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科学研究費助成事業　　研究成果報告書

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研究課題名（和文）Rationally designed catalysis for the enantioselective activation of alkenes

研究課題名（英文）Rationally designed catalysis for the enantioselective activation of alkenes

研究代表者
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交付決定額（研究期間全体）：（直接経費）　　13,500,000円

研究成果の概要（和文）：We conducted a computational study of IDPi catalysis (JACS, 2021). We developed a semi-automated seamless platform spanning with a new descriptor, predicting new catalysts (ACIE, 2023). We established the protocol for quantitatively analyzing the pocket sizes of IDPi catalysts (Nature 2024).

研究成果の学術的意義や社会的意義
While traditional approaches to optimizing catalytic processes rely on inductive and qualitative assumptions drawn from screening data, our methods provide fast and robust predictions, enabling the optimization of various catalytic reactions beyond the screening data.

研究成果の概要（英文）：Building upon the original proposal, our focus lies in understanding the behavior of catalysts and constructing a framework for the development of desired alkene activation. In order to gain deeper insights into the behavior of catalysts, we conducted a computational study of IDPi-catalyzed Mukaiyama-aldol reaction (JACS, 2021). To achieve a more efficient working protocol, we have developed a semi-automated seamless platform spanning from screening to machine learning, which incorporates a newly-developed molecular fragment descriptor. This approach has enabled efficient and robust virtual screening. Using training data with moderate selectivities, we have designed and validated new catalysts demonstrating higher selectivities in a challenging asymmetric tetrahydropyran synthesis via enantioselective hydroalkoxylation (ACIE, 2023). We have also achieved to establish the protocol for quantitatively analyzing the pocket sizes of IDPi catalysts (Nature 2024).

研究分野：Asymmetric catalysis

キーワード：Organocatalysis　Machine learning　Computational chemistry　Asymmetric catalysis

1. 研究開始当初の背景

The applicants investigated the catalytic enantiocontrol of carbocations generated by the activation of alkenes. The key scientific question in this project was summarized as follows: How can we design and develop a general methodology to activate simple alkenes by generating carbocations, while controlling chemo- and enantio-selectivities of their transformations?

Olefins represent one of the most fundamental and ubiquitous classes of organic functionalities in chemical synthesis. The rudimentary nature and abundance of this moiety are owed to its ease of accessibility, as simple olefins are obtained in a single step from crude oil by steam cracking. Alkenes can also be chemically accessed from a variety of functional groups on both industrial and laboratory scales. Despite their simplicity, olefins are versatile intermediates with diverse synthetic applications, some of which have even been recognized with Nobel Prizes: olefin metathesis, the Heck reaction, Sharpless-Katsuki asymmetric epoxidation, Sharpless dihydroxylation, Ziegler-Natta polymerization, and Noyori asymmetric hydrogenation. Among the diverse uses of alkenes, electrophilic activations of olefins are among the most valuable and important transformations. Especially hydrofunctionalizations are prized due to their conceptual simplicity, perfect atom economy, and added value to the obtained products. Therefore, this type of transformation has been extensively studied, and a variety of such transformations, including asymmetric ones, have been developed in the last decades. These enantioselective variants were mainly investigated with transition metal catalysis in combination with chiral ligands, albeit with limited substrate classes. Recently, some asymmetric radical catalysis has also emerged to achieve hydrofunctionalizations, yielding complementary anti-Markovnikov products. However, targeted transformations in this project still remained in their infancy in terms of reactivity and selectivities.

2. 研究の目的

The purpose of this project was to develop a general methodology for enantioselective functionalizations of olefins using Brønsted or Lewis acid catalysis. Although asymmetric counteranion-directed catalysis (ACDC), conceptualized by our group, was predominantly utilized in combination with oxocarbenium or iminium cations, this proposal aimed to expand the ACDC concept towards an even more fundamental challenge of asymmetric catalysis: the enantio-induction of carbocations by chiral counteranions.

3. 研究の方法

To achieve these goals, catalysts with higher acidities and modifiable microenvironments were designed and synthesized. Additionally, a synthetic robot, theoretical calculations, and machine learning were employed to accelerate the screening process, resulting in a more efficient and rational design of asymmetric catalysis.

4. 研究成果

Building upon the original proposal, our focus lies in understanding the behavior of catalysts and constructing a framework for the development of desired alkene activation.

In order to gain deeper insights into the behavior of catalysts, particularly the effects of nitrogen substituents of IDPi catalysts, we chose the Mukaiyama-aldol reaction as an example. We conducted a computational study using the GRRM program to describe the observation of a peculiar switch in enantioselectivity depending on the nitrogen substituents. This research has been documented in the literature (J. Am. Chem. Soc. 2021, 143, 14475-14481).

To enhance the development of a more efficient working protocol, we have developed a semi-automated seamless platform spanning from screening to machine learning, which incorporates a newly-developed molecular fragment descriptor.
While traditional approaches to optimizing catalytic processes rely on inductive and qualitative assumptions drawn from screening data, recent advancements in machine learning models offer a more quantitative evaluation of experimental data. However, these models can be expensive due to the required quantum chemical calculations. To circumvent these costs, 2D descriptors such as fragment counts or binary fingerprints, which depict general structural features, could be utilized. Despite the accessibility and cost-effectiveness of binary fingerprint descriptors, their predictive performance has been limited.
To address this limitation, we have developed a machine learning model that utilizes fragment descriptors fine-tuned for asymmetric catalysis, representing cyclic or polyaromatic hydrocarbons. This approach has enabled efficient and robust virtual screening. Using training data with moderate selectivities, we have designed and validated new catalysts demonstrating higher selectivities in a challenging asymmetric

tetrahydropyran synthesis via enantioselective hydroalkoxylation. During this study, we utilized a robotic system to acquire training data with efficiency and precision. Further details of this work are available in our publication (Angew. Chem. Int. Ed. 2023, 62, e2022186).

We have also achieved to establish the protocol for quantitatively analyzing the pocket sizes of IDPi catalysts. Traditionally, heteroatoms or aromatic substructures in substrates and reagents have been necessary to facilitate effective interactions with chiral catalysts. While confined acids have recently emerged as powerful tools for homogeneous asymmetric catalysis, catalyzing asymmetric reactions with purely aliphatic hydrocarbons, both as substrates and products, has remained unachieved. We developed an IDPi-catalyzed asymmetric cationic shift of aliphatic alkenyl cycloalkanes to cycloalkenes with excellent regio- and enantioselectivity. During our investigation into such catalytic asymmetric cationic shifts of aliphatic hydrocarbons, we identified a potential correlation between the pocket size of the anion and stereoselectivities, albeit without quantitatively measuring each catalyst's pocket size. Building upon this observation, we employed the SambVca program to ascertain the Percent Buried Volume (%Vbur) of each anion, using a simplified substrate as a cation. As a result, we successfully validated the correlation between these two parameters. (*Nature* **2024**, *625*, 287–292).

５．主な発表論文等

〔雑誌論文〕　計6件（うち査読付論文　6件／うち国際共著　5件／うちオープンアクセス　2件）

１．著者名 Wakchaure Vijay N.、DeSnoo William、Laconsay Croix J.、Leutzsch Markus、Tsuji Nobuya、Tantillo Dean J.、List Benjamin	４．巻 625
２．論文標題 Catalytic asymmetric cationic shifts of aliphatic hydrocarbons	５．発行年 2024年
３．雑誌名 Nature	６．最初と最後の頁 287～292
掲載論文のDOI（デジタルオブジェクト識別子） 10.1038/s41586-023-06826-7	査読の有無 有
オープンアクセス オープンアクセスとしている（また、その予定である）	国際共著 該当する

１．著者名 Sidorov Pavel、Tsuji Nobuya	４．巻 30
２．論文標題 A Primer on 2D Descriptors in Selectivity Modeling for Asymmetric Catalysis	５．発行年 2023年
３．雑誌名 Chemistry -A European Journal	６．最初と最後の頁 e202302837
掲載論文のDOI（デジタルオブジェクト識別子） 10.1002/chem.202302837	査読の有無 有
オープンアクセス オープンアクセスではない、又はオープンアクセスが困難	国際共著 －

１．著者名 Tsuji Nobuya、Sidorov Pavel、Zhu Chendan、Nagata Yuuya、Gimadiev Timur、Varnek Alexandre、List Benjamin	４．巻 62
２．論文標題 Predicting Highly Enantioselective Catalysts Using Tunable Fragment Descriptors**	５．発行年 2023年
３．雑誌名 Angewandte Chemie International Edition	６．最初と最後の頁 e2022186
掲載論文のDOI（デジタルオブジェクト識別子） 10.1002/anie.202218659	査読の有無 有
オープンアクセス オープンアクセスとしている（また、その予定である）	国際共著 該当する

１．著者名 Zhou Hui、Properzi Roberta、Leutzsch Markus、Belanzoni Paola、Bistoni Giovanni、Tsuji Nobuya、Han Jung Tae、Zhu Chendan、List Benjamin	４．巻 145
２．論文標題 Organocatalytic DYKAT of Si-Stereogenic Silanes	５．発行年 2023年
３．雑誌名 Journal of the American Chemical Society	６．最初と最後の頁 4994～5000
掲載論文のDOI（デジタルオブジェクト識別子） 10.1021/jacs.3c00858	査読の有無 有
オープンアクセス オープンアクセスではない、又はオープンアクセスが困難	国際共著 該当する

1．著者名 Zhou Hui、Han Jung Tae、Noethling Nils、Lindner Monika M.、Jenniches Judith、Kuehn Clemens、Tsuji Nobuya、Zhang Li、List Benjamin	4．巻 144
2．論文標題 Organocatalytic Asymmetric Synthesis of Si-Stereogenic Silyl Ethers	5．発行年 2022年
3．雑誌名 Journal of the American Chemical Society	6．最初と最後の頁 10156～10161
掲載論文のDOI（デジタルオブジェクト識別子） 10.1021/jacs.2c04261	査読の有無 有
オープンアクセス オープンアクセスではない、又はオープンアクセスが困難	国際共著 該当する

1．著者名 Amatov Tynchtyk、Tsuji Nobuya、Maji Rajat、Schreyer Lucas、Zhou Hui、Leutzsch Markus、List Benjamin	4．巻 143
2．論文標題 Confinement-Controlled, Either syn- or anti-Selective Catalytic Asymmetric Mukaiyama Aldolizations of Propionaldehyde Enolsilanes	5．発行年 2021年
3．雑誌名 Journal of the American Chemical Society	6．最初と最後の頁 14475～14481
掲載論文のDOI（デジタルオブジェクト識別子） 10.1021/jacs.1c07447	査読の有無 有
オープンアクセス オープンアクセスではない、又はオープンアクセスが困難	国際共著 該当する

〔学会発表〕　計2件（うち招待講演　1件／うち国際学会　2件）

1．発表者名 Benjamin List
2．発表標題 Strong and Confined Acids: Universal Catalysts for Selective Synthesis?
3．学会等名 4th ICReDD International Symposium（国際学会）
4．発表年 2022年

1．発表者名 Benjamin List
2．発表標題 Asymmetric Organocatalysis
3．学会等名 2021 Nobel Prize Lectures（招待講演）（国際学会）
4．発表年 2021年

〔図書〕　計0件

〔産業財産権〕

〔その他〕

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６．研究組織

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７．科研費を使用して開催した国際研究集会

〔国際研究集会〕　計0件

８．本研究に関連して実施した国際共同研究の実施状況

共同研究相手国	相手方研究機関