Parallel kinetic resolution via bromocyclization reaction enabled by Lewis/Brønsted base concerted catalysis of chiral bisphosphine oxide

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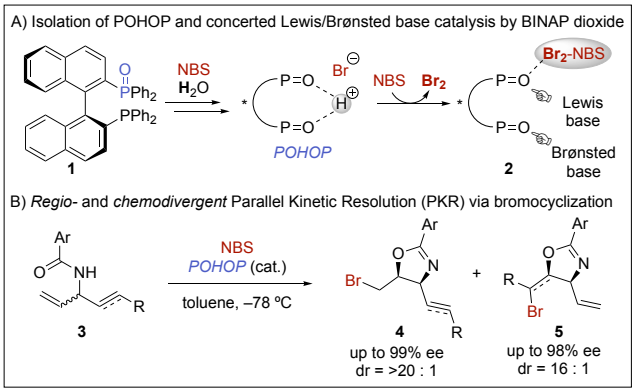
We recently reported the desymmetrization of bisallylic amides through an enantioselective bromocyclization using (*S*)-BINAP monoxide (**1**).[1)] However, the catalytic role of **1** has remained unclear. Then, the catalytic mechanism of the above reactions was examined in detail by control experiments, X-ray analysis, NMR studies and CryoSpray MS analysis. **1** was transformed to a key catalyst precursor, proton-bridged bisphosphine oxide complex (POHOP). The thus-formed the POHOP further reacts with NBS to afford BINAP dioxide (**2**) and molecular bromine (Br_2) simultaneously. While the resulting Br_2 is activated by NBS to form a more reactive brominating reagent (Br_2-NBS), **2** serves as a bifunctional catalyst, acting as both a Lewis base that reacts with Br_2-NBS to form a chiral brominating agent, and also as a Brønsted base for activation of the substrate (Fig. A.).

By taking advantage of this novel concerted Lewis/Brønsted base catalysis, we have successfully developed *regiodivergent* parallel kinetic resolution (PKR) of racemic allylic amides (**3**) via bromocyclization (Fig. B.). When **3** having two different alkenes was employed as a substrate, both enantiomers of **3** were transformed into two distinct cyclization products (**4** and **5**) in a highly stereoselective manner via concurrent resolution processes. Moreover, the catalyst also promoted *chemodivergent* PKR of racemic ene-yne **3** to provide the corresponding products (**4** and **5**), regardless of the electronic difference between alkene and alkyne. To our knowledge, these are the first examples of *regio-* and *chemodivergent* PKRs via halocyclization.[2)]



1) Nagao, Y.; Hisanaga, T.; Egami, H.; Kawato, Y.; Hamashima, Y. *Chem. Eur. J.* **2017**, *23*, 16758.
2) Hirokawa, R.; Yamashita, K. and Hamashima, Y. *et al*., *Manuscript submitted*.