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Catalytic Transfer Hydrogenation of Nitroalkenes to Primary Amines

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Catalytic Transfer Hydrogenation of Nitroalkenes to Primary Amines

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April 25, 2016

Submitted to the faculty of Ursinus College in fulfillment of the requirements for Honors in Chemistry
To my parents, Dennis and Maureen, for their love and support
Abstract
This work describes synthetic methodology development in organic chemistry. The goal of this work is to demonstrate new ways of making biologically-relevant molecules that are in line with the principles of green chemistry (chemical practices which seek to be, regarding human and environmental health, benign by design). To this end, a new method has been developed toward the introduction of primary amine functionalities into organic molecules from readily-available aldehydes, via reduction of nitroalkene intermediates. Traditional methods of reducing nitroalkenes to primary amines require harsh conditions, often produce stoichiometric amounts of metal salt waste, and present significant safety challenges to the chemist. The method described herein employs metal-catalysis to effect this same transformation under mild conditions.
Acknowledgements

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1. Introduction

1.1 The Modern Pharmaceutical Industry
1.1.1 Challenges for Green Chemistry

The modern pharmaceutical industry has grown from its nascent beginnings in ancient apothecaries, which proffered plant extracts and isolates, into an almost trillion dollar per annum business sector, which regularly produces countless unique medicines annually, many of which are synthetic or semi-synthetic in origin. While natural products still constitute a sizable portion of the pharmaceuticals in use today (the alkaloids from the opium poppy Papaver somniferum are a representative example), as the industry has grown, demand for many natural products has outpaced supply from their natural sources. The main aim of total synthesis is to addresses this issue through synthetic chemistry by discovering ways to produce natural products in the laboratory. Accordingly, along with the advent of synthetic pharmaceuticals, organic synthesis has become an integral part of the industry. By its very nature, the pharmaceutical industry specializes in complex, fine chemicals. Consequently, the multi-step reactions employed in pharmaceutical synthesis generate a disproportionate amount of chemical waste compared to other sectors of the chemical industry, see Table 1.

Table 1: Waste by chemical industry sector

<table>
<thead>
<tr>
<th>Industry segment</th>
<th>Annual production (Te)</th>
<th>kg By-products/kg products (E-factor)</th>
<th>Approx. total waste (Te)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oil refining</td>
<td>$10^6$–$10^8$</td>
<td>$\sim 0.1$</td>
<td>$10^6$</td>
</tr>
<tr>
<td>Bulk chemicals</td>
<td>$10^4$–$10^6$</td>
<td>$&lt; 1–5$</td>
<td>$10^5$</td>
</tr>
<tr>
<td>Fine chemicals</td>
<td>$10^2$–$10^4$</td>
<td>$5$ to $&gt; 50$</td>
<td>$10^4$</td>
</tr>
<tr>
<td>Pharmaceuticals</td>
<td>$10$–$10^3$</td>
<td>$25$ to $&gt; 100$</td>
<td>$10^3$</td>
</tr>
</tbody>
</table>
Much of the waste produced by the pharmaceutical industry is considered to be hazardous waste and thus requires specialized disposal. The amount of waste produced per unit of product noted in the table above specifically exemplifies the inefficiencies associated with synthetic organic chemistry, where less-than-quantitative yields over dozens of steps significantly decrease overall yield. While inefficiencies are to a certain extent inescapable, many existing processes can be greatly improved. Several examples exist where solvent waste and byproducts were greatly reduced through conscious choices in production and research. Ibuprofen represents a striking example of green chemistry in the pharmaceutical industry. A six-step process for the synthesis of Ibuprofen has since been replaced by the more atom-economical, cleaner Hoechst–Celanse process. The latter process (Figure 1) produces much less waste but at the expense of using hazardous HF as a solvent/catalyst. Trade-offs such as these (efficiency and waste-reduction over hazards) and others are common when evaluating multiple synthetic routes to chemical products. Other possible trade-offs are cost, time, atom-economy, energy usage, etc.
1.1.2 The Importance of Optical Isomers
Recently asymmetric synthesis has become a major area of research in organic chemistry. The biological applications of asymmetric synthesis are obvious. Individual enantiomers of pharmacologically-active compounds display unique activity. Sometimes a simple difference in potency between enantiomers is observed, where one enantiomer is potent and the other less so or completely inactive. Moreover, each enantiomer may possess either desirable or unwanted
biological activity, as exemplified with the enantiomers of thalidomide, see Figure 2. In the case of thalidomide, the unwanted enantiomer is toxic, causing birth deformities. Asymmetric (chiral) synthesis is important because it selectively produces only one – desirable – enantiomer. From the point of view of green chemistry and maximizing efficiency, asymmetric synthesis is necessary if single enantiomers of compounds are required. The alternative option – chiral resolution – is inefficient and wasteful since 50% of the product is unwanted and must be sold or disposed of. Much work has been done in the area of asymmetric synthesis; notable examples include the 2001 Nobel-Prize winning work of Noyori Ryoji and William S. Knowles on asymmetric hydrogenation and that of K. Barry Sharpless on enantioselective (Sharpless) epoxidation. Many pharmaceuticals are now marketed as single enantiomers.
1.2 Amines

1.2.1 Pharmacologically-active Amines
The amine functionality is one of the most ubiquitous in compounds possessing biological activity. Indeed, the amine functionality by definition defines alkaloids, a diverse class of natural products, often with biological activity, which exhibit basic properties due to amine nitrogen atoms. Figure 3 shows some common alkaloids.

Figure 2: Select chiral compounds and their associated biological activity

Figure 3: Some common alkaloids
Due to the profound importance of amines as biologically-active compounds, it should come as no surprise that many pharmaceuticals – synthetic, semi-synthetic, and natural – possess basic nitrogen atoms of this unique functionality. Figure 4 shows the presence of amines in some of the most popular pharmaceuticals today.

Figure 4: Highly successful amine pharmaceuticals. From left, Atorvastatin (Lipitor); Fluoxetine (Prozac); Oxycodone

1.2.2 The Synthesis of Primary Amines – Motivation
In light of the importance of the amine functionality in pharmaceuticals, the synthetic routes to primary amines will be discussed. Figure 5 depicts common routes to primary amines from various functionalities.

Figure 5: Common synthetic routes to primary amines
Starting from either the corresponding nitrile or amide, reduction to the primary amine may be accomplished with lithium aluminum hydride (LAH). While the reaction is effective, the hazards associated with LAH and the solvents commonly employed in its reactions leave much to be desired in terms of green chemistry. LAH is a pyrophoric compound requiring special handling precautions. Moreover, it is typically employed in excess as a suspension in comparatively-large volumes of extremely flammable, peroxide-forming ethers such as diethyl ether and tetrahydrofuran. Accordingly, the atom-economy of reactions involving LAH is poor: inorganic Li and Al salts are produced as waste. The associated hazards of reactions using LAH limit the attractiveness for the reduction of nitriles and amides in the synthesis of primary amines, especially on an industrial scale.

Reductive amination is another viable route to the synthesis of primary amines, yet it is not a method without its own shortcomings. At the laboratory scale, reductive amination may be performed using specialized hydride reagents with weakened hydricity; examples include NaCNBH$_3$ and Na(OAc)$_3$BH. Both reagents are pyrophoric, water-sensitive solids and NaCNBH$_3$ presents an acute toxicity hazard owing to the presence of a labile CN functionality. Upon acidic workup in reductive amination reactions involving NaCNBH$_3$ as the reducing agent, HCN is evolved.
Figure 6: Reductive amination of ketones and aldehydes

The synthesis of amines from alkyl azides is an efficient method of preparing primary amines. However, the formation of the alkyl azide (one step prior to the reduction to the primary amine) likely results from an $S_{N}2$ reaction at saturated carbon, employing a good source of the azide ion and necessitating the use of a leaving group (low atom-economy). Moreover, metal azides – such as NaN$_3$ – are highly toxic.

Figure 7: Retrosynthesis of alkyl azides. LG is a $S_{N}2$-type leaving group

Saturated nitro compounds (nitroalkanes) are useful intermediates in the synthesis of amines. They may be reduced to the corresponding primary amine with Pd/C and H$_2$, or under transfer
hydrogenation conditions.\textsuperscript{5,13,14,15,16} Nitroalkanes have few efficient methods for their preparation. One common method employs expensive silver nitrite and is low-yielding.\textsuperscript{6} Some methods include reduction of the corresponding nitroalkene,\textsuperscript{16} or S\textsubscript{N}2-type reactions with nitrite salts in polar aprotic solvents.\textsuperscript{6} In summary, no method for amine synthesis is without its flaws.

1.3 Nitroalkenes
1.3.1 As Intermediates in Organic Synthesis
\(\alpha,\beta\)-unsaturated nitroalkenes are important intermediates in the introduction of a wide variety of functional groups.\textsuperscript{16} They are intermediates to nitroalkanes, oximes\textsuperscript{17}, ketones, nitroso compounds, ketones, nitronates compounds (useful in the Nef reaction), and as reactive Michael acceptors. However, as intermediates in the synthesis of primary amines, they are used infrequently. One explanation for this is their lack of reactivity toward reducing agents, requiring harsh conditions that are likely to destroy labile functional groups. Some methods for the reduction of \(\alpha,\beta\)-unsaturated nitroalkenes to primary amines include LAH in ethereal solvents or reduction with \(\text{Bu}_3\text{SnH}\).\textsuperscript{6,18,19} Hydrogenation is seldom used since the pressures typically employed (100 atm) are highly dangerous.

1.4 Transfer Hydrogenation
1.4.1 Transfer Hydrogenation in Green Chemistry
Transfer hydrogenation reactions represent useful synthetic methods for the reduction of various functional groups because of their experimentally-simple nature: common glassware may be used and no special apparatus are required. Moreover, hydrogen is generated \textit{in situ} or hydride equivalents react in such a manner to yield the same products as in traditional hydrogenation
reactions with molecular hydrogen. Transfer hydrogenation reagents such as 2-propanol, ethanol, and formic acid derivatives are easily handled. As a result, transfer hydrogenation reactions are inherently safer than the analogous reactions employing molecular hydrogen as the reducing agent, especially when hydrogenation is performed under pressure. Hazard minimization, in the form of safer reactants and conditions, is the primary “green” aspect of transfer hydrogenation chemistry. In addition to replacements for reactions involving molecular hydrogen, traditional hydride-donor compounds such as NaBH₄, LiAlH₄ may be replaced by transfer hydrogenation reagents in various synthetic transformations, thus avoiding the use of pyrophoric compounds. Hazard minimization is obvious when comparing the former two reagents, both of which are toxic and water-sensitive, to alternative reducing agents such as ammonium formate or 2-propanol.

1.4.2 Formic Acid and Formate Salts as Transfer Hydrogenation Reagents
Formic acid and its salts are versatile reagents for the reduction of organic compounds. An important goal in organic synthesis is the development of methods for chemoselective reduction under mild conditions.²⁰ Formic acid and its derivatives have been utilized in the reduction of various functionalities in organic synthesis, with the choice of catalyst and reaction conditions defining reactivity. The term *transfer hydrogenation* has been used to describe the addition of hydrogen atoms to a substrate via a molecule other molecular hydrogen or hydride agents. Formic acid, when in the presence of Pd/C, decomposes into H₂ and CO₂, see Figure 8.²¹ In catalytic transfer hydrogenations employing formic acid as the H-donor, one molecule of formic acid can be viewed as equivalent to one molecule of molecular hydrogen. The formate anion, however, is a source of “hydride” anions rather than hydrogen molecules, see Figure 8. This can be understood in the reduction of various functional groups with alkali metal formates, such as potassium
formate, where proton sources are not provided by the cation$^{22,23}$. Formate appears to be a more potent H-donor than formic acid and mechanistically, reductions using formate may proceed in a similar fashion to other hydride-transfer reagents, such as NaBH$_4$. The more potent reducing ability of formate compared to formic acid may be explained by the structures of the two reagents. The formate anion bears a negative charge, which in the transition state of a transfer hydrogenation reaction, contributes a partial negative charge to the H atom, thereby increasing its reactivity and nucleophilicity. Since formic acid is neutral, no charge-related effects can increase the hard nucleophilic character of the carbon-bonded H atom. Consequently, transfer hydrogenations employing formic acid usually require harsher conditions than reductions employing formate.

![Chemical structures](image.png)

**Figure 8:** Hydrogen equivalency of formic acid and the formate ion

Traditional methods affecting the reductions discussed herein typically require the use of hazardous hydride donors or hydrogenation under high pressure. These techniques are undesirable for many reasons: there are significant hazards associated with handling hydride donors and high pressure H$_2$; hydride donors are expensive and usually employed in excess; and hydrogenation
under high pressure requires extensive safety precautions and specialized apparatus. Transfer hydrogenation, by comparison, utilizes mild conditions, inexpensive reagents, is simple, and safer than the aforementioned methods. Transfer hydrogenation using formic acid derivatives especially, offers a new paradigm for the reduction of organic substrates that is in line with the principles of green chemistry.

A common application of formic acid derivatives as reducing agents is the Leuckart-Wallach reaction, where a ketone or aldehyde is reductively alkylated with ammonium formate or a formic acid derivative to give the \(N\)-formyl amine, which can be hydrolyzed to the free amine.\(^6\) This reaction is an important synthetic route to primary amines that avoids the use of reactive hydride reagents. The Leuckart-Wallach reaction requires no catalyst, yet high temperature conditions are necessary to effect reaction. The Leuckart-Wallach reaction has been applied to many substrates, such as, aromatic, aromatic-aliphatic, alicyclic, and aliphatic-heterocyclic ketones, and high-boiling aliphatic ketones and aldehydes.\(^6\) Figure 9 shows the reaction scheme for the Leuckart-Wallach reaction performed on a ketone.

![Figure 9: The Leuckart-Wallach reaction, shown with intermediate steps\(^6\)](image-url)
1.5 Transfer Hydrogenation of Nitroalkenes to Primary Amines
Motivated to develop a new synthetic method toward primary amines that operates under mild conditions and is in line with the principles of green chemistry, nitroalkenes were chosen as synthetically-useful intermediates toward this goal. Nitroalkenes are an uncommon intermediate in the synthesis of primary amines owing to the harsh conditions required to effect reduction, however they are easily-prepared from aldehydes or ketones with a nitroalkane via the Henry reaction,\textsuperscript{16} see Figure 10. A few examples of the transfer hydrogenation of nitroalkenes are reported in the literature,\textsuperscript{17,24,25} though to the author's knowledge none exist for the preparation of primary amines from nitroalkenes. The products are typically oximes, or nitroalkanes.\textsuperscript{17,24,25}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure10.png}
\caption{Synthesis of primary amines from nitroalkenes. Retrosynthesis of nitroalkenes via the Henry reaction (nitro-aldol)\textsuperscript{26}}
\end{figure}
2. Experimental

2.1 Preparation of Substituted Nitroalkenes

Substituted nitroalkenes were prepared according to general methods published in the literature. All melting point measurements were recorded on a Thomas-Hoover instrument and are uncorrected.

2.1.1 β-nitrostyrene; 2-phenynitroethene

\[
\text{\begin{align*}
\text{PhCHO} & \quad \text{MeNO}_2 \\
\text{NaOH, MeOH} & \quad \rightarrow \text{PhC} = \text{CHNO}_2
\end{align*}}
\]

To a 2-L 3-necked flask fit with a thermometer, mechanical stirrer, and dropping funnel there was added nitromethane (61 g, 54 mL, 1 mol, 1 equiv.), redistilled benzaldehyde (106 g, 101 mL, 1 mol, 1 equiv.), and methanol (200 mL). The flask was cooled to ~-10 °C with an external ice/salt bath. To the dropping funnel, there was added a cold solution of 42 g NaOH in 100 mL of water. With vigorous stirring, the NaOH solution was added to the flask at such a rate that the internal temperature was held between 10–15 °C (2–3 drops/second). A white precipitate was observed to form. After addition was complete, the flask containing yellow solids was allowed to stand in the ice/salt bath for 15 minutes before being diluted with 700 mL of ice-water. With vigorous stirring, the reaction mixture was then poured into 500 mL of 4 M HCl. The yellow precipitate was filtered under reduced pressure and washed with cold water until free of chlorides (AgNO₃). The solids were melted on a hot water bath; subsequent cooling on ice produced two layers. The aqueous layer was decanted and the solids recrystallized from 85 mL boiling EtOH. A second
recrystallization from 80 mL boiling EtOH yielded, after washing with 20 mL cold EtOH, 93.4 g of product as yellow needles, mp 53–56 °C.

2.1.2 4-methyl-β-nitrostyrene; 2-(4-methylphenyl)-nitroethene

![Chemical structure of 4-methyl-β-nitrostyrene]

To a 100-mL round-bottom flask equipped with a magnetic stir bar and water-cooled condenser was added p-tolualdehyde (10.0 g, 9.02 mL, 83 mmol, 1 equiv.), nitromethane (20 mL, 0.37 mol, 4.5 equiv.), and ammonium acetate (1.38 g, 18 mmol, 0.22 equiv.). The mixture was stirred and heated at a gentle reflux for 1.5 hours. The reaction mixture was concentrated by rotary evaporation under reduced pressure to yield a small amount of dark red liquid, which was poured into 40 mL isopropanol (IPA), yielding yellow/brown solids. These solids were recrystallized from about 50 mL boiling IPA to yield, after washing with 30 mL cold IPA, 6.89 g of crystalline product as yellow needles, mp 106–108 °C.

2.1.3 2,5-dimethoxy-β-nitrostyrene; 2-(2,5-dimethoxyphenyl)-nitroethene

![Chemical structure of 2,5-dimethoxy-β-nitrostyrene]

To a 100-mL round-bottom flask equipped with a magnetic stir bar and water-cooled condenser
there was added 2,5-dimethoxybenzaldehyde (15.37 g, 92.6 mmol, 1 equiv.), nitromethane (30 mL, 0.55 mol, 6 equiv.), and ammonium acetate (1.54 g, 20 mmol, 0.22 equiv.). The mixture was stirred and heated at a gentle reflux for 2.5 hours. The excess solvent/reagent was removed by rotary evaporation under reduced pressure to yield orange solids. These solids were triturated with a small amount of IPA, then recrystallized from boiling IPA to yield 14.00 g of crystalline product as shimmering, fluffy orange needles.

2.1.4 3,4-dimethoxy-β-nitrostyrene; 2-(3,4-dimethoxyphenyl)-nitroethene

![Reaction Scheme]

To a 250-mL round-bottom flask equipped with a magnetic stir bar there was added 3,4-dimethoxybenzaldehyde (16.5 g, 99.3 mmol, 1 equiv.) and 70 mL acetic acid. The resulting solution was treated with nitromethane (11.5 mL, 167 mmol, 1.7 equiv.) and ammonium acetate (6.25 g, 81.1 mmol, 0.8 equiv.). The mixture was stirred and heated on an oil bath at 100 °C for 45 minutes. The flask was removed from heat and with good stirring 150 mL H₂O was added. The yellow precipitate was filtered under reduced pressure, triturated with a small amount of MeOH, and recrystallized from boiling IPA/acetone to yield 6.44 g of product as bright yellow crystals, mp 141–143 °C.
2.1.5 β-methylnitrostyrene; 1-(4-methylphenyl)-2-nitropropene

\[
\begin{array}{c}
\text{苯甲醛} \\
\text{乙基硝基} \\
\text{硝基乙酸} \\
\end{array}
\]  \[
\rightarrow
\begin{array}{c}
\text{苯乙烯} \\
\text{硝基} \\
\text{硝基乙酸} \\
\end{array}
\]

To a 250-mL round-bottom flask equipped with a magnetic stir bar and water-cooled condenser was added benzaldehyde (10.6 g, 0.16 mL, 0.1 mol, 1 equiv.), nitroethane (9.0 g, 8.6 mL, 0.12 mol, 1.2 equiv.), ammonium acetate (4.62 g, 60 mmol, 0.6 equiv.), and 70 mL acetic acid. The mixture was stirred and heated at reflux for 2 hours. The flask was removed from heat, allowed to cool for a few minutes, and then with good stirring the amber solution was poured into 250 mL ice/water and allowed to stir for 72 hours. The off-white precipitate was filtered under reduced pressure and dried on the filter to yield 8.17 g of crystalline product as light yellow needles, mp 61–63 °C.

2.2 Catalysis and Catalyst Preparation

2.2.1 Di-μ-chloro-dichlorobis(η\textsuperscript{5}-pentamethylcyclopentadienyl)dirhodium (III); pentamethylcyclopentadienylrhodium(III) chloride dimer; (RhCp\textsuperscript{+}Cl\textsubscript{2})\textsubscript{2}\textsuperscript{27}

\[
\text{RhCl}_3 \\
\text{MeOH, reflux under Ar}
\]  \[
\text{RhCl}_3 \\
\text{MeOH, reflux under Ar}
\]

To a 15-mL round-bottom flask equipped with a magnetic stir bar, water-cooled condenser, and
argon gas inlet adapter there was added rhodium (III) chloride hydrate (250 mg, 1.05 mmol, 1 equiv.), methanol (7.5 mL), and pentamethylcyclopentadiene (0.15 g, 173 µL, 1.1 mmol, 1 equiv.). The flask was purged with argon for 5 minutes. The flask was then heated at reflux under argon atmosphere for 48 hours with stirring. After cooling to room temperature, the red precipitate was filtered off onto a frit. The filtrate was reduced in volume to ~ 1 mL to afford a second crop of product, and filtered. The combined solids were washed with 3X small portions of Et₂O to yield the desired product as red solids of suitable purity (¹H NMR) for the applications described in this work. The yield according to the literature is 95 %.

2.2.2 (N-monotoluenesulfonyl)ethylenediamine; TsEN Ligand

An aqueous solution of 60 % ethylenediamine (by volume, 45 mL) was prepared by diluting ethylenediamine (27 mL, 24 g, 0.5 mol, 2.5 equiv.) to 45 mL with water. A separate solution of 25 mL 60 % ethylenediamine and 50 mL water was prepared. To the second solution there was added a small amount of methyl red pH indicator, followed by 12 M HCl until just acidic (about 40 mL was required to begin to turn the solution red from orange). This solution was placed in a 1-L round-bottom flask fitted with a magnetic stir bar and pressure-equalizing dropping funnel. To the flask a solution of p-toluenesulfonyl chloride (38 g, 0.2 mol, 1 equiv.) in diethyl ether (200 mL)
was added. While stirring rapidly, a solution of 20 mL of 60 % ethylenediamine in 300 mL water was added via the dropping funnel dropwise at such a rate that the reaction mixture remained faintly acidic (just barely red). The addition should, take about 4 hours. Over time a white precipitate formed. After addition was complete, the mixture was allowed to stir for 48 hours. The reaction mixture was concentrated under reduced pressure to ~ 200 mL, cooled on ice, and filtered under reduced pressure to remove (N-N'-ditoluenesulfonyl)ethylenediamine. Concentrated ammonia solution (60 mL) was added to the filtrate, yielding a white precipitate of (N-monotoluenesulfonyl)ethylenediamine, which after cooling on ice was filtered under reduced pressure and dried on the filter. The crude product was then purified by recrystallization from 20 mL boiling H₂O (a seed crystal was required), which yielded after washing with 3X 25 mL cold H₂O, followed by 3X 10 mL Et₂O, the desired product, mp 127–129 °C.

### 2.2.3 Synthesis of Phenethylamine from β-nitrostyrene

![Chemical reaction image]

To a 50-mL 3-neck round bottom flask equipped with a magnetic stir bar and water-cooled condenser there was added in sequence (RhCp*Cl₂)₂ (4.13 mg, 0.0066 mmol, 0.001 equiv.); TsEN (3.13 mg, 0.01467 mmol, 0.0022 equiv.); methanol (3.4 mL); and triethylamine (38 µL). The flask was heated on an oil bath at 70 °C for 1 hour and the solvent removed under reduced pressure. β-nitrostyrene (1.00 g, 6.66 mmol, 1 equiv.) dissolved in 2 mL EtOAc was added, followed by the azeotrope of formic acid (1.35 mL, 35.8 mmol, 5.4 equiv.) and triethylamine (2.0 mL, 14.3 mmol),
which was prepared by adding the former to the latter dropwise while stirring on ice. The flask was stirred at 28 °C for 24 hours; gas evolution occurred. The EtOAc was removed under reduced pressure and a solution of ammonium formate (2.1 g, 33.3 mmol, 5 equiv.) in 15 mL MeOH was added. Under a countercurrent of argon, Pd/C (355 mg, 0.3 mmol Pd, 0.05 mol equiv. Pd) was added. The flask was stirred at room temperature at 1600 rpm while open to air for 24 hours. Gas evolution was observed. The reaction mixture was filtered, first through a frit to remove the bulk of the catalyst, washing with methanol, then through a pad of celite to remove catalyst fines, washing with methanol. The filtrate was stripped of solvent by rotary evaporation under reduced pressure. The residue was suspended in 30 mL water and 10 mL EtOAc and the aqueous layer acidified with 4 mL conc. HCl (pH <5). After separating the phases, the aqueous layer was extracted with 2X 7 mL EtOAc, which removed all color from the aqueous layer. The aqueous layer was then made strongly basic with 25 % NaOH and extracted with 3X 7 mL EtOAc. The organic layers were pooled, dried over MgSO₄, and the solvent removed under reduced pressure. The residue was dissolved in 40 mL anhydrous Et₂O and saturated with anhydrous HCl gas. The fine white suspension was cooled on ice for a few minutes before being filtered under reduced pressure. After washing with 10 mL Et₂O and air-drying, 435 mg of white solids were obtained (41 %), mp 217–219 °C. Product identity was further confirmed by ¹H NMR. See the Appendix for ¹H NMR spectra related to this reaction.

2.2.4 Pd(II)-catalyzed Reduction of β-nitrostyrene
Palladium (II)-catalyzed reduction of β-nitrostyrene under transfer hydrogenation conditions was unsuccessful. Both Pd(OAc)₂ and Pd(PPh₃)₂Cl₂ were tested as homogenous catalysts, however both decomposed to elemental Pd upon gentle heating. Therefore, due to their instability, studies
involving these complexes were discontinued.

2.2.5 Pd/C-catalyzed Reduction of β-nitrostyrene
Moreover, Pd/C was screened as a catalyst for the reduction of β-nitrostyrene under transfer hydrogenation conditions. I hypothesized that, since Pd/C is known to reduce both C-C double bonds in addition to nitro groups, it might catalyze the reduction of nitroalkenes. However, no phenethylamine was isolated from studies involving Pd/C as the sole catalytic species. Further studies of the chemical literature indicated that oximes are typically formed rather than amines in the transfer hydrogenation of nitroalkenes.17 The literature also revealed that β-nitrostyrene specifically is unreactive toward Pd/C-catalyzed transfer hydrogenation.17

2.2.6 Mg/Zn-catalyzed reduction β-nitrostyrene
Mg- and Zn-catalyzed reduction of β-nitrostyrene under transfer hydrogenation conditions was unsuccessful. Both metal catalysts failed to reduce β-nitrostyrene to phenethylamine in the presence of Pd/C and ammonium formate.

3. Discussion

3.1 Rh- and Pd-catalyzed Reduction of Nitroalkenes
Reduction of β-nitrostyrene to the corresponding nitroalkane, 2-phenylnitroethane, was observed via 1H NMR analysis. This transformation has been previously reported and was able to be reproduced in this work.25 Using a Rh–Pd catalyst system with an azeotropic mixture of
triethylamine and formic acid (triethylammonium formate, TEAF, 5:2 HCO₂H:NEt₃) and ammonium formate as transfer hydrogenation reagents, phenethylamine was produced in about 50 % yield from β-nitrostyrene. This result was shown to be reproducible when the reaction conditions were reproduced. I hypothesize that the reaction mechanism for this transformation proceeds according to the scheme shown in Figure 13, wherein the C-C double bond is first reduced via a Rh-H species and the nitro group reduced catalytically over Pd metal.

**3.2 Pd(II)-catalyzed Reduction of Nitroalkenes**

In light of the catalytic transfer hydrogenation methods employing homogenous Pd(II) catalysts in the reduction of unsaturated substrates, I screened Pd(II) compounds for catalytic activity in the reduction of β-nitrostyrene. Pd(II) compounds are known to catalyze the reductive amination of ketones and aldehydes. Moreover, since Pd(II) coordinates with alkenes, I hypothesized that such coordination with the C–C double bond in nitroalkenes would render the electrophilic, activated alkene more susceptible to reduction. Coordination of Pd(II) to the double bond was hypothesized to reduce electron density about the alkenyl carbon atoms, rendering them more electrophilic than the uncoordinated double bond, and thus more susceptible to transfer hydrogenation via metal-hydride species generated in situ.

Screened Pd(OAc)₂ and Pd(PPh₃)₂Cl₂ for catalytic activity with β-nitrostyrene. Reduction of the palladium compounds to Pd metal was observed upon gentle heating just above room temperature. In light of these results suggesting an instability of Pd(II) in the presence of β-nitrostyrene, I chose to pursue studies with more stable catalytic species. I am unsure of the decomposition process for the reduction of Pd(II) to Pd metal, however, coordination of the nitro group to Pd(II) may be
3.3 Pd/C-catalyzed Reduction of Nitroalkenes

Unsaturated nitro compounds (nitroalkenes) may also be reduced by catalytic transfer hydrogenation. A solution of nitroalkene in methanol/THF at room temperature is subjected to palladium-catalyzed transfer hydrogenation via ammonium formate to furnish the corresponding oxime in high yields, see Figure 11. Yields >80% are typically achieved when this methodology is applied to aromatic nitroalkenes. The reduction proceeds under mild conditions at room temperature, with reactions typically complete in less than one hour. The reduction of nitroalkenes to oximes, the former of which may be readily prepared by Henry reactions, is a useful transformation in the synthesis of primary amines.

![Chemical Structure](image)

**Figure 11:** Reduction of α,β-unsaturated nitroalkenes to oximes. Nitroalkenes conjugated with an aromatic ring are rapidly reduced to oxime products.β-nitrostyrene, however, is unreactive toward reduction to the corresponding aldoxime under the reported reaction conditions. This may be due to the resonance-stabilization of the highly-conjugated nitroalkene system.
3.4 Mg- and Zn-catalyzed Reduction of Oximes
Accordingly, transfer hydrogenation of oximes, prepared from the Pd/C-catalyzed reduction of nitroalkenes described above in Figure 11, would constitute a facile synthetic strategy for primary amines from nitroalkenes. This was the hypothesis in pursuing studies involving step-wise reduction of β-nitrostyrene first to the corresponding oxime, then to the amine. At least two methods for the transfer hydrogenation of oximes have been reported. Both methods employ active metals as catalysts – either Mg or Zn metal in conjunction with ammonium formate – to furnish primary amines from oximes in good yield (>80%). Reaction conditions for the Mg-catalyzed reaction are shown in Figure 12. The reaction is typically complete in less than one hour at room temperature. 

Figure 12: Reduction of oximes to amines using ammonium formate and catalytic magnesium metal

3.5 Rh and Pd-catalyzed Transfer Hydrogenation of β-nitrostyrene: Dual-Catalyst System in One Pot
This work has demonstrated success in employing two unique metal catalysts to in turn effect two unique transfer hydrogenation reactions. The yields of phenethylamine from β-nitrostyrene are reasonable, but I believe they can have the potential to be improved. Since both metal catalysts are
present during the reduction of the nitro group of the intermediate nitroalkane, 2-phenylnitroethane, I cannot state for certain that Pd/C is the sole catalytic species in the reduction of the nitro group, even though such conclusions accord with theory. A distinct metal species or group of species which might be produced under the reaction conditions could be the active catalyst in the reduction of the nitro group.

3.6 The Effect of Reducing Agent
Since many different transfer hydrogenation reagents are known to effect a wide variety of transformations, I tested various reducing agents in our studies on the reduction of β-nitrostyrene. Formic acid and its derivatives are commonly employed in transfer hydrogenation reactions. The azeotrope of formic acid triethylamine has been used in the reduction of many different functional groups,\textsuperscript{32} and ketones in asymmetric transfer hydrogenation.\textsuperscript{33} Ammonium formate has been employed similarly.\textsuperscript{34} In our studies TEAF was unable to reduce 2-phenylnitroethane to phenethylamine in the presence of Pd/C and [RhCp\textsuperscript{+}Cl\textsubscript{2}]\textsubscript{2}-TsEN, though surprisingly ammonium formate effects this transformation under similar conditions. Solvent effects might explain this surprising difference in reactivity in light of the structural similarities between the two reducing agents.

3.7 Solvent Effects
Various solvent systems were tested during the course of this research. Aprotic solvents such as EtOAc and THF were screened in reaction trials. As were EtOAc/water mixtures, MeOH, TEAF as solvent/reactant, and HCO\textsubscript{2}H as solvent/reactant. The only solvent system that consistently
yielded reasonable amounts of product was EtOAc and MeOH. These solvents were employed for the [Rh]-catalyzed and Pd-catalyzed reaction steps, respectively. Solvents are known to play a crucial role in transfer hydrogenation reactions,\textsuperscript{32} which might explain the lack of reactivity with certain reducing agents and solvent systems which otherwise were hypothesized to give positive results based on theory. The ability of the solvent to dissolve the transfer hydrogenation reactant, as well as wet the Pd/C catalyst is believed to be crucial to the success of the reaction. The only solvent system that efficiently dissolved the reactants and suspended the Pd/C catalyst was methanol.

### 3.8 Work-Up Procedures

Several work-up procedures were employed when isolating the amine products of the above reactions. The presence of two free amine species in the reaction mixture (triethylamine and the product) presented a challenge for product isolation. First, a series of acid-base extractions were employed to remove triethylamine and the homogenous catalyst species, however these procedures were somewhat inefficient in terms of time economy and the amount of auxiliary substances used (acids, bases, water, and organic solvents). For this method to be applicable on an industrial scale, lengthy aqueous extractions are unsuitable. Moreover, it was noted that phenethylamine is appreciably soluble in water. In order to obviate product losses associated with aqueous-extractions, a water-free work-up procedure was developed.

#### 3.8.1 Work-Up Procedure via Extractions

The reaction mixture is filtered through a glass frit (medium porosity) to recover the bulk Pd/C
catalyst and the solids washed with MeOH. The filtrate is filtered again through a pad of celite to remove catalyst fines, and the celite washed with MeOH. The filtrate is stripped of solvent by rotary evaporation under reduced pressure to yield a residue of crude product, which is dissolved in a mixture of dilute HCl and EtOAc (~10:1) such that the aqueous layer is acidic (pH<5). The upper organic layer is separated and the aqueous layer extracted 2X with EtOAc, removing nearly all color from the aqueous layer. The aqueous layer is made strongly basic with 25% NaOH and extracted 3X with EtOAc. The organic extracts are pooled, dried over MgSO₄, and stripped of solvent by rotary evaporation under reduced pressure. The residue is dissolved in anhydrous Et₂O and gassed with anhydrous HCl to form the corresponding amine HCl salt, which is removed by filtration and washed with Et₂O. The amine HCl thus isolated is sufficiently pure for most purposes but may be purified further by recrystallization from boiling MeCN as necessary. Analysis via melting point and ¹H NMR (D₂O) may be used to confirm product identity and purity.

3.8.2 Work-Up Procedure without Extractions
The reaction mixture is filtered through a glass frit (medium porosity) to recover the bulk Pd/C catalyst and the solids washed with MeOH. The filtrate is made basic with concentrated NH₄OH, filtered through a pad of celite to remove catalyst fines, and the celite washed with MeOH. The filtrate is stripped of solvent by rotary evaporation under reduced pressure to yield a residue of crude product, which is purified by dissolving in EtOAc, gassing with anhydrous HCl, diluting the solids with anhydrous Et₂O, removing the crude amine HCl solids by filtration, and triturating with a small amount of MeCN. The amine HCl salt thus isolated is sufficiently pure for most purposes but may be purified further by recrystallization from boiling MeCN as necessary. Analysis via melting point and ¹H NMR (D₂O) may be used to confirm product identity and purity.
3.9 Proposed Mechanism of Reaction

I have developed a hypothesis for the mechanism of the transfer hydrogenation of β-nitrostyrene to phenethylamine under the reaction conditions described in 2.D.D, see Figure 13. I believe a rhodium hydride intermediate reduced the C-C double bond in the fashion of Michael addition. Pd-catalyzed reduction of the nitro group is then hypothesized to occur. The nitro group reduction probably proceeds via formate as the reactive species, or via H₂ as the reactive species that is generated in situ upon decomposition of ammonium formate.
Figure 13: Proposed mechanism for the catalytic transfer hydrogenation of β-nitrostyrene to phenethylamine with Rh- and Pd-catalysis
4. Further Work

4.1 Expanding Substrate Scope
The most exciting potential for this work is expanding its applications. For this synthetic method to be useful for the reduction of nitroalkenes under mild conditions, many nitroalkene substrates other than β-nitrostyrene must be screened for reactivity. To this end, I have prepared a number of such compounds, bearing aromatic and alkyl substituents. Isoxazoles, furan-derived aromatic nitroalkenes, alkyl-substituted nitroalkenes, aliphatic nitroalkenes, and aromatic substituted nitroalkenes are all possible substrates for this synthetic method. Chemists have already developed catalytic methods for the transfer hydrogenation of the C-C double bond in nitroalkenes bearing various substitution patterns. By applying the method described in this work, these substrates might be able to be reduced further under mild, catalytic conditions to the corresponding saturated amino derivatives. In investigating the reactivity of substituted nitroalkenes, there is also the potential to investigate the chemoselectivity of this method as well.

4.2 Chiral Diamine Ligands for Asymmetric Transfer Hydrogenation
One possibility for extending this work is employing the catalytic method described herein to the asymmetric synthesis of primary amines. An α-substituted nitroalkene can be reduced to the corresponding nitroalkane enantioselectively, followed by direct reduction to the primary amine with ammonium formate and Pd/C. The asymmetric synthesis of β-alkyl substituted nitroalkanes from nitroalkenes has been reported, employing a pentamethycyclopentadienyl Ir catalyst
bearing a chiral $N$-monotolylated ethylenediamine ligand – a complex analogous to the Rh catalyst employed in this work. Extending these previous results to $\alpha$-substituted nitroalkenes suggests a promising route to the asymmetric synthesis of primary amines.

4.3 Attaching the Rhodium Catalyst to an Inert Support for Easier Recovery

It is well known that homogenous catalysts can be covalently bonded to inert supports for easier recovery and to simplify reaction conditions. Error! Bookmark not defined. Especially important with expensive Rh catalysis, catalyst recovery and reuse should be areas for further research with this synthetic methodology. One possible connection point from the catalyst to a silica support for example, could be the aromatic ring of the $p$-toluenesulfonyl group on the ethylenediamine-derived ligand. The bonding atom might be far enough away from the active Rh center so as to minimize steric problems, and would not be in the ethylenediamine backbone (which could be used to introduce ligand chirality in future studies).

5. Conclusions

5.1 Toward Benign Organic Synthesis

A catalytic synthetic method for the preparation of phenethylamine from benzaldehyde (the addition of a CH$_2$-NH$_2$ functionality, via the intermediate nitroalkene) under transfer hydrogenation conditions is reported. This method avoids the use of pyrophoric, toxic, stoichiometric reducing agents that necessarily generate metal salt waste. From benzaldehyde, the
only byproducts of this synthetic method for phenethylamine are CO₂, H₂O, and NH₃. This method also employs EtOAc and MeOH as solvents instead of ethers, which avoids the danger of explosive peroxide formation. Moreover, the reduction of β-nitrostyrene to phenethylamine can be performed in one-pot, interestingly with two separate catalytic metal species. This synthesis is an example of applied green chemistry in organic synthesis, which offers advantages over previously-reported methods in terms of safety, waste production, and scalability. Financial expenses associated with Rh-catalysis prevented us from running trials on larger scales, however the gram scale does work and larger scale reactions could potentially simplify work-up since the chemist could purify products via distillation – thereby eliminating the need for auxiliary substances employed in acid/base extractions, and the necessity of separating triethylamine from the primary amine product.

**Appendix: ¹H NMR Spectra**

All NMR spectra were recorded on an Anasazi Eft-60 (60 MHz) instrument.
Spectrum 1: $^1$H NMR spectrum (CDCl$_3$) of the crude reaction mixture containing 2-phenyl nitroethane, before addition of Pd/C and ammonium formate. See 2.2.3
**Spectrum 2:** $^1$H NMR spectrum (D$_2$O) of phenethylamine HCl
Spectrum 3: $^1$H NMR spectrum (D$_2$O) of phenethylamine HCl spiked with an authentic sample.

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