Gold(I)-Catalyzed Ring-Opening Hydroamination of Methylene cyclopropanes with Aniline Derivatives

by

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Thesis submitted in partial fulfillment of the requirements for the degree of Master of Science in the Department of Chemistry in the Graduate School of Duke University

2017
ABSTRACT

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Abstract

Methylenecyclopropanes (MCPs) are highly strained and serve as useful building blocks in organic synthesis. When activated by a gold catalyst, subsequent nucleophilic attack can result in ring-opening (ring-expansion) of the cyclopropane moiety. Gold(I)-catalyzed ring-opening of bicyclic MCPs at the distal carbons of the cyclopropane results in either an exo or internal cyclic allylic amine, with exo double bonds providing an important handle for further functionalization in natural product synthesis.

This work explores the scope of bicyclic MCP ring opening reactions with aniline derivatives with the goal of optimizing for the exocyclic allylic amine. Although nonpolar solvent resulted in a clean and fast reaction, the selectivity between isomers was minimal. With increasing polarity of coordinating solvents there was an increase in selectivity for the desired isomer, but with reaction rates slowing dramatically. Lewis basicity of the aniline nucleophile proved to be a crucial aspect in the progress of the reaction, with electron rich anilines failing to proceed. Variation of ring size showed that larger ring sizes of bicyclic MCPs favor the competing reaction, anti-Markovnikov hydroamination of the olefin, with the cyclooctyl MCP showing complete selectivity for this competing reaction. Overall, ring opening reactions of bicyclic MCPs with electron deficient aniline derivatives proved to offer high selectivity and moderate to high yields.
towards six and seven-membered exocyclic allylic anilines.
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1.1 Introduction

1.1.1 Recent Progress in Gold(I)-Catalyzed Ring-Opening of Methylenecyclopropanes

Methylenecyclopropanes (MCPs) are highly strained molecules, giving them adequate reactivity to serve as useful building blocks in natural product synthesis.\(^1\) MCPs can undergo a variety of reactions, including ring-opening reactions due to the release of cyclopropyl ring strain which provides a thermodynamic driving force.\(^3\) Gold-catalyzed reactions of MCPs can be grouped into four main classes, two of which involve the C–C bond cleavage of the cyclopropyl moiety (Scheme 1). The cyclopropane ring can either be broken at the olefin’s proximal bond (C\(_2\)–C\(_3\)) or (C\(_2\)–C\(_4\)) or its distal bond (C\(_3\)–C\(_4\)) with electrophilic and nucleophilic attacks generally occurring at C\(_1\) or C\(_2\).

![Scheme 1: Potential Gold-catalyzed Reaction Pathways with MCPs](image-url)
In 2006, Shi showed that in the presence of a gold(I) catalyst, a powerful soft Lewis acid, they were able to achieve a domino ring-opening/ring-closing hydroamination of MCPs with sulfonamides to provide a route to pyrrolidine derivatives. They propose a mechanism involving a cationic gold(I) complex coordinating the alkene of the MCP, which then undergoes an intermolecular hydroamination that results in proximal bond cleavage and gives the corresponding homoallylic sulfonamide, regenerating the catalyst. Further activation of this olefin by the Gold(I) complex led to an intramolecular hydroamination to produce the pyrrolidine derivative (Scheme 2).

![Scheme 2: Gold(I)-Catalyzed Domino Ring-Opening/Ring-Closing Hydroamination of MCPs.](image)

Shi has also demonstrated intramolecular nucleophilic addition to MCPs bearing a nucleophilic group. Starting with 2-(arylmethylene)cyclopropylcarbinols, in the presence of a gold(I) catalyst, the corresponding 4-substituted isoxazolidine derivatives were obtained (Scheme 3). This reaction achieved high yields with highly regioselective cleavage of the C–C proximal bond of the cyclopropyl ring.
In 2008, Fensterbank and Malacria reported a structure dependent rearrangement of their bicyclic MCP. They found that the length of the methylene spacer between the cyclopropyl moiety and the nucleophile was critical to the outcome of the reaction (Scheme 4).\textsuperscript{8} When n = 1, they speculated that the electron depletion of the methylenecyclopropane induced by coordination of gold promoted elimination of an allylic proton. The electrons then redistribute into the system to give distal bond cleavage and eliminate water, resulting in an exocyclic double bond. This compound rearranges into a more stable conjugated ketone.\textsuperscript{8} With longer tethers (n = 2,3), nucleophilic attack of the alcohol at the double bond or the cyclopropane moiety (proximal bond cleavage) results, giving a tricyclic ketone or spiro compound, respectively.

Scheme 3: Gold(I)-Catalyzed Intramolecular Hydroamination and Ring-Opening Reaction of 2-(arylmethylene)cyclopropylcarbinols.
Less common is the case with complete selectivity for distal bond (C3–C4) cleavage. In 2010, after taking inspiration from a diacetoxylation pathway for MCPs in the presence of iodosobenzene diacetate via a Pd(II)/Pd(IV) catalytic cycle, Zhang developed an alternative methodology catalyzed by Au(I) and Au(III) complexes (Scheme 5). In this reaction, activation of MCP by Au(I) induces a nucleophilic attack by acetate (AcO−) to give distal bond cleavage to afford an allylic gold(I) species. This undergoes oxidative addition with iodosobenzene to provide a gold(III) intermediate, with subsequent reductive elimination producing the diacetoxylated product.

```
R1
R2
+ Phl(OAc)2 [PMe3]AuCl HOAc, 60 °C

Scheme 4: Gold(I)-Catalyzed Cycloisomerization of bicyclic MCP and the Effects of the Methylene Chain Length.
```

```
R1
R2

Scheme 5: Gold-Catalyzed Diacetoxylation of MCPs in the Presence of Phl(OAc)2.
```
Although significant developments of ring-opening reactions of MCPs in the presence of other transition metals, such as nickel, rhodium, palladium, and ruthenium have been made in the last few decades, less attention has been given to gold-catalyzed chemistry of MCPs and there is still much room for growth in this area of research. Distal bond cleavage remains especially elusive and has the potential to offer a much larger scope of reactivity.

1.1.2 Hydroamination of MCPs with Anilines

Gold(I)-catalyzed hydroamination has been an ongoing focus in the Widenhoefer group, with ACPs and MCPs providing a unique and reactive olefin moiety. These substrates are characteristic for their ability to undergo anti-markovnikov hydroamination, as seen in Scheme 6. In the exploration of scope for the hydroamination of these ACPs and MCPs, it was found that certain substrates underwent an unusual ring-opening pathway to form allylic amine derivatives (Scheme 7). The gold(I)-catalyzed reaction with 4-nitroaniline with MCP 1.1a underwent the ring-opening reaction instead of the desired anti-Markovnikov hydroamination reaction. While the reaction with nitroaniline showed complete selectivity for the ring-opening pathway, there was a mixture of two allylic amine products, with favorability for the exocyclic product.
Mechanistically, initial nucleophilic attack by aniline on the distal cyclopropane carbon (Carbon 3) of a gold-π-MCP complex I with concomitant distal cyclopropyl C–C bond cleavage affords complex II (Figure 1). This intermediate can directly undergo protodeauration to give the endocyclic product. The exocyclic products can be achieved through either allylic rearrangement of intermediate II or γ-protonation of II could also lead to complex IV. In the case of the allylic rearrangement to afford a gold-(methylenecycloheptane) complex III, subsequent protodeauration yields an exocyclic allylic aniline product.\textsuperscript{13}
Current, the origin of the selectivity between the allylic amine isomers is unknown, but the proposed distal bond cleavage makes this system unique. The focus of this work is to optimize the reaction conditions to favor the exocyclic double bond, determine the scope and limitations of the aniline nucleophile, and explore ring size and substitution effects of the MCP on the reaction.

1.2 Optimization of Reaction Conditions Towards the Exocyclic Allylic Aniline Isomer.

1.2.1 Initial Solvent Screen
The first step in the optimization of the ring opening reaction of MCPs was to investigate solvent effects. 4-Nitroaniline with the cyclohexyl MCP, 1.1a was used as the starting point for this investigation since the original reaction (Scheme 7) showed preference for the exocyclic product and it was formed in high yield. Nonpolar solvents, such as toluene and dioxane, favored fast reaction times and gave excellent yields, but the selectivity for the exocyclic product was minimal or nonexistent (Table 1, entries 1, 5, and 10). Chlorinated or highly polar solvents resulted in complex mixtures; both dichloroethane (DCE) and nitromethane gave fast consumption of MCP, but the crude mixture contained at least three undesired products, leading to the low isolated yields (Table 1, entries 7 and 9). Lewis basic, coordinating solvents, led to an increase in selectivity of the desired exocyclic product with higher polarity as shown when looking at THF and DME compared with dioxane at 70 °C (Table1, entries 1, 2, and 3). Unfortunately, with this increased selectivity came a more sluggish reaction which ultimately resulted in low to moderate yields. Increasing the temperature for the DME reaction resulted in a lower selectivity for the desired product (entry 6). Overall, Lewis basic solvents with moderate to high polarity gave the best selectivity with acetonitrile at 80 °C and DME at 70 °C, both giving a 10:1 preference for the exocyclic allylic aniline. Both these parameters were carried forward in the next optimization steps.
Table 1: Solvent Screen for the Optimization of the Exocyclic Allylic Aniline Product in the Gold-catalyzed Ring-opening Reaction of MCPs

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Temp. (°C)</th>
<th>Rxn Time (h)</th>
<th>Ratio of A:B</th>
<th>Isolated Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Dioxane</td>
<td>70</td>
<td>20</td>
<td>2:1</td>
<td>82</td>
</tr>
<tr>
<td>2</td>
<td>THF</td>
<td>70</td>
<td>28</td>
<td>6:1</td>
<td>61</td>
</tr>
<tr>
<td>3</td>
<td>DME</td>
<td>70</td>
<td>&gt;72&lt;sup&gt;a&lt;/sup&gt;</td>
<td>10:1</td>
<td>27</td>
</tr>
<tr>
<td>4</td>
<td>CPME</td>
<td>80</td>
<td>36</td>
<td>1.5:1</td>
<td>50&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>5</td>
<td>Dioxane</td>
<td>80</td>
<td>12</td>
<td>4:1</td>
<td>75</td>
</tr>
<tr>
<td>6</td>
<td>DME</td>
<td>80</td>
<td>40&lt;sup&gt;a&lt;/sup&gt;</td>
<td>6:1</td>
<td>45</td>
</tr>
<tr>
<td>7</td>
<td>DCE</td>
<td>80</td>
<td>3</td>
<td>1.5:1&lt;sup&gt;b&lt;/sup&gt;</td>
<td>32&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>8</td>
<td>Acetonitrile</td>
<td>80</td>
<td>50&lt;sup&gt;a&lt;/sup&gt;</td>
<td>10:1</td>
<td>41</td>
</tr>
<tr>
<td>9</td>
<td>Nitromethane</td>
<td>80</td>
<td>4</td>
<td>Complex Mixture</td>
<td>—</td>
</tr>
<tr>
<td>10</td>
<td>Toluene</td>
<td>80</td>
<td>18</td>
<td>1:1</td>
<td>95</td>
</tr>
</tbody>
</table>

<sup>a</sup>) Reactions failed to proceed after these time points, but were not complete. <sup>b</sup>) 3 undesired products were also produced. <sup>c</sup>) Total yield, 85%; isolated yield calculated based on GC areas.

1.2.2 Preliminary Salt screen

Prior to moving on to catalyst screening, a preliminary counter ion screen was conducted in order to try to speed up the reaction. The results can be seen in Table 2. Triflate and tetrafluoroborate were chosen as the initial screening counterions. Triflate gave
neither an improvement to reaction time or the ratio of A:B in either solvent. BF$_4^-$ showed improved selectivity for the exocyclic product (A). Although the reaction had > 20:1 selectivity, it failed to proceed after 54 hours with much of the aniline left unconsumed. The reaction in DME provided a modest boost to selectivity, but showed a much-improved reaction rate of 24 hours and a yield of 60 %.

Table 2: Initial Counterion Screen in DME and Acetonitrile Towards Selective Ring-opening Products.

<table>
<thead>
<tr>
<th>Counter Ion (X$^-$)</th>
<th>Rxn Time (h)</th>
<th>Ratio of A:B</th>
<th>Solvent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Triflate$^-$</td>
<td>54$^a$</td>
<td>9:1</td>
<td>DME</td>
</tr>
<tr>
<td>BF$_4^-$</td>
<td>24</td>
<td>12:1</td>
<td>DME</td>
</tr>
<tr>
<td>BF$_4^-$</td>
<td>54$^a$</td>
<td>&gt;20:1</td>
<td>Acetonitrile</td>
</tr>
<tr>
<td>Triflate$^-$</td>
<td>54$^a$</td>
<td>9:1</td>
<td>Acetonitrile</td>
</tr>
</tbody>
</table>

$^a$ Reactions were not progressing appreciably and stopped.

1.2.3 Gold(I) Catalyst Screen

In order to screen alternative gold catalysts, a number of additional reactions were carried out. The active gold complexes were generated in situ from the corresponding gold chloride complexes and silver tetrafluoroborate after evaluation of a reaction where the catalyst was generated in-situe rather than using a pre-made catalyst showed it did not
hinder reactivity or isomer selectivity. Along with CyJohnPhos (L1), the original ligand, JohnPhos (L2), IPr (L3), and IMes (L4) were tested. The results can be seen in Table 3. Both CyJohnPhos (L1) and IPr (L3) saw a substantial competing reaction with the anti-Markovnikov hydroamination product (C). Although the ratio of the exocyclic product to the internal allylic amine product were the highest, at >20:1 in the case of IPr, 80% of the starting materials converted to C, rather than A and B. Although this competing reaction was less prevalent with L1 and L2, yield was still compromised by anti-Markovnikov hydroamination pathway. JohnPhos (L2) results in the least preference for the exocyclic product, but the competing reaction that yields C was minimal, at ~ 10% of the final products. The reaction also proved to be the fastest under those conditions.

The selectivity and rate of the reaction can be attributed to the buried volume of the corresponding gold species, with decreased buried volume providing the best regioselectivity of the allylic amine isomers. Comparing L1 and L2 also suggests that increasing buried volume increases reactivity, with JohnPhos (L2) catalyst reacting substantially faster than CyJohnPhos (L1) catalyst. Comparing the cationic gold catalysts of IPr (L3) and IMes (L4) also showed this relationship, with (L4)Au+ taking much longer for the reaction to go to completion. Although buried volume plays a part in the rate of reaction, there was no obvious correlation of the reaction rate and buried volume showing that bonding also plays a crucial role in the reaction rate. There is also no correlation between buried volume and the amount of the competing anti-Markovnikov pathway. Although there appears to be a correlation between buried volume and percentage of competing anti-Markovnikov product from reactions with L1-L3, including a smaller buried volume with L4 removes the correlation. Interestingly, using an N-heterocyclic
carbene (NHC), such as IPr, generated the anti-Markovnikov hydroamination product as the major product at 75%, which was the expected product in our group’s previous study of gold(I)-catalyzed hydroamination of MCPs with anilines.

Table 3: Reaction Conditions and Possible Products for the Catalyst Screen for the Ring-opening Hydroamination of MCP 1.1a.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ligand</th>
<th>Rxn Time (h)</th>
<th>Ratio of A:B:C</th>
<th>Isolated Yield (%)</th>
<th>% Buried Vol.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>L1</td>
<td>24</td>
<td>12:1:3</td>
<td>58</td>
<td>46.7</td>
</tr>
<tr>
<td>2</td>
<td>L2</td>
<td>15</td>
<td>10:1:1</td>
<td>73</td>
<td>50.9</td>
</tr>
<tr>
<td>3</td>
<td>L3</td>
<td>20</td>
<td>&gt;20:1:75</td>
<td>15</td>
<td>39.0</td>
</tr>
<tr>
<td>4</td>
<td>L4</td>
<td>48</td>
<td>&gt;20:1:20</td>
<td></td>
<td>31.2</td>
</tr>
</tbody>
</table>

Percent Buried Volume calculated for (L)AuCl complexes with a L-Au bond length of 2.25 Å.14
1.2.4 Secondary Counterion Screen

After finding JohnPhos to be the best ligand for the catalytic system, the ratio of exo to endo allylic amine still remained modest at only 10:1. Based on the original counterion screen, the counterion plays a large part in the regioselectivity of the reaction. Additional counterions were tested by generating the catalyst in situ and observing conversion and product ratio in the reaction by gas chromatography (GC) (Table 4). The reaction with silver perchlorate proceeded at a similar rate as silver tetrafluoroborate reaction, but only had modest selectivity for the exocyclic product. The reaction with silver hexafluorophosphate provided a comparable rate, while also providing an excellent selectivity of 18:1, the highest observed during the screening process.

Table 4: Secondary Counterion Screen for the Ring-opening Reaction of 1.1a Towards Favoring the Exocyclic Double Bond, A.

<table>
<thead>
<tr>
<th>Counter Ion (X⁻)</th>
<th>Rxn Time (h)</th>
<th>Ratio of A:B</th>
<th>Isolated Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ClO₄⁻</td>
<td>20</td>
<td>8:1</td>
<td>—</td>
</tr>
<tr>
<td>PF₆⁻</td>
<td>18</td>
<td>18:1</td>
<td>65</td>
</tr>
</tbody>
</table>

2.5 Miscellaneous Reaction Optimization Parameters
The optimal reaction conditions identified are shown in Scheme 8. Unfortunately, when moving away from the highly electron withdrawing \( p \)-nitroaniline, to \( p \)-(trifluoromethyl)aniline a competing reaction proceeded more quickly than the desired ring-opening reaction. \( P \)-(trifluoromethyl)aniline was consumed in the reaction, but did not result in the desired product. Instead, the product was characterized by mostly \( sp^2 \)-hybridized carbons as indicated by the NMR spectra of product. This suggests the possibility of a competing aniline coupling reaction. This was a very minor product (<10%) for \( p \)-nitroaniline in DME, but was non-existent in dioxane. In order to prevent compromising the scope of anilines tolerable in the optimized catalytic system, DME was switched for dioxane as the solvent. Scheme 9 describes the two sets of reaction conditions that were used to synthesize the ring-opened products of a broad range of substituted anilines.

![Scheme 8: Optimized Reaction Conditions of the Gold(I)-catalyzed Hydroamination of MCP 1.1a with 4-nitroaniline.](image-url)
One set of conditions used for the ring-opening hydroamination of MCP 1.1a used the preformed cationic gold catalyst (Method A) and the other generated it in situ from the corresponding gold chloride complex with the silver salt (Method B). The preformed gold catalyst used in Method A had a high selectivity between the exocyclic and endocyclic isomers with a ratio of >20:1. This high selectivity is compromised by a much longer reaction time, with the reaction not going to completion until 50 hours and resulting in 77% yield. Generating the catalyst in situ in Method B still led to high selectivity at 20:1, but the reaction time was shortened to 12 hours and gave 85% isolated yield. It was also found that with more Lewis basic anilines, such as p-(trifluoromethyl)aniline that the reaction of 1.1a failed to proceed appreciably with method A, but was went to 50% completion under Method B conditions. This shows that although silver may not be important for the regioselectivity of the reaction, it is still a crucial component for the reaction rate.

To ensure that silver was not promoting a background reaction leading to the same exo- and endocyclic allylic amine products, a control reaction was completed according to Scheme 11, with MCP 1.1a and 4-nitroaniline reacted with silver hexafluorophosphate. No
depletion of MCP or aniline or production of a new compound was observed after 12 hours, indicating that silver alone is not catalyze the ring-opening hydroamination.

![Scheme 11: Control Reaction to Determine if Silver is Contributing to a Background Reaction in the Gold(I)-catalyzed Hydroamination of MCP 1.1a](image)

One final consideration for the reaction of MCPs with anilines catalyzed by a gold(I) species is the equivalents of MCP. For many of the reactions of MCP 1.1a, 1.1 equivalents of MCP was sufficient for the reaction to proceed to completion. However, with some of the more electron withdrawing or sterically encumbered anilines, such a ortho- substituted anilines, isomerization of the MCP occurs, leading to depletion of reactive MCP to three unreactive hydrocarbons, as indicated by GC analysis. The products resulting from the isomerized MCP were unable to react further and therefore decreased the number of equivalents of reactive MCP present in the reaction Possible compounds resulting from this isomerization of MCP 1.1a can be seen in figure 2.

![Figure 2: Possible Structures Resulting from the Isomerization of MCP 1.1a.](image)
In previous hydroamination studies within the Widenhoefer group, silver generated catalysts were avoided due to suspicions that silver was contributing to the isomerization of MCPs. To confirm whether the silver salt or the generated silver species causes this MCP isomerization two control reactions were completed. MCP 1.1a and 2-nitroaniline were tested with silverhexafluorophosphate in order to determine if the silver salt alone causes isomerization of MCPs (Scheme 12). 2-nitroaniline was used over the 4-nitroaniline because the reaction with the former resulted in isomerization of the MCP, whereas the reaction with 4-nitroaniline did not see isomerization in the reaction where the cationic gold catalyst was generated \textit{in situ}. In the reaction outlined in Scheme 12, there was no cyclic allylic amine product formation and no MCP isomerization observed without the presence of the gold catalyst.

![Scheme 12: Control Reaction with 2-nitroaniline and AgPF\(_6\) to determine if Silver plays an Active Role in MCP Isomerization.](image)

To determine if the MCP isomerization was a result of generated silver species in the reaction, 2-nitroaniline was tested with the acetonitrile complex according to Scheme 13. GC analysis showed MCP isomerization in the reaction without the presence of silver, suggesting this isomerization is not the result of silver in the reaction.
1.3. Aniline Scope in the Ring-Opening of MCPs

1.3.1 Substitution patterns: Inductive vs. Resonance Effects

To explore the scope of aniline for the ring-opening hydroamination of MCP 1.1a, catalyzed by the cationic JohnPhos gold species, a variety of substituted anilines were subjected to optimal reaction conditions as shown in Scheme 14. Reactions employing anilines with strong electron withdrawing groups proceeded with high selectivity for the exocyclic allylic amine. However, when employing more Lewis basic anilines under optimized reaction conditions, the reactions failed to proceed at appreciable rates. For example, the reaction with 4-bromoaniline only gave 15% yield of the desired, ring-opened products after increasing the temperature to 100 °C and running the reaction for 72 hours. Reactions with MCP 1.1a and aniline failed to proceed at all under these optimized conditions, presumably because the binding to the gold complex was too strong to proceed with the desired transformation.
Anilines with groups at the 2- or 4- positions, that could withdraw electron density through both resonance and inductive effects showed much higher reactivity under optimized catalytic conditions and also higher selectivity for the exocyclic product than anilines with groups that could only withdraw electron density through inductive effects. Both 2-nitroaniline and 4-nitroaniline proceeded much faster and had higher selectivity than the 3-nitroaniline (Scheme 14). 2-nitroaniline took longer to react than 4-nitroaniline, in the reaction with MCP 1.1a under optimized reaction conditions, but this may be due to...
the higher amount of MCP isomerization, as indicated by GC analysis, in the former case which required the addition of a second equivalent of MCP mid-reaction. Interestingly, when the aniline was substituted with two nitro groups, in the case of 2,4-dinitroaniline, the reaction with MCP 1.1a under optimized catalytic conditions had reduced selectivity and gave much poorer conversion (Scheme 14). Apart from the selectivity, the reaction of 2,4-dinitroaniline with MCP 1.1a stopped midway, even with additional MCP equivalents added to account for isomerization.

![Figure 3: Trend of Reaction Progress Dependent on the Lewis Basicity of the Starting Aniline. Catalyzed by Method B Conditions and Showing the Major, Exocyclic Allylic Product (A).](image)

Groups that could only withdraw electron density through inductive effects, such as 4-CF₃- and 3,5-bis(CF₃)-anilines were tolerated in the reaction with MCP 1.1a, catalyzed by optimized conditions, but gave longer reaction times, slightly lower selectivity, and lower yields (Scheme 14). Figure 3 shows that although regioselectivity between the exo and endocyclic allylic amine products does not suffer relative to less basic anilines such as 4-nitroaniline, increased Lewis basicity of the aniline starting compounds correlates with decreased reactivity and lower overall yield under optimized catalytic conditions. Increasing the proximity of the substituent to the amine group gives much
higher conversion compared with groups located in the meta- or para- positions (with respect to the amine). All of these results support the idea that having an electron withdrawing group is crucial for the reaction of MCPs with anilines catalyzed by Lewis acidic gold complexes by preventing binding to the active gold catalyst. These Werner complexes, as shown in Figure 4, results from a non-productive ligand exchange and are problematic due to the kinetic stability of the gold-nitrogen bond.

![Figure 4: Non-productive Ligand Exchange in Gold-catalyzed Reactions to Yield Werner Complexes.](image)

### 1.3.2 Effects of N-alkylation

The effects of N-alkylation of 4-nitroaniline can be seen in Scheme 15. Although the reaction with MCP 1.1a under optimized catalytic conditions proceeded to completion, giving higher yield than the parent reaction with 4-nitroaniline, the regioselectivity suffered, giving a preference of the exocyclic product of 2:1. This result suggests that when N-alkylation is present, the reaction has a higher preference for the direct protodeauration pathway. To further probe this effect, larger alkyl groups should be examined. Theoretically, larger groups should favor the endocyclic allylic amine, but it may also prevent reactivity.
1.3.3 Effects of ortho-substitution of the Aniline of the Gold(I)-catalyzed Ring-Opening Hydroamination of MCPs

In the cases of 2-nitroaniline and 2-methyl-4-nitroaniline in the reaction with MCP 1.1a under optimized catalytic conditions, selectivity for the exocyclic allylic aniline was not harmed compared to the parent reaction with 4-nitroaniline. This reactivity and selectivity suggests that weaker electron withdrawing groups should be tolerated at the ortho-positions, even if these weakly electron withdrawing groups failed to proceed for reactions including the meta- or para- substituted aniline isomers. 2-methyl-4-fluoroaniline was also investigated in the reaction with MCP 1.1a under optimized catalytic conditions, but the reaction failed to proceed, even with higher temperatures. Theoretically, a fluorine atom has a similar electron withdrawing effect as a CF$_3$ group.$^{14}$ An ortho substituted methyl group does not compromise selectivity but also slows the ring-opening hydroamination reaction down, and this was enough to stop the reaction from proceeding appreciably.
1.4. Methylene cyclopropane (MCP) Scope

1.4.1 The Effects of Ring Size on the Rate and Selectivity of the Gold(I)-catalyzed Ring-opening Hydroamination of MCPs

In order to study the scope of the MCPs, reactions were run with varying ring size of the bicyclic MCP 1.1a-1.4a with 4-nitroaniline under optimized catalytic conditions according to Scheme 14, where n = 1–4. When n = 1, the MCP 1.2a and 4-nitroaniline under optimized catalytic conditions underwent the ring-opening reaction with exclusive formation of the exocyclic product (3.1a), in 87 % yield. The reaction was completed in 8 hours, compared to the parent reaction of the 6-membered MCP, 1.1a which was completed in 12 hours. This increased reactivity can be attributed to the added ring strain of the cyclopentyl moiety that is released during the reaction compared to MCP 1.1a. To ensure that this extra ring strain was not sufficient to promote an un-catalyzed reaction, a control reaction was conducted according to Scheme 17. The reaction of 1.2a with 4-nitroaniline did not proceed under un-catalyzed conditions, therefore the added ring strain alone promoted a faster gold-catalyzed reaction.
Unfortunately, when \( n \) was increased to 3 and 4, with the starting cycloheptyl (1.3a) and cyclooctyl (1.4a) MCPs, the reaction with 4-nitroaniline under optimised catalyzed conditions either generated a mixture of product an undesired product. Cycloheptyl MCP (1.3a) with 4-nitroaniline results under catalytic conditions resulted in a 3:1 mixture of the desired exocyclic allylic amine (6.1a) to the undesired hydroamination product (6.1c) to give a combined yield of 80%. In the case of cyclooctyl MCP 1.4a, the nine-membered product was not formed, but instead, the anti-Markovnikov hydroamination product, 7.1c resulted exclusively at 85%. This lack of ring-opening hydroamination in the case of larger bicyclic MCPs suggests that the release of ring strain in the other cycle is also important.
for promoting distal bond cleavage and that this type of ring cleavage would not be possible in mono-cyclic MCPs.

With the cyclopentyl MCP 1.2a showing higher reactivity than the parent reaction, MCP 1.1a with 4-nitroaniline under optimized catalytic conditions, a few anilines were employed that had failed with the cyclohexyl MCP 1.1a, as seen in Scheme 18. The 2-methyl-4-fluoroaniline had failed to proceed in the reaction with 1.1a under catalytic conditions due to the decreased reactivity caused by the methyl group, but the reaction with cyclopentyl MCP 1.2a lead to complete conversion in 24 hours, showing complete selectivity for the exocyclic allylic amine (3.2a). However, moving towards more basic anilines, such as 4-bromoaniline under optimized catalytic conditions lead to a mixture of products, with the ring-opening products in a ratio of 6:1 favoring the exocyclic product 3.3a, and 30% of the products as the results of anti-Markovnikov hydroamination (3.3c).

Scheme 18: Gold(I)-catalyzed Ring-Opening Hydroamination of Cyclopentyl MCP 1.2a with Select Aniline Derivatives.
1.4.2 Substitution Effects on the Distal Carbon of the MCP of the Gold(I)-catalyzed Hydroamination of MCPs

Since the proposed mechanism for the ring-opening hydroamination involves attack at carbon 3 or 4, a methyl group at the distal carbon of they cyclopropane was used to determine regioselectivity of nucleophilic attack and to see the effects on the isomeric ratio in the reaction of 1.1b with 4-nitroaniline under optimized catalytic conditions. The possible products of this gold-catalyzed ring-opening reaction as a function of nucleophilic attacked can be seen in Scheme 19. G.C. analysis of the reaction of 1.2a with 4-nitroaniline under optimized catalytic conditions showed there were two major products formed, in a ratio of 4:1. The 1H NMR spectrum of these products lacked the alkenyl protons that would be expected for 4.1b, and the presence of two methyl singlets near 2.0 ppm confirms the formation of 4.1c and 4.1d. This NMR evidence indicates that nucleophilic attack prefers the less substituted tertiary carbon over the carbon that should have a partial positive charge under the acidic conditions. This selectivity may also be due to the formation of the more thermodynamically favorable tetrasubstituted double bond. Furthermore, this added stability of the potential tetrasubstituted olefin may explain why the selectivity between the exocyclic and endocyclic products is less pronounced in the reaction of MCP 1.1b, compared with MCP 1.1a.
With the unsubstituted cyclopentyl MCP 1.2a having a higher reactivity and selectivity than the reaction of the cyclohexyl MCP 1.1a, a methyl-substituted cyclopentyl MCP 1.2b was employed under the optimized reaction conditions, as seen in Scheme 20. The reaction of 1.2b with 4-nitroaniline proceeded with attack at the less substituted carbon to give excellent selectivity for the exocyclic product.

Scheme 20: Products Resulting from the Gold(I)-Catalyzed Ring-opening Hydroamination of the Methyl-substituted Cyclopentyl MCP 1.2b.

1.5 Deuterium Labeling Experiments

To gain insight into the mechanism of the gold(I)-catalyzed ring-opening hydroamination of bicyclic MCPs, 4-nitroaniline-\(\text{-N, N-d}_2\) was subjected to optimized
catalytic conditions. Based on the proposed reaction mechanism (Figure 1), the deuterium should be incorporated into the allylic carbon of the major product (A) and into the methyl group of the minor product (B), as seen in Scheme 21.

Scheme 21: Predicted Products for the Gold(I)-catalyzed Ring-opening Reaction with Duterio 4-nitroaniline Based on the Proposed Mechanism.

Utilizing deuterio-\textit{p}-nitroaniline, the reaction was carried out with MCP 1.1a under standard reaction conditions according to Scheme 23. The product resulting from the reaction saw no deuterium incorporation at the amine group, but saw 60\% deuterium incorporation at the expected allylic carbon based on $^1$H NMR integrations and splitting of adjacent groups. No deuterium incorporation was seen in the methylene group or of the group alpha to nitrogen, but other resonances were not sufficiently resolved to determine if deuterium incorporation had occurred. The reaction also proceeded slower than the parent reaction, but did not compromise selectivity, suggesting protodeauration as the rate-limiting step.
To determine deuterium incorporation for the endocyclic product, the reaction of 1.1a with 4-nitroaniline was carried out in toluene with [CyJohnphosANCMe]SbF$_6$ to maximize the amount of minor, endocyclic allylic amine product. Unfortunately, the mixture of products made it impossible to accurately ascertain if deuterium had been incorporated in the methyl group. Nevertheless, the reaction to produce the desired exocyclic product agrees with the proposed mechanism.

1.6 Conclusions and Outlook

The gold(I)-catalyzed ring-opening reaction of MCPs was optimized and explored. Although Lewis basic anilines were not tolerated in the developed catalytic system and a competing hydroamination of the MCP at carbon 1 occurred with larger ring sizes of the MCP, this method still adds to the limited scope of distal bond cleavage of MCPs promoted by Lewis acidic gold complexes. During optimization, it was found that silver plays a crucial role in promoting the reaction without compromise the selectivity for the desired exocyclic allylic amine. Anilines with electron withdrawing groups were necessary, with
groups that withdraw electron density through both resonance and inductive effects giving the best selectivity and rates.

Deuterium experiments agree with the proposed mechanism, but further mechanistic insight is warranted to confirm this. Also, initial hits with the more basic anilines suggests there is room for optimization around a reaction that is not limited by the substitution or electronics of the aniline. Overall, a system that promotes the distal bond cleavage of bicyclic MCPs was achieved with high selectivity in most cases and with moderate to excellent yields to provide facile synthesis to six- and seven-membered exocyclic allylic amines.
1.7 General Methods

Reactions were performed under an atmosphere of nitrogen employing standard Schlenk or dry box methods unless otherwise noted. Catalytic reactions were performed in flame-dried heavy wall reaction tubes under an atmosphere of dry nitrogen. NMR spectra were obtained on Varian spectrometers operating at 500 MHz for $^1$H NMR and 125 MHz for $^{13}$C NMR at 25 °C in CDCl$_3$ unless noted otherwise. Gas chromatography was performed on a Hewlett-Packard 5890 gas chromatograph equipped with a 20 m 0.25 mm polydimethylsiloxane capillary column and FID detector. Ratios of constitutional isomers were established by GC integrals of crude reaction mixtures and confirmed by $^1$H NMR. Flash column chromatography (FCC) was performed with 200-400 mesh silica gel (EM). Thin layer chromatography was performed on silica gel 60 F254. Room temperature is 23 °C.

Reagents were obtained through major chemical suppliers and used without further purification. Diethyl ether, THF, 1,4-dioxane, toluene, and methylene chloride were purified by passage through columns of activated alumina under nitrogen. Gold catalysts [(L1)Au(NCMe)]$^+$SbF$_6^-$, [(L1)Au(NCMe)]$^+$TfO$^-$, [(L1)Au(NCMe)]$^+$BF$_4^-$, [(L2)Au(NCMe)]$^+$SbF$_6^-$, and [(L2)Au(NCMe)]$^+$PF$_6^-$ were prepared as reported by Echavarren.$^{15}$ All other gold complexes were generated in-situ with the corresponding gold chloride and the silver salt. [(L1)AuCl] was purchased and used without further purification. [(L2)AuCl], [(L3)AuCl], and [(L4)AuCl] were synthesized according to known procedures. Methylene cyclopropanes (MCPs) 1.2a$^{16}$, 1.2b$^{16}$, 1.1a$^{16}$, 1.1b$^{16}$, 1.1c$^{16}$,
1.3a\textsuperscript{17}, 1.4a\textsuperscript{17}, were synthesized employing known procedures.

### 1.7.1 Ring-opening Hydroamination of MCPs

**2-methylene-N-(4-nitrophenyl)cycloheptan-1-amine (2.1a) and 2-methyl-N-(4-nitrophenyl)cyclohept-2-en-1-amine (2.1b).**

**Procedure A:** To a flame-dried conical vial $[(\text{L2})\text{Au(NCMe)}]^+\text{PF}_6^-$ (6.9 mg, 0.01 mmol) and 4-nitroaniline (28 mg, 0.20 mmol) were combined in 2 mL of dioxane. MCP 1.1a (26 mg, 0.22 mmol) was added, the reaction capped, and purged with $\text{N}_2$ for 1 minute. The reaction was stirred at 80 °C for 24 hours and increased to 90 °C until the reaction was complete at 80 hours. The reaction was filtered through a short silica plug and eluted with ethyl acetate. Volatile material was removed under vacuum and purified via flash column chromatography to yield a yellow-orange oil (38 mg, 0.15 mmol, 77%). Ratio of a:b = >20:1

**Procedure B:** To a flame-dried conical vial $[(\text{L2})\text{AuCl}]$ (5.3 mg, 0.01 mmol), silver hexafluorophosphate (2.8 mg, 0.011 mmol), and 4-nitroaniline (28 mg, 0.20 mmol) were combined in 2 mL of dioxane in the glovebox. MCP 1.1a (26 mg, 0.22 mmol) was added to the reaction. The reaction was stirred in the dark at 80 °C for 12 hours. The reaction was filtered through a short silica plug and eluted with ethyl acetate. The volatiles were removed under vacuum and purified via flash column chromatography to yield a yellow-orange oil (41.0 mg, 0.17 mmol, 85%). Ratio of a:b = 20:1

TLC (hexanes – EtOAc = 6:1): $R_f = 0.40$. $^1\text{H NMR}: \delta 8.18 – 8.00 (d, J = 8.7 \text{ Hz}, 2 \text{ H}), 6.58 – 6.44 (d, J = 8.7, 2 \text{ H}), 5.78 – 5.72 (m, 0.04 \text{ H}), 5.00 (s, 1 \text{ H}), 4.94 (s, 1 \text{ H}), 4.62 (bs, 1\text{H}), 4.01 – 3.98 (m, 1 \text{ H}), 2.31 (ddt, J = 44.2, 13.7, 6.5 \text{ Hz}, 2\text{H}), 2.14 – 1.98 (m,
2 H), 1.77 – 1.31 (m, 6H). $^{13}$C{$^1$H} NMR: δ 152.4(+), 149.5(+), 128.0(+), 126.5(+), 112.4(−), 110.9(+), 57.7(+), 33.4(−), 30.7(−), 25.6(−), 25.0(−), 22.7(−). HRMS calcld (found) for C$_{14}$H$_{18}$N$_2$O$_2$ (M-H): 245.1296 (245.1295).

Figure 5: $^1$H–$^1$H COSY spectrum of 2.1a.

2-methylene-$N$-(4-nitrophenyl)cycloheptan-3-$d$-1-amine (2.1a–d) [(L2)AuCl] (5.3 mg, 0.01 mmol), silver hexafluoroantimonate (3.8 mg, 0.011 mmol), and d$_2$-4-nitroaniline (14 mg, 0.20 mmol) were combine with MCP 1.1a (26 mg, 0.22 mmol) according to procedure B to afford a yellow oil (27.2 mg, .11 mmol, 55 %) after 20 hours. a:b = >20:1. TLC (hexanes – EtOAc = 6:1): $R_f$ = 0.40. $^1$H NMR (400 MHz): δ 8.18 – 8.00 (d, $J = 8.7$ Hz, 2 H), 6.58 – 6.44 (d, $J = 8.7$, 2 H), 5.78 – 5.72 (m, 0.04 H), 5.05 – 4.98 (m, 1 H), 4.94 (s, 1 H), 4.57 (d, $J = 6.9$ Hz, 1 H), 4.02 (td, $J = 7.4$, 5.1 Hz, 1 H), 2.41
- 2.23 (m, 1.4 H), 2.17 – 2.08 (m, 1H), 2.06 (s, .5H), 1.92 – 1.86 (m, .5H), 1.78 – 1.45 (m, 6H). $^{13}$C$^{1}$H NMR (400MHz): δ 152.3, 149.5, 126.2, 126.3, 112.4, 111.7, 57.7, 35.9 (d, $^1J_{C-D}$ = 2.1 Hz), 33.2, 28.3, 27.5, 25.3 (d, $^1J_{C-D}$ = 2.3 Hz), 21.3. HRMS calcd (found) for C$_{14}$H$_{17}$DN$_2$O$_2$ (MH$^+$): 248.3172 (_______).

2-methylene-N-phenylcycloheptan-1-amine (2.2a). [(L2)AuCl] (5.3 mg, 0.01 mmol), silver hexafluoroantimonate (3.8 mg, 0.011 mmol), and aniline (20 mg, 0.20 mmol) were combine with MCP 1.1a (26 mg, 0.22 mmol) according to procedure B to afford a beige oil (16.4 mg, 0.08 mmol, 37 %). TLC (hexanes – EtOAc = 15:1): R$_f$ = 0.46. $^1$H NMR: δ 7.16 (t, $J$=7.5, 2H), 6.67 (t, $J$ = 7.3 Hz, 1H), 6.60 – 6.53 (m, 2 H), 5.14 – 4.98 (m, 1 H), 4.89 (d, $J$ = 1.7 Hz, 1 H), 3.94 (dd, $J$ = 7.7, 4.8 Hz, 1 H), 3.82 (br s, 1 H), 2.41 – 2.31 (m, 1 H), 2.31 – 2.22 (m, 1 H), 2.14 – 2.00 (m, 1 H), 1.80 – 1.42 (m, 8 H). $^{13}$C$^{1}$H NMR: δ 151.1, 147.4, 129.0, 116.9, 113.3, 111.5, 57.9, 36.2, 33.3, 28.5, 27.8, 25.5. HRMS calcd (found) for C$_{14}$H$_{19}$N (MH$^+$): 202.3202 (_______).

2-methylene-N-(3-nitrophenyl)cycloheptan-1-amine (2.3a) and 2-methyl-N-(3-nitrophenyl)cyclohept-2-en-1-amine (2.3b) [(L2)AuCl] (5.3 mg, 0.01 mmol), silver hexafluorophosphate (2.8 mg, 0.011 mmol), and 3-nitroaniline (28.0 mg, 0.20 mmol) were combine with MCP 1.1a (26 mg, 0.22 mmol) according to procedure B to afford a yellow-orange oil (30 mg, 0.12 mmol, 60%) in 24 hours. Ratio of a:b = 10:1. TLC (hexanes – EtOAc = 15:1): R$_f$ = 0.32. $^1$H NMR (400 MHz): δ 7.48 (dd, $J$ = 8.0 Hz, 1.4 Hz, 1H), 7.33 (t, $J$ = 2.3 Hz, 1H), 7.24 (t, $J$ = 8.0 Hz, 1H), 6.80 (dd, $J$ = 8.1, 2. Hz, 1H), 5.85 – 5.76 (m, .09H), 5.03 (d, $J$ = 1.3 Hz, 1H), 4.91 (d, $J$ = 1.4 Hz, 1H), 4.45 (bs, .1H), 4.17 (bs, 1H), 4.00 – 3.93 (m, 1H), 2.40 – 2.21 (m, 2.2H), 2.19 – 2.01 (m, 2.2H), 1.72 –
1.61 (m, 4.4H), 1.54 – 1.44 (m, 2.2H), 1.40 – 1.31 (m, 1H). $^{13}$C$\{^1$H} NMR: $\delta$ 149.9, 149.2, 148.0, 129.5, 119.1, 112.2, 111.6, 107.1, 57.9, 36.1, 33.2, 28.4, 27.6, 25.4. HRMS calcd (found) for C$_{14}$H$_{18}$N$_2$O$_2$ (MH$^+$): 247.3172 (______).

2-methylene-$N$-(2-nitrophenyl)cycloheptan-1-amine (2.4a) and 2-methyl-$N$-(2-nitrophenyl)cyclohept-2-en-1-amine (2.4b). [(L$_2$)AuCl] (5.3 mg, 0.01 mmol), silver hexafluorophosphate (2.8 mg, 0.011 mmol), and 2-nitroaniline (29.0 mg, 0.21 mmol) were combine with MCP 1.1a (26 mg, 0.22 mmol) according to procedure B. An additional portion of MCP (10 mg, .10 mmol) was added mid reaction to accommodate MCP isomerization and afforded a yellow-orange oil (48 mg, .19mmol, 85%) in 18 hours. Ratio of a:b = >20:1. TLC (hexanes – EtOAc = 20:1): $R_f$ = 0.35. $^1$H NMR: $\delta$ 8.34 (bs, 1H), 8.18 (d, $J$ = 8.6 Hz, 1H), 7.39 (t, $J$ = 7.9 Hz, 1H), 6.75 (d, $J$ = 8.8 Hz, 1H), 6.63 (t, $J$ = 7.8 Hz, 1H), 5.05 (s, 1H), 4.95 (s, 1H), 4.20 – 4.09 (m, 1H), 2.33 (ddt, $J$ = 47.3, 14.2, 6.7 Hz, 2H), 2.15 – 2.04 (m, 2H), 1.86 – 1.58 (m, 7H). $^{13}$C$\{^1$H} NMR: $\delta$144.7, 136.0, 126.8, 115.2, 115.0, 112.5, 57.6, 36.1, 33.1, 27.8, 27.2, 25.5. HRMS calcd (found) for C$_{14}$H$_{18}$N$_2$O$_2$ (MH$^+$): 247.3172 (______).

$N$-(2,4-dinitrophenyl)-$N$-methyl-2-methylenecycloheptan-1-amine (2.5a) and $N$-(2,4-dinitrophenyl)-$N,2$-dimethylocyclohept-2-en-1-amine (2.5b). [(L$_2$)AuCl] (5.3 mg, 0.01 mmol), silver hexafluorophosphate (2.8 mg, 0.011 mmol), and 2,4-dinitroaniline (36.6 mg, 0.20 mmol) were combine with MCP 1.1a (26 mg, 0.22 mmol) according to procedure B. An additional portion of MCP (10 mg, 0.10 mmol) was added mid reaction to accommodate MCP isomerization and afforded an oily, yellow solid (26.2 mg, 0.09 mmol, 45%) after 18 hours. Ratio of a:b = 15:1. TLC (hexanes – EtOAc = 8:1): $R_f$ =
0.35. ¹H NMR: δ 9.15 (d, J = 9.5 Hz, 1 H), 8.23 (dd, J = 9.5, 2.6 Hz, 1 H), 6.81 (d, J = 9.5 Hz, 1 H), 5.88 – 5.82 (m, 0.06 H), 5.03 (s, 1 H), 5.00 (s, 1 H), 4.66 (bs, 1H), 4.23 (t, J = 6.5 Hz, 1 H), 2.62 (s, 0.18 H), 2.40 – 2.26 (m, 3 H), 2.14 (td, J = 8.7, 4.2 Hz, 1H), 1.88 – 1.80 (m, 1H), 1.74 – 1.68 (m, 5H). ¹³C{¹H} NMR: δ 148.4, 147.5, 136.0, 130.1, 124.3, 123.9, 115.1, 113.5, 58.4, 35.8, 33.1, 27.8, 27.2, 25.3. HRMS calcd (found) for C₁₄H₁₇N₃O₄ (M-H⁻): 290.1146 (290.1148).

N-methyl-2-methylene-N-(4-nitrophenyl)cycloheptan-1-amine (2.6a) and N₂-methyl-N-(4-nitrophenyl)cyclohept-2-en-1-amine (2.6b). [(L₂)AuCl] (5.3 mg, 0.01 mmol), silver hexafluorophosphate (2.8 mg, 0.011 mmol), and N-methyl-4-nitroaniline (31.0 mg, 0.20 mmol) were combine with MCP 1.1a (26 mg, 0.22 mmol) according to procedure B to afford an oily, yellow solid (48 mg, 0.18 mmol, 90%) after 24 hours. Ratio of a:b = 2:1. TLC (hexanes – EtOAc = 8:1): Rf = 0.38. ¹H NMR: δ 8.18 – 8.06 (m, 3.0 H), 6.64 (d, J = 9.5 Hz, 3.0 H), 5.82 – 5.77 (m, 0.5 H), 5.01 – 4.99 (m, 1 H), 4.70 (s, 1 H), 4.56 – 4.49 (m, 1H), 4.48 – 4.44 (m, .5H), 2.97 (s, 1.5H), 2.89 (s, 3H), 2.54 – 2.46 (m, 1 H), 2.39 – 2.29 (m, 1.5 H), 2.22 – 2.11 (m, .5 H), 1.99 – 1.83 (m, 6 H), 1.79 – 1.70 (m, .5 H), 1.68 – 1.60 (m, 1H), 1.57 (s, 1.5 H), 1.52 – 1.40 (m, 3.5 H). ¹³C{¹H} NMR: δ 154.1, 148.2, 128.6, 126.3, 113.2, 110.4, 110.1, 63.6, 41.0, 35.6, 33.3, 31.5, 30.5, 29.1, 29.0, 27.6, 21.7. HRMS calcd (found) for C₁₅H₂₀N₂O₂ (MH⁺): 261.1597 (_________).

N-(2-methyl-4-nitrophenyl)-2-methylene cycloheptan-1-amine (2.7a) and 2-methyl-N-(2-methyl-4-nitrophenyl)cyclohept-2-en-1-amine (2.7b). [(L₂)AuCl] (5.3 mg, 0.01 mmol), silver hexafluorophosphate (2.8 mg, 0.011 mmol), and 2-methyl-4-
nitroaniline (30.4 mg, 0.20 mmol) were combine with MCP 1.1a (26 mg, 0.22 mmol) according to procedure B to afford a yellow oil (52 mg, 0.18 mmol, 90%) after 24 hours.

Ratio of a:b = >20:1. TLC (hexanes – EtOAc = 6:1): Rf = 0.35. ¹H NMR: δ 8.02 (d, J = 9.0 Hz, 1 H), 7.99 (s, 1 H), 6.62 (d, J = 9.0 Hz, 1 H), 5.83 – 5.70 (m, 0.06 H), 5.01 (s, 1 H), 4.92 (s, 1 H), 4.41 (bs, 1H), 4.13 – 4.02 (m, 1H), 2.40 – 2.26 (m, 2H), 2.22 (s, 3H), 2.14 (td, J = 8.7, 4.2 Hz, 1H), 1.79 – 1.60 (m, 3H), 1.48 – 1.19 (m, 5H).

¹³C{¹H} NMR: δ 149.7, 145.6, 138.1, 126.0, 124.5, 123.8, 112.2, 109.1, 57.6, 36.1, 33.3, 28.2, 27.5, 25.5.

HRMS calcd (found) for C₁₅H₂₀N₂O₂ (M−H−): 259.1452 (259.1453).

2-methylene-N-(4-(trifluoromethyl)phenyl)cycloheptan-1-amine (2.8a) and 2-methyl-N-(4-(trifluoromethyl)phenyl)cyclohept-2-en-1-amine (2.8b).

[(L₂)AuCl] (5.3 mg, 0.01 mmol), silver hexafluorophosphate (2.8 mg, 0.011 mmol), and 4-(trifluoromethyl)aniline (32.2 mg, 0.20 mmol) were combine with MCP 1.1a (26 mg, 0.22 mmol) according to procedure B to afford a clear oil (22 mg, 0.08 mmol, 41%) after 24 hours. Ratio of a:b = 18:1. TLC (hexanes – EtOAc = 20:1): Rf = 0.28. ¹H NMR: δ 7.36 (d, J = 8.5 Hz, 2H), 6.54 (d, J = 8.5 Hz, 2H), 5.01 (s, 1 H), 4.90 (s, 1H), 4.21 – 4.08 (m, 1H), 3.94 (bs, 1H), 2.62 (s, .18H), 2.29 (ddt, J = 50, 14.7, 6.8 Hz, 1H), 2.11 – 1.98 (m, 2H), 1.72 – 1.60 (m, 4H), 1.39 – 1.11 (m, 2H), .90 (ddt J = 14.4, 7.2, 2.0 Hz, 1H).

¹³C{¹H} NMR: δ 150.3, 149.8, 126.4, 126.1, 112.3, 111.9, 111.6, 57.6, 36.1, 33.2, 28.4, 27.6, 25.4. HRMS calcd (found) for C₁₅H₁₈F₃N(M−H−): 268.1319 (268.1321).

N-(3,5-bis(trifluoromethyl)phenyl)-2-methylene cycloheptan-1-amine (2.9a) and N-(3,5-bis(trifluoromethyl)phenyl)-2-methylcyclohept-2-en-1-amine (2.9b).

[(L₂)AuCl] (5.3 mg, 0.01 mmol), silver hexafluorophosphate (2.8 mg, 0.011 mmol), and
3,5-bis(trifluoromethyl)aniline (45.8 mg, 0.20 mmol) were combine with MCP 1.1a (26 mg, 0.22 mmol) according to procedure B. An additional portion of MCP (10 mg, 0.10 mmol) was added mid reaction to accommodate MCP isomerization and afforded a clear, yellow oil (46 mg, 0.14 mmol, 70%) after 24 hours. TLC (hexanes – EtOAc = 20:1): \( R_f = 0.40 \). \(^1\)H NMR: \( \delta 7.10 \) (s, 1H), 6.87 (s, 2H), 5.82 – 5.77 (m, 0.06 H), 5.02 (s, 1 H), 4.93 (s, 1 H), 4.33 – 4.20 (m, 1H), 4.00 – 4.87 (m, 1H), 2.29 (ddt, \( J = 43.3, 13.8, 6.4 \) Hz, 2 H), 2.14 – 2.00 (m, 1 H), 1.75 – 1.61 (m, 5 H), 1.37 – 1.15 (m, 1 H), 0.94 – 0.84 (m, 1 H). \(^{13}\)C \( \{^1\)H\} NMR: \( \delta 149.5, 147.8, 132.14 \) (q, \( J = 32.6 \) Hz, 2C), 123.6 (q, \( J = 272.5 \) Hz, 2C), 112.5, 112.4, 109.8, 57.9, 36.0, 33.0, 28.5, 27.7, 25.3. HRMS calcd (found) for \( \text{C}_{16}\text{H}_{17}\text{F}_6\text{N(MH}^+\text{)}\): 338.3166 (_________).

2-methylene-N-(2-(trifluoromethyl)phenyl)cycloheptan-1-amine(2.10a) and 2-methyl-N-(2-trifluoromethyl)phenyl)cyclohept-2-en-1-amine (2.10b). [(L2)AuCl] (5.3 mg, 0.01 mmol), silver hexafluorophosphate (2.8 mg, 0.011 mmol), and 4-(trifluoromethyl)aniline (32.2 mg, .20 mmol) were combine with MCP 1.1a (26 mg, .22 mmol) according to procedure B to afford a clear oil (29.6 mg, .11 mmol, 55%) after 24 hours. Ratio of a:b = \( >20:1 \). TLC (hexanes – EtOAc = 15:1): \( R_f = 0.40 \). \(^1\)H NMR: 8.18 (d, \( J = 8.6 \) Hz, 1H), 7.58 (bs, 1H), 7.39 (t, \( J = 7.9 \) Hz, 1H), 6.75 (d, \( J = 8.8 \) Hz, 1H), 6.63 (t, \( J = 7.8 \) Hz, 1H), 5.05 (s, 1H), 4.95 (s, 1H), 4.20 – 4.09 (m, 1H), 2.33 (ddt, \( J = 45.3, 14.3, 6.2 \) Hz, 2H), 2.15 – 2.04 (m, 2H), 1.86 – 1.58 (m, 7H). \(^{13}\)C \( \{^1\)H\} NMR: \( \delta 144.7, 136.0, 126.8, 115.2, 115.0, 112.5, 57.6, 36.1, 33.1, 27.8, 27.2, 25.5. HRMS calcd (found) for \( \text{C}_{15}\text{H}_{15}\text{F}_3\text{N(MH}^+\text{)}\): 270.1463 (_________).

Methyl 2-((2-methylene cycloheptyl)amino)benzoate (2.11a) and Methyl 2-((2-
methylcyclohept-2-en-1-yl)amino)benzoate (2.11b). [(L2)AuCl] (5.3 mg, 0.01 mmol), silver hexafluorophosphate (2.8 mg, 0.011 mmol), and methyl 2-aminobenzoate (30.2 mg, 0.20 mmol) were combine with MCP 1.1a (26 mg, .22 mmol) according to procedure B to afford a clear oil (18 mg, 0.07 mmol, 35%) after 30 hours. Ratio of a:b = >20:1. TLC (hexanes – EtOAc = 20:1): Rf = 0.40. 1H NMR: δ 7.10 (s, 1H), 6.87 (s, 2H), 5.82 – 5.77 (m, 0.06 H), 5.02 (s, 1 H), 4.93 (s, 1 H), 4.33 – 4.20 (bs, 1H), 4.00 – 4.87 (m, 1H), 2.29 (ddt, J = 42.8, 13.3, 6.2 Hz, 2 H), 2.14 – 2.00 (m, 1 H), 1.75 – 1.61 (m, 5 H), 1.37 – 1.15 (m, 1 H), 0.94 – 0.84 (m, 1 H). 13C{1H} NMR: δ 149.5, 147.8, 132.14 (q, J = 32.6 Hz, 2C), 123.6 (q, J = 272.5 Hz, 2C), 112.5, 112.4, 109.8, 57.9, 36.0, 33.0, 28.5, 27.7, 25.3. HRMS calcd (found) for C16H21NO2 (MH+): 260.1644 (_________).

N-(2-methylenecyclohexyl)-4-nitroaniline (3.1a). [(L2)AuCl] (5.3 mg, 0.01 mmol), silver hexafluorophosphate (2.8 mg, 0.011 mmol), and 4-nitroaniline (28 mg, 0.20 mmol) were combine with MCP 1.2a (21 mg, 0.22 mmol) according to procedure B to afford an oily, yellow solid (40.4 mg, 0.17 mmol, 87 %) after 8 hours. TLC (hexanes – EtOAc = 5:1): Rf = 0.35. 1H NMR: δ 7.97 (d, J=9.2, 2H), 6.43 (t, J = 9.2 Hz, 2H), 4.69 (s, 1 H), 4.61 (s, 1H), 3.77 – 3.67 (m, 1H), 3.53 – 3.38 (bs, 1H), 2.43 – 2.28 (m, 1H), 2.07 – 1.98 (m, 2 H), 1.87 – 1.70 (m, 3 H), 1.59 – 1.44 (m, 2 H), 13C{1H} NMR: δ 152.8, 147.3, 137.6, 126.3, 111.5, 106.9, 56.2, 35.0, 34.2, 27.9, 25.1. HRMS calcd (found) for C13H16N2O2 (MH+): 232.1212 (_________).

4-fluoro-2-methyl-N-(2-methylenecyclohexyl)aniline (3.2a) and 4-fluoro-2-methyl-N-(2-methylcyclohex-2-en-1-yl)aniline (3.2b). [(L2)AuCl] (5.3 mg, 0.01 mmol), silver hexafluorophosphate (2.8 mg, 0.011 mmol), and 4-fluoro-2-methylaniline
(25 mg, 0.20 mmol) were combine with MCP 1.2a (21 mg, 0.22 mmol) according to procedure B to afford a clear oil (40.4 mg, 0.18 mmol, 92%) after 24 hours. Ratio of a:b = 1:0. TLC (hexanes – EtOAc = 20:1): R_f = 0.32. ^1^H NMR: δ 7.97 (d, J=9.2, 2H), 6.43 (t, J = 9.2 Hz, 2H), 4.69 (s, 1H), 4.61 (s, 1H), 3.77 – 3.67 (m, 1H), 3.53 – 3.38 (bs, 1H), 2.43 – 2.28 (m, 1H), 2.07 – 1.98 (m, 2 H), 1.87 – 1.70 (m, 3 H), 1.59 – 1.44 (m, 2 H), ^1^C{^1^H} NMR: δ 152.8, 147.3, 137.6, 126.3, 111.5, 106.9, 56.2, 35.0, 34.2, 27.9, 25.1. HRMS calcd (found) for C_{14}H_{18}FN (MH^+): 220.1495 (_________).

4-bromo-N-(2-methylenecyclohexyl)aniline (3.3a), 4-bromo-N-(2-methylcyclohex-2-en-1-yl)aniline (3.3b), and N-bicyclo[3.1.0]hexan-6-ylmethyl)-4-bromoaniline (3.3c). [(L2)AuCl] (5.3 mg, 0.01 mmol), silver hexafluorophosphate (2.8 mg, 0.011 mmol), and 4-bromoaniline (34.4 mg, 0.20 mmol) were combine with MCP 1.2a (21 mg, 0.22 mmol) according to procedure B to afford an oily, yellow solid (31.9 mg, 0.12 mmol, 60%) after 24 hours. Ratio of a:b:c = 6:1:3. TLC (hexanes – EtOAc = 15:1): R_f = 0.35. ^1^H NMR: δ 7.97 (d, J=9.2, 2H), 6.43 (t, J = 9.2 Hz, 2H), 4.69 (s, 1H), 4.61 (s, 1H), 3.77 – 3.67 (m, 1H), 3.53 – 3.38 (bs, 1H), 2.43 – 2.28 (m, 1H), 2.07 – 1.98 (m, 2 H), 1.87 – 1.70 (m, 3 H), 1.59 – 1.44 (m, 2 H), ^1^C{^1^H} NMR: δ 152.8, 147.3, 137.6, 126.3, 111.5, 106.9, 56.2, 35.0, 34.2, 27.9, 25.1. HRMS calcd (found) for C_{13}H_{16}NB (MH^+): 232.1212 (_________).

3-methyl-2-methylene-N-(4-nitrophenyl)cycloheptan-1-amine (4.1c) and 2,3-dimethyl-N-(4-nitrophenyl)cyclohept-2-en-1-amine (4.1d). [(L2)AuCl] (5.3 mg, 0.01 mmol), silver hexafluorophosphate (2.8 mg, 0.011 mmol), and 4-nitroaniline (28 mg, 0.20 mmol) were combine with MCP 1.1b (27 mg, 0.22 mmol) according to procedure B
to afford an oily, yellow solid (40.4 mg, 0.17 mmol, 87%) after 6 hours. Ratio of c:d = 4:1. TLC (hexanes – EtOAc = 5:1): R_f = 0.35. ^1^H NMR: δ 8.05 (d, J=8.9, 2.5 H), 6.51 (d, J = 9.2 Hz, .5H), 6.40 (d, J =8.9 Hz, 2.0 H), 5.02 (s, 1 H), 4.91 (s, 1H), 4.70 (bs, 1H), 4.61 (bs, .25 H), 3.91 – 3.85 (m, 1H), 3.77 – 3.72 (m, .25H), 2.50 (dt, J =11.7, 6.5 Hz, .5 H), 2.40 – 2.29 (m, 1.25H), 2.20 – 2.08 (m, 2 H), 2.04 (s, .75H), 1.89 (dt, J = 13.1, 6.2 Hz, 1.5 H), 1.81 (s, .75H), J = 1.76 – 1.63 (m, 2.25H), 1.64 – 1.48 (m, 5 H), 1.29 – 1.20 (m, 2 H), ^1^C({^1^H}) NMR: δ154.6, 153.4, 152.4, 152.2, 137.9, 126.4, 112.3, 111.8, 111.3, 108.2, 58.6, 55.7, 37.9, 37.3, 37.0, 36.6, 36.2, 26.8, 25.7, 24.7, 23.1, 21.2. HRMS calcd (found) for C_{15}H_{20}N_{2}O_{2} (M-H): 259.145 (259.1451).

**N-(3-methyl-2-methylenecyclohexyl)-4-nitroaniline (5.1a)** and **N-(2,3-dimethylcyclohex-2-en-1-yl)-4-nitroaniline (5.1b).** [(L2)AuCl] (5.3 mg, 0.01 mmol), silver hexafluorophosphate (2.8 mg, 0.011 mmol), and 4-nitroaniline (28 mg, 0.20 mmol) were combine with MCP 1.2b (22 mg, 0.22 mmol) according to procedure B to afford an oily, yellow solid (41.8 mg, 0.17 mmol, 85 %) after 4 hours. Ratio of a:b = >20:1. TLC (hexanes – EtOAc = 5:1): R_f = 0.35. ^1^H NMR: δ 8.06 (d, J = 8.8 Hz, 2 H), 6.53 (d, J = 8.8 Hz, 2 H), 4.86 (s, 1 H), 4.82 (s, 1 H), 4.59 (bs, 1 H), 4.11 (t, J = 6.9 Hz, 1 H), 2.54 – 2.44 (m, 1 H), 1.94 – 1.84 (m, 2 H), 1.74 (td, J = 11.9, 5.3 Hz, 3 H), 1.62 (s, 3 H), 1.59 – 1.44 (m, 2 H), ^1^C({^1^H}) NMR: δ152.7, 152.6, 137.9, 126.3, 111.6, 107.7, 54.9, 35.1, 34.2, 29.1, 25.3. HRMS calcd (found) for C_{14}H_{18}N_{2}O_{2} (MH^+): 247.1440 (_________).

**2-methylene-N-(4-nitrophenyl)cyclooctan-1-amine (6.1a), (Z)** 2-methyl-N-(4-nitrophenyl)cyclooctan-2-en-1-amine (6.1b), and **N-(bicycle[5.1.0]octan-8-ylmethyl)-4-nitroanilne (6.1c).** [(L2)AuCl] (6.1mg, 0.01 mmol), silver hexafluorophosphate (3.0 mg,
0.011 mmol), and 4-nitroaniline (28 mg, 0.20 mmol) were combined in 2 mL of dioxane. MCP 1.3a (27 mg, 0.22 mmol) was added to the reaction and was stirred in the dark at 80 °C for 10 hours according to procedure B to afford an oily yellow solid. Ratio a:b:c = 3:0:1. TLC (Hexanes – EtOAc = 5:1): R_f = 0.35. \(^1\)H NMR: \(\delta\) 8.13 – 7.98 (m, 2.5 H), 6.59 – 6.42 (m, 2.5 H), 5.02 (s, 1H), 4.96 (s, 1H), 4.54 (bs, 1 H), 3.98 (t, \(J = 6.8\) Hz, 1 H), 3.10 – 3.12 (m, .5 H), 2.23 – 2.08 (m, 2H), 2.07 – 1.90 (m, 2H), 1.88 – 1.79 (m, 2.5 H), 1.78 – 1.66 (m, 1 H), 1.42 – 1.24 (m, 2 H), 1.20 – 0.95 (m, 5H). \(^{13}\)C{\(^1\)H} NMR: \(\delta\) 152.3, 137.8, 126.5, 126.3, 111.6, 111.0, 53.9, 39.0, 32.8, 31.7, 30.3, 29.6, 29.3, 25.8, 23.1, 22.6, 21.2, 14.0, 13.6. HRMS calcd (found) for C_{15}H_{20}N_{2}O_{2} (MH\(^+\)): 261.1597 (_________).

### 1.7.2 Anti-Markovnikov Hydroamination of MCPs

**N-(bicyclo[4.1.0]heptan-7-ylmethyl)-4-nitroaniline (5.1).** To a flame-dried conical vial [(L\(^3\)AuCl) (6.1mg, 0.01 mmol), silver hexafluorophosphate (3.0 mg, 0.011 mmol), and 4-nitroaniline (28 mg, 0.20 mmol) were combined in 2 mL of dioxane in the glovebox. MCP 1.1a (26 mg, 0.22 mmol) was added to the reaction and was stirred in the dark at 80 °C for 10 hours. The reaction was cooled and filtered through a short silica plug, which was eluted with ethyl acetate. Volatile material was removed under vacuum and purified via flash column chromatography to yield an orange solid (43.4 mg, .18 mmol, 80%). TLC (Hexanes – EtOAc = 5:1): R_f = 0.40. \(^1\)H NMR: \(\delta\) 8.07 (d, \(J = 9.1\) Hz, 2 H), 6.50 (d, \(J = 9.1\) Hz, 2 H), 4.60 (bs, 1 H), 3.03 (dd, \(J = 6.6\) Hz, 4.9 Hz, 2 H), 1.96 – 1.82 (m, 2 H), 1.70 – 1.60 (m, 2 H), 1.21 – 1.09 (m, 4H), .92 (ddd, \(J = 1.4\) Hz, 2.4 Hz, 6.9 Hz, 2 H), .78 (ddd, \(J = 2.3\) Hz, 3.4 Hz, 8.0 Hz, 1H). \(^{13}\)C{\(^1\)H} NMR: \(\delta\) 127.2, 111.2, 49.0, 24.1, 23.6, 22.1, 17.0. HRMS calcd (found) for C_{14}H_{18}N_{2}O_{2} (M-H\^-): 245.1296
N-(bicyclo[6.1.0]nonan-9-ylmethyl)-4-nitroaniline (5.2). [(L2)AuCl] (5.3 mg, 0.01 mmol), silver hexafluorophosphate (2.8 mg, 0.011 mmol), and 4-nitroaniline (28.0 mg, 0.20 mmol) were combine with MCP 1.4a (30 mg, 0.22 mmol) according to procedure B to afford a yellow solid (50 mg, 0.18 mmol, 91%). TLC (hexanes – EtOAc = 5:1): Rf = 0.28. ¹H NMR: δ 8.06 (d, J = 8.7 Hz, 2 H), 6.50 (d, J = 8.7 Hz, 2 H), 5.02 (bs, 1 H), 1.96 (d, J = 14.3 Hz, 2 H), 1.71 – 1.56 (m, 5 H), 1.51 – 1.31 (m, 5 H), 1.16 – .96 (m, 3H), .86 (d, J = 9.3 Hz, 2 H). ¹³C{¹H} NMR: δ 152.6, 137.8, 126.4, 35.3, 28.9, 28.3, 26.4, 22.4, 13.1. HRMS calcd (found) for C₁₆H₂₂N₂O₂ (M-H⁻): 273.1609 (273.1608).
References


