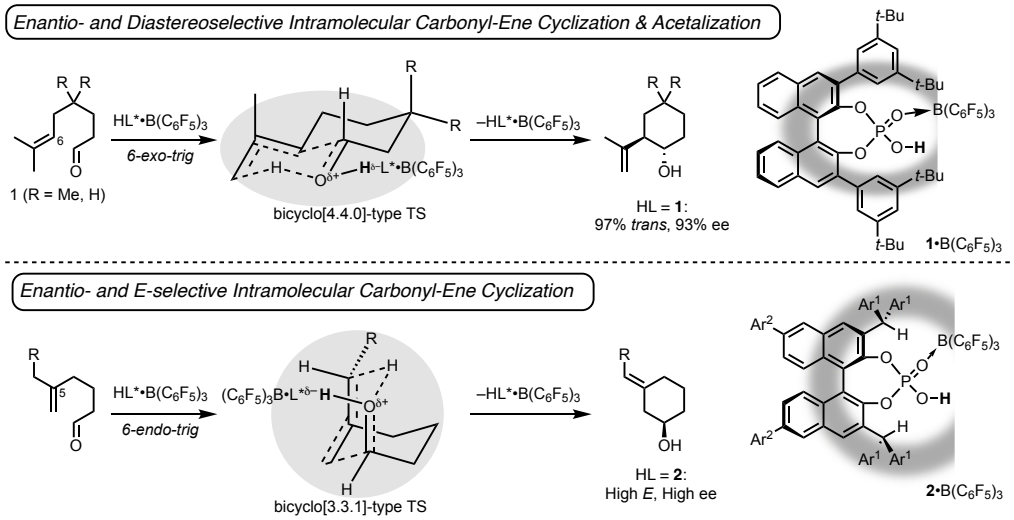
Rational Design of Lewis Acid-Assisted Chiral Brønsted Catalysts for Enantioselective Carbonyl–Ene Cyclization Reactions

([1]*Graduate School of Engineering, Nagoya University*, [2]*Graduate School of Pharmaceutical Sciences, Kobe Pharmaceutical University*) ○Jianhao Huang,[1] Manabu Hatano,[2] Kazuaki Ishihara[1]

Keywords: Carbonyl–Ene Cyclization, Brønsted Acid, Chiral Phosphoric Acid Catalyst, Boron Lewis Acid Catalyst

Carbonyl–ene cyclizations represent a remarkably efficient strategy for constructing carbon–carbon bonds with perfect atom economy. However, despite their potential, enantioselective catalytic variants—particularly those involving non-substituted or low-reactive substrates—continue to pose significant challenges. Our research group's advancements in Lewis-acid-assisted chiral Brønsted acids (LBAs) have effectively addressed these limitations, enhancing both reactivity and selectivity.[1]

This study elucidates using tris(pentafluorophenyl)borane-assisted chiral phosphoric acids as LBA catalysts for intramolecular carbonyl–ene cyclizations. These catalysts facilitate the formation of 6-*exo-trig* cyclizations with elevated enantio- and diastereoselectivities, even for conventionally unreactive substrates. Notably, 5-*exo-trig* cyclization and its tandem acetalization reactions have been developed, achieving unprecedented levels of stereocontrol. Furthermore, innovations in catalyst design, such as 3,3'-diarylmethyl-modified LBAs, enable 6-*endo-trig* cyclizations with exceptional enantio- and *E*-selectivities, thus broadening applications to challenging non-Thorpe–Ingold substrates.[2] These findings underscore the transformative impact of LBA catalysts in overcoming traditional barriers in carbonyl–ene cyclizations, presenting versatile and efficient tools for contemporary asymmetric synthesis.



1) H. Ishihara, J. Huang, T. Mochizuki, M. Hatano, K. Ishihara *ACS Catal.* **2021**, *11*, 6121–6127.
2) J. Huang, K. Ishihara, to be submitted.