Title
Discovery of Ruthenium Tris-phosphine Complexes for Poly-alcohol Functionalization and Alkene Hydroamination

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Discovery of Ruthenium Tris-phosphine Complexes for Poly-alcohol Functionalization and Alkene Hydroamination

By

Christopher Kimball Hill

A dissertation submitted in partial satisfaction of the requirements for the degree of
Doctor of Philosophy
in
Chemistry
in the
Graduate Division
of the
University of California, Berkeley

Committee in charge:
Professor John F. Hartwig, Chair
Professor T. Don Tilley
Professor Niren Murthy

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Christopher Kimball Hill
Abstract

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This dissertation describes the discovery and development of new ruthenium cis-triphosphine coordination complexes and their application towards catalytic functionalization of alcohols, ketones, and alkenes. Ruthenium-mediated transfer dehydrogenation of alcohols and subsequent complex ketone functionalization reactions enable the modification of the structures of complex molecules bearing multiple alcohol functionalities. Alteration of the ruthenium catalyst X-type scaffold generates a coordination complex that activates select amines for the direct Markovnikov hydroamination of terminal alkenes. Unactivated terminal alkenes bearing a diversity of functional groups and limiting amounts of alkene can be employed with acceptable yield. Internal alkenes undergo hydroamination with a selectivity that targets tandem isomerization-hydroamination.

Chapter 1 surveys ruthenium-catalyzed hydrogenation and borrowing hydrogen chemistry with an emphasis on hydrogen transfer-mediated alcohol functionalization. Possible mechanisms of hydrogen transfer are considered and kinetic and thermodynamic considerations regarding hydrogen transfer and hydrogenation reactions are analyzed. This chapter then presents a survey of direct hydroamination reactions of alkenes with late metals and known hydroamination systems with ruthenium catalysts. Precedent in the fields of hydrogen transfer chemistry and hydroamination is described with an emphasis on the synthetic systems of highest utility or closest analogy to the transformations presented in this thesis. The utility, scope, and mechanism of known hydrogen transfer mediated functionalization reactions and seminal contributions to this field are described.

Chapter 2 presents the discovery and development of a new class of ruthenium cis-trisphosphine complexes bearing triflate ligands which catalyze a diverse array of organic transformations. The synthesis of this class of complexes is described in addition to select stoichiometric reactions of these complexes. This chapter presents the application of newly developed ruthenium catalysts towards the selective dehydrogenation of secondary alcohols in diverse complex polyhydroxylated natural products. The epimerization of select secondary alcohols in complex natural products is
described. Several mechanistic experiments are given which support insight into the hydrogen transfer catalysts we have developed. Furthermore, this chapter covers the development of complex ketone functionalization chemistries to convert complex ketones to diverse functionalized complex molecules. In particular the description of chemistries for the incorporation of nitrogen based functional groups into complex ketones are presented.

**Chapter 3** presents the development of a new catalytic hydroamination system of terminal alkenes which tolerates limiting amounts of alkene and which enables the modification of a diverse scope of alkene substrates. The synthesis of a new class of catalysts based on a ruthenium trisphosphine scaffold with triflimide X-type ligands is presented along with their catalytic application. A synthetic route a novel osmium analog of the primary ruthenium scaffold is described. Several mechanistic experiments are presented to interpret the high reactivity of the system relative to previous systems in order to explain how a ruthenium catalyst has an activity that supersedes previous rhodium, iridium, and gold-based systems for hydroamination. Empirical observations including the generation of catalytic quantities of unsaturated intermediates in the hydroamination reaction, the tolerance of diverse solvents of widely varied dielectric properties, and the incorporation of deuterium at numerous locations in the starting materials and products the reaction are analyzed. Nuclear magnetic resonance spectroscopic and X-ray crystallographic studies are shown as preliminary support of a borrowing hydrogen type hydroamination mechanism and to support a preliminary proposal regarding the identity of ruthenium complexes along the catalytic cycle of hydroamination.
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Chapter 1:

Innovation in the science of borrowing hydrogen catalysis and alkene hydroamination and the role of ruthenium homogeneous catalysis
1.1 Introduction

Hydrogenation was one of the first catalytic processes studied, due to the ubiquity of hydrogen atoms in organic molecules and unsaturated functional groups that are the reactive sites for this catalytic process. Examples of catalytic electrochemical, chemical, and biological processes exist that incorporate hydrogen into unsaturated molecules. Individual steps of hydrogenation reactions can include addition of a hydride, protonation, or hydrogen atom transfer. The reverse processes for removing hydrogen from organic molecules also occur. Hydrofunctionalization reactions are related to hydrogenation reactions in that a hydrogen is incorporated into the products of hydrofunctionalization along with a different molecular fragment, usually based on a B, C, N, O, or S atom (Figure 1).

Transfer hydrogenation is a well-established category of hydrogenation reaction whereby organic or inorganic substrates besides hydrogen gas or protons are employed as a source of hydrogen. The development of transfer hydrogenation reactions has been enabled by the discovery of new catalysts that overcome the inherent kinetic barriers of this process.

Figure 1: Generalized hydrofunctionalization of unsaturated molecular fragments

The development of catalysts for hydrogenation and hydrofunctionalization reactions is facilitated by a combination of analysis of precedent and empirical study and guided by hypotheses connecting desired modes of reactivity and potential catalysts structures. Empirical studies can be strategically designed to examine reaction variables that are difficult to predict. The thermodynamics of a select organic reaction can be estimated, but the activity of a catalyst depends upon the concerted effect of multiple complex molecular fragments. This complexity of catalytic mechanisms leads to opportunities for the design and discovery of new reactivity, selectivity, and mechanisms.

The present thesis is an outgrowth of basic research towards the discovery of new catalysts. The primary goal of this research was aimed at generating highly active and practical catalysts for the selective modification of functionalized organic molecules. Processes were sought whereby transition-metal coordination complexes would catalyze the modification of complex organic molecules as nature does with enzymes. Our compounds of ruthenium with phosphorus-based ligands enabled us to approach this goal with a small set of well-characterized cases.
1.2 Categories of hydrogen transfer and previous studies

The transfer of a hydrogen atom equivalent between molecules can proceed via uncoupled electron and proton transfer (ET and PT), proton-coupled-electron-transfer (PCET), hydrogen atom transfer (HAT), or proton and hydride transfer (PT and HT, H₂ transferred).¹⁰⁻¹³¹⁴ This mechanistic categorization differs from statistical theoretical methods that characterize hydrogenation from a larger population-scale perspective.¹⁵ Each of the above mechanistic routes has been demonstrated catalytically and the conditions of reactions that occur by these processes are in general distinct from one another. The requirements of metabolism drove the evolution of hydrogenase and oxidase enzymes,¹⁶,¹⁷ the availability of heterogeneous catalysts derived from metal oxides led to early growth in catalytic alkene, nitrogen oxide, and carbonyl hydrogenation, and placing electrodes in various acids provided early conditions for hydrogen gas production and other reduction chemistries.¹⁸

The four possible mechanisms of hydrogen transfer with ruthenium complexes, based upon previous research, are shown in Figure 5. These include transfer via a ruthenium hydride intermediate, via an Oppenauer-type 6- or 8-membered transition state, by hydrogen atom abstraction,¹⁹,²⁰,²¹ or via electrophilic activation-oxidation. Homogeneous catalysts based on ruthenium and other second-row and third-row late metals are expected to transfer hydrogen heterolytically, as a proton and hydride. Accordingly, the present thesis describes catalytic process based upon the assumption that heterolytic hydrogen transfer mechanisms 1 and 2 from Figure 4 are the only relevant mechanisms for discussion and analysis of reactions catalyzed by ruthenium(II) precursor complexes (under mild pH and redox conditions).¹,²²–²⁴

The transfer of hydrogen to and from organic molecules has a large impact on the overall shape of the molecule. Moreover, the transfer of hydrogen from a molecule to produce unsaturated functionality can enable the diversification of a compound via hydrofunctionalization reactions or other addition or substitution reactions at the newly formed unsaturated positions. Ultimately this sequence can generate a set of derivatives of greater variety than is possible via known single step reactions.²⁵

The processes of dehydrogenation and hydrogenation can be mechanistically combined in a tandem process called borrowing hydrogen. Alcohols are the most common substrates for borrowing hydrogen catalysis based upon the abundance of catalytic methods for the dehydrogenation of simple alcohols, as well as the abundance of reductive modification chemistries for ketones and aldehydes, such as aldol condensation-reduction or reductive amination. Therefore, alcohol to amine conversion and the alpha alkylation of alcohols are the hallmark reactions of borrowing hydrogen chemistry. Ruthenium, rhodium, and iridium are common catalysts for borrowing hydrogen functionalization.
1.3 Borrowing hydrogen catalysis

A system composed of [Cp*IrCl2]2 in combination with base has been used successfully by Fugita, Williams, and other researchers for the amination of unhindered primary alcohols with select aliphatic amine sources. Beller has shown that a simple iron catalyst at 200 °C can catalyze the amination of unhindered and unfunctionalized primary alcohols with aniline, although the synthetic utility of this system and other such systems of first row metals are limited by the harsh reaction conditions. Williams has published one of the most active catalysts for borrowing hydrogen amination of unhindered secondary alcohols with a combination of a ruthenium chloride precursor and DPPF ligand, the combination of which tolerates select aliphatic and aromatic amines. Yamaguchi has demonstrated the other system of highest
activity and functional group tolerance for borrowing hydrogen amination which is composed of 
Cp*Ir(NH$_3$)$_3$X (X = halide) and can catalyze the borrowing hydrogen amination of a variety of 
unhindered and unfunctionalized primary and secondary alcohols with select aliphatic and 
aromatic amines under an aqueous reflux.$^{29}$ Despite a massive growth in interest and an 
abundance of publications in this area, the scope of borrowing hydrogen chemistry has been 
limited by low reaction rates derived from the need for multiple reactions to be catalyzed under 
the same conditions and the presence of only catalytic quantities of unsaturated intermediates 
and active reducing agents at any given point in the reactions. The scope of these reactions has 
been limited because given slow reaction rates, the rate with hindered and functionalized 
substrates is depressed to such an extent that significant yields have not been obtained (Figure 3).

Figure 3: (Top) Borrowing hydrogen amination is most facile with unhindered primary 
alcohols and non-oxidizable amines (Bottom) Hindered alcohols do not undergo borrowing hydrogen amination with known catalyst systems

![Figure 3](image.png)

Figure 4: (Top) Jonathan Williams’ and (Bottom) Ryohei Yamaguchis’ systems for the 
borrowing hydrogen amination of alcohols

![Figure 4](image.png)

1.4 Catalytic transfer hydrogenation for complex molecule functionalization

Polyoxygenated hydrocarbons bearing one or more hydroxyl groups comprise a large set of natural 
and synthetic compounds, often with potent biological activity. In synthetic chemistry, alcohols 
are important precursors to carbonyl groups, which then can be converted to a wide range of
oxygen- or nitrogen-based functionality (Figure 5). Therefore, the selective conversion of a single hydroxyl group in natural products to a ketone would enable the selective introduction of unnatural functionality (Figure 6). However, the methods known to convert a simple alcohol, or even an alcohol in a molecule containing multiple protected functional groups, are not suitable for selective reactions of complex polyol structures. This thesis describes a new ruthenium catalyst with unique efficacy for the selective oxidation of a single hydroxyl group among many in unprotected polyol natural products. This oxidation enables the introduction of nitrogen-based functional groups into such structures lacking nitrogen atoms and enables selective alcohol epimerization by stepwise or reversible oxidation and reduction.

**Figure 5:** (Top) Dehydrogenation of alcohols is a substrate-activating strategy which enables the diversification of alcohols with greater scope than can be achieved with single step reactions

**Figure 6:** Motivational example of dehydrogenation of a complex alcohol to enable novel derivatization

However, catalysts are not known that selectively oxidize one hydroxyl group among many in a range of polyol natural products. Scattered examples of the oxidation of polyol natural products have been published, but no catalyst or conditions has been broadly applicable to this synthetic
goal. Classical methods lead to mixtures of products and existing catalysts oxidize unhindered primary C-H bonds to form aldehydes over hindered secondary C-H bonds in the core of the structures to form ketones. Thus, we sought a combination of catalyst and reagent that would be sufficiently mild and selective for the oxidation of secondary alcohols in polyol natural products.

1.5 Catalytic direct hydroamination

Hydrofunctionalization reactions of alkenes enable rapid coupling of alkenes with molecules containing C-H or X-H bond without additional byproducts. Nitrogen-containing compounds often are more valuable than similar compounds lacking nitrogen atoms. Therefore, the incorporation of nitrogen into synthetic and natural feedstock chemicals via hydroamination is expected to generate compounds of high utility. Previously, the synthetically useful application of hydroamination in synthesis has been limited by the need for excess alkene, narrow substrate scope, expensive Ir and Au catalysts, and the inability to form free primary amine products. Nevertheless, the most fundamental hydroamination reaction and therefore a primary goal of hydroamination research is the formal addition of ammonia to an unactivated alkene (Figure 7).

Figure 7: Hydroamination to enable generalized free primary amine synthesis

The hydroamination reaction between an amine and an alkene is the simplest and most atom economic way to incorporate nitrogen into a carbon framework. This process could provide a valuable alternative to the more common methods of synthesizing amines, such as reductive amination of carbonyls and cross coupling of amines with aryl and alkyl halides. Previous studies of alkene hydroamination have been restricted to the use of excess quantities of the alkene component, which has prevented the application of these reactions to functionally diverse alkenes. To this end we sought to develop an alkene hydroamination catalyst that is sufficiently active to enable the alkene component to be the limiting reagent, while providing access to alkenes bearing diverse functional groups.

Direct hydroamination requires activation of either the amine or alkene component because amines and alkenes are both nucleophilic. An additional issue we recognized is that many amines outcompete alkenes for binding to the active sites of transition metal catalysts to such an extent that hydroamination via alkene binding is precluded. Hydroamination adducts in general are near to thermoneutral relative to their amine and alkene precursors. Due to the greater electron withdrawing capability of heterocyclic arylamines, the thermodynamics for addition of these substrates to alkenes is more favorable than addition of alkylamine or aniline derivatives lacking a nitrogen in the aromatic ring. Acid-catalyzed hydroaminations favor internal and cyclic and alkenes with higher substitutions. Some transition metal-catalyzed hydroaminations demonstrate this same reactivity pattern. Cobalt-catalyzed formal hydroamination reactions, which
utilize reagents that render the reactions atom-uneconomical, exhibit improved reactivity for internal alkenes over terminal and diminished reactivity for styrene derivatives.  

The hydroamination of unactivated terminal alkenes with branched selectivity is restricted to the attachment of specialized nitrogen reagents, such as indoline, indole, urea derivatives, or heterocyclic amines. The most common catalysts for direct coupling of amines and terminal alkenes are generated from Ir or Au with biaryl bisphosphine ligands. These systems form products with low to moderate enantioselectivity, and the reactivity and limited functional group tolerance is generally low. Only alkyl substituents and noncoordinating aprotic functionality are tolerated, and solvent quantities of alkene are generally required. Linear-selective hydroamination has been achieved for various terminal alkenes with photoredox catalysis and vinylarenes with ruthenium based catalysis, but even in these cases excess alkene has been employed. The establishment of a highly active hydroamination catalyst that enables the conversion of limiting and functionalized terminal alkenes to branched amines is required to achieve a synthetically useful method for this transformation. The synthetic utility would be expanded even further if the method can be extended towards the generation of free primary amines (Figure 7).

Ruthenium complexes catalyze both Markovnikov and anti-Markovnikov hydroamination, although the former selectivity appears to be more general. Wakatsuki and coworkers demonstrated that ruthenium carbonyl and various acids promote the hydroamination of alkynes to imines, yet full reduction to the amine was not observed, even in the presence of hydrogen sources like amines and alcohol solvents. Importantly, Herzon developed well defined catalysts for the functionalization of terminal alkynes. Angelici’s ruthenium dimer \{(eta-5-C₅H₅)₂(SiMe₂)₂\-[Ru₂(CO)₃(C₂H₄)H⁺][BF₄]⁻\} catalyzes the hydroamination of alkynes with aryl amines with Markovnikov selectivity and catalyzes the stoichiometric hydroamination of ethylene with excess aryl amine. The mechanistic proposal for this catalytic hydroamination follows protonation of a μ-coordinated alkyne, nucleophilic attack of the amine, deprotonation of the resulting cationic ammonium-alkene complex, and dissociation of the product enamine from the coordination sphere. In contrast to these catalysts, Hartwig’s ruthenium catalyst system Ru(COD)(2-methylallyl)₂/DPPPent/HOTf catalyzes anti-Markovnikov hydroamination of vinylarenes by the unique mechanism of arene binding and nucleophilic attack. C-H bond formation occurs instead of C-N bond formation with some ruthenium and iridium catalysts. Alkylation alpha to nitrogen with alkenes is a competing process with hydroamination in some ruthenium and other late metal-based systems.

In the present thesis, we describe a new ruthenium trisphosphine catalyst that overcomes these limitations and facilitates selective intermolecular hydroamination of terminal unactivated alkenes with a single equivalent each of alkene and amine. Secondary alkyl heteroarylamine products are obtained via a single atom economic transformation, and a one pot procedure for the synthesis of primary amine products by cleavage of the N-heteroaryl linkage is shown. The hydroamination reaction likely proceeds by a novel borrowing hydrogen type mechanism for hydroamination.
1.6 References


29. Kawahara, R., Fujita, K. & Yamaguchi, R. N-Alkylation of Amines with Alcohols Catalyzed by a Water-Soluble Cp*Iridium Complex: An Efficient Method for the


Chapter 2:

Invention of novel trisphosphine ruthenium complexes for the site-selective oxidation and epimerization of complex polyols and the development of amination chemistries for the derivatization of complex ketone products.
2.1 Introduction

The controlled modification of natural products enables chemists to alter the physical properties and resulting functions of these complex molecules. Selective reaction at a specific hydroxyl group in a polyhydroxylated molecule, particularly one that is less reactive toward classical reagents, is a synthetic challenge due to competing, undesirable side reactions and the lack of selectivity for reaction at one of multiple identical functional groups. Catalysts or reagents that differentiate between the same functional groups in different environments are needed to achieve selective, direct functionalization of such structures. To this end, catalysts based on peptides have been developed that selectively acylate, phosphorylate or sulfonate one alcohol over others in complex polyols,\textsuperscript{1,2,3} and rhodium complexes catalyze reactions at the hydroxyl groups in polyol structures,\textsuperscript{3} but these reactions attach substituents to the oxygen atom. They do not form bonds to the carbon at which the hydroxyl group is bound.\textsuperscript{1,2,3} If a single alcohol among many could be oxidized selectively to a ketone, then a wide range of reactions that would replace the original hydroxyl group, restructure the rings of the natural product, or add substituents at the position of the C-H bond alpha to the hydroxyl group could be conducted.

However, catalysts are not known that selectively oxidize one hydroxyl group among many in a range of polyol natural products. Scattered examples of the oxidation of polyol natural products have been published, but no catalyst or conditions has been broadly applicable to this synthetic goal. Classical methods lead to mixtures of products and existing catalysts oxidize unhindered primary C-H bonds to form aldehydes over hindered secondary C-H bonds in the core of the structures to form ketones (vide infra). Thus, we sought a combination of catalyst and reagent that would be sufficiently mild and selective for the oxidation of secondary alcohols in polyol natural products.

The design of coordination complexes to catalyze organic transformation requires applying predictive knowledge of about 20 reaction variables which can be derived from drawing analogies to precedent in the literature, applying fundamental theorems, and learning from experimental coverage of unpredictable variables. The fundamental insight underlying all the ruthenium chemistry reported here is that coordination sites must be accessible and have high lability. In a mixed solution of molecules numerous things can access a binding site on a metal center and it must be ensured that the functionality intended to react has an opportunity to bind the catalyst. This is ensured by high lability. Furthermore, it must be ensured that upon binding, the functionality has the opportunity to react further or the reaction will not proceed. In order to address this problem unhindered and strongly donating ligands were employed such that cis coordination of these ancillary ligands is favored. Ruthenium(II) complexes were sought in order to accommodate a sufficient number of highly donating ligands to place one opposite to every substitutable site on the metal center, and weakly coordinating anions were selected for these positions under the influence of the trans effect and the trans influence simultaneously (“trans phobia”). Anions that effectively engage in hydrogen bonding were selected to accommodate rapid proton transfer chemistries in the outer sphere of the complexes.

Although many catalysts for the oxidation of alcohols are known, few catalyze the oxidation of hindered secondary alcohols. We envisioned that the oxidation of secondary alcohols over primary
alcohols could be achieved by conducting a transfer dehydrogenation with a ketone as acceptor. Base-activated Ru(p-cymene)(Ts-DPEN),\textsuperscript{4} Shvo’s catalyst,\textsuperscript{5,6} Ru(PPh\textsubscript{3})Cl\textsubscript{2} with KOH, and Ru-MACHO with KOH have been reported to catalyze the dehydrogenation of simple unhindered secondary alcohols, such as cycloalkanols with no beta substituents, or secondary alcohols with one beta substituent in some cases, but are not reported to catalyze the dehydrogenation of more hindered alcohols containing two beta substituents. We found that Ru-MACHO with KOH and Shvo’s dimer are able to oxidize this type of hindered model substrate under forcing conditions (see section 2.16) but not at temperatures that are likely to tolerate highly functionalized molecules. Thus, to achieve the formation of ketone units in polyol natural products, a complex that catalyzes the oxidation of hindered secondary alcohols over primary alcohols is needed.

To create such a catalyst, we investigated ruthenium complexes containing a combination of weakly coordinating anions and unhindered, strongly donating phosphines. The ruthenium center would be a relatively soft, mild Lewis acid that would not lead to indiscriminate decomposition, the labile anions would allow formation of an alkoxide from the alcohol with a weak base at low temperatures, and the small phosphines would allow reaction at hindered secondary alcohols. By using acetone as the oxidant, the oxidation of primary alcohols to aldehydes would be uphill thermodynamically and the selectivity of the process could favor oxidation of a hindered secondary alcohol over a primary alcohol without the radicals intermediates of classical methods for preferential oxidation of secondary alcohols that would be unselective for one alcohol over others in a complex structure. Here, we show that such a ruthenium complex catalyzes the selective dehydrogenation of secondary alcohols in more than a dozen natural products having a wide range of structures and that the resulting ketones can be converted by subsequent catalytic processes to final products containing nitrogen-based functionality and with restructured ring systems.

2.2 Development of Catalysts and Conditions for the Selective Oxidation of Hindered Secondary Alcohols

The target reaction of transfer dehydrogenation was selected and a series of ruthenium catalysts was developed through multiple catalyst generations to facilitate this reaction. Thereafter, reactivity observations guided the application of these catalysts towards ketone reduction and alcohol epimerization.

Several sequential phases of catalyst development described in the Sections 2.3 and 2.4 led to the new ruthenium complex [Ru(PEt\textsubscript{3})\textsubscript{6}(OTf)\textsubscript{3}][OTf] (Figure 3a). Initially, the precursor Ru(DMSO)\textsubscript{4}(OTf)\textsubscript{2} was generated in acetone solvent and treated with various phosphine ligands to give potential catalysts. The complexes resulting from the addition of unhindered alkylphosphines PEt\textsubscript{3}, PMePh\textsubscript{2}, and PEt\textsubscript{2}(p-Me\textsubscript{2}N-Ph) all gave active catalysts for dehydrogenation of the hindered model alcohol diisopropylcarbinol. Thereafter a synthesis of a series of catalyst precursors without DMSO ligands was developed (Ru-1, Ru-2, Ru-3), and the activity of these complexes was found to be an order of magnitude greater than that of the system generated in-situ. Initial results of the oxidation of the model, hindered alcohol are shown in Figure 3B. In contrast to prior transition-metal catalysts that do not oxidize such hindered secondary alcohols, this ruthenium complex converted dicyclohexylcarbinol to the corresponding ketone at room temperature in only 3 h. The same oxidation also occurred when 1,4-cyclohexanedione or
trifluoroacetophenone were used as stoichiometric oxidants and the reaction is run in trifluoroethanol solvent.

2.3 1st generation catalyst

[Ru(DMSO)$_4$Cl$_2$] (48 mg, 0.10 mmol) and AgOTf (51 mg, 0.20 mmol, 2 equiv) were weighed into a 1 dram vial, and acetone (1 mL) was added. The mixture was stirred at 65 °C for 90 minutes and then filtered to give a solution of [Ru(DMSO)$_4$(OTf)$_2$] (0.1 M). To this solution, phosphine (0.2 mmol for monophosphines or 0.1 mmol for bisphosphines) (e.g. for PEt$_3$, 30 μL, 0.20 mmol, 2 equiv) and DMAP (12 mg, 0.10 mmol, 1 equiv) were added, and the mixture was briefly stirred to generate a solution of active catalyst. For reactions run without amine, the same procedure was used to generate a stock catalyst solution, but DMAP was omitted. Alcohol oxidation reactions were conducted by dissolving the substrate alcohol (0.1 mmol) and dodecane internal standard (0.05 mmol) in acetone solvent (0.46 mL) and then adding measured aliquots of the catalyst solution (0.0040 mmol, 40 μL of 0.10 M solution, 4% catalyst) to generate reaction solutions (0.2 M). The reactions were then heated at 65 °C until completion. A series of monophosphine and bisphosphine ligands were investigated using this system, and the results for oxidation of a series of model alcohols is shown in Tables S1 and S2. This catalyst system enables oxidation of hindered secondary alcohols but is less active than later generations of the catalyst.
Figure 1: Model alcohol oxidations with 1st generation catalysts containing monophosphine ligands

\[
\begin{align*}
R_2CHOH & \quad 4\% \,[\text{Ru}] + 2 \text{ Phosphines +/- 1 DMAP} \quad 65^\circ C, \text{Acetone} \\
& \quad \rightarrow \quad R_2C=O
\end{align*}
\]

Conditions: 0.2M \( R_2COH \) (65 equivalents acetone)
* 1 catalytic equivalent DMAP

Substrate Conversion (reaction time):

- **A**: 88% (1 hr)
- **B**: 58, 88, 98% (1, 3, 10 hrs)
- **C**: 45, 98% (10, 48 hrs)
- **D**: 85, 99% (10 hrs: 50, 500 eq. acetone)
- **E**: 62, 79% (10 hrs: 50, 500 eq. acetone)
- **F**: 24, 84% (10 hrs: 50, 500 eq. acetone)
- **G**: 45, 84% (10 hrs: 50, 500 eq. acetone)
- **H**: 23, 64% (10 hrs: 50, 500 eq. acetone)

Monophosphine ligand:

- **A**: 87% (1 hr)
- **B**: 9, 26% (1, 4 hrs)

Phosphines leading to inactive complexes:

- **A**: 87% (1 hr)
- **B**: 24, 95% (1, 20 hrs)

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Figure 2: Model alcohol oxidations with 1st generation catalysts containing bisphosphine ligand

\[
\text{R}_2\text{CHOH} \xrightarrow{\text{4\% [Ru] + 1 Bisphosphine +/- 1 DMAP}} \text{R}_2\text{C}=\text{O}
\]

65 °C, Acetone

Substrate Conversion (Reaction time)

\[
\text{OH} \quad \text{OH}
\]

A: 81, 87\% (1.8 hrs)
A*: 86, 87\% (1.8 hrs)
B: no rxn
B*: 49, 94\% (1, 8 hrs)

Bisphosphine Ligand:

A*: 90\% (1 hr)
A*: trace, 31\% (1.8 hrs)
A*: 85, 90\% (1.8 hrs)
B*: no rxn
B*: 90, 98\% (1.8 hrs)

Phosphines leading to inactive complexes:

2.4 2nd generation catalyst:

The DMSO-free precursor [Ru$_2$(PEt$_3$)$_6$(OTf)$_3$][OTf] (Ru-2) was developed. Alcohol oxidations in pure acetone catalyzed by this species were much faster than those catalyzed by the 1st generation catalyst. To generate a stock solution of the active catalyst, equimolar [Ru] precursor and NMM are combined in acetone solvent. For example to make a 0.01 M stock solution of active catalyst, Ru-2 (7.5 mg, 0.0050 mmol) and NMM (1.1 μL, 0.010 mmol) were combined in acetone (1 mL). To conduct a model alcohol oxidation, dicyclohexylcarbinol (7.9 mg, 0.040 mmol), dodecane internal standard (4.5 μL, 0.020 mmol, 0.5 equiv), and acetone (110 μL) were combined in a one-dram vial. Then, an aliquot of active catalyst stock solution (0.010 M, 40 μL, 1% [Ru], NMM) was added. The vial was capped, and the mixture was allowed to stand at room temperature for 3 hours and then exposed to air to halt the reaction. GC analysis showed 98% conversion to of the starting alcohol to dicyclohexylketone.

The reactions of many (non-basic) simple and complex alcohols conducted in 1:1 TFE:acetone solvent were much faster than those in neat acetone, and this change to the medium enabled many
oxidations to be conducted with lower catalyst loadings. See, for example, the oxidation of dicyclohexylcarbinol by Ru-2 in 1:1 acetone:TFE solvent (Figure 3).

Figure 3. Model alcohol oxidation and catalyst synthesis.
(a) Synthesis of the ruthenium catalyst for alcohol transfer dehydrogenation. (b) Mild oxidation of a hindered secondary alcohol is enabled by the catalyst Ru-2. (c) Reactions of primary and secondary alcohols show the selectivity for oxidation of secondary alcohols over primary alcohols. Conversions are shown in parentheses. (d) The mild reduction of a hindered ketone is enabled by Ru-2 with iPrOH as reductant.

Reaction yields for oxidation of individual alcohols:
- 84% (85%)
- 98% (98%)
- 7% (16%)
- 5% (12%)
- 2% (2%)

Reaction yields for competitive oxidation of pairs of alcohols:
- 64% (64%) *82% (62%)
- 15% (16%) *13% (27%)
- 69% (70%)
- 88% (91%)
- 51% (54%)
- 75% (77%)
- 24% (58%)
- 13% (58%)
- 2% (12%)
- 2% (2%)

Selectivity:
- 4.3 (4.0)
- 6.3 (3.0)
- 4% loading
- 11.5 (7.8)
- 6% (9%)
- 24% (27%)
- 10 min reaction
- (45.5) 2.1 (0.9)
- 8% loading
- 5.9 (5.9)
- 8% loading, 65°C
- 2.1 (0.9)
- 8% loading
- 65°C
- 13% (27%)

Reaction yields for stoichiometric ketone acceptors:
The reactions of a series of primary and secondary alcohols with acetone as hydrogen acceptor and Ru-2 as catalyst are shown in Figure 3C. These results show that the oxidation of secondary alcohols occurs over the oxidation of primary alcohols. The individual reactions of primary alcohols occur to low conversion over a time that leads to full conversion of secondary alcohols, and reactions with a mixture of primary and secondary alcohols preferentially convert the secondary alcohol to the ketone.

2.5 Selective Oxidation of Polyol Natural Products to Ketone Derivatives

Figure 4 summarizes the transfer dehydrogenation of thirteen polyol natural products. This figure shows the products from the oxidation reactions and the configuration of the alcohol unit that underwent oxidation. These reactions occur with several classes of natural products, including steroids, diterpenoids, sesquiterpenoids, iridoids, carbohydrates, alkaloids, and macrolides, showing the broad applicability of the catalyst system. The ruthenium catalysts we developed display a remarkable selectivity for the oxidation of a single secondary alcohol within each natural product in Figure 4 and for reaction at the alcohol over auxiliary functionality. The reactions of these natural products revealed guidelines for predicting the site selectivity of the oxidations. The reactions catalyzed by Ru-2 with acetone as hydrogen acceptor led to oxidation of secondary alcohols in these structures over primary alcohols, presumably due to the mild oxidizing ability of the ruthenium catalyst. This catalyst also senses subtle differences between the steric and electronic properties of secondary alcohols, leading to remarkable selectivity for oxidation of one secondary alcohol over other secondary alcohols.

In general, the ruthenium catalyst was selective for the more electron rich of the secondary alcohols and in most cases for the less hindered of the secondary alcohols. For example, the catalyst reacts with secondary alcohols containing less than two hydroxy or alkoxy groups on the carbon atoms beta to the hydroxyl group, but it does not react with alcohols containing two or more oxygen-based substituents at these positions. Primary alcohols containing a single oxygen atom on the beta carbon are not oxidized by this system. Due to this effect of electron-withdrawing substituents, the catalyst tolerates polyoxygenated moieties, such as sugars, attached to molecules via glycosidic bonds. In contrast, deoxy-sugars are selectively oxidized to the corresponding ketones by the catalyst system. In general, dione products from oxidation of multiple alcohols were not observed, due to the high sensitivity of the catalyst to differences in the properties of various alcohols. The use of a dehydrogenation process with ketone as acceptor, rather than a conventional oxidation with oxygen, peroxide, or amine oxide, creates a tolerance for olefins, amides, esters, enoates, epoxides, acetals, amines, phenols, and carbohydrates in elaborate topological settings.

The examples in Figure 4A show the selectivity for oxidation of secondary alcohols over primary alcohols and the selectivity for one secondary alcohol over others in polyol structures. Dehydrogenation of andrographolide with Ru-2 occurred selectively at the hindered secondary alcohol at the 3-position to form the corresponding ketone in 65% yield (1a). This secondary alcohol reacts over the secondary alcohol at the 14-position because of electron withdrawing groups nearby C(14). The iridoid glycoside aucubin underwent oxidation catalyzed by Ru-2 at the
Figure 4. Examples of the site-selective oxidation of polyol natural products.

(a) The oxidations of this series of natural products shows that the reactions occur at secondary over primary alcohols in complex structures (b) The oxidations of this series of natural products containing multiple secondary alcohols show that the reactions occur at one secondary alcohol over other secondary alcohols (c) Thermodynamically less favorable oxidations and selective dehydrogenations with stoichiometric amounts of acceptor occur with trifluoroacetophenone as acceptor. Allylic isomerization occurs over oxidation in the presence of a ruthenium catalyst containing the bidentate phosphine.
secondary alcohol of the cyclopentenol to form ketone **1b** in 87% yield; the primary allylic alcohol remained untouched, and the glycoside unit was stable because each alcohol in a glycoside has two or more beta oxygen atoms. Catalyst **Ru-1**, which is apparently more oxidizing than **Ru-2**, generates about ~4% aldehyde, but **Ru-2** is fully selective for formation of the ketone. The oxidation of D-glucal occurred selectively to give a vinylogous ester in 88% yield (**1c**). In contrast to those in a fully oxygenated carbohydrate, one hydroxyl group in D-glucal bears only one beta-oxygen atom and, therefore, undergoes oxidation by **Ru-2**. The oxidation of kirenol formed the natural product 15-dehydro-kirenol (**1d**) in a single step in 54% yield.\(^7\) This selectivity appears to be controlled by a combination of the relative reactivity of secondary versus primary alcohols and the reactivity of one secondary alcohol over another. The alpha hydrogen of the cyclohexanol portion of this molecule experiences 1,3 eclipsing interactions with axial methyl and hydroxymethyl groups (Figure 3), leading to oxidation at the less electron-rich secondary alcohol at C15. Chelation of the 1,2 diol could also favor selective oxidation at the 15-position, helping to overcome the electronic deactivation of this secondary alcohol by the proximal primary alcohol. As is usually observed in our system, the secondary alcohol was oxidized preferentially over the primary alcohols.

Oxidation of ouabain occurred with remarkable selectivity for one of many hydroxyl groups. Ouabain contains eight hydroxyl groups, one in a primary alcohol, five in secondary alcohols and two in tertiary alcohols. Under the conditions with acetone as hydrogen acceptor and **Ru-2** as catalyst, the oxidation of ouabain occurred at a single secondary alcohol to give a mono-ketone product in 92% yield (**1e**). The glycosidic functionality was fully tolerated, due to the deactivation of each of these hydroxyl groups by an adjacent glycosidic oxygen atom or hydroxyl substituents. The primary alcohol, again, was less reactive than the secondary alcohol with acetone as acceptor and **Ru-2** as catalyst. The alpha hydrogen on the secondary alcohol of ring C has 1,3-diaxial relationships with the hydroxymethyl substituent and a methyl substituent and, therefore, is less accessible sterically than the hydrogen that reacts (Figure 3). Treatment of the keto-ouabain product with NH2OSO3H yielded 1-keto-ouabagenin (**3a**) in 80% yield (Section 2.22), exposing a less hindered alcohol and providing a route to a useful keto-cardenolide core structure.

The examples in Figure 2B show that small differences in the electronic and steric environments of the hydroxyl groups in polyols containing only secondary alcohols lead to large effects on the site selectivity. For example, the dehydrogenation of fusidic acid methyl ester yielded a single ketone derivative in 97% yield (**1f**). Both hydroxyl groups of this natural product are sterically hindered, but one alcohol is slightly more hindered due partly to a 1,3 eclipsing arrangement of the alpha hydrogen of the hydroxyl group on the C ring with a gamma methyl group, and oxidation occurs at the less hindered of the two (Figure 5). Steric effects also control the selectivities for oxidation of digoxigenin, although the difference in steric properties in this case is more pronounced. The alcohol in this structure lacking vicinal substituents undergoes oxidation (**1g**), while the alpha hydrogen of the other hydroxyl group bears a gauche 1,2 interaction and an eclipsing 1,3 interaction blocking the site (Figure 5). Cholic acid methyl ester is selectively dehydrogenated at the hydroxy group lacking beta substituents or 1,3 eclipsing interactions between the alpha hydrogen and another substituent (**1h** and Figure 5). Finally, the reaction of forskolin illustrates the strong effect of the electronic properties of two secondary alcohols on
Figure 5. Examples of the 1,3 eclipsing interactions that influence the selectivity of the dehydrogenation of certain polyols.
Steric occlusion of the alpha hydrogen or the hydroxyl group of alcohols present in complex molecules by distal substituents with an eclipsing 1,3 relationship decreases the rate of oxidation at these sites. The site of dehydrogenation is shown in bold.

selectivity. One of the secondary alcohols of forskolin is flanked by a quaternary carbon beta to the alcohol, and the other is flanked by a vicinal acetate. In this case, oxidation occurs at the more electron-rich alcohol, even though it is more sterically hindered (1i).

Sterically accessible vicinal diols react when they lack additional, proximal oxygen atoms. When reactive, they undergo dehydrogenation to hydroxy ketones without epimerization of the adjacent alcohol. For example, the oxidation of estriol with Ru-2 yielded the α-hydroxyketone product 1j resulting from dehydrogenation of the more sterically accessible alcohol in 97% yield. However, the polyketide mupirocin methyl ester reacted in 70% yield (1k) at the methyl carbinol over the alcohols in the vicinal diol. This vicinal diol unit of mupirocin methyl ester is less electron rich than that in estriol due to the oxygen of the tetrahydropyran ring, and the methyl carbinol is sterically accessible.

The oxidation of deacetylbaccatin III, which is the core of taxol and a precursor to docetaxel contains an α-hydroxyketone unit that inhibited the catalyst activity under our standard conditions. The α-hydroxyketone unit bound to the catalyst in pure acetone solvent to form a ruthenium alkoxide, which was characterized by single crystal X-ray diffraction (Section 2.14). However, reaction in a mixture of acetone and trifluoroethanol (added to labilize the alkoxide) led to the selective oxidation of the secondary allylic alcohol to a single ketone product in 70% yield (1l). In concert, the secondary alcohol of the hydroxyketone underwent full epimerization, presumably from a reversible retro-aldol process.8

The catalyst Ru-2 reacts with remarkable tolerance for primary allylic alcohols and α-hydroxyenoates. The oxidation of iridoid glycoside genipin and the macrolide brefeldin demonstrate the ability to oxidize a secondary alcohol without isomerization of a primary or secondary allylic alcohol in the same molecule to the corresponding aldehyde or ketone. Brefeldin underwent
selective oxidation in 87% yield at the alcohol on the 5-membered ring to form 1m. In contrast, reaction of this same compound with the catalyst generated from Cy2P(CH2)4PCy2 and Ru(DMSO)4(OTf)2 led to selective isomerization of the allylic alcohol to the corresponding ketone 1q. Genipin underwent oxidation by Ru-2 at the secondary alcohol over the primary allylic alcohol to form lactone 1n directly; prior oxidation to the lactone required protection and deprotection of the primary allylic alcohol.9

Figure 2C shows oxidations that were conducted with ketones having oxidation potentials that are higher than that of acetone. Trifluoroacetophenone can be used in stoichiometric quantities as oxidant in various solvents in place of acetone when a more strongly oxidizing acceptor is required. For example, selective lactonization of the diterpenoid lagochiline to the natural product lagochirsine (1o) occurred in 40% yield with two equivalents of trifluoroacetophenone in dioxane solvent and Ru-2 as catalyst, whereas the reaction with acetone as oxidant gave an acetonide product derived from the 1,3 diol moiety. The lactonization occurred after dehydrogenation of the relatively exposed primary alcohol, driven by formation of a five membered ring. Previously, the oxidation of lagochiline formed products from oxidation of multiple hydroxyl groups.10 Trifluoroacetophenone in excess quantities also can be used to increase the rate of some slow and thermodynamically less favorable oxidations. For example, the oxidation of ivermectin with acetone as hydrogen acceptor occurred in <10% yield, but the same reaction with 20 equivalents of trifluoroacetophenone in dioxane formed a ketone (1p) in 54% isolated yield. The other secondary alcohol in this structure bears multiple oxygen atoms on adjacent carbon atoms, so is unreactive to our system.

The catalyst we discovered for the selective generation of a ketone unit in these natural products provides the potential to create derivatives of these natural products from modification at a single site. For example, we sought to use the ketone to incorporate nitrogen-containing functionality by reductive amination. However, catalytic aminations of hindered alcohols in complex polyols have not been reported, and the array of functionality in most natural products would be unlikely to tolerate the reaction temperatures, oxidants, and bases used in the catalytic oxidation and amination with published catalytic systems. We also sought to modify the ring systems by insertions of nitrene units by a Beckman rearrangement to form lactams. However, the lack of Beckman rearrangements of such hindered and functionalized structures necessitated the development of conditions for this process.

2.6 Selective Transformations of the Keto-Derivatives of Polyol Natural Products

Figure 6 shows the formation of products containing nitrogen-based functionality from selected examples of the ketones formed by our alcohol dehydrogenation. To demonstrate the potential of the oxidation and amination to occur on complex structures, we studied reactions of 3-keto-andrographolide. The arylamine derivative 2f was prepared from ketone 2e by retro-aldol cleavage of the hydroxymethyl group, followed by reductive amination with the iridium catalyst Cp*IrCl(N-(4-dimethylaminophenyl)-2-pyridylcarboxamide) (Ir-1)11 and arylammonium triflate. Classic reductive amination conditions with 2e gave diastereomeric mixtures of amination product or side reactions at the enoate functionality, including isomerization, reduction, or conjugate addition. The 7-membered lactam 2d was prepared by reaction of the ketone with NH2OSO3H in TFE (aq). This process is driven by the excellent leaving group ability of sulfate in aqueous trifluoroethanol,
which dissolves nonpolar substrates. In other solvents, the oxime was obtained as the main product. Again, more classical methods involving initial formation of the oxime gave isomerization of the enoate functionality, elimination of the hydroxy group on the 5-membered ring, and other decomposition reactions. Yet, initial formation of the oxime did allow us to isolate a product 2c containing a fused isoxazole group after formation of an oxime and subsequent treatment with TsCl.

This sequence of oxidation and amination was applied to several additional natural products. Figure 6B shows the reaction of keto-fusidic acid methyl ester with NH$_2$OSO$_3$H to form 7-membered lactams 2h and 2i directly. Reaction of the same ketone with ammonium formate catalyzed by Ir-1 led to a diastereoselective reductive amination to form the free primary amine 2j. Figure 3C shows that the reductive amination of the dehydrogenation product of D-glucal with the ammonium salt of 2,6-difluoroaniline, as well as the amine derivative of lithocholic acid, catalyzed by Ir-1 gave diastereomERICALLY pure amine products 2l and 2m in one-step from concomitant reduction of the carbon-carbon double bond and reductive amination of the ketone.

In addition to these reactions involving a single ketone formed by alcohol oxidation, we developed a route from complex vicinal diols to lactams. As shown in Figure 6D, the hydroxyketone derived from the oxidation of estriol was directly converted to amide 2p in a redox-neutral reaction under reductive amination conditions with Ir-1 and ammonium formate. This ketone intermediate was

**Figure 6. Oxidation and amination of structurally complex polyol natural products.**

(a) Incorporation of nitrogen-based functional groups into andrographolide occurs by formation of oxime derivatives and catalytic reductive amination. (i) NH$_2$OH-HCl, pyridine, 40 °C, 4 h (ii) TsCl, NEt$_3$, THF, 40 °C, 2 days (iii) NH$_2$OSO$_3$H, 1:1 0.01% TFA:TFE, 50°C, 24 h. (iv) NH$_2$OSO$_3$H, 1:1 2.5% NaHCO$_3$(aq):TFE, 50 °C, 40 min, then 80 °C, 60 min (v) 2 SmI$_2$, methyl acrylate, 4:1 THF:TFE, 65°C, 25 min (vi) 3% Ir-1, Cs$_2$NH$_2$, HCO$_2$H, MeOH, 65 °C (b) Incorporation of nitrogen-based functional groups into fusidic acid methyl ester is achieved by direct conversion of the ketone formed by oxidation to the corresponding lactam and by catalytic and diastereoselective reductive amination of this ketone to the free amine. (vii) NH$_2$OSO$_3$H, 1:1 H$_2$O:HFIP, 50 °C, 20 min, then 80 °C, 30 min. Then 1:1 H$_2$O:Me$_2$CO, 80 °C, 10 min (viii) 2.5% Ir-1, NH$_4$O$_2$CH, MeOH, 65°C, 4 h (c) Incorporation of nitrogen-based functional groups into D-glucal is achieved by catalytic and diastereoselective reductive amination. Conjugation of two natural products was achieved by this approach. (ix) 2.5% Ir-1, C$_3$H$_4$F$_2$NH$_2$O$_2$CH, MeOH, 65 °C, 10 h (x) Ir-1, lithocholic amine, HCO$_2$H, MeOH, 65 °C, 20 h (d) Incorporation of nitrogen-based functional groups into estriol is achieved by one step catalytic conversion of the hydroxyketone to the corresponding lactam or by the combination of Baeyer-Villiger oxidation and reductive amination to yield N-substituted lactams. (xi) 3% Pt-1, H$_2$O$_2$ (aq), THF, rt, 2 days or 3% Pt-1, H$_2$O$_2$ (aq), THF, 45 °C, 6 h (77% yield) (xii) R = H, 2.5% Ir-1, NH$_4$O$_2$CH, MeOH, 65 °C, 4 h ; R = Ph, 2.5% Ir-1, PhNH$_2$O$_2$CH, MeOH, 12 h (xiii) 2.5% Ir-1, NH$_4$O$_2$CH, MeOH, 65 °C, 4 h.
also suitable for conversion to esters by catalytic chemistry. Baeyer-Villiger oxidation of keto-estriol occurred with H₂O₂ as oxidant and [Pt(dppb)(OH)]₂[BF₄]₂ (Pt-1)¹² as catalyst to generate acetal 2o in 84% yield, followed by treatment of the acetal product with Ir-1 and ammonium formate salts (NH₃RO₂CH for R = H, Ph) led directly to N-substituted lactam derivatives 2p and 2q in 78% and 77% yield, respectively.
Our catalyst system not only catalyzes the transfer of hydrogen from hindered alcohols to acetone with isopropanol as byproduct, it catalyzes the reverse transfer of hydrogens from isopropanol to hindered ketones, such as pinacolone (Figure 3D), suggesting the potential to epimerize a single hydroxy groups in complex polyols with a single catalyst. For example, the ketone generated from the dehydrogenation of fusidic acid methyl ester was reduced by catalytic Ru-2 and isopropanol to give 3-epi-fusidic acid methyl ester (4a) in 80% yield, with the remaining material identified as the parent fusidic acid methyl ester (Figure 7A). Likewise, ouabain, which was selectively oxidized with acetone, was reduced with isopropanol catalyzed by Ru-2 to form 1-epi-ouabain (4b) in 90% yield. With other polyols, such as D-glucal and andrographolide, reduction of the ketone regenerated the starting natural product. A one-step epimerization also occurred in some cases. For example, the site selective epimerization of fusidic acid methyl ester at the C-3 position catalyzed by Ru-2 occurred in 84% yield, while that of ouabain occurred at the C-1 position in 60% yield (Figure 7). While Shvo’s catalyst, which is widely used for dynamic kinetic resolutions,13 also catalyzed epimerization of fusidic acid methyl ester at 70 °C to give 84% of the C-3 epimer, it did not react with ouabain up to the decomposition temperature of 100 °C. The combination of (Ph5Cp)Ru(CO)Cl and KOtBu, which also has been used to epimerize simple alcohols,14,15 did not react with either of these molecules (Section 2.13).

2.7 Comparison to Alternative Methods for Alcohol Oxidation Applied to Polyol Natural Products

Although the catalytic oxidation of alcohols has been the subject of much research, few studies have targeted the oxidation of complex polyols. Instead, most studies focus on the reactions of unhindered benzylic and allylic alcohols, linear alkanols, or cyclohexanols.16–20 In the most recent and arguably most impressive example, a series of polyglycosides were oxidized by Waymouth’s catalyst in 30-60% yields at the terminal sugar.21 Prior to this study, the polyketide antibiotic mupirolcin methyl ester was oxidized by the combination of TEMPO, NaOCl, and KBr to give only 31% yield of a monoxygenation product,22 and the labdane diterpene forskolin was oxidized by stoichiometric CrO3/pyridine in 80% yield,24 whereas another labdane diterpene, andrographolide, was oxidized to the 3-ketone in only 5% yield under optimized conditions.23 These studies illustrate that the conditions developed for reaction of one structure do not translate to the oxidation of another structure of the same or different class, and some molecules have resisted selective oxidation under all known conditions.24–27

To assess in more detail the suitability of known procedures with classical stoichiometric reagents and modern catalysts for the selective oxidation of a broader range of polyols, we conducted reactions on several representative densely functionalized structures of Section 2.5: andrographolide, ouabain, mupirolcin methyl ester, and kirenol ((Section 2.16). Each of these four natural products gave mixtures of products with classic reagents, and no conditions gave a significant yield of the ketone product obtained from reaction with Ru-1 or Ru-2 as catalyst and acetone as hydrogen acceptor. Reactions we conducted with simple published substrates occurred as described with both classical reagents. However, the reactions under these conditions with the four selected natural products gave complex mixtures. Andrographolide reacted with Dess Martin’s Periodinane (DMP) to oxidize the primary alcohol over the secondary alcohols to generate a
**Figure 7. Reduction of complex ketones and one-step epimerization of complex alcohols.**

(a) Reduction of complex ketones with isopropanol enables site-selective epimerization within polyol natural products. (b) Site-selective epimerization of complex polyols is achieved in one step with Ru-2 as catalyst in the absence of acceptor.

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**mixture of 49% aldehyde, 35% keto-aldehyde, and only 3% of the ketone.** N-Bromosuccinimide in acetone, tested because of the selective oxidation of simple bile acids,

Swern oxidation converted 65% of andrographolide to an unknown structure lacking a ketone or aldehyde, and Oppenhauer conditions with trifluoroacetone catalyzed by AlEt₂OEt gave little to
no conversion. The oxidation of mupirocin, ouabain methyl ester and kirenol also gave mixtures of products with these oxidation systems. The reaction of mupirocin with DMP gave unselective oxidation to a complex mixture of products (at least five), the $^1$H NMR spectrum of which contained multiple new olefin resonances signaling elimination processes. Reaction of the same substrate with AlEt$_2$OEt/trifluoroacetone or the Swern reagent formed a mixture of many products with low selectivity. Oxidation of ouabain with DMP formed one or more aldehyde products in 45% yield from oxidation of the primary alcohol, along with multiple additional products. The Swern reagent and AlEt$_2$OEt/trifluoroacetone gave full, unselective conversion to multiple products bearing olefins, as determined by $^1$H NMR spectroscopy. The reaction of kirenol with DMP gave decomposition to a mixture of several products, two of which contain aldehyde functionality, whereas reaction with AlEt$_2$OEt/trifluoroacetone gave full decomposition to multiple products bearing new olefins.

The ability of modern oxidation and alternative transfer dehydrogenation catalysts to oxidize andrographolide, mupirocin methyl ester, and ouabain selectively was also assessed. The reaction of andrographolide with benzoquinone and catalytic [Pd(neocuproine)(OAc)]$_2$[OTf]$_2$, which was reported to oxidize secondary over primary alcohols in 1,2 and 1,3 diols units, gave products that were similar to those of the reaction of DMP (65% aldehyde, 30% keto-aldehyde, no 3-ketone). The attempted oxidation of the same substrate with Ru-MACHO and KOH led to low conversion. Shvo’s dimer oxidized andrographolide under optimized conditions to 43% 3-ketone along with three other major products in 32%, 19%, and 4% yield derived from oxidation of the primary alcohol with a concomitant side reaction, loss of the hydroxy-enoate functionality, and loss of the 1,1 disubstituted olefin, respectively. Ru-MACHO and KOH led to decomposition of mupirocin methyl ester. Oxidation of mupirocin methyl ester by Shvo’s dimer occurred concomitantly with multiple side reactions, such that little product from selective oxidation of the alcohol to the ketone occurred. Waymouth’s catalyst gave low conversion of ouabain to multiple products, while the combination of Ru-MACHO and KOH led to decomposition of ouabain without oxidation. Shvo’s dimer led to no conversion of ouabain, up to temperatures at which auto-decomposition occurs.

2.8 Mechanistic Analysis of Kinetic vs Thermodynamic Origins of Selectivity

The mechanism of ruthenium-catalyzed transfer dehydrogenations is generally thought to begin by displacement of one of the labile ligands with alcohol and generation of a ruthenium alkoxide. When a tertiary amine is included in the reactions, the generation of alkoxide could occur by deprotonation of the bound alcohol by amine. In TFE solvent, no base is needed for alcohol oxidation to proceed (Figure 3B), and generation of the alkoxide could occur by elimination of HOTf stabilized by a substrate alcohol. H-Hydrogen elimination from the alkoxide would then generate the ketone and a ruthenium hydride. The resulting hydride would insert acetone to form an isopropoxide complex that undergoes protonolysis to initiate a second cycle.

To examine whether the observed selectivity for oxidation of secondary over primary alcohols results from a kinetic selectivity or whether it results from a thermodynamic selectivity due to reversible oxidation of the primary alcohol and irreversible oxidation of the secondary alcohol we conducted a deuterium labeling study (Section 2.17). The dehydrogenation of andrographolide, estriol, ouabain, and fusidic acid methyl ester were conducted with 5 equivalents of isopropanol-
$d_8$ added as a source of deuteride. No deuterium was incorporated into any positions of the product molecules. An analogous experiment was conducted with a combination of cyclohexanol and 2-methyl-pentanol in acetone in the presence of 5 equivalents of isopropanol-$d_8$ (Section 2.17). Under these conditions, no oxidation of the primary alcohol was observed and no deuterium was incorporated into the position $\alpha$ to oxygen in the primary alcohol that would signal reversible oxidation. Only oxidation of cyclohexanol was observed, and just 1-2% deuterium was incorporated into the position $\alpha$ to oxygen in the unreacted cyclohexanol. This results indicate that the presence of excess acceptor leads to kinetic selectivity for the oxidation of alcohols in both complex and simple substrates with the catalyst we report, in these cases a specific hindered secondary alcohol over a primary alcohol.

2.9 General Procedure for Alcohol Oxidation

(Under N$_2$) Equimolar Ru-2 and NMM were combined in acetone or TFE to form a solution. This solution was then added to a solution of alcohol starting material in acetone or a mixture of acetone and TFE in a vial, along with a magnetic stir bar if the starting alcohol is not fully dissolved at room temperature. The vial was then sealed and heated at 65 °C for several hours, with stirring if applicable. The reaction was then cooled to room temperature and evaporated to dryness. The residue was then purified by recrystallization or column chromatography on silica gel.

2.10 Conclusion and Future Directions

The selective oxidation of one secondary alcohol among many can be used strategically in target-oriented synthesis to alleviate the need for protective groups to dictate site selectivity. The present catalyst solves this challenge and provides a platform for further advancements in hydrogen transfer reactions based on X-H bond functionalization. Alcohols are the most common functional group in natural products because of the selective hydroxylation of C-H bonds by P450 enzymes. Amino groups are less common because of the lack of enzymes for direct amination. Yet, nitrogen-based functionality can impart favorable properties for biological activity. We have shown that catalytic reactions on polyol natural products create new complex architectures that could create new leads for medicine, molecular biology, and agroscience. The ability to precisely epimerize the site of an OH group, to convert an OH group to an NH group, or to incorporate nitrogen into the ring system or chain provides the ability to combine Nature’s spectacular synthetic prowess to create complex architectures with modern catalytic, synthetic chemistry as a means to create unnatural products with enhanced physical properties and function over those provided solely from biosynthetic pathways.

2.11 General Experimental Details

Equipment and Methods

All air-sensitive manipulations were conducted in a nitrogen-filled glovebox or by standard Schlenk techniques under nitrogen. All glassware were heated in an oven and cooled under an inert atmosphere prior to use. NMR spectra were acquired on 400 MHz, 500 MHz, 600 MHz, 700 MHz, or 900 MHz Bruker instruments operated by the College of Chemistry or QB3/Department of Molecular Biology at the University of California, Berkeley. NMR spectra were processed with MestReNova 9.0 (Mestrelab Research SL). Chemical shifts are reported in ppm and referenced to
residual solvent peaks (CHCl₃ in CDCl₃: 7.26 ppm for ¹H and 77.36 ppm for ¹³C). Coupling constants are reported in hertz. GC analyses were obtained on an Agilent 6890 GC equipped with an HP-5 column (25 m x 0.20 mm ID x 0.33 m film) and an FID detector. GC yields were calculated using dodecane as the internal standard. High resolution mass spectra were obtained at the QB3/Chemistry Mass Spectrometry Facility operated by the Department of Molecular Biology and the College of Chemistry, University of California, Berkeley. Elemental analyses were obtained via the Microanalytical Facility operated by the College of Chemistry, University of California, Berkeley. X-ray crystal structures were obtained via X-ray Crystallography Facility operated by the College of Chemistry, University of California, Berkeley.

Chemicals

Substrates were purchased from Sigma-Aldrich and used without further purification unless mentioned otherwise. Ruthenium trichloride hydrate was purchased from Strem Chemicals. Dry acetone and trifluoroethanol were purchased from Acros Organics, Inc. Deacetylbaccatin III, aucubin, kirenol, fusidic acid, ivermectin, and genipin were purchased from AvaChem Scientific, Inc. Brefeldin A, forskolin, and phorbol were purchased from LC Laboratories. Digoxigenin was purchased from Santa Cruz Biotechnology, Inc. Lagochiline was purchased from Cayman Chemical. Andrographolide, estriol, ivermectin, and d-glucal were purchased from AK Scientific. Mupirocin methyl ester prepared following the published procedure.² [Pt(dpbb)(OH)][BF₄]² (Pt-1) was prepared following published procedures.³⁰,³¹ Cp*IrCl(N-(4-dimethylaminophenyl)-2-pyridylcarboxamide) (Ir-1) was prepared following published procedures.¹¹,³² Waymouth’s catalyst [Pd(neocuproine)(OAc)][OTf]₂, was prepared according to literature procedures.³³,³⁴

2.12 Procedures for the alcohol oxidation and ketone reduction reactions reported Figure 3

Oxidation of secondary alcohols:

With acetone acceptor: To generate a stock solution of the active catalyst, equimolar [Ru] precursor and NMM were combined in TFE:acetone solvent. To make a 0.01 M stock solution of active catalyst, Ru-2 (7.5 mg, 0.0050 mmol) and NMM (1.1 μL, 0.010 mmol) were combined in 1:1 TFE:acetone (1 mL). To conduct a model alcohol oxidation, dicyclohexylcarbinol (7.9 mg, 0.040 mmol), dodecane internal standard (4.5 μL, 0.020 mmol, 0.5 equiv), and 1:1 TFE:acetone (192 μL) were combined in a one-dram vial. Then, an aliquot of active catalyst stock solution (0.01 M, 9 μL, 0.2% [Ru], NMM) was added, and the vial was capped. The mixture was allowed to stand at room temperature for 3 hours and then exposed to air to halt the reaction. GC analysis showed 99% conversion of the starting alcohol to dicyclohexylketone.

With stoichiometric acceptors: To generate a stock solution of the active catalyst, equimolar [Ru] precursor and NMM were combined in TFE solvent. To make a 0.01 M stock solution of active catalyst, Ru-2 (7.5 mg, 0.0050 mmol) and NMM (1.1 μL, 0.010 mmol) TFE (1 mL). To conduct a model alcohol oxidation, dicyclohexylcarbinol (19 mg, 0.10 mmol), 3,5-dimethylanisole internal standard (4.5 μL, 0.020 mmol, 0.5 equiv), acceptor (trifluoroacetophenone: 16 μL, 0.11 mmol, 1.1 equiv or 1,4-dicyclohexylketone: 12 mg, 0.11 mmol, 1.1 equiv) and TFE (40 μL) were combined in a one-dram vial. Then, an aliquot of active catalyst stock solution (20 μL, 0.01 M [Ru], 0.1% Ru-2, 0.2% NMM) was added, and the vial was capped. The mixture was allowed to stand at room temperature for 4 hours and then exposed to air to halt the reaction. GC analysis showed 99.5% conversion of the starting alcohol to dicyclohexylketone.
Relative rates for oxidation of primary versus secondary alcohols:

For reactions involving a single alcohol undergoing oxidation, 0.1 mmol alcohol and 0.05 mmol dodecane internal standard were combined in acetone to form a 0.2 M solution upon addition of an acetone solution of equimolar Ru-2 and NMM (0.001 mmol [Ru], 0.001 mmol NMM). For reactions involving two alcohols undergoing oxidation competitively in the same vessel, 0.05 mmol of each alcohol was used, while the rest of the procedure was the same as that for reactions of the single alcohols, except as noted Figure 3. The amount of remaining substrate alcohol and product aldehyde or ketone was determined via GCMS, by comparison to the dodecane internal standard.

Reduction of hindered ketone:

To generate a stock solution of the active catalyst, equimolar [Ru] precursor and NMM were combined in TFE. To make a 0.01 M stock solution of active catalyst, Ru-2 (7.5 mg, 0.0050 mmol) and NMM (1.1 μL, 0.010 mmol) were combined in TFE (1 mL). Pinocarone (13 μL, 0.1 mmol) and 3,5-dimethylanisole internal standard (14 μL, 0.1 mmol) were dissolved in 1:1 TFE:isopropanol (380 μL) and then an aliquot of catalyst solution (20 μL, 0.01M [Ru], 0.2% Ru-2, 0.4% NMM) in TFE was added. The reaction was then heated at 45 °C for 3 hours, and then allowed to cool to room temperature. GC analysis showed 99% conversion to of the starting ketone to methy-tert-butyl carbinol.

2.13 Procedure for a model hindered ketone reductive amination reaction with Ir-1:

Hindered ketone amination:

R = H: Diisopropylketone (4.3 μL, 0.030 mmol), ammonium formate (3.8 mg, 0.060 mmol, 2 equiv), formic acid (1.1 μL, 0.030 mmol, 1 equiv), Ir-1 (0.4 mg, 0.0006 mmol, 2%), and dodecane internal standard (3.4 μL, 0.015 mmol, 0.5 equiv) were weighed into a vial, and a magnetic stir bar was added. MeOH (150 μL) was then added, the vial was capped, and the reaction was heated at 65 °C for 15 hours.

For R = (CH₂)₅CH₃: Diisopropylketone (4.3 μL, 0.03 mmol), n-hexylamine (5.1 μL, 0.060 mmol, 1.3 equiv), formic acid (2.8 μL, 0.075 mmol, 2.5 equiv), and Ir-1 (0.4 mg, 0.0006 mmol, 2%), and dodecane internal standard (3.4 μL, 0.015 mmol, 0.5 equiv) were weighed into a vial, and a magnetic stir bar was added. TFE (150 μL) was then added, the vial was capped, and the reaction was heated at 65 °C for 15 hours.

After allowing the reactions to cool to room temperature, ethyl acetate, KOH solution (1M), and brine were added. The organic and aqueous phases were allowed to separate. GC analysis of the organic phase showed an 85% yield for R = H and 80% yield for R = (CH₂)₅CH₃.
2.14 Model catalytic oxidation comparisons

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Catalyst</th>
<th>Substrate</th>
<th>Solvent</th>
<th>Temperature, Time</th>
<th>Ketone Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2% [Ru(COD)Cl] 1 KOtBu</td>
<td>cyclohexanol</td>
<td>acetone</td>
<td>30°C, 4 h</td>
<td>72%</td>
</tr>
<tr>
<td>2</td>
<td>2% [Ru(COD)Cl] 1 KOtBu</td>
<td>trans-2-methyl-cyclohexanol</td>
<td>acetone</td>
<td>30°C, 4 h</td>
<td>25%</td>
</tr>
<tr>
<td>3</td>
<td>2% [Ru(COD)Cl] 1 KOtBu</td>
<td>cyclohexanol</td>
<td>acetone</td>
<td>30°C, 4 h</td>
<td>13%</td>
</tr>
<tr>
<td>4</td>
<td>4% Ru(p-cymene)(Ts-DPEN)Cl, 1 KOtBu</td>
<td>diisopropylcarbinol</td>
<td>acetone</td>
<td>30°C, 4 h</td>
<td>0%</td>
</tr>
<tr>
<td>5</td>
<td>4% Ru(p-cymene)(Ts-DPEN)Cl, 1 KOtBu</td>
<td>trans-2-methyl-cyclohexanol</td>
<td>acetone</td>
<td>30°C, 4 h</td>
<td>none</td>
</tr>
<tr>
<td>6</td>
<td>4% Ru(p-cymene)(Ts-DPEN)Cl, 1 KOtBu</td>
<td>diisopropylcarbinol</td>
<td>acetone</td>
<td>30°C, 4 h</td>
<td>18%</td>
</tr>
<tr>
<td>7</td>
<td>4% Ru(p-cymene)(DM-SEGphos)(DPEN)Cl, 1 KOtBu</td>
<td>cyclohexanol</td>
<td>acetone</td>
<td>30°C, 4 h</td>
<td>40%</td>
</tr>
<tr>
<td>8</td>
<td>4% Ru(p-cymene)(DM-SEGphos)(DPEN)Cl, 1 KOtBu</td>
<td>trans-2-methyl-cyclohexanol</td>
<td>acetone</td>
<td>30°C, 4 h</td>
<td>18%</td>
</tr>
<tr>
<td>9</td>
<td>5% Ru(COD)Cl, 5% KOtBu</td>
<td>diisopropylcarbinol</td>
<td>acetone</td>
<td>30°C, 4 h</td>
<td>none</td>
</tr>
<tr>
<td>10</td>
<td>5% Ru(COD)Cl, 5% L1, 1 KOtBu</td>
<td>benzyl alcohol</td>
<td>acetone/toluene</td>
<td>25°C, 16 h</td>
<td>99%</td>
</tr>
<tr>
<td>11</td>
<td>5% Ru(COD)Cl, 5% L1, 1 KOtBu</td>
<td>butanol</td>
<td>acetone/toluene</td>
<td>25°C, 16 h</td>
<td>77%</td>
</tr>
<tr>
<td>12</td>
<td>5% Ru(COD)Cl, 5% L1, 1 KOtBu</td>
<td>3-pentanol</td>
<td>acetone/toluene</td>
<td>25°C, 16 h</td>
<td>99%</td>
</tr>
<tr>
<td>13</td>
<td>5% Ru(COD)Cl, 5% L1, 1 KOtBu</td>
<td>cyclohexanol</td>
<td>acetone/toluene</td>
<td>25°C, 16 h</td>
<td>91%</td>
</tr>
<tr>
<td>14</td>
<td>5% Ru(COD)Cl, 5% L1, 1 KOtBu</td>
<td>diisopropylcarbinol</td>
<td>acetone/toluene</td>
<td>25°C, 16 h</td>
<td>66%</td>
</tr>
<tr>
<td>15</td>
<td>5% Ru(COD)Cl, 5% L1, 1 KOtBu</td>
<td>2-methyl-cyclohexanol</td>
<td>acetone/toluene</td>
<td>25°C, 16 h</td>
<td>28%</td>
</tr>
<tr>
<td>16</td>
<td>2.5 % Ru(p-cymene)(Ts-DPEN)Cl, 2.75% KOH</td>
<td>diisopropylcarbinol</td>
<td>acetone</td>
<td>30°C, 8 h</td>
<td>23%</td>
</tr>
<tr>
<td>17</td>
<td>2.5 % Ru(p-cymene)(Ts-DPEN)Cl, 2.75% KOH</td>
<td>trans-2-methyl-cyclohexanol</td>
<td>acetone</td>
<td>50°C, 8 h</td>
<td>28%</td>
</tr>
<tr>
<td>18</td>
<td>2.5 % Ru(p-cymene)(Ts-DPEN)Cl, 2.75% KOH</td>
<td>trans-2-methyl-cyclohexanol</td>
<td>acetone</td>
<td>70°C, 8 h</td>
<td>32%</td>
</tr>
<tr>
<td>19</td>
<td>2.5 % Ru(p-cymene)(Ts-DPEN)Cl, 2.75% KOH</td>
<td>cyclohexanol</td>
<td>acetone</td>
<td>80°C, 8 h</td>
<td>67%</td>
</tr>
<tr>
<td>20</td>
<td>2.5 % Ru(p-cymene)(Ts-DPEN)Cl, 2.75% KOH</td>
<td>diisobutylcarbinol</td>
<td>acetone</td>
<td>80°C, 4 h</td>
<td>40%</td>
</tr>
<tr>
<td>21</td>
<td>2.5 % Ru(p-cymene)(Ts-DPEN)Cl, 2.75% KOH</td>
<td>diisopropylcarbinol</td>
<td>acetone</td>
<td>80°C, 4 h</td>
<td>33%</td>
</tr>
<tr>
<td>22</td>
<td>2.5 % Ru(p-cymene)(Ts-DPEN)Cl, 2.75% KOH</td>
<td>diisopropylcarbinol</td>
<td>acetone</td>
<td>80°C, 4 h</td>
<td>11%</td>
</tr>
<tr>
<td>23</td>
<td>5 % Ru(p-cymene)(Ts-DPEN)Cl, 5.5% KOH</td>
<td>acetone</td>
<td>50°C, 4 h</td>
<td>trace</td>
<td></td>
</tr>
<tr>
<td>24</td>
<td>5 % Ru(p-cymene)(Ts-DPEN)Cl, 5.5% KOH</td>
<td>acetone</td>
<td>80°C, 16 h</td>
<td>none</td>
<td></td>
</tr>
<tr>
<td>25</td>
<td>5 % Ru(p-cymene)(Ts-DPEN)Cl, 5.5% KOH</td>
<td>acetone</td>
<td>80°C, 16 h</td>
<td>none</td>
<td></td>
</tr>
<tr>
<td>26</td>
<td>2.5 % Ru(p-cymene)Cl</td>
<td>trans-2-methyl-cyclohexanol</td>
<td>acetone</td>
<td>80°C, 4 h</td>
<td>78%</td>
</tr>
<tr>
<td>27</td>
<td>2.5 % Ru(p-cymene)Cl</td>
<td>trans-2-methyl-cyclohexanol</td>
<td>acetone</td>
<td>80°C, 4 h</td>
<td>95%</td>
</tr>
<tr>
<td>28</td>
<td>2.5 % Ru(p-cymene)Cl</td>
<td>diisopropylcarbinol</td>
<td>acetone</td>
<td>80°C, 4 h</td>
<td>39%</td>
</tr>
<tr>
<td>29</td>
<td>4% Ru-MACHO, 4% KOH</td>
<td>cyclohexanol</td>
<td>acetone/toluene</td>
<td>50°C, 5 h</td>
<td>75%</td>
</tr>
<tr>
<td>30</td>
<td>4% Ru-MACHO, 4% KOH</td>
<td>trans-2-methyl-cyclohexanol</td>
<td>acetone/toluene</td>
<td>50°C, 5 h</td>
<td>86%</td>
</tr>
<tr>
<td>31</td>
<td>4% Ru-MACHO, 4% KOH</td>
<td>cyclohexanol</td>
<td>acetone/toluene</td>
<td>80°C, 5 h</td>
<td>11%</td>
</tr>
<tr>
<td>32</td>
<td>4% Ru-MACHO, 4% KOH</td>
<td>trans-2-methyl-cyclohexanol</td>
<td>acetone/toluene</td>
<td>80°C, 5 h</td>
<td>8%</td>
</tr>
<tr>
<td>33</td>
<td>4% Ru-MACHO, 4% KOH</td>
<td>diisopropylcarbinol</td>
<td>acetone/toluene</td>
<td>80°C, 5 h</td>
<td>65%</td>
</tr>
<tr>
<td>34</td>
<td>4% Ru-MACHO, 4% KOH</td>
<td>diisopropylcarbinol</td>
<td>acetone/toluene</td>
<td>80°C, 5 h</td>
<td>6%</td>
</tr>
<tr>
<td>35</td>
<td>4% Ru(PPh)Cl, 8% KOH</td>
<td>cyclohexanol</td>
<td>acetone/toluene</td>
<td>50°C, 5 h</td>
<td>8%</td>
</tr>
<tr>
<td>36</td>
<td>4% Ru(PPh)Cl, 8% KOH</td>
<td>trans-2-methyl-cyclohexanol</td>
<td>acetone/toluene</td>
<td>50°C, 5 h</td>
<td>4%</td>
</tr>
<tr>
<td>37</td>
<td>4% Ru(PPh)Cl, 8% KOH</td>
<td>diisopropylcarbinol</td>
<td>acetone/toluene</td>
<td>50°C, 5 h</td>
<td>none</td>
</tr>
<tr>
<td>38</td>
<td>4% Ru(PPh)Cl, 8% KOH</td>
<td>cyclohexanol</td>
<td>acetone/toluene</td>
<td>80°C, 5 h</td>
<td>none</td>
</tr>
<tr>
<td>39</td>
<td>4% Ru(PPh)Cl, 8% KOH</td>
<td>trans-2-methyl-cyclohexanol</td>
<td>acetone/toluene</td>
<td>80°C, 5 h</td>
<td>0%</td>
</tr>
<tr>
<td>40</td>
<td>4% Ru(PPh)Cl, 8% KOH</td>
<td>diisopropylcarbinol</td>
<td>acetone/toluene</td>
<td>80°C, 5 h</td>
<td>none</td>
</tr>
<tr>
<td>41</td>
<td>2% Shvo's catalyst</td>
<td>cyclohexanol</td>
<td>acetone/toluene</td>
<td>50°C, 5 h</td>
<td>74%</td>
</tr>
<tr>
<td>42</td>
<td>2% Shvo's catalyst</td>
<td>trans-2-methyl-cyclohexanol</td>
<td>acetone/toluene</td>
<td>50°C, 5 h</td>
<td>70%</td>
</tr>
<tr>
<td>43</td>
<td>2% Shvo's catalyst</td>
<td>cyclohexanol</td>
<td>acetone/toluene</td>
<td>80°C, 5 h</td>
<td>30%</td>
</tr>
<tr>
<td>44</td>
<td>2% Shvo's catalyst</td>
<td>trans-2-methyl-cyclohexanol</td>
<td>acetone/toluene</td>
<td>80°C, 5 h</td>
<td>78%</td>
</tr>
<tr>
<td>45</td>
<td>2% Shvo's catalyst</td>
<td>diisopropylcarbinol</td>
<td>acetone/toluene</td>
<td>80°C, 5 h</td>
<td>86%</td>
</tr>
<tr>
<td>46</td>
<td>2% Shvo's catalyst</td>
<td>diisopropylcarbinol</td>
<td>acetone/toluene</td>
<td>80°C, 5 h</td>
<td>95%</td>
</tr>
</tbody>
</table>
Notes:
1) The use of strong bases such as KOH and KO\textsubscript{Bu} in acetone solvent invariably leads to aldol side products derived from the acetone.
2) The reactions were run at 0.2M concentration.
3) The catalysts were preformed.
4) Racemic trans-2-methyl-cyclohexanol was employed along with racemic mixtures of chiral catalysts.

2.15 Isolation of [Ru]-alkoxide

Deacetylbaaccatin III (11 mg, 0.02 mmol) was combined with acetone (0.3 mL) and a magnetic stir bar in a one dram vial. Then a solution of Ru-2 (15 mg, 0.01 mmol) and triethylamine (4.2 μL, 0.03 mmol, 1.5 equiv) in acetone (0.3 mL) was added and the mixture was stirred to form a solution. The vial was capped and heated at 50 °C for 30 minutes, and turned to a deep purple color. The reaction was allowed to cool to room temperature and then diluted with 1 mL of diethyl ether. The solution was then filtered, layered with diethyl ether, and placed at -30 °C. Large deep-purple crystals formed over several weeks. X-ray crystallography revealed the purple complex to be [Ru(PEt\textsubscript{3})\textsubscript{3}(DAB III alkoxide)][OTf].
2.16 Procedures for Complex Epimerization Reactions

Fusidic acid methyl ester epimerization:

*With Ru-2 (Figure 7B):* See procedure for this reaction and isolated yield in Section 6. $^1$H NMR Yield = 84% epi-fusidic acid methyl ester.

*With Shvo’s catalyst:* Fusidic acid methyl ester (20 mg, 0.04 mmol) was combined with Shvo’s catalyst (1.7 mg, 1.5 μmol, 4 mol %), toluene (150 μL), and a magnetic stir bar in a 4 mL vial, and the resulting mixture was stirred to form a solution. The vial was capped, and the reaction was heated at 70 °C for 3 hours with stirring. The reaction was then allowed to cool to RT, and all of the volatile materials were evaporated by rotary evaporation. The crude product was NMR spectroscopy with chloroform-$d$. $^1$H NMR result (70 °C): 84% epi-fusidic acid methyl ester obtained.

*With (Ph$_5$Cp)Ru(CO)$_2$Cl/KO'Bu:* Fusidic acid methyl ester (20 mg, 0.04 mmol) was combined with THF (50 μL) and a magnetic stir bar in a 4 mL vial, and the resulting mixture was stirred to form a solution. Then a solution of (Ph$_5$Cp)Ru(CO)$_2$Cl (2 mg, 3.2 μmol, 8.0 mol %) and KO'Bu (0.35 mg, 3.1 μmol, 7.8 mol %) in THF (50 μL) was added as an aliquot from a stock solution. The vial was capped, and the reaction was heated at 70 °C or at 70 °C for 3 hours with stirring. The reaction was then allowed to cool to RT, and all of the volatile materials were evaporated by rotary evaporation. The crude product was NMR spectroscopy with chloroform-$d$. $^1$H NMR result (50 °C or 70 °C): No conversion.

Ouabain epimerization:

*With Ru-2 (Figure 7B):* Ouabain octahydrate (30 mg, 0.06 mmol) was combined with TFE (60 μL) and a magnetic stir bar in a 4 mL vial, and the resulting mixture was stirred to form a solution. Then a solution of Ru-2 (5 mg, 6.6 μmol, 8.0 mol %) and NMM (0.75 μL, 13 μmol, 16 mol %) in TFE (40 μL) was added from a stock solution. The vial was capped, and the reaction was heated at 70 °C for 11 hours with stirring. The reaction was then allowed to cool to RT, and all of the volatile materials were evaporated by rotary evaporation. The crude product was analyzed NMR spectroscopy in methanol-$d_4$. $^1$H NMR Yield = 60% epi-ouabain.

*With Shvo’s catalyst:* Ouabain octahydrate (15 mg, 0.03 mmol) was combined with Shvo’s catalyst (1.8 mg, 1.7 μmol, 8 mol %), THF (100 μL) and a magnetic stir bar in a 4 mL vial, and the resulting mixture was stirred to form a solution. The vial was capped, and the reaction was heated at 70 °C or at 100 °C for 11 hours with stirring. The reaction was then allowed to cool to RT, and all of the volatile materials were evaporated by rotary evaporation. The crude product was NMR spectroscopy in methanol-$d_4$. $^1$H NMR result (70 °C or 100 °C): No conversion.

*With (Ph$_5$Cp)Ru(CO)$_2$Cl/KO'Bu:* Ouabain octahydrate (15 mg, 0.03 mmol) was combined with THF (50 μL) and a magnetic stir bar in a 4 mL vial, and the resulting mixture was stirred to form a solution. Then a solution of (Ph$_5$Cp)Ru(CO)$_2$Cl (1.05 mg, 1.7 μmol, 8.0 mol %) and KO'Bu (0.18 mg, 1.6 μmol, 7.8 mol %) in THF (50 μL) was added as an aliquot from a stock solution. The vial was capped, and the reaction was heated at 50 °C or at 70 °C for 11 hours with stirring. The reaction was then allowed to cool to RT, and all of the volatile materials were evaporated by rotary evaporation. The crude product was NMR spectroscopy in methanol-$d_4$. $^1$H NMR result (50 °C or 70 °C): No conversion.
### 2.17 Complex Molecule Oxidation Comparisons

**Table 1: Classical Oxidation Reactions:**

<table>
<thead>
<tr>
<th>Molecule</th>
<th>Oxidant</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Andrographolide</td>
<td>DMP(^b)</td>
<td>49% aldehyde, 35% keto-aldehyde, 8% 3-ketone product.</td>
</tr>
<tr>
<td>Andrographolide</td>
<td>Waymouth’s catalyst(^c)</td>
<td>65% aldehyde, 30% keto-aldehyde, no 3-ketone.</td>
</tr>
<tr>
<td>Andrographolide</td>
<td>NBS/Acetone(^d)</td>
<td>Complex mixture of many products.</td>
</tr>
<tr>
<td>Andrographolide</td>
<td>Jones Reagent(^23)</td>
<td>1.5% aldehyde, 2% keto-aldehyde, 5% 3-ketone.</td>
</tr>
<tr>
<td>Andrographolide</td>
<td>Swern Reagent(^e)</td>
<td>65% conversion to an unknown. No 3-ketone or aldehyde product.</td>
</tr>
<tr>
<td>Andrographolide</td>
<td>AlEt₂OEt/trifluoroacetone(^f)</td>
<td>No conversion to 3-ketone or aldehyde.</td>
</tr>
<tr>
<td>Andrographolide</td>
<td>Ru-MACHO/KOH(^g)</td>
<td>Low conversion of starting material. 43% 3-ketone, 32% of aldehyde with an additional side reaction generating a new olefin, 19% of a product that underwent loss of the hydroxy-enoate functionality in addition to alcohol oxidation, and 4% of a product that has lost the 1,1 disubstituted olefin.</td>
</tr>
<tr>
<td>Andrographolide</td>
<td>Shvo’s catalyst(^h)</td>
<td>No conversion to 3-ketone or aldehyde.</td>
</tr>
<tr>
<td>Mupirocin M.E.</td>
<td>DMP(^i)</td>
<td>Complex mixture of many (5-6) products, no 13-ketone.</td>
</tr>
<tr>
<td>Mupirocin M.E.</td>
<td>TEMPO/NaOCl/KBr(^22)</td>
<td>11%, 11%, and 31% of the 7,13-diketone, 7-ketone, and 13-ketone</td>
</tr>
<tr>
<td>Mupirocin M.E.</td>
<td>Swern Reagent(^i)</td>
<td>Mixture of many products. No 13-ketone.</td>
</tr>
<tr>
<td>Mupirocin M.E.</td>
<td>AlEt₂OEt/trifluoroacetone(^k)</td>
<td>Mixture of many products. No 13-ketone.</td>
</tr>
<tr>
<td>Mupirocin M.E.</td>
<td>Ru-MACHO/KOH(^l)</td>
<td>90% conversion. Decomposition to 4 or more products. No 13-ketone.</td>
</tr>
<tr>
<td>Mupirocin M.E.</td>
<td>Shvo’s catalyst(^m)</td>
<td>94% conversion into a mixture of 2 products which result from 13-oxidation in addition to undiagnosed side reactions. 13-keto-mupirocin methyl ester was not obtained. The remaining 6% was starting material (2%) or converted into another compound without 13-oxidation.</td>
</tr>
</tbody>
</table>
Ouabain DMP\textsuperscript{n} 73\% conversion. Multiple products, no 1-ketone.

Ouabain Waymouth’s catalyst\textsuperscript{o} Low conversion to multiple products. No 1-ketone.

Ouabain Swern Reagent\textsuperscript{p} Full conversion to multiple products. New olefin peaks are present. No 1-ketone or aldehyde product.

Ouabain AlEt\textsubscript{2}OEt/trifluoroacetone\textsuperscript{q} Full conversion to multiple products. New olefin peaks are present. No 1-ketone or aldehyde product.

Ouabain Ru-MACHO/KOH\textsuperscript{r} 45\% conversion to a modified structure without oxidation. Likely an isomer of ouabain.

Ouabain Shvo’s catalyst\textsuperscript{s} Low conversion of starting material. No oxidation.

Kirenol DMP\textsuperscript{t} 75\% conversion to multiple products, no 15-ketone.

Kirenol AlEt\textsubscript{2}OEt/trifluoroacetone\textsuperscript{u} Full conversion to mixture of several products, no 15-ketone.

D-glucal AlEt\textsubscript{2}OEt/trifluoroacetone\textsuperscript{v} No conversion to vinylogous ester

**Conditions and Procedures for classical alcohol oxidation reactions.** (a) Standard procedures from previous reports were used (DMP, Waymouth’s catalyst, NBS/acetone, Swern reagent, AlEt\textsubscript{2}OEt/trifluoroacetone\textsuperscript{37}). In several cases, the oxidation procedures were adapted to the use of THF, dioxane, or CH\textsubscript{3}CN solvent to dissolve the substrate. For all of the reactions applied to complex substrates, the literature results were first reproduced in the original solvent or the substitute solvent. The reactions of complex molecules were monitored by thin layer chromatography. After completion, the reactions were analyzed by NMR spectroscopy of the crude reaction. Trimethoxybenzene (0.5 equiv) was added after the reaction prior to the workup as an internal standard. (b) CH\textsubscript{3}CN, 1.25 equiv DMP, RT, 1 h (c) 9:1 CH\textsubscript{3}CN:H\textsubscript{2}O, 2.5\% [Pd(neocuproine)(OAc)]\textsubscript{2}[OTf]\textsubscript{2}, 1 equiv benzoquinone, 50 °C, 2 h (d) 2.5:1 acetone:H\textsubscript{2}O, 1.1 NBS, 40 °C (e) THF, 1.5 equiv DMSO/(COCl)\textsubscript{2} (-78 °C, 20 min), then NEt\textsubscript{3} (-78 °C to RT) (f) dioxane, 0.3 equiv AlEt\textsubscript{2}OEt, 5 equiv trifluoroacetone, RT, 21 h (g) Me\textsubscript{2}CO, 4\% Ru-MACHO, 4\% KOH ([Ru] premixed at RT for 15 min with KOH), 80 °C, 4 h (h) Me\textsubscript{2}CO, 4\% Shvo dimer (8\% [Ru]), 65 °C, 3.5 h (i) DCM, 1.25 equiv DMP, 0 °C to RT, 3 h (j) DCM, 1.5 equiv DMSO/(COCl)\textsubscript{2} (-78 °C, 20 min), then NEt\textsubscript{3} (-78 °C to RT) (k) DCM, 0.3 equiv AlEt\textsubscript{2}OEt, 5 equiv trifluoroacetone, RT, 24 h (l) 1:1 Me\textsubscript{2}CO:toluene, 4\% Ru-MACHO, 4\% KOH ([Ru] premixed at RT for 15 min with KOH), 65 °C, 4 h (m) 1:1 Me\textsubscript{2}CO:toluene, 2\% Shvo dimer (4\% [Ru]), 65 °C, 4 h (n) THF, 1.25 equiv DMP, 0 °C to RT, 3 h (o) 9:1 CH\textsubscript{3}CN:H\textsubscript{2}O, 2.5\% [Pd(neocuproine)(OAc)]\textsubscript{2}[OTf]\textsubscript{2}, 1 equiv benzoquinone, 50 °C, 5 h (p) THF, 1.5 equiv DMSO/(COCl)\textsubscript{2} (-78 °C, 20 min), then NEt\textsubscript{3} (-78 °C to RT) (q) dioxane, 0.3 equiv AlEt\textsubscript{2}OEt, 5 equiv trifluoroacetone, RT, 21 h (r) Me\textsubscript{2}CO, 4\% Ru-MACHO, 4\% KOH ([Ru] premixed at RT for 15 min with KOH), 80 °C, 3 h (s) Me\textsubscript{2}CO, 2%
Shvo dimer (4% [Ru]), 80 °C, 3 h (t) THF, 1.25 equiv DMP, RT, 2 h (u) dioxane, 0.3 equiv AlEt2OEt, 5 equiv trifluoroacetone, RT, 30 h (v) dioxane, 0.3 equiv AlEt2OEt, 5 equiv trifluoroacetone, RT, 21 h.

2.18 Deuterium Incorporation Tests

Complex substrates (main text): To make a 0.01 M stock solution of active catalyst, **Ru-2** (7.5 mg, 0.0050 mmol) and NMM (1.1 μL, 0.010 mmol) were combined in acetone-$d_6$ (1 mL). Andrographolide (5.0 mg, 0.014 mmol) was combined with acetone-$d_6$ (250 μL), isopropanol-$d_8$ (5.5 μL, 0.072 mmol, 5 equiv), and a magnetic stir bar in a 1 dram vial. Then catalyst solution (5.7 μL, 0.1 M [Ru]) was added, the vial was capped, and the reaction was heated at 65 °C for 3 hours with stirring and then cooled to RT. The solvent was fully evaporated. Both $^1$H and $^2$H NMR were then conducted on the product in methanol solvent with chloroform internal standard. Analogous procedures were used to test for deuterium incorporation during the dehydrogenation of estriol (5 mg, 1.3% [Ru], 200 μL acetone-$d_6$, 65 °C, 3h), ouabain (5 mg, 3.5% [Ru], 250 μL acetone-$d_6$, 65 °C, 3h), and fusidic acid methyl ester (5 mg, 3% [Ru], 140 μL acetone-$d_6$, 65 °C, 2h).

Deuterium incorporation into a combination of 2-methyl-1-pentanol and cyclohexanol (Section 2.8):

2-methyl-1-pentanol (5 μL, 0.05 mmol), cyclohexanol (5 μL, 0.05 mmol), isopropanol-$d_8$ (5 μL, 0.05 mmol), and dodecane internal standard (5 μL, 0.05 mmol) were combined acetone-$d_6$ (400 μL). Then an aliquot of acetone-$d_6$ solution of equimolar **Ru-2** and NMM (10 μL, 0.1 M, 0.001 mmol [Ru], 0.001 mmol NMM, 2 mole % [Ru] versus each alcohol) was added. The vial was capped and reacted at room temperature for 10 minutes, then exposed to air and analyzed by GCMS. No conversion of 2-methyl-1-pentanol to aldehyde occurred under these conditions and no deuterium was incorporated into the remaining starting alcohol. 60% conversion of cyclohexanol to cyclohexanone occurred, and the remaining cyclohexanol showed 1.5% incorporation of deuterium.

2.19 Procedures for the synthesis of metal complexes and spectral data:

**cis-[Ru(DMSO)$_4$Cl$_2$]**. A modification of the known procedure reported by Wilkinson yields this compound with improved convenience, purity, and reproducibility at multi-gram scale. In a 500 mL flask, 2.50 g of RuCl$_3$-xH$_2$O was combined with DMSO (12 mL) and NPr$_3$ (2.25 mL) along with a magnetic stir bar. The system was placed under a reflux condenser and flushed with N$_2$ for 5 minutes at room temperature with stirring. Then, the solution was heated with stirring at 145 °C for 6-7 minutes in an oil bath. During this time, a mild reflux occurred, and the color changed from black to green to dark red/yellow. The flask was removed from the bath, and the solution was allowed to cool to room temperature, at which point the product crystallized from solution. Acetone (40 mL) was added under nitrogen, and the solution was allowed to stand for 20 minutes to allow precipitation to be complete. Under air, the product was collected by filtration and rinsed with acetone and ether and dried under vacuum. Larger crystals were obtained by recrystallization from minimal hot DMSO. To do so, the material was dissolved in ~7 mL DMSO at 165 °C in a 20 mL vial and then removed from the heat. The product crystallized at room temperature in the dark. The supernatant was removed, the crystals were rinsed with acetone, and then ether, and then the crystals were dried under high vacuum. Yield = 3.30 g (71%). Analytical data matched those in the literature. The combined supernatants from this synthesis were saved in an open flask under
Addition of acetone to the supernatant and recrystallization of the precipitate from DMSO yielded additional pure product (12%). Combined yield = 3.69 g (83%).

*Note: the addition of alkylamine is hypothesized to prevent decomposition of the target product by removing acidic by-products (increasingly problematic at >1g scale for the Wilkinson synthesis) from the reaction and serving as a mild reductant of Ru(III) to Ru(II).*

**[Ru₂Cl₃(PPh₂Me)₆][Cl] (Ru-1-Cl)**

cis-[Ru(DMSO)₄Cl₂] (630 mg, 1.30 mmol), PPh₂Me (0.798 mL, 4.29 mmol, 3.3 equiv), and MeOH (16 mL) were combined and stirred at room temperature for 90 minutes. Over this period, the supernatant turned orange brown and then yellow. The solid was removed by filtration, rinsed with ether, and dried under vacuum. The supernatant was placed in the freezer (-30 °C) overnight, after which time additional crystalline product was collected by filtration. Yield = 831 mg (83%).

1H NMR (600 MHz, chloroform-d1) δ 7.27 (t, J = 7.5 Hz, 6H), 7.07 (m, 12H), 7.02 (m, 12H), 1.82 (m, 9H). 13C NMR (151 MHz, chloroform-d) δ 136.70 (m), 132.93, 129.58, 127.95, 19.88 (m). Anal. Calc’d C:60.63 H:5.09 Found C:60.34 H:5.18.

**[Ru₂Cl₃(PEt₃)₆][Cl] (Ru-2-Cl)**

cis-[Ru(DMSO)₄Cl₂] (1.00 g, 2.06 mmol), PEt₃ (1.0 mL, 6.8 mmol, 3.3 equiv), and MeOH (4 mL) were combined and heated at 65 °C for 90 minutes with stirring. Over this period, all the material dissolved, and the supernatant turned green and then bright yellow/orange. The reaction solution was allowed to cool to RT and then was transferred to a larger flask under N₂ and slowly diluted with 250 mL 5:1 ether: pentane to crystallize the product. The yellow needles thus formed were collected by filtration (the filtration can be done under air) and rinsed once with ether, then pentane, and then dried under high vacuum. Yield = 885 mg (81%).

1H NMR (400 MHz, chloroform-d) δ 1.92 (m, 36H), 1.21 (m, 54H). 13C NMR (151 MHz, methylene chloride-d2) δ 20.44, 10.35. Anal. Calc’d C:41.07 H:8.62 Found C:41.13 H:8.46.

**[Ru₂Cl₃(PEt₂(p-Me₂N-Ph))₆][Cl] (Ru-3-Cl)**

cis-[Ru(DMSO)₄Cl₂] (1.00 g, 2.06 mmol), PEt₂(p-Me₂N-Ph) (1.4 mL, 6.8 mmol, 3.3 equiv) and MeOH (4 mL) were combined and stirred at 65 °C for 90 minutes. The solution was then allowed to return to RT, and then kept to -30 °C overnight. During this time yellow crystalline product formed. The supernatant was transferred to another vial, along with an ether rinse (2 mL). The supernatant was placed back into the freezer, and more crystals formed over 24 hours, which were rinsed with ether. The combined product was dried by high vacuum. Combined yield = 1.37 g (83%) 1H NMR (600 MHz, methanol-d₄) δ 7.00 – 6.83 (m, 12H), 6.62 (d, J = 8.3 Hz, 12H), 3.00 (s, 36H), 2.41 – 2.12 (m, 24H), 1.04 – 0.71 (m, 36H). 13C NMR (151 MHz, methanol-d₄) δ 152.10, 135.34, 120.72 (m), 112.63, 40.48, 24.39 (m), 10.13. Anal. Calc’d C:53.81 H:7.79 N:5.10. The product structure was confirmed by x-ray crystallography.
Figure 8: X-ray crystal structure of Ru-3-Cl

![X-ray crystal structure of Ru-3-Cl](image)

\[ \text{[Ru}_2\text{(OTf)}_3(\text{PPh}_2\text{Me})_6][\text{OTf}] \] (Ru-1)

\[ \text{[Ru}_2\text{Cl}_3(\text{PPh}_2\text{Me})_6][\text{Cl}] \] (Ru-1-Cl) (170 mg, 0.110 mmol) and AgOTf (113 mg, 0.440 mmol, 4 equiv) were combined in TFE (2 mL) and stirred at RT overnight (or 65 °C for 2 hours). The solution was then filtered and the solvent was evaporated to form a residue. The residue was triturated with isopropyl ether (2 x 0.8 ml), and dried under high vacuum. Yield = 210 mg (95%) red powder. \(^1\)H NMR (500 MHz, chloroform-\(d_2\)) \(\delta 7.55 \text{ (t, } J = 7.3 \text{ Hz, 6H)}, 7.45 \text{ (m, 12H)}, 7.36 \text{ (t, } J = 7.3 \text{ Hz, 12H)}, 2.09 \text{ (m, 9H)}\). \(^13\)C NMR (126 MHz, acetone-\(d_6\)) \(\delta 133.59 \text{ (m)}, 133.10 \text{ (m)}, 130.01 \text{ (m)}, 15.54 \text{ (m)}\). The intensity of the triflate CF\(_3\) signal in the \(^13\)C NMR spectrum was too low to observe. Anal. Calc’d C:49.25 H:3.93 Found C:49.12 H:4.18.

\[ \text{[Ru}_2\text{(OTf)}_3(\text{PEt}_3)_6][\text{OTf}] \] (Ru-2)

\[ \text{[Ru}_2\text{Cl}_3(\text{PEt}_3)_6][\text{Cl}] \] (Ru-2-Cl) (1.0 g, 0.95 mmol) and AgOTf (976 mg, 3.80 mmol, 4 equiv) were combined in TFE (5 mL) and stirred at RT overnight (or 65 °C for 2 hours). The reaction solution was then filtered and concentrated to ~1.5 mL. Isopropyl ether (10 mL) was added, and the product was allowed to crystallize overnight. The supernatant was removed, and the crystalline product was rinsed with isopropyl ether (1 mL) and then dried by high vacuum. Yield = 1.32 g (92%) yellow-orange crystals. \(^1\)H NMR (600 MHz, methylene chloride-\(d_2\)) \(\delta 1.97 \text{ (s, 18H)}, 1.23 \text{ (m, 27H)}\). \(^13\)C NMR (151 MHz, methylene Chloride-\(d_2\)) \(\delta 20.44, 10.35\). The intensity of the triflate CF\(_3\) signal in the \(^13\)C NMR spectrum was too low to observe. Anal. Calc’d C:31.87 H:6.02 S:8.51 Found C:31.76 H:6.16 S:8.18. The identity of the product was confirmed by x-ray crystallography (see Figure 3 for structure).

\[ \text{[Ru}_2\text{(OTf)}_3(\text{PEt}_2(\text{p-Me}_2\text{N-Ph}))_6][\text{OTf}] \] (Ru-3)

\[ \text{[Ru}_2\text{Cl}_3(\text{PEt}_2(\text{p-Me}_2\text{N-Ph}))_6][\text{Cl}] \] (Ru-3-Cl) (102 mg, 0.0640 mmol) and AgOTf (66 mg, 0.26 mmol, 4 equiv) were combined in acetone (1.5 mL) and stirred at RT overnight. The solution was then filtered and concentrated to ~0.75 mL, layered with pentane, and allowed to precipitate overnight. Then the supernatant was removed, and the product was dried under high vacuum. Yield = 114 mg (87%) yellow-orange powder. \(^1\)H NMR (600 MHz, acetone-\(d_6\)) \(\delta 7.24 \text{ (m, 12H)}, 6.78\)
2.20 Procedures for Substrate Preparation and Spectral Data

**Fusidic acid methyl ester.** Fusidic acid (1.655 mmol, 878 mg) was dissolved in 54 mL of a 2:1 mixture of toluene:methanol. TMS diazomethane was added dropwise until a yellow color persisted (2.5 mmol, 1.25 mL, 2 M in ether). The resulting mixture was stirred for 2 hours at room temperature. The reaction was then quenched with acetic acid (30 μL) and neutralized with 5% bicarbonate solution. The mixture was diluted with dichloromethane, and the bicarbonate layer was removed. The dichloromethane layer was washed two times with brine and dried over Na₂SO₄. Removal of volatile materials yielded pure methyl fusidate. Yield = 886 mg (98%). ¹H NMR (600 MHz, chloroform- d) δ 5.84 (d, J = 8.5 Hz, 1H), 5.08 (t, J = 7.2 Hz, 1H), 4.34 (m, 1H), 3.75 (m, 1H), 3.64 (s, 3H), 3.03 (d, J = 11.6 Hz, 1H), 2.48 (m, 1H), 2.41 (m, 1H), 2.31 (dt, J = 13.1, 3.2 Hz, 1H), 2.22 – 2.07 (m, 4H), 2.03 (m, 1H), 1.97 (s, 3H), 1.91 – 1.80 (m, 2H), 1.80 – 1.71 (m, 2H), 1.67 (s, 3H), 1.62 – 1.47 (m, 7H), 1.41 (d, J = 3.5 Hz, 1H), 1.37 (s, 3H), 1.32 (d, J = 3.5 Hz, 1H), 1.27 (d, J = 14.3 Hz, 1H), 1.18 – 1.04 (m, 2H), 0.97 (s, 3H), 0.92 (d, J = 6.8 Hz, 3H), 0.90 (s, 3H). ¹³C NMR (151 MHz, chloroform- d) δ 170.65, 170.29, 148.04, 132.51, 130.42, 123.01, 74.36, 71.29, 68.27, 51.33, 49.15, 48.67, 43.84, 39.40, 39.03, 37.10, 36.27, 36.09, 35.53, 32.55, 30.30, 29.97, 28.89, 28.24, 25.67, 24.22, 22.57, 20.93, 20.67, 17.80, 17.71, 15.87. HRMS (ESI+) calc’d for [C₃₂H₅₀O₆Na⁺]: 553.3500, found: 553.3497.

2.21 Procedures for Alcohol Dehydrogenation and Product Spectral Data

**General procedure (II) for alcohol oxidation**

The procedure was conducted under an N₂ atmosphere. The catalyst precursor (Ru-1, Ru-2, or Ru-3) was dissolved in acetone or the specified reaction solvent, and an equimolar amount of NMM was added. The resulting solution was quickly mixed to generate the active catalyst. This solution of the catalyst was then added to a solution or slurry of the substrate alcohol in the specified reaction solvent in a vial or flask containing a magnetic stir bar. For the reactions in which a homogeneous solution did not form at room temperature (estriol, kirenol, ouabain, brefieldin), the starting materials composed of large crystals were crushed, sonicated in the reaction solvent, or pre-stirred in the reaction solvent to improve the rate of dissolution and reaction. The reactions were all heated at the indicated temperature for the indicated time. For reactions that
were homogeneous upon mixing, stirring was not necessary. Reactions that began as slurries were stirred vigorously with one or more magnetic stir bars. Small-scale reactions were conducted in Teflon capped one, two, or five dram glass vials, while larger-scale reactions were conducted in a sealed Schlenk flask or a round bottom flask fit with a reflux condenser. All of the reported reactions became fully homogeneous before completion. Upon completion, the solvent was evaporated by rotary evaporation, and the product was purified by recrystallization or column chromatography. Care was taken to premix the ruthenium precursor and the base in the reaction solvent before addition of the solution of catalyst to the solution or slurry of the substrate alcohol. The selectivity of the oxidation reactions was lower if the substrate was mixed with the catalyst precursor prior to mixing the catalyst precursor and amine.

### 3-keto-andrographolide (1a) and 3,19-keto-aldehyde-andrographolide
Andrographolide (1.10 g, 3.14 mmol) was combined with acetone (50 mL), TFE (11 mL), THF (11 mL), and a magnetic stir bar in a 250 mL Schlenk flask, and the resulting mixture was stirred to form a slurry. Then, a solution of Ru-2 (90 mg, 1.9 mol %, 0.06 mmol) and NMM (13 μL, 3.8 mol %, 0.12 mmol) premixed in acetone (5 mL) was added. The flask was sealed. The reaction was heated at 65 °C for 3 hours and then cooled to RT. The solvent was fully evaporated. Then the residue was dissolved in 15 mL THF and silica gel (10 g) was added. The solvent was fully evaporated by rotary evaporation to deposit the crude product on the silica gel. The product was then purified by silica gel chromatography with 2% MeOH in CHCl3 (until 3,19-keto-aldehyde-andrographolide and trace 19-aldehyde-andrographolide elute) and then with 2% to 3.5% MeOH in CHCl3 (3-keto-andrographolide elutes). Yields: **3-keto-andrographolide (1a)** (720 mg, 65%) and **3,19-keto-aldehyde-andrographolide** (220 mg, 20%). Spectral data of this product match those published previously (28,44). Highly crystalline 3-keto-andrographolide was obtained by dissolving the product in minimal ethyl acetate at 80 °C, layering with hot hexane, and allowing the mixture to cool and crystallize for several hours. The supernatant was concentrated to obtain a second crop. Yield = 642 mg (58%) of transparent crystals.

### 6-keto-aucubin (1b)
Aucubin (9.4 mg, 0.027 mmol) was combined with acetone (2 mL) and a magnetic stir bar in a one dram vial, and the resulting mixture was stirred to form a slurry. Then, a solution of Ru-2 (1.02 mg, 0.7 μmol, 2.5%) and NMM (0.15 μL, 1.4 μmol, 5%) in 0.7 mL of acetone was added. The vial was capped, and the reaction was heated at 65 °C for 1 hour. The reaction was allowed to cool, and all of the volatile materials were evaporated. The crude product was purified by silica
gel chromatography, eluting with 0 to 15% MeOH in CHCl₃. Yield = 8.2 mg (87%). ¹H NMR (600 MHz, methanol-d₄) δ 6.39 (dd, J = 6.0, 2.4 Hz, 1H), 6.22 (s, 1H), 5.16 (dd, J = 6.0, 3.7 Hz, 1H), 4.88 (d, J = 6.7 Hz, 1H), 4.79 (d, J = 18.9 Hz, 1H), 4.68 (d, J = 7.9 Hz, 1H), 4.40 (d, J = 18.7 Hz, 1H), 3.86 (d, J = 12.1 Hz, 1H), 3.65 (dd, J = 12.0, 5.4 Hz, 1H), 3.37 (dd, J = 9.0, 9.0 Hz, 1H), 3.29 − 3.16 (m, 5H). ¹³C NMR (151 MHz, methanol-d₄) δ 207.92, 182.58, 142.33, 128.50, 102.47, 100.22, 98.27, 78.36, 77.92, 74.90, 71.52, 62.70, 62.61, 47.04, 45.62. HRMS (ESI+) calcd for [C₁₅H₂₀O₉Na⁺]: 367.1000, found: 367.0998. IR (neat) (cm⁻¹) 1700.1, 1648.0, 1618.8.

3-keto-D-glucal (1c)

D-glucal (150 mg, 1.03 mmol) was combined with 1:1 acetone:TFE (13 mL) in a 20 mL vial, along with a magnetic stir bar, and the resulting mixture was stirred to form a solution. Then, a solution of Ru-2 (12 mg, 0.0080 mmol, 0.75 mol %) and NMM (1.7 μL, 0.015 mmol, 1.5 mol %) in 1:1 acetone:TFE (2 mL) was added. The vial was capped, and the reaction was heated at 65 °C for 4 hours with stirring. The reaction was allowed to cool to RT, and all of the volatile materials were evaporated. The crude product was purified by silica gel chromatography, eluting with 25 to 45% ethyl acetate in hexanes. Yield = 130 mg (88%) white solid.

Alternative procedure: D-glucal (150 mg, 1.03 mmol) was combined with 1 acetone (13 mL) in a 20 mL vial, along with a magnetic stir bar, and the resulting mixture was stirred to form a solution. Then, a solution of Ru-3 (34 mg, 0.016 mmol, 1.6 mol %) and NMM (3.4 μL, 0.030 mmol, 3 mol %) in 1 acetone (2 mL) was added. The vial was capped, and the reaction was heated at 65 °C for 3 hours with stirring. The reaction was allowed to cool to RT, and all of the volatile materials were evaporated. The crude product was purified by silica gel chromatography, eluting with 25 to 45% ethyl acetate in hexanes. Yield = 127 mg (86%). Spectral data match a previous report.²⁴

15-keto-kirenol (1d)

Kirenol (50 mg, 0.148 mmol) was combined with acetone (2.7 mL) and a magnetic stir bar in a two-dram vial, and the resulting mixture was stirred to form a slurry. Then, a solution of Ru-1 (7.4 mg, 3.7 μmol, 2.5%) and NMM (0.80 μL, 7.4 μmol, 5%) in acetone (1 mL) was added. The vial was capped, and the reaction was heated at 65 °C for 1 hour with stirring. The reaction was then allowed to cool to RT, and all of the volatile materials were evaporated. The crude product was
purified by silica gel chromatography, eluting with a gradient of 10% MeOH in CHCl₃ to 20% MeOH in CHCl₃. Yield = 27 mg (54%). Analytical data match the reported natural product.7

1-keto-ouabain (1e)

Ouabain octahydrate (1.00 g, 1.37 mmol) was combined with acetone (30 mL) in a 150 mL Schlenk flask, along with a magnetic stir bar, and the resulting mixture was stirred to form a fine slurry. A solution of Ru-2 (36.2 mg, 0.024 mmol, 1.75%) and NMM (5.3 μL, 0.048 mmol, 3.5%) in acetone (7 mL) was then added. The flask was sealed, and the reaction was heated at 65 °C for 3.5 hours and then cooled to RT. The solvent was concentrated to ~12-13 mL under reduced pressure and then transferred to a 20 mL vial along with a THF rinse of the reaction flask. The solution was then dried down to a residue by rotary evaporation. The residue was recrystallized by dissolving it in minimal CH₃CN (10-12 mL) at 85 °C and then immediately removing the reaction from heat and allowing the solution to cool to RT overnight during which time white microcrystalline solid formed (700 mg). The supernatant was transferred into a second vial and then concentrated (to ~4 mL), and additional microcrystalline product formed (36 mg). The supernatant was removed and the product dried under high vacuum. Combined yield = 736 mg (92%). ¹H NMR (600 MHz, methanol-d₄) δ 5.92 (s, 1H), 5.02 (d, J = 18.4 Hz, 1H), 4.92 (d, J = 18.4 Hz, 1H), 4.81 (s, 1H), 4.48 (s, 1H), 4.40 (d, J = 12.1 Hz, 1H), 4.18 (d, J = 12.2 Hz, 1H), 4.16 (td, J = 13.5, 4.3, 1H), 3.72 (bs, 1H), 3.69 (dq, J = 12.4, 6.2 Hz, 2H), 3.56 (dd, J = 9.5, 3.2 Hz, 1H), 3.44 (dd, J = 13.8, 4.4 Hz, 1H), 3.37 (t, J = 9.5 Hz, 1H), 2.87 (dd, J = 9.2, 5.4 Hz, 1H), 2.65 (dd, J = 15.5, 3.0 Hz, 1H), 2.52 (d, J = 13.9 Hz, 1H), 2.32 – 2.17 (m, 3H), 2.06 (d, J = 13.7 Hz, 1H), 1.97 (td, J = 12.6, 4.2 Hz, 1H), 1.91 (dp, J = 14.7, 5.8, 4.7 Hz, 1H), 1.80 (dd, J = 12.6, 9.6 Hz, 1H), 1.77 – 1.71 (m, 2H), 1.68 (dd, J = 13.1, 4.3 Hz, 1H), 1.60 (d, J = 13.7 Hz, 1H), 1.53 – 1.40 (m, 2H), 1.28 (d, J = 6.2 Hz, 3H), 0.93 (s, 3H). ¹³C NMR (151 MHz, methanol-d₄) δ 215.47, 177.61, 177.04, 118.14, 101.27, 85.55, 82.03, 78.33, 75.28, 73.77, 72.32, 72.27, 70.48, 67.27, 61.76, 59.75, 51.72, 51.35, 51.13, 49.97, 45.13, 40.25, 36.06, 35.75, 33.25, 27.89, 24.93, 17.97, 17.33.. HRMS (ESI+) calcd for [C₂₀H₄₂O₁₂Na⁺]: 605.2568, found: 605.2578. IR (neat) (cm⁻¹) 1726.3, 1687.0 (shoulder), 1621.8.
3-keto-fusidic acid methyl ester (1f)

Fusidic acid methyl ester (244 mg, 0.460 mmol) was combined with 1:1 acetone:TFE (6 mL) and a magnetic stir bar in a 20 mL vial, and the resulting mixture was stirred to form a solution. Then a solution of Ru-2 (5.2 mg, 3.5 μmol, 0.75 mol %) and NMM (0.76 μL, 6.9 μmol, 1.5 mol %) in 1:1 acetone:TFE (1 mL) was added. The vial was capped, and the reaction was heated at 60 °C for 4 hours with stirring. The reaction was then allowed to cool to RT, and all of the volatile materials were evaporated by rotary evaporation. The crude product was purified by silica gel chromatography, eluting with 1:1 hexanes:ethyl acetate. Yield = 237 mg (97%) of a transparent solid. **Alternative procedure:** Fusidic acid methyl ester (530 mg, 1 mmol) was combined with acetone (9 mL) and a magnetic stir bar in a 20 mL vial, and the resulting mixture was stirred to form a solution. A solution of Ru-3 (30.8 mg, 0.75 mol %, 0.015 mmol [Ru]) and NMM (3.3 μL, 3 mol %, 0.03 mmol) in acetone (1 mL) was then added. The vial was capped. The reaction was heated at 50 °C for 4 hours and then cooled to RT. The solvent was removed under reduced pressure, and the residue was purified by silica gel column, eluting with 1:1 hexanes: ethyl acetate. Yield = 501 mg (94.8%) of transparent solid. Spectral data match the reported product.26

3-keto-digoxigenin (1g)

Digoxigenin (8 mg, 0.02 mmol) was combined with acetone (0.2 mL) in a one dram vial, along with a magnetic stir bar. The resulting mixture and was stirred to form a solution. Then, a solution of Ru-2 (0.15 mg, 0.11 μmol, 0.5 %) and NMM (0.023 μL, 0.21 μmol, 1%) in acetone (0.1 mL) was added. The vial was capped, and the reaction was heated at 65 °C for 70 minutes with stirring. The reaction was allowed to cool to RT, and all of the volatile materials were evaporated. Addition of several drops of ethyl acetate led to crystallization, yielding pure product. Yield = 7 mg (87.5%) transparent crystals. Analytical data match those of the reported compound.39
3-keto-cholic acid methyl ester (1h)

Cholic acid methyl ester (250 mg, 0.590 mmol) was combined with acetone (5.5 mL) in a one dram vial, along with a magnetic stir bar, and the resulting mixture was stirred to form a solution. Then, a solution of Ru-2 (3.3 mg, 2.2 μmol, 0.38%) and NMM (0.5 μL, 4 μmol, 0.8%) in acetone (1 mL) was added. The vial was capped, and the reaction was heated at 35 °C for 4 hours with stirring. The reaction was allowed to cool to RT, and all of the volatile materials were removed. The crude product was purified by silica gel chromatography with EA/hexanes. Yield = 234 mg (94%). Analytical data for the product matches those reported previously.40

1-keto-forskolin (1i)

Forskolin (12 mg, 0.030 mmol) was combined with 1:1 acetone:TFE acetone (0.41 mL) and a magnetic stir bar in a one dram vial. The resulting mixture was stirred to form a solution. Then, an aliquot of 0.01 M active catalyst stock solution was added (0.88 μmol, 90 μL, 1.5% Ru-2, 3% NMM). The 0.01 M stock solution of active catalyst was made by combining Ru-2 (8 mg, 0.005 mmol) and NMM (1.1 μL, 0.010 mmol) in 1:1 acetone:TFE (1 mL). The vial was capped, and the reaction was heated at 65 °C for 2.5 hours with stirring. The reaction was allowed to cool to RT, and all of the volatile materials were evaporated. The crude product was purified by silica gel chromatography, eluting with 85:15 DCM:MTBE. Yield = 10.5 mg (88%). Analytical data for the product match those reported previously.27

16-keto-estriol (1j)

Estriol (288 mg, 1 mmol) was combined with acetone (12 mL) in a 20 mL vial, along with a magnetic stir bar, and the resulting mixture was stirred to form a slurry. Then, a solution of Ru-2
(9.4 mg, 0.0065 mmol, 0.63%) and NMM (1.4 μL, 0.013 mmol, 1.3%) in acetone (2 mL) were added. The vial was capped, and the reaction was heated at 65 °C for 5 hours with stirring. During this period, the reaction mixture becomes fully homogeneous. The reaction was allowed to cool to RT, and all of the volatile materials were removed. Then CH₃CN (4 mL) was added to the residue and the mixture was stirred at RT for 1 hour. The white powder precipitate was collected by filtration, and rinsed with CH₃CN, and dried under vacuum. The supernatant was evaporated and triturated with CH₃CN (2 x 300 μL), and then dried under vacuum. Combined yield = 277 mg (97%) of a white powder. ¹H NMR (600 MHz, methanol-d₄) δ 7.08 (d, J = 8.4 Hz, 1H), 6.55 (dd, J = 8.4, 2.5 Hz, 1H), 6.48 (d, J = 2.3 Hz, 1H), 3.82 (s, 1H), 2.86 – 2.73 (m, 2H), 2.42 – 2.22 (m, 3H), 2.01 (dt, J = 12.3, 3.0 Hz, 1H), 1.92 – 1.77 (m, 2H), 1.67 (m, 1H), 1.59 (td, J = 12.9, 3.6 Hz, 1H), 1.55 – 1.44 (m, 2H), 1.38 (tq, J = 12.0, 6.5 Hz, 1H), 0.76 (s, 3H). ¹³C NMR (151 MHz, methanol-d₄) δ 217.06, 154.65, 137.21, 130.73, 125.56, 114.68, 112.43, 85.94, 43.75, 43.72, 42.42, 37.81, 36.12, 35.15, 29.11, 27.38, 25.79, 10.55. HRMS (ESI-) calcd for [C₁₈H₂₁O₃-]: 285.1496, found: 285.1492. IR (neat) (cm⁻¹) 1740.8.

13-keto-mupirocin methyl ester (1k)

Mupirocin methyl ester (100 mg, 0.190 mmol) was combined with acetone (1.5 mL) in a one dram vial, forming a solution. Then, a solution of Ru-2 (15 mg, 9.5 μmol, 5%) and NMM (2.1 μL, 19 μmol, 10%) in acetone (0.5 mL) was added. The vial was capped and the reaction was heated at 50 °C for 3.5 hours. The reaction was cooled to RT, and all of the volatile materials were evaporated. The crude product was purified by silica gel chromatography, eluting with 50 to 55% ethyl acetate in hexanes. Yield = 70 mg (70%). Analytical data match those of the reported compound.²²

7-epi-13-keto-deacetylbaccatin III (1l)

Deacetylbaccatin III (100 mg, 0.184 mmol) was combined with TFE (2 mL), MgOTf₂ (105 mg, 0.322 mmol, 1.75 equiv), and trifluoroacetophenone (516 μL, 3.67 mmol, 20 equiv) in a two dram
A vial, along with a magnetic stir bar, and the resulting mixture was stirred to form a slurry. Then, a solution of Ru-2 (49 mg, 0.032 mmol, 17.5%) and NMM (7 μL, 0.64 mmol, 35%) in 0.5 mL TFE was added. The vial was capped, and the reaction was heated at 85 °C for 6 hours with stirring. The reaction was allowed to cool to RT, and the vial contents were transferred to a separatory funnel, along with ethyl acetate (30 mL). The mixture was extracted with saturated bicarbonate (3 mL) and then brine (3 mL). The organic layer was collected, and a second extraction with ethyl acetate (30 mL) was conducted. The combined organic phases were dried with Na₂SO₄, filtered through a glass-fritted funnel, and the organic solvent was evaporated. The crude product was then purified by silica gel chromatography with 10 to 22% ethyl acetate in hexanes. Yield 71 mg (71%) of a white solid. 1H NMR (600 MHz, chloroform-d) δ 8.08 (d, J = 7.8 Hz, 2H), 7.65 (t, J = 7.4 Hz, 1H), 7.51 (t, J = 7.7 Hz, 2H), 5.79 (d, J = 7.2 Hz, 1H), 5.62 (s, 1H), 4.91 (dd, J = 9.3, 3.3 Hz, 1H), 4.59 (d, J = 11.8 Hz, 1H), 4.42 (d, J = 8.9 Hz, 1H), 4.37 (d, J = 8.9 Hz, 1H), 4.19 (s, 1H), 4.03 (d, J = 7.2 Hz, 1H), 3.67 (dd, J = 11.0, 3.4 Hz, 1H), 3.03 (d, J = 19.8 Hz, 1H), 2.68 (d, J = 19.8 Hz, 1H), 2.39 (dd, J = 15.9, 9.4 Hz, 1H), 2.29 (m, 1H), 2.27 (s, 3H), 1.99 (s, 3H), 1.84 (s, 1H), 1.69 (s, 3H), 1.24 (s, 3H), 1.15 (s, 3H). 13C NMR (151 MHz, chloroform-d) δ 213.27, 198.07, 172.34, 167.04, 157.36, 139.42, 134.22, 130.18, 129.08, 129.00, 82.26, 81.88, 79.74, 79.33, 77.72, 75.45, 73.59, 58.36, 43.16, 42.69, 40.12, 35.55, 32.43, 22.04, 18.08, 16.54, 13.88. HRMS (ESI+) calcd for [C₂₉H₃₄O₁₀Na⁺]: 565.2044, found: 565.2049. IR (neat) (cm⁻¹) 1718.8, 1691.2, 1663.8, 1605.8. Product confirmed by x-ray crystallography.

**Figure 9: X-ray crystal structure of 7-epi-10-keto-DAB III (2d)**
**13-keto-brefeldin A (1m)**

Brefeldin (25 mg, 0.089 mmol) was combined with 1:1 acetone:TFE (2.5 mL) in a one dram vial, along with a magnetic stir bar, and the resulting mixture was stirred to form a slurry. Then, a solution of Ru-1 (3.6 mg, 1.8 μmol, 2%) and NMM (0.4 μL, 3.6 μmol, 4%) in 1:1 acetone:TFE (0.5 mL) was added. The vial was capped, and the reaction was heated at 65 °C for 2.5 hours with stirring. The reaction was allowed to cool to RT, and all of the volatile materials were removed. The crude product was purified by silica gel chromatography, eluting with 3.5% MeOH in CHCl₃. Yield = 21.4 mg (87%). 

1H NMR (600 MHz, chloroform-d) δ 7.38 (dd, J = 15.7, 3.5 Hz, 1H), 5.96 (dd, J = 15.7, 1.9 Hz, 1H), 5.81 (ddd, J = 15.0, 9.6, 5.1 Hz, 1H), 5.20 (dd, J = 15.3, 9.2 Hz, 1H), 4.91 (dt, J = 11.6, 7.2, 5.3 Hz, 1H), 4.23 (d, J = 9.4 Hz, 1H), 2.83 (dd, J = 19.1, 8.5 Hz, 1H), 2.69 (p, J = 9.6 Hz, 1H), 2.53 (dd, J = 18.9, 8.4 Hz, 1H), 2.19 (ddd, J = 19.2, 10.5, 1.8 Hz, 1H), 1.99-2.14 (m, 3H), 1.94 – 1.80 (m, 3H), 1.74 (dt, J = 16.1, 8.1 Hz, 1H), 1.54 (dtt, J = 10.4, 7.5, 3.8 Hz, 1H), 1.27 (d, J = 6.3 Hz, 3H), 1.04 (tdd, J = 13.2, 6.8, 3.5 Hz, 1H). 

13C NMR (151 MHz, chloroform-d) δ 216.00, 166.10, 150.50, 135.29, 132.48, 118.63, 76.83, 71.38, 50.06, 46.70, 45.00, 42.64, 34.48, 31.74, 26.57, 20.86. HRMS (ESI-) calcd for [C₁₆H₂₁O₄]: 277.1445, found: 277.1445.

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**Genipin lactone (1n)**

Genipin (100 mg, 0.44 mmol) was combined with acetone (10 mL) and a magnetic stir bar in a one-dram vial, and the resulting mixture was stirred to form a solution. Then, a solution of Ru-2 (18 mg, 12 μmol, 2.8%) and NMM (2.7 μL, 24 μmol, 5.5%) in acetone (1 mL) was added. The vial was capped, and the reaction was heated at 65 °C for 3 hours with stirring. The reaction was cooled to RT, and all of the volatile materials were evaporated. The crude product was purified by silica gel chromatography with 95:5 CHCl₃:CH₃CN. Yield = 69 mg (69%). Analytical data match those of the reported compound.⁹
Lagochirsine (lagochiline spirolactone) (1o)

Lagochilin (10 mg, 0.028 mmol) was combined with trifluoroacetophenone (7.86 μL, 0.056 mmol, 2 equiv), dioxane (0.2 mL), and a magnetic stir bar in a one dram vial, and the resulting mixture was stirred to form a solution. Then a solution of Ru-2 (1.2 mg, 0.7 μmol, 2.5%) and NMM (0.15 μL, 1.4 μmol, 5%) in dioxane (0.1 mL) was added. The vial was capped and the reaction was heated at 100 °C for 4 hours with stirring. The reaction was cooled to RT and all of the volatile materials were evaporated. The crude product was purified by silica gel chromatography with 20:1 EA:MeOH. Yield = 4 mg (40%). 1H NMR (600 MHz, chloroform-d) δ 4.31 (d, J = 8.7 Hz, 1H), 4.09 (d, J = 8.7 Hz, 1H), 3.70 (dd, J = 9.6, 3.0 Hz, 1H), 3.60 (dd, J = 11.2, 4.2 Hz, 1H), 3.45 (d, J = 10.1 Hz, 1H), 2.95 (d, J = 17.1 Hz, 1H), 2.83 (s, 1H), 2.51 (d, J = 17.1 Hz, 1H), 2.28 (s, 1H), 2.14 – 2.01 (m, 3H), 1.79 – 1.63 (m, 4H), 1.63 – 1.61 (m, 2H), 1.49 (dd, J = 11.8, 3.2 Hz, 1H), 1.42 (d, J = 11.2 Hz, 3H), 1.38 – 1.21 (m, 4H), 0.94 (s, 3H), 0.90 (s, 3H), 0.81 (d, J = 6.6 Hz, 3H). 13C NMR (151 MHz, chloroform-d) δ 174.85, 94.12, 86.09, 78.51, 76.84, 72.53, 42.43, 42.15, 42.10, 41.51, 37.85, 36.10, 31.39, 30.43, 29.75, 26.87, 21.68, 17.79, 17.54, 11.34. HRMS (ESI-) calcd for [C16H21O4-]: 277.1445, found: 277.1445. IR (neat) (cm⁻¹) 1774.1.

5-keto-ivermectin (1p)

Ivermectin (35 mg, 0.04 mmol) was combined with dioxane (0.1 mL) and a magnetic stir bar, and the resulting mixture was stirred to form a solution. Then, a solution of Ru-2 (3.3 mg, 2.2 μmol, 5.5%), NMM (0.49 μL, 4.4 μmol, 11%), and trifluoroacetophenone (112 μL, 0.800 mmol, 20 equiv) in dioxane (0.1 mL) was added. The vial was capped, and the reaction was heated at 100 °C for 2.5 hours with stirring. The reaction was cooled to RT, and all of the volatile materials were evaporated. The trifluoroacetophenone was evaporated under high vacuum at 80 °C. The crude
product was purified by silica gel chromatography with 2.5:1 hexanes:ethyl acetate. Yield = 19 mg (54%). 1H NMR (900 MHz, chloroform-d) δ 6.57 (m, 1H), 5.93 (dt, J = 11.1, 2.2, 1H), 5.79 (dd, J = 15.1, 9.9 Hz, 1H), 5.72 (dd, J = 15.1, 11.2 Hz, 1H), 5.45 – 5.37 (m, 2H), 4.99 (d, J = 11.5 Hz, 1H), 4.78 (d, J = 3.4 Hz, 1H), 4.76 (dd, J = 14.4, 2.2 Hz, 1H), 4.73 (dd, J = 14.4, 2.2 Hz, 1H), 4.07 (s, 1H), 3.95 (s, 1H), 3.86 (s, 1H), 3.83 (dq, J = 11.1, 2.2, 1H), 3.77 (dq, J = 11.1, 6.1 Hz, 1H), 3.68 (dd, J = 15.1, 11.5, 4.1, 2.0 Hz, 1H), 3.62 (dd, J = 11.4, 8.6, 4.9 Hz, 1H), 3.58 (m, 1H), 3.48 (dd, J = 11.5, 8.9, 4.8 Hz, 1H), 3.43 (s, 3H), 3.42 (s, 3H), 3.25 (dd, J = 9.1, 9.1 Hz, 1H), 3.22 (dd, J = 9.0, 1.6 Hz, 1H), 3.19 – 3.15 (ddd, J = 9.1, 9.1, 1.5, 1H), 2.53 (dq, J = 13.9, 7.0, 2.9 Hz, 1H), 2.48 (d, J = 1.7 Hz, 1H), 2.37 – 2.31 (m, 2H), 2.31 – 2.20 (m, 3H), 2.00 (ddd, J = 12.1, 4.7, 1.7 Hz, 1H), 1.90 (m, 3H), 1.78 (d, J = 11.1 Hz, 1H), 1.67 (d, J = 13.1 Hz, 1H), 1.59 – 1.56 (m, 2H), 1.55 – 1.48 (m, 6H), 1.49 – 1.37 (m, 4H), 1.28 (d, J = 6.2 Hz, 3H), 1.26 (d, J = 6.3 Hz, 3H), 1.17 (d, J = 7.0 Hz, 3H), 0.94 (t, J = 7.4 Hz, 3H), 0.86 (d, J = 6.8 Hz, 3H), 0.85 (m, 1H), 0.79 (d, J = 5.9 Hz, 3H). 13C NMR (151 MHz, chloroform-d) δ 192.22, 172.54, 139.27, 138.09, 138.00, 137.04, 135.27, 124.82, 121.99, 118.54, 98.69, 97.68, 94.98, 82.10, 81.83, 81.01, 80.62, 79.54, 78.37, 76.93, 76.33, 70.03, 69.56, 68.32, 67.46, 67.44, 56.65, 56.55, 46.83, 41.40, 40.08, 37.09, 35.93, 35.66, 34.69, 34.39, 34.24, 31.41, 28.23, 27.51, 20.24, 18.59, 17.84, 17.60, 15.60, 15.32, 12.59, 12.28. HRMS (ESI-) calcd for [C48H71O14-]: 871.4849, found: 871.4840. IR (neat) (cm⁻¹) 1719.0, 1679.9.

![Image of 2,3-dihydro-1-keto-brefeldin A (1q) molecule](image-url)

2,3-dihydro-1-keto-brefeldin A (1q)

[Ru(DMSO)4Cl2] (24 mg, 0.050 mmol) and AgOTf (25 mg, 0.10 mmol, 2 equivalents) were weighed into a one-dram vial, and acetone (1 mL) was added. The mixture was stirred at 65 °C for 90 minutes and then filtered to give a solution of [Ru(DMSO)4(OTf)2] (0.05 M). To this solution, 1,4-bis-(dicyclohexylphosphino)butane (23 mg, 0.050 mmol, 1 equiv) was added, and the mixture was stirred for 5 minutes to generate a solution of active catalyst. An aliquot (36 μL, 0.050 M, 1.8 μmol [Ru], 5%) of this catalyst solution was then added to a slurry of Brefeldin A (10 mg, 0.036 mmol) in 1:1 acetone:DCE (1 mL) with a magnetic stir bar in a one dram vial. The vial was then capped, and the mixture was heated at 65 °C for 25 min. The reaction was then cooled to RT, and all of the volatile materials were evaporated. The crude product was purified by silica gel chromatography with 4% MeOH in CHCl3. Yield = 9 mg (90%). 1H NMR (500 MHz, chloroform-d) δ 5.55 (ddd, J = 15.1, 10.0, 4.9 Hz, 1H), 5.33 (dd, J = 15.3, 8.9 Hz, 1H), 4.78 (m, 1H), 4.42 (m, 1H), 3.08 – 2.93 (m, 2H), 2.80 (ddd, J = 14.9, 8.0, 4.0 Hz, 1H), 2.67 (p, J = 9.3 Hz, 1H), 2.58 (ddd, J = 17.2, 9.0, 3.6 Hz, 1H), 2.35 (ddd, J = 15.7, 8.5, 4.4 Hz, 2H), 1.98 (m, 2H), 1.86 (m, 2H), 1.58 – 1.39 (m, 5H), 1.28 (m, 1H), 1.19 (d, J = 6.4 Hz, 3H). 13C NMR (126 MHz, chloroform-d) δ 210.86, 172.79, 133.21, 132.06, 72.45, 71.69, 56.41, 47.02, 42.66, 39.44, 38.80, 32.52, 31.02, 29.40, 24.08, 19.50. HRMS (ESI+) calcd for [C16H25O4+] : 281.1747, found: 281.1749.
2.22 Procedures for the Synthesis of Derivatives and Spectral Data

1-keto-oubagenin (2a)

Keto-ouabain (125 mg, 0.215 mmol), hydroxylamine-o-sulfonic acid (56.0 mg, 0.490 mmol, 2.3 equiv), and 10:1 TFE:H₂O (2.5 mL) were combined in a one dram vial, along with a magnetic stir bar. The vial was capped, and the reaction was heated at 50 °C for 12 hours. After this time, the volatile materials were evaporated under vacuum at 65 °C. Then the residue was dissolved in 1:10:89 28% NH₄OH:MeOH:THF, and filtered through a plug of Na₂SO₄. The solvents were then fully evaporated. The residue was taken up in THF and silica gel was added (~1.5 g), and the product was deposited onto the silica gel by rotary evaporation. Silica gel chromatography, eluting with 3.5 to 7% MeOH in CHCl₃ yielded deglycosyl-keto-ouabain. Yield = 75 mg (80%) white powder. 

\[ \text{1H NMR (500 MHz, chloroform-}d \text{)} \delta 5.92 (s, 1H), 5.02 (d, J = 18.4 Hz, 1H), 4.91 (d, J = 18.4 Hz, 1H), 4.37 (d, J = 11.8 Hz, 1H), 4.31 (d, J = 11.8 Hz, 1H), 3.88 (td, J = 11.1, 4.3 Hz, 1H), 3.44 – 3.29 (m, 2H), 2.90 – 2.83 (m, 1H), 2.70 (dt, J = 15.1, 3.3 Hz, 1H), 2.44 (dt, J = 13.7, 4.5 Hz, 2H), 2.31 – 2.18 (m, 3H), 2.10 – 2.03 (m, 1H), 1.95 – 1.84 (m, 2H), 1.83 – 1.74 (m, 2H), 1.72 – 1.61 (m, 3H), 1.54 – 1.40 (m, 2H), 0.91 (s, 3H). \]

\[ \text{13C NMR (126 MHz, chloroform-}d \text{)} \delta 215.32, 177.56, 177.06, 118.19, 85.47, 84.13, 75.28, 71.99, 67.00, 61.87, 58.90, 51.70, 51.33, 51.00, 50.00, 47.51, 40.33, 37.75, 36.69, 33.18, 27.90, 24.94, 17.31. \]

\[ \text{HRMS (ESI+) calcd for [C}_{23}\text{H}_{32}\text{O}_8\text{Na}^+: 459.1989, found: 459.1985. IR (neat) (cm}^{-1}) 1722.7, 1684.2, 1620.0. \]

Andrographolide-3-oxime (2b)

3-keto-andrographolide (mmol) and 1.05 NH₂OH-HCl (1.05 equiv) were weighed into a 20 mL vial. Pyridine (2.8 mL) was added, followed by a magnetic stir bar. The vial was capped and heated at 40 °C for 2.5 hours, and then cooled to room temperature. The reaction mixture was fully dried down and then the resulting residue was recrystallized from hot 49:49:2 benzene:MeOH:benzene:NEt₃ (65 °C). The supernatant was removed, and the product was rinsed with cold 1:1 MeOH/benzene mixture, and then dried under high vacuum to obtain a white solid (75 mg). The combined supernatant was concentrated, and more product crystallized from solution (12 mg), which was rinsed with cold MeOH/benzene mixture and then dried by high vacuum. Combined yield = 87 mg (73%). 

\[ \text{1H NMR (600 MHz, methanol-}d₄) 6.85 (td, J = 6.8, 1.8 Hz, 1H), \]
5.02 (d, J = 6.0 Hz, 1H), 4.92 (s, 1H), 4.71 (s, 1H), 4.47 (dd, J = 10.2, 6.1 Hz, 1H), 4.16 (dd, J = 10.3, 2.1 Hz, 1H), 3.85 (d, J = 11.1 Hz, 1H), 3.41 (d, J = 11.2 Hz, 1H), 3.24 (ddd, J = 15.3, 5.1, 3.5 Hz, 1H), 2.68 – 2.57 (m, 2H), 2.45 (ddd, J = 13.0, 4.2, 2.5 Hz, 1H), 2.13 (ddd, J = 15.3, 13.1, 5.3 Hz, 1H), 2.04 (td, J = 13.0, 4.9 Hz, 1H), 1.99 – 1.87 (m, 3H), 1.59 (dd, J = 13.0, 2.6 Hz, 1H), 1.48 (qd, J = 13.0, 4.2 Hz, 1H), 1.36 (td, J = 13.1, 5.0 Hz, 1H), 1.22 (s, 3H), 0.89 (s, 3H). 13C NMR (151 MHz, methanol-d4) δ 172.60, 164.13, 149.13, 148.66, 129.90, 109.44, 76.13, 66.66, 66.12, 57.58, 57.03, 47.33, 40.35, 38.92, 38.30, 25.82, 25.70, 22.36, 18.78, 15.21. HRMS (ESI+) calcd for [C20H30NO5+]: 364.2118, found: 364.2119. IR (neat) (cm⁻¹) 1740.2, 1722.6, 1673.7, 1643.9.

Andrographolide isoxazole (2c)

Method A (Figure 6, reaction): Andrographolide-3-oxime (45 mg, 0.13 mmol) was dissolved in THF, and NEt3 (35 μL) was added, followed by TsCl (31 mg, 0.163 mmol, 1.3 equiv). The reaction was stirred for 36 hours at 40 °C, after which time a second portion of NEt3 and TsCl were added. The reaction was heated at 40 °C for another 36 hours. Then, the reaction was allowed to cool to RT and filtered, and the solvent was evaporated. Chromatography on silica gel, eluting with a gradient of 0 to 5% MeOH in DCM gave 3,19-andrographolide isoxazole (25 mg, 55%).

Method B (Figure 6, reaction): 3-keto-andrographolide (50 mg, 0.144 mmol) was combined with NH2OSO3H (33 mg, 0.288 mmol, 2 equiv) in 1:1 TFE:0.01% TFA(aq) (2.5 mL) and stirred at 50 °C for 24 hours. The reaction was then allowed to cool to RT, and saturated NaHCO3 (2 mL) was added. The mixture was then extracted with 4:1 EA:THF (3 x 10 mL). The organic extracts were combined, dried over Na2SO4, and filtered, and the solvent was evaporated. The resulting residue was purified by silica gel chromatography with 0 to 5% MeOH in CHCl3. Yield = 24.5 mg (49%).

Method C: The product was isolated as a side product from the synthesis of andrographolide lactam (Figure 6). 1H NMR (600 MHz, methanol-d4) δ 6.84 (td, J = 6.7, 1.8 Hz, 1H), 5.03 (m, 1H), 4.97 (q, J = 1.3 Hz, 1H), 4.74 (q, J = 1.3 Hz, 1H), 4.47 (dd, J = 10.2, 6.1 Hz, 1H), 4.16 (dd, J = 10.2, 2.1 Hz, 1H), 4.01 (d, J = 7.8 Hz, 1H), 3.96 (d, J = 7.8 Hz, 1H), 2.70 – 2.56 (m, 4H), 2.43 (ddd, J = 12.9, 4.3, 2.4 Hz, 1H), 2.14-1.99 (m, 3H), 1.81 – 1.74 (m, 2H), 1.69 (ddt, J = 12.8, 5.6, 2.9 Hz, 1H), 1.42 (qd, J = 13.1, 4.3 Hz, 1H), 1.25 (s, 3H), 0.76 (s, 3H). 13C NMR (151 MHz, methanol-d4) δ 172.56, 167.52, 148.74, 148.00, 130.07, 110.50, 78.83, 76.12, 66.66, 55.66, 54.29, 53.13, 41.18, 38.34, 35.20, 26.21, 26.11, 24.94, 18.11, 13.96. HRMS (ESI+) calcd for [C20H28NO4+]: 346.2013, found: 346.2013. IR (neat) (cm⁻¹) 1721.8, 1675.8, 1647.7. Product confirmed by x-ray crystallography.
Andrographolide lactam (2d)

3-keto-andrographolide (108 mg, 0.310 mmol) was combined with hydroxylamine-o-sulfonic acid (70 mg, 0.62 mmol, 2 equiv) and 1:1 TFE:2.5% NaHCO₃(aq) in a 20 mL vial along with a magnetic stir bar. The vial was flushed with N₂, capped, and stirred at 50 °C for 40 minutes then at 80 °C for 1 hour. The reaction was then allowed to cool to RT and was concentrated with a rotary evaporation under vacuum to a volume of 1.5 mL. Saturated NaHCO₃ (2 mL) and brine (5 mL) were then added, and the mixture was extracted with 3:1 EA:THF three times (50 mL each). The organic extracts were combined, dried over Na₂SO₄ and filtered, and the solvent was evaporated. The resulting residue was purified by silica gel chromatography, eluting with 0 to 5% MeOH in CHCl₃ (with 0.2% NH₄OH added to the CHCl₃) to elute andrographolide isoxazole (38 mg, 35% yield) and then with 5 to 8% MeOH in CHCl₃ to elute the target lactam. Yield = 36 mg (32%). The product elutes in a fairly broad band with a yield lower than is expected by NMR spectroscopy (NMR yield = 45%).

1H NMR (600 MHz, methanol-4) δ 6.84 (td, J = 6.6, 1.7 Hz, 1H), 5.03 (d, J = 6.1 Hz, 1H), 4.95 (s, 1H), 4.72 (s, 1H), 4.47 (dd, J = 10.2, 6.2 Hz, 1H), 4.16 (dd, J = 10.2, 2.1 Hz, 1H), 3.73 (d, J = 10.9 Hz, 1H), 3.50 (d, J = 10.9 Hz, 1H), 2.70 – 2.61 (m, 3H), 2.45 – 2.38 (m, 2H), 2.20 (dd, J = 8.2, 5.7 Hz, 1H), 2.12 – 2.05 (m, 2H), 1.96 – 1.90 (m, 2H), 1.83 (ddd, J = 14.6, 7.8, 2.9 Hz, 1H), 1.53 (qd, J = 13.1, 4.3 Hz, 1H), 1.35 (s, 3H), 0.95 (s, 3H).

13C NMR (151 MHz, methanol-d4) δ 178.90, 172.57, 148.94, 148.63, 129.89, 109.71, 76.11, 66.70, 66.69, 61.27, 55.89, 53.67, 43.01, 38.55, 36.87, 32.20, 27.89, 27.79, 26.28, 17.76. HRMS (ESI+) calcd for [C₂₀H₂₉NO₅Na⁺]: 386.1938, found: 386.1934. IR (neat) (cm⁻¹) 1738, 1671, 1632, 1570 (shoulder). The product structure was confirmed by x-ray crystallography.
Figure 11: X-ray crystal structure of Andrographolide lactam (2d)

Dehydroxymethyl-andrographolide (2e)

3-keto-andrographolide (100 mg, 0.287 mmol) was combined with methyl acrylate (200 μL, 2.21 mmol, 8 equiv), TFE (2 mL), and a magnetic stir bar in a 20 mL vial and stirred to form a solution. SmI₂ in THF (0.1 M, 6 mL, 2 equiv) was then added, the vial was capped, and the mixture was heated at 65 °C with stirring for 25 minutes. The reaction was then allowed to cool to room temperature, and saturated bicarbonate solution (5 mL) was added. The mixture was extracted with ethyl acetate (3 x 15 mL), and the combined organic layers were dried over Na₂SO₄, filtered, and the solvent was concentrated to ~8 mL. Silica gel (~2 g) was added and the solvent was removed by rotary evaporation to deposit the product onto the silica gel. Chromatography on silica gel, eluting with 0 to 3% MeOH in CHCl₃ yielded the dehydroxymethyl ketone (38 mg, 40% yield) as a white solid. ¹H NMR (500 MHz, methanol-d₄) δ 6.87 (td, J = 6.7, 1.7 Hz, 1H), 5.03 (d, J = 6.1 Hz, 1H), 4.99 (s, 1H), 4.77 (s, 1H), 4.47 (dd, J = 10.2, 6.1 Hz, 1H), 4.16 (dd, J = 10.2, 2.1 Hz, 1H), 2.76 – 2.66 (m, 2H), 2.58 (td, J = 14.7, 14.3, 6.0 Hz, 1H), 2.44 (ddd, J = 13.2, 4.2, 2.4 Hz, 1H), 2.40 (dq, J = 6.1, 12.2, 1H), 2.30 (ddd, J = 14.5, 4.7, 2.5 Hz, 1H), 2.16 (ddd, J = 12.9, 6.3, 2.4 Hz, 1H), 2.13 – 2.05 (m, 2H), 1.85 (ddt, J = 13.0, 5.3, 3.0 Hz, 1H), 1.61 (td, J = 13.6, 4.7 Hz, 1H), 1.50 (ddd, J = 12.2, 12.2, 3.4 Hz, 1H), 1.32 (qd, J = 13.1, 4.3 Hz, 1H), 1.01 (s, 3H), 0.98 (d, J = 6.5 Hz, 3H). ¹³C NMR (126 MHz, chloroform-d) δ 213.89, 171.19, 147.66, 147.05, 128.52, 108.71, 108.71, 108.71, 108.71, 108.71, 108.71, 108.71, 108.71, 108.71, 108.71, 108.71, 108.71, 108.71, 108.71, 108.71, 108.71, 108.71, 108.71. HRMS (ESI-) calcd for [C₁₀H₁₅O₄]: 317.1758, found: 317.1754. IR (neat) (cm⁻¹) 1725.9, 1708.3, 1678.0. The product structure was confirmed by x-ray crystallography.
Figure 12: X-ray crystal structure of De-hydroxymethyl-andrographolide (2e)

3-(N-phenyl)amino-dehydroxymethyl-andrographolide (2f)

1e (19 mg, 0.060 mmol) was combined with aniline (16 μL, 0.18 mmol 3 equiv), formic acid (9 μL, 0.24 mmol, 4 equiv), Ir-1 (1.7 mg, 0.0028 mmol, 4.5 %), and TFE (0.5 mL) in a small Schlenk flask, along with a magnetic stir bar. The flask was sealed and heated at 65 °C with stirring for 19 hours. The flask was periodically exposed to Schlenk line N₂ until carbon dioxide pressure buildup ceased (after 5 minutes, 10 minutes, 30 minutes, and 1 hour the flask was briefly opened to N₂ and then resealed). The reaction was then cooled to room temperature and saturated NaHCO₃ solution (1 mL) was added. The mixture was extracted with 3:1 ethyl acetate:THF (4 x 4 mL). The organic extracts were dried over Na₂SO₄, filtered and dried down to a residue. The residue was purified by silica gel chromatography, eluting with CHCl₃ followed by a gradient of 0% to 0.5% CH₃OH in CHCl₃. Yield = 10.6 mg (45%). ¹H NMR (900 MHz, methanol-d₄) δ 7.05 (t, J = 7.8 Hz, 2H), 6.93 – 6.88 (m, 1H), 6.65 (d, J = 7.9 Hz, 2H), 6.52 (t, J = 7.2 Hz, 1H), 5.01 (d, J = 5.9 Hz, 1H), 4.93 (s, 1H), 4.70 (s, 1H), 4.45 (dd, J = 10.2, 6.1 Hz, 1H), 4.16 (dd, J = 10.2, 1.9 Hz, 1H), 3.56 – 3.52 (m, 1H), 2.72 (ddd, J = 16.7, 6.9, 2.9 Hz, 1H), 2.59 (ddd, J = 17.2, 11.4, 6.7 Hz, 1H), 2.46 – 2.41 (m, 1H), 2.15 (td, J = 13.2, 5.1 Hz, 1H), 2.12 (d, J = 10.9 Hz, 1H), 1.85 (dq, J = 13.6, 2.8 Hz, 1H), 1.83 – 1.77 (m, 2H), 1.67 (tt, J = 13.9, 3.7 Hz, 1H), 1.61 (td, J = 12.1, 3.2 Hz, 1H), 1.56 (dt, J = 12.7, 3.2 Hz, 1H), 1.51 (td, J = 13.6, 3.5 Hz, 1H), 1.14 (qd, J = 12.9, 4.3 Hz, 1H), 0.94 (d, J = 6.8 Hz, 3H), 0.78 (s, 3H). ¹³C NMR (226 MHz, methanol-d₄) δ 172.74, 150.20, 149.88, 149.50, 129.98, 129.64, 116.95, 113.96, 109.19, 76.20, 66.63, 55.75, 54.70, 46.61, 40.29, 38.44, 35.93, 33.78, 27.93, 27.16, 25.74, 17.33, 12.72. HRMS (ESI+) calcd for [C₂₅H₃₄NO₃⁺]: 396.2533, found: 396.2528.
Fusidic lactam (2h, 2i)

3-keto-methyl fusidate (80 mg, 0.15 mmol) was combined with hydroxylamine-o-sulfonic acid (26 mg, 0.23 mmol, 1.5 equiv) in 1:1 HFIP:H2O (1.9 mL) along with a magnetic stir bar. The resulting solution was heated at 50 °C with stirring for 20 minutes and then at 80 °C for 30 minutes. The reaction was then cooled to room temperature, and saturated bicarbonate (3 mL) was added. The mixture was extracted with 1.5:1 ethyl acetate:THF (4 x 8 mL). The organic layers were filtered through Na2SO4 in a glass fritted filter, collected, and dried down into a 25 mL round bottom schlenk flask. To the residue 1:1 acetone:H2O (10 mL) was added, the flask was sealed and heated at 80 °C for 10 minutes with stirring, and then cooled to room temperature. Brine (3 mL) was added to the mixture and then it was extracted with 1.5:1 ethyl acetate:THF (4 x 10 mL). The combined organic extracts were dried over Na2SO4, filtered, and concentrated to 10 mL. Silica gel (~1.5 g) was added and then the solvent was fully evaporated by rotary evaporation to deposit the product onto the silica gel. Silica gel chromatography, eluting with 2.25% MeOH in DCM yielded purified fusidic lactam. 1h eluted first. Yield = 38 mg (46%). 1H NMR (900 MHz, chloroform-d) δ 5.86 (d, J = 8.3 Hz, 1H), 5.42 (d, J = 4.6 Hz, 1H), 5.08 (t, J = 6.9 Hz, 1H), 4.40 (s, 1H), 3.64 (s, 3H), 3.41 (h, J = 6.5 Hz, 1H), 3.03 (d, J = 11.9 Hz, 1H), 2.56 (ddd, J = 14.0, 10.4, 2.6 Hz, 1H), 2.52 – 2.37 (m, 4H), 2.29 (dt, J = 13.1, 2.7 Hz, 1H), 2.15 (dd, J = 14.4, 8.7 Hz, 1H), 2.12 (dt, J = 14.8, 7.4 Hz, 1H), 2.04 (dt, J = 14.8, 7.4 Hz, 1H), 1.97 (s, 3H), 1.94 (m, 1H), 1.92 – 1.82 (m, 3H), 1.67 (s, 3H), 1.60 (s, 3H), 1.52 (s, 1H), 1.49 (m, 1H), 1.33 – 1.28 (m, 4H), 1.26 (d, J = 3.6 Hz, 1H), 1.18 (d, J = 6.6 Hz, 3H), 1.16 – 1.06 (m, 2H), 1.13 (s, 3H), 0.92 (s, 3H). 13C NMR (226 MHz, chloroform-d) δ 176.41, 170.66, 170.48, 148.27, 132.80, 130.97, 123.14, 77.36, 74.42, 67.98, 51.58, 49.15, 48.65, 48.62, 48.08, 44.09, 39.80, 39.31, 39.25, 36.58, 35.56, 33.77, 32.64, 29.10, 28.36, 25.88, 25.74, 22.79, 22.56, 21.11, 20.93, 18.18, 17.91. HRMS (ESI+) calcd for [C32H49NO5Na+] : 566.3452 found: 566.3443. IR (neat) (cm^-1) 1715.6, 1650.5. Next an impurity eluted, followed by 1i. 1i partially overlapped with the impurity and the impure fractions were purified by a second column, eluting with 2% MeOH in DCM. Combined yield = 11 mg (13%). 1H NMR (900 MHz, chloroform-d) δ 5.87 (d, J = 8.2 Hz, 1H), 5.59 (t, J = 6.2 Hz, 1H), 5.08 (t, J = 6.6 Hz, 1H), 4.44 (s, 1H), 3.65 (s, 3H), 3.50 (m, 1H), 3.21 (m, 1H), 3.01 (d, J = 12.1 Hz, 1H), 2.49 – 2.41 (m, 3H), 2.32 (p, J = 7.4 Hz, 1H), 2.27 (d, J = 13.2 Hz, 1H), 2.17 – 2.11 (m, 2H), 2.04 (dt, J = 14.5, 7.8 Hz, 1H), 1.99 (d, J = 4.9 Hz, 1H), 1.98 (s, 3H), 1.92 (td, J = 13.0, 2.2 Hz, 2H), 1.84 (t, J = 10.6 Hz, 1H), 1.71 – 1.66 (m, 4H), 1.60 (s, 3H), 1.46 – 1.40 (m, 2H), 1.33 (d, J = 14.2 Hz, 1H), 1.28 (s, 3H), 1.24 (d, J = 7.2 Hz, 3H), 1.19 (m, 1H), 1.13 (s, 3H), 1.12 (m, 1H), 1.03 (td, J = 13.8, 5.8 Hz, 1H), 0.94 (s, 3H). 13C NMR (226 MHz, chloroform-d) δ 180.56, 170.60, 170.50, 148.44, 132.78, 131.07, 123.17, 74.36, 68.40, 51.60, 49.25, 48.11, 44.16, 43.80, 42.99, 39.48, 39.35, 39.23, 38.66, 37.99, 36.86, 36.35, 29.13, 28.35, 26.04, 25.89, 24.21, 23.60, 21.12, 18.27, 17.92, 16.92. HRMS (ESI+) calcd for [C32H49NO5Na+] : 566.3452 found: 566.3447. IR (neat) (cm^-1) 1716.8, 1641.2.
3-amino-fusidic acid methyl ester (2j)

3-keto-methyl fusidate (50 mg, 0.094 mmol), ammonium formate (18 mg, 0.29 mmol, 3 equiv), and Ir-1 (1.4 mg, 0.0024 mmol, 2.5%) were weighed into a small Schlenk flask, along with a magnetic stir bar. MeOH (300 μL) and acetic acid (5.4 μL, 0.094 mmol, 1 equiv) were then added. The mixture was heated at 60 °C with stirring for 4 hours. The flask was periodically exposed to Schlenk line N2 until carbon dioxide pressure buildup ceased (after 5 minutes, 10 minutes, and 1 hour the flask was briefly opened to N2 and then resealed). After the reaction, 5% Na2CO3 (1 mL) was added, and the mixture was extracted with ethyl acetate (3 x 2.5 mL each). The organic fractions were combined, dried over Na2SO4, and filtered, and the solvent was evaporated. Preparative reverse phase HPLC with a C18 column, eluting with a gradient of 0 to 95% CH3CN in H2O yielded pure 3-amino-fusidic acid methyl ester (39 mg, 73%). 1H NMR (600 MHz, chloroform-d) δ 5.83 (d, J = 8.4 Hz, 1H), 5.07 (m, 1H), 4.32 (s, 1H), 3.62 (s, 3H), 3.02 (d, J = 11.6 Hz, 1H), 2.92 (s, 1H), 2.46 (m, 1H), 2.40 (m, 1H), 2.27 (d, J = 13 Hz, 1H), 2.21-2.07 (m, 3H), 2.06-1.98 (m, 2H), 1.96 (s, 3H), 1.90 (m, 1H), 1.82 (m, 1H), 1.73 – 1.51 (m, 1H), 1.45 (d, J = 12.4 Hz, 2H), 1.36 (s, 3H), 1.25 (d, J = 14.0 Hz, 1H), 1.15-1.04 (m, 2H), 0.96 (s, 3H), 0.88 (s, 3H), 0.84 (d, J = 7 Hz, 3H). 13C NMR (126 MHz, chloroform-d) δ 170.90, 170.51, 148.30, 132.69, 130.39, 123.15, 74.52, 68.18, 51.55, 51.54, 49.35, 48.77, 44.02, 39.56, 39.12, 37.30, 35.88, 35.78, 35.70, 32.14, 30.20, 30.12, 29.02, 28.44, 25.88, 24.14, 23.38, 21.12, 20.99, 17.89, 17.80, 16.57. HRMS (ESI+) calcd for [C32H52NO5+]: 530.3840, found: 530.3830.

1,2-dihydro-3-(N-2,6-difluorophenyl)amino-D-glucal (2l)

Keto-d-glucal (20 mg, 0.14 mmol) was combined with 2,6-difluoro aniline (31 μL, 0.29 mmol, 2 equiv), formic acid (16 μL, 0.42 mmol, 3 equiv), Ir-1 (2.6 mg, 0.0042 mmol, 3%), MeOH (0.20 mL), and a magnetic stir bar in a 5 mL Schlenk flask. The reaction was heated at 65 °C under nitrogen for 16 hours. The flask was periodically exposed to Schlenk line N2 until carbon dioxide pressure buildup ceased (after 5 minutes, 10 minutes, and 1 hour the flask was briefly opened to N2 and then resealed). After the reaction, the mixture was neutralized by the addition of NEt3 (30 μL) in 1:1 THF:ethyl acetate, filtered through a plug of basic alumina, and the solvent was evaporated. Preparative reverse phase HPLC with a C18 column, eluting with a gradient of 0 to 95% CH3CN in H2O yielded pure 1,2-dihydro-3-(N-2,6-difluorophenyl)amino-D-glucal (2l).
evaporated. The product was isolated by silica gel chromatography, eluting with 25 to 50% ethyl acetate in hexanes. Yield = 29 mg (80%) oil. $^1$H NMR (600 MHz, chloroform-$d$) $\delta$ 6.91 – 6.77 (m, 3H), 3.96 – 3.88 (m, 2H), 3.86 – 3.69 (m, 5H), 3.50 (ddd, $J = 9.5, 5.8, 3.8$ Hz, 1H), 2.88 (d, $J = 8.0$ Hz, 1H), 2.12 (t, $J = 6.1$ Hz, 1H), 1.92 – 1.83 (m, 1H), 1.78 (dq, $J = 14.4, 2.8$ Hz, 1H). $^{13}$C NMR (151 MHz, chloroform-$d$) $\delta$ 155.24, 124.51, 120.76, 111.87, 76.76, 76.68, 68.00, 63.55, 61.46, 54.38, 30.10. HRMS (ESI+) calcd for [C$_{12}$H$_{16}$F$_2$NO$_3$$^+$]: 260.1093, found: 260.1091.

![Image](image.png)

1,2-dihydro-3-(N-lithocholic)amino-D-glucal (2m)

Keto-d-glucal (8.2 mg, 0.057 mmol) was combined with lithocholic amine (25 mg, 0.068 mmol, 1.2 equiv), formic acid (5.4 μL, 0.14 mmol, 2.5 equiv), Ir-l (1 mg, 0.0017 mmol, 3%), and methanol-d$_4$ (500 μL) in a small Schlenk flask. The flask was sealed and heated at 60 ºC under nitrogen for 20 hours. The flask was periodically exposed to Schlenk line N$_2$ until carbon dioxide pressure buildup ceased (after 10 minutes, 30 minutes, and 1 hour the flask was briefly opened to N$_2$ and then resealed). Then the reaction was cooled to room temperature and saturated bicarbonate was added (0.8 mL). The mixture was extracted (3 x 3 mL) with CHCl$_3$. The organic phases were combined, dried over Na$_2$SO$_4$, and dried down. The product was isolated by silica gel chromatography with 0 to 15% MeOH in 1:4 benzene:CHCl$_3$. Yield = 12 mg (43%) plus recovered d-glucal (3 mg, 35%). $^1$H NMR (500 MHz, chloroform-$d$) $\delta$ 3.83 – 3.51 (m, 6H), 3.00 (s, 1H), 2.67 (s, 1H), 2.51 (s, 1H), 2.04 (d, $J = 11.2$ Hz, 1H), 1.97 – 1.73 (m, 5H), 166 - 1.63 (m, 2H), 1.55 – 1.24 (m, 14H), 1.24 – 1.06 (m, 7H), 1.05 – 0.91 (m, 7H), 0.71 (s, 3H). $^{13}$C NMR (126 MHz, chloroform-$d$) $\delta$ 76.90, 71.01, 66.76, 61.80, 60.93, 56.55, 56.25, 55.15, 48.05, 47.88, 42.48, 42.13, 40.49, 40.16, 35.84, 35.76, 35.62, 35.07, 34.28, 33.26, 29.78, 28.02, 26.96, 26.27, 25.79, 23.88, 22.54, 20.55, 17.78, 11.08. HRMS (ESI+) calcd for [C$_{30}$H$_{53}$DNO$_5$$^+$]: 493.4110, found: 493.4100.

![Image](image.png)

Estriol lactol (2o)

Keto-estriol (50 mg, 0.17 mmol) was combined with THF (0.5 mL), [Pt(dppb)(OH)]$_2$[BF$_4$]$_2$ (8 mg, 5.5 μmol, 3 %), 30% H$_2$O$_2$(aq) (35 μL, 0.35 mmol, 2 equiv), and a magnetic stir bar in a one dram vial. The mixture was stirred at room temperature with monitoring by TLC. During the first 20 minutes, the vial was kept with a loose cap to allow for gas evolution. After 20 minutes gas
evolution ceased and the vial was capped. After one day a second aliquot of H₂O₂ (aq) (35 μL, 0.35 mmol, 2 equiv) was added. After 2 days the reaction was determined to be complete. Additional THF was then added (1 mL) and the reaction mixture was eluted through a plug of Na₂SO₄ followed by a rinse of THF (1 mL). To the solution silica gel (~1 g) was added and the product was deposited onto the silica gel by rotary evaporation. Chromatography on silica gel with 5% MeOH in DCM yielded the acid-lactol (46.5 mg, 84%).

**Alternative procedure:** Keto-estriol (100 mg, 0.35 mmol) was combined with THF (1 mL), [Pt(dppb)(OH)]₂[BF₄]₂ (16 mg, 11 μmol, 3 %), 30% H₂O₂(140 μL, 2.8 mmol, 4 equiv), and a magnetic stir bar in a one dram vial. The mixture was stirred at room temperature for 20 minutes until gas evolution ceased. Then the vial was capped and heated at 45 °C with monitoring by TLC. After 6 hours the reaction was determined to be complete and cooled to room temperature. Additional THF was then added (1 mL) and the reaction mixture was eluted through a plug of Na₂SO₄ followed by a rinse of THF (1 mL). To the solution silica gel (~1 g) was added and the product was deposited onto the silica gel by rotary evaporation. Chromatography on silica gel with 5% MeOH in DCM yielded the acid-lactol (86 mg, 77%).

**Note regarding isomeric forms and NMR characterization:** At room temperature in solution, the product is in rapid equilibrium between 3 different isomeric forms: an acid-aldehyde and both possible hemiacetal epimers. NMR studies were conducted at -40 °C in order to observe all three species (in a 1.4:1:1 ratio, respectively). In addition to the study of ¹H and ¹³C NMR spectra for the product, ¹H-¹³C HSQC and comparison of the product ¹³C spectrum to the ¹³C spectra of other estriol derivatives enabled all of the ¹³C peaks to be located. 5 out of the 6 aromatic ¹³C peaks for the hemiacetal epimers are superposed, and the aromatic phenol ¹³C peak is superposed for all 3 isomeric forms. 3 of the aliphatic ¹³C peaks are superposed for the hemiacetal epimers. 3 distinct ¹³C peaks in the 9 to 16 ppm range correspond to the –CH₃ group in the three different isomeric forms. ¹H NMR (500 MHz, tetrahydrofuran-d₈) δ 11.82 – 11.39 (m, 1H), 9.34 (s, 1H), 8.79 – 8.59 (m, 3H), 7.37 (s, 1H), 7.08 (s, 4H), 6.55 – 6.47 (m, 3H), 6.42 (s, 3H), 5.19 – 5.04 (m, 2H), 2.81 – 2.60 (m, 8H), 2.48 – 2.27 (m, 6H), 2.26 – 2.05 (m, 6H), 1.97 – 1.83 (m, 6H), 1.57 – 1.50 (m, 1H), 1.48 – 1.16 (m, 12H), 1.04 – 0.81 (m, 9H). ¹³C NMR (126 MHz, tetrahydrofuran-d₈) δ 206.35, 174.97, 170.77, 170.03, 156.66, 156.64, 156.64, 156.66, 137.95, 137.94, 137.94, 137.86, 130.72, 130.62, 130.34, 127.32, 127.06, 115.60, 115.59, 115.55, 113.80, 113.70, 113.68, 105.23, 103.37, 51.33, 43.96, 43.89, 43.77, 41.73, 41.67, 40.43, 39.94, 39.88, 37.63, 37.17, 36.38, 35.60, 35.31, 33.77, 32.85, 32.37, 31.97, 31.13, 30.87, 30.83, 27.75, 26.98, 26.79, 26.71, 26.49, 26.48, 15.81, 13.31, 9.94. HRMS (ESI-) calcd for [C₁₈H₂₁O₄]: 301.1445, found: 301.1444. IR (neat, RT) (cm⁻¹) 1695.4, 1672.5, 1606.2. Additional confirmation of the structure of this product was obtained by transforming it into lactam derivatives 2p and 2q in high yield under reductive amination conditions.

![Estriol-N-H-lactam (2p)](image)

**Estriol-N-H-lactam (2p)**

**Method A (Figure 7 reaction xviii):** Keto-estriol (25 mg, 0.087 mmol) was combined with ammonium formate (17 mg, 0.26 mmol, 3 equiv), acetic acid (5 μL, 0.087, 1 equiv), Ir-1 (1.32
mg, 2.2 μmol, 2.5%), MeOH (200 μL), and a magnetic stir bar in a small Schlenk flask. The reaction was heated at 60 °C under nitrogen for 4 hours. The flask was periodically exposed to Schlenk line N₂ until carbon dioxide pressure buildup ceased (after 5 minutes, 10 minutes, 30 minutes, and 1 hour the flask was briefly opened to N₂ and then resealed). Upon completion, the reaction was cooled to room temperature and saturated bicarbonate was added (2 mL). The mixture was extracted with ethyl acetate (3 x 10 mL). The organic phases were combined, dried over Na₂SO₄, and dried down. The product was isolated by silica gel chromatography with 0 to 5% MeOH in CHCl₃. Yield = 13.5 (54%).

**Method B (Figure 7 reaction xvi):** Estriol-acid-lactol (11 mg, 0.036 mmol) was combined with ammonium formate (7 mg, mmol, 3 equiv), formic acid (1.4 μL, 1 equiv), Ir-1 (0.6 mg, mmol, 2.5%), MeOH (700 μL), and a magnetic stir bar in a 5 mL Schlenk flask. The reaction was heated at 60 °C under nitrogen for 4 hours. The flask was periodically exposed to Schlenk line N₂ until carbon dioxide pressure buildup ceased (after 10 minutes, 30 minutes, and 1 hour the flask was briefly opened to N₂ and then resealed). Yield = 8.5 mg (78%). ¹H NMR (600 MHz, methanol-d₄) δ 7.10 (d, J = 8.5 Hz, 1H), 6.55 (d, J = 8.5 Hz, 1H), 6.49 (s, 1H), 3.04 (d, J = 12.0 Hz, 1H), 2.95 (d, J = 12.0 Hz, 1H), 2.81 – 2.75 (m, 2H), 2.56 (dd, J = 18.1, 5.8 Hz, 1H), 2.38 – 2.32 (m, 1H), 2.27 (t, J = 9.6 Hz, 1H), 2.01 – 1.91 (m, 2H), 1.74 – 1.67 (m, 1H), 1.57 (td, J = 11.9, 11.2, 5.8 Hz, 1H), 1.51 – 1.39 (m, 2H), 1.32 – 1.19 (m, 2H), 0.99 (s, 3H). ¹³C NMR (151 MHz, methanol-d₄) δ 174.99, 156.13, 138.62, 132.03, 127.20, 115.87, 113.93, 56.57, 44.42, 44.12, 41.50, 38.17, 33.38, 33.29, 30.78, 27.05, 26.98, 16.25. HRMS (ESI+) calcd for [C₁₈H₂₄NO₂⁺]: 286.1702, found: 286.1797. IR (neat) (cm⁻¹) 1740.6, 1673.1, 1644.5.

**Estriol-N-phenyl-lactam (2q)**

Estriol-acid-lactol (19 mg, 0.063 mmol) was combined with aniline (12 μL, 2 equiv), formic acid (7 μL, 3 equiv), Ir-1 (mg, mmol, 2.5%), MeOH (1 mL), and a magnetic stir bar in a 5 mL Schlenk flask. The reaction was heated at 60 °C under nitrogen for 12 hours. During the first 4 hours the flask was left open to the Schlenk line via a reflux condenser to allow for the release of carbon dioxide. During the reaction, a white precipitate formed. After the reaction, the mixture was neutralized by the addition of 30 μL triethylamine. The resulting mixture was then filtered to collect the white solid product in a glass-fritted funnel. The product was rinsed with methanol twice and then dried under high vacuum. Yield = 18.5 mg (77%) white powder. ¹H NMR (600 MHz, dimethylformamide-d₇) δ 9.19 (s, 1H), 7.41 (t, J = 7.7 Hz, 2H), 7.33 (d, J = 7.7 Hz, 2H), 7.26 (t, J = 7.4 Hz, 1H), 7.14 (d, J = 8.4 Hz, 1H), 6.67 – 6.62 (m, 1H), 6.59 – 6.55 (m, 1H), 3.63 (d, J = 11.5 Hz, 1H), 3.20 (d, J = 11.4 Hz, 1H), 2.79 (dd, J = 10.1, 5.5 Hz, 2H), 2.64 (dd, J = 17.8, 5.9 Hz, 1H), 2.35 (d, J = 10.1 Hz, 1H), 2.28 (d, J = 10.2 Hz, 1H), 2.13 (dd, J = 17.8, 12.7 Hz, 1H), 1.99 (dt, J = 11.7, 5.9 Hz, 1H), 1.76 – 1.68 (m, 2H), 1.52 – 1.37 (m, 2H), 1.28 (dt, J = 10.8, 6.2 Hz, 2H), 1.12 (s, 3H). ¹³C NMR (151 MHz, dimethylformamide-d₇) δ 174.99, 156.81, 145.45, 138.55, 131.55, 129.84, 127.47, 127.23, 127.14, 116.04, 114.06, 65.68, 44.88, 43.74, 41.10, 37.66,
3.40, 3.44, 3.66, 3.90, 3.87, 1.60. HRMS (ESI+) calcd for [C_{24}H_{28}NO_{2}^+] : 362.2115, found: 362.2115.

\[ \text{Me} \quad \text{Me} \quad \text{Me} \quad \text{HO} \]
\[ \text{HO} \quad \text{H} \quad \text{OAc} \quad \text{OMe} \]

3-epi-fusidic acid methyl ester (3a)

**Method A:** 3-keto-fusidic acid methyl ester (83 mg, 0.16 mmol) was combined with 1:3 iPrOH:TFE (3.1 mL) and a magnetic stir bar in a 20 mL vial, and the resulting mixture was stirred to form a solution. Then a solution of Ru-2 (4.8 mg, 3.2 μmol, 2.0 mol %) and NMM (0.76 μL, 6.4 μmol, 4.0 mol %) in TFE (0.2 mL) was added from a stock solution. The vial was capped, and the reaction was heated at 65 °C for 1 hour with stirring. The reaction was then allowed to cool to RT, and all of the volatile materials were evaporated by rotary evaporation. The crude product was purified by silica gel chromatography, eluting with 15% to 18% ethyl acetate in hexanes. Yield = 67 mg (82%) of a transparent solid.

**Method B:** Fusidic acid methyl ester (40 mg, 0.08 mmol) was combined with TFE (80 μL) and a magnetic stir bar in a 20 mL vial, and the resulting mixture was stirred to form a solution. Then a solution of Ru-2 (4.6 mg, 3.0 μmol, 4.0 mol %) and NMM (0.75 μL, 6.1 μmol, 8.0 mol %) in TFE (80 μL) was added from a stock solution. The vial was capped, and the reaction was heated at 70 °C for 11 hours with stirring. The reaction was then allowed to cool to RT, and all of the volatile materials were evaporated by rotary evaporation. The crude product was purified by silica gel chromatography, eluting with 15% to 18% ethyl acetate in hexanes. Yield = 32 mg (80%) of a transparent solid.

**1H NMR (700 MHz, chloroform-d)** δ 5.83 (d, J = 8.4 Hz, 1H), 5.07 (t, J = 6.8 Hz, 1H), 4.33 (s, 1H), 3.63 (s, 3H), 3.12 (td, J = 10.5, 5.3 Hz, 1H), 3.00 (d, J = 12.0 Hz, 1H), 2.50 – 2.37 (m, 2H), 2.27 (d, J = 13.2 Hz, 1H), 2.17 – 2.08 (m, 2H), 2.01 (dq, J = 15.1, 7.4 Hz, 1H), 1.97 (s, 3H), 1.94 – 1.82 (m, 3H), 1.77 – 1.72 (m, 2H), 1.70 – 1.67 (m, 1H), 1.66 (s, 3H), 1.62 (td, J = 12.9, 12.4, 4.2 Hz, 1H), 1.58 (s, 3H), 1.54 (s, 1H), 1.53 – 1.48 (m, 1H), 1.38 (ddt, J = 16.7, 12.6, 6.5 Hz, 1H), 1.32 (s, 1H), 1.31 (s, 3H), 1.29 – 1.22 (m, 2H), 1.11 (tq, J = 13.6, 6.7 Hz, 2H), 0.99 (s, 3H), 0.95 (d, J = 6.2 Hz, 3H), 0.89 (s, 3H). **13C NMR (151 MHz, chloroform-d)** δ 170.80, 170.52, 148.18, 132.72, 130.62, 123.15, 76.64, 74.48, 68.43, 51.55, 49.13, 48.82, 44.01, 43.02, 39.75, 39.53, 39.19, 36.86, 36.01, 34.41, 32.91, 31.73, 29.04, 28.40, 25.87, 24.32, 23.83, 21.10, 21.10, 17.89, 17.87, 15.49. HRMS (ESI+) calcd for [C_{32}H_{50}O_{6}Na^+] : 553.3500, found: 553.3497.
1-epi-ouabain (3b)

1-keto-ouabain (45 mg, 0.77 mmol) was combined with 1:3 iPrOH:TFE (1.7 mL) and a magnetic stir bar in a 4 mL vial, and the resulting mixture was stirred to form a solution. Then a solution of Ru-2 (2 mg, 2.8 μmol, 1.8 mol %) and NMM (0.30 μL, 6.4 μmol, 3.6 mol %) in TFE (100 μL) was added from a stock solution. The vial was capped, and the reaction was heated at 65 °C for 1 hour with stirring. The reaction was then allowed to cool to RT, and all of the volatile materials were evaporated by rotary evaporation. The crude product was purified by silica gel chromatography, eluting with 15% to 25% methanol in dichloromethane. Yield = 41 mg (90%) of a transparent solid. ^1H NMR (700 MHz, methanol-d_4) δ 5.93 (s, 1H), 5.02 (d, J = 18.0 Hz, 1H), 4.92 (d, J = 18.0 Hz, 1H), 4.34 (d, J = 11.4 Hz, 1H), 4.21 (s, 1H), 4.14 (d, J = 11.4 Hz, 1H), 3.90 (td, J = 10.8, 4.9 Hz, 1H), 3.79 (dd, J = 3.2, 1.7 Hz, 1H), 3.69 – 3.63 (m, 2H), 3.40 (t, J = 9.4 Hz, 1H), 2.88 (dd, J = 8.4, 5.3 Hz, 1H), 2.30 (td, J = 13.4, 3.2 Hz, 1H), 2.19 (ddt, J = 19.0, 12.8, 6.2 Hz, 3H), 2.04 (d, J = 12.8 Hz, 1H), 1.98 (m, 1H), 1.94 (td, J = 14.1, 4.9 Hz, 1H), 1.89 (dd, J = 9.7, 12.0 Hz, 1H), 1.83 (m, 1H), 1.74 (tt, J = 13.0, 7.4 Hz, 3H), 1.60 – 1.47 (m, 3H), 1.29 (m, 1H), 1.28 (d, J = 6.3 Hz, 3H), 0.90 (s, 3H). ^13C NMR (151 MHz, methanol-d_4) δ 176.11, 175.63, 116.73, 99.24, 83.96, 78.41, 73.82, 73.69, 72.46, 71.02, 71.00, 69.17, 64.51, 63.97, 60.96, 50.24, 48.97, 48.82, 45.72, 39.12, 35.45, 34.36, 34.09, 31.83, 28.97, 26.20, 23.86, 16.56, 15.47. HRMS (ESI+) calcd for [C_{29}H_{44}O_{12}Na^+]: 607.2725, found: 607.2726.

2.23 List of Abbreviations

DCE, dichloroethane
DCM, dichloromethane
DMAP, p-dimethylamino-pyridine
DMP, Dess Martin’s Periodinane
DMSO, dimethylsulfoxide
DPPB, 1,4-bis(diphenylphosphino)butane
HFIP, hexafluoroisopropanol
Ir-1, Cp*IrCl(N-(4-dimethylaminophenyl)-2-pyridylcarboxamide)
MeOH, methanol
MTBE, methyl tert-butyl ether
Mupirocin M.E., Mupirocin methyl ester
NBS, N-bromo succinimide
NMM, N-methyl-morpholine
Pt-1, [Pt(DPPB)(OH)]_2[BF_4]_2
2.24 References


29. Yi, C. S., He, Z. & Guzei, I. A. Transfer hydrogenation of carbonyl compounds catalyzed by a ruthenium-acetamido complex: Evidence for a stepwise hydrogen transfer


Chapter 3:

Hydroamination of Functionalized Unactivated Alkenes with Limiting Alkene
3.1 Introduction

Hydrofunctionalizations of alkenes enable rapid coupling of molecules by joining the X-H or C-H bond with alkenes, two of the most common functional groups of organic molecules. Nitrogen containing compounds are among the most important molecules for applications from medicine to materials. Therefore, the addition of N-H bonds to alkenes, in particular, has the potential to become an important method to prepare compounds containing alkyl-nitrogen bonds. However, existing metal-catalyzed hydroaminations are limited in many cases by the need for excess alkene, narrow scope of alkene and amine or amine derivative, expensive catalysts, and inability to form free primary amine products. We describe a new ruthenium trisphosphine complex that overcomes these limitations by catalyzing intermolecular hydroamination of terminal unactivated alkenes with a single equivalent of the alkene and an amine that serves as an ammonia surrogate. Preliminary mechanistic data suggest that the hydroamination reaction proceeds by a novel mechanism related to dehydrogenation processes.

The hydroamination of an alkene with an amine is a simple and atom economic method to form amines from one of the most common chemical feedstocks. This process could provide a valuable alternative to the more common methods of synthesizing amines, such as reductive amination of carbonyls and reaction of alkyl halides with cyanide, azide or phthalimide and reduction or deprotection of the substitution product. However, applications of alkene hydroaminations have been limited to intramolecular processes, to intermolecular processes with strained or conjugated alkenes, or to intermolecular processes requiring excess quantities of the alkene component. The use of excess of alkene is suitable for reactions involving simple commodity alkenes and complex amines but it is not suitable for reactions in which a simple amine or ammonia surrogate would add to a more complex alkene as part of a multi-step synthesis. The use of excess quantities of amine component is suitable for hydroaminations with ammonia, as in the hydroamination of isobutylene to form tert-butyl amine in a commercial process catalyzed by an acidic heterogeneous system, however these systems require high pressures and temperatures and significant excesses of amine (2-6 equivalents) are employed to generate even low conversions (10-20%) of product based on the alkene component.

Thermal, intermolecular hydroaminations are more limited than intramolecular hydroaminations and have been reported primarily (for intramolecular hydroamination catalyzed by lanthanides or early transition-metal complexes, see references 11–19) with late transition metal catalysts and conjugated alkenes, such as dienes, acrylic acid derivatives, and vinyl arenes. The most common catalysts for direct, thermal, intermolecular coupling of amines and unactivated terminal alkenes form the product of Markovnikov addition and consist of Ir and Au catalysts with biaryl bisphosphine ligands. Reactions of unconjugated alkenes catalyzed by the iridium complexes generated from [Ir(COE)Cl]2 and (S)-DTBM-SEGPHOS with 20 equivalents and 8 equivalents of alkene, respectively, and those of the gold-complexes generated from Ph3PAuCl and AgOTf with 4 and 60 equivalents of alkene, respectively. Biaryl bisphosphine ligands have enabled reactions to occur with low to moderate enantioselectivity, but catalysts based on these ligands have displayed only moderate reactivity and limited functional group tolerance. In general, only alkyl groups, aryl groups and other nonpolar functionality have been tolerated by these hydroamination systems.
Additions of N-H bonds to unconjugated alkenes with photoredox catalysts also have been reported, and these reactions can occur with anti-Markovnikov selectivity. However, these reactions, too, have required excess of the alkene and are likely to be challenging to conduct on large scale for potential applications.\textsuperscript{27,28} The photoredox system \([\text{Ir(dF(Me)ppy)}_2(\text{dtbbpy})][\text{PF}_6]\)\textsuperscript{27} catalyzes the addition of secondary amines to unactivated alkenes with 3-5 equivalents of alkene. Reactions of the more activated vinylarenes occur with mesityl-\(N\)-Me-acridinium, \((\text{PhS})_2\) and lutidine as catalyst with 1.5 equivalents of olefin when the nitrogen source is a pyrazole, indazole, or triazole. Reaction of the unconjugated cyclic alkene 1-methylcyclopentene occurred with limiting alkene, but 3 equivalents of HNTf\(_2\) were required.\textsuperscript{29,30}

Two general classes of mechanisms have been followed by most late transition-metal catalysts for alkene hydroamination. The first involves attack of a nitrogen nucleophile on a bound alkene, followed by protonation of the resulting amino-alkyl intermediate. The second involves oxidative addition of an N-H bond, followed by migratory insertion of the alkene and reductive elimination. Cationic rhodium, iridium and gold systems react by the first pathway,\textsuperscript{31} whereas neutral iridium complexes have reacted by the second pathway. Ruthenium complexes that are most relevant to the work reported here catalyze additions to terminal alkynes but have not been shown to catalyze additions to alkenes, let alone unconjugated alkenes with the alkene as limiting reagent.

Recently, the requirement of excess olein has been addressed by using alkenes that contain a carboxylic acid unit modified by a substituent that binds to the metal center.\textsuperscript{32–34} While valuable in some cases, the final product must contain a carbonyl group in the appropriate position for this strategy to be followed. We considered that the catalytic intermediates could be stabilized by coordination of a Lewis basic group bound to the amine, rather than the alkene. By following this strategy, the substrate containing an N-H bond could serve as an ammonia equivalent by conventional removal of the substituent on nitrogen and the scope of alkene could be broadened. Moreover, because hydroamination is nearly thermoneutral, this substituent could alter the thermodynamics of the reaction to favor addition by rendering the N-H bond weaker and more acidic than the N-H bond in ammonia itself.

We report the hydroamination of unstrained, unconjugated alkenes with a 1:1 ratio of alkene and amine catalyzed by a triflimide-bound ruthenium-trisphosphine complex and an aminopyridine as the N-H donor. The precatalyst consists of a fac-trisphosphine ruthenium core with weakly coordinating triflimide anions. This structure can readily bind alkenes and amines at the coordination sites occupied by the weakly coordinating anions. The amine possesses appropriate electronic properties for addition and potential abilities to coordinate the ruthenium through the pyridyl nitrogen.

3.2 Hydroamination of limiting quantities of terminal alkenes with tolerance of a variety of functional groups

To create a ruthenium catalyst for alkene hydroamination, we selected the catalyst precursor \([\text{Ru}_2(\text{PEt}_3)_6(\text{OTf})_3][\text{OTf}]\), which we developed recently for hydrogen transfer between alcohols and ketones. We examined reactions of amines that could form strained, chelated rings, based on the hypothesis that binding of one amine to two open coordination sites might preclude the binding of additional amines (for the solid-state structure determined by X-ray diffraction, of
such a complex made from the dinuclear species $[\text{Ru}((\text{PEt}_3)_6(\text{OTf})_3][\text{OTf}]^{35}$, see Figure 1). Such chelation also could stabilize amido hydrido complexes from oxidative addition of an N-H bond or amino-alkyl species from attack on a bound alkene, and the strain of a small chelate ring would allow the bound amine or amide to be reactive. To test these hypotheses, the reactions of octene with a series of amines, amides, heterocycles, and amino-heterocycles bearing 1,3-heteroatom functionality, such as pyrazole, sulfonamide, acetamide, and aminopyridine, were studied. These experiments showed that 2-aminopyridine was unusually reactive toward ruthenium-catalyzed hydroamination and led to the highest yields of addition products from this series of potential reagents with limiting quantities of alkene.

**Figure 1: $[\text{Ru}((\text{PEt}_3)_3(\text{OTf})(\kappa^2-1\text{-Me-3-aminopyrazole})][\text{OTf}]$.**


To examine the effect of catalyst architecture on the yield of hydroamination, we synthesized (Figure 2A) and studied (Figure 2B) the catalytic activity of a series of ruthenium-phosphine complexes bearing triflimide X-type ligands. Higher yields of products from hydroamination were observed with complexes containing triflimide as the weakly bound X-type ligand on ruthenium than with triflate. The trisphosphine scaffold that led to the highest reactivity was $[(\text{PEt}_3)_3\text{Ru}]$. The single-component catalyst $\text{Ru}((\text{PEt}_3)_3(\text{NTf})_2$ combined these features and catalyzed with high activity the hydroamination of unactivated terminal alkenes (Figure 2).
**Figure 2: Synthesis of ruthenium triflimide complexes ligated by phosphines and their evaluation for hydroamination of unactivated terminal and internal alkenes.**

A) Synthesis of ruthenium phosphine triflimide and triflate complexes  
B) Evaluation of ruthenium complexes for hydroamination  
C) Structure of complex 1b determined by single-crystal X-ray diffraction showing both an $\eta^1$ and $\eta^2$ bound triflimide ligand and three cis-coordinated PEt$_3$ ligands. *with twice the [Ru] loading.

A

\[
\begin{align*}
\text{cis-RuDMSO}_4\text{Cl}_2 & \xrightarrow{1-12 \text{ h} \atop \text{rt to } 80^\circ \text{C}} \text{phosphine ligand} \\
\text{cis-Ru(PMe}_3\text{)}_4\text{Cl}_2 & \text{ cis-Ru(PMe}_3\text{)}_4\text{NTf}_2 \\
\text{Ru(PEt}_3\text{)}_3\text{NTf}_2 & \text{ or catalyst-NTf}_2 \\
\text{Ru(PnPr}_3\text{)}_3\text{NTf}_2 & \text{ yield } 3a \\
\text{Ru(PnBu}_3\text{)}_3\text{NTf}_2 & \text{ yield } 3b \\
\text{Ru(PMePh}_2\text{)}_3\text{NTf}_2 & \text{ or alkene isomerization} \\
\text{Ru(N(CH}_2\text{PEt}_2\text{)}_3\text{NTf}_2 & \text{ yield } 3a \\
\text{cis-Ru(Et}_2\text{P(CH}_2\text{)}_4\text{PEt}_2\text{)}_2\text{Cl}_2 & \text{ yield } 3b \\
\text{cis-Ru(Et}_2\text{P(CH}_2\text{NiBuCH}_2\text{)}\text{PEt}_2\text{)}_2\text{Cl}_2 &
\end{align*}
\]

The results of hydroaminations of a series of terminal unactivated aliphatic alkenes with the parent aminopyridine is shown in Figure 3. Functional groups that were tolerated on the alkene include alkyl, aryl, aromatic halogens, aliphatic halogens, amide, ester, ketone, tertiary alcohol, methyl ether, disubstituted alkene, and trisubstituted alkene. A test of the functional group tolerance by conducting reactions in the presence of a series of added compounds bearing diverse functional groups (Figure 4)\textsuperscript{36} showed that the hydroamination reaction also tolerates two phenols, amines, added phosphine (one catalytic equivalent), a trimethylsilyl enol ether, a tetrahydrothiofuran, a furan, and a pyridine additive. The yields were lower in the presence of an added diene, or ketone.
Figure 3: Hydroamination of unstrained, unconjugated alkenes.

Hydroamination of terminal aliphatic alkenes is facile, and the selective hydroamination of terminal alkenes occurs when both terminal and internal alkenes are present in the substrate.

Modified conditions: *The reaction was run at 100 ºC. 10% [Ru]. 15% [Ru]
Figure 4: Examination of the tolerance of the hydroamination to various functional groups.

1-dodecene (11 µL, 9 mg, 0.05 mmol), 2-amino-5-methylpyridine (5.5 mg, 0.05 mmol), catalyst (2.5 mg, 0.0025 mmol, 5 mol % 1b), 2-fluorotoluene standard (5.5 mg, 0.05 mmol, 1 equiv), dichlorobenzene (35 µL), and an additional reagent (0.05 mmol or the stated quantity in Table 1) were combined with a magnetic stir bar in a one-dram vial to form a solution. The vial threads were wrapped with 1 layer of Teflon tape, the vial was capped, and the resulting mixture was heated at 80 °C with stirring for 48 hours. The reaction was allowed to cool to room temperature. Yields were determined by GC, and side products were determined by GCMS and NMR spectroscopy.

\[
\text{decyl} + \text{H}_2\text{N}^+\text{Py} + \text{additive} \xrightarrow{5\% \text{Ru(PEt}_3)_3\text{NTf}_2, \text{DCB, 80 }^\circ\text{C, 48 h}} \text{HN}^+\text{Py} \text{R} \quad \text{Py} = \text{p-Me aminopyridine}
\]

List of additives and associated yields of 3a (with side products shown)

<table>
<thead>
<tr>
<th>Additive</th>
<th>Yield (%)</th>
<th>Side Products</th>
</tr>
</thead>
<tbody>
<tr>
<td>no additive</td>
<td>71%</td>
<td></td>
</tr>
<tr>
<td>PhOH</td>
<td>62%</td>
<td></td>
</tr>
<tr>
<td>iPr</td>
<td>60%</td>
<td></td>
</tr>
<tr>
<td>iBu</td>
<td>42%</td>
<td>32% 3a, 3b</td>
</tr>
<tr>
<td>H$_2$NCF$_3$PEt$_3$</td>
<td>60%</td>
<td></td>
</tr>
<tr>
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<tr>
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<td></td>
</tr>
<tr>
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<td>plus 30% BHA1</td>
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<tr>
<td>CyOH</td>
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<td></td>
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<tr>
<td>Cy-Cy</td>
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<tr>
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<td>32% but least isomerization</td>
</tr>
<tr>
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<td></td>
</tr>
<tr>
<td>H$_2$O</td>
<td>1 equiv: 25%</td>
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</tr>
</tbody>
</table>

BHA = borrowing hydrogen adduct
Tertiary alcohols are completely tolerated and the yields of reactions in dry tert-butanol were the same as those in DCB. The yield was lower when the reaction was conducted with added secondary alcohols (Figure 4). Oxidation and amination of secondary alcohols occurred as major competing processes in the presence of these additives. Reactions in the presence of primary alcohols also occurred with competing processes. Reactions conducted with the added primary alcohol 5-hexene-1-ol in place of the alkene under the conditions of the reactions in Figure 4 led to the amination of the primary alcohol and formation of N-(5-methylpyridin-2-yl)hexanamide as the major products. This amide is formed by oxidative amidation and concomitant reduction of the alkene.

Terminal alkenes underwent hydroamination with complete selectivity over internal alkenes in molecules bearing both types of alkenes. This selectivity contrasts that observed for formal hydroamination with copper and cobalt, as well as by photocatalysts, which are more reactive toward more substituted alkenes than less substituted alkenes.37

Conjugated alkenes, including vinylarenes, enones, enamines, and enamides, also underwent hydroamination catalyzed by this ruthenium system. No reaction was observed in the absence of the ruthenium catalyst under the same conditions. Vinylarenes underwent hydroamination to yield branched products. For example, the hydroamination of vinylferrocene gave the corresponding branched amine in 61% yield (Table 2). Enones and acrylamides underwent addition under slightly modified conditions that included a catalytic LiO{Bu additive (Figure 5). Ru(P{Et})3(NTf2)2 and [Ru2(P{Et})6(OTf)3][OTf] also catalyzed the hydroamination of the internal alkene, 2-octene (Figures 2 and 6). The formation of a single isomer and the formation of <5% product from the reaction of cis or trans 4-octene implies that 2-octene reacts by initial isomerization to 1-octene (Figure 6). To achieve yields that are comparable to those of reactions with terminal alkenes, two equivalents of alkene and higher catalyst loadings were required.

Nevertheless, the addition of the aminopyridine to 2-decene and 2,5−dimethyl-3-hexene gave the addition products in high yield. The same conditions with cycloheptene or 4-octene (cis or trans) gave less than 5% yield and the reaction of 2-norbornene gave no product (Supplementary information). The higher reactivity of 2-alkenes than other internal alkenes indicates that isomerization to the terminal position is slower than the hydroamination of terminal alkenes and 2-alkenes are likely to isomerize to generate both 1- and 3-alkenes, with the addition occurring after isomerization of the internal alkene to a small amount of the reactive terminal alkene.

Alkene isomerization of 2,5-dimethyl-3-hexene to the disubstituted terminal alkene is more thermodynamically favorable than isomerization of 3-octene to the terminal alkene. We propose that this more favorable isomerization causes the reaction of 2,5-dimethyl-3-hexene to occur in higher yield than the reaction of 3-octene. However, the temperature for this addition was higher than that to the mono-substituted terminal alkenes. Addition to 1,1-disubstituted terminal alkenes lead to only trace amounts of product at temperatures below 100 °C but are reactive within the temperature range in which alkene isomerization occurs at a rate competitive with hydroamination.

To achieve the formal hydroamination with ammonia, the 2-aminopyridyl group of the initial alkyl aminopyridine product was removed. This group is known to be cleaved by hydrogenation to generate an amidine, which can be cleaved in-situ to generate the free amine product. This
sequence was performed with the two substrates shown in Figure 7. A convenient sequence was developed, involving ruthenium catalyzed hydroamination, silica filtration, hydrogenation, and purification of the bench-stable amidine intermediate. The hydrogenation to the amidine occurs readily with 10% PtO$_2$ catalyst (Figure 7). The pure amidine then was cleaved with hydrazine to generate the free primary amine (Figure 7).

**Figure 5: Hydroamination of activated alkenes.**
Styrene derivatives undergo hydroamination with Markovnikoff selectivity. Enones and enamides undergo hydroamination when catalytic amounts of base are added, but in no yield with only base added and lower yield when only [Ru] is added. $^a$Reaction run at 100 °C. *10% [Ru].

**Figure 6: Hydroamination of internal alkenes to generate 2-substituted products exclusively.**
The formation of 2-substituted products, indicates that isomerization preceded Markovnikov addition to the terminal alkene.
Figure 7. Synthesis of primary amines by ruthenium-catalyzed hydroamination.
Cleavage of the pyridyl protecting group leads to a primary amine product. The amidine or the final amine can be purified, depending on the substrate or synthetic goal. It can be convenient to purify the amidine and cleave this compound for use of the amine generated in situ. The yields shown refer to a sequence in which the amidine was purified. Similar yields were obtained from a sequence in which the amidine cleavage is performed before purification of the amine.

We considered that this hydroamination process could occur by an initial oxidative amination and subsequent reduction of an unsaturated intermediate. A small quantity of ketone (5%) was detected in each case after the reaction is complete. An aminoalkyl intermediate formed by insertion of the alkene into a metal amide or nucleophilic attack on the coordinated alkene could undergo beta hydrogen elimination to generate an enamine which would undergo reduction by the released ruthenium hydride with or without concomitant tautomerization of the initially formed enamine. To assess whether the hydroamination reaction proceeds by direct addition to the alkene or by the mechanism involving initial oxidative amination, we performed mechanistic experiments (Figures 8-10). The reaction between an amine and alkene was conducted in the presence of acetone to test whether the product derived from transiminization of our proposed imine intermediate would occur. This reaction led to the product from reductive amination of acetone and, more important, the ketone derived from the starting alkene also was observed in greater quantity than under the normal reaction conditions (20% versus 5%). Control experiments were performed in which water and the alkene were combined under the reaction conditions in the absence or presence of amine. No alcohol or ketone was obtained in the absence of amine and in the presence of added water the amount of ketone was the same as the small quantity obtained under the standard reaction conditions. (5% ketone). In the presence of the added trifluoroethylamine or p-anisidine, the yield of product from hydroamination was the same as that in the absence of added amine, and small amounts of imines (5% imine) derived from these two added amines was observed after the reaction. These experiments together show that the alkene does not undergo Wacker oxidation as a side reaction to form the ketone side product or the increased quantity of ketone observed in the reaction with added acetone. Thus, this production of ketone derived from the alkene supports a reaction mechanism by which an imine is a reaction intermediate and this intermediate imine can undergo transimination to generate acetone imine or to generate imines derived from trifluoroethylamine or p-anisidine. To test if the ruthenium complex would catalyze reduction of an imine intermediate, we conducted the reaction of 2-octanone, 4-methyl-2-aminopyridine, and hydrogen gas with 1b. Full conversion to the amine product occurred, and no concomitant reduction of the ketone to an alcohol was observed (Figure 9D).
Figure 8: Observation of ruthenium phosphine complexes by $^{31}$P and $^{19}$F NMR spectroscopy and modified reaction conditions to narrow down mechanistic possibilities. (A) Addition of aminopyridine to Ru(PEt$_3$)$_3$(NTf$_2$)$_2$ (1b) generates an amine bound ruthenium which likely undergoes further deprotonation. [Ru](H$_2$NP$_2$)[NTf] is a transient intermediate hypothesized to occur by analogy to the formation of [Ru(PEt$_3$)$_3$(OTf)(k$_2$-1-Me-3-aminopyrazole)]OTf from N-Me-3-aminopyrazole and [Ru$_2$(PEt$_3$)$_6$(OTf)$_3$][OTf] (B) The triflimide $^{19}$F signal in the NMR shifts to match that of free triflimide upon the addition of aminopyridine to Ru(PEt$_3$)$_3$(NTf$_2$)$_2$ at room temperature. Heating Ru(PEt$_3$)$_3$(NTf$_2$)$_2$ in the presence of two or more equivalents of aminopyridine generates a characteristic set of two doublets in the $^{31}$P NMR which match a [Ru] bound by two phosphines in a cis configuration.

A

Identified by x-ray diffraction (Figure 1)

B

$^{19}$F NMR confirms the substitution of NTf$_2$ by p-Me-2-aminopyridine at room temperature

Possible active species, requiring further characterization

$^{31}$P NMR of indicates the formation of a new ruthenium phosphine complex under catalytic conditions. This spectrum shows two doublets. The complex only forms in substantial amounts upon heating with two equivalents of p-Me-2-aminopyridine at >50 °C. The complex thus formed is stable after returning the solution to room temperature after heating and the spectrum shown was take at room temperature. When the reaction mixture was cooled down further to <20 °C the doublets disappeared and the spectrum reverted to that of unheated starting materials.
Because the ruthenium is Lewis acidic, reaction with the amine could generate a protic acid, and this protic acid could be envisioned to catalyze the addition, as observed previously with some combinations of substrates containing N-H bonds and transition-metal complexes. Several observations are inconsistent with this pathway: the aminopyridine reagent should quench this acid, no reaction was observed with norbornene, and internal alkenes were less reactive than terminal alkenes. Nevertheless, we conducted experiments to determine if the reaction of terminal alkenes were occurring with an acid catalyst generated from the ruthenium and aminopyridine. To do so, we conducted the reaction of 1-octene and 2-aminopyridine with 20% triflic acid or triflimide as catalyst at 100 °C and 140 °C. This reaction gave no product from hydroamination of the linear aliphatic alkene, and the starting alkenes and amines were fully recovered (Section 3.12).

To determine the structure of potential reaction intermediates, the hydroamination reaction was performed between the deuterated analog of the aminopyridine and alkene, as shown in a time plot of deuterium incorporation (Figure 10). Deuterium was incorporated rapidly into both the alkene starting material in the allylic position and into the aminopyridine starting material at the 3-position, but not into any other positions of the compounds in significant amounts during the first 30 minutes of reaction. Upon measurable conversion of the alkene to the amine, deuterium was incorporated into the positions alpha and beta to the nitrogen in the product. The deuterium incorporation into the position alpha to the amine and into the methyl group beta to the amine support an unsaturated enamine intermediate, which undergoes reduction, either with or without prior tautomerization to an imine. in order to account for the deuterium at these positions. The deuterium incorporated into the methylene position in the product that is beta to the amine is present due to incorporation of deuterium into the allylic position of the starting alkene (Figure 10). The greater amount of deuterium alpha and beta to the amine in the product than at these positions in the starting alkene indicates that the reaction may proceed via an enamine and imine intermediate. The lower amount of deuterium in the product after 48 hours than after three hours is due to the continued exchange at these positions over the course of the reaction.

A deep mechanistic understanding of the hydroamination will require further studies into the speciation of the active catalyst. However, a general process might involve a positively charged ruthenium complex which is first bound by an aminopyridine. Coordination to the cationic center will make the N-H bond of the aminopyridine ligand more acidic and readily deprotonated. The resulting amide could then insert a coordinated alkene to form an aminoalkyl ligand. Such alkene insertion into an amide has been observed with a series of late transition-metal complexes of amide and sulfonamide complexes. In the present case, the [Ru]-alkyl formed by insertion then could react by several paths, including protonation to form the amine or β-hydrogen elimination to form an enamine which tautomerizes to an imine. This intermediate imine then could undergo reduction by the hydrogen “borrowed” in the first step. The preliminary mechanistic data and typical slow protonation of cationic metal-alkyl complexes support this pathway. Further alkene functionalizations could be developed that occur by this novel mechanism, including enantioselective additions that would occur by a stereoselective hydrogenation step.
Figure 9: Hypothesized route towards the generation of side products from Ruthenium-catalyzed hydroamination and modifications of the standard reaction conditions which generate novel side products.

(A) Addition of acetone to the reaction leads to products derived from transimination. (B) Sampling the reaction for analysis always generates a small quantity (~5%) of free ketone, indicating that an imine is present. (C) Addition of 1 equivalent of other amines, including para anisidine or trifluoroethylamine, leads to the generation of imines from transimination that do not undergo further reduction under the reaction conditions. (D) Reaction of a ketone with p-Me-2-aminopyridine and hydrogen gas in the presence of 1b gives exclusively the amine product of reductive amination.
**Figure 10: Incorporation of deuterium in the products of hydroamination.**

(A) Conducting the reaction in the presence of protic deuterium sources led to incorporation of deuterium in the starting materials and products of hydroamination at select positions. Rapid deuterium incorporation occurs into the allylic alkene positions but not into the alkene, indicating that the deuterium incorporation into the product is likely to derive from tautomerization and reduction of an unsaturated intermediate. (B) Mechanistic outline for the incorporation of deuterium into the position alpha to the amine in the product and into the methyl group beta to the amine in the product.

### Table

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<th>% D substitution at 30m</th>
<th>% D substitution at 3h</th>
<th>% D substitution at 48h</th>
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### Oxidative amination and reduction:

\[
\begin{align*}
D_2N^-Py + \text{R} & \xrightarrow{[\text{Ru}][\text{NTf}_2]} \text{DN}^-Py \\
& \xrightarrow{[\text{Ru}][\text{NTf}_2]} \text{DN}^-Py
\end{align*}
\]

### Hydride-proton exchange:

\[
[\text{Ru}]H + [D_2NPy][\text{NTf}_2] \rightarrow [\text{Ru}]D + [D_2NPy][\text{NTf}_2]
\]
3.3 Experiments and procedures

3.4 Purification of organic starting materials
Alkenes were stored over 4Å molecular sieves under an atmosphere of nitrogen gas for 2 days or longer prior to use in catalytic reactions. Boldenone undecylenate was purified by chromatography with 20% ethyl acetate in hexanes prior to use. In general, any alkenes which showed <99% purity by NMR and GC were purified by chromatography or distillation prior to use. Aminopyridines were recrystallized by dissolving in a minimal amount of a mixture of ethyl acetate and hexanes at 75 °C, hot filtration with a syringe filter to remove any colored material, and allowing the aminopyridine to crystallize over 1-24 hours at room temperature. The supernatant was removed, and the aminopyridines were rinsed with a mixture of ethyl acetate and hexanes and then hexanes alone. The solid was then dried under high vacuum overnight and stored in a desiccator or under nitrogen gas. Commercial 5-MeO-2-aminopyridine was darkly colored and was resistant to recrystallization, so this aminopyridine was purified by silica gel column chromatography with 50% ethyl acetate in hexanes to generate a pure yellow oil.

3.5 Synthesis of [Ru(PEt₃)₃(OTf)(κ²-1-Me-3-aminopyrazole)]OTf (Figure 1)
[Ru(PEt₃)₆(OTf)₃][OTf] (15 mg, 0.0075 mmol) was combined with 1-Me-3-amino-pyrazole (1.5 mg from 1M solution 0.015 mmol, 2 equivalents) in trifluoroethanol (1 mL). The mixture was stirred for 5 minutes at room temperature and filtered through a syringe filter into a 1 dram vial. The resulting yellow solution was layered with di-isopropyl ether (3 mL). During 1-2 days, crystals formed. The crystals were collected and characterized by X-ray diffraction.

3.6 Notes about catalyst conditions:
It was found that the order of addition does not significantly influence the outcome of the reaction. In general, the solids were added to the vials first, followed by liquids. For volatile alkenes, the solvent was added before the alkene. The reactions turn dark amber in color immediately upon dissolving the catalyst and amine together and addition of the alkene in general does not change the color. The reaction does not initiate at room temperature. If water impurity is present the reactions do not turn a dark amber color upon dissolution and may even appear yellow if there is enough water to completely inhibit the reaction. Chelating protic substrates which were unreactive for hydroamination turn the reaction solution bright red or purple in color as opposed to dark amber when combined with catalyst under the reaction conditions. The inhibitory effect of water is lessened in ethereal solvents such as dioxane and the reaction color in these solvents is yellow even in the absence of protic impurities. It was found that stirring does not influence the rate of the reactions because they are homogeneous. Stir bars were included when the reactions did not readily form a homogeneous solution at room temperature, as indicated in the following procedures.

3.7 Conditions for the examination of catalysts for hydroamination of alkenes (Figure 2)
Conditions A: 1-dodecene (44 µL, 34 mg, 0.20 mmol), 2-amino-5-methylpyridine (22 mg, 0.20 mmol), catalyst (4.0 µmol, 2 mol % [Ru], for example 4.0 mg of 1b), and dichlorobenzene (60 µL) were combined with a magnetic stir bar in a one-dram vial to form a solution. The vial threads were wrapped with 1 layer of Teflon tape, the vial was capped, and the resulting mixture was heated at 80 °C with stirring for 48 hours. The reaction was allowed to cool to room
temperature, and yields were determined by NMR and GC with dichlorobenzene as the internal standard.

**Conditions B:** 2-Octene (16 µL, 11 mg, 0.10 mmol), 2-amino-5-methylpyridine (11 mg, 0.10 mmol), catalyst (15 µmol, 15 mol % [Ru], for example 15 mg of 1b), and dichlorobenzene (40 µL) were combined with a magnetic stir bar in a one-dram vial to form a solution. The vial threads were wrapped with 1 layer of Teflon tape, the vial was capped, and the resulting mixture was heated at 120 °C with stirring for 48 hours. The reaction was allowed to cool to room temperature, and yields were determined by gas chromatography.

### 3.8 Preparation of select complexes for in situ examination of catalyst activity from isolated chloride precursors:
The complexes 1a and 1d-1h were generated for in situ for examination of catalyst activity, either for convenience or because the products were oily metal species for which crystallization conditions could not be established. To establish the conditions for in-situ catalyst examination, a procedure was developed that gave comparable yields for model catalyst 1b when this catalyst was generated in-situ instead of used after isolation (88% of the yield for in-situ generated catalyst was obtained for catalyst 1b compared to when isolated crystalline catalyst was employed). This method was applied to the transformation of isolated chloride precursors to triflimide derivatives for the catalyst examinations shown in Figure 2. In these cases, the purity and identity of the ruthenium triflimide complex was verified by NMR spectroscopy. To generate ruthenium triflimide complexes in-situ, dimeric ruthenium chloride precursor (0.02 mmol), AgNTf₂ (31 mg, 0.08 mmol, 2 equiv relative to [Ru]), trifluoroethanol (0.50 mL), and a magnetic stir bar were combined in a 1 dram vial. The vial was capped and heated at 80 °C for 2 h with stirring and then allowed to cool to room temperature. The solution was filtered with a syringe filter, and the volatile materials were evaporated from the supernatant under high vacuum fully to form a residue. This residue was then triturated with isopropyl ether, which was removed. The resulting residue was dried by high vacuum and then used directly for the reaction as a stock solution in DCB.

### 3.9 Test for catalytic Wacker-type oxidation
1-dodecene (22 µL, 17 mg, 0.10 mmol), water (1.8 µL, 0.10 mmol), Ru(PEt₃)₃(NTf₂)₂ (10 mg, 0.01 mmol, 10 mol % [Ru]), and dichlorobenzene (60 µL) were combined with a magnetic stir bar in a one-dram vial to form a solution. The vial threads were wrapped with 1 layer of Teflon tape, the vial was capped, and the resulting mixture was heated at 100 °C with stirring for 48 hours. The reaction was allowed to cool to room temperature, and yields were determined by NMR and GCMS.

### 3.10 Conditions for the investigation of the catalytic reaction by NMR for the identification of catalytic intermediates
**Reaction A:** 1-dodecene (14 µL, 10 mg, 0.06 mmol, 4 catalyst equiv), 2-amino-5-methylpyridine (7.0 mg, 0.03 mmol, 2 catalyst equiv), Ru(PEt₃)₃(NTf₂)₂ (15 mg, 0.015 mmol), chlorobenzene (440 µL), and benzene-d₆ (110 µL) were combined with a magnetic stir bar in a one-dram vial, and the resulting mixture was stirred vigorously to form a homogeneous solution. The mixture was transferred into a J-young tube and sealed. NMR spectra of the mixture were obtained prior to any heating. The reaction was then heated at 80 °C and NMR spectra were taken after 10
minutes, 90 minutes, 12 hours, and 24 hours. High temperature and low temperature \(^1\text{H}\), \(^{19}\text{F}\), and \(^{31}\text{P}\) NMR studies were performed on the reactions from each of these time points.

**Reaction B:** Same as Reaction A except that alkene was omitted from the reaction, which led to analogous spectra of the ruthenium complexes visible in the \(^{31}\text{P}\) NMR.

### 3.11 Conditions for the detection of transiminization-reduction products upon the addition of ketone to the hydroamination reaction

During the examination of the reaction tolerance to various functional groups, it was found that imines derived from primary amine additives were present in the reaction mixtures (Figure 9C). These reactions were conducted following the conditions of the robustness test shown in Figure 3. The formation of imines was also observed under conditions identical to those in which no 2-AP was added with 1 equivalent of p-anisidine or 1 equivalent of trifluoroethylamine added.

### 3.12 Determination of catalyst activity after the catalytic hydroamination

1-Dodecene (44 µL, 34 mg, 0.20 mmol), 2-amino-5-methylpyridine (22 mg, 0.20 mmol), Ru(PEt₃)₃(NTf₂)₂ (10 mg, 0.01 mmol, 10 mol % [Ru]), dichlorobenzene (60 µL) were combined with a magnetic stir bar in a one-dram vial, and the resulting mixture stirred to form a homogeneous solution. The vial threads were wrapped with 1 layer of Teflon tape, the vial was capped, and the resulting mixture was heated at 80 °C with stirring for 48 hours. The reaction was allowed to cool to room temperature, taken into a nitrogen-filled glovebox, and an aliquot was removed for GC analysis. Additional 1-dodecene (44 µL, 34 mg, 0.20 mmol) and 2-amino-5-methylpyridine (22 mg, 0.20 mmol) were then added to the reaction, the vial was capped, and the reaction was heated for an additional 24 hours at 80 °C with stirring. The reaction was allowed to cool to room temperature and a second aliquot removed for GC analysis.

### 3.13 Procedure for evaluation of deuterium incorporation into products (Figure 10)

**Test A (performed with replicate reactions):** 1-Dodecene (133 µL, 101 mg, 0.60 mmol), N-D₂-2-amino-5-methylpyridine (79 mg, 0.72 mmol, 1.2 equiv), Ru(PEt₃)₃(NTf₂)₂ (31 mg, 5 mol % [Ru]), benzene-\(\text{d}_6\) (51 mg, 0.60 mmol, 1 equiv), and 1,2-dichlorobenzene (300 µL) were combined with a magnetic stir bar in a one dram vial, and the resulting solution was stirred to form a homogeneous solution. This stock solution was then distributed into 5 vials to generate 5 identical replicate reactions at 0.1 mmol scale. One reaction was examined by \(^1\text{H}\) and \(^2\text{H}\) NMR spectroscopy as a standard prior to heating. For the other 4 reaction vials, the vial threads were wrapped with 1 layer of Teflon tape each, the vials were capped, and the resulting mixtures were heated at 65 °C with stirring for 5 minutes, 30 minutes, 3 hours, and 48 hours. The reactions were allowed to cool to room temperature and were examined by \(^1\text{H}\) and \(^2\text{H}\) NMR with chloroform-\(\text{d}_1\) or chloroform as the NMR solvents respectively.

**Test B:** Same as test A except with allylbenzene as the alkene component.

### 3.14 Test for potential acid-catalyzed hydroamination

**Test A:** 1-dodecene (22 µL, 17 mg, 0.10 mmol), 2-amino-5-methylpyridine (11 mg, 0.10 mmol), HNTf₂ (0.02 mmol, 20 mol %), and dichlorobenzene (60 µL) were combined with a magnetic stir bar in a one-dram vial, and the resulting solution was stirred to form a homogeneous solution. The vial threads were wrapped with 1 layer of Teflon tape, the vial was capped, and the
resulting mixture was heated at 80 °C with stirring for 48 hours. The reaction was allowed to cool to room temperature and analyzed by GC.
Test B: Same as test A except at 120 °C.
Test C: Same as test A except with HOTf (0.02 mmol, 20 mol %) instead of HNTf2.
Test D: Same as test C except at 120 °C.

3.15 Procedures for the synthesis of metal complexes and spectral data

General notes regarding the synthesis of ruthenium phosphine chloride complexes
In polar protic solvents, such as methanol and trifluoroethanol, the cis-[Ru(DMSO)4Cl2] precursor undergoes rapid substitution by 2, 3, or 4 equivalents of sterically unhindered phosphines to generate chloride bridged dimers and monomeric cis dichloride complexes. If the product does not precipitate from methanol or trifluoroethanol under the reaction condition or upon cooling to room temperature, the addition of ethereal solvents can induce precipitation and crystal formation. If this does not yield product, the solvent for the reaction can be chosen to be water, which enables rapid substitution and isolation of the product complexes under air. All of the syntheses shown follow one of these scenarios.

cis-Ru(PMe3)4Cl2
 cis-[Ru(DMSO)4Cl2] (243 mg, 0.5 mmol), PMe3 (1M in toluene, 2.2 mL, 2.2 mmol, 4.4 equiv), and trifluoroethanol (2 mL) were combined and heated at 100 °C for 2 hours with stirring. Over this period, all the material dissolved, and the supernatant turned bright yellow/orange. The reaction solution was allowed to cool to RT, concentrated to 1.5 mL under vacuum, and layered with iPr2O (10 mL). Light yellow crystals formed over one day. The supernatant was removed, the crystals were rinsed with iPr2O (2 x 1 mL) and then pentane (1 mL) and dried under high vacuum. Yield = 207 mg (87%). 1H NMR (600 MHz, chloroform-d) δ 1.56 (t, J = 3.2 Hz, 9H), 1.47 (m, 9H). 13C NMR (151 MHz, chloroform-d) δ 23.34 (ddt, J = 17.1, 12.7, 2.4 Hz), 18.96 (t, J = 14.0 Hz). δ 31P NMR (243 MHz, chloroform-d) δ 11.27 (t, J = 33.0 Hz), -10.58 (t, J = 33 Hz). Anal. Calc’d C:30.26 H:7.62 Found C:30.45 H:7.84.

[Ru2(PEt3)6Cl3][Cl]
Synthesized by the reported procedure.35 cis-[Ru(DMSO)4Cl2] (3.00 g, 6.18 mmol), PEt3 (3.00 mL, 20.4 mmol, 3.30 equiv), and MeOH (10 mL) were combined and heated at 65 °C for 90 minutes with stirring. Over this period, all the material dissolved, and the supernatant turned green and then bright yellow/orange. The reaction solution was allowed to cool to RT and then the reaction solution was layered under nitrogen atmosphere onto 600 mL of 3:1 diethyl ether:pentane in a 1 L flask and the flask was slowly swirled to mix over 5 minutes time. The yellow needles thus formed were collected by filtration (the filtration can be done under air) and rinsed once with ether, then pentane, and then dried under high vacuum. Yield = 2.88 g (88%). 1H NMR (400 MHz, chloroform-d) δ 1.92 (m, 36H), 1.21 (m, 54H). 13C NMR (151 MHz, methylene chloride-d2) δ 20.44, 10.35. δ 31P NMR (162 MHz, chloroform-d) δ 34.06. Anal. Calc’d C:41.07 H:8.62 Found C:41.13 H:8.46.

[Ru2(PPr3)6Cl3][Cl]
cis-[Ru(DMSO)4Cl2] (243 mg, 0.500 mmol), PPr3 (310 µL, 248 mg, 1.55 mmol, 3.10 equiv), and a magnetic stir bar were added to a small Schlenk flask in a N2 filled glove box. Outside the
drybox, degassed H₂O (800 µL) was added via syringe under nitrogen pressure. Then, the Schlenk flask was sealed and heated in an oil bath at 100 °C for 2 hours with vigorous stirring. The reaction begins biphasic and becomes green before the product precipitates as a yellow solid. The reaction flask was then allowed to cool to room temperature, opened under air, and the solid product was crushed with a spatula until finely divided. The suspension was collected by filtration on a glass fritted filter, rinsed with H₂O (3 x 1 mL), and then rinsed with hexanes (3 x 1 mL). The product was dried under N₂ gas flow for 90 minutes, and then transferred to a vial. The vial was placed under high vacuum for 12 hours at 85 °C to fully dry the solid, which was transferred to a N₂ atmosphere for storage. Yield = 281 mg (86%). 1H NMR (600 MHz, chloroform-d) δ 1.76 (m, 36H), 1.57 (m, 36H), 0.99 (t, J = 7.2 Hz, 54H). 13C NMR (151 MHz, chloroform-d) δ 32.48 (m), 19.13 (m), 16.34 (m, apparent quartet). 31P NMR (243 MHz, chloroform-d) δ 29.16. Anal. Calc’d C:49.69 H:9.73. Found C:49.87 H:9.60.

[Ru₂(P₈Bu₃)₆Cl₃][Cl]
cis-[Ru(DMSO)₄Cl₂] (243 mg, 0.500 mmol), PBu₃ (380 µL, 314 mg, 1.55 mmol, 3.10 equiv), and a magnetic stir bar were added to a small Schlenk flask in a N₂ filled glove box. Outside the box, degassed H₂O (800 µL) was added via syringe under nitrogen pressure. The Schlenk flask was then sealed and heated in an oil bath at 100 °C for 2 hours with vigorous stirring. The reaction begins biphasic and becomes green before the product precipitates as a yellow solid. The reaction flask was then allowed to cool to room temperature, opened under air, and the solid product was crushed with a spatula until finely divided. The suspension was collected by filtration on a glass fritted filter, rinsed with H₂O (3 x 1 mL), and then rinsed with hexanes (3 x 1 mL). The product was dried under N₂ gas flow for 90 minutes, and then transferred to a vial. The vial was placed under high vacuum for 12 hours at 85 °C to fully dry the solid, which was transferred to a N₂ atmosphere for storage. Yield = 356 mg (91%). 1H NMR (600 MHz, chloroform-d) δ 1.87 (m, 36H), 1.55 (m, 36H), 1.36 (h, J = 7.3 Hz, 36H), 0.93 (t, J = 7.3 Hz, 54H). 13C NMR (151 MHz, chloroform-d) δ 30.00 (m), 27.72, 25.05 (m), 13.81. 31P NMR (243 MHz, chloroform-d) δ 29.94. Anal. Calc’d C:55.51 H:10.48. Found C:55.66 H:10.44.

[Ru₂(PMePh₂)₆Cl₃][Cl]
Synthesized by the reported procedure.35 cis-[Ru(DMSO)₄Cl₂] (630 mg, 1.30 mmol), PPh₂Me (0.798 mL, 4.29 mmol, 3.3 equiv), and MeOH (16 mL) were combined and stirred at room temperature for 90 minutes. Over this period, the supernatant turned orange brown and then yellow. The solid was separated by filtration, rinsed with ether, and dried under vacuum. The supernatant was placed in the freezer (-30 °C) overnight, after which time additional crystalline product was collected by filtration. Combined yield = 831 mg (83%). 1H NMR (600 MHz, chloroform-d) δ 7.27 (t, J = 7.5 Hz, 12H), 7.07 (m, 24H), 7.02 (m, 24H), 1.82 (m, 18H). 13C NMR (151 MHz, chloroform-d) δ 136.70 (m), 132.93, 129.58, 127.95, 19.88 (m). 31P NMR (243 MHz, chloroform-d) δ 18.93. Anal. Calc’d C:60.63 H:5.09 Found C:60.34 H:5.18.

[Ru₂(N(CH₂PEt₂)₃)₂Cl₃][Cl]
cis-[Ru(DMSO)₄Cl₂] (169 mg, 0.350 mmol), N(CH₂PEt₂)₃ (114 mg, 0.350 mmol, 1.02 equiv), MeOH (1 mL), and a magnetic stir bar were combined in a 4 mL vial and heated at 65 °C for 5 hours with stirring. The reaction was allowed to cool to room temperature. The solution then was transferred to a 20 mL vial and layered with ⁴Pr₂O (12 mL). Over 12 hours a light yellow
microcrystalline powder precipitated, which was collected by filtration, rinsed with \( \text{^3} \text{Pr}_2 \text{O} \) (2 x 0.5 mL) and dried under high vacuum. Yield = 83 mg (71%). \(^1\text{H} \) NMR (600 MHz, chloroform-\(d_2 \)) \( \delta \) 2.87 (s, 12H), 2.19 (h, \( J = 9.8, 9.1 \) Hz, 12H), 1.80 (dt, \( J = 15.1, 7.5 \) Hz, 12H), 1.18 (p, \( J = 7.2 \) Hz, 36H). \(^{13}\text{C} \) NMR (151 MHz, methylene chloride-\(d_2 \)) \( \delta \) 47.94, 20.59, 8.68. \(^{31}\text{P} \) NMR (243 MHz, chloroform-\(d_2 \)) \( \delta \) 28.08. Anal. Calc’d C:36.37 H:7.33 N:2.83 Found C:36.53 H:7.19 N:2.64.

cis-Ru(\text{Et}_2\text{PCH}_2\text{N(}\text{Bu}\text{)CH}_2\text{PEt}_2\text{)}_2\text{Cl}_2

cis-[Ru(DMSO)_4\text{Cl}_2] (165 mg, 0.340 mmol), \text{Et}_2\text{PCH}_2\text{N(}\text{Bu}\text{)CH}_2\text{PEt}_2\) (189 mg, 0.680 mmol, 2 equiv), and a magnetic stir bar were combined in a small Schlenk flask. Degassed water (0.5 mL) was added outside the glove box, the flask was sealed, and the reaction was heated at 100 \(^\circ\text{C} \) for 1 hour with vigorous stirring. The reaction was allowed to cool to room temperature and then trititated with water (3 x 400 \mu L), then with ether (4 x 1 mL), and then with pentane (2 x 1 mL). During trititation, the solid was finely divided with a spatula. The solid was then placed under high vacuum for 12 hours at 80 \(^\circ\text{C} \) to fully dry and was transferred to a \text{N}_2 atmosphere for storage. Yield = 202 mg (82%). \(^1\text{H} \) NMR (500 MHz, chloroform-\(d_2 \)) \( \delta \) 3.17 (dt, \( J = 13.0, 3.5 \) Hz, 2H), 3.10 (t, \( J = 12.2 \) Hz, 2H), 2.83 (dt, \( J = 12.2 \) Hz, 4H), 2.34 (dd, \( J = 13.4, 3.5 \) Hz, 2H), 2.24 (dd, \( J = 12.2, 6.1 \) Hz, 2H), 2.13 (ddd, \( J = 15.0, 7.7, 3.5 \) Hz, 4H), 1.91 (ddq, \( J = 14.7, 7.6, 3.7 \) Hz, 2H), 1.74 (tt, \( J = 10.0, 5.7 \) Hz, 2H), 1.45 (d, \( J = 15.1, 7.5 \) Hz, 2H), 1.25 (p, \( J = 7.5 \) Hz, 6H), 1.18 – 1.04 (m, 18H), 0.89 (dd, \( J = 10.7, 6.5 \) Hz, 12H). \(^{13}\text{C} \) NMR (151 MHz, chloroform-\(d_2 \)) \( \delta \) 73.37 (p, \( J = 4.4 \) Hz), 55.47 (t, \( J = 17.3 \) Hz), 54.66, 26.69 (m), 26.11 (m), 21.05 (m), 20.95 (m), 17.74 (t, \( J = 13.2 \) Hz), 17.54 (t, \( J = 12.2 \) Hz), 10.22 (t, \( J = 3.5 \) Hz), 9.34 (t, \( J = 1.8 \) Hz), 9.22 (t, \( J = 3.8 \) Hz), 8.23 (t, \( J = 2.8 \) Hz). \(^{31}\text{P} \) NMR (202 MHz, chloroform-\(d_2 \)) \( \delta \) 22.26 (t, \( J = 34.1 \) Hz), -1.22 (t, \( J = 34.1 \) Hz). Anal. Calc’d C:46.28 H:9.15 N:3.85 Found C:46.30 H:9.08 N:3.79.

cis-Ru(\text{Et}_2\text{P(CH}_2\text{)}_4\text{PEt}_2\text{)}_2\text{Cl}_2

cis-[Ru(DMSO)_4\text{Cl}_2] (150 mg, 0.310 mmol), \text{Et}_2\text{P(CH}_2\text{)}_4\text{PEt}_2\) (160 mg, 0.680 mmol, 2.20 equiv), and MeOH (1 mL) were combined in a 1 dram vial along with a magnetic stir bar. The vial was capped and heated at 65 \(^\circ\text{C} \) for 14 hours with stirring. Over this period, all the material dissolved, and the reaction turned bright red and then orange in color. Upon completion of the reaction, the solution color turned yellow upon cooling to room temperature. The reaction mixture was transferred to a 20 mL vial and layered with isopropyl ether (19 mL) and allowed to stand while yellow crystals formed over 2 days. The supernatant was removed, the crystals rinsed with isopropyl ether (2 x 0.5 mL) and then pentane (1 mL), and then dried by high vacuum. Yield = 165 mg (83%). \(^1\text{H} \) NMR (600 MHz, methylene chloride-\(d_2 \)) \( \delta \) 2.20-2.75 (m, 8H), 1.45-2.05 (m, 20H), 0.95-1.35 (m, 28H). \(^{13}\text{C} \) NMR (151 MHz, methylene chloride-\(d_2 \)) \( \delta \) 27.97(m), 24.57(m), 24.10(m), 23.88(m), 22.50(m), 22.27(m), 20.68(m), 18.83(m), 11.35(m), 10.60(m), 9.85(m), 8.35(m). \(^{31}\text{P} \) NMR (243 MHz, CD_2Cl_2) \( \delta \) 32.27 (t, \( J = 29 \) Hz), 4.62 (t (broadened), 2P, \( J = 29 \) Hz). Anal. Calc’d C:45.00 H:9.15 N:3.85 Found C:45.30 H:9.08 N:3.79.

Ru(\text{PEt}_3)_3(\text{NTf}_2)_2 \ (\text{Ru-2-NTf}_2)

[Ru_2Cl_3(\text{PEt}_3)_6][\text{Cl}] \ (\text{Ru-2-Cl}) (800 mg, 0.760 mmol) and AgNTf_2 (1.28 g, 3.04 mmol, 4.00 equiv) were combined in TFE (4.00 mL) and stirred at 65 \(^\circ\text{C} \) for 3 hours. The reaction solution was then filtered, and the solid was rinsed with TFE (300 \mu L). The filtrate was concentrated to ~1.5 mL, isopropyl ether (17 mL) was added, and the product was allowed to crystallize overnight. The supernatant was removed. The product was then recrystallized one time: the
microcrystalline initial product was dissolved in 2.5 mL TFE at 65 °C, allowed to cool to RT, and layered with isopropyl ether (17 mL). The product crystallized overnight. The supernatant then was removed, and the crystalline product was rinsed with isopropyl ether (1 mL) and pentane (1 mL), and then dried by high vacuum. Yield = 1.39 g (90%) large orange crystals. \( ^1\)H NMR (600 MHz, methylene chloride-\(d_2\)) \(\delta\) 1.89 (m, 36H), 1.23 (m, 54H). \( ^{13}\)C NMR (151 MHz, methylene chloride-\(d_2\)) \(\delta\) 119.64 (q, \(J = 320\) Hz), 20.14 (m), 9.38 (q, \(J = 2.2\) Hz). \( ^{31}\)P NMR (243 MHz, CD\(_2\)Cl\(_2\)) \(\delta\) 46.20. \( ^{19}\)F NMR (376 MHz, CD\(_2\)Cl\(_2\)) \(\delta\) -79.07. Anal. Calc’d C:26.01 H:4.47 N:2.76 Found C:25.91 H:4.49 N:2.70. The identity of the product was confirmed by x-ray crystallography.

**Ru(PPr\(_3\))\(_3\)(NTf\(_2\))\(_2\)**

\[ [\text{Ru}_2\text{Cl}_3(\text{PPr}_3)_6][\text{Cl}] \] (131 mg, 0.100 mmol), AgNTf\(_2\) (154 mg, 0.400 mmol, 4 equiv), and TFE (750 µL) were combined with a magnetic stir bar in a 4 mL vial, which was capped. The resulting solution was stirred at 50 °C for 3 hours. The reaction solution was then filtered and concentrated to a residue. To this residue a 1:1 mixture of isopropyl ether:pentane (3 mL) was added, and the supernatant (containing ~90% of the material from the residue) was transferred into a new vial and allowed to stand overnight. The product crystallized out during this period. The supernatant was removed, and the product was rinsed with 2:1 pentane: isopropyl ether (1 mL) and then dried by high vacuum. Yield = 140 mg (61%) large orange crystals. \( ^1\)H NMR (500 MHz, chloroform-\(d\)) \(\delta\) 1.80 (m, 18H), 1.59 (m, 18H), 1.04 (t, \(J = 7.0\) Hz, 27H). \( ^{13}\)C NMR (126 MHz, chloroform-\(d\)) \(\delta\) 30.08 (m), 19.05, 16.34 (m). (The triflimide carbon signal in this case was too minor to detect in the spectrum). \( ^{19}\)F NMR (376 MHz, CD\(_2\)Cl\(_2\)) \(\delta\) -79.02. Anal. Calc’d C:32.60 H:5.56 N:2.45 Found C:32.46 H:5.59 N:2.44.

### 3.16 Procedures for the synthesis of amine products and spectral data

**General notes regarding the synthesis of organic products**

Because the yields of hydroamination are limited by alkene isomerization, reactions were run until complete conversion of the alkene for the majority of molecules. Conditions were selected to be at temperatures low enough to minimize isomerization of the alkene but high enough for practical reaction times.

**5-methyl-N-(octan-2-yl)pyridine-2-amine**

1-octene (31 µL, 23 mg, 0.20 mmol), 2-amino-5-methylpyridine (22 mg, 0.20 mmol), and Ru(PEt\(_3\))\(_3\)(NTf\(_2\))\(_2\) (10 mg, 0.010 mmol, 5.0 mol %) were combined with DCB (40 µL) and a magnetic stir bar in a one dram vial. The vial was capped, and the resulting mixture was heated at 80 °C with stirring for 48 hours. The reaction was allowed to cool, and all of the volatile materials were evaporated. The crude product was purified by silica gel chromatography, eluting with 15% ethyl acetate in hexanes. Yield = 28 mg (62%). \( ^1\)H NMR (600 MHz, chloroform-\(d\)) \(\delta\) 7.88 (s, 1H), 7.23 (dd, \(J = 8.4, 2.2\) Hz, 1H), 6.28 (d, \(J = 8.4\) Hz, 1H), 4.16 (d, \(J = 8.1\) Hz, 1H), 3.67 (m, 1H), 2.16 (s, 3H), 1.57 – 1.24 (m, 10H), 1.17 (d, \(J = 6.4\) Hz, 3H), 0.87 (t, \(J = 6.9\) Hz,
5-methyl-N-(dodecan-2-yl)pyridine-2-amine
1-dodecene (34 mg, 0.20 mmol), 2-amino-5-methylpyridine (22 mg, 0.20 mmol), and Ru(PEt₃)₃(NTf₂)₂ (10 mg, 0.01 mmol, 5.0 mol %) were combined with DCB (40 μL) and a magnetic stir bar in a one dram vial. The vial was capped, and the resulting mixture was heated at 80 °C with stirring for 48 hours. The reaction was allowed to cool, and all of the volatile materials were evaporated. The crude product was purified by silica gel chromatography, eluting with 15% ethyl acetate in hexanes. Yield = 35 mg (63%). ¹H NMR (600 MHz, chloroform-d) δ 7.87 (m, 1H), 7.21 (dd, J = 8.5, 2.4 Hz, 1H), 6.27 (d, J = 8.4 Hz, 1H), 4.21 (d, J = 8.6 Hz, 1H), 3.66 (dh, J = 8.5, 6.4 Hz, 1H), 2.14 (s, 3H), 1.51 (dddd, J = 12.9, 10.0, 6.5, 5.2 Hz, 1H), 1.44 (dddt, J = 12.9, 9.5, 6.0 Hz, 1H), 1.39 – 1.31 (m, 2H), 1.30 – 1.22 (m, 14H), 1.16 (d, J = 6.4 Hz, 3H), 0.87 (t, J = 7.0 Hz, 3H). ¹³C NMR (151 MHz, chloroform-d) δ 156.81, 147.94, 138.43, 138.42, 121.07, 106.36, 47.45, 37.39, 32.00, 29.77, 29.71, 29.43, 26.17, 22.78, 21.05, 17.44, 14.21, 14.20. GC-MS (EI⁺): 276 (M), 261 (M-CH₃), 135 ([N-ethyl-5-methylpyridin-2-amine]⁺).

5-methyl-N-(1-phenylpropan-2-yl)pyridine-2-amine
Allylbenzene (46 μL, 0.40 mmol), 2-amino-5-methylpyridine (22 mg, 0.2 mmol), and Ru(PEt₃)₃(NTf₂)₂ (10 mg, 0.01 mmol, 5.0 mol %) were combined with DCB (40 μL) and a magnetic stir bar in a one dram vial. The vial was capped, and the resulting mixture was heated at 80 °C with stirring for 48 hours. The reaction was allowed to cool, and all of the volatile materials were evaporated. The crude product was purified by silica gel chromatography, eluting with 15% ethyl acetate in hexanes. Yield = 30 mg (66%). ¹H NMR (600 MHz, chloroform-d) δ 7.92 (s, 1H), 7.29 (t, J = 7.5 Hz, 2H), 7.24 (dd, J = 8.4, 2.4 Hz, 1H), 7.23 – 7.17 (m, 3H), 6.32 (d, J = 8.4 Hz, 1H), 4.24 (d, J = 8.6 Hz, 1H), 4.03 (dq, J = 8.7, 6.7 Hz, 1H), 2.92 (dd, J = 13.4, 5.1 Hz, 1H), 2.75 (dd, J = 13.4, 7.1 Hz, 1H), 2.17 (s, 3H), 1.16 (d, J = 6.5 Hz, 3H). ¹³C NMR (151 MHz, chloroform-d) δ 156.42, 148.05, 138.65, 138.50, 129.69, 128.41, 126.35, 121.55, 106.94, 48.34, 42.72, 20.34, 17.53. GC-MS (EI⁺): 226 (M), 211 (M-CH₃), 135 ([N-ethyl-5-methylpyridin-2-amine]⁺).
5-methyl-N-(1-(4-fluoro-phenyl)propan-2-yl)pyridine-2-amine
p-fluoro-allylbenzene (27 mg, 27 μL, 0.20 mmol), 2-amino-5-methylpyridine (22 mg, 0.20 mmol), Ru(PEt$_3$)$_3$(NTf$_2$)$_2$ (10 mg, 10 μmol, 5.0 mol %), were combined with DCB (40 μL) and a magnetic stir bar in a one dram vial. The vial was capped, and the resulting mixture was heated at 80 °C with stirring for 48 hours. The reaction was allowed to cool, and all of the volatile materials were evaporated. The crude product was purified by silica gel chromatography, eluting with 15% ethyl acetate in hexanes. Yield = 27 mg (56%). $^1$H NMR (600 MHz, chloroform-$d$) δ 7.92 (s, 1H), 7.24 (d, J = 8.4 Hz, 1H), 7.14 (dd, J = 8.0, 5.8 Hz, 2H), 6.96 (t, J = 8.6 Hz, 2H), 6.29 (d, J = 8.4 Hz, 1H), 4.14 (d, J = 7.8 Hz, 1H), 4.01 (m, 1H), 2.87 (dd, J = 13.6, 6.9 Hz, 1H), 2.17 (s, 3H), 1.14 (d, J = 6.4 Hz, 3H). $^{13}$C NMR (101 MHz, chloroform-$d$) δ 162.90, 160.48, 156.34, 148.03, 138.52, 134.33 (d, J = 3.2 Hz), 131.05 (d, J = 7.7 Hz), 121.65, 115.27, 115.06, 107.01, 48.31, 41.83, 20.31, 17.52. GC-MS (EI+): 244 (M), 229 (M-CH$_3$), 135 ([N-ethyl-5-methylpyridin-2-amine]•).

N-(1-(3,4-dimethoxyphenyl)propan-2-yl)-5-methylpyridin-2-amine
3,4-Dimethoxy-allylbenzene (36 mg, 0.20 mmol), 2-amino-5-methylpyridine (22 mg, 0.20 mmol), Ru(PEt$_3$)$_3$(NTf$_2$)$_2$ (10 mg, 0.010 mmol, 5.0 mol %), and DCB (40 μL) were combined along with a magnetic stir bar in a one dram vial. The vial was capped, and the resulting mixture was heated at 80 °C with stirring for 48 hours. The reaction was allowed to cool, and all of the volatile materials were evaporated. The crude product was purified by silica gel chromatography, eluting with 40% ethyl acetate in hexanes. Yield = 30 mg (52%). $^1$H NMR (600 MHz, chloroform-$d$) δ 7.91 (d, J = 2.3 Hz, 1H), 7.23 (dd, J = 8.5, 2.4 Hz, 1H), 6.79 (d, J = 8.1 Hz, 1H), 6.72 (dd, J = 8.1, 2.0 Hz, 1H), 6.70 (d, J = 2.0 Hz, 1H), 6.29 (d, J = 8.4 Hz, 1H), 4.23 (d, J = 8.6 Hz, 1H), 4.01 (hept, J = 6.5 Hz, 1H), 3.85 (d, J = 10.2 Hz, 6H), 2.83 (dd, J = 13.5, 5.3 Hz, 1H), 2.72 (dd, J = 13.6, 6.8 Hz, 1H), 2.17 (s, 3H), 1.16 (d, J = 6.5 Hz, 3H). $^{13}$C NMR (151 MHz, chloroform-$d$) δ 156.51, 148.88, 147.98, 147.70, 138.52, 131.22, 121.69, 121.56, 112.98, 111.29, 107.08, 56.05, 55.99, 48.37, 42.27, 20.48, 17.52. GC-MS (EI+): 286 (M), 135 ([N-ethyl-5-methylpyridin-2-amine]•).

N,N-diethyl-9-((5-methylpyridin-2-yl)amino)decanamide
9-decenoic acid diethyl amide (45 mg, 0.20 mmol), 2-amino-5-methylpyridine (22 mg, 0.20 mmol), Ru(PEt$_3$)$_3$(NTf$_2$)$_2$ (10 mg, 0.010 mmol, 5.0 mol %), and DCB (40 μL) were combined
along with a magnetic stir bar in a one dram vial. The vial was capped, and the resulting mixture was heated at 80 °C with stirring for 48 hours. The reaction was allowed to cool, and all of the volatile materials were evaporated. The crude product was purified by silica gel chromatography, eluting with 40% ethyl acetate in hexanes. Yield = 44 mg (66%). $^1$H NMR (600 MHz, chloroform-d) $\delta$ 7.86 (s, 1H), 7.21 (dd, J = 8.4, 2.4 Hz, 1H), 6.27 (d, J = 8.4 Hz, 1H), 4.18 (d, J = 8.6 Hz, 1H), 3.65 (dq, J = 8.3, 6.2 Hz, 1H), 3.34 (q, J = 7.1 Hz, 2H), 3.27 (q, J = 7.1 Hz, 2H), 2.26 (d, J = 8.5 Hz, 1H), 2.24 (d, J = 8.5 Hz, 1H), 2.14 (s, 3H), 1.60 (p, J = 7.5 Hz, 2H), 1.50 (m, 1H), 1.43 (m, 1H), 1.39 – 1.21 (m, 8H), 1.14 (t, J = 6.5 Hz, 6H, 2 methyl groups), 1.08 (t, J = 7.1 Hz, 3H). $^{13}$C NMR (151 MHz, chloroform-d) $\delta$ 172.42, 156.77, 147.85, 138.51, 121.13, 106.44, 47.45, 42.06, 40.12, 37.33, 33.23, 29.59, 29.52, 29.49, 26.10, 25.55, 21.05, 17.45, 14.49, 13.21. GC-MS (EI+): 333 (M), (M-CH3), 318 ([N-ethyl-5-methylpyridin-2-amine]+).

5-((5-methylpyridin-2-yl)amino)-2-phenylhexan-2-ol
2-phenylhex-5-en-2-ol (35 mg, 0.20 mmol), 2-amino-5-methylpyridine (22 mg, 0.20 mmol), Ru(P(Ph)$_3$)(NTf)$_2$ (20 mg, 0.020 mmol, 10 mol %), and DCB (40 μL) were combined along with a magnetic stir bar in a one dram vial. The vial was capped, and the resulting mixture was heated at 80 °C with stirring for 48 hours. The reaction was allowed to cool, and all of the volatile materials were evaporated. The crude product was purified by silica gel chromatography, eluting with 40% ethyl acetate in hexanes. Yield = 29 mg (42%, 52:48 dr). The peaks derived from diastereomer 1 are labelled and those derived from diastereomer 2 are given without labels. $^1$H NMR (400 MHz, chloroform-d) $\delta$ 7.88 (s, 1H), 7.87 (s, 1H, diastereomer 1), 7.47 (d, J = 8.1 Hz, 4H, both diastereomers), 7.34 (d, J = 7.7 Hz, 2H, diastereomer 1), 7.32 (d, J = 7.7 Hz, 2H), 7.22 (m, 4H, both diastereomers), 6.26 (d, J = 8.5 Hz, 2H, both diastereomers), 4.11 (s, 2H, both diastereomers), 3.89 (h, J = 6.0 Hz, 2H, both diastereomers), 2.16 (s, 6H, both diastereomers), 1.91 (t, J = 7.5 Hz, 4H, both diastereomers) 1.52 (s, 6H, both diastereomers), 1.50 – 1.38 (m, 4H, both diastereomers), 1.25 (s, 2H, both diastereomers), 1.10 (d, J = 6.4 Hz, 6H, both diastereomers). $^{13}$C NMR (101 MHz, chloroform-d) $\delta$ 156.34 (diastereomer 1), 156.13, 148.77, 148.45 (diastereomer 1), 146.63 (diastereomer 1), 146.61, 138.98 (diastereomer 1), 138.93, 128.20 (diastereomer 1), 128.17, 126.40 (diastereomer 1), 126.36, 125.01, 124.95 (diastereomer 1), 121.35, 121.30 (diastereomer 1), 107.90, 107.71 (diastereomer 1), 74.87, 74.62 (diastereomer 1), 48.11, 47.51 (diastereomer 1), 39.83 (diastereomer 1), 39.65, 32.56 (diastereomer 1), 32.12, 31.42 (diastereomer 1), 31.08, 29.85, 21.66, 21.41 (diastereomer 1), 17.48 (diastereomer 1). GC-MS (EI+): 284 (M), 135 ([N-ethyl-5-methylpyridin-2-amine]+).
Aminopyridyl boldenone undecylenate

Boldenone undecylenate (91 mg, 0.20 mmol), 2-amino-5-methylpyridine (22 mg, 0.20 mmol), Ru(PEt3)3(NTf2)2 (61 mg, 0.030 mmol, 15 mol %), and DCB (60 μL) were combined along with a magnetic stir bar in a one dram vial. The vial was capped, and the resulting mixture was heated at 80 °C with stirring for 72 hours. The reaction was allowed to cool, and all of the volatile materials were evaporated. The crude product was purified by silica gel chromatography, eluting with a gradient of 20% to 60% ethyl acetate in hexanes. Yield = 39 mg (34%). Both diastereomers gave identical NMR and mass spectra. 1H NMR (500 MHz, chloroform-d) δ 7.87 (s, 1H), 7.23 (dd, J = 10.2 Hz, 1H), 6.28 (d, J = 8.5 Hz, 1H), 6.22 (dd, J = 10.1, 1.5 Hz, 1H), 6.06 (s, 1H), 4.58 (t, J = 8.5 Hz, 1H), 4.18 (d, J = 8.4 Hz, 1H), 3.66 (hept, J = 6.6 Hz, 1H), 2.46 (td, J = 13.4, 4.7 Hz, 1H), 2.36 (d, J = 12.6 Hz, 1H), 2.27 (t, J = 7.5 Hz, 2H), 2.15 (s, 3H), 1.94 (d, J = 14.2 Hz, 2H), 1.86 – 1.54 (m, 9H), 1.54 – 1.41 (m, 4H), 1.38-1.32 (m, 2H), 1.31 – 1.24 (m, 6H), 1.22 (s, 3H), 1.16 (d, J = 6.3 Hz, 3H), 1.10 – 0.98 (m, 4H, 0.85 (s, 3H). 13C NMR (151 MHz, chloroform-d) δ 186.43, 173.93, 168.99, 156.20, 155.80, 146.54, 139.37, 127.67, 124.06, 121.28, 106.83, 82.14, 52.36, 50.02, 47.69, 43.64, 42.89, 37.28, 36.66, 35.45, 34.63, 33.19, 32.84, 29.66, 29.48, 29.28, 29.20, 27.59, 26.11, 25.17, 23.80, 22.48, 20.98, 18.85, 17.42, 12.28. ESI-MS (+): Calc. for C36H53O3N2: 561.4051. Found: 563.4048.

N-(1-(cyclohex-3-en-1-yl)ethyl)-5-methylpyridin-2-amine

4-ethenyl-cyclohexene (26 µL, 22 mg, 0.20 mmol), 2-amino-5-methylpyridine (22 mg, 0.20 mmol), Ru(PEt3)3(NTf2)2 (10 mg, 0.010 mmol, 5.0 mol %), and DCB (40 μL) were combined along with a magnetic stir bar in a one dram vial and stirred to form a solution. The vial was capped, and the resulting mixture was heated at 100 °C with stirring for 48 hours. The reaction was allowed to cool, and all of the volatile materials were evaporated. The crude product was purified by silica gel chromatography, eluting with 15% ethyl acetate in hexanes. Yield = 27 mg (61%). 1H NMR (600 MHz, chloroform-d) δ Major isomer: 7.88 (s, 1H, major), 7.22 (dd, J = 8.5, 2.4 Hz, 1H, major), 6.30 (d, J = 8.4 Hz, 1H, major), 5.67 (m, 2H, major), 4.19 (d, J = 9.3 Hz, 1H, major), 3.67 (h, J = 7 Hz, 1H, major), 2.20 – 1.98 (m, 3H, major), 2.16 (s, 3H, major), 1.88 – 1.83 (m, 2H, major), 1.69 (m, 1H, major), 1.28 (m, 1H, major), 1.16 (t, J = 6.4 Hz, 3H, major). Minor isomer: 7.88 (s, 1H), 7.22 (dd, J = 8.5, 2.4 Hz, 1H), 6.29 (d, J = 8.4 Hz, 1H), 5.67 (m, 2H), 4.24 (d, J = 9.3 Hz, 1H), 3.67 (h, J = 7 Hz, 1H), 2.20 – 1.98 (m, 3H), 2.16 (s, 3H), 1.90 (m, 1H), 1.78 (m, 1H), 1.71 (m, 1H), 1.36 (m, 1H), 1.16 (t, J = 6.4 Hz, 3H). 13C NMR (151 MHz, chloroform-d) δ 156.99, 156.90 (major), 147.83 (major), 147.82, 138.48 (major), 138.47, 127.20,
(E)-N-(hept-5-en-2-yl)-5-methylpyridin-2-amine
1,5-heptadiene (19 mg, 0.20 mmol), 2-amino-5-methylpyridine (22 mg, 0.20 mmol), Ru(PEt3)3(NTf2)2 (10 mg, 0.010 mmol, 5.0 mol %), and DCB (35 μL) were combined along with a magnetic stir bar in a one dram vial and stirred to form a solution. The vial was capped, and the resulting mixture was heated at 80 °C with stirring for 48 hours. The reaction was allowed to cool, and all of the volatile materials were evaporated. The crude product was purified by silica gel chromatography, eluting with 15% ethyl acetate in hexanes. Yield = 27 mg (67%).

\[
\begin{align*}
\text{HN} & \quad \text{N} \\
& \quad \text{O}
\end{align*}
\]

1H NMR (600 MHz, chloroform-\(d\)) \(\delta\) 7.88 (s, 1H), 7.23 (d, \(J = 8.5\) Hz, 1H), 6.28 (d, \(J = 8.3\) Hz, 1H), 5.50 – 5.30 (m, 2H), 4.19 (bs, 1H), 3.69 (dt, \(J = 13.8, 7.0\) Hz, 1H), 2.16 (s, 3H), 2.14 – 2.00 (m, 2H), 1.71 – 1.43 (m, 5H), 1.18 (d, \(J = 6.4\) Hz, 3H). 13C NMR (151 MHz, chloroform-\(d\)) \(\delta\) 156.58, 147.74, 138.35, 130.68, 125.22, 121.07, 106.26, 46.90, 37.06, 29.11, 20.89, 17.87, 17.31, 135. GC-MS (EI+): 204 (M), 185 (M-CH3), 149 (M-butene), 135 ([N-ethyl-5-methoxypyridin-2-amine]+).

5-methoxy-N-(octan-2-yl)pyridin-2-amine
1-octene (31 μL, 23 mg, 0.20 mmol), 2-amino-5-methylpyridine (22 mg, 0.20 mmol), Ru(PEt3)3(NTf2)2 (10 mg, 0.010 mmol, 5.0 mol %), and DCB (40 μL) were combined along with a magnetic stir bar in a one dram vial and stirred to form a solution. The vial was capped, and the resulting mixture was heated at 80 °C with stirring for 48 hours. The reaction was allowed to cool, and all of the volatile materials were evaporated. The crude product was purified by silica gel chromatography, eluting with 25% ethyl acetate in hexanes. Yield = 33 mg (68%).

\[
\begin{align*}
\text{HN} & \quad \text{N} \\
& \quad \text{O}
\end{align*}
\]

1H NMR (600 MHz, chloroform-\(d\)) \(\delta\) 7.80 (d, \(J = 3.0\) Hz, 1H), 7.09 (dd, \(J = 3.0, 1\) Hz, 1H), 6.33 (d, \(J = 9.0\) Hz, 1H), 4.05 (s, 1H), 3.77 (s, 3H), 3.64 (dt, \(J = 11.2, 5.1\) Hz, 2H), 1.53 (dddd, \(J = 12.8, 9.9, 6.3, 5.1\) Hz, 1H), 1.49 – 1.40 (m, 1H), 1.41 – 1.31 (m, 2H), 1.33 – 1.21 (m, 6H), 1.17 (d, \(J = 6.4\) Hz, 3H), 0.87 (t, \(J = 7.0\) Hz, 3H). 13C NMR (151 MHz, chloroform-\(d\)) \(\delta\) 153.88, 148.55, 133.84, 125.80, 107.39, 56.70, 48.00, 37.49, 31.97, 29.50, 26.21, 22.76, 21.14, 14.22. GC-MS (EI+): 236 (M), 221 (M-CH3), 151 ([N-ethyl-5-methoxypyridin-2-amine]+).
N-(dodecan-2-yl)-5-(methylthio)pyridin-2-amine
1-dodecene (34 mg, 0.20 mmol), 5-(methylthio)pyridin-2-amine (28 mg, 0.20 mmol), Ru(PEt3)3(NTf2)2 (10 mg, 0.010 mmol, 5 mol %), and DCB (40 μL) were combined along with a magnetic stir bar in a one dram vial and stirred to form a solution. The vial was capped, and the resulting mixture was heated at 100 °C with stirring for 48 hours. The reaction was allowed to cool, and all of the volatile materials were evaporated. The crude product was purified by silica gel chromatography, eluting with 40% ethyl acetate in hexanes. Yield = 26 mg (42%). 1H NMR (600 MHz, chloroform-d) δ 8.12 (d, J = 2.2 Hz, 1H), 7.47 (dd, J = 8.7, 2.4 Hz, 1H), 6.29 (d, J = 8.7 Hz, 1H), 4.44 (d, J = 8.3 Hz, 1H), 3.73 – 3.66 (m, 1H), 2.35 (s, 3H), 1.49 (ddtd, J = 25.4, 13.2, 9.7, 5.9 Hz, 2H), 1.34 (dtt, J = 18.8, 8.4, 4.9 Hz, 2H), 1.29 – 1.22 (m, 14H), 1.17 (d, J = 6.4 Hz, 3H), 0.87 (t, J = 7.0 Hz, 3H). 13C NMR (151 MHz, chloroform-d) δ 157.61, 151.41, 141.33, 119.93, 106.98, 47.46, 37.30, 32.02, 29.74, 29.71, 29.70, 29.44, 26.17, 22.79, 21.00, 20.43, 14.23. GC-MS (EI+): 308 (M), 292 (M-CH4), 167 ([N-ethyl-5-(methylthio)pyridin-2-amine]).

N-(dodecan-2-yl)-5-(4-methylpiperazin-1-yl)pyridin-2-amine
1-dodecene (34 mg, 0.20 mmol), 5-(4-methylpiperazin-1-yl)pyridin-2-amine (39 mg, 0.20 mmol), Ru(PEt3)3(NTf2)2 (10 mg, 0.010 mmol, 5.0 mol %), and DCB (40 μL) were combined along with a magnetic stir bar in a one dram vial and stirred to form a solution. The vial was capped, and the resulting mixture was heated at 100 °C with stirring for 48 hours. The reaction was allowed to cool, and all of the volatile materials were evaporated. The crude product was purified by silica gel chromatography, eluting with 40% ethyl acetate in hexanes. Yield = 34 mg (47%). 1H NMR (600 MHz, chloroform-d) δ 7.78 (d, J = 2.8 Hz, 1H), 7.18 (dd, J = 9.0, 2.9 Hz, 1H), 6.33 (d, J = 8.9 Hz, 1H), 4.18 (s, 1H), 3.63 (h, J = 6.4 Hz, 1H), 3.06 – 3.01 (m, 4H), 2.60 – 2.55 (m, 4H), 2.35 (s, 3H), 1.52 (dddt, J = 16.1, 12.2, 5.7 Hz, 1H), 1.44 (dddd, J = 13.0, 6.4, 4.2 Hz, 1H), 1.41 – 1.31 (m, 2H), 1.30 – 1.23 (m, 14H), 1.16 (d, J = 6.3 Hz, 3H), 0.87 (t, J = 7.0 Hz, 3H). 13C NMR (151 MHz, chloroform-d) δ 153.93, 139.41, 137.58, 129.34, 107.18, 55.34 (2C), 51.17 (2C), 47.87, 46.25, 37.48, 32.05, 29.83, 29.75 (3C), 29.47, 26.25, 22.82, 21.16, 14.26. GC-MS (EI+): 360 (M), 345 (M-CH3), 219 ([N-ethyl-5-(4-methylpiperazin-1-yl)pyridin-2-amine]).
**N-(1-(3,4-dimethoxyphenyl)ethyl)-5-methylpyridine-2-**

3,4-dimethoxy-vinylbenzene (33 mg, 0.20 mmol), 2-amino-5-methylpyridine (22 mg, 0.20 mmol), Ru(PEt₃)₃(NTf₂)₂ (10 mg, 0.010 mmol, 5.0 mol %), DCB (40 μL), and a magnetic stir bar were combined in a one dram vial to form a solution. The vial was capped, and the resulting mixture was heated at 80 °C with stirring for 48 hours. The reaction was allowed to cool, and all of the volatile materials were evaporated. The crude product was purified by silica gel chromatography, eluting with 20% ethyl acetate in hexanes. Yield = 35 mg (64%). ¹H NMR (600 MHz, chloroform-d) δ 7.90 (s, 1H), 7.16 (d, J = 10.0 Hz, 1H), 6.90 (d, J = 10.7 Hz, 2H), 6.81 (d, J = 8.1 Hz, 1H), 6.14 (d, J = 8.4 Hz, 1H), 4.76 (d, J = 5.5 Hz, 1H), 4.61 (p, J = 6.5 Hz, 1H), 3.85 (s, 6H), 2.14 (s, 3H), 1.52 (d, J = 6.7 Hz, 3H). ¹³C NMR (151 MHz, chloroform-d) δ 156.18, 149.13, 147.89, 147.42, 138.56, 137.48, 121.82, 117.72, 111.17, 109.04, 106.45, 76.98, 55.86, 55.82, 51.97, 24.46, 17.31. GC-MS (EI+): 272 (M), 267 (M-CH₃), 165 (M-[p-Me-aminopyridine]+).

**N-(ethyl-naphthalene-2-yl)-5-methylpyridin-2-amine**

(31 mg, 0.20 mmol), 2-amino-5-methylpyridine (22 mg, 0.20 mmol), Ru(PEt₃)₃(NTf₂)₂ (20 mg, 0.020 mmol, 10 mol %), and DCB (60 μL) were combined along with a magnetic stir bar in a one dram vial. The vial was capped, and the resulting mixture was heated at 100 °C with stirring for 48 hours. The reaction was allowed to cool, and all of the volatile materials were evaporated. The crude product was purified by silica gel chromatography, eluting with 40% ethyl acetate in hexanes. Yield = 34 mg (65%). ¹H NMR (600 MHz, chloroform-d) δ 7.93 – 7.90 (m, 1H), 7.84 – 7.77 (m, 4H), 7.50 (dd, J = 8.5, 1.7 Hz, 1H), 7.45 (pd, J = 6.8, 1.5 Hz, 2H), 7.11 (dd, J = 8.4, 2.4 Hz, 1H), 6.16 (d, J = 8.5 Hz, 1H), 4.95 (d, J = 5.9 Hz, 1H), 4.83 (p, J = 6.6 Hz, 1H), 2.12 (s, 3H), 1.61 (d, J = 6.8 Hz, 3H). ¹³C NMR (151 MHz, chloroform-d) δ 156.44, 148.03, 142.55, 138.55, 133.64, 132.85, 128.60, 127.95, 127.78, 126.18, 125.69, 124.58, 124.35, 122.06, 106.50, 52.49, 24.64, 17.48. GC-MS (EI+): 262 (M), 155 (M-[p-Me-aminopyridine]+).
N-(ethylferrocene-2-yl)-5-methylpyridin-2-amine
(42 mg, 0.20 mmol), 2-amino-5-methylpyridine (22 mg, 0.20 mmol), Ru(PEt3)3(NTf2)2 (20 mg, 0.020 mmol, 10 mol %), and DCB (40 μL) were combined along with a magnetic stir bar in a one dram vial and stirred to form a solution. The vial was capped, and the resulting mixture was heated at 80 °C with stirring for 48 hours. The reaction was allowed to cool, and all of the volatile materials were evaporated. The crude product was purified by silica gel chromatography, eluting with 40% ethyl acetate in hexanes. Yield = 39 mg (61%). 1H NMR (600 MHz, chloroform-d) δ 7.95 (s, 1H), 7.27 – 7.24 (m, J = 2.0 Hz, 1H), 6.34 (d, J = 8.4 Hz, 1H), 4.66 (m, 1H), 4.55 (d, J = 8.2 Hz, 1H), 4.20 (s, 5H), 4.18 (m, 2H), 4.13 (dt, J = 7.7, 1.7 Hz, 2H), 2.18 (s, 3H), 1.52 (d, J = 6.5 Hz, 3H). 13C NMR (151 MHz, chloroform-d) δ 156.41, 147.93, 138.53, 121.54, 107.08, 93.38, 68.58 (5C), 67.88, 67.62, 67.08, 66.15, 45.75, 21.37, 17.55. GCMS: (EI+): 320 (M), 305 (M-CH3), 213 (M-[p-Me-aminopyridine]+).

4-((5-methylpyridin-2-yl)amino)nonan-2-one
(E)-non-3-en-2-one (28 mg, 0.20 mmol), 2-amino-5-methylpyridine (22 mg, 0.20 mmol), Ru(PEt3)3(NTf2)2 (10 mg, 0.010 mmol, 5.0 mol %), lithium tert butoxide (0.6 mg, 20 µL of a 30 mg/mL suspension in dioxane, 3.5 mol %), and DCB (40 μL) were combined along with a magnetic stir bar in a one dram vial. The vial was capped, and the resulting mixture was heated at 100 °C with stirring for 48 hours. The reaction was allowed to cool, and all of the volatile materials were evaporated. The crude product was purified by silica gel chromatography, eluting with 40% ethyl acetate in hexanes. Yield = 35 mg (70%). 1H NMR (600 MHz, chloroform-d) δ 7.87 (s, 1H), 7.21 (dd, J = 8.4, 1.8 Hz, 1H), 6.32 (d, J = 8.4 Hz, 1H), 4.36 (d, J = 9.3 Hz, 1H), 4.17 (dt, J = 15.0, 7.3 Hz, 1H), 2.66 (t, J = 5.9 Hz, 2H), 2.15 (d, J = 6.9 Hz, 7H), 1.61 – 1.50 (m, 2H), 1.40 (m, 1H), 1.36 – 1.19 (m, 6H), 0.85 (t, J = 6.5 Hz, 4H). 13C NMR (151 MHz, chloroform-d) δ 208.53, 156.45, 147.53, 138.69, 121.68, 107.32, 48.52, 48.43, 35.40, 31.85, 30.95, 26.02, 22.69, 17.50, 14.14. GCMS: (EI+): 248 (M), 191 (M-[acetone]+).
p-methyl-amino-pyridinyl Crotamiton

Crotamiton (41 mg, 0.20 mmol), 2-amino-5-methylpyridine (22 mg, 0.20 mmol), Ru(PEt3)3(NTf2)2 (10 mg, 0.010 mmol, 5 mol %), lithium tert butoxide (0.6 mg, 20 µL of a 30 mg/mL suspension in dioxane, 3.5 mol %) and DCB (40 µL) were combined along with a magnetic stir bar in a one dram vial and stirred to form a solution. The vial was capped, and the resulting mixture was heated at 80 °C with stirring for 48 hours. The reaction was allowed to cool, and all of the volatile materials were evaporated. The crude product was purified by silica gel chromatography, eluting with 40% ethyl acetate in hexanes. Yield = 39 mg (62%). 1H NMR (600 MHz, chloroform-d) δ 7.84 (s, 2H), 7.31 – 7.27 (m, 2H), 7.25 – 7.00 (m, 8H), 6.34 – 6.28 (m, 2H), 4.82 – 4.73 (m, 2H), 4.17 – 4.05 (m, 4H), 3.25 – 3.16 (m, 2H), 2.30 (dd, J = 15.4, 4.9 Hz, 2H), 2.22 – 2.10 (m, 12H), 2.03 (dd, J = 15.2, 6.6 Hz, 2H), 1.21 (d, J = 6.5 Hz, 6H), 1.11 (td, 6H). 13C NMR (151 MHz, chloroform-d) (rotamer 1 refers to one of the two diatereotopic conformations arising from the presence rotamers in the chiral racemic compound) δ 171.02, 171.00 (rotamer 1), 156.17, 156.14 (rotamer 1), 147.49, 147.49 (rotamer 1), 140.74 (rotamer 1), 140.65, 138.32, 138.32 (rotamer 1), 135.74 (rotamer 1), 135.73, 131.50, 131.45(rotamer 1), 129.35, 129.25 (rotamer 1), 128.28, 128.27 (rotamer 1), 127.10 (rotamer 1), 127.02, 121.31, 121.28 (rotamer 1), 107.25, 107.15 (rotamer 1), 44.83, 44.82 (rotamer 1), 42.95 (rotamer 1), 42.85, 39.93, 39.87 (rotamer 1), 29.66, 20.71, 20.67 (rotamer 1), 17.50 (rotamer 1), 17.46 (rotamer 1), 17.32, 12.83, 12.78. GC-MS (El+): 311 (M), 135 ([N-ethyl-5-methylpyridin-2-amine]?).

3.17 Deprotection of masked primary amine to free primary amine

5-methyl-N-(dodecan-2-yl)pyridine-2-amine (28 mg, 0.10 mmol), PtO2 (2.3 mg, 10% [Pt]), acetic acid (150 µL), and a stir bar were combined in a one dram vial, flushed with nitrogen outside of the glove box, and capped with a septa capped vial. A balloon of hydrogen gas was inserted through the septa cap via a needle and the reaction was heated at 30 °C for 18 hours. The reaction was made basic by the addition of 10% KOH solution until reaching pH 12, and then extracted with 2:1 ethyl acetate:tetrahydrofuran (4 x 2 mL). The combined extracts were dried over Na2SO4, dried down, and purified through a short reverse phase silica column with 40% EtOH in H2O. The pure amidine residue, occurring as a 2:1 mixture of trisubstituted: disubstituted amidine, was then treated with 1M hydrazine in THF (0.15 mmol, 1.5 equiv) at 80 °C for 20 minutes to generate 2-dodecanamine in 95% yield generated in situ. Addition of 1 M potassium carbonate solution at pH 9 and extraction with 2:1 EA:THF (4 x 1 mL) yields pure 2-dodecanamine. Alternatively the crude amidine was treated with 1M hydrazine in THF (0.15 mmol, 1.5 equiv) at 80 °C for 20 minutes and then allowed to cool to room temperature, dried down fully, and purified by reverse phase chromatography, eluting with 10% to 50% EtOH in H2O. Yield = 8.0 mg (51%) for the full sequence.
3.18 List of Abbreviations
2-AP, 2-amino-5-methylpyridine
DCB, dichlorobenzene
DCE, dichloroethane
DCM, dichloromethane
DMSO, dimethylsulfoxide
GC, gas chromatography
GCMS, gas chromatography-mass spectrometry
HFIP, hexafluoroisopropanol
MeOH, methanol
NMR, nuclear magnetic resonance
THF, tetrahydrofuran
TLC, thin layer chromatography

3.19 References
11. Klauber, E. G. et al. Group 5 Metal Binaphtholate Complexes for Catalytic Asymmetric


