Brønsted Acid Catalysis

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A Chiral *N*-Phosphinyl Phosphoramide: Another Offspring for the Sage Phosphoric Acid Progenitor**

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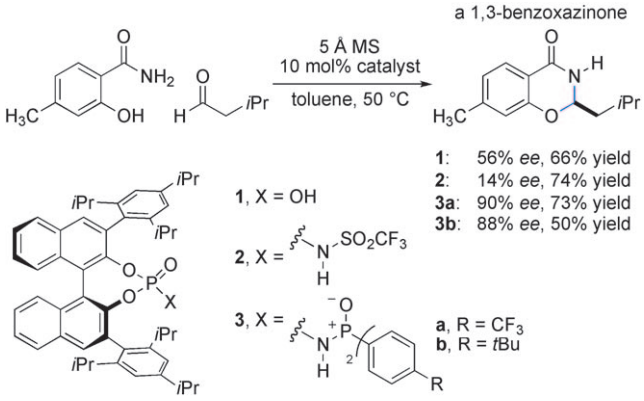
Brønsted acids · heterocycles · *N,O*-acetals · organocatalysis · phosphoramides

In a current publication, List and co-workers report the enantioselective intramolecular cyclization of hydroxy acylimines leading to bicyclic *N*-acyl *N,O*-acetals.[1] A new reagent was developed to accomplish this, that is, a chiral nonracemic *N*-phosphinyl phosphoramide, **3**, that (presumably) accelerates the overall reaction and differentially accelerates formation of one enantiomeric form of the product. This study extends the utility of chiral phosphoric acid catalysis[2] in oxygen additions to azomethines, an area pioneered by Antilla et al.[3,4] At stake here is the efficiency with which biologically active small molecules known as 1,3-benzoxazinones, bearing a chiral *N,O*-acetal, can be prepared. Indeed, an enantioselective preparation of the analgesic chlorothenoxazine is accomplished in a single step using catalyst **3a**.

Their study begins with the use of chiral phosphoric acid catalyst **1** ((*S*)-trip), which delivered the benzoxazine derived from isovaleraldehyde in a 3:1 enantiomeric ratio (e.r.) favoring the (*R*)-*N,O*-acetal (Scheme 1). It is possible that

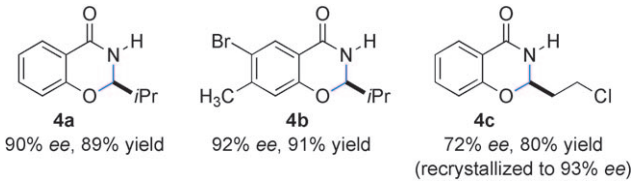


Scheme 1. Development of a chiral *N*-phosphinyl phosphoramide-catalyzed enantioselective acetalization.

modifications to the binaphthyl 3,3′-substituents could have improved enantioselection, as they did previously with the same transformation using *ortho*-amino benzamides,[5] but the authors decided to instead modify the phosphorous substituent. This approach provides more immediate access to catalyst derivatives, but may come at the expense of any enantioselection since the changes drastically alter the catalyst's cavity and the hydrogen bond that is presumably key to reactivity. The behavior of a sulfonamide derivative, **2**,[6] was not encouraging, and a phosphonamide (not shown) provided an improvement to enantioselection but not rate. However, phosphinamide **3** derivatives delivered improvement to both selectivity and reactivity.

An investigation of the effect that electron-deficient aryl substituents at phosphinamide phosphorous might have on reactivity and enantioselectivity uncovered a needed increase in reactivity. In this comparison, similar enantioselectivity is obtained with either catalyst **3b** or **3a**, but the latter could be optimized to a 90% yield using an excess of aldehyde.

This catalyst became the reagent of choice to survey the suitability of a range of substrates for the transformation. Notable examples from the preliminary scope include α-substituted aldehydes, such as isobutyraldehyde, which provided benzoxazinone **4a** (Scheme 2) in 89% yield and 90% *ee*



Scheme 2. Representative benzoxazines prepared using a chiral *N*-phosphinyl phosphoramide catalyst.

(95:5 e.r.). This aldehyde was used to create a variety of 1,3-benzoxazinones generally at the level of 94:6 e.r. or greater (e.g., **4b**). In a final demonstration, the authors prepared the analgesic chlorothenoxazine (**4c**) in 80% yield and in a single step from 3-chloropropanal in 86:14 e.r.

Although purely speculative, a stereochemical model is advanced that proposes discrete roles for the catalyst N–H bond and phosphinamide oxygen. Specifically, these two points establish hydrogen bonds to the substrate through

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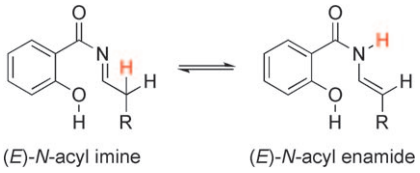
complementary contacts with the azomethine nitrogen and phenol hydrogen, respectively. This effectively twists the substrate about the exocyclic benzoyl carbon–carbon bond, thereby guiding addition of the phenol oxygen to the iminium carbon. This model is consistent with the configuration of the products, but mechanistic studies for these catalysts remain limited.[7] That an acylimine is a key intermediate is consistent with the demonstration that the e.r. of the product formed is the same, whether the substrate is an *ortho*-hydroxy benzamide–aldehyde combination, or an *N*-acyl enamide (Scheme 3). However, these experiments do not seem to



Scheme 3. Tautomeric forms of *N*-acyl enamide.

narrow the key intermediate to only an *N*-acyl imine; it remains a possibility that the catalyst protonates the *N*-acyl enamide as the oxygen adds—in concert rather than stepwise.

Beyond the practical value associated with access to enantioenriched 1,3-benzoxazines for which phosphoramide **3a** is the optimal catalyst, a complement of diverse new tools (including a bisphosphoramide) can now be applied elsewhere. One basic investigation that seems worthy of broader study[8] is the relative acidity within and across classes of Brønsted acids.[9] It should be noted that the "acidity" of a given catalyst, as defined by pK_a, is not necessarily related directly to its activity or selectivity.[7b,10]

In the broader context of biomimetic asymmetric catalysis, this catalyst motif is a new platform with which we might advance on our grand challenges. Catalyst design is the key that will eventually unlock the myriad of reaction types we cannot yet effect. Barton conveniently encapsulated the spirit of this subdiscipline of enantioselective catalysis in 1973 when he pontificated:

"*I can foresee also a great deal of work on the synthesis of molecules which will imitate more closely the chemical synthesizing powers of enzymes. I do not believe that you have to have a great big protein in order to get this kind of effect. I suspect a much smaller molecule with the right kind of three-dimensional structure will do the same sort of thing, but these kinds of molecules are quite unknown yet in organic chemistry, and obviously we have to make them.*"[11]

Extrapolating forward in the Barton style, chiral Brønsted acids that provide hydrogen bonds with different electronic character, and a fashionable three-dimensional environment, constitute a solid step toward the imitation of nature's most prized chemical transformations.[12] List's new catalyst broadens the class of phosphoric acid-derived Brønsted acids first described by Akiyama and Terada, and unlocks the door to a novel enantioselective 1,3-benzoxazine synthesis.

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