeOH. <sup>b</sup>Reactions run in PhMe. <sup>c</sup>Conversions to 13 and 60 and DE (diastereomeric excess) determined by HPLC equipped with a chiral reverse phase column.
Table 12. Solvent screen of selected 5% Ru/C catalyst in hydrogenation of 12

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>% 13</th>
<th>% DE</th>
<th>% DEa</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>EtOH</td>
<td>96.1</td>
<td>70.2</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>MeOH</td>
<td>96.0</td>
<td>67.9</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>iPrOH</td>
<td>94.1</td>
<td>71.3</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>EtOAc</td>
<td>93.2</td>
<td>71.1</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>TFE</td>
<td>62.6</td>
<td>65.8</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>iPrOAc</td>
<td>60.0</td>
<td>67.5</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>MEK</td>
<td>37.3</td>
<td>62.3</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>MIBK</td>
<td>30.1</td>
<td>63.2</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>THF</td>
<td>60.2</td>
<td>73.2</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>2-Me-THF</td>
<td>50.3</td>
<td>69.7</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>CPME</td>
<td>9.4</td>
<td>61.0</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>DME</td>
<td>63.9</td>
<td>69.8</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>PhMe</td>
<td>1.9</td>
<td>53.4</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>PhCF3</td>
<td>4.4</td>
<td>56.4</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>PhCl</td>
<td>0.8</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>DCE</td>
<td>1.0</td>
<td>N/A</td>
<td></td>
</tr>
</tbody>
</table>

*Conversions to 13 and DE (diastereomeric excess) determined by HPLC equipped with a chiral reverse phase column.

3.5 Hydrogenation of artemisinic acid with 5% Ru/C catalyst in different systems

Based on the findings from the catalyst and solvent screens conducted at Merck & Co., we applied the highly effective 5% Ru/C catalyst to three different systems: a continuous flow reactor, a batch reactor and a continuous stirred tank reactor (CSTR). The heterogeneous catalyst was pursued over the promising homogeneous ones due to its potential to be recovered and recycled, an attractive
cost saving attribute of the material. We initially sought to exploit the advantages of continuous operations for this transformation; namely, inverting the catalyst-substrate stoichiometry to achieve a high instantaneous contact of catalyst, while holding its amount used to a minimum. To that end, we envisioned filling a packed bed reactor with the 5% Ru/C material and carrying out the continuous hydrogenation of 12 in EtOH using a ThalesNano H-Cube Mini (Figure 33). This reactor operated as a hydrogen source generator, which produced gaseous hydrogen on demand via electrolysis of water. Challenges with that system, however, led us to work on optimizing batch conditions to maximize both the production of 13 and recycled catalyst. Finally, in an effort to retain the benefits of continuous processes, but circumvent the difficulties associated with the packed bed reactor, we explored conducting the hydrogenation in a CSTR.

3.5.1 Design of experiment (DOE) in a continuous packed bed reactor: H-Cube Mini

A DOE, which is a systematic approach of investigating the relationships between multiple variables within a particular process and an output variable of interest, was conducted to ascertain the optimal parameters to effect the hydrogenation of 12 (Table 13). The highest and lowest values available by the ThalesNano H-Cube Mini for each parameter were evaluated: flow rate, temperature and pressure. Through this methodology, 11 experiments were conducted. For each experiment, a 70 mm catalyst cartridge was packed with 200 mg of 5% Ru/C and 200 mg of Ti shavings; the percent conversions and stereoselectivity are an average of results generated from 5 aliquots collected over a 25-minute period.
The DOE indicated that in every experiment the same unknown by-product was formed, which was detectible by HPLC. (Chapter 3.6 will discuss our efforts to elucidate the identity of this molecule). With regard to results of the DOE, the reaction conditions had a perceptible affect on the diastereomeric selectivity of the hydrogenation (Table 13). Specifically, the reactions carried out at the lowest flow rates generated the highest excess in the desired diastereomer of 13 (entries 1, 7 and 9, Table 13). Conversely, the highest flow rate, 3 mL/min, not only afforded the least stereoselective hydrogenations of the DOE, with the exception of entry 5, it insuffciently converted 12 to product regardless of the temperature and pressure combination (entries 5, 6, 8 and 10). Entries 2–4 represented the midpoint values of each parameter evaluated. Experiments employing this flow rate, temperature and pressure values were repeated three times to check for reproducibility. While there was some variance in the conversion to 13 in entries 2–4, the percentage of the desired diastereomer produced was approximately 65%. The experiments conducted at 0.1 mL/min (entries 1, 7, 9 and 11) provided the highest chiral purity of 13; entries 1 and 9 generated the desired product with the highest diastereomeric excess.

Within the 0.1 mL/min experiments, the other two parameters, temperature and pressure, proved to be significant contributors to the production of the over-reduced product (60). The only temperature and pressure combination that did not afford prodigious amounts of 60 at 0.1 mL/min was 100°C and 5 bar, entry 1, which delivered a 69.55% conversion of 12 to (R,R)-dihydroartemisinic acid (13).
Table 13. DOE with 5% Ru/C in the continuous hydrogenation of 12

<table>
<thead>
<tr>
<th>Entry</th>
<th>Flow Rate (mL/min)</th>
<th>Temp (°C)</th>
<th>Pressure (bar)</th>
<th>% 12b</th>
<th>% 60b</th>
<th>% By-Productb</th>
<th>% 13b</th>
<th>% DEb</th>
<th>% Conversion to (R,R) – DHAA (13)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.1</td>
<td>100</td>
<td>5</td>
<td>0.00</td>
<td>23.68</td>
<td>4.17</td>
<td>72.14</td>
<td>92.80</td>
<td>69.55</td>
</tr>
<tr>
<td>2</td>
<td>1.5</td>
<td>60</td>
<td>50</td>
<td>4.05</td>
<td>4.84</td>
<td>11.68</td>
<td>79.43</td>
<td>69.60</td>
<td>67.36</td>
</tr>
<tr>
<td>3</td>
<td>1.5</td>
<td>60</td>
<td>50</td>
<td>6.22</td>
<td>2.94</td>
<td>13.34</td>
<td>77.49</td>
<td>68.80</td>
<td>65.40</td>
</tr>
<tr>
<td>4</td>
<td>1.5</td>
<td>60</td>
<td>50</td>
<td>16.26</td>
<td>1.75</td>
<td>14.49</td>
<td>78.38</td>
<td>66.00</td>
<td>62.72</td>
</tr>
<tr>
<td>5</td>
<td>3</td>
<td>25</td>
<td>100</td>
<td>57.85</td>
<td>0.19</td>
<td>7.88</td>
<td>34.08</td>
<td>72.66</td>
<td>29.42</td>
</tr>
<tr>
<td>6</td>
<td>3</td>
<td>100</td>
<td>100</td>
<td>40.20</td>
<td>0.29</td>
<td>22.98</td>
<td>36.53</td>
<td>53.20</td>
<td>27.98</td>
</tr>
<tr>
<td>7</td>
<td>0.1</td>
<td>25</td>
<td>5</td>
<td>0.00</td>
<td>81.84</td>
<td>4.85</td>
<td>13.31</td>
<td>84.00</td>
<td>12.25</td>
</tr>
<tr>
<td>8</td>
<td>3</td>
<td>100</td>
<td>5</td>
<td>90.15</td>
<td>0.14</td>
<td>3.15</td>
<td>6.57</td>
<td>49.50</td>
<td>4.91</td>
</tr>
<tr>
<td>9</td>
<td>0.1</td>
<td>25</td>
<td>100</td>
<td>0.39</td>
<td>96.15</td>
<td>1.93</td>
<td>1.53</td>
<td>90.40</td>
<td>1.46</td>
</tr>
<tr>
<td>10</td>
<td>3</td>
<td>25</td>
<td>5</td>
<td>99.67</td>
<td>0.00</td>
<td>0.02</td>
<td>0.32</td>
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<td>0.21</td>
</tr>
<tr>
<td>11</td>
<td>0.1</td>
<td>100</td>
<td>100</td>
<td>0.70</td>
<td>97.58</td>
<td>1.55</td>
<td>0.17</td>
<td>70.00</td>
<td>0.15</td>
</tr>
</tbody>
</table>

*All reactions were run in ethanol with 0.015 M solution of 12. Conversions to (remaining 12), 60, the by-product, 13 and DE (diastereomeric excess) determined by HPLC equipped with a chiral reverse phase column.
3.5.1.1 Simplex method optimization studies

Based on the promising results displayed at 0.1 mL/min, 100°C and 5 bar, we explored the effect of varying the flow rate while holding the other two parameters constant. Fixing the temperature and pressure at 100°C and 5 bar, we incrementally adjusted the flow rate from 0.1 mL/min to 0.7 mL/min and observed any changes in the production of 13 (Table 14). Increasing the flow rate to greater than 0.5 mL/min (entries 1 and 2) provided incomplete conversion of starting material (12) at this temperature and pressure, most likely due to the decreased residence time. While 0.3 mL/min (entry 3) and 0.1 mL/min (entry 4) both produced near complete conversion to 13, 0.1 mL/min proved to hydrogenate the exocyclic methylene group with higher stereoselectivity.

Table 14. Affect of flow rate on the conversion to (R,R)-DHAA (13)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Flow Rate (mL/min)</th>
<th>% 12b</th>
<th>% 60b</th>
<th>% By-Productb</th>
<th>% 13b</th>
<th>% DEb</th>
<th>% Conversion to (R,R) – DHAA (13)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.7</td>
<td>18.59</td>
<td>0.46</td>
<td>20.97</td>
<td>59.92</td>
<td>56</td>
<td>46.73</td>
</tr>
<tr>
<td>2</td>
<td>0.5</td>
<td>25.07</td>
<td>0.93</td>
<td>18.48</td>
<td>55.51</td>
<td>55.6</td>
<td>43.18</td>
</tr>
<tr>
<td>3</td>
<td>0.3</td>
<td>0</td>
<td>3.55</td>
<td>4.09</td>
<td>92.34</td>
<td>65.2</td>
<td>76.27</td>
</tr>
<tr>
<td>4</td>
<td>0.1</td>
<td>6.56</td>
<td>0.23</td>
<td>93.15</td>
<td>79.8</td>
<td>83.74</td>
<td></td>
</tr>
</tbody>
</table>

*a*All reactions were run at 100°C and 5 bar in ethanol with 0.015 M solution of 12. The percent conversions and diastereometric excess are an average of results generated from 5 aliquots collected over a 20-minute period. *b*Conversions to (remaining 12), 60, the by-product, 13 and DE (diastereomeric excess) determined by HPLC equipped with a chiral reverse phase column.
Given the promising data generated in the DOE and flow rate study we then employed the simplex method to optimize the continuous production of \((R,R)\)–dihydroartemisinic acid (13). A simplex is a geometrical shape in which the number of vertices is equal to one more than the number of dimensions in factor space.\(^{137}\) In our case, the factors represented the aforementioned reaction parameters. We elected to evaluate two of those parameters, temperature and pressure, and hold flow rate constant at 0.1 mL/min, which resulted in a factor space of two and a simplex that formed a triangle. The vertices of our initial equilateral triangle are labeled in figure 34. One vertex of the triangle represented the best temperature and nearly the best pressure conditions from the previous studies; the other two vertices were selected because the DOE results indicated that high temperature and low pressure had a positive affect on suppressing the amount of 60, but that low temperature and high pressure failed to produce 13 in high quantity. In anticipation of conducting further experiments, 10 bar was the lowest pressure values we could use to study the reflection point of the 125°C and 19 bar experiment if necessary. This was our justification for carrying out an experiment at 100°C and 10 bar instead of at 100°C and 5 bar.

![Figure 34. Simplex used in the optimization of \((R,R)\)–DHAA (13) production](image-url)
Since the H-Cube Mini was not able to exceed temperatures greater than 100°C, we integrated the heating block of a ThalesNano X-Cube into the H-Cube Mini to test the reactions at temperatures above 100°C. The three experiments represented by the vertices in figure 34 at 0.1 mL/min were conducted (Table 15). Of the three investigated, the reaction at 150°C and 10 bar fared the worst, delivering only 31.4% of \((R,R)\)-DHAA (13). Following the procedure outlined by the simplex method, a reflection point for this experiment was calculated by substituting the parameter values into the equations below (Equation 2).

**Table 15. Simplex method optimization of \((R,R)\)-DHAA (13) production**

<table>
<thead>
<tr>
<th>Entry&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Temp (°C)</th>
<th>Pressure (bar)</th>
<th>% 12&lt;sup&gt;b&lt;/sup&gt;</th>
<th>% 60&lt;sup&gt;b&lt;/sup&gt;</th>
<th>% By-Product&lt;sup&gt;b&lt;/sup&gt;</th>
<th>% 13&lt;sup&gt;b&lt;/sup&gt;</th>
<th>% DE&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Conversion to ((R,R))–DHAA (13)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>150</td>
<td>10</td>
<td>14.02</td>
<td>0.04</td>
<td>19.39</td>
<td>66.55</td>
<td>-5.50</td>
<td>31.44</td>
</tr>
<tr>
<td>2</td>
<td>125</td>
<td>19</td>
<td>1.83</td>
<td>1.99</td>
<td>3.58</td>
<td>92.61</td>
<td>60.40</td>
<td>74.27</td>
</tr>
<tr>
<td>3</td>
<td>100</td>
<td>10</td>
<td>1.79</td>
<td>3.89</td>
<td>0.65</td>
<td>93.35</td>
<td>77.60</td>
<td>82.90</td>
</tr>
</tbody>
</table>

<sup>a</sup>All reactions were run at 0.1 mL/min in ethanol with 0.015 M solution of 12. The percent conversions and diastereometric excess are an average of results generated from 5 aliquots collected over a 20-minute period. <sup>b</sup>Conversions to (remaining 12), 60, the by-product, 13 and DE (diastereomeric excess) determined by HPLC equipped with a chiral reverse phase column.

\[
R = C + (C - W)
\]

\[
C = \frac{1}{2}(N + B)
\]

R – reflection; C – centroid; W – worst response; B – best response; N – next to best

**Equation 2. Simplex method’s calculation of new vertex**

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The new, reflected vertex represented a temperature of 95°C and a pressure of 17 bar. While the hydrogenation results under these conditions were closer to those exhibited by the other two vertices (entry 2 and 3, Table 15), it afforded a 69.4% conversion to the desired isomer of 13. After several iterations of reflecting the “worst” performing vertex and carrying out those experiments, the simplex experiments revealed the temperature and pressure combination in entry 3 provided superior conversion and stereoselectivity to the others. Thus, we concluded that we were working in the region of maximum operability as it relates to this system.

3.5.1.2 Catalyst deactivation study

In parallel with optimization studies, we conducted a longitudinal study to explore the recyclability of the 5% Ru/C catalyst. With the objective of commercialization in full view, we elected to investigate the longevity of the catalyst at 1.5 mL/min, 60°C and 50 bar, conditions that afforded modest conversion to the desired diastereomer of 13 (entries 2–4, Table 13) and a superior throughput to the reaction run at 0.1 mL/min (entry 1, Table 13). During the time study, an aliquot was collected every 10 minutes (for a 5 minute period) and subjected to HPLC analysis. Results indicated that the catalytic activity of 5% Ru/C quickly decreased after 10 minutes of use (Figure 35). While not as rapid, the stereoselectivity also declined during that 2-hour interval. We hypothesized that the significant drop off in conversion was either due to leaching of Ru or intense packing of the material in the fixed bed reactor, which resulted in channeling, and thereby lowered the surface
area of catalyst exposed to the substrate. Visible inspection of the catalyst after the reaction showed an extremely compacted pellet. (All hydrogenation reactions we conducted using the H-Cube Mini produced a similar outcome).

![Figure 35](image)

**Figure 35.** Longitudinal study of 5% Ru/C activity; (60°C, 50 bar, 1.5 mL/min)

To test for leaching, we analyzed the supernatant of the product for Ru at minute 10, 20, 30, 60 and 120. ICP-OES results indicated that for the 10, 20 and 30-minute aliquots collected, each contained between 160 – 180 ppb of Ru (Figure 36). In considering the low concentrations of Ru in the product samples and the packing of the catalyst in the fixed bed reactor, we concluded that the deactivation of 5% Ru/C was predominately a result of a loss in the catalyst’s surface area and not leaching of the metal. To confirm this hypothesis, we inverted the catalyst column
and ran subsequent hydrogenation experiments, observing renewed activity for a limited period of time.

**Figure 36.** Ru concentration in the product stream of the hydrogenation longitudinal study; (60°C, 50 bar, 1.5 mL/min)

Interested in whether substituting the 5% Ru/C catalyst, in the powdered form, for pelletized Ru/C catalysts could remedy the extreme catalyst packing, we sought out other Ru catalysts from the same suite. These Ru catalysts, varying in form and loading, were evaluated in the H-Cube Mini (Table 16). Entries 1 and 2 were reiterations of pervious experiments using the 5% Ru/C Strem (BASF) 44-4065 ESCAT 4401 catalyst. Entry 3 employed a different powderized Ru catalyst from that extensively investigated in previous studies (and in entries 1 and 2). Neither its conversion nor its stereoselectivity was as favorable, however. Entries 4
through 11 all explored catalysts that were non-powderized; these catalysts were either pelletized or pressed into hard irregularly shaped flakes. Compared to the powdered catalysts, these non-powdered catalysts showed little conversion to product over the 20-minute period that each was examined. Moreover, the diastereometric excess afforded by the non-powdered catalysts was inferior to the 5% Ru/C identified at Merck & Co.

Table 16. Screen of additional Ru/C catalyst in hydrogenation of 12

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Flow Rate (mL/min)</th>
<th>Temp (°C)</th>
<th>Pressure (bar)</th>
<th>% 12</th>
<th>% 60</th>
<th>% By-Product</th>
<th>% 13</th>
<th>% DE</th>
<th>% Conversion to (R,R) – DHAA (13)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5 % Ru/C #2531260</td>
<td>1.5</td>
<td>60</td>
<td>50</td>
<td>2.1</td>
<td>0</td>
<td>19.5</td>
<td>78.38</td>
<td>66</td>
<td>51.73</td>
</tr>
<tr>
<td>2</td>
<td>5 % Ru/C #2531260</td>
<td>0.1</td>
<td>100</td>
<td>5</td>
<td>0.0</td>
<td>3.88</td>
<td>0</td>
<td>96.12</td>
<td>79.6</td>
<td>76.51</td>
</tr>
<tr>
<td>3</td>
<td>5% Ru/C #SE 172421</td>
<td>0.1</td>
<td>100</td>
<td>5</td>
<td>31.7</td>
<td>0</td>
<td>1.16</td>
<td>67.14</td>
<td>71.6</td>
<td>48.07</td>
</tr>
<tr>
<td>4</td>
<td>0.5 % Ru/C</td>
<td>0.1</td>
<td>100</td>
<td>5</td>
<td>90.5</td>
<td>0</td>
<td>3.52</td>
<td>5.96</td>
<td>36.8</td>
<td>2.19</td>
</tr>
<tr>
<td>5</td>
<td>1 % Ru/C</td>
<td>0.1</td>
<td>100</td>
<td>5</td>
<td>73.7</td>
<td>0</td>
<td>4.71</td>
<td>21.59</td>
<td>52</td>
<td>11.23</td>
</tr>
<tr>
<td>6</td>
<td>0.5 % Ru/C</td>
<td>0.1</td>
<td>100</td>
<td>5</td>
<td>94.0</td>
<td>0</td>
<td>1.98</td>
<td>4</td>
<td>36</td>
<td>1.44</td>
</tr>
<tr>
<td>7</td>
<td>1 % Ru/C</td>
<td>0.1</td>
<td>100</td>
<td>5</td>
<td>70.2</td>
<td>0</td>
<td>13.85</td>
<td>15.94</td>
<td>34</td>
<td>5.42</td>
</tr>
<tr>
<td>8</td>
<td>1 % Ru/C</td>
<td>0.1</td>
<td>100</td>
<td>15</td>
<td>89.3</td>
<td>0</td>
<td>28.12</td>
<td>9.11</td>
<td>56.4</td>
<td>5.14</td>
</tr>
<tr>
<td>9</td>
<td>1 % Ru/C</td>
<td>0.1</td>
<td>100</td>
<td>25</td>
<td>87.8</td>
<td>0</td>
<td>1.98</td>
<td>10.22</td>
<td>58</td>
<td>5.93</td>
</tr>
<tr>
<td>10</td>
<td>1 % Ru/C</td>
<td>0.1</td>
<td>100</td>
<td>100</td>
<td>55.6</td>
<td>1.96</td>
<td>6.6</td>
<td>35.89</td>
<td>60.8</td>
<td>21.82</td>
</tr>
<tr>
<td>11</td>
<td>1 % Ru/C</td>
<td>0.1</td>
<td>100</td>
<td>100</td>
<td>41.0</td>
<td>7.51</td>
<td>6.53</td>
<td>44.95</td>
<td>63.33</td>
<td>28.47</td>
</tr>
</tbody>
</table>

All reactions were carried out in ethanol with 0.015 M solution of 12. The fixed bed reactors were filled with 200 mg of catalysts and were combined with equal mass amounts of titanium shavings, except for entries 10 and 11 (200 mg and 387 mg of catalyst, respectively). aConversions to (remaining 12), 60, the by-product, 13 and DE (diastereomeric excess) were generated from 5 aliquots collected over a 20-minute period and determined by HPLC equipped with a chiral reverse phase column.
We hypothesized that the failure to hydrogenate the starting material was
due to the lower catalyst loading combined with the relative loss in surface area,
which is an inherent property of the pelletized form. The results of this study also
indicated that increasing the catalyst loading (entry 11) to generate more of \textbf{13}
significantly augmented the hydrogenation of both the endocyclic as well as the
exocyclic olefin, to form \textbf{60}, with less of a conversion to the desired
dihydroartemisinic acid product (\textbf{13}).

3.5.1.3 Evaluating (\textit{R},\textit{R})–dihydroartemisinic acid formation by $^1$H NMR

Following the simplex method optimization studies, we sought to validate
the hydrogenation results by analyzing them using an orthogonal analytical method.
We chose to utilize $^1$H NMR data, quantifying conversion and stereoselectivity
relative to an internal standard. We analyzed the product mixture of a reaction
carried out at 1.5 mL/min, 60° C and 50 bar as well as at 0.1 mL, 100° C and 10 bar,
the conditions that produced that highest conversion to \textit{(R,R)}-DHAA (\textbf{13}) in
previous experiments. Unfortunately, the $^1$H NMR results indicated substantially
less of the desired diastereomer of \textbf{13} than the HPLC did: yields of 57.1 \% and
51.3\%, respectively. Upon closer evaluation, both spectra showed a minimal
amount of \textbf{12} and the by-product present; the identifiable, diagnostic peaks were
those of the vinylic hydrogens located on the endocyclic olefin of the diastereomers
of \textbf{13}. Since the over-reduced molecule (\textbf{60}) possesses no discernable peaks via $^1$H
NMR, yet it was present in the HPLC traces, we attributed the relatively lower
amounts of \textbf{13} seen on $^1$H NMR to the higher production of inconspicuous \textbf{60}. From
1H NMR, the formation of 60 appeared to be much higher than previously observed on via HPLC. We concluded that the low amounts of 60 observed on HPLC were due to the lack of a chromophore on the over-reduced product relative to the other molecules.

Aware of this phenomenon, we reran some of the other experiments executed in the DOE, and analyzed them by 1H NMR with an internal standard. We also co-loaded higher amounts of Ti shavings into the catalyst cartridge in attempt to reduce the substrate's exposure to the catalyst at any one time. Despite these efforts, results revealed the highly exacting nature of this transformation when conducted in a packed bed reactor: either the residence time (and associated conditions) was too large, which rendered sizable amounts of 60 and the by-product, or it was too small, which left unreacted 12. Based on these findings, we concluded that this process represented an ideal “Goldilocks” scenario; we needed to find the ideal conditions to reduce the exocyclic double bond without reducing the endocyclic one. Additional experiments, which included varying the substrate concentration, were ineffective. Accordingly, with the presence of two double bonds, ascertaining the right combination of conditions to chemoselectively hydrogenate the exocyclic methylene, without forming the by-product or leaving behind unreacted starting material (12) proved inaccessible in this system.

3.5.2 Batch reactor

Considering the challenges this transformation exhibited in a continuous flow packed bed reactor, with regard to catalyst deactivation (packing and
channeling) as well as nonselective hydrogenation, we sought to develop a high-yielding batch process that demonstrated excellent recyclability of the catalyst. While the formation of 60 was possible, we theorized that by reversing the catalyst-substrate stoichiometry, 12 would encounter a smaller amount of catalyst at any one time, thereby decreasing the probably that the less reactive endocyclic olefin would also be hydrogenated. Many experiments with different combinations of catalyst loading values (ranging from 1 to 4 mol%), hydrogen pressure values (ranging from 10 to 30 bar) and temperatures (25°C or 30°C) where conducted in the HEL ChemSCAN high-pressure batch reactor (Figure 30). Results indicated that across all of the experiments the diastereomeric ratio afforded by the 5% Ru/C catalyst was nearly consistent and comparable to that seen in the HTE at Merck & Co., approximately 85:15. At 25°C and 20 bar with 1.5 mol% of catalyst the desired diastereomer of 13 was delivered in a 73.2% yield, which represented the highest yielding set of conditions evaluated in this study. The HPLC trace showed no formation of 60 in that reaction, but did reveal the presence of 12 and the by-product. In an effort to convert the small amount of remaining starting material to product we carried out subsequent reactions with higher catalyst loadings. Increasing the catalyst loading to 1.5 and 2 mol%, however, led to the formation of 60. Thus, under the aforementioned temperature and pressure with 1.25 mol% of 5% Ru/C, we concluded that we were essentially operating within the optimal set of conditions to form \((R,R)\)-dihydroartemisinic acid (13).

Next, we investigated the recyclability of the 5% Ru/C catalyst. We found that the catalyst could be used in five unique reactions before a considerable
decrease in activity occurred (Table 17). ICP-OES was employed to test for ruthenium leaching. The elemental analysis technique revealed that less than 100 ppb of ruthenium was present in each product mixture.

### Table 17. Recyclability study of 5% Ru/C in the batch hydrogenation of 12

<table>
<thead>
<tr>
<th>Entry</th>
<th>Recycle</th>
<th>% 12</th>
<th>% 60</th>
<th>% By-Product</th>
<th>% 13</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.00</td>
<td>0.00</td>
<td>7.14</td>
<td>92.86</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>1.80</td>
<td>0.00</td>
<td>6.63</td>
<td>90.11</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>2.00</td>
<td>0.00</td>
<td>8.14</td>
<td>91.88</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>1.03</td>
<td>0.00</td>
<td>8.55</td>
<td>90.00</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>1.89</td>
<td>0.00</td>
<td>8.26</td>
<td>88.42</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>8.76</td>
<td>0.00</td>
<td>15.15</td>
<td>76.00</td>
<td></td>
</tr>
</tbody>
</table>

*All reactions were carried out at 20 bar and 25 °C with 1.25 mol% catalyst in 0.015 M ethanol solution of 12. *After each reaction the product mixture was centrifuged, the catalyst was isolated and washed once prior to reuse. *Conversions to (remaining 12), the by-product and 13 were determined by 1H NMR. *The conversion to 60 was determined by HPLC equipped with a chiral reverse phase column.

### 3.5.3 Continuous stirred tank reactor (CSTR)

Finally, we explored the hydrogenation of 12 using the 5% Ru/C catalyst identified at Merck & Co. in a CSTR (Figure 37). A CSTR is a continuous, open system reactor that operates by constantly delivering reagents to the vessel while periodically removing the vessel’s contents. In theory, the reactor’s contents are agitated so intensely that complete uniformity is established within the system, allowing it to function in a steady state.
Since the packed bed reactor was implicated in the over-reduction of 13 and the deactivation of the catalyst, we envisioned that by suspending the catalyst in the solvent, in the form of a slurry, we could alleviate those issues while still harnessing some of the benefits of a continuous reactor. The CSTR, fabricated by HEL, was outfitted with a 0.2-micron frit on the exit line, which served to keep the catalyst within the vessel. This CSTR was designed to expel material once the temperature differential between the probes reached an inputted minimum; at that point, contents were discharged from the vessel until an inputted maximum temperature differential was reestablished. An initial screen included a 10 mol% loading of 5% Ru/C, a flow rate of 0.1 mL/min, a temperature at 40°C and 30 bar of hydrogen gas. Under these parameters, HPLC analysis showed that at several different intervals,
the effluent contained an average of 78.8% unreacted 12 (entry 1, Table 18). Consequently, in an effort to consume more starting material, we repeated the hydrogenation under the same set of conditions, but increased the catalyst loading to 20 mol%. While the amount of 12 in the effluent decreased to an average of 18.2%, 60 and the by-product appeared in large quantities (entry 2, Table 18). That both the unconsumed starting material and the over-reduced product were present concurrently in the effluent, these experiments once again revealed the highly sensitive nature of this transformation, particularly as it related to the reactor system in which it was carried out.

![Table 18. CSTR screen in the hydrogenation of 12](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst Loading (mol%)</th>
<th>%12</th>
<th>%60</th>
<th>%By-Product</th>
<th>%13</th>
<th>%DE</th>
<th>% Conversion to (R,R)-DHAA (13)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>10</td>
<td>78.84</td>
<td>0</td>
<td>3.42</td>
<td>17.73</td>
<td>59.84</td>
<td>14.17</td>
</tr>
<tr>
<td>2</td>
<td>20</td>
<td>18.2</td>
<td>3.37</td>
<td>9.27</td>
<td>69.17</td>
<td>59.58</td>
<td>55.19</td>
</tr>
</tbody>
</table>

*All reactions were carried out at 0.1 mL/min, at 30 bar and 40°C in a 0.015 M ethanol solution of 12. ‡This value was calculated relative to the amount of initial 12 in reactor. §Conversions to (remaining 12), 60, the by-product and 13 were determined by HPLC equipped with a chiral reverse phase column.

While these studies demonstrated that a CSTR does not appear to be suitable for conducting a hydrogenation on this substrate, it did support our earlier hypothesis that the deactivation of the catalyst in the fixed bed reactor was due to packing, not leaching. One experiment, which included 10 mol% loading of 5%
Ru/C, a flow rate of 2 mL/min, a temperature at 18°C and 30 bar of hydrogen gas, showed no indication of a decrease in catalyst activity after 205 minutes.

3.6 Isolation and identification of the by-product

In the course of performing the hydrogenation studies, a by-product continually appeared in the product mixture, detectable on HPLC as well as 1H NMR. While this substance was formed using all three-reactor systems, in the presence of many different heterogeneous catalysts, it was generated most abundantly during some undisclosed transfer hydrogenation experiments. In an effort to elucidate its structure, and in so doing determine how to minimize its production, we isolated this compound using column chromatography impregnated with silver nitrate and subjected it to mass spectrometry as well as comprehensive 1D and 2D NMR studies.

Following isolation and purification, mass spectrometry revealed a parent peak at m/z = 234. While this substance shared the same mass as 12 it had a distinctly different chromatographic retention time. In fact, the HPLC trace showed two nearly baseline resolved peaks that integrated to 8.8 to 1.2: it was these peaks to which the by-product was assigned. Both the by-product and 12 were observable on the HPLC at 254 nm, while 13 and 60 were detectable at 210 nm. The differences in absorptivity provided some insight into the nature of the by-product’s chromophore. We hypothesized that since the only substantial chromophoric groups on 12 were the double bonds, and the reduction of one of them resulted in
the inability to absorb at 254 nm, then the by-product most likely would not be a reduced form of 12. The mass spectrometry data supported this conjecture.

The $^1$H NMR of the isolated by-product revealed the same large peaks at 5.05 ppm and 3.91 ppm that had been present on the previous spectra of product mixtures. The diagnostic vinyl region also included a small peak at 5.29 ppm, which was identified as an impurity associated with the lone vinyl hydrogen on the undesired diastereomer of 13 and a smaller peak at 4.95 ppm. The $^{13}$C NMR displayed numerous peaks beyond the aliphatic region, but four most prominently: one at 175.6 ppm, attributed to a carbonyl carbon, and three in the vinyl region at 153.9 ppm, 134.0 ppm and 124.2 ppm. $^{13}$C-HSQC revealed that the proton at 5.05 ppm was located on the carbon at 124.2 ppm, which was a positive peak on DEPT-135, strongly suggesting that the peak represented a vinyl methine carbon. $^{13}$C-HSQC also showed that the proton at 3.91 ppm was correlated to an aliphatic carbon at approximately 41 ppm. This carbon was positive on DEPT-135 as well, intimating that it was also a methine carbon, especially since it integrated 1-to-1 with the proton at 5.05 ppm. A COSY 2D NMR experiment, also performed on the by-product, indicated that the vinylic proton at 5.05 ppm and the aliphatic proton at 3.91 ppm were coupled. (Refer to the appendix for the NMR spectra).

The DEPT-135 also prominently displayed four negative and six additional positive peaks in the aliphatic region, which were assigned to four methylene carbons and a combination of methine and methyl carbons, respectively. With 11 of the 15 carbon atoms that constitute the cis-decalin skeleton of 12 unequivocally identified, we speculated that since the DEPT-135 spectrum was devoid of any
additional peaks that the four remaining carbons that form the molecular skeleton were quaternary. The peak at 175.6 ppm, which we initially denoted the carbonyl carbon, was absent on the DEPT-135 spectrum, validating this assignment.

Based on the NMR data we were confident that two of the remaining three carbons were vinylic and quaternary: the peaks at 153.9 ppm and 134.01 ppm. One of those carbons, we reasoned, was the other carbon bound to the methine carbon at 124.2 ppm. The second vinylic, quaternary carbon, however, did not have an identifiable vinylic carbon to which it was bound; this unassigned carbon represented the fifteenth carbon atom in the molecule. Although we could not definitively identify the fifteenth carbon due to the other peaks associated with the impurities, we deduced that since the DEPT-135 revealed that all of the peaks beyond the aliphatic region (except for the peak at 124.2 ppm) were quaternary that the remaining carbon atom must also be quaternary and bound to the aforementioned vinylic carbon.

In general, hydrogenation reactions are characterized as clean reactions, producing little in the way of by-products. However, “double-bond migration can take place in competition with reduction,”92 as depicted in figure 12, leading to the formation of undesired products. Studies have ascertained that double-bond migration tends to occur when the surface concentration of hydrogen on the catalyst is low.139

Given all of the data analysis and the information published in the literature on the nature of hydrogenations, we proposed three possible structures for the by-product (Figure 38). While each of these structures fit within our spectral
interpretations, only one was plausible upon closer inspection. A literature search revealed that compound 61 did not match our $^1$H NMR data, which allowed us to quickly eliminate that option. Next, particular attention was dedicated to the proton at 3.91 ppm, given how far downfield it appeared for an aliphatic moiety. Aware that it was coupled to the only vinylic proton in the molecule, compound 62 seemed reasonable. However, the chemical shift of the methine group at 3.91 ppm provided some significant insights into the position of the two olefins. Analogous molecules to compound 62 that possess highly conjugated π-systems are not known to contain terminal allylic protons, like the one bonded to C-4, shifted that far downfield. A proton bound to a sp$^3$ hybridized carbon separating two olefins in a non-conjugated system, however, experiences greater deshielding, as indicated on the $^1$H NMR spectrum of valerenic acid and other 1,4 pentadiene containing molecules. As a sesquiterpenoid, valerenic acid is structurally analogous to compound 63. Its methine proton, allylic to both olefins, is located at 3.54 ppm. While the proton attached to C-6 in the by-product spectrum is slightly further downfield, the location of this corresponding proton in valerenic acid rationalized its assignment. Ultimately, the published characterization of valerenic acid, combined with our spectral data and the known tendencies for double bonds to isomerize during hydrogenations, especially during hydrogen starved transfer hydrogenations, provided strong evidence that compound 63 represented the molecular structure of the by-product.

The proposed by-product structure led us to speculate that the two nearly baseline resolved peaks observed on the HPLC, with a relative abundance of 8.8 to
1.2, corresponded to the E and Z isomer of compound 63. This hypothesis was corroborated by an orthogonal data point: the two HPLC peaks shared the same integration ratio as the peaks at 5.05 ppm and 4.95 ppm displayed on the by-product $^1$H NMR spectrum. We considered that these represented the C-6 proton peaks on the two configurational isomers of compound 63. This not only provided insight into the unexplained impurity on the NMR, but it further validated our purposed by-product structure, compound 63.

![Figure 38. Proposed by-product structures](image)

Given the proposed by-product structure as compound 63, we were interested in the stereochemical outcome upon exposing it to hydrogenation conditions. We reasoned that since tetra-substituted olefins are more stable than di-substituted ones, it would be thermodynamically unfavorable for compound 63 to isomerize back to 12, and therefore it might exist as a dead end product or a reactive intermediate. While 12 demonstrated the ability to preferentially generate the desired diastereomer of 13 in the absence of a chiral catalyst, we questioned whether the by-product possessing the tetra-substituted olefin would function
similarly or if hydrogenating it with 5% Ru/C would deliver a racemic mixture of 13. We speculated that if the latter were true, then any formation of the by-product as a reactive intermediate could scramble the stereochemistry, lowering the chiral purity of the desired dihydroartemisinic acid product (13).

To test this, we subjected the isolated by-product (63) to the optimal batch hydrogenation conditions identified in Chapter 3.5.2. After multiple attempts, however, HPLC analysis showed no conversion of the by-product to either 13 or 60. While tetra-substituted olefins are more stable than their di-substituted counterparts, rendering them less reactive toward hydrogenation, the tetra-substituted olefin should be susceptible to reduction. That no consumption of the by-product was detected led us to question if any remaining silver from the separation deleteriously affected the reaction. Therefore, at a minimum, these hydrogenation results suggest that further investigations into the presence or function of silver should be considered. If the metal's presence is found to be innocuous, then more work into elucidating the structure of the by-product should be pursued.

3.7 Conclusions

Our efforts to identify an efficient and cost-effective commercially available catalyst to facilitate the asymmetric hydrogenation of 12 ultimately led us to a thorough evaluation of a heterogeneous 5% Ru/C catalyst in three different reactor systems. The work exposed the challenges inherent to this transformation, despite
not necessitating a chiral catalyst to effect the asymmetric induction. Conducting the reaction in an expeditious manner, one that obviates the laborious, interruptive separation and isolation steps, as exemplified in the continuous packed bed reactor and CSTR, proved to deliver too much over-reacted product, form the by-product or leave behind too much unconsumed starting material, or produce a mixture of the three. Moreover, this powdered catalyst proved unsuitable for a fixed bed reactor. Given the complexity of this reaction, particularly within these systems, we concluded that a traditional batch reactor is the optimal system to conduct this specific hydrogenation.

Finally, our work has also identified and purposed a structure for the formation of a by-product implicated in this transformation that to date has not been reported in the literature.

3.7.1 Space-time-yield results: comparison to prior work

By definition, space-time-yield (STY) is the quantity of material produced per reactor volume during a designated interval of time. It is a metric often used to express the overall efficiency of a process. In comparing our work with the 5\% Ru/C catalyst in the continuous fixed bed reactor to previous efforts in this area, our process is reasonably competitive, despite the lower yield to the desired diastereomer of 13 (Table 19). If a solution to the catalyst packing and concomitant deactivation could be ascertained, our continuous process holds some potential for commercialization, especially given its cost and safety profile. Additionally, this
regime has the capability of being easily integrated into a downstream continuous photooxygenation process, forming a novel continuous multistep operation.

Table 19. Comparison of VCU conditions hydrogenation to other processes

<table>
<thead>
<tr>
<th>Group</th>
<th>Catalyst</th>
<th>Reducing Agent</th>
<th>Conditions</th>
<th>Process</th>
<th>% Conv.</th>
<th>DR</th>
<th>STY (mol L⁻¹ h⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amyris⁹</td>
<td>[RhCl(PPh₃)₃][0.05 mol%]</td>
<td>H₂</td>
<td>25°C; 22 bar; 6 hrs; MeOH</td>
<td>batch</td>
<td>99</td>
<td>95:5</td>
<td>0.023</td>
</tr>
<tr>
<td>Sanofi-Aventis³</td>
<td><a href="dmf">RuCl₂(R)-dtbm-Segphos</a>₂ [0.01 mol%]</td>
<td>H₂</td>
<td>80°C; 47 bar; 19 hrs; PhMe</td>
<td>batch</td>
<td>100</td>
<td>94:6</td>
<td>N/A</td>
</tr>
<tr>
<td>Sanofi-Aventis³</td>
<td>N/A</td>
<td>N₂H₄</td>
<td>40°C; 7 hrs; H₂O/iPrOH (4:1) pH 8.1 - 8.4 (KOH)</td>
<td>batch</td>
<td>90</td>
<td>93:7</td>
<td>0.023</td>
</tr>
<tr>
<td>Kappe et. al.¹⁴</td>
<td>N/A</td>
<td>N₂H₄</td>
<td>60°C; 20 bar; 0.6 hrs; iPrOH</td>
<td>continuous</td>
<td>97</td>
<td>97:3</td>
<td>0.56</td>
</tr>
<tr>
<td>VCU</td>
<td>5% Ru/C</td>
<td>H₂</td>
<td>60°C; 50 bar; 0.1 hrs; EtOH</td>
<td>continuous</td>
<td>89:11</td>
<td>0.22</td>
<td></td>
</tr>
</tbody>
</table>

3.8 Experimental

3.8.1 General remarks

All reactions were conducted under ambient conditions unless otherwise indicated. Hydrogenation reactions performed at VCU were conducted using a combination of systems, which included: a ThalesNano H-Cube Mini, continuous flow reactor, a HEL ChemSCAN, a parallel high-pressure reaction system, and a custom designed HEL CSTR. The HTE hydrogenation studies performed at VCU were conducted on a custom-built high-pressure reactor designed to accommodate two-96 reactor well plates. The hydrogenation reactions conducted at Boehringer-
Ingelheim were carried out on a HEL Cat24, a high-pressure reactor system. The reagents were purchased from commercial suppliers including Sigma Aldrich, Inorganic Ventures and Strem Chemicals Inc. (BASF), as well as from collaborating chemists at Boehringer-Ingelheim and Clinton Health Access Initiative; all were used as received. Elemental analysis was performed on a Varian Vista MPX Axial ICP-OES. The chiral purity of the hydrogenation reactions were monitored using a Waters ACQUITY UPLC M-Class system equipped with a chiral, reverse phase column (ID-3, 4.6 mm X 15 cm, 3-micron particle size) acquired from Chiral Technologies. Both $^1$H NMR and $^{13}$C NMR spectra were obtained on a Varian Mercury 300 MHz, Bruker 400 MHz NMR or Bruker 600 MHz NMR spectrometer using CDCl$_3$ as solvents. Mass spectrometry data was acquired on a Micromass Waters QTOF-2 mass spectrometer.

3.8.2 General method for BIPI ligand screen

In a glove box, 0.02 equivalents of the metal catalyst and 0.024 equivalents of the ligand (as indicated within the tables presented in chapter 3.2) were charged to test tubes compatible with the HEL Cat24. 0.5 mL aliquot of a 12 stock solution (0.0426 M, 1 eq.) was then removed and transferred into the test tubes, along with stir bars. The test tubes were loaded into the reactor vessel, capable of accommodating up to 24 test tubes. The vessel was then sealed and plugged within the glove box, and transferred into the CAT block inside the fume hood. The reaction vessel was purged with gaseous nitrogen and back filled with gaseous...
hydrogen three times before finally being pressurized to 24 bar. The reaction was heated to 65°C (unless otherwise indicated) overnight. Additional hydrogen gas was added to the system as needed to maintain constant pressure. Conversion and stereoselectivity of the product were monitored by HPLC.

3.8.2.1 HPLC method performed at Boehringer-Ingelheim

4 minute run time; Halo Rp Amide; 4.6 mm X 15 cm, 2.7-micron particle size; isocratic mobile phase, 30:70 A to B, A= 0.1% H₃PO₄ (aqueous), B = acetonitrile; flow rate of 1.5 mL/min at 25°C; 5 μL injection volume; elution times of the diastereomers: 2.51 minutes and 2.68 minutes; observed at 210 nm.

3.8.3 General method for HTE screen of catalysts at Merck & Co.

Experiments were conducted using protocols developed at Merck & Co.

3.8.4 General methods for evaluating 5% Ru/C catalyst in the hydrogenation of artemisinic acid within different reactor systems

3.8.4.1 Continuous flow reactor

0.200 g of 5% Ru/C (Strem Chemicals Inc., BASF; lot # 25312600) and 0.200 g of titanium shavings were combined in a cartridge (70 mm in length) with one end
pre-sealed with 8 μm filters. Once packed, the other end of cartridge was sealed with 8 μm filters, and it was then loaded into the ThalesNano H-Cube Mini. The HPLC pump was primed and the system was sufficiently flushed with EtOH. A 15 mM stock solution of 12 in 200 mL of EtOH was prepared in a volumetric flask and fed into the ThalesNano H-Cube Mini by the piston pumps at flow rates between 0.1 mL/min and 3 mL/min, under pressures that ranged from 5 bar to 100 bar and at temperatures between 25°C and 100°C (specified within the tables presented in chapter 3.5.1). Once the system had reached a stable state (as indicated on the display), the first 7.5 mL of the product stream was discarded prior to collecting the outlet stream continuously in 5-minute increments over a 25-minute duration. The fractions were monitored by HPLC (the procedure is included below). 3 mL of product solution was concentrated under reduced pressure, dissolved in CDCl₃ along with internal standard dimethyl sulfone (0.0444 mmol) before analyzing by ¹H NMR. Upon comparison, the spectra collected was identical to that reported in the literature.¹⁴²

3.8.4.2 Batch reactor

In a HEL ChemSCAN 20 mL hastelloy autoclave, a 5 mL portion of a 15 mM stock solution of 12 in EtOH and 0.00372 g of 5% Ru/C (Strem Chemicals Inc., BASF; lot # 25312600) were combined. The hastelloy autoclave was screwed onto the ChemSCAN unit by hand. The vessel was pressurized with hydrogen gas to 30 bar, vented and pressurized again with hydrogen gas to 20 bar. The reactor was heated
to 25°C for 18 hours with overhead agitation. Additional hydrogen gas was injected into the reactor as necessary to maintain a constant pressure. At the conclusion of the reaction, the hydrogen gas was vented from the autoclave and it was allowed to cool to RT. The reaction contents were transferred to a 20 mL scintillation vial and an internal standard, dimethyl sulfone (0.0368 mmol), was charged to the vial and stirred until it dissolved upon inspection. The heterogeneous catalyst was then allowed to completely collect at the bottom of the vial. The supernatant was transferred to another scintillation vial by a syringe. The solution was concentrated on a rotary evaporator and the resulting material was dissolved in CDCl$_3$ and monitored by $^1$H NMR. Upon comparison, the spectra collected was identical to that reported in the literature.\textsuperscript{142} In the case that the heterogeneous catalyst was subject to further recycles, the catalyst was washed by transferring it into a 50 mL conical vial with 50 mL of EtOH. The suspended mixture was centrifuged at 4,200 rpm and the supernatant was decanted. The resulting solid catalyst was dried under vacuum.

3.8.4.3 Continuous stirred tank reactor

150 mL of 15 mM solution of 12 in EtOH was charged to a 200 mL hastelloy grade C276 reactor, followed by 0.600 g of 5% Ru/C (Strem Chemicals Inc., BASF; lot # 25312600). The vessel was placed into the reactor block and sealed. The contents were stirred via overhead agitation at 800 rpm for 1 hour prior to the system reaching desired pressure and temperature, 30 bar and 60°C. At that point, the substrate was fed into the system at flow rate of 0.1 mL/min. The product was
discharged from the vessel when the temperature differential between the thermocouple submerged in the reacting solution and thermocouple residing above it was less than or equal to 1°C. Once, the difference in temperatures between the probes returned to 1.3°C the system stopped draining the contents. The product stream was monitored by HPLC (the procedure is included below).

3.8.4.4 Chiral HPLC method performed at VCU and Merck & Co.

12 minute run time; ID-3, 4.6 mm X 15 cm, 3-micron particle size; isocratic mobile phase, 60:40 A to B, A= 0.02% HClO₄/150 mM NaClO₄ (aqueous), B = acetonitrile, flow rate of 1.5 mL/min at 25°C; 5 μL injection volume; elution times of the diastereomers: 6.25 minutes and 6.70 minutes; observed at 210 nm and 254 nm.

3.8.5 Transfer hydrogenation procedure to render by-product 63

To a stirred solution of 12 (0.050 g, 0.214 mmol, 1 eq.) in 5 mL of MeOH in a 20 mL scintillation vial equipped with a stir bar, formic acid (0.092 g, 2.00 mmol, 10 eq.) was charged dropwise. Ammonium formate (0.0699 g, 3.00 mmol, 15 eq.) was added to the vial, followed by 10% Pd/C (0.0039 g, 0.0037 mmol, 0.0173 eq.). The
solution was allowed to stir. After two hours, the reaction was heated to 50°C and that temperature was maintained for 24 hours. At the conclusion of the reaction, the heterogeneous catalyst was removed and the supernatant, containing the product mixture, was concentrated by rotary evaporator. The product was then dissolved in a solution of dichloromethane, MeOH and acetic acid, before being precipitated in water, collected and lyophilized. The resulting off-white solid was then purified by column chromatography (the procedure is included below) and the fractions of interest were concentrated under vacuum. $^1$H NMR diagnostic peaks (CDCl$_3$): $\delta = 5.07$ (s, 1H), 3.93 (s, 1H) ppm. $^{13}$C NMR (CDCl$_3$): $\delta = 175.4, 153.9, 134.0, 124.2, 119.5, 41.8, 35.3, 28.2, 27.8, 25.6, 25.07, 23.5, 19.4, 15.4$ ppm.

3.8.5.2 Column chromatography method to isolate the by-product (63)

An aqueous solution (2:1 water: MeOH) of 1 g of silver nitrate in 6 mL of water/MeOH was mixed with 4.5 g of silica C-18 and stirred with a stir bar for 10 minutes. The mixture was dried in an oven at 150°C for 1 hour. The beaker was wrapped in aluminum foil and left out in the hood overnight. A column (30 cm long with a 1 cm diameter) was packed with a cotton ball, sand, and then the impregnated silica powder (dissolved in 35 mL of 2:8 water: MeOH). It was topped off with sand. The sample was added to the top. Air was used to push the eluting solvent, a 2:8 solution of water: MeOH, through the column. Thin layer chromatography was conducted on the collected fractions.
CHAPTER IV

THE APPLICATION OF A COMMERCIALLY AVAILABLE PHOTOSENSITIZER FOR THE CONTINUOUS PHOTOOXYGENATION OF DIHYDROARTEMISINIC ACID TO ARTEMSININ

4.1 Background and prior work

4.1.1 An explanation of photochemistry

Photochemistry is a branch of chemistry that involves the interaction of light with matter. Chemical reactions that involve light are ubiquitous, and are an important aspect of many chemical processes that include: photosynthesis, photodynamic therapy, and radical polymerization reactions. As scientists have gained a deeper understanding of photochemistry and its capacity to improve the quality of life, research has rendered new devices, more environmentally friendly sources of energy as well as innovative industrial applications.\textsuperscript{143}

The quantum theory states that the energy of matter is quantized, meaning that the energy within matter occupies distinct, specific levels. The gap between the quantized energy levels of matter can correspond to the energy of ultraviolet and visible light. Accordingly, matter is capable of absorbing light energy, in the form of a photon, which can promote an electron to a higher energy state provided that the photon has energy that corresponds to the energy difference between the electronic states. The process that moves an electron from a lower energy level to a higher,
more electronically excited one is destructive to the photon supplying the energy. The photon’s energy is conserved, however, as it becomes a part of the electronically excited species’ total energy. The absorbing matter, possessing a higher energetic state, is much more inclined to participate in a reaction or other chemical process, such as electron transfer, than in its ground state.

Exciting an electron can engender a chemical transformation, such as when the human body synthesizes vitamin D from 7-dehydrocholesterol in the dermis during exposure to sunlight. In other cases, an electronically excited molecule can transfer its energy or an electron to another molecule in the ground state as long as certain requirements are met. Conversely, an excited electron can become deactivated through light emission, known as luminescence, or the release of heat energy.

Matter, in all of its various forms, does not absorb light equally. Molecules that absorb light possess chromophores, which are moieties within molecules whose distance between electronic energy levels is of the same order as the energy of visible or ultraviolet light. In molecular organic chemistry, chromophores are functional groups that typically undergo π to π* and n to π* electronic transitions upon encounter with electromagnetic radiation in the visible or ultraviolet range. In general, molecules that contain conjugated π-systems tend to absorb light much more intensely than isolated alkenes. This occurs because the energy gap between the highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO) in a conjugated system narrows, which reduces the amount of energy required to initiated a π to π* transition. In general, the greater
the number of linearly conjugated polyenes present in a molecule, the lower the energy needed to promote an electron to a higher electronic state. For example, a diene's lowest energy absorption band occurs at 217 nm, in the ultraviolet region of the electromagnetic spectrum. Comparatively, a molecule with eight alternating double and single bonds possesses a lowest energy absorption band in the visible region at 410 nm. Thus, electromagnetic radiation with wavelengths in the visible range, such as red, green, or blue light, possess sufficient energy to promote an electron to a higher electronic state, provided the transition gap is of the same order. Molecules that possess these signature-conjugated π-systems are excellent candidates for use as photocatalysts, provided they meet other requirements as well.

While organic molecules lacking π-systems can experience σ to σ* electronic transitions, this transition requires energy that cannot be supplied by ultraviolet or visible light, but rather by inaccessible far-ultraviolet light. Thus, organic molecules without π bonds tend not to absorb much visible light. In addition to transitions in a molecule's electronic state, light absorption can also initiate nuclear motion, causing changes in the vibrational and rotational states.

4.1.2 The chemistry of singlet oxygen: generation and application

The concept of singlet oxygen (\( ^1O_2 \)) was first proposed in 1924. A highly reactive electrophile, singlet oxygen is an electronically excited form of molecular oxygen in its ground state, known as triplet oxygen (\( ^3O_2 \)). It can be generated
through several different photochemical and chemical methods as well as in biological processes.\textsuperscript{146,147}

Singlet oxygen is photochemically generated when triplet oxygen interacts with an electronically excited molecule, usually a photocatalyst, and a transfer of energy ensues that promotes molecular oxygen into its excited state, as seen in the Jablonski diagram represented in figure 39. In order for a photocatalyst to excite molecular oxygen, the photocatalyst must have a triplet excited state of its own that is equal to or exceeds 95 kJ/mol, which corresponds to the energy difference between the ground state and the excited state of molecular oxygen.\textsuperscript{145}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{jablonski_diagram.png}
\caption{Jablonski diagram; the process through which molecular triplet oxygen is promoted to the higher energy, singlet oxygen state}
\end{figure}

There are two singlet oxygen states. From an electronic configuration perspective, the difference between each of the two singlet oxygen states and triplet
oxygen state involves the spin as well as the location of the electrons in the molecules’ degenerative \( \pi \)-antibonding orbitals. In ground state diatomic oxygen (\( 3\Sigma_g^- \)), the two electrons in the molecule’s \( \pi \)-antibonding orbitals have parallel spin and are unpaired, as predicted by Hund’s Rule. In the higher energy singlet oxygen state, the electronic configuration remains identical to the ground state except the electrons in the molecule’s \( \pi \)-antibonding orbitals possess antiparallel spin. This species, represented as \( ^1\Sigma_g^+ \), is approximately 195 kJ/mol higher in energy than molecular oxygen in the ground state. This form of singlet oxygen, however, quickly relaxes to the lower energy singlet oxygen state, denoted \( ^1\Delta_g \), as the two electrons in the molecule’s \( \pi \)-antibonding orbitals pair up with antiparallel spins, leaving one vacant degenerative orbital (Figure 40). This lower-lying singlet oxygen state remains 95 kJ/mol higher in energy compared to molecular oxygen in ground state. Accordingly, it is a highly reactive, electrophilic species.

\[ \begin{array}{cccc}
\pi^* & \pi^* & \pi^* & \pi^* \\
3\Sigma_g^- & ^1\Sigma_g^+ & ^1\Delta_g & \end{array} \]

**Figure 40.** Representation of the location and spin of electrons within the \( \pi \)-antibonding molecular orbitals in molecular oxygen’s triplet and singlet states

While there are two singlet excited states, the form that predominates is the energetically lower one, \( ^1\Delta_g \). While \( ^1\Delta_g \) singlet oxygen lasts longer than \( ^1\Sigma_g^+ \) singlet
oxygen, it too is very short-lived. In PhMe for example, the lifetime of $^1\Delta_g$ singlet oxygen is $2.9 \times 10^{-5}$ seconds. In a protic solvent, like EtOH, it remains excited for $9.7 \times 10^{-6}$ seconds.\textsuperscript{148} Despite its short lifetime, chemists have been able to use singlet oxygen to construct complex organic molecules through the oxidation of heteroatoms, ene reactions and cycloadditions for the last fifty years.\textsuperscript{147, 149, 150} Many natural products, including artemisinin (1), have been biomimetically synthesized through a reaction with photochemically induced singlet oxygen.\textsuperscript{147}

### 4.1.3 Photochemical batch syntheses of artemisinin

Cognizant of the biosynthetic pathway that furnishes artemisinin (1) in *Artemisia annua*, research teams have devoted much attention to synthetically preparing the antimalarial agent through biomimetic methods. Over the last four decades, teams have sought to produce 1 through an ene reaction involving a highly electrophilic oxygen species, singlet oxygen. Many of these research groups have employed a similar strategy for installing the endoperoxide core: a photochemical generation of singlet oxygen followed by an acid-mediated cyclization involving triplet oxygen to deliver the final target. What differentiated the approaches were the starting points, as well as the intermediate to which singlet oxygen was installed along the synthetic route. For those who pursued a total synthesis, the structure of the commercially available starting materials greatly varied. For the groups who sought after a semi-synthetic methodology, however, many began with a common starting point: artemisinic acid (12).
In 1983, Schmid and Hofheinz published the first total synthesis to artemisinin (1). They began the synthetic sequence from readily available (−)-isopulegol (5) (Scheme 1 and Figure 41). Following 11 steps, a critical intermediate possessing an enol ether was constructed (6). This species then reacted with singlet oxygen through an ene reaction to introduce the essential hydroperoxide moiety onto the molecule (7). This methodology established a precedent for installing artemisinin’s oxygenated core: a reaction with photochemically generated singlet oxygen, via exposure of a photocatalyst to light in the presence of triplet oxygen. In this particular procedure, methylene blue, dissolved in a halogenated solvent, dichloromethane, served as the photosensitizer. Following the photooxygenation, the intermediate peroxide underwent an acid-induced cyclization to deliver 1. The oxygenation and cyclization steps combined to produce an 18% yield.74

In 1992, Acton and Roth reported a semi-synthetic batch procedure to convert 13 to 1 that built upon their 1989 publication and utilized similar photochemical methods as Schmid and Hofheinz.77,78 Methylene blue was again selected as the photosensitizer. Upon irradiation by a street lamp, the dye, dissolved in a mixture of methylene chloride and acetone at 0°C, generated singlet oxygen that then reacted with 13 to produce 14. What differentiated this approach from the Schmid and Hofheinz’s scheme was the substrate on which the singlet oxygen was installed: dihydroartemisinic acid (13), which was generated by reducing 12 sourced from Artemisia annua. After a solvent switch to petroleum ether and removal of the sensitizer, the intermediate peroxide was left standing, exposed to air at room temperature for up to 4 days with catalytic amounts of trifluoroacetic
During this time, a second oxygen molecule reacted with the oxidized intermediate to install the essential endoperoxide core, followed by a cyclization to furnish the natural product. Several variations of this general reaction procedure were conducted to afford 1 in isolated yields of 17-32% (Figure 41).\textsuperscript{77}

In 1990, and Vonwiller disclosed a similar semi-synthetic approach involving photochemistry. However, this group elected to use rose bengal as the photocatalyst. In this procedure, rose bengal, dissolved in acetonitrile, was irradiated with a tungsten lamp at -30°C to quantitatively consume 13 and produce the allylic hydroperoxide (14) and a mixture of other regioisomers. The mixture of these species was esterified to form the methyl ester derivatives. Subsequently, the intermediate mixture was diluted with dichloromethane at -20°C and treated with copper triflate. This copper catalyst served to initiate a proposed redox reaction that converted the allylic hydroperoxide to 1,2 dioxetane, a four-membered heterocycle, and placed a resulting radical on the adjacent bridgehead carbon. This transient radical species was then intercepted with a mole of oxygen to install a second hydroperoxide moiety onto the cis-decalene ring. This species then underwent a ring opening to deliver a dicarbonyl hydroperoxide. The resulting intermediate was warmed to room temperature, which initiated the intramolecular cyclization/condensation reaction to furnish 1 in a 29% isolated yield (Figure 41).\textsuperscript{75}

In 2003 and in 2010, Yadav and coworkers reported a total synthesis of the natural product that built upon the aforementioned work, specifically the use of photochemical means to generate singlet oxygen and install the oxygenated core.\textsuperscript{67,76} Both approaches commenced with commercially available starting materials (+)-
isolimonene (64) and (R)-(+)‐Citronellal (8), respectively. In their first synthesis, an ether enol immediate (65), structurally similar to the one constructed by Schmid and Hofheinz was fashioned after 9 steps. It was then subjected to a comparable photooxygenation. In their second synthesis, a structurally dissimilar immediate (9), the methyl ester of 13, was constructed in 8 steps. This cis‐decalene species underwent a photooxygenation similar to the process executed by Acton and Roth. In both approaches, however, rose bengal served as the photosensitizer. Additionally, both hydroperoxide intermediates were converted to artemisinin (1) by an acid‐mediated ring closure reaction. (Figure 41).
Figure 41. A compilation of the pioneering small-scale, batch approaches to artemisinin (1), highlighting the photooxygenation and concomitant cyclization steps.

Following decades of incremental advancements by numerous research groups on the benchtop, the scientists at Sanofi revealed the first large, industrial scale photochemical production of artemisinin (1). Modeled after the small-scale process originally established by Acton and Roth, this robust operation transformed a mixed anhydride of 13 into 1 by comparable photochemical methods. A singlet oxygen ene reaction generated by light, air and the photosensitizer,
tetraphenylporphyrin (TPP), in an immersion well reactor at -10°C converted the anhydride of dihydroartemisinic acid (66) into the hydroperoxide intermediate (14). TFA then induced a Hock cleavage and rearrangement sequence that installed a second hydroperoxide moiety and a simultaneous cyclization to furnish 1 in 41% yield (Scheme 33). In 2013, the first year of production, Sanofi’s industrial scale photochemical operation manufactured 35 tons of artemisinin (1) (Figure 42).83

Scheme 33. Sanofi large-scale batch photoxygenation process to artemisinin (1)

83 Figure 42. An image of the photoreactor set-up used by Sanofi in the industrial-scale batch process of artemisinin (1) in Garessio, Italy
4.1.4 Photochemistry in continuous operations

The benefits of conducting chemical syntheses in continuous flow operations are well documented. Among them is its increased photochemical efficiency as compared to batch processes. As mentioned, in order for photochemical reactions to occur, light-responsive molecules must be exposed to ultraviolet or visible electromagnetic radiation. If the transmission of that light into a photoreactor is not uniform or does not fully penetrate it, the molecule’s exposure to photons is compromised, which can lead to lower product yields and selectivities.

This phenomenon is described by the Beer-Lambert law: \( A = \varepsilon cl \), where the absorption of the light \( A \) is related to the molar absorptivity \( \varepsilon \) of the light-absorbing molecule, the concentration of the molecule in solution \( c \), and the distance the light passes through the solution \( l \). The relationship between transmittance, the inverse of absorption, and the radius of the reactor at different photosensitizer concentrations is illustrated in figure 43.

![Figure 43](image)

**Figure 43.** Light transmission as a function of distance from radiation source in a homogeneous photocatalytic reaction
From this graph, it is evident that the percentage of a reaction solution capable of being irradiated is inversely correlated to the size of the photoreactor, as the intensity of light decreases rapidly with increasing distance from the source. Accordingly, in large-scale batch reactors the transmission of radiation is limited to a small space immediately surrounding the light source, leaving a majority of the reaction contents “in the dark.” The attenuation of light poses several challenges when scaling up a process. Due to poor photon transport, large volume batch reactions need to run for longer durations to ensure sufficient irradiation. This not only slows down the process, but it also contributes to the formation of by-products, as uneven over-radiation of the reaction mixture tends to occur.

For these reasons, the generation of singlet oxygen by dye-sensitized photoexcitation of molecular oxygen is more efficient in continuous flow operations. As mentioned, the small diameter of continuous photoreactors increase the surface-to-volume ratio, which for photochemical application improves the uniformity in energy distribution and enables optimal photon transport to the light-absorbing molecules. There are several continuous photoreactor designs that effectively enable this outcome (Figure 44). One set up positions light emitting diodes (LEDs) or other light sources directly above a microflow reactor plate while the reactant mixture and homogeneous sensitizer are pumped through micrometer-sized channels (A). Another system transports a mixture of reactants and a homogeneous photocatalyst through millimeter-sized, transparent tubing that is wrapped around a light source (B). As of 2016, there were 20 studies that used micro- or macroflow photoreactors to conduct syntheses with in situ generated singlet oxygen. A third
design flows a reactant mixture through a very narrow glass packed bed reactor filled with a heterogeneous photocatalyst that is surrounded by LED or another lamp (C).

Figure 44. Continuous micro- and macroflow systems for the generation of singlet oxygen

Just as continuous photoreactors are advantageous from a light absorption perspective, they are equally beneficial from a multiphase mass transfer standpoint. The overall performance of any reaction depends on the degree of mixing. Accordingly, the efficiency of photochemical oxygenations is in part driven by the rate at which gaseous oxygen diffuses into the liquid phase, and subsequently interacts with the other components in the mixture. "The driving force for the gas-liquid mass transfer of" oxygen is the "concentration gradient, which is governed by
thermodynamic and chemical equilibria." One approach to improving this process is to minimize the transport distances by maximizing the interfacial area. Traditional batch reactors, such as mechanically agitated reactors, possess "poorly defined interfacial contact areas." Conversely, in certain continuous flow reactors, gas bubbles are interspersed between liquid slugs in a uniform flow pattern, a regime referred to as a Taylor flow (slug flow). This phenomenon increases the liquid's surface area and creates internal circulations in the bulk liquid phase, which enables rapid mass transfer of oxygen and improved mixing between the two phases.

Continuous photochemical reactors also possess all of the other advantages inherent to continuous flow processing: improved safety, increased reproducibility, faster heat exchange, and greater capabilities to telescope multiple reactions. For these reasons, conducing photochemical oxygenations continuously has received significant attention as of late. Perhaps, one of the most chemically elegant and medicinally impactful applications of this technology has been the seminal work of Seeberger et al. in the continuous semi-synthetic production of artemisinin (1).

4.1.5 Continuous photochemical syntheses of artemisinin

In 2012, Seeberger and co-workers reported the first continuous semi-synthetic process from dihydroartemisinic acid (13) to artemisinin (1) (Scheme 34). Their photoreactor platform included small diameter transparent tubes coiled around a medium pressure mercury lamp (450 W) that were cooled to 25°C by an
immersion well. Through the tubes a solution of 13, molecular oxygen, and TPP in dichloromethane were pumped. The reactant mixture’s proximity to the light source resulted in highly efficient illumination of the entire solution, delivering 1.5 mmol of the desired tertiary allylic hydroperoxide (14) per minute in 75% yield. Telescoping the steps, the oxygenated intermediate stream intersected a continuous injection of TFA, which protonated the terminal oxygen on 14 and initiated the Hock cleavage. The ratio of 1 to undesired side-products was highly dependent on reaction conditions. The Hock cleavage process was heated to 60°C. Purification of the product stream by chromatography produced 1 in a 39% overall yield from 13. Using this particular photooxygenation flow process, Seeberger estimated that 200 g of artemisinin (1) could be produced each day.\textsuperscript{85}

\textbf{Scheme 34.} Seeberger \textit{et. al} first generation continuous photooxygenation process to artemisinin (1)
In 2013, Seeberger and co-workers built upon their earlier work and reported an optimized continuous process to 1 from 13 (Scheme 35). The improved procedure substituted the medium pressure mercury lamp for a monochromatic LED, the photocatalyst, TPP, for 9,10 dicyanoanthracene (DCA), and the solvent, DCM, for PhMe. By exchanging the light sources the platform became more energy efficient for two principle reasons. First, a less powerful cooling system was required since LEDs generate less heat. Second, the LEDs used for this system emit light at 420 nm, the absorption maximum for DCA. While mercury lamps emit a broad spectrum of visible light, only a portion of the radiation can excite the photocatalyst. The optimized process wrapped the transparent tubing in two layers around a glass plate, which was positioned proximate to the LED module. This tubing, which contained the substrate, oxygen, photocatalyst (DCA) and TFA, was cooled to minus 20°C, a temperature found to improve the photo-induced ene reaction: a 84% yield of desired hydroperoxide isomer (14) was achieved from 13. The solvent, DCM, was substituted because PhMe reduced the formation of unwanted by-products during the Hock cleavage and concomitant cyclization, affording 1 from the intermediate peroxide 14 in 81% yield. It was determined that this part of the continuous process only necessitated temperatures around 25°C, a significant decrease in energy from the first generation process. Combining the photochemical oxygenation and the acid-induced Hock cleavage steps in flow, the Seeberger group afforded 1 in a 65% overall yield.86
Scheme 35. Seeberger et al. optimized continuous photooxygenation process to artemisinin (1)

Building on Seeberger’s continuous flow regime, Poliakoff et al. assembled a continuous photoreactor platform equipped with a packed bed reactor filled with an heterogeneous photocatalyst, TPP immobilized onto Amberlyst-15, that was surrounded by a transparent cooling jacket and white LEDs. This insoluble photocatalyst not only offered the advantages inherent to heterogeneous catalysts, it served two functions essential to the transformation: it generated singlet oxygen for the ene reaction and acted as the Brønsted acid to initiate the Hock cleavage. This process used supercritical carbon dioxide (scCO₂) as the solvent due to its low cost, renewable benefit coupled with its ability to support a longer singlet oxygen lifetime. In this set up, 13, dissolved in PhMe, was joined to a T-mixer along with a mixture of molecular oxygen and scCO₂. The reactant mixture was then passed through the packed bed containing the immobilized catalyst. As mentioned, the entire transformation from 13 to 1 occurred within the packed bed reactor. While
one pass through the photoreactor afforded a 25% yield to the anti-malarial agent (1), subjecting the effluent to the reactor three addition times delivered 1 in 51% yield from 13 (Scheme 36).\textsuperscript{84}

\textbf{Scheme 36}. Poliakoff \textit{et al} continuous photooxygenation process to artemisinin (1)

4.1.6 \textit{A heterogeneous photosensitizer: rose bengal on polystyrene}

Ever since scientists discovered the principles that constitute photodynamic action,\textsuperscript{162} dyes have been used to convert light energy to chemical energy in the production of singlet oxygen.\textsuperscript{163} Organic dyes such as rose bengal (67), eosin erythrosin blue and methylene blue are several effective photosensitizers that have been extensively studied and used. Over several decades, many synthetic applications of dye-sensitized oxidation have been reported.\textsuperscript{145}
While singlet oxygen can be generated through many different methods, photochemical formation of this electronically excited molecule particularly with dyestuffs continues to be a highly popular approach in synthetic applications. This is due to its operational simplicity, controllability and low environmental impact; all that is required is an appropriate light source, the dye, and gaseous oxygen. Despite these functional conveniences, some limitations of photooxidation exist: insolubility of the dye in many nonpolar solvents, photobleaching of the dye, deleterious interactions between the dye and the substrate, and inherent difficulties separating the dye from the product. In an effort to circumvent these challenges, many research groups have immobilized organic dyes and other sensitizers onto solid supports. The resulting heterogeneous photocatalysts possess several advantages over the unbound sensitizers. First, they demonstrate operability in solvents in which the homogeneous dye is insoluble and therefore unable to efficiently convert triplet oxygen to its electronically excited state. Second, they show improved stability toward the destructive effects of photobleaching. Lastly, the solid supported dyes can be easily separated from the product mixture and reused in subsequent reactions without appreciable loss in functionality.

With the benefits of heterogeneous photocatalysts in mind, Schaap et al. worked toward this end, and in 1973 reported the first preparation of polymer-bound rose bengal. The procedure, adopted from Merrifield’s approach to polypeptide synthesis, reacted chloromethylated styrene-divinylbenzene copolymer beads and the disodium salt of rose bengal (67) (Scheme 37). Through reactions with the relatively nucelophilic carboxylate or phenolate group on rose
bengal and the electrophilic methylene group adjacent to the chlorine atom on the polymer, the dye was attached to the copolymer beads via ester or ether linkages.\textsuperscript{169}

![Scheme 37](image)

**Scheme 37.** Schaap *et al.* preparation of polymer-supported rose bengal (67)

Analysis Schaap's work revealed that 16.5\% of the chloromethyl groups had been converted to the rose bengal derivative. This material was then tested for application in what the researchers considered to be an “authentic” singlet oxygen reaction: the photooxidation of 2,3 diphenyl-p-dioxene (68) (Scheme 38). In this reaction, singlet oxygen underwent a 1,2 cycloaddition with 68 to furnish the oxygenated product (69) in 100\% yield after 4 hours.\textsuperscript{165} Absorption spectroscopy of the product mixture revealed that no rose bengal (67) had leached off of the polymer into solution. Control studies were then conducted to test the whether the oxygenation had transpired as a result of photochemically generated singlet oxygen by the heterogeneous sensitizer.\textsuperscript{164, 165} The addition DABCO, a singlet oxygen quencher, to the reaction had a deleterious affect, yielding 15\% of 69. Meanwhile, the presence of a free radical inhibitor, 2,6-di-tert-butylcresol did not impact the
reaction, delivering \(69\) in 100% yield. Subsequently, the ability of the heterogeneous photosensitizer to photochemically generate singlet oxygen in a solvent that was otherwise incompatible with the homogeneous form was investigated by substituting the polymer-bound rose bengal for the free rose bengal (67). A suspension of homogeneous rose bengal (67) in dichloromethane proved unable to efficiently catalyze the reaction, yielding only 4% of 69. The results of these experiments strongly suggested that the polymer immobilized rose bengal was not only able to catalyze the photooxidation of an alkene, it could do so much more efficiently than in the homogeneous form and without appreciable leaching from the support in various solvents.

Scheme 38. Photooxygenation of 2,3 diphenyl-\(p\)-dioxene (68) with polymer supported rose bengal

To examine the versatility of this heterogeneous sensitizer in photooxidations, a scope of study was conducted. In addition to 1,2 cycloadditions, singlet oxygen can participate in 1,4 cycloadditions with conjugated dienes and in ene reactions
with olefins. Examples of each reaction type were executed with polymer-bound rose bengal and demonstrated delivery to the intended products in good yields. With regard to ene reactions, the generation of singlet oxygen from various sources has shown that while the general product distribution of allylic hydroperoxide isomers is similar, there are slight variations in the ratio of the products. Polymer-based rose bengal was thus examined against various photochemical as well as non-photochemical sources of singlet oxygen in the peroxidation of 1,2-dimethylcyclohexene. Results indicated that despite minimal variation in isomers formed, heterogeneous rose bengal performed along the same lines as the other sources.

While other photosensitizers, including eosin, fluorescein, chlorophyllin and hematoporphyrin, were anchored onto the surface of polymer beads, the results from the photooxidation of substrate with these materials were significantly less efficacious than polymer-bound rose bengal.

The quantum yield for the generation of singlet oxygen by heterogeneous rose bengal in dichloromethane was empirically evaluated: a value of 0.43. Comparatively, the quantum yield of singlet oxygen formation by homogeneous rose bengal generated in a polar solvent in which the dye dissolves, such as MeOH, was found to be approximately twice as large: 0.76. An investigation into the cause of this difference rejected the hypothesis that the polymeric backbone of the heterogeneous sensitizer was either reacting with the singlet oxygen or quenching its production. However, subsequent studies offered several explanations. It was found that for lightly functionalized polymers the solution viscosity controlled the
quantum yield of singlet oxygen formation as it governed the rate of oxygen diffusion into the rose bengal sites through the polymer matrix; the higher the solution's viscosity, the lower the quantum yield. For more highly functionalized polymers, aggregations between rose bengal molecules bound to the same polymer have been implicated in decreasing the quantum yield of singlet oxygen formation.

Separate studies postulated that the smaller quantum yields were the result of the insoluble polymers dispersing the incident light.

Despite the lower quantum yield of singlet oxygen produced by Schaap's polymer-bound rose bengal, the advantages of this heterogeneous sensitizer are numerous, and arguably exceed those offered by the homogeneous form. In an effort, however, to improve the quantum yield of singlet oxygen formation of the polymer-bound sensitizer, rose bengal was covalently immobilized onto a different polymer from originally used. This material's ability to photosensitize the oxidation of phenol to benzoquinone was tested. The quantum yield of singlet oxygen formation was found to be 0.73.

4.1.7 Significance of work

Fully aware of artemisinin's (1) essential role in treating malaria and the need to produce it as affordably as possible, many research teams have pursued biomimetic strategies that react photochemically generated singlet oxygen and followed by the addition of acid and triplet oxygen to deliver the anti-malarial drug. Photooxygenation is an economically appealing approach because it includes
molecular oxygen, an inexpensive, abundant reactant, as well as photons of visible light, which can be considered traceless, environmentally benign “reagents.” As mentioned, several processes of this type have been conducted in batch as well as in continuous flow operations.

We sought to adapt Seeberger and coworkers’ continuous flow methodology to a packed bed photoreactor system, and in so doing identify and utilize a commercially available, effective and recyclable heterogeneous photocatalyst to generated singlet oxygen in situ. At the time our research began, the work of Poliakoff et al had not been published. Regardless, we pursued a system devoid of scCO₂, since scCO₂ necessitates high energy demanding, specialized equipment. Our aim was to maximize the benefits of continuous flow chemistry and heterogeneous catalysis and design a low cost, scalable system to transform 13 to 1, with the potential of sequencing it to the asymmetric hydrogenation step. Ultimately, it was the goal of this project to increase global access of artemisinin (1) by improving the economics associated with this process.

4.2 High throughput screen: identifying a homogeneous photocatalyst

As the primary aim of this project, we sought to identify a photocatalyst capable of facilitating the photooxygenation of dihydroartemisinic acid (13) more efficiently and economically than those cited in the literature. In collaboration with scientists at Merck & Co. we initially explored a diverse range of homogeneous photocatalysts, which included: acridinium-based sensitizers, organometallic
photocatalysts, specifically derivatives of tris(bipyridine)ruthenium(II), Ru(bpy)$_3$, as well as other organic dyes. In this work, we also evaluated numerous Lewis and Brønsted acids, which are necessary in converting the oxygenated intermediate (14) to artemisinin (1).

The ability of the homogeneous photocatalysts and acids to form 1 were monitored exclusively by analyzing the formation of the product, and not any reactive intermediates. The preliminary screen revealed that the acridinium-based photocatalysts appeared to degrade the substrate. The many derivatives of Ru(bpy)$_3$, distinct by the substituents bound to the bipyridine rings, demonstrated efficacy in this transformation, especially Ru(bpy)$_3$(PF$_6$)$_2$. While the organic dyes exhibited the ability to catalyze the reaction, Ru(bpy)$_3$(PF$_6$)$_2$ was superior.

With an effective sensitizer in hand, we expanded our evaluation of Ru(bpy)$_3$(PF$_6$)$_2$. A 24-vial batch photoreactor, which was designed and fabricated in-house by scientists at Merck & Co., expedited the screen (Figure 45), as it enabled us to conduct 24 reactions at once. The reactor was comprised of three main parts: a manifold plumbed with gas lines that delivered oxygen overtop of the vials, a vial block with holes drilled into the bottom, and a plate, on which the block sat, with 24 individual blue LEDs that were focused up into the block.
Ru(bpy)$_3$(PF$_6$)$_2$, was screened in different organic acid and nonpolar solvent combinations (Table 20). Since oxygen is highly soluble in fluorinated solvents, we elected to evaluate trifluorotoluene (CF$_3$Ph) and perfluorodecalin (PFD) in addition to PhMe and dichloromethane. A comparatively weaker and stronger organic acid, acetic acid (AcOH) and methanesulfonic acid (MeSO$_3$H), respectively, were screened against the process-tested TFA. In addition to the organometallic photocatalyst, DCA was examined in parallel, serving as a benchmark in the study given its demonstrated effectiveness (entries 1–12).

With remarkably similar results to the work published by Seeberger et al., DCA in both PhMe and CH$_2$Cl$_2$ in the presence of TFA produced a 52.42% and 64.90% yield to 1, respectively (entries 4 and 9). Comparatively, the yields to 1 in the fluorinated solvents were lower (entries 3 and 10). The decrease in
performance could most likely be attributed to the insolubility of the substrate and catalyst in those solvents.

Overall, the photooxygenation experiments with Ru(bpy)$_3$(PF$_6$)$_2$ were not as effective in producing 1 as DCA (entries 13 – 24). However, in the presence of TFA in dichloromethane it formed 1 in a promising 81.18% yield (entry 21). As with DCA, Ru(bpy)$_3$(PF$_6$)$_2$ in the fluorinated solvents was unable to generate any substantial amount of product. In general, AcOH and MeSO$_3$H proved ineffective toward the formation of artemisinin.
Table 20. Preliminary screen of photocatalysts, acids and solvents

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Acids</th>
<th>Solvent</th>
<th>% 1&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>DCA</td>
<td>AcOH</td>
<td>PhMe/PFD</td>
<td>2.06</td>
</tr>
<tr>
<td>2</td>
<td>DCA</td>
<td>AcOH</td>
<td>PhMe</td>
<td>2.06</td>
</tr>
<tr>
<td>3</td>
<td>DCA</td>
<td>TFA</td>
<td>PhMe/PFD</td>
<td>42.78</td>
</tr>
<tr>
<td>4</td>
<td>DCA</td>
<td>TFA</td>
<td>PhMe</td>
<td>52.42</td>
</tr>
<tr>
<td>5</td>
<td>DCA</td>
<td>MeSO&lt;sub&gt;3&lt;/sub&gt;H</td>
<td>PhMe/PFD</td>
<td>18.71</td>
</tr>
<tr>
<td>6</td>
<td>DCA</td>
<td>MeSO&lt;sub&gt;3&lt;/sub&gt;H</td>
<td>PhMe</td>
<td>2.06</td>
</tr>
<tr>
<td>7</td>
<td>DCA</td>
<td>AcOH</td>
<td>CH&lt;sub&gt;2&lt;/sub&gt;Cl&lt;sub&gt;2&lt;/sub&gt;</td>
<td>10.28</td>
</tr>
<tr>
<td>8</td>
<td>DCA</td>
<td>AcOH</td>
<td>CF&lt;sub&gt;3&lt;/sub&gt;Ph</td>
<td>2.06</td>
</tr>
<tr>
<td>9</td>
<td>DCA</td>
<td>TFA</td>
<td>CH&lt;sub&gt;2&lt;/sub&gt;Cl&lt;sub&gt;2&lt;/sub&gt;</td>
<td>64.90</td>
</tr>
<tr>
<td>10</td>
<td>DCA</td>
<td>TFA</td>
<td>CF&lt;sub&gt;3&lt;/sub&gt;Ph</td>
<td>2.06</td>
</tr>
<tr>
<td>11</td>
<td>DCA</td>
<td>MeSO&lt;sub&gt;3&lt;/sub&gt;H</td>
<td>CH&lt;sub&gt;2&lt;/sub&gt;Cl&lt;sub&gt;2&lt;/sub&gt;</td>
<td>11.60</td>
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<tr>
<td>12</td>
<td>DCA</td>
<td>MeSO&lt;sub&gt;3&lt;/sub&gt;H</td>
<td>CF&lt;sub&gt;3&lt;/sub&gt;Ph</td>
<td>2.06</td>
</tr>
<tr>
<td>13</td>
<td>Ru(bpy)₃(PF&lt;sub&gt;6&lt;/sub&gt;)&lt;sub&gt;2&lt;/sub&gt;</td>
<td>MeSO&lt;sub&gt;3&lt;/sub&gt;H</td>
<td>PhMe/PFD</td>
<td>2.06</td>
</tr>
<tr>
<td>14</td>
<td>Ru(bpy)₃(PF&lt;sub&gt;6&lt;/sub&gt;)&lt;sub&gt;2&lt;/sub&gt;</td>
<td>AcOH</td>
<td>PhMe</td>
<td>2.06</td>
</tr>
<tr>
<td>15</td>
<td>Ru(bpy)₃(PF&lt;sub&gt;6&lt;/sub&gt;)&lt;sub&gt;2&lt;/sub&gt;</td>
<td>TFA</td>
<td>PhMe/PFD</td>
<td>7.85</td>
</tr>
<tr>
<td>16</td>
<td>Ru(bpy)₃(PF&lt;sub&gt;6&lt;/sub&gt;)&lt;sub&gt;2&lt;/sub&gt;</td>
<td>TFA</td>
<td>PhMe</td>
<td>2.06</td>
</tr>
<tr>
<td>17</td>
<td>Ru(bpy)₃(PF&lt;sub&gt;6&lt;/sub&gt;)&lt;sub&gt;2&lt;/sub&gt;</td>
<td>MeSO&lt;sub&gt;3&lt;/sub&gt;H</td>
<td>PhMe/PFD</td>
<td>2.06</td>
</tr>
<tr>
<td>18</td>
<td>Ru(bpy)₃(PF&lt;sub&gt;6&lt;/sub&gt;)&lt;sub&gt;2&lt;/sub&gt;</td>
<td>MeSO&lt;sub&gt;3&lt;/sub&gt;H</td>
<td>PhMe</td>
<td>2.06</td>
</tr>
<tr>
<td>19</td>
<td>Ru(bpy)₃(PF&lt;sub&gt;6&lt;/sub&gt;)&lt;sub&gt;2&lt;/sub&gt;</td>
<td>AcOH</td>
<td>CH&lt;sub&gt;2&lt;/sub&gt;Cl&lt;sub&gt;2&lt;/sub&gt;</td>
<td>17.91</td>
</tr>
<tr>
<td>20</td>
<td>Ru(bpy)₃(PF&lt;sub&gt;6&lt;/sub&gt;)&lt;sub&gt;2&lt;/sub&gt;</td>
<td>AcOH</td>
<td>CF&lt;sub&gt;3&lt;/sub&gt;Ph</td>
<td>2.06</td>
</tr>
<tr>
<td>21</td>
<td>Ru(bpy)₃(PF&lt;sub&gt;6&lt;/sub&gt;)&lt;sub&gt;2&lt;/sub&gt;</td>
<td>TFA</td>
<td>CH&lt;sub&gt;2&lt;/sub&gt;Cl&lt;sub&gt;2&lt;/sub&gt;</td>
<td>81.18</td>
</tr>
<tr>
<td>22</td>
<td>Ru(bpy)₃(PF&lt;sub&gt;6&lt;/sub&gt;)&lt;sub&gt;2&lt;/sub&gt;</td>
<td>TFA</td>
<td>CF&lt;sub&gt;3&lt;/sub&gt;Ph</td>
<td>2.06</td>
</tr>
<tr>
<td>23</td>
<td>Ru(bpy)₃(PF&lt;sub&gt;6&lt;/sub&gt;)&lt;sub&gt;2&lt;/sub&gt;</td>
<td>MeSO&lt;sub&gt;3&lt;/sub&gt;H</td>
<td>CH&lt;sub&gt;2&lt;/sub&gt;Cl&lt;sub&gt;2&lt;/sub&gt;</td>
<td>28.73</td>
</tr>
<tr>
<td>24</td>
<td>Ru(bpy)₃(PF&lt;sub&gt;6&lt;/sub&gt;)&lt;sub&gt;2&lt;/sub&gt;</td>
<td>MeSO&lt;sub&gt;3&lt;/sub&gt;H</td>
<td>CF&lt;sub&gt;3&lt;/sub&gt;Ph</td>
<td>2.06</td>
</tr>
</tbody>
</table>

<sup>a</sup>All reactions conduct under 0.55 bar of oxygen gas at ambient temperature, irradiated under blue visible light. <sup>b</sup>Assay yield to artemisinin (1) determined by using a calibrated curve generated on a HPLC equipped with a reverse phase column.
Given the high yielding results of Ru(bpy)$_3$(PF$_6$)$_2$ in CH$_2$Cl$_2$ with TFA, we evaluated a plethora of different inorganic and organic acids in an effort to identify an acid better suited for this reaction. 24 different Lewis acids were screened (Table 21). Yet, with the exception of indium (III) chloride (entry 5) and zinc triflate (entry 10), the Lewis acids proved completely ineffective. Accordingly, we concluded that Lewis acids were not applicable for this transformation and turned to investigating a diverse set of Brønsted acids (Table 22). While oxalic acid, trichloroacetic acid (TCA) and HBF$_4$-Et$_2$O (entries 8, 10 and 13) exhibited modest yields to 1, none of the Brønsted acids were competitive to the initial experiment conducted in TFA. The large discrepancy in yields between entry 21 in table 20 and the previously reported work with TFA led us to repeat the experiment to determine if the first pass was an anomaly. Unfortunately, we were unable to reproduce the preliminary results (entry 20, Table 22).

Due to the reproducibility issues with Ru(bpy)$_3$(PF$_6$)$_2$ in TFA, coupled with work that was published immediately following our experiments, which included use of the same organometallic photocatalyst and acid, combined with our interests in heterogeneous catalysis, we discontinued any further evaluation of homogeneous photosensitizers. Despite the confluence of factors that ultimately led us to halt this aspect of the project, we gained significant insights into identifying the most suitable acid and solvents for this transformation as a result of these studies. Most notably, we ascertained that TFA was superior to any other of the nearly 50 acids screened, and was therefore optimal for this reaction. These studies also corroborated the work of Seeberger et al., which found the fluorinated solvents
to be impractical because of solubility constraints. We applied this acquired knowledge to future research investigating heterogeneous photocatalysts.

Table 21. Lewis acid screen in the photooxygenation to 1

<table>
<thead>
<tr>
<th>Entry</th>
<th>Acid</th>
<th>% 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>FeCl₃</td>
<td>2.06</td>
</tr>
<tr>
<td>2</td>
<td>ZnCl₂</td>
<td>2.06</td>
</tr>
<tr>
<td>3</td>
<td>MnBr₂</td>
<td>2.06</td>
</tr>
<tr>
<td>4</td>
<td>CsCl</td>
<td>2.06</td>
</tr>
<tr>
<td>5</td>
<td>InCl₃</td>
<td>40.06</td>
</tr>
<tr>
<td>6</td>
<td>MnCl₂</td>
<td>2.06</td>
</tr>
<tr>
<td>7</td>
<td>TiCl₂</td>
<td>2.06</td>
</tr>
<tr>
<td>8</td>
<td>TeCl₄</td>
<td>2.06</td>
</tr>
<tr>
<td>9</td>
<td>AlF₃</td>
<td>2.06</td>
</tr>
<tr>
<td>10</td>
<td>Zn(OTf)₂</td>
<td>27.37</td>
</tr>
<tr>
<td>11</td>
<td>Ln(OTf)₂</td>
<td>2.06</td>
</tr>
<tr>
<td>12</td>
<td>In(OH)₃</td>
<td>2.06</td>
</tr>
<tr>
<td>13</td>
<td>TiF₄</td>
<td>2.06</td>
</tr>
<tr>
<td>14</td>
<td>SnCl₂</td>
<td>18.05</td>
</tr>
<tr>
<td>15</td>
<td>AlCl₃-6H₂O</td>
<td>2.06</td>
</tr>
<tr>
<td>16</td>
<td>FeCl₂</td>
<td>2.06</td>
</tr>
<tr>
<td>17</td>
<td>InBr₃</td>
<td>2.06</td>
</tr>
<tr>
<td>18</td>
<td>BiBr₃</td>
<td>10.05</td>
</tr>
<tr>
<td>19</td>
<td>BiCl₃</td>
<td>2.06</td>
</tr>
<tr>
<td>20</td>
<td>Mn(OTf)₂</td>
<td>2.06</td>
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<tr>
<td>21</td>
<td>Sn(OTf)₂</td>
<td>2.06</td>
</tr>
<tr>
<td>22</td>
<td>ScCl₂</td>
<td>2.06</td>
</tr>
<tr>
<td>23</td>
<td>Ca(OTf)₂</td>
<td>2.06</td>
</tr>
<tr>
<td>24</td>
<td>LiOTf</td>
<td>12.64</td>
</tr>
</tbody>
</table>

*All reactions conducted in CH₂Cl₂ with Ru(bpy)₃(PF₆)₂ under 0.55 bar of oxygen gas at ambient temperature. Assay yield to artemisinin determined using a calibrated curve generated on a HPLC equipped with a reverse phase column.
Table 23. Brønsted acid screen in the photooxygenation to 1

<table>
<thead>
<tr>
<th>Entry</th>
<th>Acid</th>
<th>% 1&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Glutamic</td>
<td>2.06</td>
</tr>
<tr>
<td>2</td>
<td>4-NO₂-BzOH</td>
<td>2.06</td>
</tr>
<tr>
<td>3</td>
<td>CN-AcOH</td>
<td>17.00</td>
</tr>
<tr>
<td>4</td>
<td>TsOH</td>
<td>12.36</td>
</tr>
<tr>
<td>5</td>
<td>Boric</td>
<td>2.06</td>
</tr>
<tr>
<td>6</td>
<td>Maleic</td>
<td>2.06</td>
</tr>
<tr>
<td>7</td>
<td>BzOH</td>
<td>2.06</td>
</tr>
<tr>
<td>8</td>
<td>oxalic</td>
<td>32.47</td>
</tr>
<tr>
<td>9</td>
<td>methyl sulfonic</td>
<td>2.06</td>
</tr>
<tr>
<td>10</td>
<td>TCA</td>
<td>33.90</td>
</tr>
<tr>
<td>11</td>
<td>fumaric</td>
<td>2.06</td>
</tr>
<tr>
<td>12</td>
<td>citric</td>
<td>2.06</td>
</tr>
<tr>
<td>13</td>
<td>HBF₄·Et₂O</td>
<td>40.56</td>
</tr>
<tr>
<td>14</td>
<td>salicylic</td>
<td>2.06</td>
</tr>
<tr>
<td>15</td>
<td>Cl-Acetic</td>
<td>9.51</td>
</tr>
<tr>
<td>16</td>
<td>Pthalic</td>
<td>2.06</td>
</tr>
<tr>
<td>17</td>
<td>succinic</td>
<td>2.06</td>
</tr>
<tr>
<td>18</td>
<td>4-OH BzOH</td>
<td>2.06</td>
</tr>
<tr>
<td>19</td>
<td>TFOH</td>
<td>2.06</td>
</tr>
<tr>
<td>20</td>
<td>TFA</td>
<td>21.10</td>
</tr>
<tr>
<td>21</td>
<td>HBF₄·H₃PO₄</td>
<td>4.61</td>
</tr>
<tr>
<td>22</td>
<td>nicotinic</td>
<td>2.06</td>
</tr>
<tr>
<td>23</td>
<td>MeO-Acetic</td>
<td>32.93</td>
</tr>
<tr>
<td>24</td>
<td>Formic</td>
<td>2.06</td>
</tr>
</tbody>
</table>

<sup>a</sup>All reactions conducted in DCM with Ru(bpy)₃(PF₆)₂ under 0.55 bar of oxygen gas at ambient temperature. <sup>b</sup>Assay yield to artemisinin determined using a calibrated curve generated on a HPLC equipped with a reverse phase column.
4.3 Batch screen of heterogeneous photocatalysts

For the many stated benefits of heterogeneous catalysis, we evaluated numerous commercially available insoluble photosensitizers in batch reactors (Table 23). Unlike our earlier work at Merck & Co., we conducted this study by separating the two chemical transformations involved in this process into the photooxygenation step (Scheme 39) and the acid-mediated Hock cleavage step (Scheme 40), in order to more directly assess the activity of the photocatalysts and the parameters specific to each step. Accordingly, we evaluated the efficacy of the heterogeneous catalysts by monitoring the appearance of its oxygenated products, the DHAA hydroperoxide isomers, 14, 70 and 71. For the preliminary screen, we were only interested in tracking the formation of isomer 14, the only isomer capable of being transformed into 1.

Several different forms of titanium dioxide (TiO₂) were investigated: anatase, nanotubes and nanopowder. Since the inorganic material possesses photocatalytic activity in the ultraviolet region of the electromagnetic spectrum, the solution was irradiated with 355 nm and 365 nm lamps for varying durations in a nonpolar and a polar solvent (entries 1–3, 6–8, 11–13 and 15). Despite adjusting the reaction conditions, TiO₂ exhibited no ability to photocatalytically oxygenate 13 under the parameters studied. Two other inorganic photosensitizers were also examined: tungsten(IV) sulfide (WS₂) and zinc (II) sulfide (ZnS). Reaction solutions in dichloromethane containing these heterogeneous substances were also irradiated at 365 nm (entries 4, 5, 9 and 10). Like TiO₂, WS₂ and ZnS were unable to produce any oxygenated product. Gratifyingly, however, rose bengal on polystyrene
demonstrated some photoactivity when exposed to white visible light in PhMe, forming 10% of 14 relative to the starting material, 13 (entry 14). With these promising results, a more in-depth evaluation of rose bengal on polystyrene ensued.

Table 23. Batch screen of heterogeneous photocatalysts in the photooxygenation to 14

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Irradiation Wavelength</th>
<th>Time</th>
<th>Solvent</th>
<th>% 14&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>TiO&lt;sub&gt;2&lt;/sub&gt; anatase</td>
<td>365 nm</td>
<td>1 hour</td>
<td>CH&lt;sub&gt;2&lt;/sub&gt;Cl&lt;sub&gt;2&lt;/sub&gt;</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>TiO&lt;sub&gt;2&lt;/sub&gt; nanotubes</td>
<td>365 nm</td>
<td>1 hour</td>
<td>CH&lt;sub&gt;2&lt;/sub&gt;Cl&lt;sub&gt;2&lt;/sub&gt;</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>TiO&lt;sub&gt;2&lt;/sub&gt; nanopowder</td>
<td>365 nm</td>
<td>1 hour</td>
<td>CH&lt;sub&gt;2&lt;/sub&gt;Cl&lt;sub&gt;2&lt;/sub&gt;</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>WS&lt;sub&gt;2&lt;/sub&gt;</td>
<td>365 nm</td>
<td>1 hour</td>
<td>CH&lt;sub&gt;2&lt;/sub&gt;Cl&lt;sub&gt;2&lt;/sub&gt;</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>ZnS</td>
<td>365 nm</td>
<td>1 hour</td>
<td>CH&lt;sub&gt;2&lt;/sub&gt;Cl&lt;sub&gt;2&lt;/sub&gt;</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>TiO&lt;sub&gt;2&lt;/sub&gt; anatase</td>
<td>365 nm</td>
<td>4 hours</td>
<td>CH&lt;sub&gt;2&lt;/sub&gt;Cl&lt;sub&gt;2&lt;/sub&gt;</td>
<td>0</td>
</tr>
<tr>
<td>7</td>
<td>TiO&lt;sub&gt;2&lt;/sub&gt; nanotubes</td>
<td>365 nm</td>
<td>4 hours</td>
<td>CH&lt;sub&gt;2&lt;/sub&gt;Cl&lt;sub&gt;2&lt;/sub&gt;</td>
<td>0</td>
</tr>
<tr>
<td>8</td>
<td>TiO&lt;sub&gt;2&lt;/sub&gt; nanopowder</td>
<td>365 nm</td>
<td>4 hours</td>
<td>CH&lt;sub&gt;2&lt;/sub&gt;Cl&lt;sub&gt;2&lt;/sub&gt;</td>
<td>0</td>
</tr>
<tr>
<td>9</td>
<td>WS&lt;sub&gt;2&lt;/sub&gt;</td>
<td>365 nm</td>
<td>4 hours</td>
<td>CH&lt;sub&gt;2&lt;/sub&gt;Cl&lt;sub&gt;2&lt;/sub&gt;</td>
<td>0</td>
</tr>
<tr>
<td>10</td>
<td>ZnS</td>
<td>365 nm</td>
<td>4 hours</td>
<td>CH&lt;sub&gt;2&lt;/sub&gt;Cl&lt;sub&gt;2&lt;/sub&gt;</td>
<td>0</td>
</tr>
<tr>
<td>11</td>
<td>TiO&lt;sub&gt;2&lt;/sub&gt; anatase</td>
<td>365 nm</td>
<td>19 hours</td>
<td>H&lt;sub&gt;2&lt;/sub&gt;O:EtOH 3:1</td>
<td>0</td>
</tr>
<tr>
<td>12</td>
<td>TiO&lt;sub&gt;2&lt;/sub&gt; nanotubes</td>
<td>365 nm</td>
<td>19 hours</td>
<td>H&lt;sub&gt;2&lt;/sub&gt;O:EtOH 3:1</td>
<td>0</td>
</tr>
<tr>
<td>13</td>
<td>TiO&lt;sub&gt;2&lt;/sub&gt; nanopowder</td>
<td>365 nm</td>
<td>19 hours</td>
<td>H&lt;sub&gt;2&lt;/sub&gt;O:EtOH 3:1</td>
<td>0</td>
</tr>
<tr>
<td>14</td>
<td>Rose bengal on polystyrene</td>
<td>white light</td>
<td>18 hours</td>
<td>PhMe</td>
<td>10</td>
</tr>
<tr>
<td>15</td>
<td>TiO&lt;sub&gt;2&lt;/sub&gt; nanotubes</td>
<td>355 nm</td>
<td>18 hours</td>
<td>CH&lt;sub&gt;2&lt;/sub&gt;Cl&lt;sub&gt;2&lt;/sub&gt;</td>
<td>0</td>
</tr>
</tbody>
</table>

<sup>a</sup>Conversion to 14 was determined by HPLC equipped with a reverse phase column.
4.4 **Batch production of artemisinin using rose bengal on polystyrene**

Although small, the successful photocatalytic conversion of 13 to 14 by rose bengal on polystyrene demanded an elaborative study. As done in the prior investigation, we disconnected the two chemical transformations and evaluated each batch process independent from one another. This methodology enabled us to sufficiently analyze and optimize each step. The aim of this work was to identify the best conditions to effect the photooxygenation step as well as the acid-induced Hock cleavage step that could be applied to a continuous flow regime.

4.4.1 **Step I: dihydroartemisinic acid to DHAA hydroperoxide**

To adequately assess the photocatalytic activity of rose bengal on polystyrene in this transformation, we exclusively monitored its capacity to oxygenate 13 and generate the hydroperoxide intermediates through an ene reaction. We were interested in its ability to selectively produce the allylic hydroperoxide isomer 14, which is the only isomer capable of being transformed into artemisinin (1). To accomplish this, we utilized 1H NMR and inspected for the diagnostic peaks of each principal isomer known to form, as reported in the literature (Scheme 39). We conducted the reactions on small scale, in 20 mL scintillation vials. Since the maximum absorbance of rose bengal occurs around 558 nm, we acquired three green LEDs that emitted near that wavelength. Although the white light used in the prior study emitted radiation at 558 nm, only a portion of the light was absorbed by rose bengal. The use of a monochromatic light that corresponded to the absorption spectrum of the heterogenized dye improved the
efficiency of the process. Therefore, the LEDs were soldered together and wrapped around the inside of a Styrofoam box (lined with aluminum foil), which served to contain the light and enable the experiments to be conducted below ambient temperature (Figure 46). A thermocouple was inserted into the top of the box, which sat on a magnetic stir plate. Each reaction vial was sparged with pure oxygen prior to commencing the experiments.

Scheme 39. Photooxygenation to DHAA hydroperoxide isomers: 14, 70 and 71

Figure 46. Batch photooxygenation set up (executed around Halloween)
In the evaluation of rose bengal on polystyrene, we elected to screen the solvents that were proven suitable for this process as well as some not yet tested. With the intent of fully integrating the continuous hydrogenation of 12 to this process, we were particularly interested in carrying out the photooxygenation process in EtOH. In addition to irradiating the rose bengal photocatalyst with a more efficient monochromatic source, we also sought to improve conversion by allowing the reactions to proceed for longer durations. Accordingly, the reaction times were expanded from 19 to 48 hours, in some cases (Table 24).

The results on this investigation were encouraging, as they revealed that with the appropriate lamp, rose bengal on polystyrene was capable of facilitating the oxygenation of 13. We observed that in the cases when the starting material was consumed that the desired allylic hydroperoxide isomer (14) was formed in high amounts relative to the other isomers or unidentified by-products (entries 1, 3 and 4). This study also revealed that the polar solvents required longer durations to consume the starting material (entries 1, 2, 4 and 7), than the nonpolar solvents (entries 3, 5 and 6). This phenomenon could be explained by the fact that the nonpolar solvents support longer singlet oxygen lifetimes. Although more sluggish, the results of the reactions conducted in EtOH or a mixture of EtOH and water were promising, especially when considering the potential to telescope this step with the continuous hydrogenation process (entries 1, 2, 4 and 7). The trend was clear, however, with respect to the relative ratio of EtOH and water: the higher percentage of water, the less conversion to product (entries 11 and 13).
Temperature, although not significantly, did seem to affect the selectivity by which 13 was oxygenated (entries 1 and 4), and was a parameter worth further evaluation. Ultimately, from this batch investigation, we concluded that rose bengal on polystyrene was a promising candidate for use in a continuous packed bed photoreactor, as it demonstrated excellent photocatalytic activity in the regioselective formation of the biologically relevant intermediate 14.

Table 24. Batch screen of RB on polystyrene in the photooxygenation of 13

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Temp. (°C)</th>
<th>Time (hours)</th>
<th>% 13&lt;sup&gt;b&lt;/sup&gt;</th>
<th>% 14&lt;sup&gt;b&lt;/sup&gt;</th>
<th>% 70&lt;sup&gt;b&lt;/sup&gt;</th>
<th>% 71&lt;sup&gt;b&lt;/sup&gt;</th>
<th>% of others&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>EtOH: H₂O (8:2)</td>
<td>0</td>
<td>42</td>
<td>0.00</td>
<td>89.29</td>
<td>3.57</td>
<td>1.79</td>
<td>5.36</td>
</tr>
<tr>
<td>2</td>
<td>EtOH</td>
<td>RT</td>
<td>48</td>
<td>2.22</td>
<td>87.78</td>
<td>4.44</td>
<td>2.22</td>
<td>3.33</td>
</tr>
<tr>
<td>3</td>
<td>PhMe</td>
<td>RT</td>
<td>22</td>
<td>0.00</td>
<td>87.36</td>
<td>0.00</td>
<td>0.00</td>
<td>12.64</td>
</tr>
<tr>
<td>4</td>
<td>EtOH: H₂O (8:2)</td>
<td>RT</td>
<td>48</td>
<td>0.00</td>
<td>87.10</td>
<td>4.30</td>
<td>2.15</td>
<td>6.45</td>
</tr>
<tr>
<td>5</td>
<td>CH₂Cl₂</td>
<td>0</td>
<td>15</td>
<td>7.56</td>
<td>84.03</td>
<td>5.88</td>
<td>1.68</td>
<td>0.84</td>
</tr>
<tr>
<td>6</td>
<td>PhMe</td>
<td>0</td>
<td>15</td>
<td>5.81</td>
<td>80.07</td>
<td>6.22</td>
<td>1.60</td>
<td>6.30</td>
</tr>
<tr>
<td>7</td>
<td>EtOH</td>
<td>0</td>
<td>15</td>
<td>2.31</td>
<td>80.00</td>
<td>6.15</td>
<td>3.08</td>
<td>8.46</td>
</tr>
<tr>
<td>8</td>
<td>THF</td>
<td>0</td>
<td>15</td>
<td>6.17</td>
<td>66.04</td>
<td>6.29</td>
<td>0.00</td>
<td>21.51</td>
</tr>
<tr>
<td>9</td>
<td>AcCN</td>
<td>0</td>
<td>15</td>
<td>9.38</td>
<td>60.47</td>
<td>14.89</td>
<td>4.06</td>
<td>11.20</td>
</tr>
<tr>
<td>10</td>
<td>EtOH</td>
<td>0</td>
<td>15</td>
<td>31.91</td>
<td>44.16</td>
<td>12.18</td>
<td>0.00</td>
<td>11.76</td>
</tr>
<tr>
<td>11</td>
<td>EtOH: H₂O (6:4)</td>
<td>RT</td>
<td>48</td>
<td>0.00</td>
<td>42.22</td>
<td>20.74</td>
<td>18.52</td>
<td>18.52</td>
</tr>
<tr>
<td>12</td>
<td>PhCF₃</td>
<td>0</td>
<td>15</td>
<td>63.46</td>
<td>32.48</td>
<td>2.45</td>
<td>0.02</td>
<td>1.59</td>
</tr>
<tr>
<td>13</td>
<td>EtOH: H₂O (1:1)</td>
<td>RT</td>
<td>48</td>
<td>0.00</td>
<td>31.33</td>
<td>14.46</td>
<td>10.04</td>
<td>44.18</td>
</tr>
</tbody>
</table>

<sup>a</sup>All reactions initially sparged with pure oxygen gas, then run under ambient pressure. <sup>b</sup>Conversions were determined by ¹H NMR.
4.4.2 Step II: DHAA hydroperoxide to artemisinin

With an effective heterogeneous photocatalyst in hand, and several compatible solvents identified, we pursued applying the reactive intermediate generated in the previous process to the acid-induced Hock cleavage. (It should be noted that the intermediate was stable in the refrigerator for several days). This second step, which converts 14 to artemisinin (1) proceeds via protonation of either oxygen on the allylic peroxide moiety of 14 (Scheme 40). If the internal oxygen is protonated then the reaction progresses down an undesired path: with a positive charge on the internal oxygen, the hydroperoxide is displaced by the adjacent carboxylic acid in the intramolecular formation of a five-membered lactone by-product (72). Conversely, if the terminal oxygen is protonated then the reaction proceeds favorably toward artemisinin (1): with a positive charge on the terminal oxygen, water is displaced by an attack on the internal oxygen from the π–electrons in the adjacent olefin, which results in a ring expansion and the formation of the hemiketal intermediate (73). A subsequent acid-catalyzed ring-opening step transforms 73 into a highly reactive enol containing species (74). If the enol tautomerizes to the aldehyde, then an intramolecular condensation reaction ensues, which generates another undesired by-product (75). However, if the enol is intercepted by triplet oxygen prior to tautomerization, then another peroxide moiety is inserted into the molecule (76). This oxygenation is then followed by a cascading reaction to install the endoperoxide bridge and cyclize two other portions of the molecule, and ultimately deliver artemisinin (1).
Scheme 40. Acid-induced transformation from 14 to artemisinin and principal side products, 72 and 75

The second step in this transformation was monitored by $^1$H NMR. We measured the success of the reaction by comparing the formation of artemisinin (1) relative to two main side products, 72 and 75, unreacted starting material (14), as well as the appearance of proton peaks that we not associated with either of the aforementioned molecules. From many different experiments performed in PhMe and EtOH, of which some are presented in Table 25, we observed that with one-half equivalence of TFA, less undesired side products were produced than with one-
equivalence of acid (entries 1, 2, 5 and 6). This result was corroborated by the work of Seeberger et al.86 This investigation also found that the presence of water was deleterious toward the formation of 1 (entries 3 and 4). The addition of a fluorinated solvent, PFD, while successful in suppressing the formation of 75 as compared to entry 5, did not consume as much of the tertiary allylic peroxide intermediate (14). This resembled previous findings at Merck & Co. Finally, it also appeared that, although conducted in different solvents, the lower temperature experiment generated more 1 with respect to the other side products (entry 1). That result was used to inform future continuous flow experiments in which we elaborated on the affects of temperature in this transformation.

Table 25. Batch screen of 14 to artemisinin (1) with TFA

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Temp. (°C)</th>
<th>TFA (equiv.)</th>
<th>Pressure (bar)</th>
<th>% 14&lt;sup&gt;a&lt;/sup&gt;</th>
<th>% 72&lt;sup&gt;a&lt;/sup&gt;</th>
<th>% 75&lt;sup&gt;a&lt;/sup&gt;</th>
<th>% 1&lt;sup&gt;a&lt;/sup&gt;</th>
<th>% of others&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PhMe</td>
<td>0°C</td>
<td>0.5</td>
<td>1</td>
<td>0.00</td>
<td>10.00</td>
<td>0.00</td>
<td>83.33</td>
<td>6.67</td>
</tr>
<tr>
<td>2</td>
<td>EtOH</td>
<td>RT</td>
<td>0.5</td>
<td>1.5</td>
<td>0.00</td>
<td>14.81</td>
<td>N/A</td>
<td>61.11</td>
<td>24.07</td>
</tr>
<tr>
<td>3</td>
<td>EtOH: H₂O (8:2)</td>
<td>RT</td>
<td>0.5</td>
<td>1.5</td>
<td>0.00</td>
<td>23.17</td>
<td>N/A</td>
<td>26.83</td>
<td>50.00</td>
</tr>
<tr>
<td>4</td>
<td>EtOH: H₂O (6:4)</td>
<td>RT</td>
<td>0.5</td>
<td>1.5</td>
<td>0.00</td>
<td>29.86</td>
<td>N/A</td>
<td>18.75</td>
<td>51.39</td>
</tr>
<tr>
<td>5</td>
<td>EtOH : PhMe (1:1)</td>
<td>RT</td>
<td>1</td>
<td>1</td>
<td>17.52</td>
<td>17.79</td>
<td>26.95</td>
<td>22.10</td>
<td>15.63</td>
</tr>
<tr>
<td>6</td>
<td>EtOH/PhMe /PFD (5:4:1)</td>
<td>RT</td>
<td>1</td>
<td>1</td>
<td>27.53</td>
<td>15.09</td>
<td>10.20</td>
<td>31.89</td>
<td>15.29</td>
</tr>
</tbody>
</table>

<sup>a</sup>Conversions were determined by <sup>1</sup>H NMR.
4.5 Continuous production of artemisinin using rose bengal on polystyrene

To evaluate the photooxygenation and subsequent acid-induced Hock cleavage reactions continuously, yet independent of each other, we employed a Vapourtec E-series system (Figure 47).

![Figure 47. Vapourtec E-series](image)

For the photooxygenation, Vapourtec fabricated a packed-bed photoreactor that was customized to meet our specifications (Figure 48). As a prototype unit, the reactor operated detached from E-series, though it was assembled with the dimensions to accommodate a 150 mm Omnifit column, which enabled the fixed bed to connect to the E-series' pumps via polytetrafluoroethylene (PTFE) tubing. Taking
the shape of a tripod, the metal reactor frame contained a 1:2 mixture of 24 LEDs that emitted at either 530 or 580 nm and ran on an input power of 90 watts. The two sets of monochromatic LEDs extended vertically along the interior of each side and faced in toward a center cylinder where the packed, transparent column of heterogeneous photocatalyst resided. In attempt to dissipate the heat generated by the lights, baffles were attached to the backside of the LEDs, which protruded outward from the reactor. We found, however, that the baffles were insufficient to keep the illuminated central manifold at ambient temperature. Therefore, to further mitigate excessive heat, we directed a stream of forced air around the column. In some instances, the compressed air was cooled through a coil of Tygon tubing in an acetonitrile and dry ice bath in order to establish a reactor temperature between 10 to 15°C.

To reduce the amount of photocatalyst unexposed to the light within the middle of the column, we inserted an inert metallic rod into the column and packed a slurry of the heterogenized rose bengal and 200-400 μm glass beads in PhMe around it (Figure 48). The glass beads served to disperse the catalyst throughout the column and prevent any extensive packing of the material. We pre-swelled the catalyst in PhMe prior to charging the fixed bed in an effort to minimize the expansion of the polystyrene within the column and any possible concomitant pressure spikes once the process commenced. These two measures combined to provide a stable and robust system that enabled the reuse of the same packed photocatalyst bed for innumerable experiments.
4.5.1 *Step I: dihydroartemisinic acid to DHAA hydroperoxide*

Given the results from the batch photooxygenation experiments, we elected to evaluate the rose bengal on polystyrene catalyst within the customized photoreactor in pure PhMe, EtOH and a 1:1 mixture of the two. A stream of the substrate and a separate stream of O₂, fed by the Vapourtec peristaltic pumps, were joined to a T-mixer prior to their delivery into the transparent column containing the catalyst (Scheme 41). A back pressure regulator (BPR) was fixed to the exit line to adjust the system pressure.
Scheme 41. Continuous photooxygenation of 13 to a mixture of hydroperoxide isomers (14, 70 and 71)

The preliminary screens we all carried out at room temperature and were monitored by comparing the presence of remaining 13 to the appearance of the oxygenated product 14 (Table 26). In an effort to maximize conversion, we initially evaluated the system at the lowest flow rates allowable by the E-series (entry 1 and 2). Despite the differences in pressure, we observed that in both trials conducted in PhMe, the product stream contained a mixture of 14 and 13 in a 97 to 3 ratio. Interested in the affect that a shorter residence time would have on conversion, we increased the flow rates of the substrate and gaseous O₂ stream that were fed into the photoreactor (entry 3). An appreciable, yet not unexpected, decrease in the
ratio between 14 and 13 was observed. Again, with our sights set on telescoping the hydrogenation process to the photooxygenation, we explored the photochemical reaction in EtOH (entry 4). Under nearly identical conditions as entry 3, the substrate dissolved in EtOH required four passes through the photoreactor to achieve a comparable conversion. The difference between these two experiments was understood to be a consequence of gaseous oxygen's increased solubility in PhMe as compared to EtOH, as well as a result of singlet oxygen's increased lifetime in PhMe.\textsuperscript{148,177} Fully aware of the affects that solvents have on the efficiency of this transformation, while maintaining our aim to directly integrate the processes, we decided to further investigate screens a 1:1 mixture of PhMe to EtOH, envisioning that we could simply intersect a stream of PhMe to the hydrogenation product stream and flow them jointly through the photoreactor. In attempt to ascertain the optimal set of parameters to oxygenate 13, we increased the amount of the heterogenized rose bengal in the column while varying the concentration of the substrate and altering the flow rates (entries 5–8). We discovered that in order to maximize conversion with this dual solvent system that the concentration of the substrate needed to be reduced along with the flow rates; two passes through the photoreactor was also required (entry 8). To verify these results and evaluate the selectivity of the photooxygenation, we repeated this experiment, although it was run between 10–15°C, and monitored the product mixture by \textsuperscript{1}H NMR (Table 27). The results revealed, again, that two passes through the photoreactor were needed to nearly consume all of 13. \textsuperscript{1}H NMR indicated a high percentage of 14 as compared
to the other principal hydroperoxide isomers 70 and 71. In fact, these values were
very competitive with previously reported results. \(^8^6\)

**Table 26. Continuous photoxygenation of 13 with RB on polystyrene**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Substrate Concentration (mM)</th>
<th>Substrate Flow Rate (mL/min)</th>
<th>O₂ Flow Rate (mL/min)</th>
<th>Pressure (bar)</th>
<th>Pass</th>
<th>% 13 (^b)</th>
<th>% 14 (^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PhMe</td>
<td>10</td>
<td>0.1</td>
<td>0.1</td>
<td>0.4</td>
<td>1</td>
<td>3</td>
<td>97</td>
</tr>
<tr>
<td>2</td>
<td>PhMe</td>
<td>10</td>
<td>0.1</td>
<td>0.1</td>
<td>3</td>
<td>1</td>
<td>3</td>
<td>97</td>
</tr>
<tr>
<td>3</td>
<td>PhMe</td>
<td>10</td>
<td>0.25</td>
<td>0.25</td>
<td>0.4</td>
<td>1</td>
<td>13</td>
<td>87</td>
</tr>
<tr>
<td>4</td>
<td>EtOH</td>
<td>10</td>
<td>0.25</td>
<td>0.25</td>
<td>0.1</td>
<td>1</td>
<td>60.1</td>
<td>39.9</td>
</tr>
<tr>
<td></td>
<td>EtOH</td>
<td>10</td>
<td>0.25</td>
<td>0.25</td>
<td>0.1</td>
<td>2</td>
<td>40.8</td>
<td>59.1</td>
</tr>
<tr>
<td></td>
<td>EtOH</td>
<td>10</td>
<td>0.25</td>
<td>0.25</td>
<td>0.1</td>
<td>3</td>
<td>29</td>
<td>71</td>
</tr>
<tr>
<td></td>
<td>EtOH</td>
<td>10</td>
<td>0.25</td>
<td>0.25</td>
<td>0.1</td>
<td>4</td>
<td>24.3</td>
<td>75.2</td>
</tr>
<tr>
<td>5</td>
<td>EtOH/PhMe</td>
<td>15</td>
<td>0.25</td>
<td>0.25</td>
<td>5</td>
<td>1</td>
<td>38.2</td>
<td>61.8</td>
</tr>
<tr>
<td>6</td>
<td>EtOH/PhMe</td>
<td>15</td>
<td>0.1</td>
<td>0.1</td>
<td>0.1</td>
<td>1</td>
<td>24.1</td>
<td>75.8</td>
</tr>
<tr>
<td></td>
<td>EtOH/PhMe</td>
<td>15</td>
<td>0.1</td>
<td>0.1</td>
<td>0.1</td>
<td>2</td>
<td>7.69</td>
<td>92.3</td>
</tr>
<tr>
<td>7</td>
<td>EtOH/PhMe</td>
<td>7.5</td>
<td>0.1</td>
<td>0.1</td>
<td>0.1</td>
<td>1</td>
<td>18.1</td>
<td>81.9</td>
</tr>
<tr>
<td>8</td>
<td>EtOH/PhMe</td>
<td>7.5</td>
<td>0.1</td>
<td>0.1</td>
<td>0.1</td>
<td>1</td>
<td>19.7</td>
<td>80.2</td>
</tr>
<tr>
<td></td>
<td>EtOH/PhMe</td>
<td>7.5</td>
<td>0.1</td>
<td>0.1</td>
<td>0.1</td>
<td>2</td>
<td>5.9</td>
<td>94.1</td>
</tr>
</tbody>
</table>

\(^a\)Entries 1 – 5 were conducted with 430 mg of catalyst; entries 6 – 8 with 1 g of catalyst. EtOH/PhMe mixture was in 1:1 ratio. All experiments conducted at RT. \(^b\)Entry 1 – 5 conversions were determined by HPLC; entry 6 – 8 conversions determined by \(^1^H\) NMR.
Table 27. Continuous photooxygenation of 13 in EtOH/PhMe (1:1) to DHAA hydroperoxide isomers (14, 70 and 71)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Pass</th>
<th>% 13</th>
<th>% 14</th>
<th>% 71</th>
<th>% 70</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>EtOH/PhMe</td>
<td>1</td>
<td>26.3</td>
<td>64.1</td>
<td>6.4</td>
<td>3.2</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>2</td>
<td>3.5</td>
<td>87.7</td>
<td>7.0</td>
<td>1.8</td>
</tr>
</tbody>
</table>

*aReaction ran between 10 and 15°C. **Conversions were determined by 1H NMR.

4.5.2 Step II: DHAA hydroperoxide to artemisinin

The hydroperoxide intermediate 14 continuously generated in the first step was subjected to TFA and O₂ in a continuous regime (Scheme 42). A stream of 14 and a separate stream of O₂, fed by the Vapourtec peristaltic pumps, were joined to a T-mixer and mixed in a 10 mL reactor coil that served as the reactor stage. A BPR was attached to the exit line to adjust the system pressure. The product mixture was evaluated by 1H NMR, through which the emergence of the major side products, artemisinin (1), and the disappearance of 14 were monitored.

The screen of the acid-catalyzed Hock cleavage step revealed an important discovery with regard to the formation of one of the major side products (Table 28). We noticed that any reaction run in EtOH produced disproportionately higher amounts of the side product 75, than was formed in its absence (entry 1 versus entry 2 or 3). We hypothesized that this side product more readily formed in hypoxic conditions given that it is a result of a tautomerization process that is in
competition with the enol reacting with triplet oxygen. And since O₂ is less soluble in EtOH than in PhMe, we speculated that the increased ratio of 75 to 1 in EtOH was a result of oxygen solubility differences. Given our desire to develop a fully continuous, telescoped process from 12 to 1 we elected to explore other options before concluding that EtOH was not viable for the second step of this process. Accordingly, we increased the pressure in the system (entry 4) and added in a small fraction of PFD (entry 5 and 7). Despite the pressure augmentation, 75 remained a significant side product; in fact, it formed in a larger percentage. We anticipated that the addition of a PFD as a co-solvent, which showed to lower conversion of the starting material when used in batch processes, could prove effective in continuous operations given the improved mixing inherent to continuous flow. The system, however, never established turbulent flow given the low flow rates, and consequently, the conversion of the allylic hydroperoxide 14 was poor. In a separate study, we immersed the 10 mL reactor coil in a sonicator in attempt to improve the mixing with the fluorinated solvent (entry 8). While that adjustment proved effective with regard to consuming the starting material, it delivered prodigious amounts of 75 as well (entry 8).

To verify that pure PhMe suppresses the formation of 75 and affords an overall cleaner reaction, we repeated the first experiment conducted in PhMe four more times and observed very similar results. As a result, we determined that the formation of 75 was not so much an O₂ solubility issue (although oxygen is more solube in PhMe than EtOH), but rather, we conjectured, it was more of a solvent polarity issue. Ultimately, these findings exposed that PhMe was a superior solvent
for this final transformation, which led us to abandon the idea of telescoping all processes from 12 to 1, since PhMe proved incompatible with the hydrogenation step.

The effects of temperature on this process were also investigated. With the prospect of commercialization considered, we determined that despite any incremental boosts in selectivity that the energy demands associated with cooling large-scale processes most likely would not offset the benefits of conducting the reaction below room temperature. The results from this study were applied to the development of a process that integrated step one and step two.

\[ 	ext{Scheme 42. Continuous acid-catalyzed conversion of 14 to artemisinin (1)} \]
Table 28. Continuous screen of 14 to 1 with TFA

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>TFA (equiv.)</th>
<th>Pressure (bar)</th>
<th>% 14b</th>
<th>% 72b</th>
<th>% 75b</th>
<th>% 1b</th>
<th>% of othersb</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PhMe</td>
<td>0.5</td>
<td>4</td>
<td>9.9</td>
<td>0.0</td>
<td>9.00</td>
<td>90.1</td>
<td>0.0</td>
</tr>
<tr>
<td>2</td>
<td>EtOH/PhMe (1:1)</td>
<td>8</td>
<td>0.1</td>
<td>0.0</td>
<td>N/A</td>
<td>21.26</td>
<td>51.9</td>
<td>26.9</td>
</tr>
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<td>EtOH/PhMe (1:1)</td>
<td>8</td>
<td>7</td>
<td>0.0</td>
<td>12.9</td>
<td>51.55</td>
<td>27.3</td>
<td>8.3</td>
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<td>4</td>
<td>EtOH/PhMe/PFD (5:4:1)</td>
<td>0.5</td>
<td>1</td>
<td>55.0</td>
<td>8.1</td>
<td>14.3</td>
<td>22.6</td>
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<td>5</td>
<td>EtOH/PhMe (1:1)</td>
<td>1</td>
<td>1</td>
<td>0.0</td>
<td>21.0</td>
<td>35.68</td>
<td>21.1</td>
<td>22.2</td>
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<td>EtOH/PhMe/PFD (5:4:1)</td>
<td>1</td>
<td>1</td>
<td>5.6</td>
<td>14.5</td>
<td>32.9</td>
<td>17.8</td>
<td>29.3</td>
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<tr>
<td>7</td>
<td>EtOH/PhMe/PFD (0.5:1.5:1)</td>
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<td>6</td>
<td>0.0</td>
<td>10.6</td>
<td>74.9</td>
<td>14.5</td>
<td>0.0</td>
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aAll reactions were conducted at RT. Entry 7 immersed the reactor coil in a sonicator. bConversions were determined by 1H NMR.

4.5.3 Fully integrating step I and step II

After comprehensively evaluating the photochemical and Hock-cleavage steps independently of each other, we merged the two steps to create a continuous process from dihydroartemisinic acid (13) to artemisinin (1) (Scheme 43). In this step up, a solution of the substrate (13) in PhMe and a separate stream of O₂, fed by the Vapourtec peristaltic pumps, were joined to a T-mixer, establishing a slug-flow regime. This stream was then delivered into the column of heterogeneous rose bengal residing within the photoreactor. A tube of cooled, compressed air was directed into the photoreactor to achieve a temperature between 10 and 15°C. The
oxygenated intermediate stream (14) was collected and recycled through the photoreactor in the same manner as described above. The second time it emerged from the packed bed photochemical unit it intersected a solution of TFA in PhMe, also fed by the Vapourtec peristaltic pumps, at a T-mixer. This mixed stream then circulated within a 10 mL coil that served as the reactor stage. A BPR attached to the other side of the reactor coil enabled us to maintain a system pressure of 4 bar. We analyzed the product stream by $^1$H NMR and an assay yield was obtained, which revealed a 56% overall yield from 13 to 1 (Table 29).\textsuperscript{178}

\textbf{Scheme 43.} Fully continuous process from 13 to artemisinin (1)
Table 29. Continuous photooxygenation of 13 to 1

<table>
<thead>
<tr>
<th>Entry</th>
<th>Temp. of Photoreactor (°C)</th>
<th>Temp. of Coil (°C)</th>
<th>Pressure (bar)</th>
<th>Solvent</th>
<th>TFA (equiv.)</th>
<th>% artemisinin&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>12</td>
<td>25</td>
<td>4</td>
<td>PhMe</td>
<td>0.5</td>
<td>56%</td>
</tr>
</tbody>
</table>

<sup>a</sup>Yield was determined by 1H NMR relative to an internal standard, dimethyl sulfone.

4.6 Conclusions

Through this work, a commercially available heterogeneous photocatalyst capable of effectively facilitating the oxygenation of 13 has been identified: rose bengal (67) on polystyrene. Moreover, we have incorporated the insoluble sensitizer into a robust continuous operation that uses a process-friendly solvent, PhMe, to deliver artemisinin (1). In addition to the catalyst being accessible through commercial sites, we have successfully reproduced a procedure to immobilize the homogeneous dye to the surface of polystyrene, demonstrating that the material can easily be generated in-house.<sup>164,165</sup>

Beyond its use in this particular ene reaction, our group has proven rose bengal on polystyrene effective toward other oxidation applications as well. These include [4+2] cycloadditions and heteroatom oxidations, which were successfully carried out on a variety of substrates. In addition to its versatility, polymer supported rose bengal also proved reusable throughout our studies. In one
particular experiment, the conversion of a substrate was maintained for over 10 hours with the same packed bed. Its demonstrated durability promises to improve process efficiency of photooxygenations, as it reduces waste and obviates the laborious repacking steps after each experiment.

4.6.1 Comparison to prior work

The process we have developed that continuously transforms dihydroartemisinic acid (13) to artemisinin (1) with the use of packed bed of rose bengal on polystyrene is very competitive with previously reported continuous processes (entry 1, Table 30). While the second-generation process developed by Seeberger et al. delivered a higher yielding reaction, it utilized a nonrecyclable homogeneous photocatalyst (entry 3). Furthermore, compared to the work of Poliakoff et al., who also employed a heterogeneous catalyst, our system produced a higher yield to artemisinin and did not incorporate the energy consuming equipment necessary to support scCO₂ (entry 4).

While we have made significant progress toward actualizing our goal of developing an economical route that transforms 13 to 1 with a heterogeneous photocatalyst, we have identified several areas that could be enhanced. First, increasing the substrate concentration and flow rate would greatly improve the productivity of our process, rendering it more commercially viable. Second, we hypothesize that flowing the peroxide intermediate (14), through a fixed bed of a heterogeneous acid instead of mixing it with a solution of TFA, might augment the
selectivity of the protonation and improve the cost and safety profile of transformation. Preliminary efforts toward this end, in which several acidic resins were evaluated, indicated that use of these substances produces promising, yet inconsistent results. Therefore, we suggest that further efforts should be devoted to this area.

Table 30. Photooxygenation of 13 to 1 continuous process comparisons

<table>
<thead>
<tr>
<th>Entry</th>
<th>Investigator</th>
<th>Photocatalyst</th>
<th>Solvent</th>
<th>Acid</th>
<th>% artemisinin</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>VCU</td>
<td>RB on polystyrene</td>
<td>PhMe</td>
<td>TFA</td>
<td>56%</td>
</tr>
<tr>
<td>2</td>
<td>Seeberger et al.</td>
<td>TPP</td>
<td>CH₂Cl₂</td>
<td>TFA</td>
<td>39%</td>
</tr>
<tr>
<td>3</td>
<td>Seeberger et al.</td>
<td>DCA</td>
<td>PhMe</td>
<td>TFA</td>
<td>65%</td>
</tr>
<tr>
<td>4</td>
<td>Poliakoff et al.</td>
<td>TPP on amberlyst</td>
<td>scCO₂/PhMe</td>
<td>N/A</td>
<td>51%</td>
</tr>
</tbody>
</table>

4.7 Experimental

4.7.1 General remarks

All reactions were conducted under ambient conditions unless otherwise indicated. The continuous photooxygenation reactions performed at VCU were conducted using a Vapourtec E-series, equipped with a customized photoreactor, designed and assembled by Vapourtec. The HTE photooxygenation studies
performed at Merck & Co. were conducted on a custom-built photoreactor designed to accommodate one-24 reactor well plate. The reagents and light sources were purchased from commercial suppliers including Sigma Aldrich and Praxair, as well as a non-profit collaborator, Clinton Health Access Initiative; all were used as received. The light sources were purchased from QPhotonics, Rapid LED and BlackLightsUSA. Reaction temperatures were recorded using J-KEM temperature controllers and thermocouples. The reactions were monitored using a Waters ACQUITY UPLC M-Class system equipped with a reverse phase column and a Bruker 400 MHz NMR or Bruker Ascend 600 MHz NMR spectrometer using CDCl₃ as the solvent.

4.7.2 General method for HTE screen of homogenous photocatalysts and acids at Merck & Co.

Experiments were conducted using established laboratory protocols.

4.7.3 Immobilization of rose bengal (67) onto Merrifield resin

Merrifield resin (2 g, 1% crosslinked, 200-400 mesh, 0.1 mmol/g), rose bengal (67) (1.57 g, 1.54 mmol) and 60 mL of DMF were added to a 250 mL round bottom flask, equipped with a stir bar, and stirred for 17 hours at 60 °C. The reaction mass was filtered and the filter cake was washed with successive aliquots of PhMe (150 mL), EtOH (150 mL), EtOH/water (1:1, 150 mL), MeOH/water (1:1,
150 mL), then MeOH (150 mL). The product was dried in an oven for 2 hours at 100 °C, which rendered a dark red solid.

4.7.3.1 Preparation of the continuous flow column with heterogeneous rose bengal

The polymer supported rose bengal was pre-swollen with PhMe prior to its addition into an Omnifit column (6.6 mm x 150 mm). A filter/plunger was inserted into one end of the column and glass beads (425 - 600 μm) were filled approximately 1 cm up the length of the column. A metal rod (3 mm x 90 mm) was placed inside the column. The immobilized photocatalyst slurry (1000 mg in PhMe) was added incrementally into the top of column while the solvent was carefully withdrawn out the other end by a syringe, though some solvent remained in the column at all times. Another portion of glass beads were added to the top of the column (1 cm in depth), prior to inserting a second filter/plunger into the top end of the column. The column was then placed within the photoreactor (1:2 mixture of 24 LEDs, 530 nm and 580 nm, 90 watts).

4.7.4 General methods for evaluating heterogeneous photocatalysts in the photooxygenation of 13 within different reactor systems

4.7.4.1 Batch reactor

13 (0.025 g, 0.105 mmol, 1 eq.), rose bengal on polystyrene (0.021 g, 1% crosslinked, 200 – 400 mesh, 0.1 mmol/g) and 5 mL of PhMe were combined in a 20
mL scintillation vial, equipped with stir bar, and capped with a rubber septum. The vial was sparged with pure gaseous oxygen (O₂ tank, 3.45 bar) by inserting a needle into the solution for 5 minutes. The reaction mixture was then placed inside a Styrofoam cooler. The bottom half of the vial was packed with ice and surrounded 3 green LED lights (566 – 569 nm, 1000 mA, 2.75 V). The cooler was placed atop a magnetic stir plate and allowed to stir for 15 hours. Additional ice was added into the cooler as necessary to maintain a constant temperature. The product mixture was removed with a syringe and expunged through a 2-micron syringe filter to separate the heterogeneous photocatalyst from the photooxygenated product. PhMe was removed under vacuum and the crude products were dissolved in CDCl₃ before monitoring by ¹H NMR. Upon comparison, the spectra collected was identical to that reported in the literature.⁸⁴

4.7.4.2 Continuous flow reactor

A 15 mM solution of 13 in PhMe was prepared in a 100 mL volumetric flask. To that solution, dimethyl sulfone was added as an internal standard (0.37 mmol). The packed bed of rose bengal supported on polystyrene (obtained from Sigma Aldrich or made in-house) was introduced into the column as described above. 13 and pure gaseous oxygen (O₂ tank; 50 PSI) were both delivered at a flow rate of 0.1 mL/min using separate peristaltic pumps contained within the flow reactor. The reagents were joined at an ethylene tetrafluoroethylene (ETFE) T-mixer and allowed to mix within 2 mL reactor coil prior to entering the column/photoreactor.
A piece of aluminum foil was used to completely surround the photoreactor, shielding the operators from unnecessary exposure of the light. The photoreactor lamp was illuminated and a compressed air line cooled through a coil of Tygon tubing in an acetonitrile and dry ice bath was used to maintain a column manifold temperature between 10 and 15 °C. The terminus of the column was fitted with a BPR in order to establish the desired system pressure. The first 4 mL were discarded and the next 3 mL were collected. PhMe was removed under vacuum and the crude products were dissolved in CDCl₃ before monitoring by ¹H NMR. Upon comparison, the spectra collected was identical to that reported in the literature.⁸⁴

4.7.5 General methods for the preparation of 1 from 1₄ within different reactor systems

4.7.5.1 Batch reactor

A solution of the photooxygenation product 1₄ (0.025 g, 0.105 mmol, 1 eq.) in 5 mL of EtOH was charged to a 100 mL Ace round bottom pressure flask, equipped with a stir bar. To that flask, an additional 5 mL of EtOH was added, along with TFA (4.05 μL, 0.052 mmol, 0.5 eq.). The round bottom pressure flask was fitted with a pressure gauge (threaded into the top). The reactor was pressurized with 1.4 bar of pure gaseous oxygen (O₂ tank, 3.45 bar) and then vented; this process was repeated two more times before the reactor was finally pressurized to 1.4 bar with gaseous oxygen. The reaction mixture was allowed to stir under pressure for 2 hours. At the conclusion of the reaction, trimethylbenzene (0.148 mmol), was added
as an internal standard. EtOH and any excess TFA were removed under vacuum and the crude products were dissolved in CDCl₃ before monitoring by ¹H NMR. Upon comparison, the spectra collected was identical to that reported in the literature.⁸⁶

4.7.5.2 Continuous flow reactor with homogeneous acid

A solution of TFA (with varying equivalency, as indicated in chapter 4.5.2) in PhMe was delivered into the system at a flow rate of 0.1 mL/min. The TFA solution fed into the photooxygenation product stream 14 (from above) at an ETFE T-mixer, and then proceeded through a 10 mL reactor coil with back pressure regulator affixed to maintain a constant pressure. The first 3 mL were discarded and the next 6 mL were collected. PhMe and any excess TFA were removed under vacuum and the crude products were dissolved in CDCl₃ before monitoring by ¹H NMR. Upon comparison, the spectra collected was identical to that reported in the literature.⁸⁶

4.7.5.3 Continuous flow reactor with heterogeneous acid

An Omnifit column (6.6 mm x 150 mm) with a filter/plunger inserted into one end was packed with a mixture of para-toluenesulfonic acid (p-TSA) immobilized on resins (1.44 g, 30-60 mesh, 2.0-3.0 mmol/g) and glass beds (5.3 g, 425 - 600 μm). After the addition, another filter/plunger was fitted into the other end. The column was connected to the exit stream of the photoreactor. The photooxygenation product stream 14 fed into the fixed bed of acid at a flow rate of 0.1 mL/min. The terminus of the column was fitted with BPR to maintain a constant
pressure. The first 3 mL were discarded and the next 6 mL were collected. PhMe was removed under vacuum and the crude products were dissolved in CDCl₃ before monitoring by ¹H NMR.
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### APPENDICES

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<th>Type</th>
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<td>237</td>
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<td>238</td>
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<td>1H NMR:</td>
<td>2-((4R,4aS,8aR,E)-4,7-dimethyl-3,4,4a,5,6,8a-hexahydonaphthalen-1(2H)-ylidene)propanoic acid (63)</td>
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<td>243</td>
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<td>COSY:</td>
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<td>244</td>
</tr>
<tr>
<td>HSQC:</td>
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<td>245</td>
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</table>
$^{13}C$ DEPT 135: 2-(((4R,4aS,8aR,E)-4,7-dimethyl-3,4,4a,5,6,8a-
hexahydonaphthalen-1(2H)-ylidene)propanoic acid (63)

$^1$H NMR: dihydroartemisinic acid (13)

$^1$H NMR: dihydroartemisinic acid hydroperoxide (14)

$^1$H NMR: artemisinin (1)
$^1$H NMR: \[(\text{tert-butoxycarbonyl)amino})\text{butanoic acid} (54)\]
CNMR: 4-(tert-butoxycarbonyl)amino)butanoic acid (54)
H NMR: tert-butyl (4-((4S,5S)-2-(dicyclohexylphosphanyl)phenyl)-4,5-diphenyl-4,5-dihydro-1H-imidazol-1-yl)-4-oxobutyl)carbamate (55)
$^{13}$C NMR: tert-butyl (4-(4S,5S)-2-(dicyclohexylphosphanyl)phenyl)-4,5-dihydro-4',5'-dihydro-1H-imidazol-1-yl)-4-oxobutyl)carbamate (55)

$^{13}$C NMR: tert-butyl (4-((4S,5S)-2-(dicyclohexylphosphanyl)phenyl)-4,5-dihydro-4',5'-dihydro-1H-imidazol-1-yl)-4-oxobutyl)carbamate (55)
H NMR: 4-((4S,5S)-2,2-dicyclohexylphosphanylidene)-4,5-dihydro-1H-imidazol-1-yl)-4-oxobutan-1-aminium chloride (56)
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C NMR: byproduct (63)
COSY byproduct (63)
HSQC: byproduct (63)
H NMR: dihydrotartemisilic acid (13)
H NMR: dihydroartemisinic acid hydroperoxide (14)
H	NMR:	artemisinin (1)

\[
\begin{align*}
  &\text{H}^3\text{C} - \text{SO}_3\text{H} \\
  &\text{O} - \text{CH}_3 \\
  &\text{O} - \text{O}
\end{align*}
\]
VITA

Daniel C. Fisher was born on August 23\textsuperscript{rd}, 1984 in Newton, PA. He grew up in Pittsford, NY an enthusiastic Philadelphia sports fan. He graduated sum laude with a B.A. from the University of Richmond in 2007. He is a founding member of Church Hill Academy in Richmond, VA. Currently, he is a member of the faculty at St. Christopher’s School in Richmond, VA, where he teaches chemistry.

Publications
