

Symposium | Asian International Symposium : Asian International Symposium - Organic Chemistry / Green Sustainable Chemistry -

🏠 Tue. Mar 19, 2024 1:00 PM - 3:40 PM JST | Tue. Mar 19, 2024 4:00 AM - 6:40 AM UTC 🏠 A1422(1422, Bldg. 14 [2F])

**[A1422-2pm] Asian International Symposium - Organic Chemistry / Green Sustainable Chemistry -**

Chair, Symposium organizer: Kazuaki Ishihara, Takashi Ohshima

📌 English 📌 Invited Lecture

1:00 PM - 1:30 PM JST | 4:00 AM - 4:30 AM UTC

[A1422-2pm-01]

Enantioselective Bromocyclization Reactions Enabled by Lewis/Brønsted Base Concerted Catalysis of Chiral Bisphosphine Oxide

○Kenji Yamashita<sup>1</sup> (1. University of Shizuoka)

📌 English 📌 Keynote Lecture

1:30 PM - 2:00 PM JST | 4:30 AM - 5:00 AM UTC

[A1422-2pm-02]

Anion-encapsulating sodium alkoxide clusters (X@RONa): structure and function as multi-functional Lewis acid catalysts

○Zhi Li<sup>1</sup> (1. ShanghaiTech University)

2:00 PM - 2:20 PM JST | 5:00 AM - 5:20 AM UTC

Break

📌 English 📌 Invited Lecture

2:20 PM - 2:50 PM JST | 5:20 AM - 5:50 AM UTC

[A1422-2pm-03]

Computation-based Strategy for the Development of Fluoroalkylation Reactions with Difluorocarbene

○Hiroki Hayashi<sup>1,2</sup> (1. WPI-ICReDD, Hokkaido Univ., 2. JST-ERATO, Hokkaido Univ.)

📌 English 📌 Asia Special Lecture

2:50 PM - 3:30 PM JST | 5:50 AM - 6:30 AM UTC

[A1422-2pm-04]

Asymmetric Carbene-Transfer Reactions Catalyzed by Low Coordination State Rhodium(I)

○Ming-Hua Xu<sup>1</sup> (1. Southern University of Science and Technology, China)

3:30 PM - 3:40 PM JST | 6:30 AM - 6:40 AM UTC

Closing Remarks

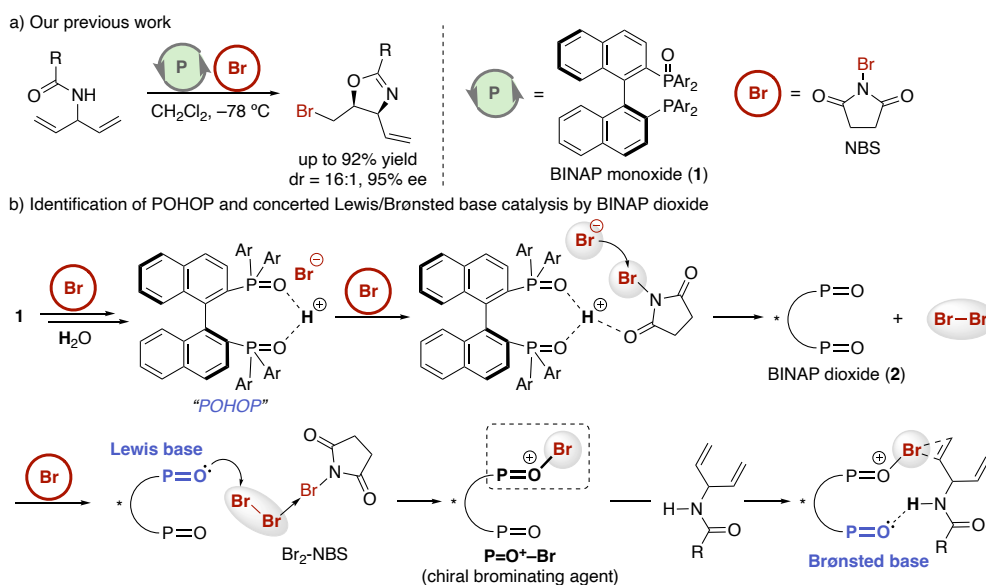
# Enantioselective Bromocyclization Reactions Enabled by Lewis/Brønsted Base Concerted Catalysis of Chiral Bisphosphine Oxide

(1. School of Pharmaceutical Sciences, University of Shizuoka) ○Kenji Yamashita<sup>1</sup>

**Keywords:** Organocatalyst; Halogenation; Asymmetric Reaction; Lewis Base; Brønsted Base

Electrophilic halo-functionalizations of carbon–carbon unsaturated bonds are one of the most synthetically attractive transformations that allow for simultaneous incorporation of two heteroatom functionalities across these unsaturated bonds. In this context, we recently reported the desymmetrization of bisallylic amides via an enantioselective bromocyclization using (*S*)-BINAP monoxide (**1**) (Scheme 1a).<sup>1</sup> However, the catalytic role of **1** has remained elusive. Then, the catalytic mechanism of the above reaction was examined in detail by several control experiments, X-ray analysis, NMR studies, and CryoSpray MS analysis. **1** was transformed to a key catalyst precursor, proton-bridged bisphosphine oxide complex “POHOP” (Scheme 1b). The thus-formed POHOP further reacts with *N*-bromosuccinimide (NBS) to afford BINAP dioxide (**2**) and molecular bromine (Br<sub>2</sub>) simultaneously. While the resulting Br<sub>2</sub> is activated by NBS through halogen bonding interaction to form a more reactive brominating reagent (Br<sub>2</sub>–NBS),<sup>2</sup> **2** serves as a bifunctional catalyst, acting as both a Lewis base that reacts with Br<sub>2</sub>–NBS to form a chiral brominating agent (P=O<sup>+</sup>–Br), and also as a Brønsted base for activating the substrate.<sup>3</sup>

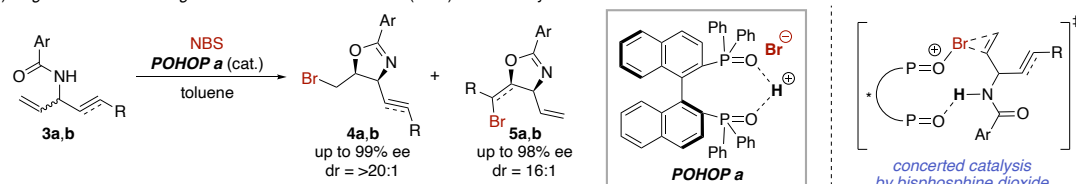
## Scheme 1. Bifunctional Catalysis of Chiral Bisphosphine Oxide



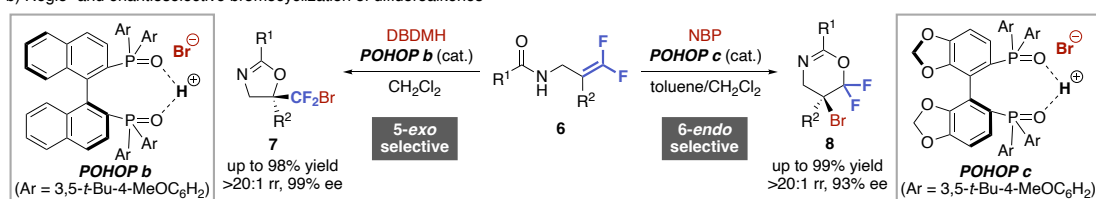
This novel catalysis of the chiral bisphosphine oxide was applicable to various highly challenging asymmetric bromocyclization reactions. For example, we have successfully developed *regiodivergent* parallel kinetic resolution (PKR) of racemic allylic amides **3a** via bromocyclization (Scheme 2a).<sup>3</sup> When **3a** having two different alkenes was employed as a substrate, **3a** was transformed into two distinct cyclization products (**4a** and **5a**) in a highly stereoselective manner via concurrent resolution processes. The catalysis could also promote *chemodivergent* PKR of racemic ene-yne **3b** to provide the corresponding products (**4b** and **5b**), regardless of the electronic difference between alkene and alkyne. To our knowledge, these are the first examples of *regio*- and *chemodivergent* PKRs via halocyclization. Furthermore, *regio*- and *enantioselective* bromocyclizations of difluoroalkenes **6**<sup>4</sup> were also demonstrated (Scheme 2b).<sup>5</sup> Owing to the extremely high electrophilicity of  $\text{P}=\text{O}^+-\text{Br}^-$  species, the cyclization of less reactive **6** proceeded smoothly even at low temperature. A particularly noteworthy feature is that *regio*- and *enantioselectivity* were greatly influenced by the solvent, the catalyst structure, and the brominating reagent. Consequently, both the 5-*exo* and 6-*endo* selective bromocyclizations became feasible, providing the corresponding oxazolines **7** or oxazines **8** bearing a tetrasubstituted difluoromethylated stereocenter in high yield with excellent *enantioselectivity*. Moreover, a gram-scale synthesis of chiral oxazoline **7** was also achieved with as little as 1 mol% of the catalyst, highlighting the synthetic utility of our protocol.

## Scheme 2. Enantioselective Bromocyclizations Using POHOP as a Catalyst Precursor

a) *Regio*- and *chemodivergent* Parallel Kinetic Resolution (PKR) via bromocyclization



b) *Regio*- and *enantioselective* bromocyclization of difluoroalkenes



1) Y. Nagao, T. Hisanaga, H. Egami, Y. Kawato, Y. Hamashima, *Chem. Eur. J.* **2017**, *23*, 16758. 2) T. Horibe, Y. Tsuji, K. Ishihara, *Org. Lett.* **2020**, *22*, 4888. 3) K. Yamashita, R. Hirokawa, M. Ichikawa, T. Hisanaga, Y. Nagao, R. Takita, K. Watanabe, Y. Kawato, Y. Hamashima, *J. Am. Chem. Soc.* **2022**, *144*, 3913. 4) E. Miller, S. Kim, K. Gibson, S. J. Derrick, D. F. Toste, *J. Am. Chem. Soc.* **2020**, *142*, 8946. 5) a) R. Hirokawa, Y. Nakahara, S. Uchida, K. Yamashita, Y. Hamashima, *Chem. Asian. J.* **2023**, *18*, e202300141. b) Y. Nakahara, R. Hirokawa, S. Uchida, K. Yamashita, Y. Hamashima, *Synlett* **2023**, *34*, 2476.

## Anion-encapsulating sodium alkoxide clusters ( $X@RONa$ ): structure and function as multi-functional Lewis acid catalysts

(<sup>1</sup>*School of Physical Science and Technology, ShanghaiTech University*) ○Zhi Li<sup>1</sup>

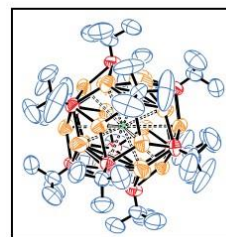
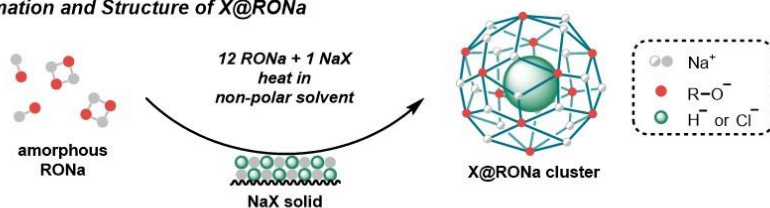
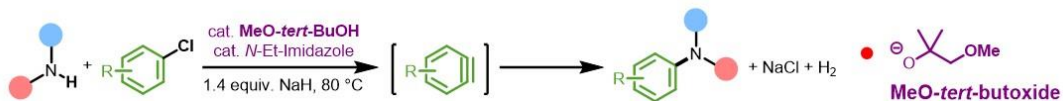
**Keywords:** sodium alkoxide clusters; benzyne; aryl amines; polyprenylquinones; Lewis acid catalysis

Sodium salts are able to aggregate into various types of polymeric or molecular substances depending on anions. We discovered that sodium *tert*-butoxide formed thermodynamically favored dodecameric anion-encapsulating molecular clusters ( $NaOt-Bu$ )<sub>12</sub>NaX, or  $X@t-BuONa$ , where X is the encapsulated anion. The synthesis could be as simple as heating NaOt-Bu and fine powder of NaCl together in a non-polar solvent. The structures of these substances were studied by X-ray crystallography and NMR. Unlike their well-known oligomeric clusters or amorphous ionic polymers, its structure consists of 12 alkoxide anions located at vertices of an icosahedron, a halide or other anion at the center, and 13 sodium cations dynamically distributed at 13 of the 20 faces.

The multi-level composition of these clusters allowed us to design clusters by changing the *tert*-butoxide to other alkoxide ligand RO as  $X@RONa$ , thus enabling their catalytic activities. The RO ligand, encapsulated X, and substrates coordinated to Na were all Lewis basic ligands that interacting with the cluster as well as each other, thus we consider the  $X@RONa$  as a new type of Lewis acid catalyst. The catalytic activity will be illustrated in the following two cases.

First,  $X@RONa$  was able to promote transition-metal-free polyprenylation of quinones through redox chain mechanism we discovered earlier.<sup>1</sup> Many biologically important polyprenylquinones were synthesized from corresponding parent quinone and polyprenyl halide as precursors and NaH as base in one step and high yield.

Second,  $X@RONa$  was applied in catalytic transition-metal-free C-N bond formation. Aryl amines are usually synthesized from transition metal-catalyzed cross coupling or C-H activations from aryl halides, triflates, or arenes. Although these methods are effective, the costs of precursors, reagents and catalysts are often too high for them to be applied in large scale synthesis. We recently discovered that  $X@RONa$  was capable of catalytically promoting benzyne formation from simple aryl chlorides, as well as the subsequent arylation of amines. From very simple and cheap aryl chlorides, alkyl amines and NaH, aryl amines can be easily synthesized in large scale. This is also a very rare case of large-scale application of benzyne.

**Formation and Structure of X@RONa****X@RONa-Catalyzed Redox Chain Polyprenylation of Quinones****X@RONa-Catalyzed Arylamine Synthesis through Benzyne**

1) X.-L. Xu, Z. Li *Angew. Chem. Int. Ed.* **2017**, 56, 8196.

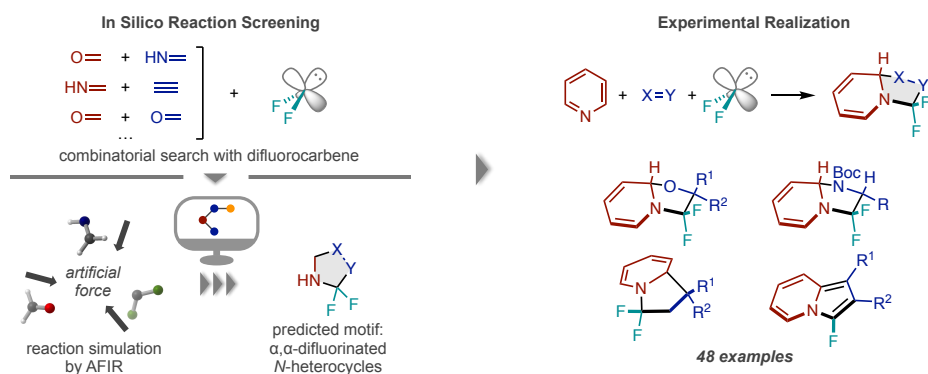
## Computation-based Strategy for the Development of Fluoroalkylation Reactions with Difluorocarbene

(WPI-ICReDD, Hokkaido University & JST-ERATO) ○Hiroki Hayashi

**Keywords:** Quantum Chemical Calculations; Reaction Development; Fluoroalkylation; Difluorocarbene; Dearomatization

Quantum chemical calculations have been an indispensable tool in synthetic methodology development. The progress of computational methods as well as computer technology has enabled the systematic exploration of reaction pathways, and their current primary role is to gain the mechanistic insight into established reactions. In this context, our group has developed an artificial force induced reaction (AFIR) method, an automated reaction path search algorithm that can explore the possible reaction pathways from single input structure. This method can create reaction path networks comprising computationally estimated reaction intermediates and products without any prior knowledge of organic transformations, showcasing its ability to predict even unknown chemical processes.<sup>1</sup>

Here, we report a strategy that leverages computational reaction simulations for the development of three-component reactions with difluorocarbene using the AFIR method. Difluorocarbene, an electrophilic carbene species useful not only for incorporating the difluoromethylene unit into organic molecules but also in the calculations due to its relatively small character, is used for *in silico* combinatorial reaction screening with two unsaturated compounds containing C=O, C=N, C=C, or C≡C bonds. These simulations suggested that the less explored three-component cycloaddition of methanimine, difluorocarbene, and the other unsaturated component would proceed preferentially to furnish  $\alpha,\alpha$ -difluorinated *N*-heterocyclic skeletons. Based on the computational results, we realized the identified reaction mode experimentally, leading to a diverse dearomative cycloaddition of pyridines with difluorocarbene and a series of unsaturated compounds (aldehydes, ketones, imines, alkenes, and alkynes).<sup>2</sup>



1) H. Hayashi, S. Maeda, T. Mita *Chem. Sci.* **2023**, *14*, 11601.

2) H. Hayashi, H. Katsuyama, H. Takano, Y. Harabuchi, S. Maeda, T. Mita *Nat. Synth.* **2022**, *1*, 804.

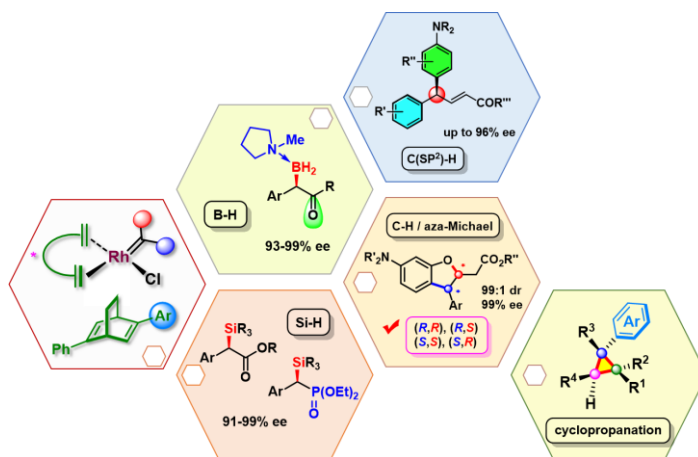
## Asymmetric Carbene-Transfer Reactions Catalyzed by Low Coordination State Rhodium(I)

Ming-Hua Xu

*Shenzhen Grubbs Institute and Department of Chemistry, Southern University of Science and Technology, Shenzhen 518055, China*

**Keywords:** Asymmetric Catalysis; Carbene-Transfer; Rhodium(I); Chiral Diene; Carbene Insertion

Transition metal-catalyzed asymmetric carbene insertion reactions have been recognized as one of the most powerful methods for the construction of C-C or C-heteroatom bonds. In recent years, our group has been interested in Rh(I)-carbene chemistry, and achieved the first asymmetric metal-carbene insertion into B-H and Si-H bonds using Rh(I)/C<sub>1</sub>-symmetric diene complexes as catalysts.<sup>1</sup> With the established Rh(I)-carbene chemistry, we also discovered that C-H insertion reaction of styryldiazoacetates with aniline derivatives could be achieved in a highly region- and enantio-selective manner.<sup>2</sup> Moreover, the rhodium(I)/chiral diene catalytic system also enables efficient asymmetric Rh(I)-carbene-directed S-H, C(sp<sup>3</sup>)-H, N-H, O-H insertions, as well as intramolecular cyclopropanations.<sup>3</sup> In this presentation, these results together with some new achievements will be described.



1) a) Chen, X. Zhang, W.-Y. Qi, B. Xu, M.-H. Xu, *J. Am. Chem. Soc.* **2015**, *137*, 5268; b) D. Chen, D.-X. Zhu, M.-H. Xu, *J. Am. Chem. Soc.* **2016**, *138*, 1498. 2) a) D.-X. Zhu, H. Xia, J.-G. Liu, L.W. Chung, M.-H. Xu, *J. Am. Chem. Soc.* **2021**, *143*, 2608; b) D.-X. Zhu, J.-G. Liu, M.-H. Xu, *J. Am. Chem. Soc.* **2021**, *143*, 8583; c) Wang, T.-Y.; Chen, X.-X.; Zhu, D.-X.; Chung, L. W.; Xu, M.-H. *Angew. Chem. Int. Ed.*, **2022**, *61*, e202207008. 3) Zhang, J.; Xu, W.; Xu, M.-H. *Angew. Chem. Int. Ed.*, **2023**, *62*, e202216799.