Efficiently novel catalysts of asymmetric propargylation by using Zn(HMDS)$_2$ with chiral ligands

Chu Thi Hien Thu
Faculty of Chemistry
Hanoi University of Science
Hanoi, Vietnam.

ABSTRACT

The asymmetric synthesis of propargyl alcohol played an essential role in fundamental organic synthesis as useful building blocks for complex molecules. Hence, there were several methods of using catalysts and ligands to enhance the chemoselectivity, rate and enantioselectivity for the synthesis of propargyl alcohol. However, the isomerization of organometallic species could cause two pathways to form both propargyl and allenyl alcohol. Zn(HMDS)$_2$ and chiral ligands were investigated, exploited and found to be not only efficient in catalyzing the propargylation but lowering the costs of catalysts as well. The mechanisms and additional factors of producing highly enantiomerical propargyl alcohol will be discussed in this paper.

Keywords: Propargylation, allenylation, asymmetric synthesis, Zn(HMDS)$_2$, allenylboronate.

1. INTRODUCTION

Catalytic asymmetric synthesis is a very attractive area and played a prominent role in chemistry due to their production of a large number of optically active chiral centers compounds for the medicine industry and academic research with only small quantity of catalysts$^{[1,4]}$.

In this synthesis route, we chose acetophenone as the prochiral starting material and used zinc hexamethyldisilane Zn(HMDS)$_2$ to catalyze the reaction between acetophenone and boronate. The challenge of this asymmetric propargylation is the rearrangement and isomerization of propargyl metal into allylzinc complexes. Therefore, not only enantioselectivity but chemoselectivity is also an important factor to drive the reaction to get high yield of propargyl alcohol.

An active allylzinc nucleophile formation based on the transmetallation of allenylboronate with zinc amide via Zimmerman-Traxler transition state$^{[5]}$. The boron-zinc exchange mechanism is a mild method to generate allyllic zinc nucleophile lead to the efficient catalytic reaction.

METHODOLOGY

1. Preparation of allenylboronate

The Grignard’s reagent following the steps from literatures synthesized as in the scheme 1$^{[6]}$.

Scheme 1. Preparation of Grignard’s reagent

After stirring for 3 hours at -78°C (by mixture of ice and acetone) and 1 hour at 0°C (ice water), the product allenyl magnesium bromide (2) was isolated and purified.

The reaction is described below by scheme 2.

Scheme 2. Synthesis of Allenylboronate

2. Asymmetric synthesis of propargyl alcohol

Several chiral ligands were used to synthesize chiral
propargyl alcohol. They were archived from chiral pool strategy or resolution methods from natural product or organic synthesis.

The Zn(HMDS)$_2$ was dissolved in THF solvent inside the vessel under argon environment, prevent catalysts from oxygen and decomposition. After that, allenylboronates (3) in THF was added to the reaction system via syringes. The "slow addition" of acetophenone (4) was carried out to completely finish the reaction after 12 hours to produce propargyl alcohol (6) and allenyl alcohol (5) as in the scheme 3.

**Scheme 3.** Synthesis of propargyl and allenyl alcohol

![Scheme 3](image)

Ligands were employed:

(7) N,N'-dibenzyl-1,2-diphenylethane-1,2-diamine
(8) Bis-oxazolines (BOX)
(9) pyridine bis-oxazoline (pyBOX)
(10) (R)-(+)2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl (BINAP)
(11) (R)-(+)6,6?-bimethyl-2,2?-bis(diphenylphosphino)-1,1'-biphenyl

**Figure 1.** Some chiral ligands were used

![Figure 1](image)

4. Results

4.1. Chemoselectivity

Under the consideration of temperature and specific ligands, the chemoselectivity was determined by the ratio of propargyl and allenyl alcohols.

<table>
<thead>
<tr>
<th>Temperature(°C)</th>
<th>Ligands</th>
<th>Yield (%)</th>
<th>5:6</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
<td>7</td>
<td>97</td>
<td>78:19</td>
</tr>
<tr>
<td>40</td>
<td>7</td>
<td>87</td>
<td>61:49</td>
</tr>
<tr>
<td>-20</td>
<td>7</td>
<td>92</td>
<td>30:72</td>
</tr>
<tr>
<td>20</td>
<td>8</td>
<td>81</td>
<td>63:18</td>
</tr>
<tr>
<td>20</td>
<td>9</td>
<td>70</td>
<td>65:5</td>
</tr>
<tr>
<td>20</td>
<td>10</td>
<td>76</td>
<td>69:7</td>
</tr>
<tr>
<td>20</td>
<td>11</td>
<td>5</td>
<td>47:10</td>
</tr>
</tbody>
</table>

* Determined by $^1$H NMR spectroscopy.

4.2. Enantioselectivity

The ratio of two enantiomers: propargyl and allenyl alcohol as below:

**Figure 2.** Structures of propargyl and allenyl alcohol

![Figure 2](image)

As it can be described and expressed by measuring ee (enantiomeric excess) through polarimeter.
Table 2. Enantioselectivity of propargyl alcohol using different chiral ligands

<table>
<thead>
<tr>
<th>Temperature(°C)</th>
<th>Ligands</th>
<th>ee&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
<td>1</td>
<td>88</td>
</tr>
<tr>
<td>20</td>
<td>2</td>
<td>72</td>
</tr>
<tr>
<td>20</td>
<td>3</td>
<td>85</td>
</tr>
<tr>
<td>20</td>
<td>4</td>
<td>62</td>
</tr>
<tr>
<td>20</td>
<td>5</td>
<td>65</td>
</tr>
</tbody>
</table>

<sup>b</sup>Determined by polarimeter.

DISCUSSIONS

1. Why we used Zn(HMDS)₂ as a catalyst for this asymmetric reaction?

Zn(HMDS)₂ can be considered as Metal Amide catalyst:

**Figure 3. Structure of Zn(HMDS)₂**

As the role of each part:

**Metal part:** Lewis acidity

- Chiral Auxiliary with Ligands

**Amide part:** Bronsted Basicity

- Steric and Electronic Tunability

2. Mechanism/Pathway I

2.1. Transmetallation and isomerization

**Scheme 4.** Transmetallation from allenylboronate to zinc amide

After the transmetallation, the isomerization of propargyl zinc amide into allenyl zinc amide complex occurred. Due to the stabilized energy, the forward direction is more favourable:

**Scheme 5.** Isomerization from propargyl zinc amide to allenyl zinc amide

2.2. Allyl-zinc amide complex reacts with ketone

Propargyl and allenyl zinc amide (16), (18) act as nucleophiles react with ketones to generate alkoxy zinc amide (17) and (19) via Zimmerman-Traxler transition state in pericyclic process<sup>53</sup>.

**Scheme 6.** Nucleophilic propargyl and allenyl zinc amide react with electrophilic ketones

Both propargyl zinc amide and allenyl zinc amide then can act as nucleophiles to react with acetophenone electrophile to generate allenyl alcohol and propargyl alcohol respectively. And the final products:

**Scheme 7.** The exchange of alkoxy zinc amides (20), (23) with boron amide (21) to give the final products (22) and (24)

2.3. Using ligands

For the asymmetric synthesis of propargyl alcohol, zinc may chelate with chiral ligands to produce chiral catalysts as shown below:

**Figure 4.** The chelating between chiral ligands with zinc ion

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They can be denoted as:

(Chiral zinc complexes)

3. Notes on other plausible mechanisms

Yi Cui et al. (2013) showed three another plausible pathways of producing propargyl and allenyl alcohol but the experiments and some explanations proved that they were not the major pathways in the reaction.

Scheme 8. The possible pathway II

The kinetic reasons are major factors to the non-tendency of this pathway to occur. The reaction between propargyl zinc amide and allenyl zinc amide occurred very fast and the rare chance of producing diallyl zinc (25) as in this mechanism.

Scheme 9: Possible pathway III

The catalytic pathway I, IV is more favored than pathways II and III as consistent in the mechanistic experiments to generate a key intermediate as nuleophilic allenyl zinc amide complex. However, the pathway IV is only different from the first mechanism that was shown in the previous part, on the final stage whether allenylboronate (3) or boron amide (21) would attack to the propargyl/allenyl zinc amide to give the final products. It seems more possibility and tendency to introduced mechanism I because the amide group in boron amide (21) is a better leaving group than the allenyl group in allenylboronates (3).

Therefore, the most consistent pathway is pathway I.

4. Additional factors and methods to enhance the yield, chemoselectivity and enantioselectivity

4.1. Control propargyl/allenyl alcohol ratio

We found that the reaction conditions such as temperature, solvents or other factors could remarkably impact the reaction outcomes.

4.1.1. Temperature

When changing the temperature of the reaction, the ratio of propargyl and allenyl alcohol also significantly changed.

We have found out that when the temperature was increased reasonably to around room temperature, the fraction of propargyl alcohol was also increased. As usual, we carried out the reaction at a mild condition (room temperature) to reduce the costs of the reaction.
However, when the temperature increased from room temperature to higher (40°C, for instance), the yield of reaction was reduced.

The explanation for that phenomenon is the higher temperature stabilizes the allenyl zinc amide complex in the isomerization equilibrium to transform into the propargyl alcohol.

4.1.2. Steric factors of alcohols

The different alcohols: pinacol, 2,2-dimethyl-1,3- propanol, ethylene glycol and 1,3-propanol were used to generate allylboronate (18), (19), (20) and (21). Due to the transmetallation of allylboronate with zinc amide to form transition state, this complex is stabilized by minimizing the steric hindrance, the different alcohols formed different chemoselectivities and enantioselectivities.

Figure 5. Structures of corresponding boronates with different alcohols

It's also to be found that allenylboronic acid 2,2-dimethyl-1,3-propanediol (19) ester gave better activity than pinacol allylboronate (6) and the yield of these alcohols were used in this reaction is based on the reaction outcomes, the proposed reason for the result is the higher steric strains and more hindrance in the more bulky and branched alcohol affected the slower rate and suppressed the exchange of boronate to zinc in the transmetallation.

Table 3. Steric effect of alcohols on propargylation and allenylation of acetophenone using zinc catalyst (Solvent: THF). Previous work⁽⁴⁾

<table>
<thead>
<tr>
<th>Temperature(°C)</th>
<th>Boronate</th>
<th>Time</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
<td>18</td>
<td>72h</td>
<td>95</td>
</tr>
<tr>
<td>20</td>
<td>19</td>
<td>110min</td>
<td>98</td>
</tr>
<tr>
<td>20</td>
<td>20</td>
<td>20min</td>
<td>&gt;99</td>
</tr>
<tr>
<td>20</td>
<td>21</td>
<td>10min</td>
<td>&gt;99</td>
</tr>
</tbody>
</table>

4.1.3. Solvents

As the previous research⁽⁴⁾ in the effect of solvents to the yields of the propargylation.

Table 4. Solvents effect on propargylation and allenylation of acetophenone using Zn(HMDS)₂

<table>
<thead>
<tr>
<th>Solvents</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>THF</td>
<td>80</td>
</tr>
<tr>
<td>Pentane</td>
<td>85</td>
</tr>
<tr>
<td>Toluene</td>
<td>53</td>
</tr>
</tbody>
</table>

Determined by ¹H NMR spectroscopy.

4.1.4. "Slow addition" method

The "Slow addition" method was used a device to transfer ketones slowly at a specific rate to the reaction system containing allylboronate and zinc amide.

The reason for this method is the equilibrium of the isomerization from propargyl zinc to allenyl zinc amide:

Scheme 11. Isomerization of propargyl zinc to allenyl zinc amide

If acetophenone is added immediately after the transfer of allylboronates to zinc amide, it would definitely react with propargyl zinc amide to form allenyl alcohol. Therefore, if we keep the concentration of ketones small enough, the concentration of the desired will be enhanced.

4.1.5. Transmetallation control???

The major stage to control the ratio of propargyl and allenyl alcohol is the transmetallation because this step is equilibrium and moreover, this step is the rate-determining step. By changing the conditions to shifting the equilibrium to forward or backward is the best way to generate propargyl or allenyl zinc amide and produce the desired products of propargyl or allenyl alcohol.

4.2. Enantioselectivity

By the investigation of different ligands were shown in figure 1, scheme. 3 and result of measuring enantiomeric excess (ee) from table 3, we could see that the best ligand among them is diamine ligand by comparing the chemo and...
enantioselectivity between them.

CONCLUSIONS

As I have shown here the effective method to synthesize highly biological active compounds with wide application in the organic synthesis by using reactive allyboronic acid 2,2-dimethyl-1,3-pronanediol ester and more economical zinc catalyst with chiral ligands.

Based on the smooth and clear exchange transmetallation of zinc amide with allenylboronates, the de-sired propargyl alcohol was archived with high yield and high ee. The results might help us to further understanding of organometallic catalysts for the selective organic synthesis with high yield.

Further researches are now in progress to discover and explore more about the asymmetric catalysts as perfectly wonderful tools to control the selectivity of products with higher biological activities with more potential applications to the real life.

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ABBREVIATIONS

1. TLC: thin layer chromatography
2. THF: Tetrahydrofuran
3. HMDS: Hexamethyldisilane
4. BOX: Bis-oxazolines
5. pyBOX: pyridine bis-oxazolines
6. BINAP: 2,2’-bis(diphenylphosphino)-1,1’-binaphthyl
7. TMS: trimethyldisilyl

REFERENCES


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