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学位論文題目 ホウ素触媒による有機分子変換反応の開発

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論文内容の要旨  
Summary of thesis contents

Catalytic hydrogenation of unsaturated compounds, such as alkenes, alkynes, aldehydes, ketones, and imines is one of the important reactions in the organic synthesis. Conventionally, transition metals such as Ni, Pd, Pt, Ru, and Rh have been used as catalysts for the hydrogenation. However, concomitant derived from transition metals in the resulting products is problematic for the synthesis of pharmaceuticals, agrochemicals, and fine chemicals. In order to overcome this problem, the development of a metal-free organocatalytic hydrogenation is highly desirable. Recently, frustrated Lewis pairs (FLPs) generated from boron reagents have appeared as efficient catalysts for the hydrogenation of imines, enamines, silyl enol ethers, and so on. However, the catalytic systems for hydrogenation of carbonyl compounds are still limited. In this thesis, the author developed the borane-catalyzed efficient hydrogenation of carbonyl compounds.

This thesis is composed of general introduction, chapters 1 and 2, and general conclusion. In the general introduction, the author describes the background about the catalytic hydrogenation reaction. In chapter 1, the author describes the borane-catalyzed hydrogenation of carbonyl compounds with the Hantzsch ester. In chapter 2, the mechanistic studies for the borane-catalyzed hydrogenation of aldehydes are describe. Finally, the author describes the general conclusion of this thesis.

### Chapter 1.

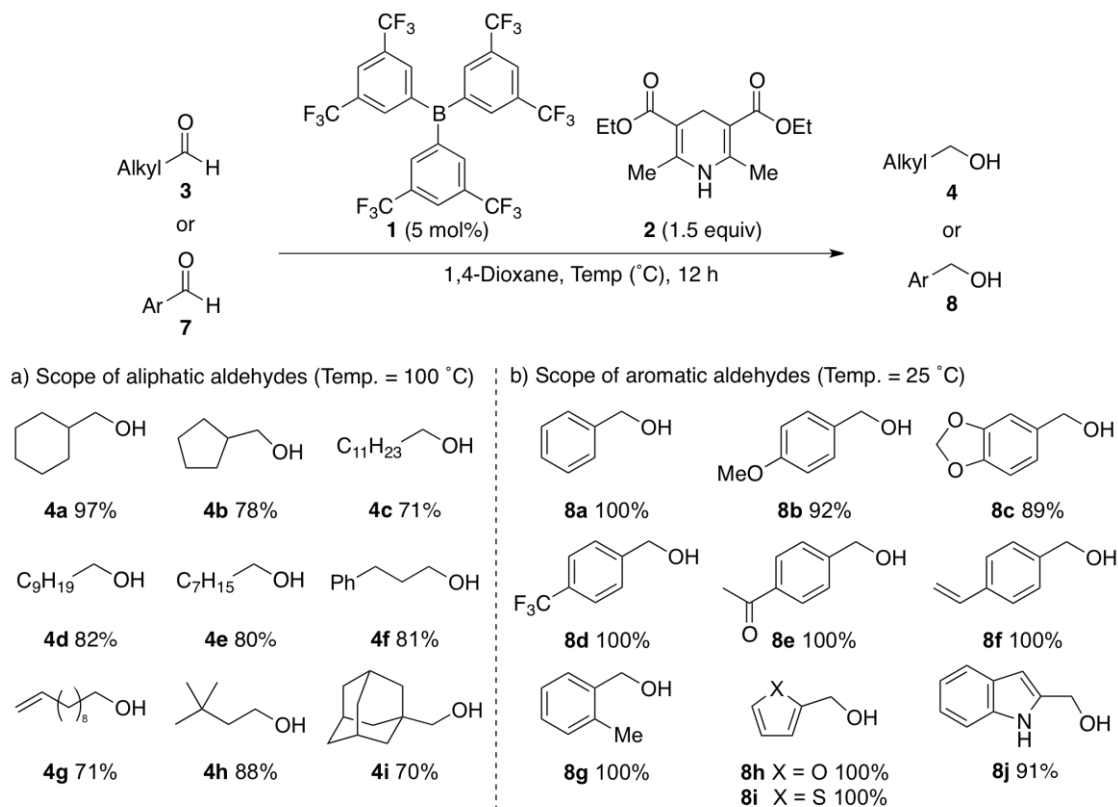
The author developed the hydrogenation of carbonyl compounds with hydrogen donors in the presence of borane catalysts. The author examined several borane catalysts and hydrogen donors for the hydrogenation of cyclohexanecarbaldehyde **3a** (Table 1). The hydrogenation of **3a** with the Hantzsch ester **2** took place in the presence of 5 mol% tris[3,5-bis(trifluoromethyl)phenyl]borane **1** in toluene at 60 °C for 12 h to give cyclohexanemethanol **4a** in 70% yield (entry 1). Under similar conditions, the reaction with B(C<sub>6</sub>F<sub>5</sub>)<sub>3</sub> and BF<sub>3</sub>•OEt<sub>2</sub> afforded **4a** in 28 and 2% yield, respectively (entries 2 and 3). No catalytic activity was observed in the hydrogenation reaction with BPh<sub>3</sub> (entry 4). The other hydrogen donors were also tested for the reaction in the presence of borane **1** as the catalyst (entry 5-8). *N*-Benzyl-1,4-dihydronicotinamide **5** was not a suitable hydrogen donor in this reaction (entry 5). The use of 5,6-dihydrophenanthridine **6** and 2-propanol led to low yield (entries 6 and 7). No desired alcohol **4a** was obtained in the reaction of **3a** with formic acid (entry 8). When the reaction was performed in 1,4-dioxane at 60 °C, desired alcohol **4a** was obtained in 78% yield (entry 9). Finally, efficient hydrogenation of cyclohexanecarbaldehyde **3a** was achieved by raising the reaction temperature to 100 °C (97% yield, entry 10).

(別紙様式 2)  
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**Table 1.** Hydrogenation of cyclohexanecarbaldehyde **3a**

Entry	Cat.	Hydrogen donors	Solvent	Temp. (°C)	Yield (%)
1	<b>1</b>	<b>2</b>	Toluene	60	70
2	B(C <sub>6</sub> F <sub>5</sub> ) <sub>3</sub>	<b>2</b>	Toluene	60	28
3	BF <sub>3</sub> ·OEt <sub>2</sub>	<b>2</b>	Toluene	60	2
4	BPh <sub>3</sub>	<b>2</b>	Toluene	60	0
5	<b>1</b>	<b>5</b>	Toluene	60	0
6	<b>1</b>	<b>6</b>	Toluene	60	13
7	<b>1</b>	<i>i</i> PrOH	Toluene	60	12
8	<b>1</b>	HCO <sub>2</sub> H	Toluene	60	0
9	<b>1</b>	<b>2</b>	1,4-Dioxane	60	78
10	<b>1</b>	<b>2</b>	1,4-Dioxane	100	97

To demonstrate the extent of substrate tolerance in this reaction system, various aldehydes were used for the hydrogenation reaction (Scheme 1a and 1b). Aliphatic aldehydes **3b-f** bearing cyclopentyl and linear alkyl groups underwent hydrogenation at 100 °C to afford the corresponding alcohols **4b-f** in 71-81% yield. Hydrogenation of 10-undecenal (**3g**) took place at the formyl unit with the olefinic group intact to give **4g** in 71% yield.

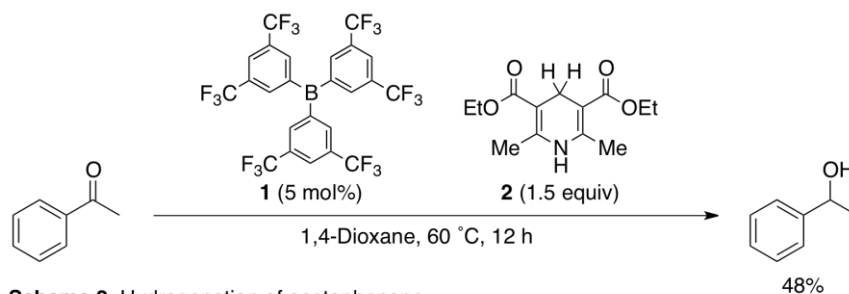


**Scheme 1.** Borane-catalyzed hydrogenation of aldehydes with the Hantzsch ester.

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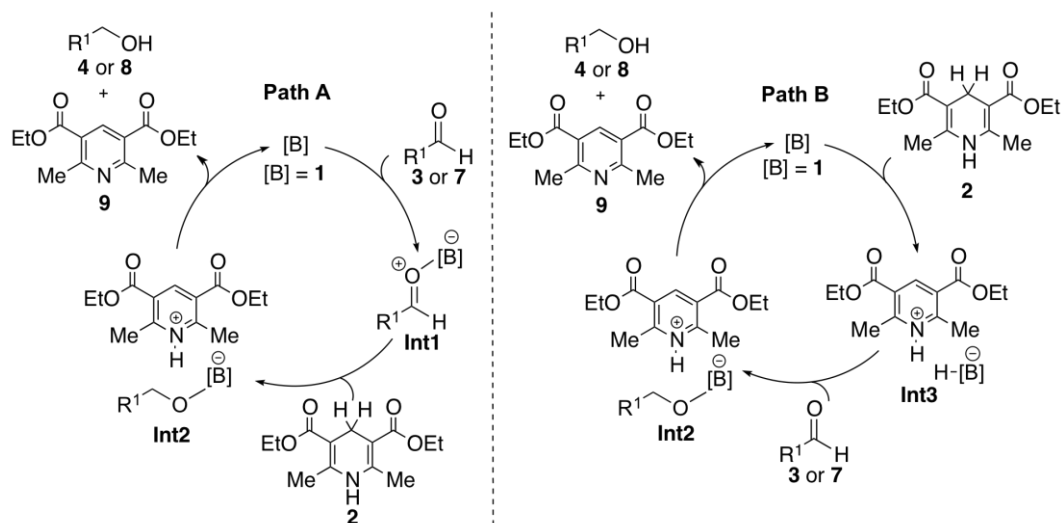
Sterically hindered aldehydes **3h** and **3i** were subjected to the reaction to afford **4h** and **4i** in 88% and 70% yield, respectively. The reaction of aromatic aldehydes **7a-d** bearing electron-donating and -withdrawing substituents on their aromatic rings was carried out at lower reaction temperature (25 °C) to give the corresponding alcohols **8a-d** in good yield. Hydrogenation of aldehydes having acetyl and alkenyl groups took place at their formyl unit with the functional groups intact to give alcohols **8e** and **8f** in quantitative yield. Ortho-tolylaldehyde (**7g**) was subjected to the hydrogenation to give alcohol **8g** in quantitatively. Aldehydes bearing 2-furyl, 2-thienyl, and 2-indolyl groups also underwent the reaction to afford the desired alcohols **8h**, **8i**, and **8j** in 100%, 100%, and 91% yield, respectively.

The hydrogenation of acetophenone with the Hantzsch ester **2** also proceeded in the presence of borane **1** at 60 °C for 12 h to give 1-phenylethanol in 48% yield (Scheme 2).



## Chapter 2.

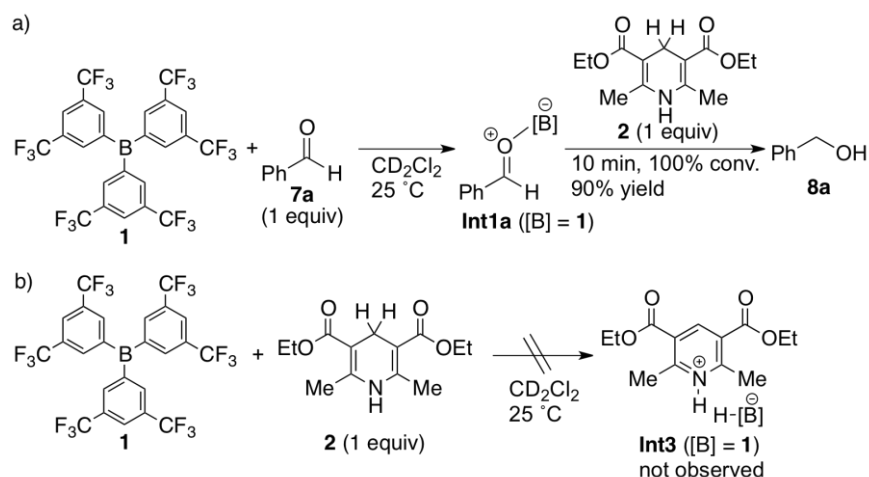
In this chapter, the author studied the reaction pathways of the borane-catalyzed hydrogenation reaction. Possible two reaction pathways of the borane-catalyzed hydrogenation of aldehydes with the Hantzsch ester **2** are shown in Scheme 3. In path A, the author assumes that the coordination of the carbonyl group of **3** and **7** to borane **1** produces the zwitterionic intermediate **Int1**. Subsequent hydrogen transfer from the Hantzsch ester **2** yields the pyridinium alkoxyborate salt **Int2**, which undergoes proton transfer to regenerate borane **1** along with the



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formation of alcohols **4** and **8**, and the Hantzsch pyridine **9**. On the other hand, in path B, hydrogen transfer from the Hantzsch ester **2** to the boron center of **1** would initially take place to afford the pyridinium hydridoborate salt **Int3**. The reaction of **Int3** with aldehydes **3** and **7** followed by proton transfer of **Int2** gives alcohols **4** and **8**, the Hantzsch pyridine **9**, and borane catalyst **1**.

To obtain a mechanistic understanding of the hydrogenation reaction, the author examined the stoichiometric reactions as shown in Scheme 4. The reaction of borane **1** with a stoichiometric amount of benzaldehyde **4a** was performed in CD<sub>2</sub>Cl<sub>2</sub> at 25 °C (Scheme 4a). <sup>1</sup>H, <sup>13</sup>C, and <sup>11</sup>B NMR spectroscopic studies of the reaction mixture showed the formation of **Int1a**. The reaction of **Int1a** with the Hantzsch ester **2** gave benzyl alcohol **6a** in 90% NMR yield. In contrast, the reaction of borane **1** with a stoichiometric amount of the Hantzsch ester **2** resulted in no **Int3** formation under similar conditions (Scheme 4b). These results supported that the reaction proceeds through the path A.



**Scheme 4.** a) Stoichiometric reaction of borane **1** with benzaldehyde **7a**. b) Stoichiometric reaction of borane **1** with the Hantzsch ester **2**.

Next, the author investigated the hydrogenation of **7a** catalyzed by borane **1**, B(C<sub>6</sub>F<sub>5</sub>)<sub>3</sub>, BF<sub>3</sub>, and BPh<sub>3</sub> using the DFT method. The author initially examined the hydrogenation reaction catalyzed by borane **1**, assuming that the Lewis acid activates the carbonyl group of **7a**. The relative energy diagram is shown in Figure 1. The Lewis acid was attached to the carbonyl oxygen atom of **7a**. The energy of **Int1a** is lower than that of the dissociated state of the three species (**1+7a+2**), by 7.8 kcal/mol (Red line). The attack of the Hantzsch ester **2** to the C=O bond in **Int1a** gives the pyridinium alkoxyborate **Int2a** via **TSa**. The activation energy of **TSa** is calculated to be 11.8 kcal/mol. The pyridinium alkoxyborate **Int2a** easily dissociates to give the product **8a**, the Hantzsch pyridine **9**, and borane **1**. To see the reasons why the catalytic activity of borane **1** was higher than that of the other borane catalysts, the author next studied the reaction in the presence of B(C<sub>6</sub>F<sub>5</sub>)<sub>3</sub>, BF<sub>3</sub>, and BPh<sub>3</sub> in place of borane **1**. The activation energy of **TSb** in the reaction catalyzed by B(C<sub>6</sub>F<sub>5</sub>)<sub>3</sub> is calculated to be 15.7 kcal/mol, which is higher than that of **TSa** (Blue line). On the other hand, the activation energy of **TSc** in the reaction

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catalyzed by  $\text{BF}_3$  is calculated to be 10.2 kcal/mol, being lower than that of **TSa** (Green line). However, the state ( $\text{BF}_3 + \mathbf{8a} + \mathbf{9}$ ) is high in energy, 34.8 kcal/mol, relative to **Int2c**. Thus, the final step is unlikely in the  $\text{BF}_3$ -catalyzed reactions. In the presence of  $\text{BPh}_3$ , the activation energy of **TSd** is calculated to be 21.6 kcal/mol (Black line), which is much higher than that of **TSa**, **TSb**, and **TSc**. These results suggest that the catalytic activity of tris[3,5-bis(trifluoromethyl)phenyl]borane **1** is higher than that of the other borane catalysts such as  $\text{B}(\text{C}_6\text{F}_5)_3$ ,  $\text{BF}_3$ , and  $\text{BPh}_3$ .

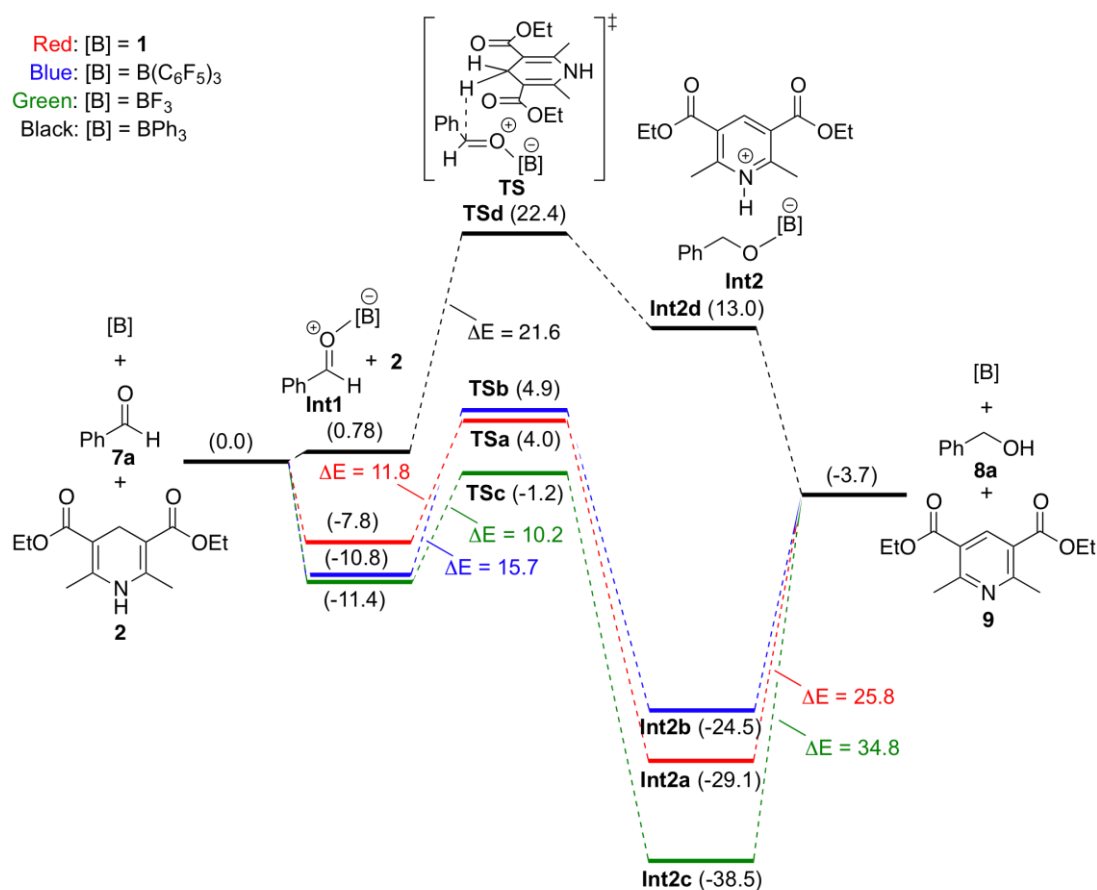


Figure 1. Energy diagram at the B3LYP/6-31G(d,p) level of theory (kcal/mol).

In conclusion, the author has developed tris[3,5-bis(trifluoromethyl)phenyl]borane-catalyzed hydrogenation of aldehydes with the Hantzsch ester **2** as the hydrogen donor. The catalyst efficiently promoted the hydrogenation of a variety of aromatic and aliphatic aldehydes. The experimental results and the calculations showed that the reaction proceeds through the activation of carbonyl groups of aldehydes with borane **1** followed by hydrogen transfer from the Hantzsch ester **2** to the boron center of **1**. The calculations also suggest that the catalytic activity of tris[3,5-bis(trifluoromethyl)phenyl]borane **1** is higher than that of the other borane catalysts such as  $\text{B}(\text{C}_6\text{F}_5)_3$ ,  $\text{BF}_3$ , and  $\text{BPh}_3$ .

(別紙様式 3)  
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### 博士論文の審査結果の要旨

#### Summary of the results of the doctoral thesis screening

水素化反応工程は有機合成プロセスにおいて基本的かつ重要な反応のひとつである。従来の触媒的水素化反応では遷移金属触媒が用いられてきた。しかしながら、本反応工程は原理的に反応生成物中への金属の残留が問題となる。本論文では、上記の問題を根幹から解決することを目的に、金属を用いない有機分子触媒を用いたカルボニル化合物の水素化反応工程開発の検討を行っている。申請者は、有機分子触媒として最近注目されている有機ホウ素化合物、そして、水素供与体としてNADH類縁体に着目し、水素化反応工程の開発を行うとともに、反応の詳細を実験化学的手法と計算科学的手法を用い明らかとしている。

本論文は序論、本論、結語から構成され、本論は2章から成っている。

序論では、従来の金属触媒を用いた水素化工程の問題点として金属の生成物中への混入を指摘し、その解決法としての有機分子触媒を用いた水素化反応の先例、本論文で開発する反応システムへの着想へと至る背景がまとめられている。

第1章では、有機ホウ素化合物を触媒として用いたカルボニル化合物の水素化反応が述べられている。各種ホウ素化合物、水素供与体等のスクリーニングを実施し、最適条件を探索した結果、触媒として電子不足な有機ホウ素化合物、水素供与体としてHantzschエステルを用いることで脂肪族アルデヒドの水素化が100℃にて進行することを見出している。本反応システムは芳香族アルデヒドに対しても有効であり、室温という穏和な条件下で水素化反応を触媒し、対応するアルコールを高収率で得ている。また、同一分子上還元される官能基(ビニル基、アセチル基など)が存在した場合も、アルデヒドのみが選択的に水素化されており、高い化学選択性を示した。また、本触媒系を他のカルボニル化合物への水素化反応へと適用している。

第2章では、第1章で実現した有機ホウ素化合物とHantzschエステルを用いたアルデヒドの水素化反応の反応機構について、実験化学的・計算化学的手法により解析し、議論している。化学両論量のホウ素化合物を用いた実験の結果から、本反応はホウ素触媒によるアルデヒドの活性化ののち、Hantzschエステルからの水素移動が起こるものと推定している。推定した反応機構の詳細を、計算化学的手法により解析している。遷移状態計算の結果から、本反応が電子不足な有機ホウ素化合物による活性化されたアルデヒドに対して、Hantzschエステルからの水素移動により進行することを明快に示している。また、第1章においてスクリーニングした一連の有機ホウ素触媒について同様の計算を行い、触媒活性の違いについて詳細に考察している。その考察は実験結果をよく説明するものである。

結論では、論文全体を総括している。

以上の結果は、有機分子触媒による水素化反応の新たな局面を切り拓くものであり、当該分野の研究の発展に大きく寄与すると期待される。また、本論文の一部は、既に査読付きの国際的学術誌一報として公表されており、語学力も十分なレベルにあると判断される。以上より、本論文は博士(理学)の学位授与に値すると審査員全員一致で判断した。