Data-driven Multi-parameter Screening of Electrochemical and Flow Reaction Conditions Using Bayesian Optimization

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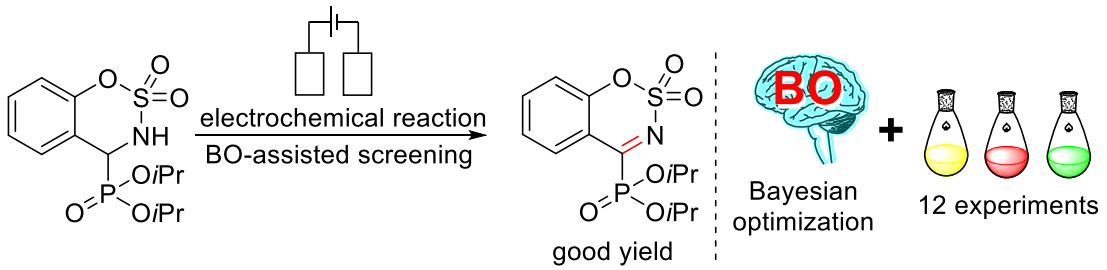
Screening and optimization of reaction conditions are inevitable processes in organic synthetic fields. However, a conventional exhaustive screening by chemists requires a lot of time, energy, and chemicals to achieve high chemical yield of product. In the case of electrochemical and flow reactions that have been attracted as unique reaction processes, involve additional parameters such as current and flow rate to be essential for the optimization. Recently, various machine-learning methods for reaction screening and optimization have been reported.[1] Among them, Bayesian optimization (BO) that has been known to accelerate the optimization process,[2] stands out as a powerful data-driven probabilistic method to predict the maximum of a black-box objective function with minimum training set. This presentation discusses our work on BO-assisted multiparameter screening of flow and electrochemical syntheses.

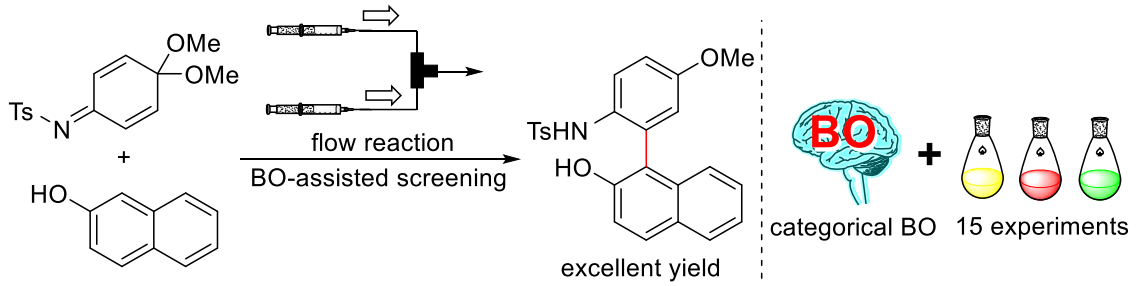
1. BO-assisted multiparameter screening of electrochemical synthesis of α- ketiminophosphonates

α-Ketiminophosphonates serve as important synthetic intermediates for the synthesis of tetrasubstituted α-aminophosphoric acids.[3] An oxidation of α-aminophosphonates with excess amount of MnO_2 are well-known method for the synthesis of α-ketiminophosphonates. In this study, we have developed an electrochemical oxidation approach for the synthesis of α-ketiminophosphonates, which offers a greener alternative. BO-assisted multi-parameter screening was applied to optimize the electrochemical oxidation process with minimizing costs, energy consumption, and chemical usage. Based on the BO and 12 experiments (including five initial data points and seven additional data points), we identified suitable five parameter values (current, conc. of the starting material and $LiClO_4$, temperature, and reaction period) that led to the desired ketimine in good yield.[4]



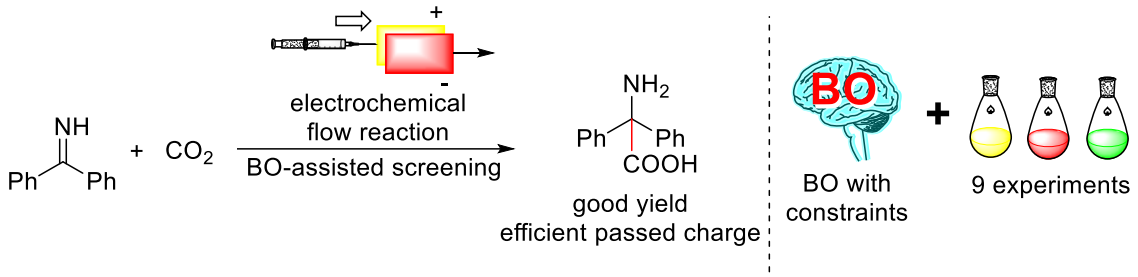
2. Data-driven parallel-screening of micromixer-type and organocatalytic conditions in the flow biaryl synthesis

Flow reactions have gained considerable attention as green processes due to their high efficiency, safety, and scalability. Although flow rate and micromixer-type significantly affects the yield in the flow system, the type of micromixer is machine-engineering non-numerical parameter and difficult to convert into the numerical representation for chemists. To address this issue, we employed one-hot encoding to treat the micromixer-type as a numerical parameter (for example, mixer A: '0' represented by 1 0 0, mixer B: '1' represented by 0 1 0, mixer C: '2' represented by 0 0 1). Using BO with the suitable acquisition function, we hypothesized the categorical parameter like the micromixer-type could be simultaneously optimized along with other numerical parameters. Using the BO system with parallel LCB (Lower Confidence Bounds) and conducting a total of 15 experiments (comprising 6 initial data points and 9 additional data points), we determined suitable reaction conditions, including micromixer-type, for TfOH-catalyzed biaryl synthesis using 2-naphthol and iminoquinone monoacetal in flow.[5] These predicted conditions did not only afford the corresponding 2-amino-2′-hydroxy-biaryl in 96% yield, but also achieve the lower temperature and reduced catalyst loading compared with the previously reported batch system.[6,7]



3. BO with constraint on passed charge for multiparameter screening of electrochemical-flow synthesis of amino acids

Electrochemical-flow synthesis offers several advantages such as a large surface-to-volume ratio, continuous production, and avoiding overoxidation/reduction. However, optimizing the reaction conditions in electrochemical-flow synthesis can become complicated due to the involvement of both electrochemical and flow reaction parameters, in addition to conventional reaction parameters. Moreover, modifying one parameter significantly affects the others because the passed charge (q) is expressed as a function of the current density, substrate concentration, and flow rate. Conditions screening of electrochemical-flow reaction is not easy task for chemists while maintaining an efficient passed charge. To overcome this issue, we performed the constrained BO-assisted screening for the electrochemical reductive carboxylation of imines in a flow microreactor. By imposing constraints on the passed charge ($2.0<q<3.0$ and $2.0<q<2.1$), we successfully identified suitable reaction parameters that resulted in the desired amino acid with high yields (90% yield, q = 2.85 Fmol^{-1}; 87% yield, q = 2.03 Fmol^{-1}).[8]



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Curriculum Vitae

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Dr. Masaru Kondo was born in Aichi, Japan. He is currently an assistant professor at Ibaraki University. He received his Ph.D. from Nagoya Institute of Technology in 2017 under the direction of Prof. Shuichi Nakamura. He was a JSPS research fellow from 2016 to 2017. He worked as a visiting student with Prof. Mark Lautens at Toronto University in 2015 and as a visiting researcher with Prof. David W. C. MacMillan at Princeton University in 2017. Then, he became an assistant professor at SANKEN, Osaka University from 2017 to 2021. From September 2023, he shifted to University of Shizuoka. His current research interest is the development of novel photoswitchable catalysts and data-driven organic syntheses.