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学 位 論 文 題 目	Brønsted Acid-initiated Formal [1,3]-Rearrangement Reaction of β-Substituted Ene-Aldimines
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(Form 3)

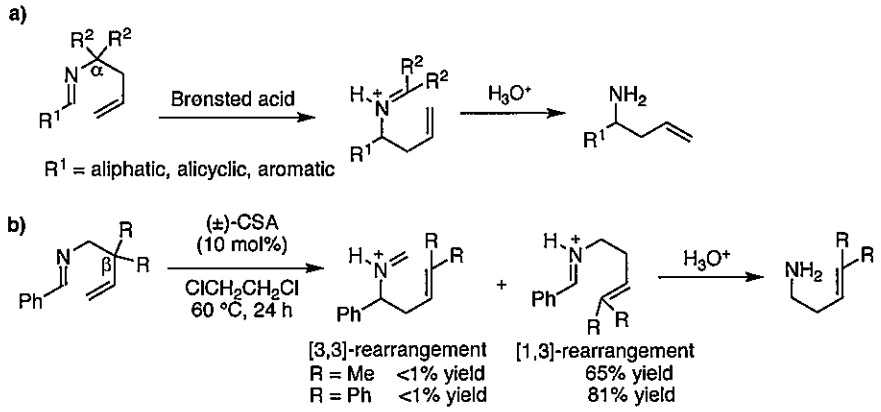
Summary of Doctoral Thesis

Chanantida JONGWOHAN

Title Brønsted Acid-initiated Formal [1,3]-Rearrangement Reaction of β-Substituted Ene-Aldimines

Homoallylic amines are one of the most important intermediates for many useful compounds because carbon-carbon double bond moiety is readily converted to a variety of functional groups. Allylation reaction of imines and rearrangement reaction of ene-imines have been developed for the syntheses of regio- and stereoselective homoallylic amines. Although these reactions show excellent level of selectivities, it has some practical limitations to synthesize 2,4,4-substituted homoallylic amino compounds. Therefore, this study for doctoral thesis is aimed to develop a new method to synthesize 2,4,4-substituted homoallylic amines and their derivatives.

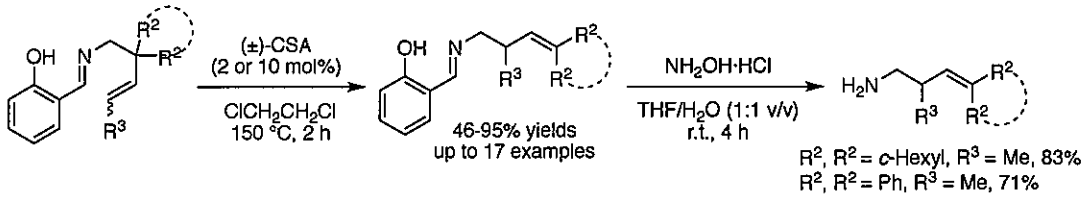
In chapter 1, importance and synthetic methodology of homoallylic amines, our discovery for formal [1,3]-rearrangement of ene-imines, and scope of this thesis are summarized as general introduction. In particular, design concept of ene-imine substrates is exemplified based on literature reviews. Then, the initial discovery of the formal [1,3]-rearrangement is clearly demonstrated. Importantly, it was found that the reaction did not provide [3,3]-rearrangement products; only [1,3]-rearrangement products were obtained (Scheme 1). These initial results were in contrast to previous reports; therefore, study of my thesis is focused on the development of formal [1,3]-rearrangement using ene-aldimines and application to 2,4,4-homoallylic amine synthesis: optimizing reaction condition, achieving broad substrate scope, demonstrating utilities, and exploring mechanism.



Scheme 1. Rearrangement reaction of ene-imines. (a) General design in previous reports; (b) our design of β-substituted ene-aldimine substrate and our discovery of

formal [1,3]-rearrangement

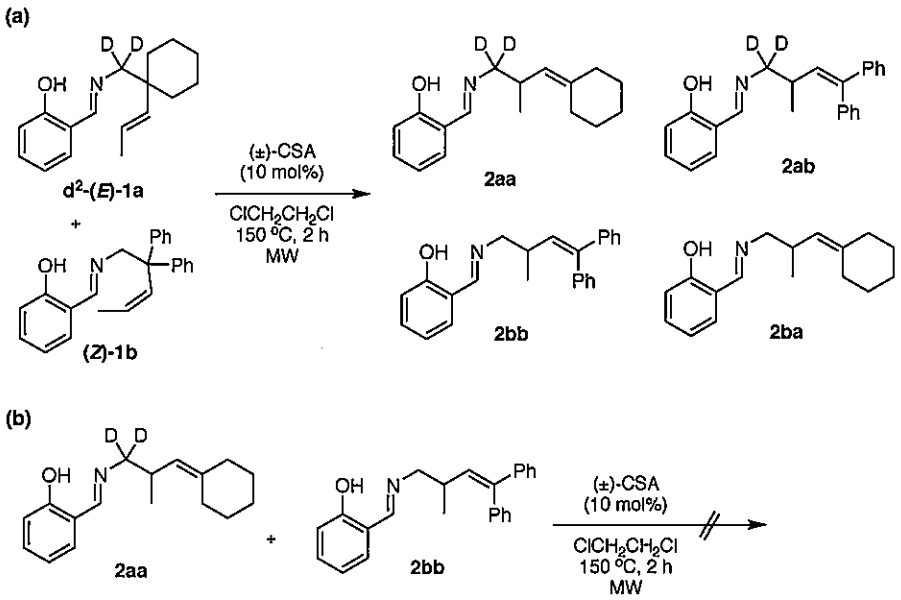
In chapter 2, experimental results for reaction developments are summarized (Scheme 2). The investigation of electronic effects on aryl group, solvent effects, Brønsted acid, and reaction temperature were carried out in this study. Brønsted acids, such as trifluoro acetic acid (TFA), phosphoric acid diphenyl ester, and (±)-10-camphorsulfonic acid (CSA) efficiently promoted the reaction in acetonitrile (MeCN) and 1,2-dichloroethane (DCE) as solvents under normal or microwave heating method. Importantly, 1 mol% catalyst loading was realized when microwave heating method was used. After optimizing the formal [1,3]-rearrangement reaction, scope of substrates was evaluated. It was demonstrated that a variety of substituents on ene-aldimine substrates were tolerated and gave corresponding rearrangement products in good to excellent yields. To establish the utilities of this rearrangement reaction, ene-imine products were subjected into hydrolysis condition to afford 2,4,4-substituted homoallylic amines. Furthermore, the obtained 2,4,4-homoallylic amines were used for the synthesis of a spiro compound and a β-amino acid precursor. Details on reaction optimization, substrate scope, and derivatization will be described in chapter 2.



Scheme 2. Development of formal [1,3]-rearrangement of β-substituted ene-aldimines to synthesize 2,4,4-substituted homoallylic amines

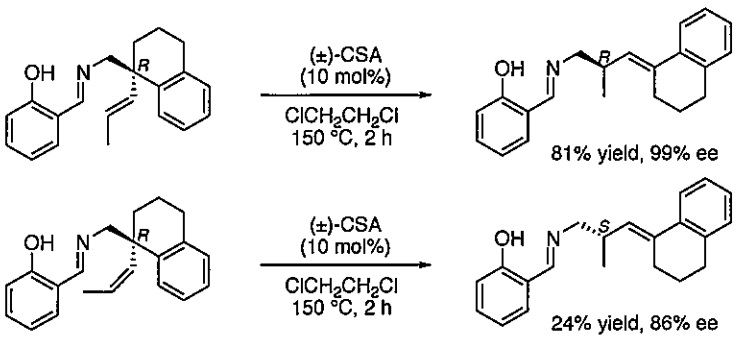
In chapter 3, experimental results for the mechanistic studies are summarized. Furthermore, details of reaction mechanism are proposed and discussed based on experimental and computational studies. This rearrangement reaction has not been reported so far, and the reaction mechanism has been unclear. Therefore, the studies were conducted to clarify the mechanism of this formal [1,3]-rearrangement. To think about the reaction pathway: either intra- or intermolecular, crossover experiments of substrates were initially examined. It was revealed that two normal- and two crossover rearrangement products were observed in a ratio of *ca.* 1:1:1:1 (Scheme 3). When the two normal rearrangement products were subjected in the presence of (±)-CSA under the heating condition, the reaction did not give the crossover products. These results suggest that C(α)–C(β) cleavage occurs during the irreversible rearrangement process, in other words, C(α)–C(β) cleavage does not proceed after the product formation. Therefore, intermolecular pathway is proposed for this formal [1,3]-rearrangement reaction. To propose details of reaction mechanism, collaborative study was carried out

with Dr. Honda in HPC SYSTEMS and Dr. Suzuki in IMS, where enormous DFT calculations were conducted. Detailed reaction mechanism, chain reaction mechanism of 2-azaallenium cation as a chain carrier, was proposed based on DFT calculations. Further discussions for the chain reaction mechanism is also summarized in chapter 3.



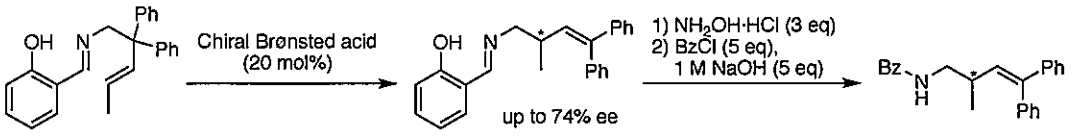
Scheme 3. Crossover experiments of (a) substrates, and (b) products

In chapter 4, studies on asymmetric formal [1,3]-rearrangement of chiral ene-aldimine substrates is summarized. According to the one of proposed mechanism in propagation step, asymmetric formal [1,3]-rearrangement of chiral ene-aldimine substrates may proceed with highly chirality transfer ratio. Furthermore, as far as we know, highly asymmetric formal [1,3]-rearrangements of ene-aldimines have not been reported. Therefore, this study gives not only a great insight into the reaction mechanism of propagation step but also opens the new entry for asymmetric rearrangement reaction of ene-imines. On the basis of the results in chapter 2, tetrahydronaphthalene was chosen as substituent on chiral substrate, and this chiral substrate was synthesized from commercially available 1-cyano-1,2,3,4-tetrahydronaphthalene. The chirality transfer experiments clearly showed that chirality at 2-position was transferred, and good to excellent enantioselectivities were obtained in the cases of both *E*- and *Z*-olefin substrates (Scheme 4). Absolute configurations of the ene-imine substrates and products were determined by single crystal X-ray diffraction analysis, derivatization, and crystal sponge method. These results supported the reaction pathway that begins with C–N bond formation in the propagation step. Moreover, DFT calculation by Dr. Suzuki showed good agreement with the experimental results of stereochemistries.



Scheme 4. Asymmetric formal [1,3]-rearrangement of chiral ene-imines with tetrahydronaphthalene unit at the β-position

In chapter 5, examinations of catalytic asymmetric formal [1,3]-rearrangement are described. During the study on chapter 2, 3, and 4, development of the formal [1,3]-rearrangement was realized in the presence of racemic Brønsted acid such as (±)-CSA. It is no doubt that catalytic asymmetric version of this reaction by chiral catalyst is ultimately challenging during the course of this study. According to the plausible mechanism in chapter 4, a well-designed chiral counter anion as chiral catalysts may give the asymmetric induction. At this point, chiral Brønsted acids were selected as one of candidates for this study. It was found that although (+)-CSA did not give any asymmetric induction at all, chiral phosphoric acid with substituents at the 3,3'-position provided good enantioselectivities of the ene-imine products (Scheme 5). Detailed studies on catalyst substituents, optimized reaction condition, and mechanistic consideration of interaction mode will be summarized in chapter 5.



Scheme 5. Enantioselective formal [1,3]-rearrangement of ene-imine promoted by chiral Brønsted acid

In chapter 6, studies for this thesis are summarized, and perspective of the formal [1,3]-rearrangement of ene-aldimines is described.

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(様式8・別紙)

Results of the doctoral thesis screening

博士論文審査結果

Name in Full
氏　　名　Chanantida JONGWOHAN

Title
論文題目　Brønsted Acid-initiated Formal [1,3]-Rearrangement Reaction of β-Substituted Ene-Aldimines

ホモアリルアミンは、生理活性物質や医薬品合成において重要な中間体である。位置選択的な置換型ホモアリルアミン合成反応の開発は、複雑な含窒素化合物の合成を可能にすることから、近年、特に注目が集まっている。既存のホモアリルアミン合成反応は、１位の一置換もしくは１位および２位の二置換のホモアリルアミンを供給できるものの、それら以外の置換様式を達成する有力な方法論には至っていない。

出願者は、既存の方法論では合成困難であった三置換ホモアリルアミンを標的分子とし、独自に見出された形式的［1, 3］-転位反応を用いて、2, 4, 4-置換型ホモアリルアミンの位置選択的かつ効率的な合成に成功した。また、有機化学実験の結果にもとづいて反応機構を提案し、共同研究者によるDFT計算の結果も踏まえ、形式的［1, 3］-転位反応の反応機構を提示した。さらに、提示した反応機構を精査し、触媒量のキラル有機分子を開始剤として用い、世界に先駆けて形式的［1, 3］-転位反応の不斉触媒化に成功した。

本学位論文は、第一章を序論、第二章から第五章を本論、第六章を結論とする全六章から構成されている。

第一章では、ホモアリルアミン化合物の有用性を踏まえ従来の合成法の適用範囲や問題点を示し、続いて、形式的［1, 3］-転位反応の発見に至る経緯と本研究の内容が簡潔にまとめられている。

第二章では、ブレンステッド酸触媒によるエン-アルジミンの形式的［1, 3］-転位反応の検討について、詳細が述べられている。出願者は、本転位反応が、2, 4, 4-置換型ホモアリルアミン合成に応用可能であることを見出した。高価な金属触媒を用いることなく、市販で入手容易な触媒量のブレンステッド酸が、形式的［1, 3］-転位反応を効率的に促進し、目的とする2, 4, 4-置換転位体が良好な収率で得られることを明らかにした。さらに、得られた転位体を種々の含窒素化合物に変換し、本反応の有用性を示した。

第三章では、形式的［1, 3］-転位反応の反応機構解明に関する実験と反応機構の提案について記述している。出願者は、交差実験の結果から、本反応が2-アザアレニウムを媒体とする分子間反応により進行していると考察した。さらに、共同研究者によるDFT計算の結果も踏まえ、本転位反応の詳細な反応機構を提示した。

第四章では、出願者が開発した形式的［1, 3］-転位の不斉反応について記述している。出願者は、1, 2, 3, 4-テトラヒドロナフチル基を有する光学的に純粋な反応基質を設計・合成し、不斉形式的［1, 3］-転位反応が、良好な不斉転写率で進行することを明らかにした。

得られた転位生成物の絶対立体配置をもとに、本反応が良好な不斉転写率で進行する要因を考察した。

第五章では、キラルブレンステッド酸を用いた触媒的不斉形式的［1, 3］-転位反応について記述している。出願者は、種々のキラルブレンステッド酸を検討し、ビナフチルリン酸存在下で本反応を行うと、良好なエナンチオ選択性が得られることを突き止めた。本成果は、エン-アルジミンを用いる触媒的不斉［1, 3］-転位反応の世界初の成功例である。

第六章では、本学位論文を総括し、本研究の展望を述べている。

以上のように、本学位論文では、従来困難であった置換型ホモアリルアミンの合成をめざして反応基質を設計し、形式的［1, 3］-転位反応による 2, 4, 4-置換ホモアリルアミン合成反応の開発に成功した。新規な結合形成位置の発見と転位反応の開拓を基盤に、従来にない置換様式のホモアリルアミン合成法を確立した。さらに、その反応機構を詳細に調べ、触媒的不斉反応にまで展開していることから、当該分野の研究の発展に大きく寄与するものと期待される。また、本論文の成果の一部は、既に一報の査読付き国際学術誌に発表されており、国際的にも高い水準の研究であると判定できる。

以上により、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。

（備考）

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