

# Chiral Brønsted Acid Catalysis

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## INTRODUCTION

The use of chiral Lewis acid catalysts is a well established, successful method of achieving asymmetric induction. Recently, the use of chiral Brønsted acid catalysts has become a growing area of investigation. In general, catalysis by chiral Brønsted acids can operate by two types of mechanisms; proton transfer prior to the rate limiting step is generally known as specific acid catalysis, and proton transfer in the rate limiting step, is termed general acid catalysis or hydrogen bond catalysis. The former is characteristic of stronger acids, such as phosphoric acids, while the latter is characteristic of weaker acids, such as thioureas. A clear line cannot be drawn between the two without detailed mechanistic study, and a catalyst that acts as a specific acid in one transformation may act as a general acid in another.<sup>1</sup>

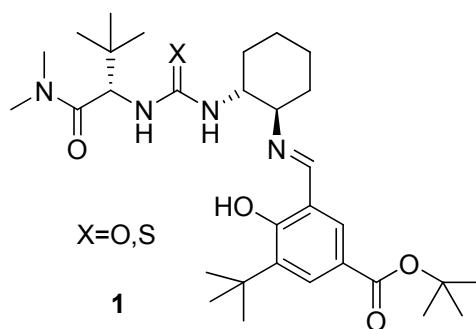
One interesting aspect of chiral Brønsted acid catalysis is that the single *s* orbital of hydrogen appears to provide few opportunities for control of transition state geometry. This perception contributed to a paucity of research in the area until fairly recently. At the same time, *achiral* Brønsted acid catalysis has been pervasive since the early days of chemistry, providing many candidate reactions that might be made asymmetric. Recent years have seen an explosion of literature studies using chiral Brønsted acid catalysts and applying them to reactions. Space does not permit the examination of every example in the literature, so this review will be limited to an examination of catalyst types, and to reactions having published mechanistic studies or particular novelty, with an emphasis on chiral phosphoric acids.

## CHIRAL UREA AND THIOUREA CATALYSIS

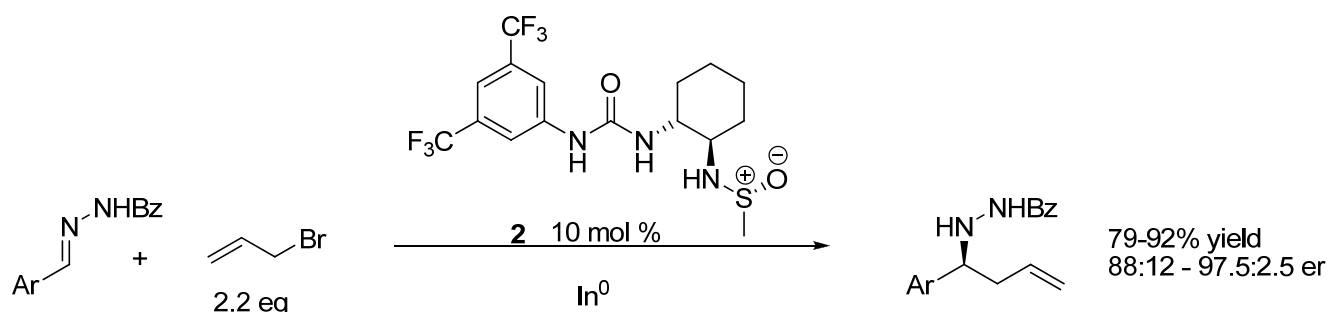
The most successful general acid catalysts are those based on the framework of Jacobsen and co-workers (Figure 1).<sup>2,3</sup> Excellent yields and enantioselectivities were obtained in the hydrocyanation of imines even at 1 mol% catalyst loading. Mechanistic investigation showed that activation of the electrophile occurs by double hydrogen bonding with the urea moiety. This highly modular design has produced a multitude of variants optimized for different reactions.<sup>4</sup> Many modifications have focused on the right hand side of the molecule, where variation of the nitrogen substituent allows introduction of tunable Lewis or Brønsted base functionality, allowing binding or activation of the nucleophile. An excellent example of this double activation is Jacobsen and co-workers' indium mediated asymmetric allylation of acylhydrazones (Scheme 1).<sup>5</sup> The proposed mechanism involves both binding of the allyl

indium reagent by the Lewis-basic sulfoxide and activation of the hydrazone by the hydrogen bond donation by the urea, giving excellent yields and enantioselectivity.

**Figure 1. Jacobsen's Urea Catalyst**



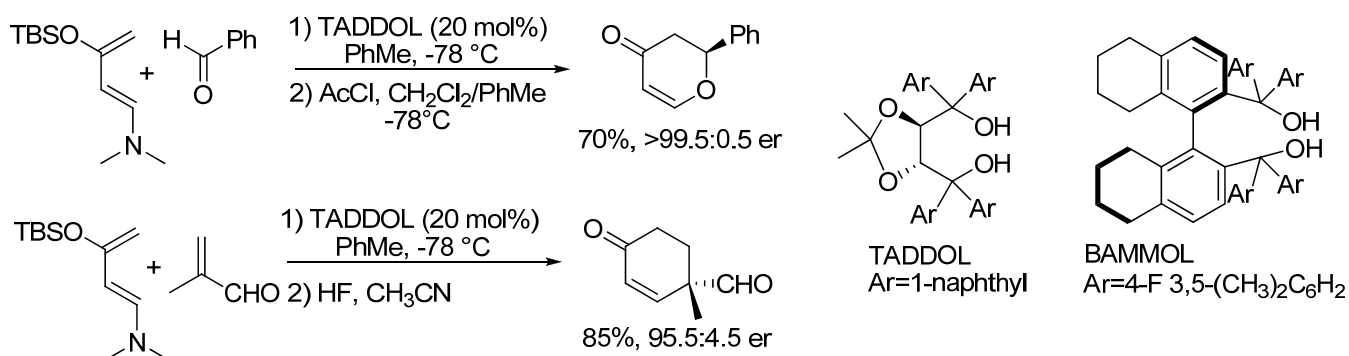
**Scheme 1. Bifunctional Urea Catalyzed Allylation**



## CHIRAL DIOLS

Rawal and co-workers have found that TADDOL<sup>6</sup> and BMMOL<sup>7</sup> derivatives can accelerate Diels-Alder<sup>8</sup> and hetero Diels-Alder reactions of very reactive amino-siloxy dienes with good to excellent enantiomeric excess. It is hypothesized that these reactions are promoted by a single hydrogen bond, donated from a hydroxyl that has been activated by accepting another hydrogen bond from its neighbor. This is supported by x-ray crystallography of a BMMOL/benzaldehyde co-crystal<sup>9</sup>.

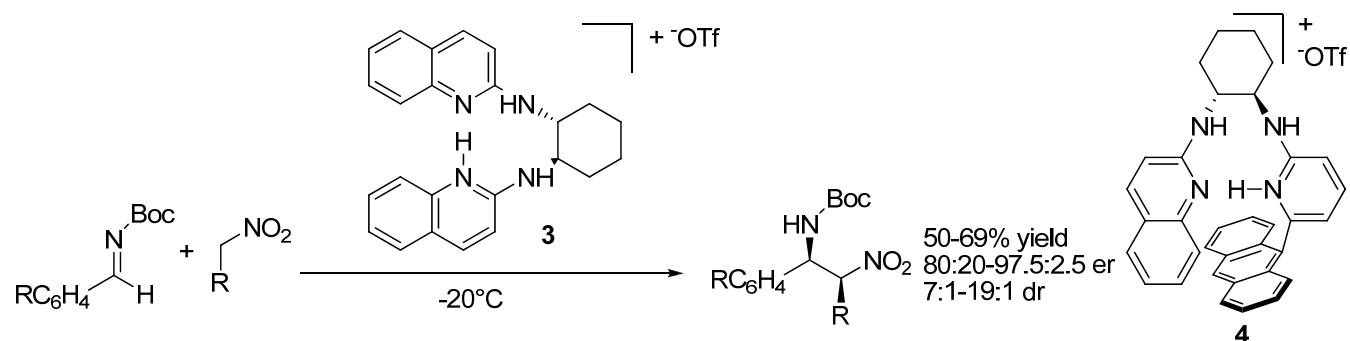
**Scheme 2. Chiral Diol Catalyzed Diels-Alder**



## AMMONIUM IONS

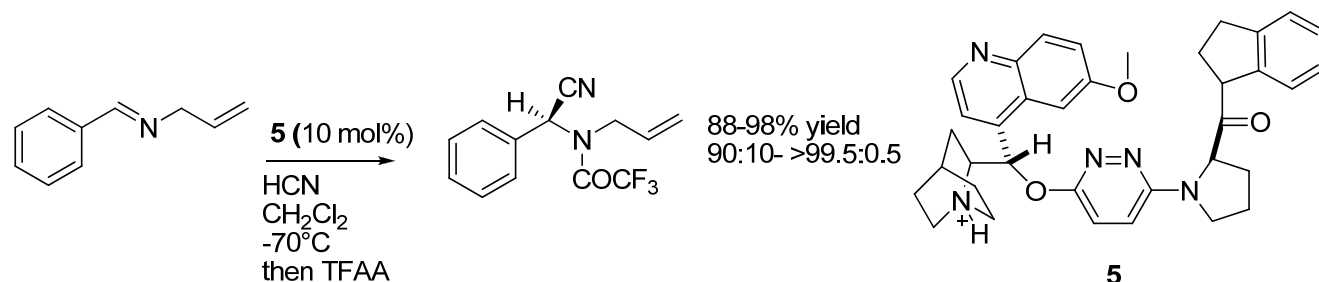
With the success of the urea catalysts, some researchers have sought stronger proton donors to achieve stronger activation of electrophiles. Several chiral ammonium ions have been used for this purpose. Johnston and co-workers have developed the quinoline derived catalyst **3**, which provides good enantioselectivity in aza-Henry reactions (Scheme 3),<sup>10</sup> and catalyst **4** that is very effective for the addition of nitroacetic acid esters to Boc-imines.<sup>11</sup> In the latter case, use of **4** is critical to prevent epimerization of the highly acidic  $\alpha$  stereocenter produced.

### Scheme 3. Chiral Ammonium Ion Catalyzed Aza-Henry Reaction



Quinoline derived catalyst (**5**), whose conjugate base is commonly used in dihydroxylation, was found by Corey and co-workers to catalyze the hydrocyanation of aryl aldimines with good enantioselectivity (Scheme 4).<sup>12</sup> It was hypothesized that the imine is bound in a chiral pocket similar to the model of the asymmetric dihydroxylation reaction.

### Scheme 4. Ammonium Ion Catalyzed Strecker Reaction

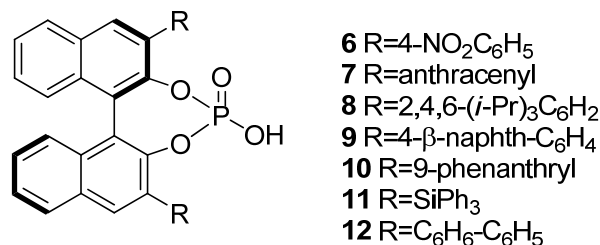


## CHIRAL PHOSPHORIC ACIDS

BINOL-derived phosphoric acid esters provide a class of stronger, sterically tunable acids. These catalysts are highly enantioselective for additions of various nucleophiles to imines, as well as promoting aza-Diels-Alder reactions and Nazarov cyclizations. While there is no single “best” catalyst, there are a few that have proven themselves to be quite versatile, in particular catalysts **10** and **11**. The

common feature of versatile catalysts is that they surround the binding site with large aryl groups to confine the substrate and transfer chirality effectively.

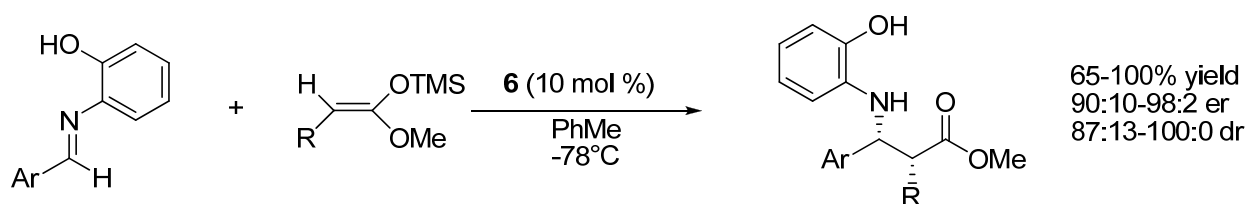
**Figure 2. Chiral Phosphoric Acid Catalysts**



### Chiral Brønsted Acid Catalysis in Mannich Reactions

One of the first and best studied asymmetric Mannich reactions was developed by Akiyama and coworkers (Scheme 5).<sup>13</sup> Previously, Akiyama had demonstrated the effectiveness of HBF<sub>4</sub> as a catalyst in the Mannich reaction. Building on this work, BINOL phosphoric acids were chosen due to their low pK<sub>a</sub> (~1.3), cyclic structure, and availability of the chiral source. The presence of an ortho hydroxyl group on the N-aryl imine was critical for both rate and enantioselectivity, consistent with a proposal of two point binding. A para-nitro phenyl substituent on the catalyst was also found to be critical to yield and enantioselectivity, suggesting a vital role of  $\pi$ -stacking in the binding of the substrate in addition to increased acidity.

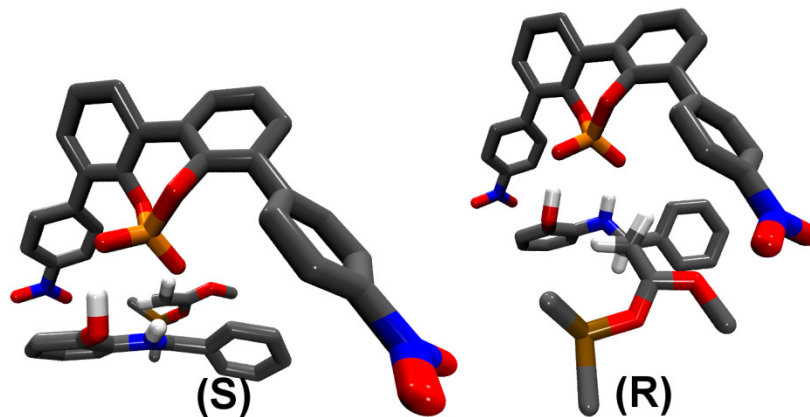
### Scheme 5. Akiyama's Asymmetric Mannich Reaction



The mechanism of this reaction was investigated by extensive DFT calculations. Two pathways were found, one monocoordinate (not shown) and the other dicoordinate, with the latter favored by 3.4 kcal/mol (Figure 3), thus supporting the two point hydrogen bonding hypothesis. Proton transfer prior to the rate limiting attack of the nucleophile was found to be rapid, with the equilibrium favoring the iminium phosphate. DFT studies therefore support a mechanism involving specific acid catalysis. Transition states leading to both enantiomers were located, in order to rationalize the enantioselectivity of the catalyst (Figure 3).<sup>14</sup> It was hypothesized that the origin of enantioselectivity is a steric interaction

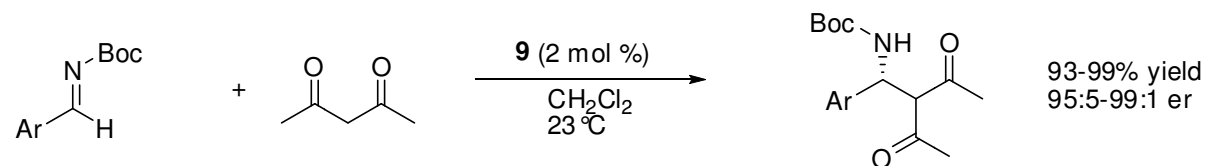
between the TMS group of the silyl ketene acetal and the catalyst in the transition state leading to the *S* product.

**Figure 3. Computed Transition States**



Two point binding can be excluded if larger more sterically shielding aryl groups are used on the catalyst. Simultaneously with Akiyama, Terada and co-workers researched similar catalysts based on 4-biaryl substituted BINOL phosphoric acids.<sup>15</sup> Their optimized catalyst (**9**) provides high enantioselectivity and yield for direct Mannich reactions of N-Boc imines, eliminating the hydrogen bond required by Akiyama's catalyst, and providing a more practical, easily cleavable protected amine without prior nucleophile formation (Scheme 6). While a full mechanistic analysis has not been published for this system, preliminary work suggests the formation of a strong hydrogen bond between the catalyst and imine at equilibrium rather than complete proton transfer, consistent with the expected lower pKa of an N-acyl iminium, compared to an N-aryl iminium.<sup>16</sup>

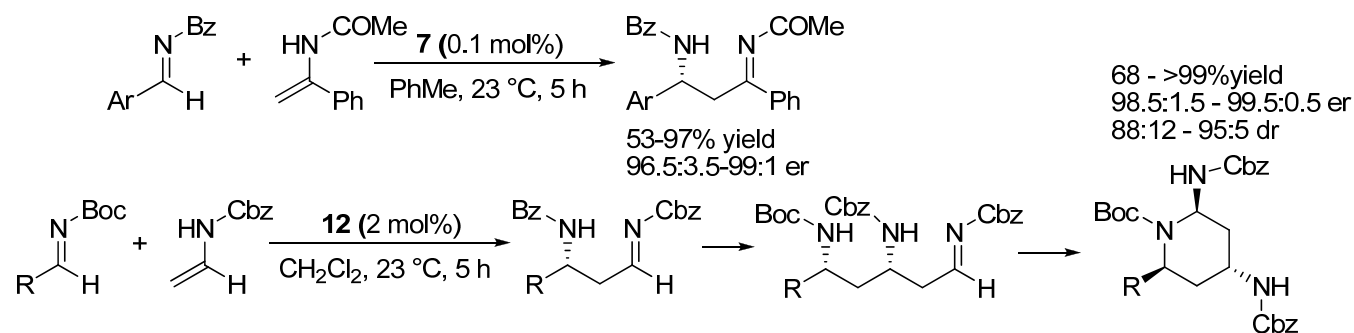
### Scheme 6. Terada's Enantioselective Mannich Reaction



### Enamine Addition Reaction

Terada has developed an enantioselective enamine addition reaction that gives excellent yields and enantioselectivities with very low catalyst loadings (Scheme 7).<sup>17</sup> While the initial report was limited to aryl imines and enamines, a subsequent report of a cascade double addition reaction/cyclization demonstrated high enantioselectivity with alkyl and glyoxylate derived imines.<sup>18</sup>

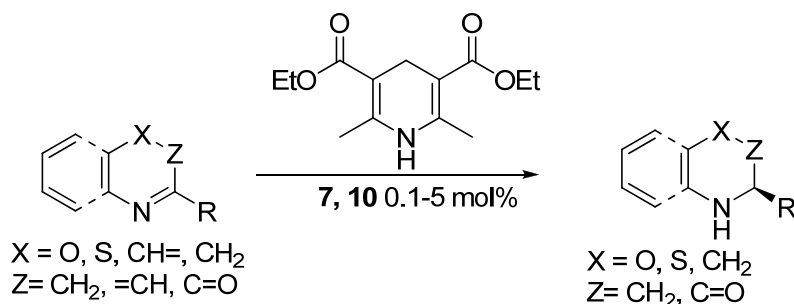
### Scheme 7. Enantioselective Enamine Addition Reaction



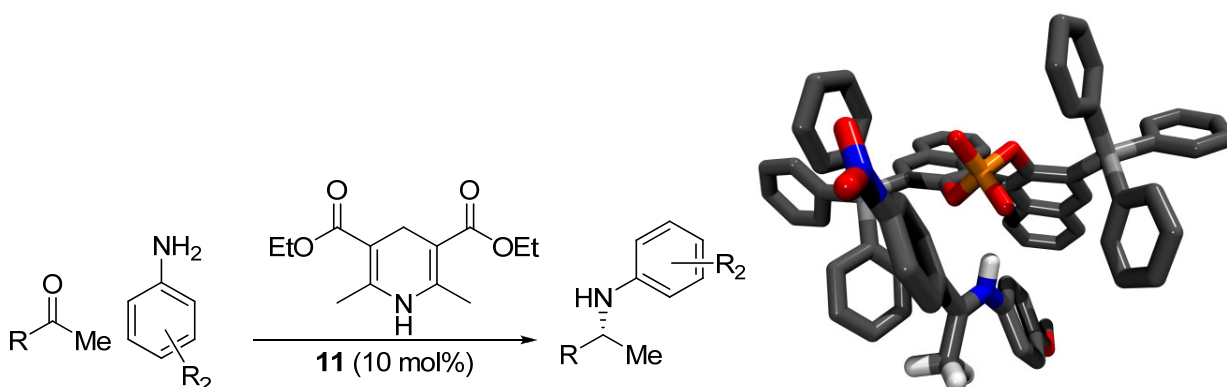
### Transfer Hydrogenation

Rueping and co-workers have developed a similar catalyst for asymmetric transfer hydrogenation of internal imines, and related heterocycles using the Hantzsch ester (Scheme 8).<sup>19,20,21</sup> Notably, the reaction is tolerant of sulfur functionality, frequently a problem with transition metal catalysts. Furthermore, the catalyst loading is quite low, in some cases the optimal loading is 0.1%, with only a small loss of selectivity at lower loadings.

### Scheme 8. Enantioselective Transfer Hydrogenation of Heterocycles



MacMillan and co-workers have produced a new catalyst (**11**) bearing triphenylsilyl groups at the 3 and 3' positions of the binaphthyl phosphoric acid. This catalyst has allowed the highly enantioselective reductive amination of methyl ketones without prior formation of an imine using the Hantzsch ester.<sup>22</sup> While limited to methyl ketones by steric interactions with the catalyst, they have demonstrated good enantioselectivity for a series of aliphatic methyl ketones. A crystal structure has been obtained of the iminium phosphate intermediate, showing clear shielding of the Re face of the imine (Figure 2).

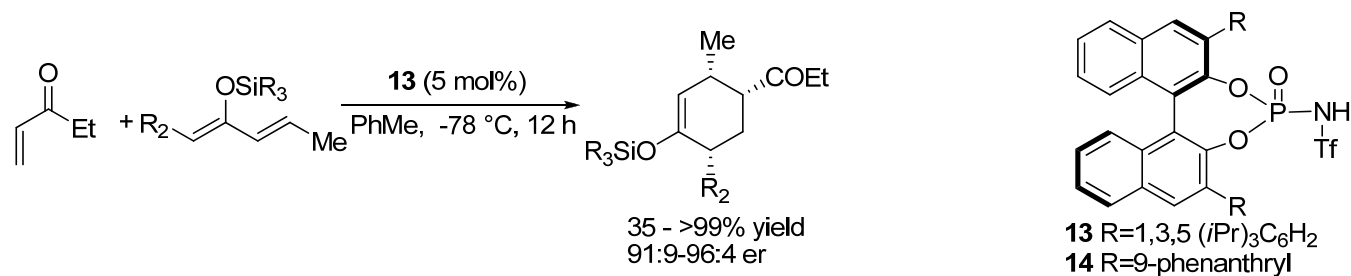


**Figure 2.** Enantioselective Reductive Amination and Structure of Iminium Phosphate Intermediate

### N-TRIFLUOROMETHYL SULFONYL PHOSPHORAMIDES

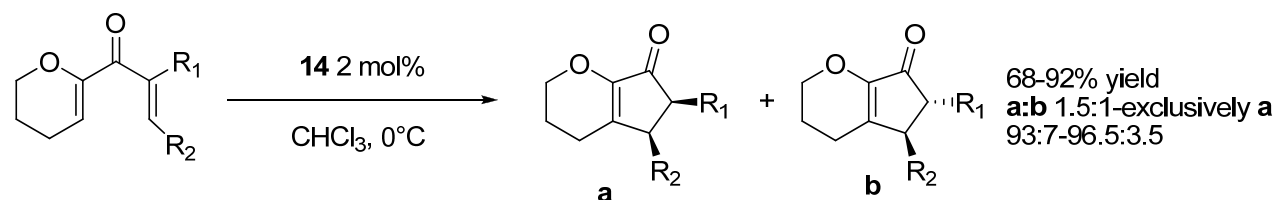
Phosphoric acids do not appear to be strong enough to efficiently activate ketones. Yamamoto and co-workers designed N-triflyl phosphoramidate catalyst **13**, which they presume to be a strong acid, for enantioselective Diels-Alder reactions of ethyl-vinyl ketone with siloxy dienes.<sup>23</sup> The analogous phosphoric acid gave no reaction, highlighting the importance of choosing an appropriate acid strength.

#### Scheme 2. Scope of Enantioselective Diels-Alder Reaction



Rueping and co-workers have developed an asymmetric Nazarov cyclization (Scheme 9).<sup>24</sup> In this case, the reactivity was increased by the use of N-triflyl phosphoramides, permitting the reduction of the reaction temperature from 60 °C to 0 °C, with increased selectivity. The product was produced with high enantioselectivity, but generally moderate to low diastereoselectivity, favoring the *cis* product. The *trans* product is accessible via mild base catalyzed epimerization.

#### Scheme 3. Enantioselective Nazarov Cyclization



## CONCLUSION

Chiral Brønsted acid catalysis is a growing area with many possibilities. The Strecker and Mannich reactions, as well as transfer hydrogenation are among the most well explored areas; however for many reactions, the potential of using chiral Brønsted acids has yet to be tapped. Catalyst structures have been identified that can be tuned to provide high yield and enantioselectivity in a variety of reactions. This has been accomplished using Brønsted acids with a variety of structures, strengths and activation mechanisms.

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