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

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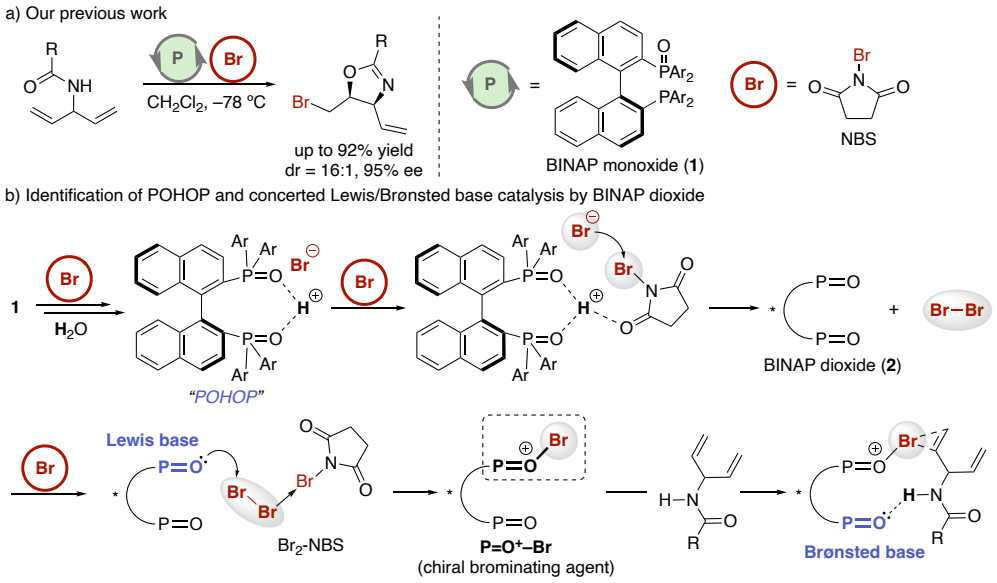
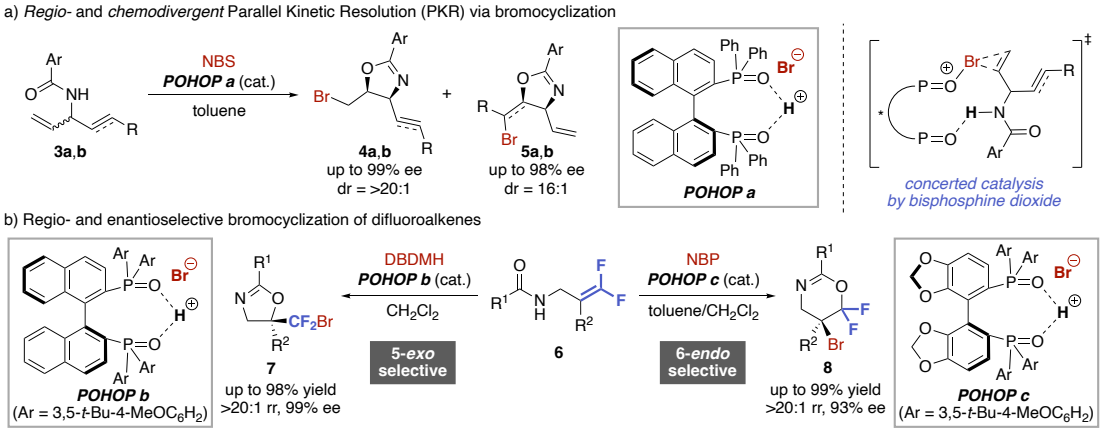
Electrophilic halo-functionalizations of carbon–carbon unsaturated bonds are one of the most synthetically attractive transformations that allow for simultaneous incorporation of two heteroatom functionalities across these unsaturated bonds. In this context, we recently reported the desymmetrization of bisallylic amides via an enantioselective bromocyclization using (*S*)-BINAP monoxide (**1**) (Scheme 1a).[1] 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_2) simultaneously. While the resulting Br_2 is activated by NBS through halogen bonding interaction to form a more reactive brominating reagent (Br_2-NBS),[2] **2** serves as a bifunctional catalyst, acting as both a Lewis base that reacts with Br_2-NBS to form a chiral brominating agent (**P=O$^+$–Br**), and also as a Brønsted base for activating the substrate.[3]

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).[3] 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**[4] were also demonstrated (Scheme 2b).[5] Owing to the extremely high electrophilicity of **P=O$^+$–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



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