A Scope on the Advantages and Limitations of Iron Catalysts in the Synthesis of Secondary Alcohols

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Abstract

The utilization of rare-earth metals such as rhodium, ruthenium, osmium, titanium, or even palladium has had great importance in the field of synthetic organic chemistry, but the lack of usage of more common, cheaper transition metal catalysts such as iron has not been quite understood. The field of using iron catalysts towards the hydrogenation of ketones to secondary alcohols became popularized because it allowed for a functional group change that could be further used in pharmaceuticals. To this modern time, not a lot has been understood as to the limitations and advantages of using a cheap, common transition metal as a catalyst, such as iron. The common problem amongst published works is in regards to iron's inability to synthesize molecules with a desired specific three-dimensional projection (stereoselectivty). Stereoselectivity is highly desired in pharmaceutical companies because it mimics natural products and molecules that our bodies make for our own defense. Iron has been disregarded as a good catalyst in stereoselective reductions, even though it is cheaper due, to certain electronic issues, and so ligands must be chemically attached to the metal. The question posed is this: will adding complex ligands to iron be more efficient economically and time-wise, than purchasing rare earth metals with minimal addition of ligands, towards the reduction of ketones into secondary alcohols with stereoselectivity.

The method of reduction has great implications in the field of synthetic organic chemistry, especially in the production of mass produced pharmaceutical drugs. Reduction, is the process of adding electrons to a molecule, for instance, the usage of O_2 to H_2O is a form of hydrogenation. The desire for reduction, especially with stereoselectivity (specific 3-D projection of elements on a molecule) is justified because in vivo (taking place within the body), substrate to enzyme binding is highly three-dimensionally specific.[1,2] Because these alcohol groups have stereoselectivity due to their chiral carbon center, it is now highly desired as a precursor to make large-scale amounts of more potent pharmaceuticals.

Chirallity is the identification of a carbon molecule attached to four different molecules. Stereoselectivity, however, is the specific three-dimensional placement of elements on a chiral carbon center (stereocenter).[2,3,4] In typical chemical reactions, the hydrogenation of a molecule with stereoselectivity produces products with enantiomers, which can be analogized as mirror-images of the same product.[2,3] Take into account looking at your left and right hands, they are, generally speaking, enantiomers of one another.

Specifically, within the body, receptors that mediate reactions only accept a specific diastereomer (molecules with multiple chiral carbon centers) in order for the effect to take place.[1, 2] For instance, in the case of Albuterol, a respiratory medication, the body reacts to a certain diastereomer (R conformation) but sees the other conformation (S) as a toxin that can go to waste.[1] In addition, it has been noted that as much as 50% of today's commercial drugs are also enantiomers or diastereomers of one another.[2] Such fact validates the idea of the high

demand for stereochemical control over product output.[1, 2] Hydrogenation of an unsaturated bond, allows for chirallity to occur because the carbon center of the unsaturated bond will now be saturated with four different elements, or substituents. In the instance of ketones, hydrogenation does lead to chirality so long as the ketone is asymmetric (carbon chains are not the same number in length) .[1,2]

In the past, hydrogen gas being bubbled through oil and in the presence of a metal such as palladium, for catalytic purposes, was the most common method of attaining a hydrogenated product.[3] It has been well noted that hydrogen gas is a volatile substance that can be more combustible than gasoline. There have been instances of explosions of hydrogen tanks in laboratory because of improper storage. Not only this, but the most common method of reduction in the past was with the usage of a reducing agent in conjunction with hydrogen gas.[3] These agents can include the following: hydride compounds, certain alcohols, acids, and boron compounds, or even compounds involving sulfur.[3,4] The safety of the researcher is at stake when conducting these experiments, which makes this popularized mechanism something of a hassle when being conducted.

In the avoidance of using volatile substances, the employment of organometallic compounds, metals that have been chemically engineered to carry attachments (ligands) on the metal, became a prominently used option to synthesize the desired compound. With that, in vitro (in a test tube) methods of hydrogenation, using reductive reagents and organometallic catalysts, were adapted and applied in avoidance of having the danger of a combustible gas in lab. Organometallic catalysts such as rhodium, ruthenium, platinum, osmium, or palladium were used quite frequently from the 1980s and the ensuing years due to their ability to produce

stereoselective products.[5] The issue with the usage of the aforementioned transition metals is the fact that they are directly placed in the region where it can be considered "Rarest metals" as shown in Figure 1, therefore economical costs come into play when trying to produce kilogram quantities of a desired product.[7] The most common question that arises from such is this: Can there be a substitute within the "Rock-forming elements" that can replace the "Rarest metals", as seen in Figure 1?[6]

The 1990s decade was very productive for the advancement of using organometallic compounds to hydrogenate ketones into alcohols. Research on the matter identified that catalysts such as osmium, ruthenium, and even iron, in the 2+ oxidative state would allow for an efficient reduction of the carbon to carbon double bonds, however the result that occurred was the production of saturated and unsaturated alcohols on some compounds.[3] What was understood was that even if efficiency was slightly lowered than the other organometallic compounds, iron was far cheaper to purchase and can be modified to run the same reactions as osmium and ruthenium.

Synthesis of alcohols from ketones was a novel reaction, yes, but for it be profitable, it was necessary to be able to have better control on how it can react in a biological system. Because of this, stereoselective control over the synthesis of these alcohols was a highly desired, yet not well understood process. Several researchers, including a Nobel Prize award-winning methodology, identified that an asymmetric, chiral ruthenium and rhodium catalyst can allow for the specific control, and high yield, of the reduction of ketones into secondary alcohols.[9,10]

Later research identified that palladium and platinum, and even titanium can conduct such stereospecific reactions with the proper ligand additions, and with less cost to the conductor of the research.[4] However, the most recent identification was that even iron can conduct this method of reduction with a 99:1 stereoselective synthesis of alcohols. Such research is something that has been highly desired, due to its innate toxicity and abundance in the environment.[10]

The opioid medications for pain relief narcotics such as hydrocodone, codeine, and dihydrocodeine, are popularized within the pharmaceutical industry and consumers. The production of which has been long desired for the simple reason being: consumers want pain relief. As seen in Scheme 2, the structure of hydrocodone contains two ketone groups, but only one of which is significant in the differentiation between hydrocodone and codeine, and a carbon to carbon double bond away between codeine and dihydrocodeine.[11,12] The oxidation of a secondary alcohol from codeine, under oxidative conditions, has lead to the inexpensive production of hydrocodone.[11] This experiment demonstrated the ability to selectively oxidize the terminal alcohol functional group, and turn it into a ketone. In a reverse reaction, the possibility of producing codeine from hydrocodone is feasible in selective reduction conditions.[10] The selectivity is dependent on the reduction of the carbonyl group forming the ketone, and also in the proper stereochemistry.[11]

In using hydrocodone as a reagent and by reducing the ketone, the codeine molecule can be formed.[12] Indicative of past research, the synthesis of codeine via reduction has not been fully identified. The utilization of an asymmetric iron catalyst which allows selective reduction, with a

99:1 selectivity rate, could prove to be beneficial in the hydrogenation into codeine. [10, 11,12] Codeine is now more useful because it can be selectively hydrogenated on its double bond between carbons to form dihydrocodeine, another opioid useful in treating pain especially in conjunction with paracetamol (acetaminophen or Tylenol) .[12]

Iron has the possibility to conduct hydrogenations of ketones into chirally active secondary alcohols with similar stereoselectivty, product yield, and mechanistic pathway as ruthenium, palladium, or other rare earth metal catalysts.[10] So what then is the issue with the substitution of iron in place of the more expensive metals? Iron just lacks the electron density as opposed to the rarer earth metals as seen in Figure 1.[6] Electron density contributes to an element's ability to coordinate with its ligands, which will then aid in the reaction with the chemicals in its environment. In the case of iron versus another metal within its column, such as ruthenium, ruthenium has a whole s and p orbital shell plus six extra d orbital electrons to coordinate with ligand attachments.[13] Iron's lack of electron density can be attributed to the metal's lack of efficiency as a catalyst in the hydrogenation of ketones. During reactions, ligands attached to the iron catalyst tend to fall apart in situ (on site or within the reaction), and the metal itself can no longer coordinate in the desired manner because it has lost its chiral control, its oxidation state, and its ability to produce the mechanism desired; all of which contributes to the detriment of the experiment. In opposition, ruthenium has an ample electron density to hold ligands together, complete the mechanism, and not "burn out" in vitro (within a test tube) when given the proper catalytic amount.[13]

However, where iron succeeds versus other rare earth metals is in vivo, being used as a catalyst for biochemical reactions.[14] Within the human body, iron acts as an oxygen acceptor that goes into the 3^+ oxidation state, being the receptor within the tetramer of globulin molecules, such as that in blood and red blood cells. This extremely important iron center is the reason that we are allowed ample oxygen throughout the body, and the removal of CO_2 from our body. Not only this, but iron is also used as an electron acceptor in Complex IV, of the Animal Electron Transport Chain in cellular respiration.[14] Without iron being where it is in this respiratory process, the generation of ATP would be hindered, our cells would become toxic due to a high build up of oxygen peroxide formation, and ultimately, our biological processes would not be possible.[14] Within these structures, iron is the metal used as the prosthetic center of these highly important proteins.[14]

In comparison, other molecules within the same column in the periodic table as iron would not be applicable because the element would be either too large or small in size, toxic for the human body, or not be as efficient with oxygen displacement as iron is.[14] Where it differs from chemical reactions conducted is that this in vivo reaction is an oxidative step and reductive step, catalyzed by several different enzymes, which are known to be much more efficient than any synthetically produced catalyst.[15]

It is well noted that iron has many limitations as a catalyst for organometallic, organic reactions. It is indeed not electron dense enough to withstand chemical reactions while maintaining its ligand attachments. Not only this, several reactions are needed to simply activate the metal, giving it the desired oxidation state for the catalyst to undergo the needed mechanisms for the reaction.

Although it has many limitations, iron has been known to have the ability to be a highly efficient catalyst in reductions of ketones into chiral, secondary alcohols if proper ligand attachments can activate the metal. Not only can it do this, iron is highly abundant, non-toxic metal to humans, and cost efficient to apply to several different studies in synthetic chemistry, inorganic chemistry, and biochemistry. Iron can replicate several mechanisms that rare earth metals can, such as that by ruthenium and osmium, especially because it is in the same periodic table column within the transition metal groups. Best of all, within the scope of this research, data would support that iron is becoming a more popular catalyst to apply to different reactions aside from just the reductions of ketones. Iron, however, is dependent on further research into cheaper methods of attaining the oxidation state desired in these reductions, with minimal amount of reactions to attach those ligands that will get the metal to its oxidation state. The advancement of this metal catalyst shows a future scope on the enhanced reduction of different functional groups such as alkenes, or even alkynes with enhanced stereoselectivity.

Iron can no longer be viewed as just as an inefficient catalyst exo vivo (outside life); it can be associated with the idea of it being an efficient, stereoselective catalyst not just biochemically, but in synthetic chemistry as well. Further research on reductions of other functional groups, is currently being discovered, and in great hopes, will provide further insight on this fairly novel area of research. With the current pattern of research, iron will be highly desired in the field of pharmaceuticals and mass production because of its potential to be a cheap, environmentally-safe, catalyst that can replicate mechanisms obtained from other organometallic catalysts.

It is with great hope that further research can be done on this subject because the possibilities and benefits from having more cost efficient materials could be endless. A lower cost of starting materials could end up having a lower cost of products. If the price of the product, which in this case is pharmaceutical narcotics, could be lowered, those less fortunate would be able to afford the medication needed for their survival. Surprisingly, in our developed country, we still struggle to provide citizens with the proper provisions for survival. Yes, it is impossible to appease everyone and their needs, but one change can go a long way in working for the advancement of humanity. With all that is wrong in the world, a small microscopic change, like changing a common metal catalyst, can have the ability pave the way to bigger changes that are undoubtedly needed in our ever expanding world.

Figure 1

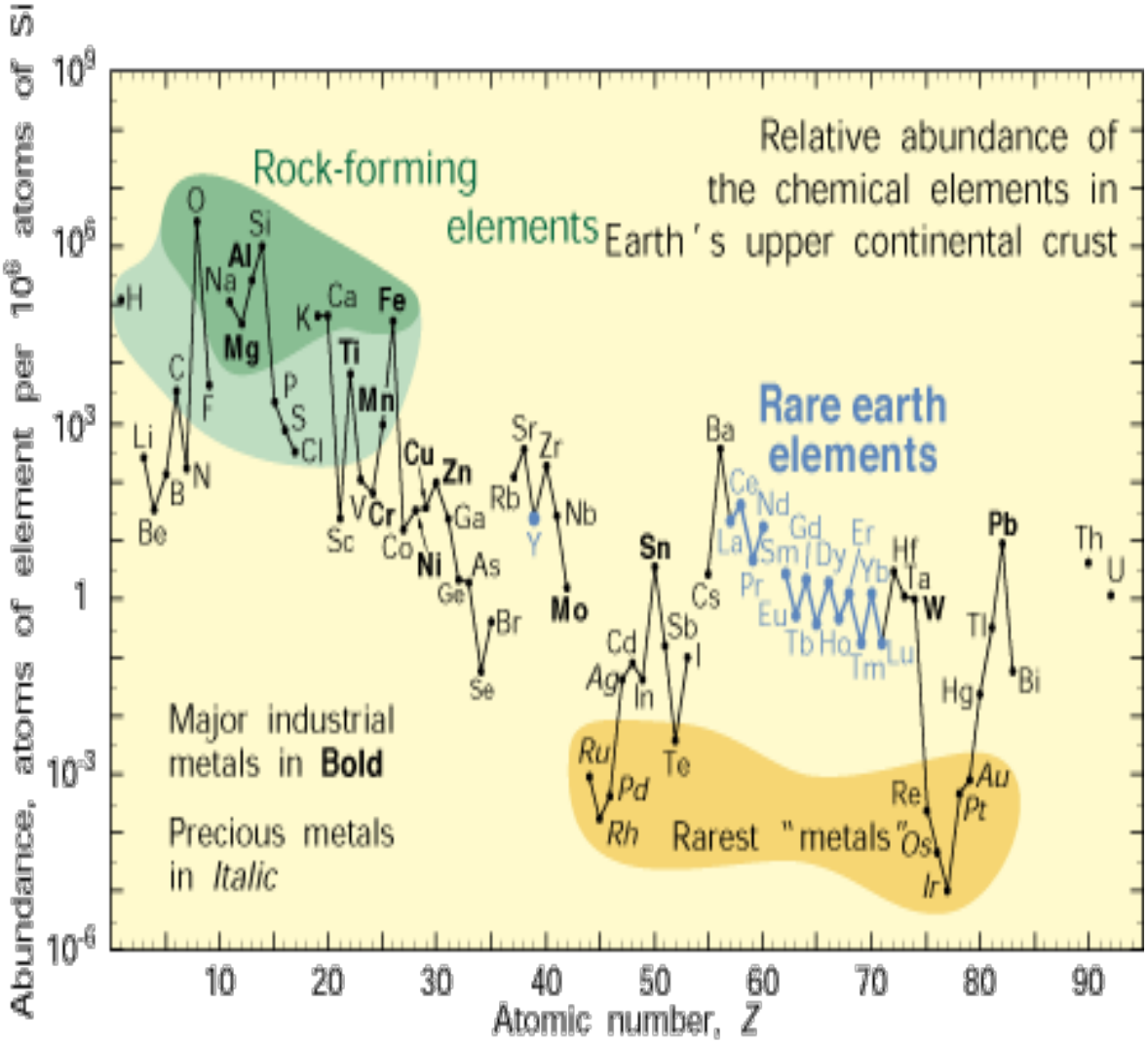
Relative abundance of the chemical elements in Earth's upper continental crust
Rock-forming elements
Rare earth elements
Major industrial metals in Bold
Precious metals in Italic
Rarest "metals"
Abundance, atoms of element per 10^6 atoms of Si
Atomic number, Z
10^9
10^6
10^3
1
10^-3
10^-6
10
20
30
40
50
60
70
80
90
H
Li
Be
B
C
N
O
F
Na
Mg
Al
Si
P
S
Cl
K
Ca
Sc
Ti
V
Cr
Mn
Fe
Co
Ni
Cu
Zn
Ga
Ge
As
Se
Br
Rb
Sr
Y
Zr
Nb
Mo
Ru
Rh
Pd
Ag
Cd
In
Sn
Sb
Te
I
Cs
Ba
La
Ce
Pr
Nd
Eu
Sm
Gd
Tb
Dy
Ho
Er
Tm
Yb
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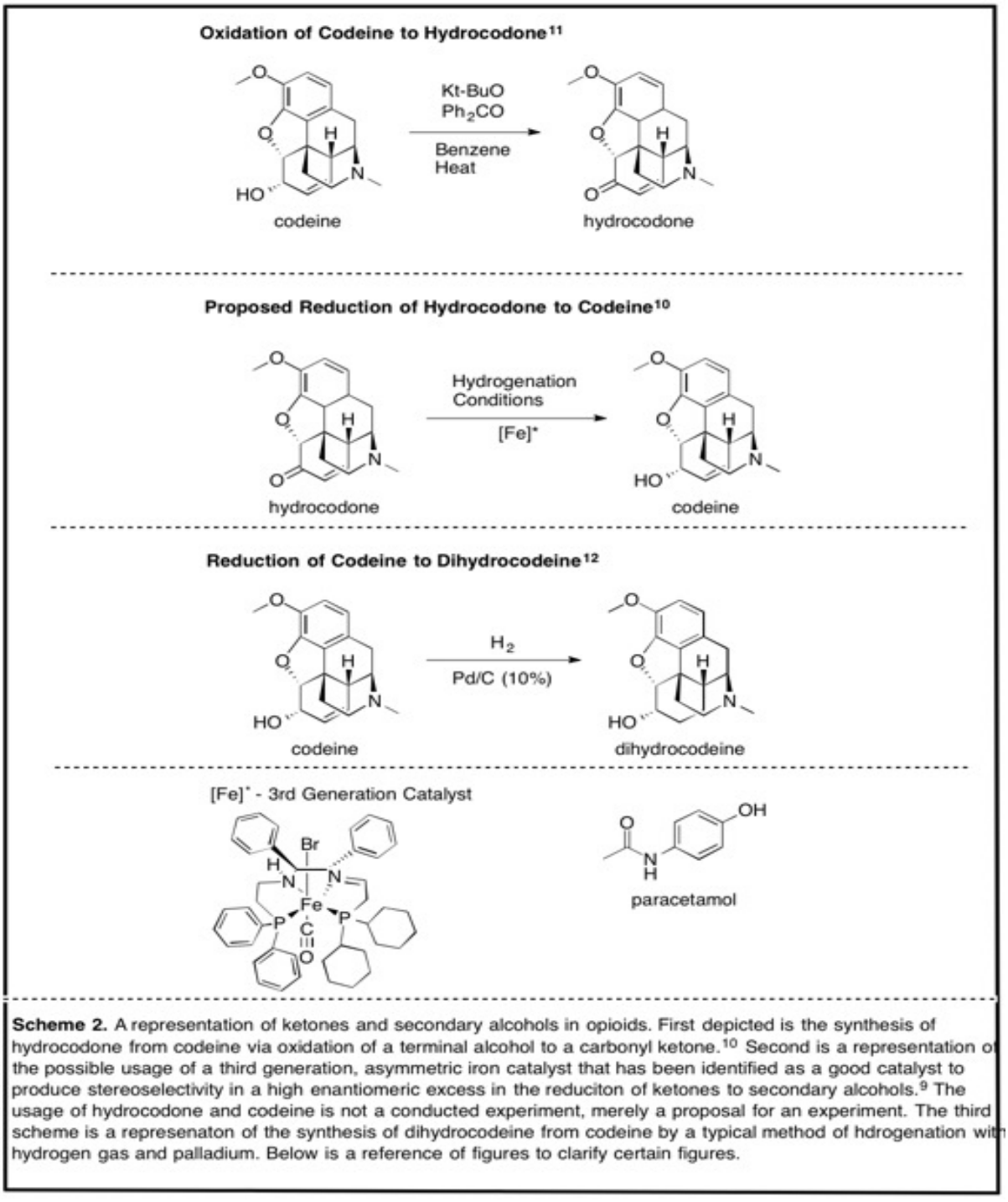
Figure 2



Scheme 2. A representation of ketones and secondary alcohols in opioids. First depicted is the synthesis of hydrocodone from codeine via oxidation of a terminal alcohol to a carbonyl ketone.[10] Second is a representation of the possible usage of a third generation, asymmetric iron catalyst that has been identified as a good catalyst to produce stereoselectivity in a high enantiomeric excess in the reduciton of ketones to secondary alcohols.[9] The usage of hydrocodone and codeine is not a conducted experiment, merely a proposal for an experiment. The third scheme is a represenaton of the synthesis of dihydrocodeine from codeine by a typical method of hdrogenation with hydrogen gas and palladium. Below is a reference of figures to clarify certain figures.

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Biography

Originally, I was born in the Philippines but immigrated at the age of six. My family and I started in Oakland but decided to move to the Central Valley, first in Ceres, then to Atwater, and finally Modesto. I graduated from Delhi High School, located in Delhi, CA; a small town of approximately 5,000 people, located right in between Turlock and Livingston. Upon graduation in 2012, I attended University of California, Merced in pursuit of a Bachelor's of Science in Biology. Currently, I am a fourth year with an emphasis in Immunology and Microbiology and an undergraduate research assistant in organometallic and organic chemistry under Benjamin Stokes, Ph.D. I work as a Student Mentor for first year students and am also a part of the Kappa Sigma Fraternity. I look forward to graduation in 2016 with hopes of obtaining a position in medical school.