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Asymmetric dearomatization enabled by chiral Brønsted acid activation of ynamides

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Chiral Brønsted acid catalysis has evolved into a powerful synthetic tool in asymmetric synthesis in the past two decades or so. However, despite the broad scope of reactions achieved by chiral Brønsted acid catalysis, they only involve the activation of a small number of functional groups. Among them, imines and carbonyls are most studied owing to the defined orientation of their lone pairs for hydrogen bonding with acids (Figure 1a). In contrast, the activation of unsaturated C–C bonds by chiral Brønsted acids toward asymmetric bond formation is much more challenging. In particular, the activation of C≡C bonds has met with limited success. While asymmetric Michael-type addition has been known by indirect activation of C≡C bonds (*e.g.*, ynones, ynoates, Figure 1b), asymmetric control initiated by direct protonation of C≡C bonds is rare. This would generate an ion pair between a carbocation and a chiral counteranion (Figure 1a). Different from the strong directionality of hydrogen bonding, asymmetric induction by counteranion typically relies on much weaker and less directional electrostatic interaction [1].

As a family of versatile electron-rich alkynes, ynamides have been recognized as a powerful building block for the synthesis of diverse cyclic compounds. However, asymmetric transformations of ynamides have been mostly limited to those with existing chirality or asymmetric induction on the electrophile [2]. Moreover, in contrast to the success of metal catalysis, the development of metal-free catalytic enantioselective processes lags behind. In this context, Ye's group achieved great progress [3], building on their extensive experience in the discovery of useful tandem reactions of ynamides [4].

In a recent study, published in *Nat. Chem.*, Ye and coworkers [5] reported their progress in addressing the above challenge by activation of ynamide C≡C bonds with a chiral phosphoric acid, enabling intramolecular asymmetric dearomatization of naphthols, phenols and pyrroles for the rapid assembly of diverse valuable spirocyclic structures with high efficiency and enantioselectivity (Figure 1c). The key to success is the formation of a keteniminium ion, which has electrostatic interaction with the chiral phosphate ion. Meanwhile, the latter has hydrogen-bonding interaction with the electron-rich arene motif. These two types of interactions allow the chiral anion to induce chirality in subsequent intramolecular nucleophilic addition. It is remarkable that this protocol is applicable to the synthesis of enantioenriched spirocyclic 2*H*-pyrroles, which are precursors to spirocyclic γ-lactams leading to useful scaffolds in bioactive molecules.

In conclusion, an elegant catalytic asymmetric dearomatization (CADA) reaction of naphthol-, phenol- and pyrrole-tethered ynamides has been developed with chiral

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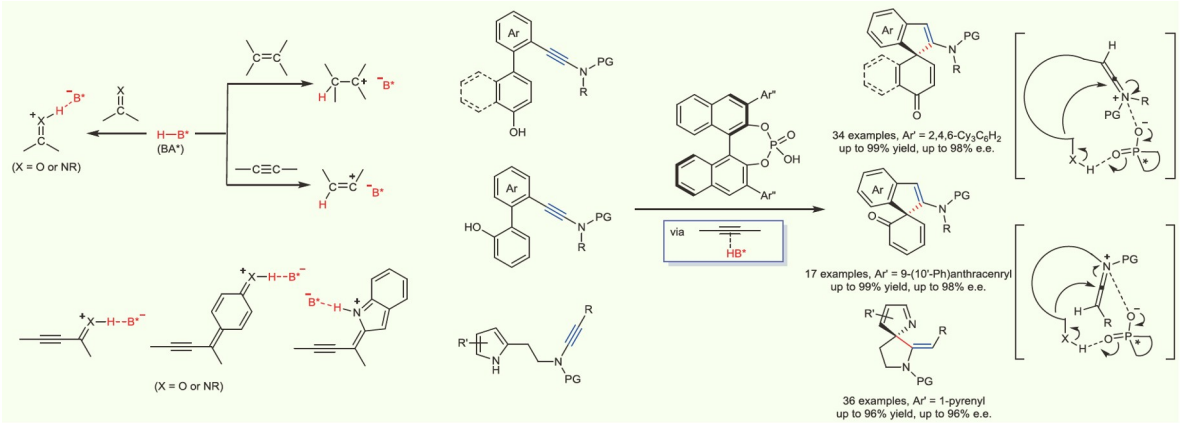

Figure 1 Asymmetric catalysis enabled by chiral Brønsted acid activation [5] (color online).

Brønsted acid catalysis. It represents a rare example of direct chiral acid activation of C≡C bonds for enantioselective bond formation. This process is expected to stimulate a more systematic exploration of catalytic asymmetric reactions of ynamides and other related alkynes.

Conflict of interest The authors declare no conflict of interest.

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