Chiral Brønsted Acids

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Asymmetric Brønsted Acid Catalysis Enabling Hydroaminations of Dienes and Allenes**

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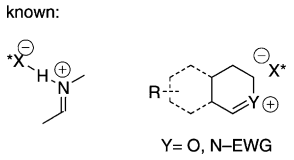
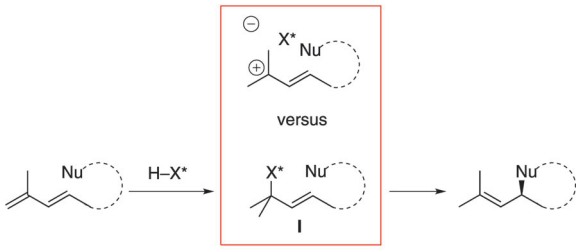
The coordination of substrates with Brønsted or Lewis acids results in an important increase of the reaction rate of numerous reactions involving unsaturated systems through the formation of more-electrophilic complexes or charged intermediates. The prochiral nature of these reaction intermediates and the need to access single enantiomers has driven the development of efficient chiral catalysts. While chiral Lewis acid catalyzed reactions are well developed, hydrogen-bonding and chiral Brønsted acid catalysis are just emerging as new strategies to induce stereoselectivity through association or ion pairing.[1] Of note, pioneering work by Jacobsen and Sigman on organocatalysis using strong hydrogen-bond donors, such as chiral thioureas, and reports by Akiyama et al., and Terada and Uragichi on chiral phosphoric acid organocatalysts have led to intense research efforts; these strategies already show broad applicability in heteroatom-containing π systems (Scheme 1).[2,3a,b] In contrast, the asymmetric Brønsted acid catalysis of reactions that involve C=C bonds remains a very challenging problem, to which important synthetic applications are linked.[4a] In a recent publication, Toste et al. unveiled a new pathway for asymmetric Brønsted acid catalysis of reactions that involve dienes or allenes (Scheme 2) and achieved highly efficient intramolecular hydroamination and hydroarylation reactivity.[5]



Scheme 1. Previous examples of chiral Brønsted acid catalysis. EWG = electron-withdrawing group.

Chiral Brønsted acid organocatalysts typically activate carbon–heteroatom unsaturated systems and rely on ion-pairing for stereoinduction. For example, hydrogen-bond donors such as chiral thioureas can either complex the nucleophile or the counteranion of the positively charged intermediate, or can act as Brønsted acids;[6] these activation manifolds occur with efficient transfer of stereochemical information. Conversely, chiral phosphoric acids possess both acidic and Lewis basic sites, thereby allowing for dual activation of the reagents and/or bidentate complexation. Hindered binol-derived phosphoric acids (binol = 2,2′-dihydroxy-1,1′-binaphthyl) and their derivatives have notably shown excellent results in the asymmetric catalysis of reactions involving prochiral imines.[3c,7]



Scheme 2. Activated intermediates in enantioselective reactions: pathways available to dienes using chiral Brønsted acids (H-X*). Nu = nucleophile.

In the work of Toste et al., binol-derived dithiophosphoric acids are used as chiral catalysts for the cyclization of nucleophiles onto activated allylic intermediates. The high yields and enantioselectivities obtained raised questions about the mechanism when compared to related reactions that rely on ion pairing.[8] Further investigations revealed that the dithiophosphoric acid added onto the diene substrate, and afforded intermediate **I** (Scheme 2). The transient positioning of the chiral conjugate base on the substrate likely results in the efficient transfer of chirality during its S_N2' displacement by an internal nucleophile. As such, stereoinduction in this system would be conceptually related to asymmetric enamine- or iminium-based organocatalysis, where the catalyst is transiently attached through covalent bonding and forms an activated substrate. This novel stereoinduction pathway was supported by the observation of intermediate **A** (Scheme 3) by TOF-MS and by reactions on strained substrates, which showed that both the addition and S_N2' displacement occur in a *syn* fashion. As discussed in the original contribution, there

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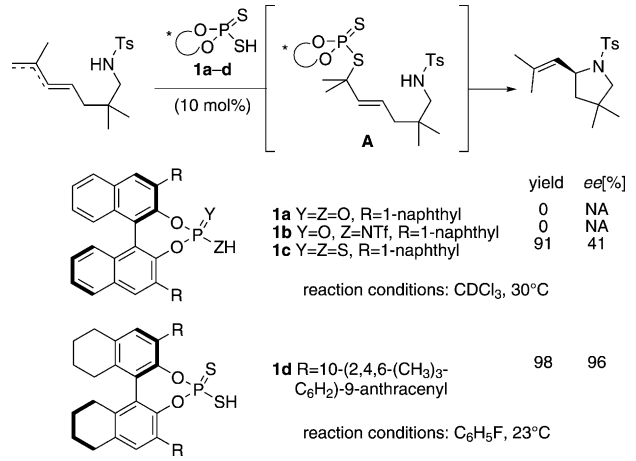
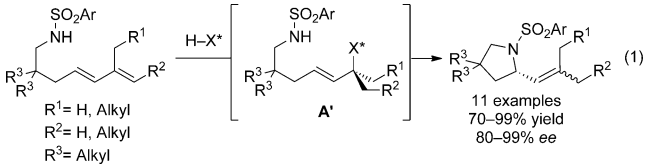


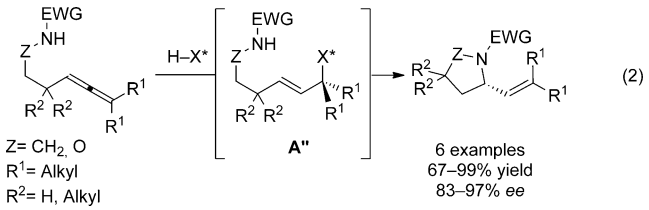
Scheme 3. Proposed mechanism and catalyst optimization. Tf = trifluoromethanesulfonyl, Ts = *p*-toluenesulfonyl.

is no definitive evidence on whether the reaction goes through a formal S_N2' or via an allylic carbocation with anionic pairing of the chiral conjugate base (Scheme 2).[5] Nonetheless, if the latter is the operating pathway, the efficiency of the stereoinduction by the chiral counterion is remarkable.

Phosphoric acid and phosphoramide organocatalysts that are typically used in ion-pairing asymmetric catalysis failed to promote the desired hydroamination reaction.[3c,4b] As such, extensive optimization of the chiral Brønsted acid was performed to obtain high yield and enantiomeric excess. The P=S bond proved necessary for any reaction to proceed (Scheme 3, Y = S), and improved results were obtained with dithiophosphoric acid **1d**. The polarizability of the sulfur atom results in the increased acidity of dithiophosphoric acid and the anion to be a competent nucleophile and afford intermediate **A**. Furthermore, bulkier binol substituents significantly improved the enantiomeric excess, presumably because the stereochemical influence of these bulkier groups reaches the site of the S_N2' attack. Further optimization afforded excellent enantioinduction (96% *ee*). Overall, Toste et al. have demonstrated the unique reactivity of the dithiophosphoric acid catalysts in a association/displacement sequence, which could be applicable to a variety of systems. This data also suggests that dithiophosphoric acids should become standard Brønsted acid catalysts in the design, screening, and optimization of reactions on π systems.

The hydroamination reaction can be performed on dienes [Eq. (1)] or allenes [Eq. (2)] with high yields and *ee* values. Various sulfonamide- and phosphoramide-based protecting groups are tolerated on the nucleophilic nitrogen atom. Additionally, the reaction conditions are mild enough to be compatible with a primary *tert*-butyldimethylsilyl ether group. Substitution is also well tolerated at both positions of the





distal alkene. In most cases, *gem*-dialkyl substituents are present on the backbone of the substrate and likely favor the cyclization owing to the Thorpe–Ingold effect. However, these substituents are not required for allene substrates. *O*-Alkylhydroxylamines can also be used as nucleophiles, thus allowing access to enantioenriched isoxazolidines. Finally, the reaction conditions were used on an electron-rich indole, which added onto the tethered allene, thus providing a fused six-membered carbocycle with comparable efficiency (one hydroarylation example, not shown).

From the perspective of hydroamination, this report is pioneering: it is the only efficient metal-free catalytic variant that yields enantioenriched pyrrolidines. Highly enantioselective intramolecular hydroaminations are rare, require metal catalysis, and are often facilitated by the Thorpe–Ingold effect.[9] These limitations can likely be linked to the recent report by Hartwig and co-workers on the thermoneutrality of intermolecular hydroamination reactions.[10] In fact, the influence of the Thorpe–Ingold effect on the alkene substrates allows for a more favorable reaction. This ensures the process is strictly under kinetic control, thus minimizing reversibility and erosion of enantiomeric excess. Analogously, allenes possess a higher ground state and their reactions are usually inherently more favorable (kinetically and thermodynamically).

At first glance, the scope of the reactivity reported may seem limited in terms of diene and allene substitution. However, this specificity translates to highly symmetrical activated intermediates [**A′** and **A″**, Eqs. (1) and (2)] through the chemo- and regioselective incorporation of HX. Such intermediates are ideally positioned for the efficient transfer of chirality in the S_N2' step, during which the allylic amine stereochemistry is set. This step also leads to the extrusion of the dithiophosphoric acid, thus highlighting the importance of the selective incorporation of HX and efficient substitution for the catalyst turnover. While this clever substrate design was probably needed to validate this strategy in asymmetric catalysis, further reaction development will undoubtedly address this key issue for broad applicability in synthesis. Current results already suggest that the cyclization of various nucleophiles and intermolecular variants of this reaction will lead to a variety of enantioenriched molecules.

Departing from traditional ion-pairing chemistry, this novel strategy in asymmetric catalysis has resulted in efficient metal-free intramolecular hydroamination reactions of dienes and allenes. The reaction using the chiral Brønsted acid probably results in a transient covalent attachment of a chiral leaving group to the allylic system and leads to efficient stereoinduction. Overall, C_2-symmetric dithiophosphoric acids such as **1d** (Scheme 3) pave the way toward a new

family of catalytic transformations involving chiral Brønsted acids.

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