様　式　Ｃ－１９、Ｆ－１９－１、Ｚ－１９　（共通）

科学研究費助成事業　　研究成果報告書

令和　６ 年　６ 月 ２５ 日現在

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研究種目： 研究活動スタート支援

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課題番号： ２２Ｋ２０５２２

研究課題名（和文） Development of Indigo Derivatives as Functional Molecules with Novel Photochemical Properties

研究課題名（英文） Development of Indigo Derivatives as Functional Molecules with Novel Photochemical Properties

研究代表者

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交付決定額（研究期間全体）：（直接経費） 2,200,000円

研究成果の概要（和文）：このプロジェクトでは、光応答性分子ツールとしてのインディゴ化合物の使用促進において大きな進歩をとげた。まず新しい赤色光フォトスイッチを構築するために、インディゴ染料の新しい銅触媒による直接官能基化を開発した。計算とデータサイエンスのアプローチにより、反応機構および構造と特性の関係についての洞察が得られた。また、薄膜におけるインディゴフォトスイッチの最初の例の実装にも成功し、材料科学におけるその可能性を実証した。さらに、光応答性分子ツールとしてのインディゴの利用の歴史と展望をまとめた総説を作成した。全体として、このプロジェクトは 3 つの論文を生み出し、インディゴ化学の新しい方向性を指摘した。

研究成果の学術的意義や社会的意義
Due to their red-light absorbance, indigo derivatives are expected to be useful in biomedicine and material science. This research has demonstrated their potential as photoresponsive molecular tools by developing new synthetic methods and building structure-property relationships.

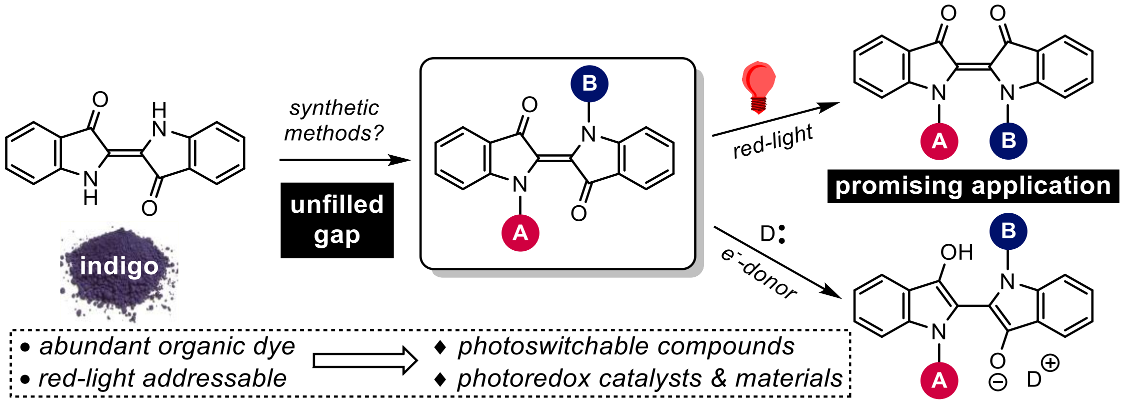
研究成果の概要（英文）：In this project, we have made significant progress in promoting the use of indigo compounds as photoresponsive molecular tools. We first developed a new copper-catalyzed direct functionalization of indigo dye to build new red-light photoswitches. Computational studies and data science approaches have provided insight on reaction mechanism and structure-property relationships. We have also successfully implemented the first example of indigo photoswitches in thin films, which demonstrates its potential in material science. Additionally, we have prepared a review to summarize the history and perspectives of utilizing indigos as photoresponsive molecular tools. Overall, this project will yield three publications and has pointed out new directions for indigo chemistry.

研究分野： organic chemistry

キーワード： indigo　photoswitch　organic synthesis　metal catalyst　data science

１．研究開始当初の背景

At the outset of this project, we aimed to develop novel synthetic methodologies to directly functionalize the indigo dye and build novel molecular structures for new photochemical properties. Indigo is one of the most abundant and ancient dyes in human history, and its blue color suggests the absorbance in red-light region. Red light-triggered chemical processes hold immense potential in biomedical and material science applications, in particular due to low energy of this long-wavelength irradiation as well as its enhanced ability to penetrate through biological medium. As opposed to other dye molecules that require lengthy derivatization to attain absorption in visible light region, indigo compounds naturally absorb red light and are thus ideal candidates for the development of photoresponsive molecular tools. However, the hurdle to achieving this goal is the lack of efficient, selective, and flexible synthetic methods to directly convert the inexpensive dye into the desired structures. As a result, the crucial part of this project was to develop such methodologies, especially by employing transition metal catalysis. Furthermore, using these novel transformations, new compounds would be synthesized, which would allow us to build the relationship between their molecular structures and photochemical properties. Gaining such understandings would significantly assist the future design of photoresponsive indigo compounds.



２．研究の目的

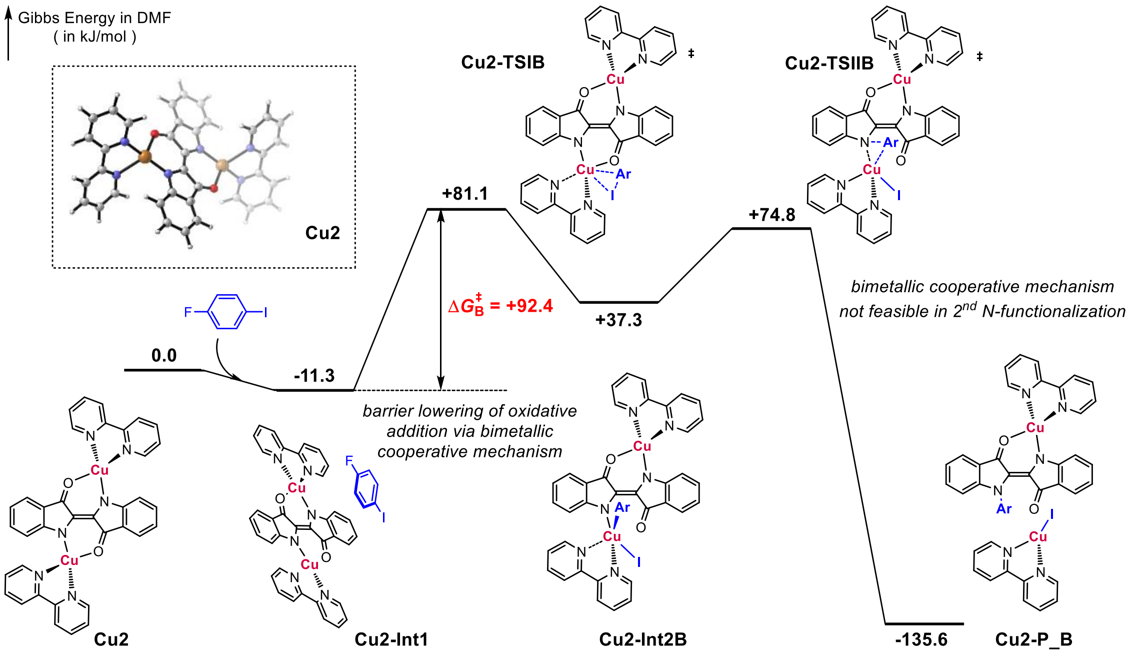
The purpose of this research project was to develop novel synthetic methodologies to convert the abundant indigo dye into functional photoresponsive molecular tools. Through these endeavors, we would first gain understanding on catalytic systems for such transformations that can be applicable to other substrates. Second, with the novel indigo derivatives, we would be able to explore new photochemical properties. It would be immensely beneficial to develop a quantitative structure-property relationship with these photoresponsive compounds. Specifically, indigos have been known to function as red-light photoswitches, but there lack strategies to control the stability of switched state (i.e. thermal half-lives of Z-isomers) while maintaining the red-light absorbance. We were thus interested in developing models to link the indigo structures to their thermal half-lives with the hope that compounds with unprecedented properties can be rationally designed. On the other hand, the utilities of these novel indigo compounds would be explored, especially in the area of material science and biomedicine.

３．研究の方法

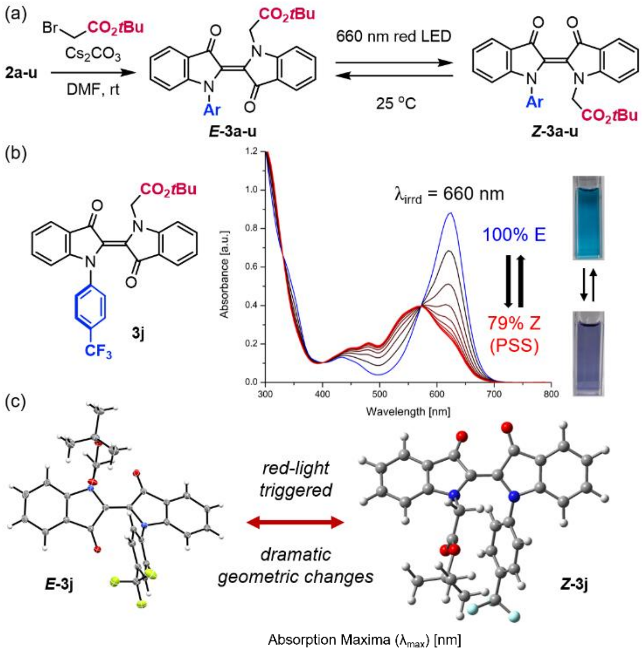
The development of synthetic methodologies was performed by using conventional optimization procedure, where the catalysts and reactions conditions were evaluated systematically through common analytical techniques such as LC and NMR. The optimized conditions were then applied to prepare a wide range of compounds carrying useful functional groups. The photochromic properties of these indigo photoswitches were studied utilizing common spectroscopic tools (UV-vis spectrometer with red-light LED). Finally, data science workflow was implemented to construct models for correlating the molecular structures with their photochemical and thermal properties.

４．研究成果

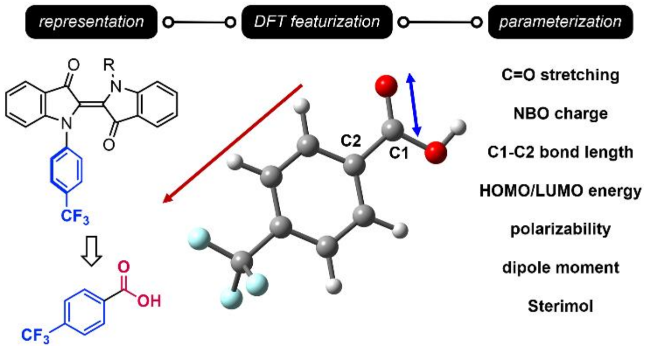
Upon reaction optimization, we identified copper as the most suitable catalyst of direct indigo *N*-arylations. The optimal conditions featuring $CuCl_2$ in combination with bipyridine as the ligand and K_3PO_4 as the base, which are all inexpensive and commercially available reagents. This method is applicable to a wide variety of functional groups, including moieties that can be further derivatized, such as aldehyde, ester, alkene, alkyne and bromide. This protocol is operationally simple and can be carried out at gram-scale. One interesting phenomenon we observed was that even when an excess of aryl iodide was utilized, only mono-*N*-arylated products were obtained, despite the presence of a second available nitrogen in indigo. To explain this exclusive selectivity, we collaborated with computation chemists and carried out DFT calculations of this reaction. The oxidative addition was identified to have the highest energy barrier. Interestingly, this barrier could be alleviated by a bis-copper-indigo intermediate, where a bimetallic cooperative mechanism through the communication was invoked and the two copper centers are electronically coupled with each other through the indigo ring. This theory then explains the ineffectiveness of the second *N*-arylation, where the formation of this bimetallic complex is not feasible. This presence of this dinuclear Cu-indigo complex was confirmed by mass spectrometry, and studies to explore the utility of this interesting compound are currently underway.



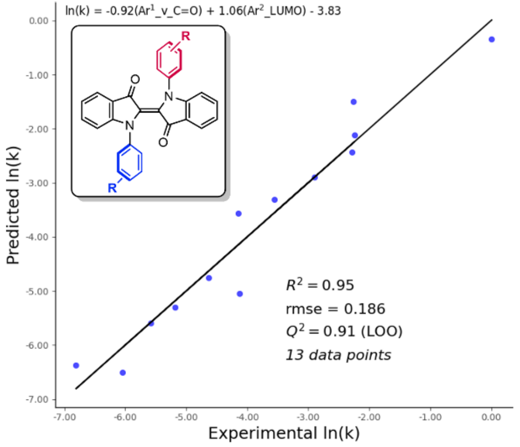
With these novel compounds in hand, we carried out further transformations to build *N*-aryl-*N'*-alkylindigo photoswitches. These compounds can all be switched by using the same 660-nm red LED to trigger the E-Z photoisomerization. The switching efficiency is generally decent (40-80% Z in PSS), and the switched state (Z-isomer) typically has a thermal half-life of 2-20 min in MeCN or toluene. These *N*-aryl-*N'*-alkylindigos also represent a new design of red-light photoswitches, where the *N*-aryl substituents are used to control the thermal half-lives, and the *N'*-alkyl groups can be utilized to attach functional moieties. To illustrate this

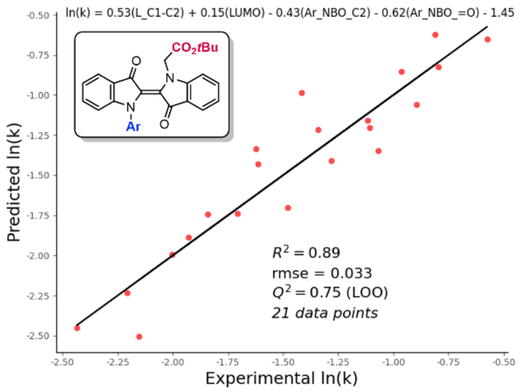


concept, we conducted preliminary studies to attach biologically relevant molecules (carbohydrate, amino acid, and biotin) to indigos through copper-catalyzed azide-alkyne cycloadditions (CuAAC). Then in the reaction mixtures, the generated coupled products were successfully switched *in situ* by using the same red LED.

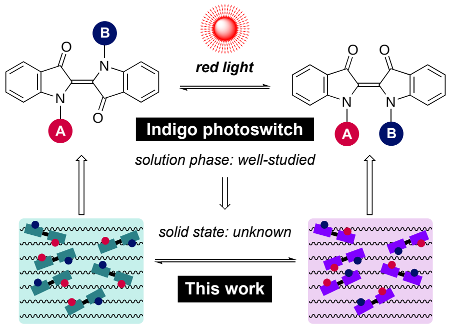


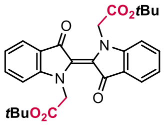
Next, in order to quantitatively understand how the structures of indigo *N*-aryl substituents influence their thermal half-lives, we then aimed to build correlative models following a modern Hammett analysis workflow. First, the *N*-aryl groups are represented as the corresponding benzoic acid derivatives, which are then subjected to simple DFT calculations. From the computational outcomes, molecular parameters, such as C=O stretching frequencies/intensities, NBO charge, and HOMO/LUMO energies, were extracted. These parameters were implemented as descriptors to construct multivariate linear regression models. With only a few parameters, a good level of correlativity could be observed. Key to this success is the ability to quantitatively represent the electronic properties of these *N*-aryl substituents by measurable properties. This workflow is thus expected to be generalizable to other photoactive systems.



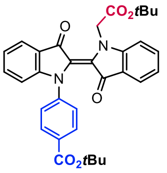


We also sought to explore the applications of indigo photoswitches during this research project. In particular, we were interested in applying indigos in photoresponsive materials, for example, to tune the material properties or trigger motion by red light. However, despite the studies of indigo photoswitching in solution state, there was no knowledge of translating such microscopic behavior to macroscopic reactivity in the solid state. One foreseeable challenge is that the E-Z isomerization of indigos requires much greater free space compared to other classes of photoswitches so it is not apparent whether indigos can successfully switch in the solid state. Fundamental understanding on how the indigo structures interact with the polymer environment would be crucial to answer these questions. We thus teamed up with the Priimagi group from Finland and Hecht group from Germany, who are specialists in photoresponsive materials.

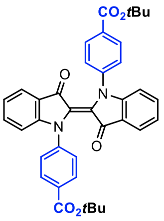




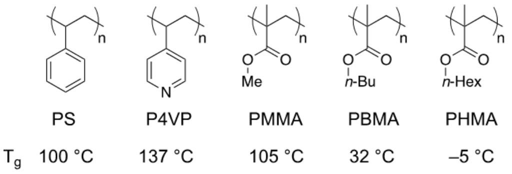
Al-tBu



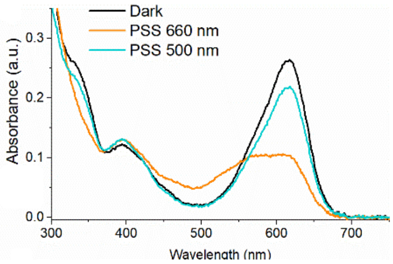
As-tBu

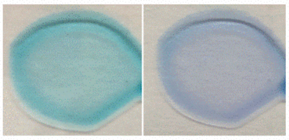


Ar-tBu

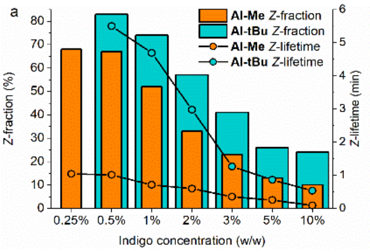


We first blended three representative indigo molecules of different *N*-substitution patterns together with various polymer matrices containing distinctive side chains and levels of softness. Excitingly, photoisomerization was observed in these thin films, as can be seen from the apparent color changes and UV-vis spectroscopy. We also observed the dependence of switching efficiency on the identity of polymer chains. In general, softer matrices resulted in higher Z% in the PSS, which is presumably due to greater degree of freedom in accommodating steric changes during E-Z isomerization processes. To further improve the switching efficiency, we replaced the Me groups in the indigo molecules with tBu groups to create even more free space from the polymer environment. Finally, we lowered the loading of indigos in the polymer thin films to decrease the interactions between the two photoswitch molecules. All these modifications eventually led to >80% Z in the PSS, which is comparable to the switching efficiency in the solution state. This study thus helped decipher parameters crucial for successful photoswtiching of indigos in the solid state and should serve as a guidance for translating microscopic photoisomerization to macroscopic material photoresponsiveness.




E-enriched

Z-enriched



In summary, in this project we addressed two challenges that are currently gapping indigo photoswitches from real applications: synthetic viability and structure-property relationship. Significant progress has been achieved on both the fundamental end as well as the application side. Two publications and one manuscript in review have resulted from this project:

1) Kuntze, K.; Viljakka, J.; Virkki, M.; Huang, C.-Y.; Hecht, S.; Priimagi, A. "Red-light photoswitching of indigos in polymer thin films" *Chem. Sci.* **2023**, *14*, 2482

2) Huang, C.-Y.; Hecht, S. "A Blueprint for Transforming Indigos to Photoresponsive Molecular Tools." *Chem. Eur. J.* **2023**, *29*, e202300981.

3) Jaiswal, A. K.; Saha, P.; Jiang, J.; Suzuki, K.; Jasny, A.; Schmidt, B. M.; Maeda, S.; Hecht, S.; Huang, C.-Y. "Accessing a Diverse Set of Functional Red-Light Photoswitches by Selective Copper-Catalyzed Indigo N-Arylation." *ChemRxiv* doi: 10.26434/chemrxiv-2024-62zmf.

５．主な発表論文等

〔雑誌論文〕　計3件（うち査読付論文　2件／うち国際共著　3件／うちオープンアクセス　2件）

１．著者名 Kuntze Kim、Viljakka Jani、Virkki Matti、Huang Chung-Yang、Hecht Stefan、Priimagi Arri	４．巻 14
２．論文標題 Red-light photoswitching of indigos in polymer thin films	５．発行年 2023年
３．雑誌名 Chemical Science	６．最初と最後の頁 2482～2488
掲載論文のDOI（デジタルオブジェクト識別子） 10.1039/D2SC06790K	査読の有無 有
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１．著者名 Huang Chung‐Yang (Dennis)、Hecht Stefan	４．巻 29
２．論文標題 A Blueprint for Transforming Indigos to Photoresponsive Molecular Tools	５．発行年 2023年
３．雑誌名 Chemistry A European Journal	６．最初と最後の頁 e202300981
掲載論文のDOI（デジタルオブジェクト識別子） 10.1002/chem.202300981	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 Jaiswal Amit K.、Saha Priya、Jiang Julong、Suzuki Kimichi、Jasny Anna、Schmidt Bernd M.、Maeda Satoshi、Hecht Stefan、Huang Chung-Yang (Dennis)	４．巻 -
２．論文標題 Accessing a Diverse Set of Functional Red-Light Photoswitches by Selective Copper-Catalyzed Indigo N-Arylation	５．発行年 2024年
３．雑誌名 ChemRxiv	６．最初と最後の頁 -
掲載論文のDOI（デジタルオブジェクト識別子） 10.26434/chemrxiv-2024-62zmf	査読の有無 無
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12件（うち招待講演　1件／うち国際学会　11件）

１．発表者名 Huang, Chung-Yang
２．発表標題 Development of Indigos as Red-Light Photoswitches
３．学会等名 Gordon Research Conference: Artificial Molecular Switches and Motors（国際学会）
４．発表年 2023年

１．発表者名
Huang, Chung-Yang

２．発表標題
Development of Indigos as Red-Light Photoswitches

３．学会等名
International Conference on Photochemistry（国際学会）

４．発表年
2023年

１．発表者名
Huang, Chung-Yang

２．発表標題
Development of Indigos as Red-Light Photoswitches

３．学会等名
ACS Fall National Meeting（国際学会）

４．発表年
2023年

１．発表者名
Huang, Chung-Yang

２．発表標題
Development of Indigos as Red-Light Photoswitches

３．学会等名
14th Indian Scientists Association in Japan Annual Symposium（招待講演）（国際学会）

４．発表年
2023年

１．発表者名
Huang, Chung-Yang

２．発表標題
Development of Indigos as Red-Light Photoswitches

３．学会等名
The 15th International Kyoto Conference on Organic Chemistry（国際学会）

４．発表年
2023年

１．発表者名
Huang, Chung-Yang

２．発表標題
Red-Light Photoswitching of Indigos in Polymer Thin Films

３．学会等名
6th ICReDD International Symposium（国際学会）

４．発表年
2023年

１．発表者名
Huang, Chung-Yang

２．発表標題
Development of Indigos as Red-Light Photoswitches

３．学会等名
10th International Symposium on Photochromism（国際学会）

４．発表年
2023年

１．発表者名
Saha, Priya

２．発表標題
Development of Indigos as Red-Light Photoswitches

３．学会等名
CSE Summer School & ALP International Symposium（国際学会）

４．発表年
2023年

１．発表者名
Saha, Priya

２．発表標題
Development of Indigos as Red-Light Photoswitches

３．学会等名
6th ICReDD International Symposium（国際学会）

４．発表年
2023年

１．発表者名 Huang, Chung-Yang
２．発表標題 Red-Light Photoswitching of Indigos in Polymer Thin Films
３．学会等名 4th ICReDD International Symposium（国際学会）
４．発表年 2023年

１．発表者名 Jaiswal, Amit Kumar
２．発表標題 Development of Indigos as Photo-responsive Molecular Tools
３．学会等名 2023 Bowei Research Conference（国際学会）
４．発表年 2023年

１．発表者名 Huang, Chung-Yang
２．発表標題 Indigos as Red-Light Photoswitches
３．学会等名 8th Hokkaido University Cross-Departmental Symposium
４．発表年 2022年

〔図書〕　計0件

〔産業財産権〕

〔その他〕

ICReDD Research News
https://www.icredd.hokudai.ac.jp/research/8687

６．研究組織

	氏名 （ローマ字氏名） （研究者番号）	所属研究機関・部局・職 （機関番号）	備考
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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