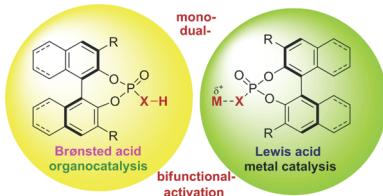


## Complete Field Guide to Asymmetric BINOL-Phosphate Derived Brønsted Acid and Metal Catalysis: History and Classification by Mode of Activation; Brønsted Acidity, Hydrogen Bonding, Ion Pairing, and Metal Phosphates

Dixit Parmar, Erli Sugiono, Sadiya Raja, and Magnus Rueping\*

Institute of Organic Chemistry, RWTH Aachen University, Landoltweg 1, 52074 Aachen, Germany



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Received: March 14, 2014

Published: September 9, 2014



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## 1. INTRODUCTION

The activation of a substrate by a chiral catalyst is now regarded as one of the most powerful strategies that can be employed in the art of asymmetric synthesis.<sup>1</sup> The development of small-molecule hydrogen-bond donors has received a tremendous amount of attention from research groups, and the quest to reach the levels of control that nature can achieve is a constant challenge.<sup>2</sup> Brønsted acids have proven themselves to be highly efficient and versatile catalysts for an ever expanding list of synthetic transformations. The ability to lower the LUMO of an electrophile via protonation and thus “activate” the substrate toward reacting with nucleophiles is the classical strategy employed. Within this vast field, the past decade has seen BINOL-derived<sup>3</sup> phosphoric acids establish themselves as one of the most prominent players.<sup>4</sup> They have achieved this status by being highly versatile catalysts and have been shown to catalyze a plethora of asymmetric transformations typically using operationally simple and mild reaction conditions. The versatile nature of the catalysts has not been solely due to their Brønsted acidity, but more often than not additional modes of activation are exhibited by them. However, when phosphoric acids are not acidic enough to activate a particular substrate, phosphoramides (prepared in one step from the parent phosphoric acid) have stepped into the limelight and have shown themselves to be equally as powerful catalysts.<sup>5</sup> It should be noted that structurally related stronger Brønsted acids known as JINGLES<sup>6</sup> and disulfonyl imides<sup>7</sup> exist, but they will not be covered within this Review.

Remarkably, considering that catalytic activity has been shown to vary greatly depending on the nature of the phosphoric acid, studies into the  $pK_a$ 's are relatively scarce. A general study of  $pK_a$ 's in DMSO on a range of chiral Brønsted acids was published by O'Donoghue and Berkessel.<sup>8</sup> Recently, a theoretical study by Cheng and Li calculated the  $pK_a$ 's of BINOL-phosphoric acid values including thiophosphoric acids, which were found to be considerably more acidic.<sup>9</sup> In 2013, Rueping and Leito disclosed a full study on establishing an acidity scale for the commonly used Brønsted acid catalysts.<sup>10</sup> The measurements were conducted in MeCN by using UV-vis spectrophotometric methods. From the measurements that were conducted in MeCN, it was found that three distinct groups of varying acidity were formed, phosphoric acids, *N*-sulfonyl phosphoramides, and sulfonyl imides (Figure 1).

In acetonitrile, phosphoric acids were found to have  $pK_a$ 's between 12 and 14, *N*-sulfonyl phosphoramides between 6 and 7, and finally the sulfonyl imides around 5. For comparison, common laboratory acids were also measured using the same techniques, and a selection of those values are shown below in Table 1.

The study also investigated the correlation between Brønsted acidity and reactivity. A Nazarov cyclization was chosen as a model reaction because no product inhibition occurred. A series of catalysts were tested, and the rates of the reactions were measured. From the data, a graph of  $-\log(k_1)$  against the  $pK_a$  of the catalyst was plotted (Figure 2).

The result was a clear relationship between the observed rate constant and the acidity of the catalyst. In general, the more acidic catalysts resulted in higher rate constants. It should be pointed out

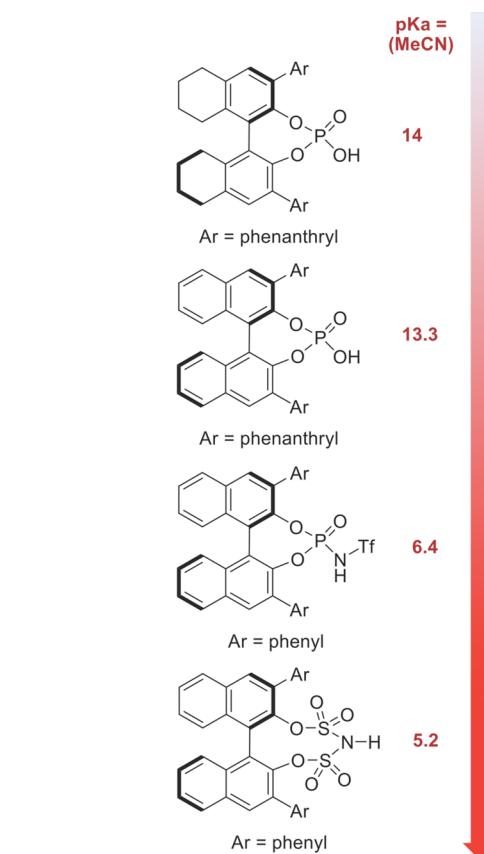


Figure 1. Acidity scale for selected BINOL-derived Brønsted acids.

Table 1.  $pK_a$ 's of Common Acids in MeCN

acid	$pK_a$ in MeCN
saccharin	14.6
picric acid	11.0
HCl	10.3
TsOH	8.5
$4\text{-NO}_2\text{C}_6\text{H}_4\text{-SO}_3\text{H}$	6.7
HBr	5.5

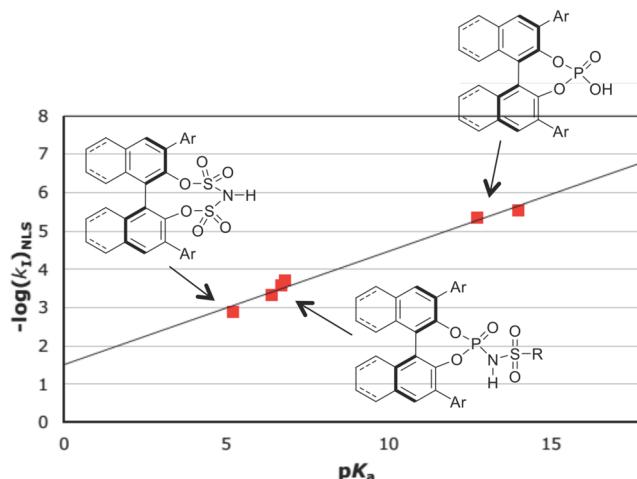


Figure 2. A plot of the rate of a reaction versus acidity of catalyst.

however that enantioselectivity is dependent on catalyst architecture. Nevertheless, activation (and thus reactivity) can be directly correlated to acidity if no catalyst inhibition occurs.

Within the vast field of organocatalysis,<sup>11</sup> chiral BINOL-derived phosphoric acids have stood strong during the test of time and are very much at the forefront of modern asymmetric chemistry today. In 2013 alone, over 100 research articles were published, which utilized them as catalysts for synthetic procedures. The main factor that has allowed them to be featured in a large number of research projects is that they are incredibly versatile and can be thought of as much more than a simple Brønsted acid. As chiral phosphoric acids attempt to cement their status as one of the essential tools for an organic chemist, we have deemed it of most importance to analyze the “mode of action” in play during reactions involving these catalysts. In many of the cases, the catalyst functions through various interactions with substrates during the key stereoselective step. Many excellent reviews exist for chiral phosphoric acids; however, they nearly all focus on the different types of reactions possible rather than the activation mode involved.<sup>12</sup> This Review will inform the interested reader of how the catalysts activate substrates and attempt to reclassify the entire history of chiral BINOL-derived Brønsted acid transformations including when combined with metal centers up until mid of 2014.

### 1.1. Phosphinic Acids—The Starting Seeds?

Sir John Cornforth, who sadly passed away last year at the age of 96, was awarded the Nobel Prize for Chemistry in 1975 for his contributions to the stereochemistry of enzyme catalyzed reactions. Although he was well-known for his work in this field, many may not be aware of his ground-breaking work on phosphinic acids. In 1962, Sir Cornforth became a codirector of Shell Research’s Milstead laboratory. Although fascinated by the way nature was able to synthesize molecules especially in a stereoselective manner, he was determined to imitate nature as best as he could.<sup>13</sup> During his time there, he began research into catalysts that would allow him to carry out the hydration of alkenes in a stereospecific manner. After a detailed analysis of the requirements of the ideal catalyst, he decided to investigate phosphinic acids containing the general structure 1 (Figure 3).

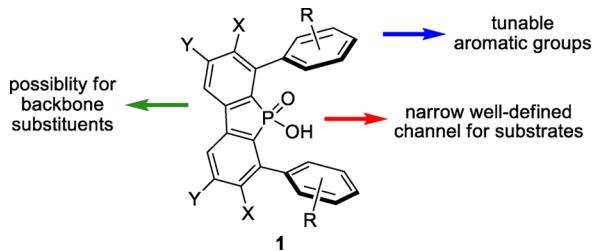


Figure 3. Phosphinic acid catalysts developed by Cornforth (1978).

Aside from containing the correct acidity required for catalysis, Cornforth was particularly attracted by the five-membered dibenzophenone derivatives for their rigidity and the possibility for the attachment of groups at appropriate positions to create a cavity for potential substrates. The correct choice of substituents, in particular with regards to the steric size of X, would potentially create a chiral axis due to restricted rotation of the benzene rings. At the time, he proposed a potential mechanism for the hydration and possible problems that may be associated with using phosphinic acid catalysts (Figure 4).

Protonation of an alkene was proposed to initially lead to a close ion-pairing between the phosphate and the newly generated carbocation (2). The desired reactivity was for this complex to then react with H<sub>2</sub>O. However, it was also envisioned

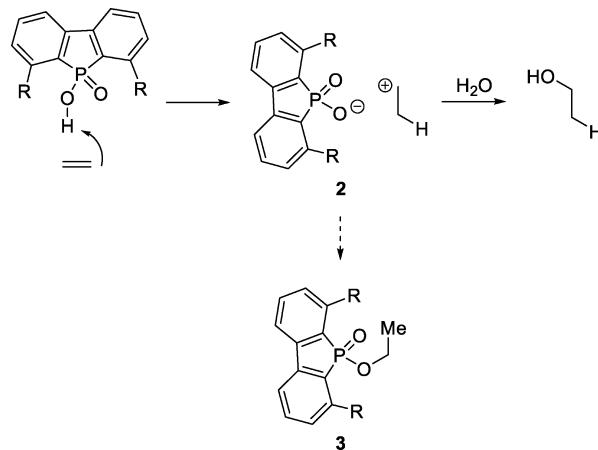


Figure 4. Potential reactivity of phosphinic acids with olefins.

that the phosphate could potentially react with the intermediate to form the corresponding ester 3 and thus deactivate the catalyst. Following his review lecture, Cornforth published a series of papers related to the synthesis of a wide variety of derivatives based around the general core structure of 1.<sup>14</sup> For the job they were designed, the catalysts performed well and were more efficient than comparable acids such as TsOH. Results on the enantioselectivity unfortunately have not been published, but nevertheless Cornforth can be considered as a true pioneer. His ideas on catalyst design and structure, even though formulated for phosphinic acids over 30 years ago, are very much valid for chiral phosphoric acids today.

### 1.2. Mechanistic Differences from the Pioneers

Although the use of BINOL-derived phosphoric acids has been known for over 40 years in organic synthesis, their usage as catalysts started only 10 years ago. Akiyama is widely credited as one of the pioneers of the field with his report in 2004 on the chiral Brønsted acid-catalyzed Mannich reaction.<sup>15</sup> Akiyama’s approach utilized 2-hydroxyphenyl imines 4 with silyl ketene acetals 5 in the presence of 10 mol % PA 15 (see section 1.4 for catalyst abbreviations) to give the Mannich products 6 (Figure 5).

The reaction proceeds smoothly with a range of substrates to give the *syn*-diastereoisomer products 6 generally in high yields and enantioselectivity. Even though no mechanistic studies had been conducted at this point, Akiyama recognized the importance of the 2-hydroxy group toward the reaction mechanism but opted at the time of publication to propose a simple monocontact mechanism. In 2007, he disclosed the results of theoretical calculations and refined the mechanism to that of a dual activation mechanism.<sup>16</sup> It was calculated that the acidic proton activates the imine by protonation, and an additional interaction between the phenol proton and the Lewis basic site on the catalyst aids to create a rigid and stronger chiral environment around the substrate. Akiyama has also shown this reaction to be easily scaled up to gram scale<sup>17</sup> and has developed a simpler catalyst,<sup>18</sup> which is also able to achieve high enantioselectivities.

Later, the group of Terada disclosed their results on the use of chiral Brønsted acids to also catalyze the Mannich reaction. Terada’s approach involved a more direct Mannich reaction of acetyl acetone 8a with N-Boc protected imines 7 (Figure 6).<sup>19</sup>

Interestingly, he found that tuning of the 3,3'-positions with bulky substituents enabled both high yields and high enantioselectivities of the corresponding secondary amine products

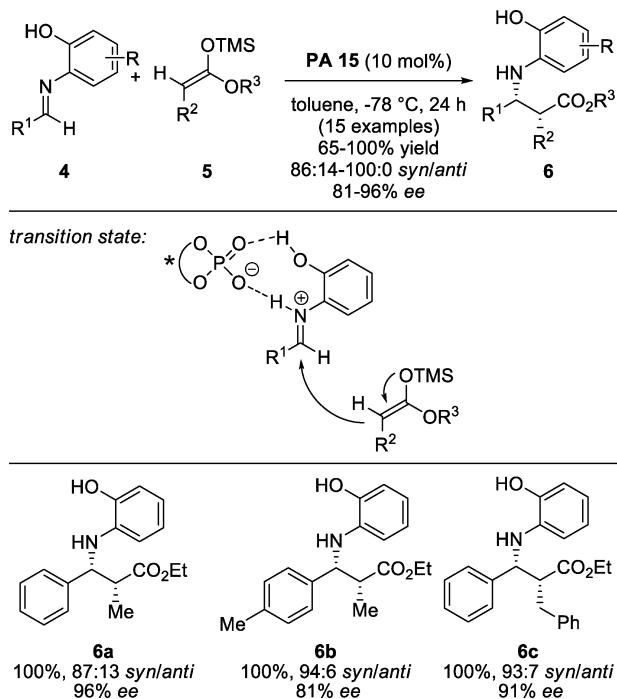


Figure 5. Mannich-type reaction by Akiyama (2004).

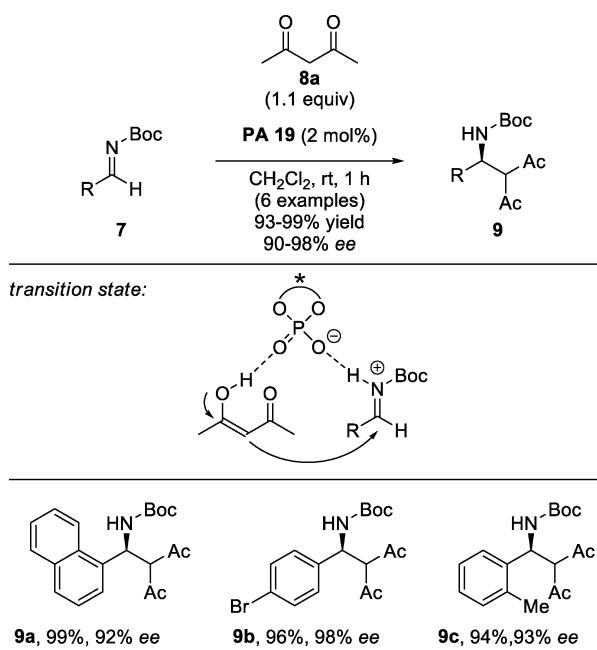


Figure 6. Direct Mannich reaction by Terada (2004).

9. That is in contrast to Akiyama's protocol where he found that the electronics of the catalyst was more important for the enantioselectivity. Mechanistic studies by Terada on the reaction mechanism proposed a simple monocontact H-bonding interaction with the imine.<sup>20</sup> It was later shown by the group of Goodman that the catalyst has a bifunctional role and activates both the imine and the nucleophile (acac) through its resonance enol form.<sup>21</sup> It should be noted that protonation is thought to occur on the nitrogen atom of the N-Boc imine; however, protonation at the more basic oxygen atom of the Boc-group cannot be fully ruled out.

This variation in mechanism for seemingly identical reactions on paper is actually more frequent than one might expect. Throughout this Review, we will come across reactions that bear the same or resemble one another in terms of the transformation occurring, but will however be controlled in very different ways by the catalyst used. We will as best as possible provide the proposed or accepted mechanism that is responsible for the enantioselectivity of the reactions covered in this Review. Where this is not possible, we will use our experienced opinion of the most likely role of the catalyst for the given reaction.

### 1.3. Historical Use of BINOL-Phosphoric Acids

Before the pioneering studies by Akiyama, the acids themselves were used as resolving agents for chiral amines. One of the earliest reports was from 1971, where a racemic mixture of amine ( $\pm$ )-10 could be reacted with BINOL-phosphoric acid (PA 1) to form a salt, which could be crystallized selectively and following a simple acid–base wash liberated the enantiopure amine (+)-10 (Figure 7).<sup>22</sup>

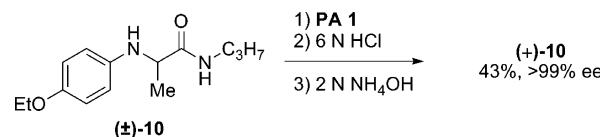


Figure 7. Resolution of chiral amines (1971).

The application was shown for a range of other amines and was found to be widely applicable. In the late 1980s and early 1990s, other research groups were also able to successfully use chiral phosphoric acids for the resolution of chiral amines.<sup>23</sup> In 2002, an interesting report on the crystallization of aliphatic  $\alpha$ -amino acids with BINOL-phosphoric acids was reported by Hirayama.<sup>24</sup> From the crystal structures obtained, it could be seen that the acids packed together in a uniform manner that created a chiral space between the molecules, which could recognize amino acids.

Although technology in the art of asymmetric synthesis has been greatly developed, the classical resolution can still be the quickest option to access enantiomerically pure materials even with the limitation of only a maximum yield of 50%. In 2009, Mikami was able to show the resolution of axial chiral gold complexes using BINOL-phosphoric acids (Figure 8).<sup>25</sup>

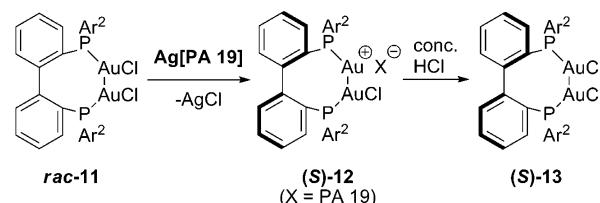


Figure 8. Resolution of gold complexes by Mikami (2009).

Starting with complexes **rac-11**, treatment with silver phosphate Ag[PA 19] led to a diastereomeric pair of which **(S)-12** could be separated and treated with concentrated acid to yield enantiopure **(S)-13**. The resolution properties of BINOL-phosphoric acids are still being exploited today. Recently, Feringa has shown that they can be used as chiral extractants to resolve primary benzylic amines on both a laboratory and an industrial scale.<sup>26</sup> Chiral phosphoric acids based on a biphenyl core have

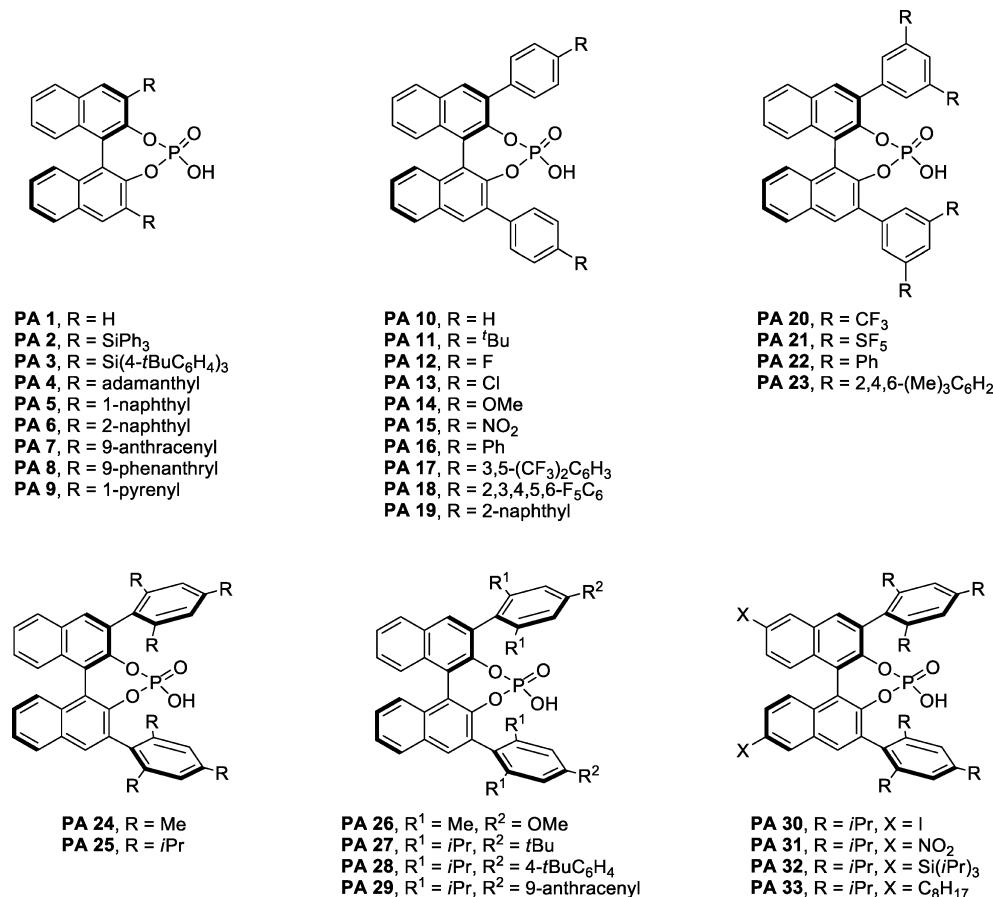


Figure 9. BINOL-phosphoric acid (PA) catalysts used in the majority of reactions.

also been shown by Feringa as being able to induce conformational changes in receptors by recognition of chiral amines.<sup>27</sup>

#### 1.4. Overview of Catalysts

For the inexperienced user of BINOL-derived catalysts, the large variety of structural variation in the literature of the catalysts can seem daunting; however, there are certain trends that can be seen that may aid the process of determining the best catalyst for a given reaction. In this section, we will introduce the catalysts that are used in this Review. It should be pointed out however that the catalysts presented below are only the ones that were taken forward by research groups for performing their enantioselective methodology. However, often many more were tested in preliminary optimization studies. So one must not consider this list exhaustive, but it should serve as an initial guide when considering which catalysts to test. The most straightforward catalysts that are encountered in the vast majority of reactions are shown in Figure 9.

PA 1 is a catalyst that has found early applications; however, most of the catalysts used nowadays contain some substitution at the 3,3'-positions. The use of silicon groups (PA 2 and PA 3) is popular at the 3,3'-positions, and these catalysts have found many applications. Generally, steric bulk at this position is highly advantageous for the enantioselectivity, and catalysts PA 5–10 are commonly seen. Catalysts PA 11–19 all contain substitution at the 4-position of a benzene ring, and these substituents have a dual role of providing bulk as well as tuning the electronics of the catalyst. Substitution at the 3,5-positions (PA 20–23) of a benzene ring is also seen, however, in much less frequency. Trisubstitution on a benzene ring (PA 24–33)

is also a major class of catalysts, which allows steric bulk to be increased dramatically. PA 25 is by far the most utilized catalyst in the literature. It is formally known as 3,3'-bis(2,4,6-triisopropylphenyl)-1,1'-binaphthyl-2,2'-diyl hydrogen phosphate but very commonly abbreviated to just TRIP.<sup>28</sup> Substitution on the backbone of the BINOL-framework (PA 30–33) is also encountered in the literature, and these groups are known for their ability to modulate other parameters of the catalyst such as electronics or solubility.

More specialized catalysts that deviate from the standard mold do feature quite often in the literature. As a general rule, these catalysts are usually highly specialized and have been developed for a specific purpose. An overview of the less commonly used catalyst architecture is shown in Figure 10.

PA 34–35 are both catalysts that contain a simplified biphenyl core, which has been shown in selected examples to be sufficient enough to function effectively. Catalysts PA 36–37 are derived from vaulted biaryl diols, which are now commercially available. They have found use in wide ranging applications usually where BINOL-derived Brønsted acids have not delivered the desired reactivity. Catalysts PA 38–39 are both very carefully designed catalysts, which have been shown in isolated examples to work and will be discussed later in this Review. The use of amine salts (PA 40–41) of the free acid is also a strategy used when a chiral anion is needed for a reaction involving iminium ion-catalysis.<sup>29</sup>

The final category for phosphoric acids is catalysts that contain multiple chiral axes (Figure 11). This is a relatively under-developed area, and only a few examples are known in the literature. The rationale for using these catalysts is usually

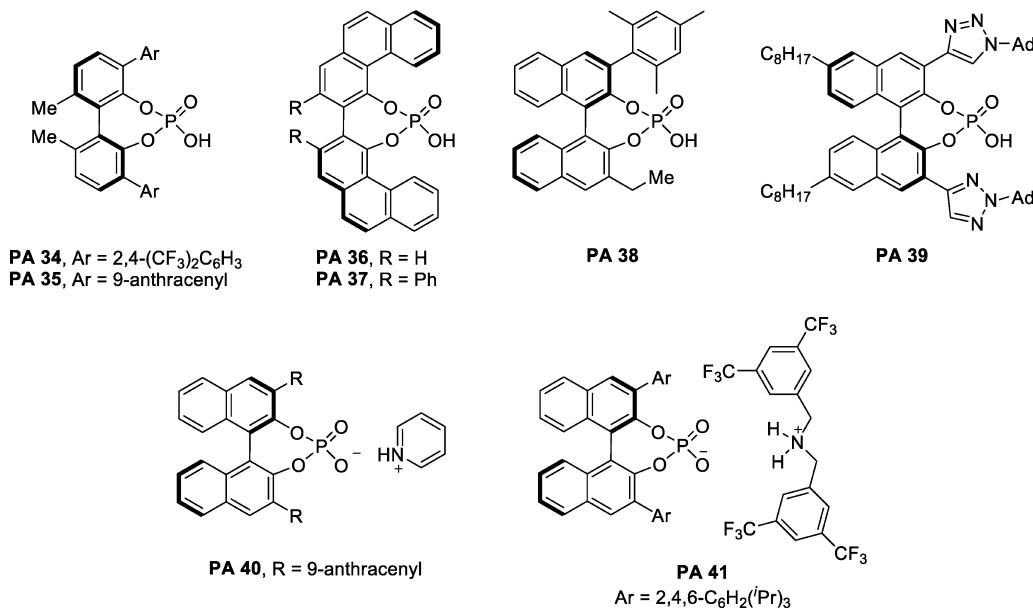


Figure 10. Miscellaneous chiral phosphoric acid catalysts.

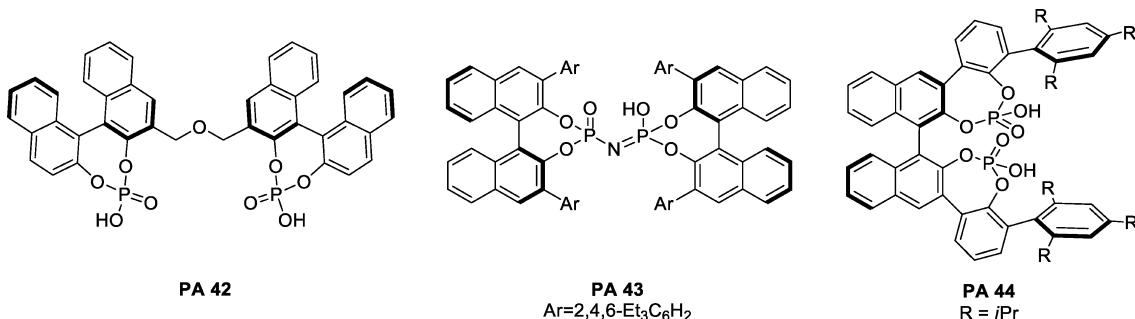


Figure 11. Multiple chiral axis containing phosphoric acid catalysts.

that they offer a second functional group, which can aid the transition state of certain reactions.

N-Phosphoramido catalysts (**NPA**) are more acidic than the phosphoric acid catalysts and have found many uses especially in cases where the substrate is notoriously more difficult to activate. An overview of the catalysts used in this Review is given in Figure 12.

Structural variety is less prevalent within this class of catalysts, and most rely on steric bulk to achieve high selectivities. Most catalysts opt to use the triflyl group on nitrogen, but some notable exceptions to this exist with **NPA 5** and **NPA 11**. Of note are the phosphorodiamidic acids, but as of yet their use has been rather limited.<sup>30</sup>

The final category within this class is the *N*-thiophosphoramido catalysts (**NTA**), which are even stronger Brønsted acids; however, their usage is rather confined. Within this Review, only two instances of their use are presented, and the catalysts used are shown in Figure 13.

A relatively new class of spiro-catalysts (**SPA**) is increasingly becoming popular in Brønsted acid catalysis. Although not strictly based on a BINOL-core, they will be covered in this review. As of yet, only a few variants exist, which are shown in Figure 14.

In the literature, it is interesting to note that most groups tend to prefer the use of the (*R*)-isomer of the catalysts, but the (*S*)-isomer, which is equally accessible, is used by some. In the

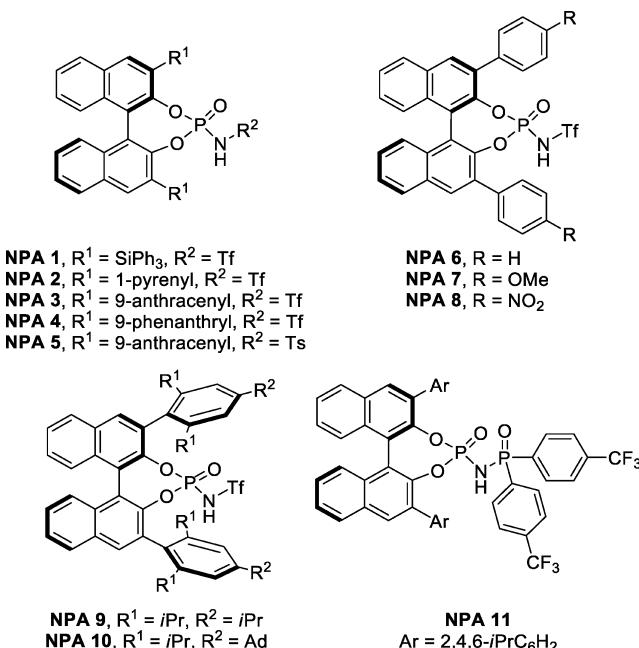
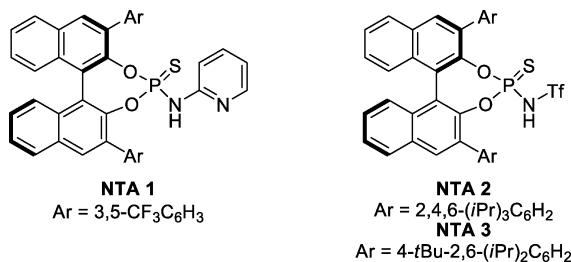


Figure 12. N-Phosphoramido catalysts used in this Review.

interest of clarity, for the majority of catalysts, the (*R*)-isomer will be the parent number, and when the (*S*)-isomer is used it

Figure 13. *N*-Thiophosphoramido catalysts used in this Review.

will be referred to as **(S)-PA** followed by the number. In a similar manner, **[H<sub>8</sub>]-PA** refers to the partially hydrogenated version of the parent catalyst (Figure 15).

### 1.5. Synthesis of Catalysts

As this Review aims to show, chiral BINOL-derived phosphoric acids (and related family members) can be used for a huge wealth of transformations, but usually their synthesis is not presented in research papers. The reason for this might be that while the scope of reactions that can be catalyzed by these catalysts continues to evolve, the synthesis of them has remained largely the same. Early reports on the synthesis of BINOL phosphoric acid (**PA 1**) involved resolutions involving chiral amines, most commonly from the cinchona alkaloid family.<sup>31</sup> For the introduction of substituents at the 3,3'-positions, the most commonly used route by research groups is shown in Figure 16.<sup>32</sup> The synthesis normally commences with commercially available BINOL **14** in either R- or S-configuration. Protection of the hydroxyl groups gives **15**, which can be processed by one of two routes. The first route sees the installation of boronic esters at the 3,3'-positions using a lithiation-borylation strategy (**16**). Alternatively, a lithiation-halogenation can also be carried out to yield **18**. Both of these intermediates can be used in cross-coupling chemistry using a Pd(0) catalyst and an appropriate coupling partner to yield **17**. Finally, deprotection (**19**) followed by phosphorylation yields the desired catalysts.<sup>31d</sup>

This generic scheme serves as the basis for nearly all of the catalysts used in the literature, and generally the steps employed are relatively straightforward and high yielding. There are however some notable examples whereby novel catalysts have been synthesized using modified procedures, usually to chiral BINOL frameworks, which then can be converted to the phosphoric acid by POCl<sub>3</sub> followed by hydrolysis.<sup>33</sup> Because the standard route involves protecting groups, several groups have disclosed more streamlined protecting group free strategies.<sup>34</sup>

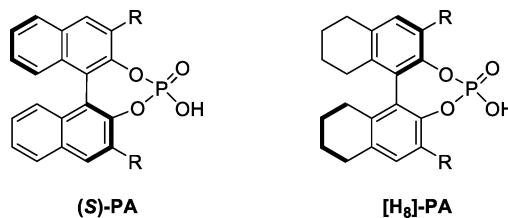


Figure 15. Alternative variants of catalysts used in this Review.

It should be highlighted that the free-acid catalysts are highly prone to picking up metal impurities, which are thought to come from the silica gel used during chromatography. This can lead to dramatic variations in results when different batches of catalyst are used, and several groups have reported on this.<sup>35</sup> The best solution to removing metal cations has been found to be an acidic wash, usually with 3–4 M HCl. List has also reported on a reliable procedure for determining the presence of impurities and on how to remove them.<sup>36</sup>

A relatively new class of chiral phosphoric acids containing a spirobiindane scaffold has been recently shown by various research groups to afford products with higher selectivity than the more simple BINOL-phosphoric acids. The synthesis of these catalysts is however noticeably longer than with the BINOL-based catalysts. Figure 17 shows the route used by research groups to access the required diol precursor, named SPINOL **24**.<sup>37</sup>

The synthesis commences with a double aldol condensation of **20** with acetone to afford **21**, which can be hydrogenated and brominated at the *para*-position to yield **22**. The bromination is required to block the *para*-position for the subsequent spirocyclization step using PPA to yield **23** in 57% yield over three steps. Removal of the bromine and deprotection of the alcohol yields *rac*-SPINOL **24**. The resolution has been shown to be possible by forming menthol esters, or more recently with cinchonidinium salts.<sup>38</sup> With the enantiopure diol in hand, standard synthetic steps as shown in Figure 16 can be used to synthesize the desired catalysts with varying substituents.

Wulff and co-workers have been the pioneers of using vaulted biaryl backbones as catalysts, and because they are structurally distinct from the classic BINOL scaffold, they can offer the possibility of higher selectivities when desired. The parent diols such as VAPOL or VANOL are commercially available; however, a dimerization–deracemization strategy has been shown on gram scale to be an effective route to substituted variants (Figure 18).<sup>39</sup>

Taking easily prepared phenol **25**, an oxidative dimerization could be performed in air to yield the dimer **26**, which could be

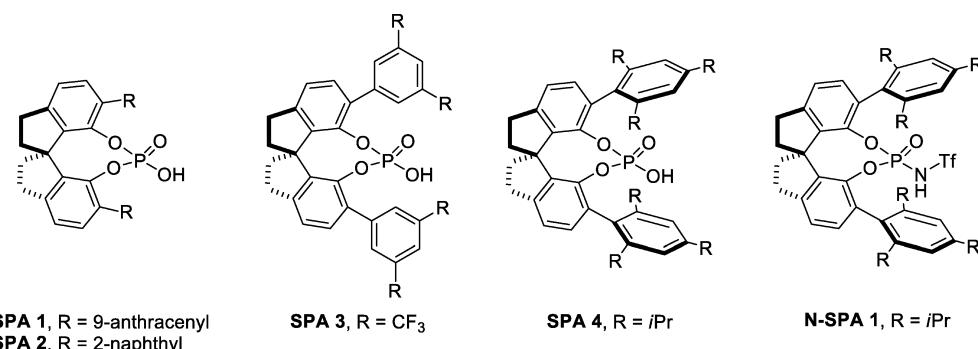
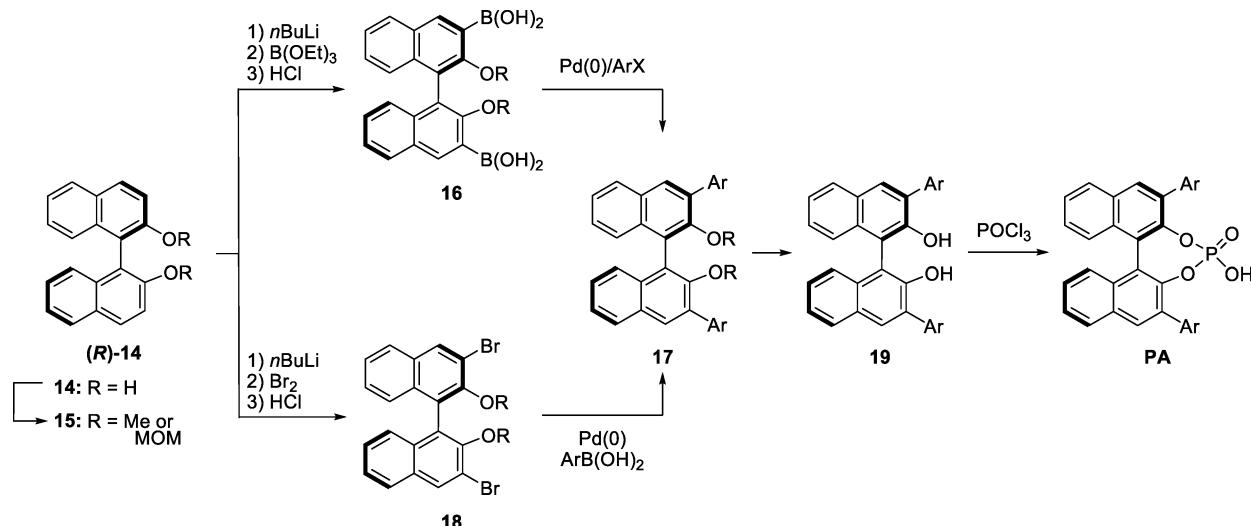
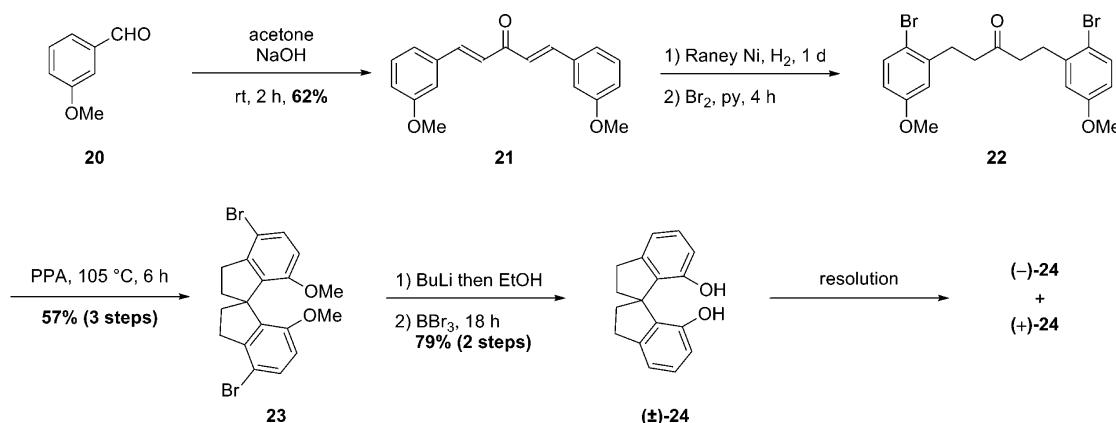


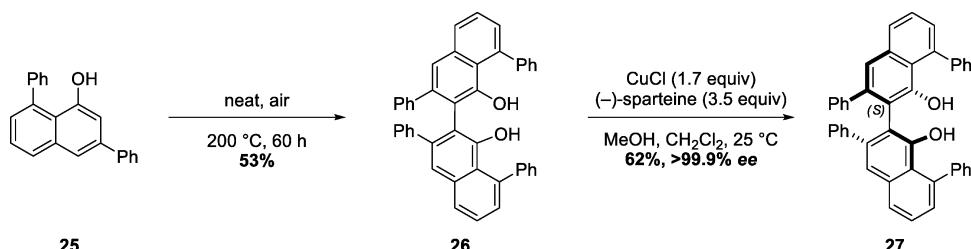
Figure 14. Spiro catalysts used in this Review.



**Figure 16.** Most commonly utilized route to chiral BINOL-derived catalysts.



**Figure 17.** Route to SPINOL backbone.



**Figure 18.** A route to vaulted biaryl diols.

deracemized using (−)-sparteine to give **27** in 62%. The reaction was carried out on a multigram scale and afforded over 3 g of the chiral diol, which could be converted to the phosphoric acid catalyst using standard procedures as mentioned previously.

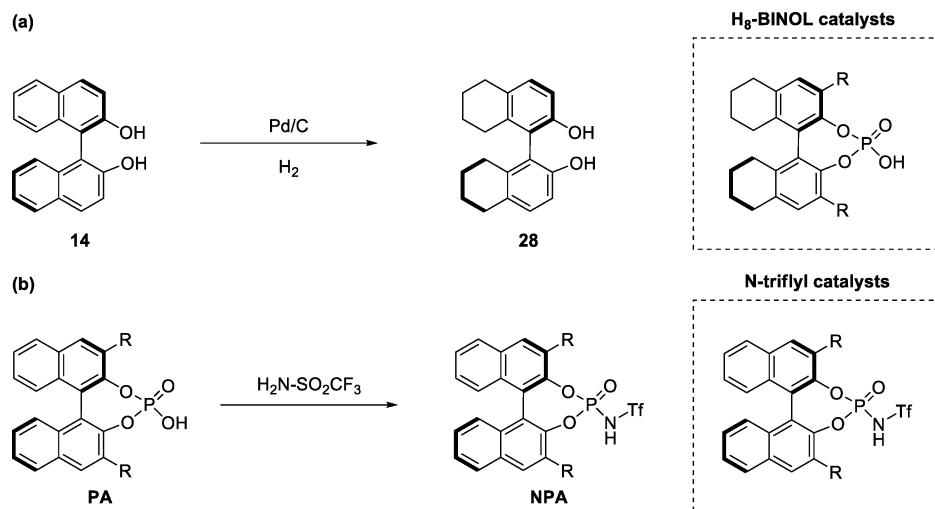
A common group of catalysts often seen used in the literature is the H<sub>8</sub>–BINOL-derived catalysts, and their synthesis is almost identical to that previously described except for a partial hydrogenation of BINOL **14** to begin the synthesis. **14** when treated with Pd/C and hydrogen gas can be partially hydrogenated to the H<sub>8</sub>–BINOL **28** usually in quantitative yields (Figure 19a).

Not only do the H<sub>8</sub>–BINOL catalysts possess different solubilities and offer slightly alternative structural conformations, but from a synthetic point of view they can be

synthesized in fewer steps. First, a high yielding bromination of the diol to 3,3'-dibromo-H<sub>8</sub>–BINOL<sup>40</sup> is well-known, and second the direct Suzuki reaction of the unprotected diol<sup>34a</sup> has been shown by Beller. Using these steps significantly improves the route by overcoming low yielding halogenations and also removes the need for protecting groups.

For the more acidic *N*-triflylphosphoramide catalysts,<sup>41</sup> a simple amidation reaction from the parent phosphoric acid yields the desired substrates (Figure 19b). This process can even be carried out in one pot with the phosphorylation of the parent diol reaction using POCl<sub>3</sub>. The Rueping group has also disclosed the synthesis of calcium salts of these types of catalysts.<sup>35c</sup>

The mentioned examples above cover the vast majority of catalysts that will be encountered in the literature; however,



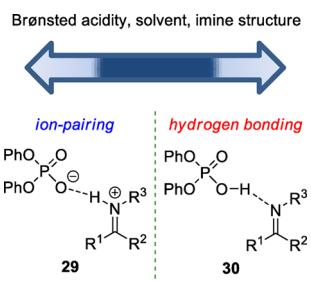
**Figure 19.** Synthetic transformations involved for the synthesis of various other catalysts.

there are some catalysts that have been specially designed for a specific purpose, for example, double axially chiral bis-phosphorylimides<sup>42</sup> developed by the Zhang group and easily recoverable catalysts<sup>43</sup> by Toy. Blechert has also shown microporous heterogeneous catalysts, which are recyclable.<sup>44</sup>

## 2. MODES OF ACTIVATION

### 2.1. Mono Activation

Elucidating the exact mechanisms involved in chiral phosphoric acid catalyzed systems is not a straightforward procedure due to the large number of possible interactions that could occur between the catalyst and the large variety of substrates used in reactions. Early work in this area suggested that the reactions proceeded via ion pairing between the substrate (most commonly an imine species) and the catalyst. However, mechanistic studies from Rueping and Gschwind have revealed that this picture is not as simple as it may seem (Figure 20).<sup>45</sup>

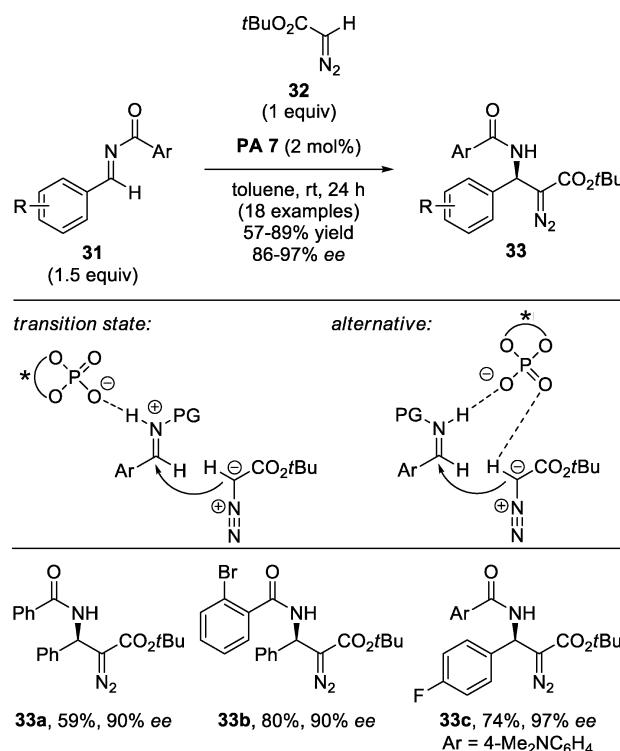


**Figure 20.** Different modes of monoactivation.

The study looked into trying to distinguish between the classically view of ion-pairing (**29**) from hydrogen bonding (**30**) using detailed NMR experiments. It was found that the nature of substituents ( $R^1$  and  $R^2$ ) played a big role in determining the amount of hydrogen bonding that was present. Unsurprisingly, the more electron-rich imines tended toward the ion-pairing species, while electron-deficient imines were prone to more hydrogen-bonding interactions.<sup>46</sup> Other factors such as Brønsted acidity and solvents also played a crucial role. It is also worth noting that both species can be involved during the course of a reaction.

In this Review, we will not aim to distinguish between ion-pairing and hydrogen bonding but for the interest of clarity will depict mechanisms as proceeding via ion-pairing even though the exact nature is unclear.

**2.1.1. Reactions with Iminium Ions.** The use of iminium ions as electrophiles for the addition of nucleophiles to imines is a well explored field, and a variety of substrates have been shown to participate very efficiently leading to useful chiral amine products.<sup>4b,47</sup> In this section, we will cover general reactions of iminium ions, which do not fall into the reaction classes of the following subsections. In 2005, Terada demonstrated the direct alkylation of  $\alpha$ -diazoesters with *N*-acylimines **31** (Figure 21).<sup>48</sup> Treating **31** with a diazoester (**32**) in the presence of 5 mol % **PA 7** gave the corresponding

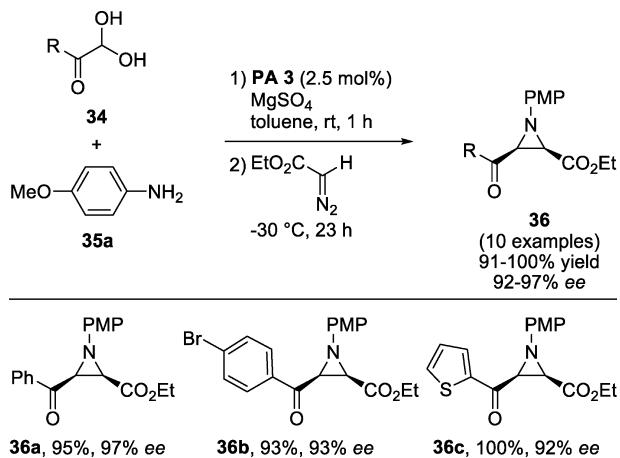


**Figure 21.** Alkylation of diazoesters with imines by Terada (2005).

alkylated secondary amides **33** in good yields and good enantiomeric excess.

The reaction was found to be facile for a range of aryl imines; however, the nature of the aromatic amide was found to have a dramatic effect on the yield and selectivity. It was found that using 4-Me<sub>2</sub>NC<sub>6</sub>H<sub>4</sub> as the aromatic amide gave the best results (cf., **33c**). A transition state that involves a single contact activation of the imine that can be intercepted by the nucleophilic diazo-species is proposed to be occurring. Alternatively, Peng has proposed a bifunctional mechanism for a related transformation with  $\alpha$ -diazomethylphosphonates, and this can also be considered a viable mechanistic pathway.<sup>49</sup>

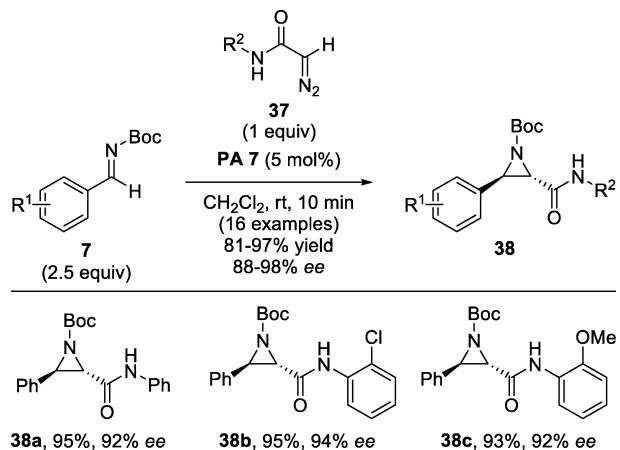
In 2009, Akiyama in fact showed that the use of 2.5 mol % PA **3** with *in situ* generated imines from the corresponding glyoxal monohydrate **34** and aryl amine **35a** furnished *cis*-aziridines **36** (Figure 22).<sup>50</sup>



**Figure 22.** Aziridination of diazoesters using imines by Akiyama (2009).

In this case, the PMP-group on the nitrogen atom is thought to increase its nucleophilicity, and hence displacement of N<sub>2</sub> occurs. A similar transition state as depicted in Figure 21 is thought to be occurring for the key stereoselective step.

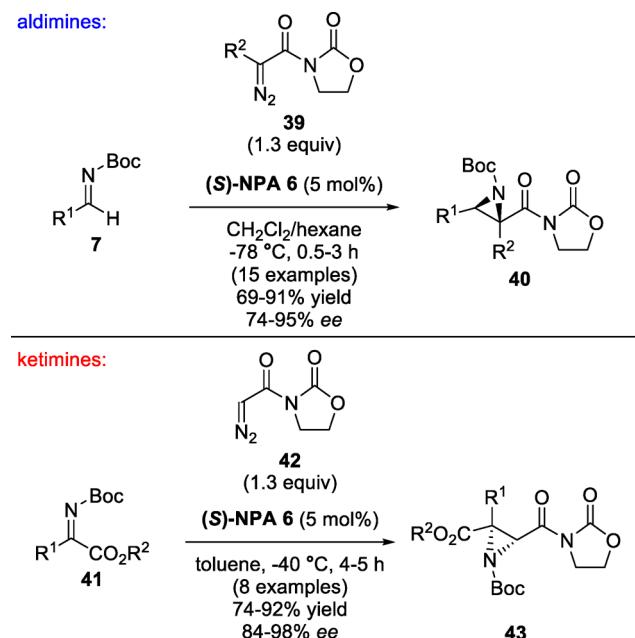
In the same year, Zhong reported the aza-Darzens reactions of diazoacetamides **37** with *N*-Boc aryl imines **7** (Figure 23).<sup>51</sup> Using 5 mol % of catalyst PA **7** at room temperature, they got a



**Figure 23.** Aziridination of diazoacetamides using imines by Zhong (2009).

rapid reaction (10 min) to yield predominantly *trans*-aziridines **38** in good yields and high enantiomeric excess. In contrast to Akiyama's report, using the diazoacetamides caused a dramatic switch from *cis*- to *trans*-products, and this may suggest that a mechanism alternative to that in Figure 21 is occurring, but no study has confirmed this.

Maruoka has also shown that the use of either substituted diazoacetamides with aldimines or unsubstituted diazoacetamides with ketimines allows access to trisubstituted aziridines (Figure 24).<sup>52</sup>



**Figure 24.** Synthesis of trisubstituted aziridines by Maruoka (2011).

Using 5 mol % of (S)-NPA **6**, a series of aldimines **7** reacted smoothly with **39** to give the aziridine products **40** in good yields and high enantiomeric excess. Alternatively, he showed that ketimines **41** could react with diazoacetamide **42** to give the corresponding products **43** also with good levels of selectivity.

In 2010, Antilla disclosed the addition of dihydropyrans **44** to *N*-acyl imines **31** using 2 mol % of PA **25** to give useful chiral derivatives **45** in good yields and selectivity (Figure 25).<sup>53</sup>

The enantioselectivity of the reaction was strongly dependent on the benzoyl group attached to the imine, and it was shown that electron-donating groups in the 4-position performed best in their study. A variety of pyrans and imines were tested and were seen to proceed efficiently. The products could be transformed into nonracemic spirocyclic compounds by treatment with *m*-CPBA followed by aqueous NaHSO<sub>3</sub>. *N*-Acyl imines have also been shown by Momiyama and Terada to be suitable for the addition of allyl silane in an enantioselective Hosomi–Sakurai reaction.<sup>54</sup>

Hydrazone derived from formaldehyde show strong nucleophilic character on the carbon atom and hence can be used as formyl-anion equivalents. Furthermore, chiral hydrazone are important intermediates that can be transformed into a variety of building blocks through simple procedures. In 2007, Rueping reported the addition of hydrazone **46** to *N*-Boc imines **7** in the presence of 10 mol % [H<sub>8</sub>]-PA **8** (Figure 26).<sup>55</sup>

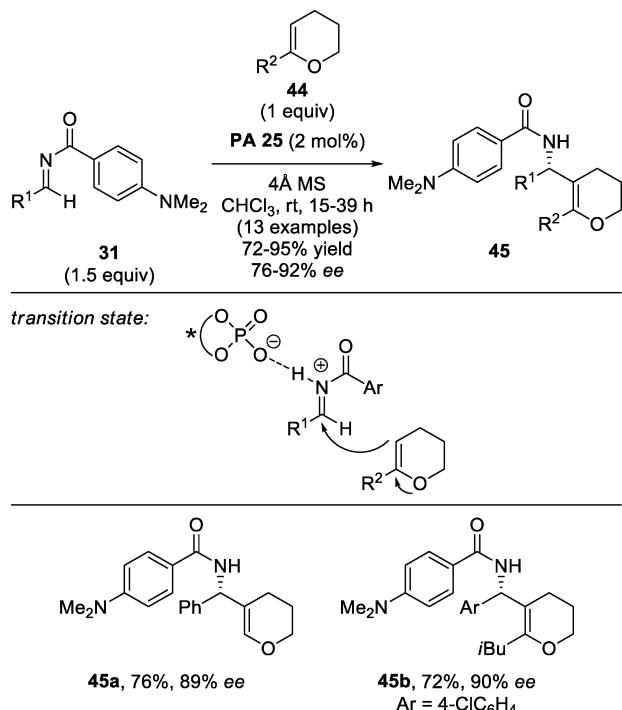


Figure 25. Addition of enol ethers into imines by Antilla (2010).

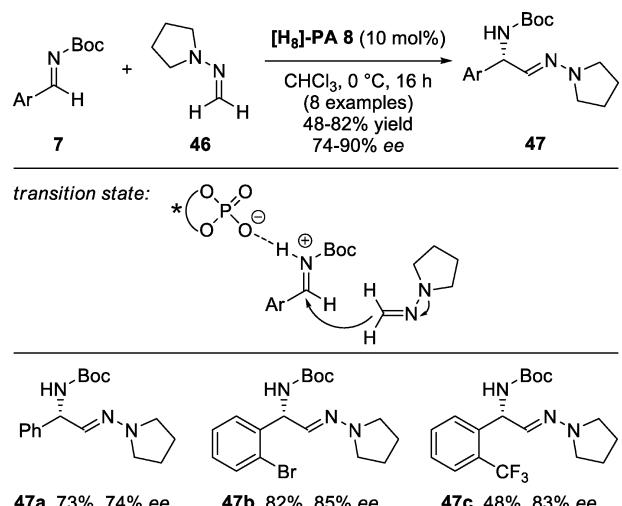


Figure 26. Addition of hydrazones into imines by Rueping (2007).

The reaction proceeds best in CHCl<sub>3</sub> at 0 °C and yields the corresponding alkylated hydrazones 47 in good yields with up to 90% enantiomeric excess. The [H<sub>8</sub>]-catalysts tested performed better than their corresponding unsaturated partners with sterically more demanding substituents at the 3,3'-positions being optimal for achieving high selectivity. It is proposed that a simple H-bonding interaction between the catalyst and the imine is responsible for the selectivity observed.

In 2010, hydrazones were also shown by Tsogoeva to be suitable electrophilic partners for the addition of TMS-CN in a Strecker reaction.<sup>56</sup> She showed that hydrazones 48 could be reacted with TMSCN in the presence of PA 15 and tBuOH to give the corresponding products 49 in good yields and selectivity (Figure 27).

The authors propose that the silicon group (from TMSCN) initially silylates the hydrazone, which then can be activated by

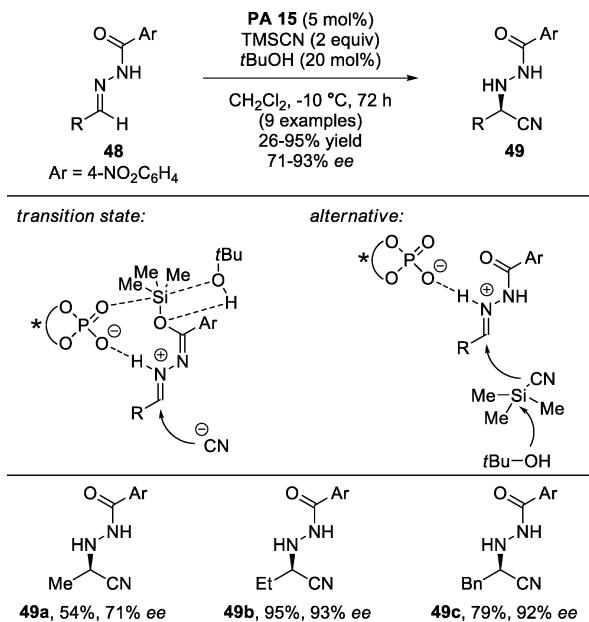


Figure 27. Strecker reaction of hydrazones by Tsogoeva (2010).

the phosphoric acid via a dual activation mode to undergo reaction with cyanide. An alternative mechanism can be envisioned, which involves monoactivation and where the tBuOH is now responsible for removing the silicon group from TMSCN. In the same year, Ma also reported a three-component asymmetric Strecker reaction.<sup>57</sup>

In 2011, Gong was able to show a rather unique example of asymmetric hydride transfer occurring in aromatic ketones 50 once they had condensed with various anilines 35. The process formally can be described as C–H activation with the generated iminium ion being trapped by the amine to afford the polycyclic compounds 51 (Figure 28).<sup>58</sup>

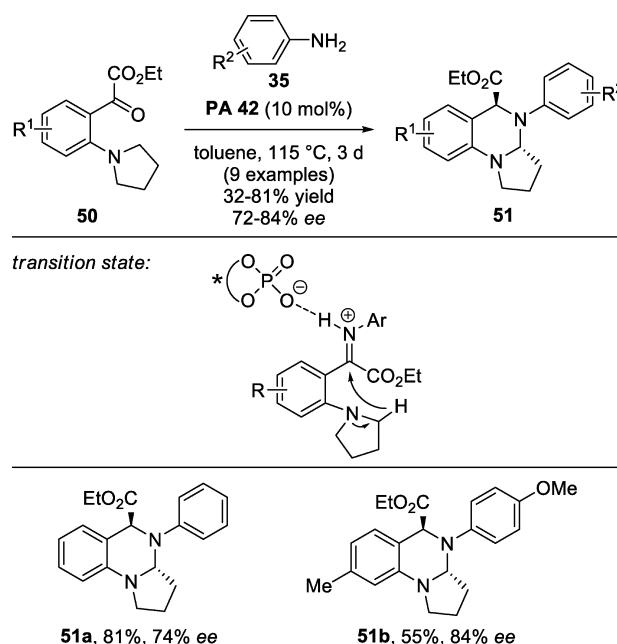


Figure 28. Asymmetric hydride transfer-cyclization by Gong (2011).

The mechanism of the process first involves the condensation of the aniline with the aromatic ketone to give an imine

species. The acid catalyst then can activate the imine to accept the hydride via 1,5-hydride transfer. Concomitant cyclization of the amine on the generated iminium yields the observed products.

Radical reactions are powerful processes that allow for the breaking and formation of bonds in a distinctive manner to generate unique products that may not be possible to access via typical ionic methods. Radical processes applied in conjunction with chiral Brønsted acids are scarce in the literature. In 2009, a rare example of such a process was shown by Kim who developed the addition of alkyl iodides to aromatic imines **52** using a radical pathway in the presence of 30 mol % NPA **9** (Figure 29).<sup>59</sup>

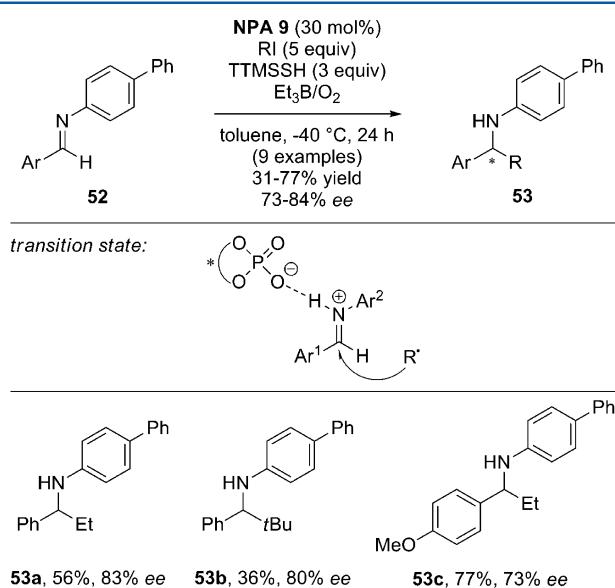


Figure 29. Addition of radicals into imines by Kim (2009).

The radicals were generated from alkyl iodides using TTMSSH, and upon addition gave secondary amines **53** in good yields and enantioselectivities. The reaction was unaffected by the electronics of the imine counterpart but suffered from the formation of byproducts, the direct addition of an ethyl radical, generated from triethylborane. The presence of the phosphoric acid was shown to accelerate product formation, and so on the basis of this we propose a monoactivation pathway involving a single interaction between the catalyst and the imine substrate. It is unclear whether the catalyst is involved in any interactions with the generated radical species, and therefore further studies into phosphoric acid-catalyzed radical reactions are certainly needed.

**2.1.2. Friedel–Crafts Reaction.** The Friedel–Crafts reaction is one of the most common and highly practical methods to form C–C bonds and introduce substitution to aromatic systems. Organocatalysis has played a large role in the development of the reaction in the past decade.<sup>60</sup> Within this area, the activation of electrophiles using chiral Brønsted acids has been an area of research that has received a great deal of attention.<sup>61</sup> Typically these electrophiles involve imine-intermediates but have also been extended to include substrates such as electron-deficient alkenes.

In 2004, Terada was the first to report an aza-Friedel–Crafts reaction between *N*-Boc imines **7** and methoxyfuran **54a** in the

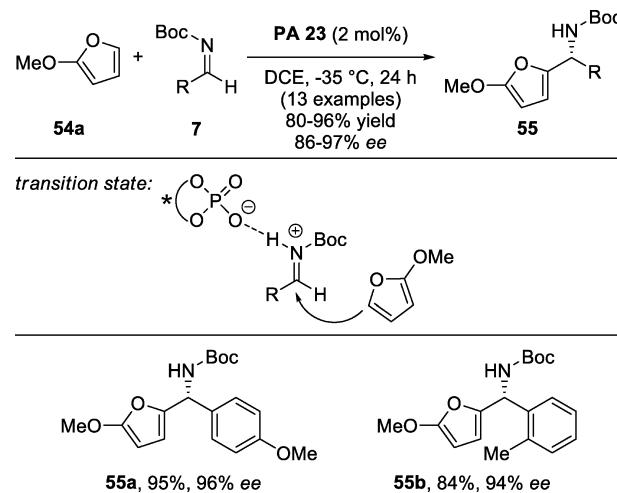


Figure 30. Friedel–Crafts reaction with furan by Terada (2004).

presence of 2 mol % of highly sterically hindered catalyst PA **23** (Figure 30).<sup>62</sup>

The reaction proceeded best in DCE at -35 °C and gave access to a variety of chiral amines **55** in excellent yields and enantioselectivities. The reaction performed well irrespective of the electronic properties of **7** and could also be carried out on a gram scale using as little as 0.5 mol % catalyst. The mechanism is thought to be monoactivation of the imine by the catalyst followed by attack by furan.

In 2007, Antilla developed the Friedel–Crafts reaction between *N*-acyl imines **31** and benzyl-protected indoles **56** (Figure 31).<sup>63</sup> The reaction was performed using 2 mol % of PA **2** and gave the corresponding products **57** in excellent

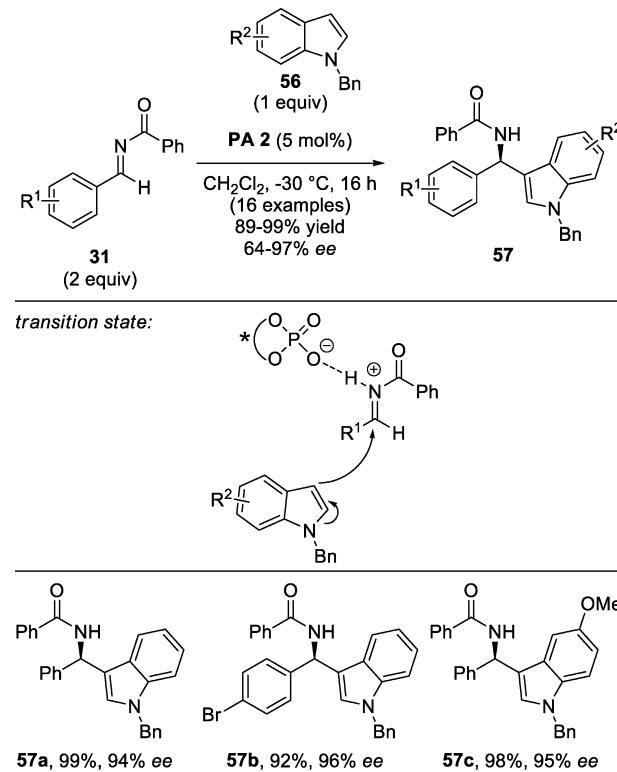


Figure 31. Friedel–Crafts reaction of *N*-acyl imines with indoles by Antilla (2007).

yields and selectivity. The scope of the reaction was broad with both electron-donating and -withdrawing substituents tolerated on the indole backbone as well as on the imine. Interestingly, the use of the free N–H indole was found to give lower yields and enantioselectivity. With that observation in mind, it is proposed that the indole component has no formal interactions with the catalyst, and the selectivity is solely due to activation of the imine component.

Almost at the same time, Terada reported a very similar reaction involving silyl-protected indoles **56** with *N*-Boc imines **7** to give Friedel–Crafts adducts **58** (Figure 32).<sup>64</sup>

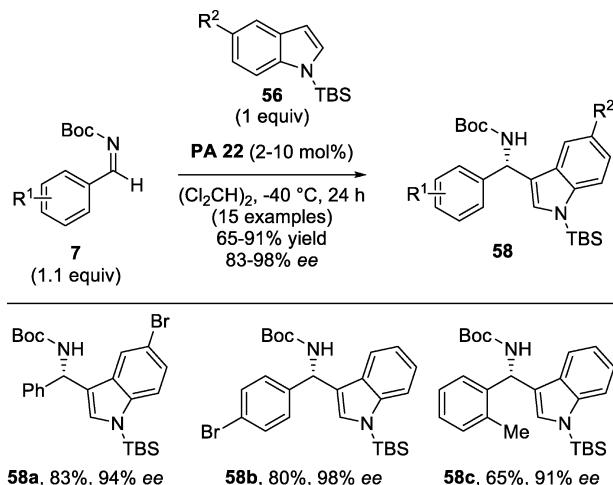


Figure 32. Friedel–Crafts reaction of *N*-Boc imines by Terada (2007).

Under quite similar reaction conditions but instead using up to 10 mol % of catalyst **PA 22**, modest to good yields and high enantioselectivities could be achieved. The report also discloses an interesting switch in the absolute stereochemistry of the products when a greater sterically demanding catalyst is used. DFT calculations at the B3LYP/6-31G\*\* level suggest that it may be attributed to the level of accessibility that reactants have toward the acidic site of the catalyst. Once again, the use of *N*-protected indoles would suggest a mechanism similar to that depicted in Figure 31 is occurring.

In 2008, Enders reported a one-pot two-step sequence to synthesize isoindolines **61** from the corresponding aromatic imines **59** (Figure 33).<sup>65</sup> The first step (a Friedel–Crafts reaction) was performed in the presence of 10 mol % of **NPA 8** at room temperature to yield the 1,2-addition to the imine product, and then the second step (aza-Michael) was performed by using DBU.

The isoindolines **61** were isolated in good to excellent yields with good selectivity being obtained under short reaction time. The authors also noticed a stereoablative kinetic resolution occurring during the reaction. Thus, when the reaction was left to run for longer periods, the enantioselectivity of the product increased but the yield decreased. The decreased yield was due to one enantiomer being consumed by reacting further with a nucleophile. Most of the examples were performed with N–H indole (**60**), but when the indole was protected (**56**) similar enantioselectivities were obtained. This would suggest that the indole proton does not interact with the catalyst, and we propose that monoactivation of the imine is responsible for the selectivity.

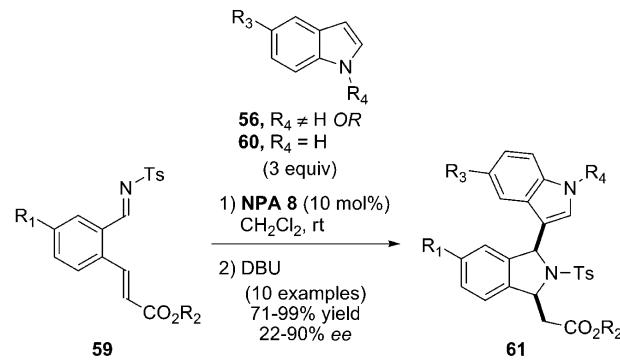


Figure 33. Synthesis of isoindolines by Enders (2008).

In 2007, Antilla disclosed a highly enantioselective Friedel–Crafts reaction of *N*-acyl imines **31** with pyrroles **62** to give alkylated products **63** in high yields and selectivity (Figure 34).<sup>66</sup>

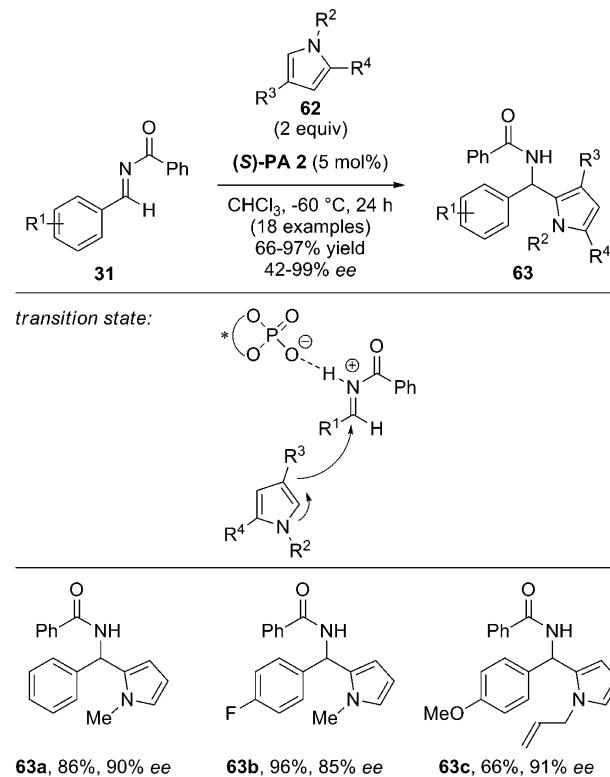


Figure 34. Friedel–Crafts reaction of *N*-acyl imines with pyrroles by Antilla (2007).

The reaction is performed at  $-60^\circ\text{C}$  in  $\text{CHCl}_3$  using 5 mol % of **(S)-PA 2**.

The reaction has a broad scope and can tolerate a range of imine substrates and electron-rich pyrroles. The nature of the group on the nitrogen atom of the pyrrole was shown to have a

dramatic effect. For example, N–H pyrrole gave almost no enantioselectivity, while bulky alkyl groups such as *i*Pr proved too demanding and the reaction did not proceed. A methyl group (or primary alkyl chains) was tolerated the best for the desired reactivity. As seen with the protected indoles, it is proposed that a simple monoactivation is occurring here to deliver the selectivity observed. Antilla has also reported on the intramolecular Friedel–Crafts reactions of pyrroles with in situ formed imines, which can be activated with chiral phosphoric acids.<sup>67</sup>

In 2010, Enders was able to carry out the Friedel–Crafts reaction between aromatic phenyl rings bearing a variety of substrates and glyoxylates imine **64a** (Figure 35).<sup>68</sup> The

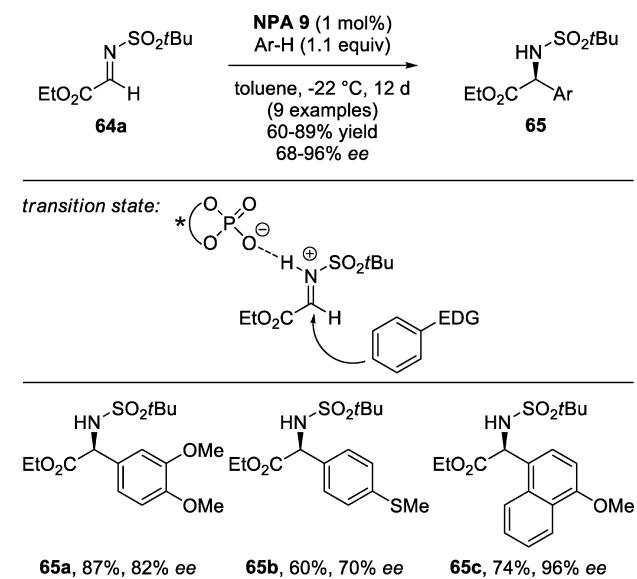


Figure 35. Friedel–Crafts reaction with arenes by Enders (2010).

aromatic coupling partner tended to be electron-donating in most cases and yielded the corresponding adducts **65** in good yields and selectivities; however, a reaction time of 12 days was required for full conversion.

The procedure was conducted with 1 mol % *N*-trifyl phosphoric acid **NPA 9** as chiral phosphoric acids showed much lower reactivity and produced almost no stereoinduction. It is worthy of note that the more acidic thio-phosphorus catalyst (**NTA 2**) gave an almost identical yield but with considerably lower enantioselectivity. It was also shown that the amine's protecting group could also be easily removed without loss of enantiopurity to yield amino acid derivatives.

In 2012, Wang demonstrated for the first time that *N*-Boc ketimines **66** derived from isatins could be employed in a highly selective coupling with protected-indoles **56** and pyrroles **62** (Figure 36).<sup>69</sup> The reaction was conducted with between 2 and 5 mol % of **PA 16** under mild conditions to yield a variety of adducts **67** generally in high yields and excellent enantiomeric excess.

The reaction performed well in a range of solvents, but Et<sub>2</sub>O proved to be optimal for obtaining the best yield and enantioselectivity. The addition of 4 Å MS was shown to have a dramatic effect on the selectivity of the reaction by minimizing the water content in the system. A broad range of isatin substrates were well tolerated under the reaction conditions. We can assume that because the indole is protected

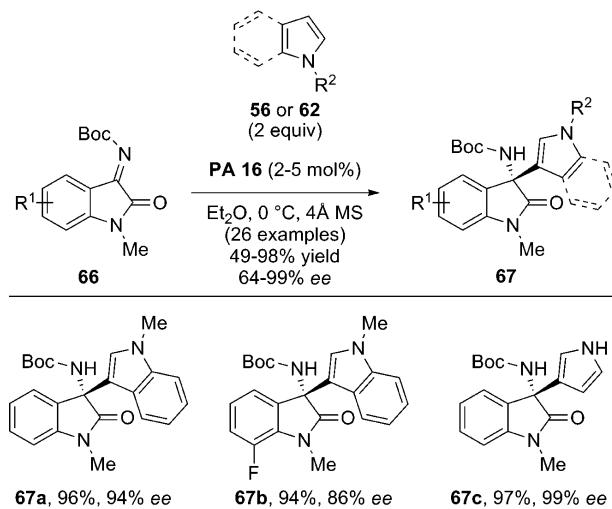


Figure 36. Friedel–Crafts reaction of *N*-Boc ketimines by Wang (2012).

it follows a transition state similar to that previously described within this category.

The activation of imine derivatives by phosphoric acids resembles a major area of research in the Friedel–Crafts reaction mainly due to the ease of activation. Alternative substrates can however be activated successfully in the presence of stronger acids such as the *N*-triflyl phosphoric acids. In 2008, Rueping showed that  $\alpha,\beta$ -unsaturated keto esters **68** could be utilized as efficient electrophiles that undergo Friedel–Crafts reactions with protected indoles (Figure 37).<sup>70</sup>

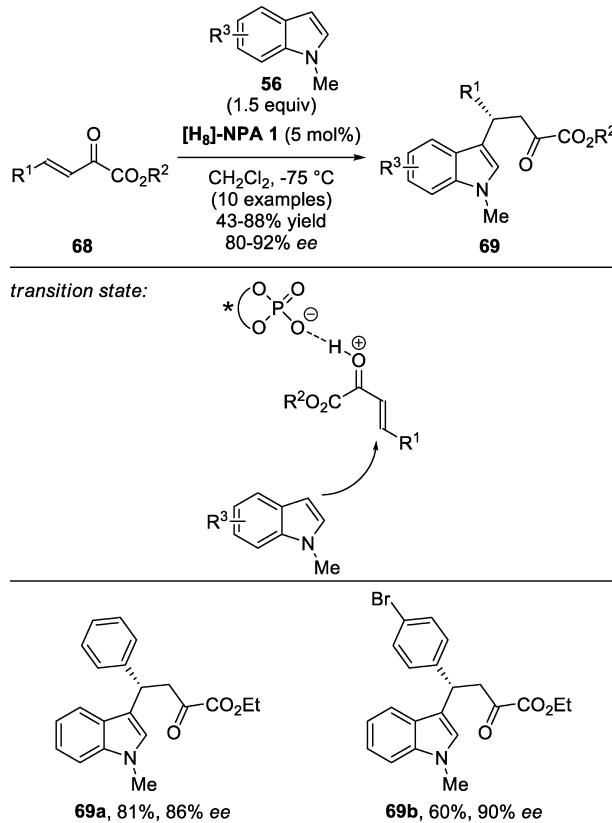


Figure 37. Friedel–Crafts reaction with  $\alpha,\beta$ -unsaturated ketones by Rueping (2008).

The reaction was conducted in the presence of 5 mol %  $[H_3]-NPA$  1 and gave the alkylated indoles 69 in modest to good yields and high enantioselectivities. Interestingly, when fully saturated catalysts were used, a byproduct (72) resulting from double addition to the carbonyl was isolated (Figure 38).

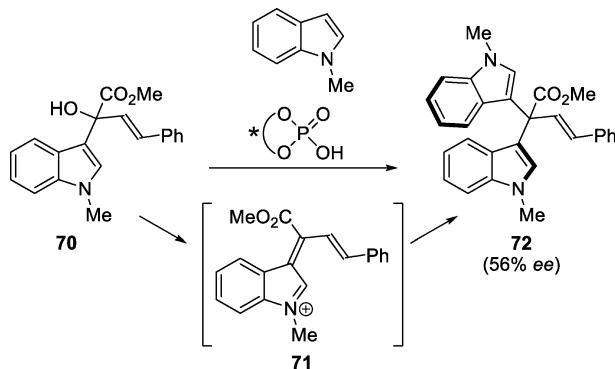


Figure 38. Double addition byproduct formation by Rueping.

It was proposed that upon addition of indole to the carbonyl, 70 is formed, which in the presence of the chiral Brønsted acid can undergo dehydration to yield the iminium intermediate 71. This highly electrophilic species can subsequently be trapped by another equivalent of indole to yield 72. The product was found to possess a chiral axis and could be obtained with modest enantiomeric excess. Other research groups have shown this highly electrophilic intermediate (71) to be a versatile reacting partner for various other nucleophiles. In 2009, You opened up the possibility of carrying out Friedel-Crafts reactions with the *in situ* generation of the protonated iminium intermediate.<sup>71</sup> In his preliminary report, an achiral phosphoric acid was shown to be suitable for the reaction of 73 with various indoles. A year later, the asymmetric variant was reported by the same group using 5 mol % of (*S*)-PA 17 (Figure 39).<sup>72</sup> The reaction was conducted in either benzene or xylene with 5 Å MS being shown to have a beneficial effect for the reaction. The mild reaction conditions provided the corresponding products 74 in good yields and with modest selectivity.

It is thought that the catalyst may increase the leaving group ability of the secondary amine via protonation and thus generating a highly electrophilic intermediate, which can be intercepted by methyl-protected indole 56a. Although the acidic proton from the catalyst is lost during the elimination step, coordination of the phosphate to the proton of the indole results in monoactivation that ultimately induces stereo-selectivity. In all cases, a racemic sample of secondary amine 73 was used, and it was noted in a single case that a modest kinetic resolution could be carried out on the starting material. It could be recovered with 49% yield and 35% ee.

You has also published a protocol for the Friedel-Crafts reaction of dihydroindoless 68 and 75 (Figure 40).<sup>73</sup> These substrates are known to react at the 2-position and were shown to do so to give the alkylated products 76 in good yields and high selectivity. The use of an unsaturated catalyst minimized any unwanted addition to the ketone.

The reaction was carried out at  $-60^\circ C$ , and this was determined to be optimal. Higher temperatures gave lower yields and selectivity. The products 76 were shown to be able to be oxidized to the indole and therefore presents a complementary

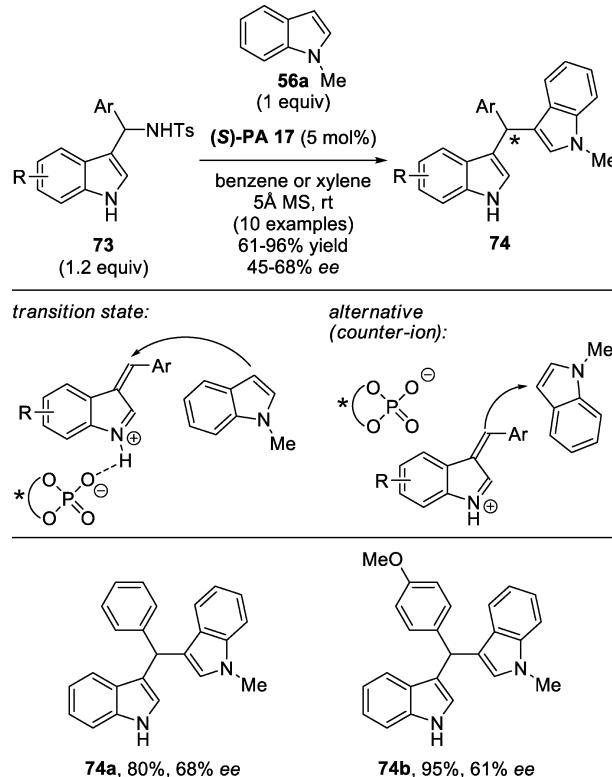


Figure 39. Friedel-Crafts reaction of  $\alpha$ -indole amines by You (2009).

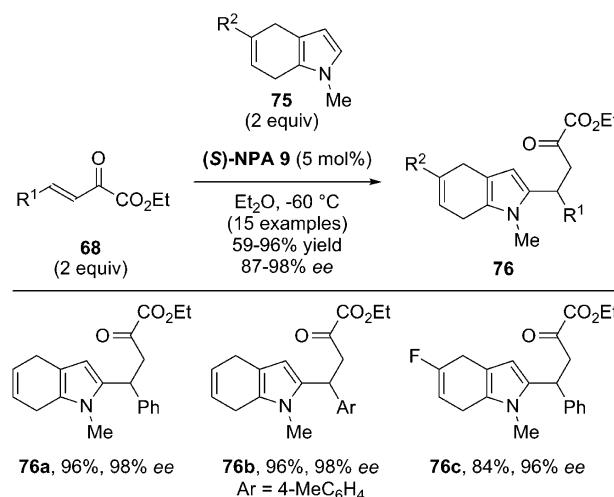
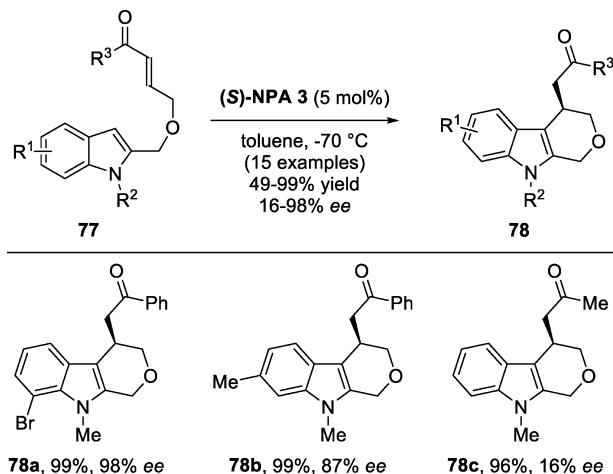


Figure 40. Friedel-Crafts reaction with dihydroindoless by You (2008).

strategy of offering reactivity at the 2-position versus the natural indole reactivity at the 3-position.

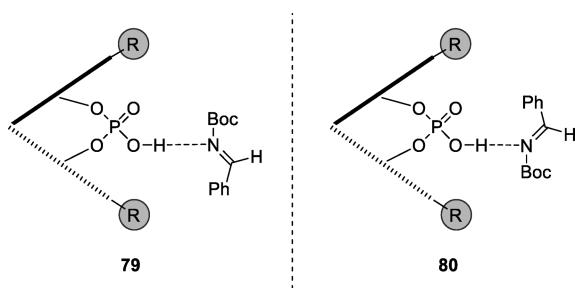
An interesting application of the Friedel-Crafts reaction was shown by You in 2011, which featured an intramolecular reaction of indole substrates 77 (Figure 41).<sup>74</sup> Treating 77 in toluene in the presence of 5 mol % (*S*)-NPA 3 initiated a cyclization to yield tricyclic products 78.

A catalyst screen revealed most catalysts gave similarly good yields, but the enantioselectivity was highly dependent on the steric bulk at the 3,3'-positions. The products 78 could be used in further transformations, thus providing useful indole building blocks. As seen with the intermolecular examples, the



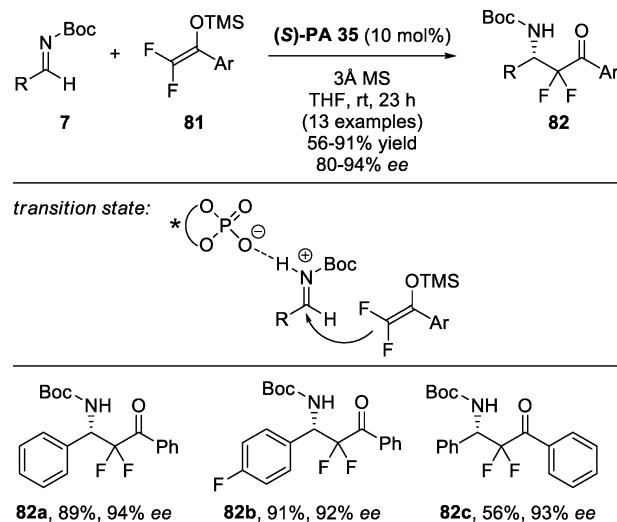
mechanism of the reaction most likely is monoactivation due to the indole being protected.

**2.1.3. Mannich Reaction.** The Mannich reaction is one of the most fundamental of organic transformations, and the products formed are highly useful and versatile intermediates. The asymmetric variant is a well-studied reaction especially within the field of organocatalysis.<sup>75</sup> The Mannich reaction is also known for kick starting the field of chiral Brønsted acid catalysis. As described earlier, the initial reports from Akiyama<sup>15</sup> and Terada<sup>19</sup> utilized different reaction modes to perform the Mannich reaction in a stereoselective manner. Although neither is thought to proceed via monoactivation, it is worth highlighting an early mechanistic study from Terada, which studied the direct Mannich reaction with acac.<sup>20</sup> At the time, it was proposed to be proceeding via monoactivation by the catalyst, where the imine could orient itself in two possible forms (Figure 42).



Although the two possible imine orientations (79 and 80) were able to explain the stereochemical outcome of the reaction, later studies by Goodman have gone on to show that the catalyst is bifunctional and is involved in coordination to the nucleophile too.<sup>21</sup>

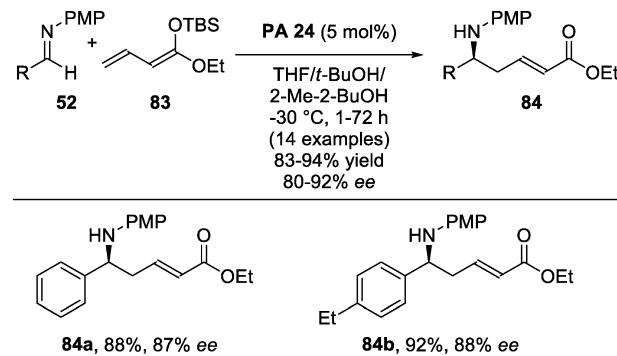
In addition to a dual and bifunctional activated Mannich reaction, single-contact monoactivation for the reaction has also been disclosed. In 2011, Akiyama disclosed a modified chiral phosphoric acid based on biphenol, as an effective catalyst for the reaction between silyl enol ethers 81 and imines 7



(Figure 43).<sup>76</sup> The reaction afforded amino-difluoroketones 82 in good yields and with excellent enantioselectivities.

During the optimization, a range of catalysts consisting of the conventional BINOL core were tested, and although some were able to give good selectivity, the yields were generally low. At this point, a simpler biphenol-based catalyst ((S)-PA 35) was tested and found to be the optimal catalyst in terms of both yield and enantioselectivity. The products 82 could also be transformed into azetidinones in three steps without any loss of optical purity. It is thought that, due to the absence of acidic protons on the nucleophile, no interaction exists between itself and the catalyst. Therefore, a single hydrogen bond to the imine from the catalyst is sufficient for activation.

In 2008, Schneider was the first to report the asymmetric vinylogous Mannich reaction of silyl ketene acetals 83 and imines 52 (Figure 44).<sup>77</sup> It was found that 5 mol % of PA 24



was the optimal choice to achieve good yields and high enantioselectivities of the corresponding  $\alpha,\beta$ -unsaturated  $\delta$ -amino esters 84. Interestingly, the use of a bulkier catalyst resulted in lower selectivity.

Alcohol solvents increased the reaction rate dramatically but predictably also led to lower enantioselectivities. To compensate for this, a solvent mixture containing an ethereal solvent could be employed. The optimal results were obtained with an unusual solvent mixture containing equal amounts of THF, tBuOH, and 2-Me-2-BuOH with the addition of 1 equiv of

water. A detailed mechanistic investigation using NMR and mass spectrometry found that protic solvents serve the purpose of capturing the cationic silicon species as its silanol derivative.<sup>78</sup> It was also shown that the imine formation could be carried out *in situ* to obtain the products **84** in similar yields and selectivity. Schneider has extended the utility of this methodology's potential by demonstrating the synthesis of a few natural products.<sup>79</sup> In 2011, Belder and Schneider reported that they had managed to miniaturize this reaction to be able to be performed on a single chip.<sup>80</sup> Recently, Schneider has also shown that the reaction can be run on a multigram scale to access a variety of substituted indolizidine-based alkaloids.<sup>81</sup>

In the same year, extension of the reaction of vinylketene silyl *N,O*-acetals **85** with imines **52** to give unsaturated amide products **86** was shown to proceed efficiently (Figure 45).<sup>82</sup>

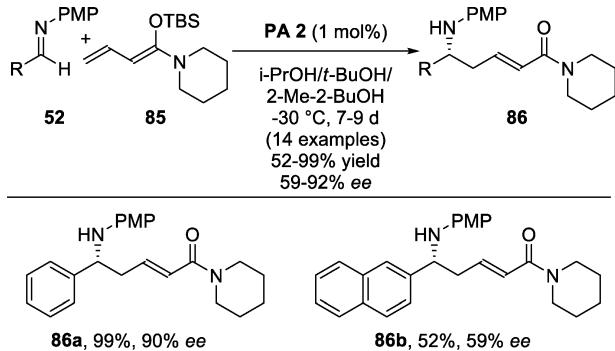


Figure 45. Vinylogous Mannich reaction of vinylketene silyl *N,O*-acetals by Schneider (2008).

Using 1 mol % of **PA 2** gave the products **86** in good yields and selectivities.

The starting imines **52** could also be prepared in the reaction pot from the corresponding aldehyde and amine and delivered the products in identical yields and selectivities. The utility of the products was also shown with various further transformations, which provided useful chiral building blocks.

In 2010, Rueping presented a rather unique Mannich reaction followed by a ketalization reaction. Taking 2-hydroxyphenyl imines **87** with cyclic enol ethers **88** in the presence of 5 mol % of  $[H_8]$ -NPA **4** furnished the polycyclic products **89** in good yields and high selectivity (Figure 46).<sup>83</sup>

Interestingly, when the 2-hydroxyphenyl group is placed directly on the nitrogen, alternative products are obtained, which do not involve participation of the hydroxyl group. A plausible explanation for this may be due to an interaction between the acidic proton and the catalyst (see dual activation section). This would render the hydroxyl group less reactive, and hence the *in situ* generated oxonium ion is intercepted by the aromatic system. In light of this, it is proposed that the desired reaction proceeds with only monocontact activation of the imine, which allows for stereoselective addition of the enol ether followed by cyclization of the hydroxyl group.

**2.1.4. 1,3-Dipolar Cycloadditions.** The 1,3-dipolar cycloaddition involves the reaction of a substrate that contains a dipole in a 1,3-relationship to undergo reaction with suitable partners to form five-membered rings. Nitrones are such compounds that possess a 1,3-dipole and when reacted with alkenes provide an efficient route to isoxazolidines.

In 2008, Yamamoto reported the 1,3-dipolar cycloaddition reaction between nitrones **90** and ethyl vinyl ether **91** (Figure 47).<sup>84</sup>

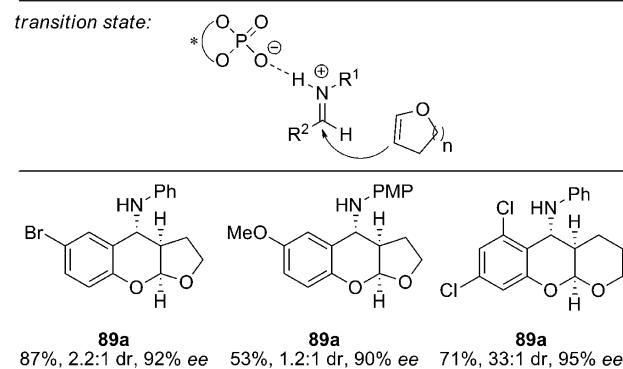
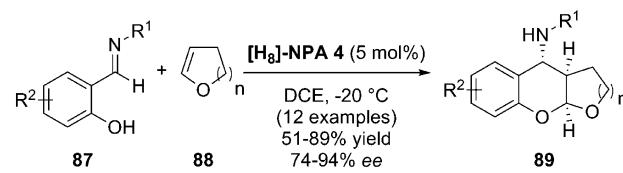


Figure 46. Mannich-ketalization reaction by Rueping (2010).

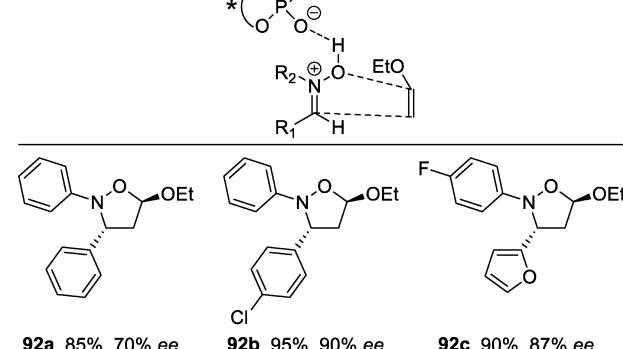
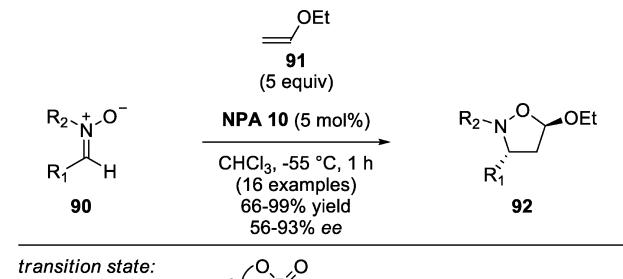


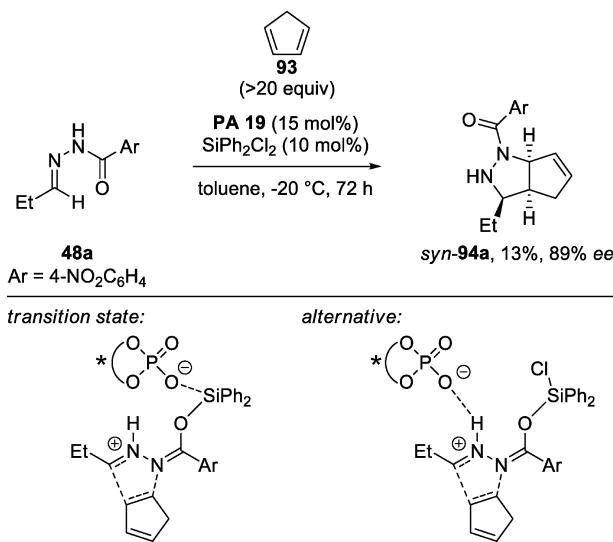
Figure 47. 1,3-Dipolar cycloaddition of nitrones by Yamamoto (2008).

In the presence of 5 mol % of highly bulky catalyst **NPA 10**, the corresponding isoxazolidines **92** could be formed in good yields and enantioselectivities.

It was noted that the steric bulk of the catalyst had a dramatic effect on the reaction, and even catalysts bearing a 9-anthryl group failed to give suitable enantioselectivity. It was also noted that electron-withdrawing groups generally provided better enantioselectivity in the reaction. The role of the Brønsted acid here is unclear as it could potentially activate both substrates through H-bonding but most likely preferentially activates the nitrone due to its more basic oxygen atom via a single contact.

In 2011, Tsogoeva reported the [3+2] cycloaddition of hydrazones with cyclopentadiene using a catalytic amount of TMSOTf (10 mol %) to give the corresponding cyclic products in good yields and with high diastereocontrol.<sup>85</sup> In this case, the silicon reagent was thought to activate the hydrazone by

silylation. It was then envisioned that a similar activation could be carried out by BINOL-phosphoric acids, to perform an asymmetric variant (Figure 48).



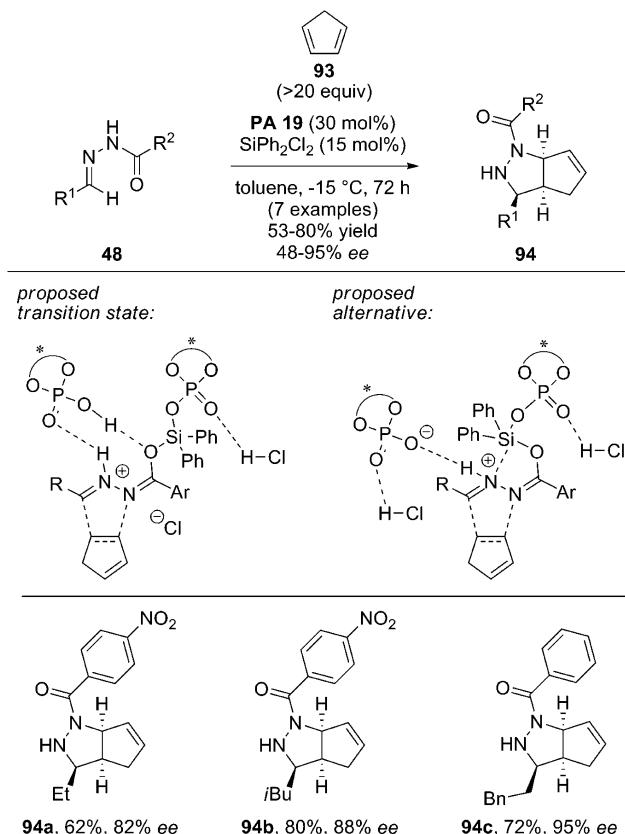
**Figure 48.** Seminal [3+2]-cycloaddition reaction of a hydrazone by Tsogoeva (2011).

The reaction of **48a** with 20 equiv of cyclopentadiene **93** in the presence of 15 mol % **PA 19** and 10 mol % **SiPh<sub>2</sub>Cl<sub>2</sub>** was performed. The desired product **94a** was obtained in an excellent 89% ee but a rather low yield of 13%. The mechanism of asymmetric induction is unclear, because the reaction conditions differ substantially from the racemic variant, and in addition the low yield suggests an alternative pathway. The authors propose an interesting coordinative interaction between the phosphoric acid and the silylated hydrazone. This would suggest that the catalyst is acting here as a chiral counterion. However, when the silicon additive was omitted entirely, the reaction still furnished the product with 47% ee, suggesting that multiple modes for enantioinduction could be operating. An alternative suggestion would be monoactivation of the imine nitrogen by the catalyst and silylation of the carbonyl by the silicon reagent. A year later the same group published the same reaction with improved yields and enantioselectivity (Figure 49).<sup>86</sup>

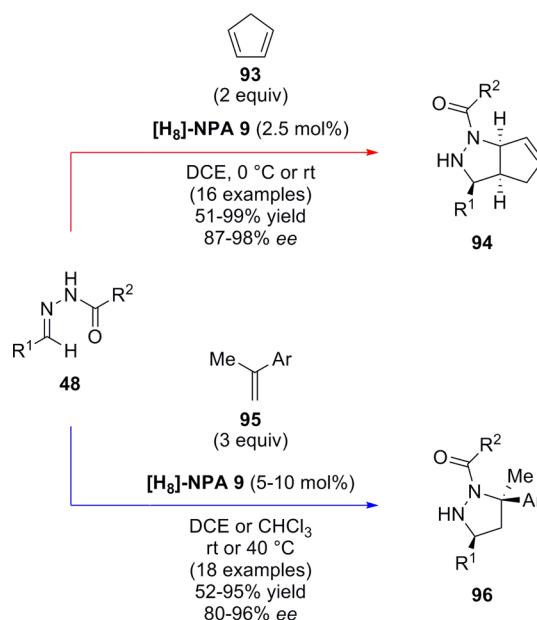
Hydrazones **48** gave after reaction with cyclopentadiene **93** the bicyclic products **94** now in yields ranging from 53% to 80%. This result is quite striking as the reaction conditions only slightly differed. The reaction was now conducted at -15 °C, and a rather high 30 mol % of catalyst **PA 19** was employed, which gave enantioselectivities in the range of 48–95%. The authors propose two possible transition states, which both involve two molecules of phosphoric acid in addition to the hydrazone, cyclopentadiene, and HCl (Figure 49).

In 2012, Rueping was able to show that the use of an *N*-triflyl phosphoramide catalyst precluded the use of any silicon containing additive and the reaction of hydrazones **48** with cyclopentadiene **93** could be conducted with just 2.5 mol % of **[H<sub>8</sub>]-NPA 9** to give the desired products **94** in high yields and enantioselectivities (Figure 50).<sup>87</sup>

The higher acidity of the catalyst is proposed to be the reason for improved reactivity, and further studies showed that the loading could even be dropped to 1 mol % without significant deterioration in selectivity or reactivity. Furthermore,



**Figure 49.** [3+2]-Cycloadditions of hydrazones in combination with a silicon additive by Tsogoeva (2012).



**Figure 50.** [3+2]-Cycloadditions of hydrazones using a *N*-triflyl amide catalyst by Rueping (2012).

the scope of the [3+2]-cycloaddition was extended to include aromatic alkene partners **95** to form pyrazolidine products **96**. This time a slightly higher loading of 5–10 mol % was utilized. The products of the reactions were shown to be suitable for numerous further transformations. The mechanism is thought to closely resemble that shown in Figure 46, but instead of a

chiral counterion, mono activation of the substrate by H-bond activation of the *N*-acyl unit occurs.

**2.1.5. Pericyclic Reactions.** Electrocyclic reactions can be a powerful tool in organic synthesis as they often provide disconnections that would not normally be possible via alternative methods. In 2009, List was able to show that chiral Brønsted acids could catalyze the cycloisomerization of  $\alpha,\beta$ -unsaturated hydrazones **97** (Figure 51).<sup>88</sup>

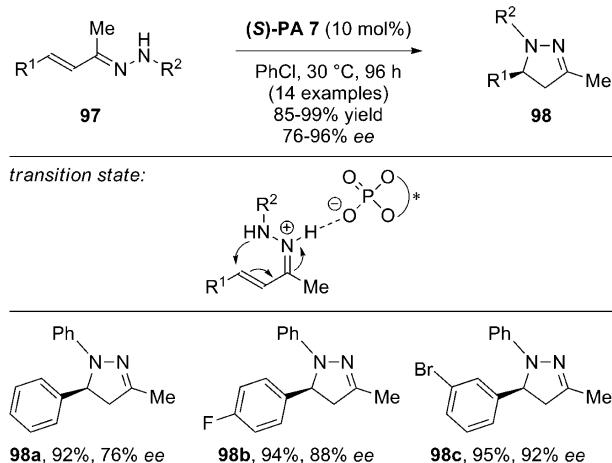


Figure 51.  $6\pi$  electrocyclization for the synthesis of pyrazolines by List (2009).

Using 10 mol % of catalyst (S)-PA 7, he was able to show that hydrazones **97** would undergo a  $6\pi$ -electrocyclization to give pyrazolines **98** in excellent yields and high enantioselectivities. A broad scope was demonstrated with both electron-donating and -withdrawing substituents being well tolerated. Aromatic substituents performed the best, but alkyl substitution was also shown to proceed in low to modest yields. Additionally, the hydrazone could be generated *in situ* from the  $\alpha,\beta$ -unsaturated ketones and the corresponding hydrazine. For the hydrazone to undergo cyclization, it must isomerize the double bond geometry from *E* to *Z*, and it is thought that the phosphoric acid can catalyze this process. The proposed mechanism involves a single H-bond activation of the imine nitrogen. The product pyrazolines are useful motifs that possess biological activity and were shown to also undergo diastereoselective alkylations.<sup>89</sup>

The Diels–Alder reaction is one of the oldest and well-studied reactions especially in conjunction with chiral catalysts, which are usually Lewis acids. Brønsted acids tend to lack the acidity to activate the substrates sufficiently and so tend to result in poor reactivity.<sup>90</sup> The development of so-called super acids has been a strongly researched area.<sup>5c,91</sup> In 2006, Yamamoto showed that the more acidic *N*-triflyl phosphoramido catalyst (S)-NPA 9 could effectively catalyze the reaction between diene **100** and dienophile **99a** (Figure 52).<sup>41</sup>

Utilizing 5 mol % of catalyst (S)-NPA 9 at  $-78^\circ\text{C}$  led to an efficient reaction to yield substituted cyclohexanes **101** in modest to good yields and excellent selectivity. In contrast, the corresponding phosphoric acid catalyst showed no reactivity. The nature of the silicon protecting group was shown to have a large effect on the yield of the reaction, with the TIPS group being superior to the TBS group (cf., **101a** versus **101b**). Nagorny has also shown that chiral phosphoric acids can catalyze the ionic [2+4] cycloadditions of unsaturated acetals.<sup>92</sup>

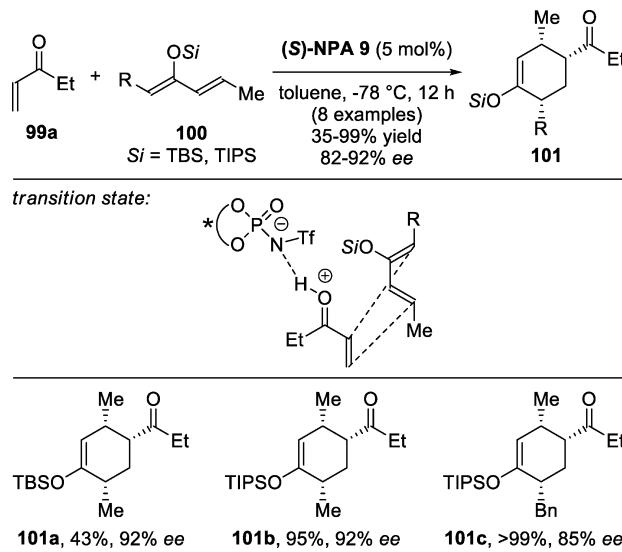


Figure 52. Diels–Alder reaction by Yamamoto (2006).

Rearrangements are a powerful way of synthesizing molecular architecture that is difficult to approach in conventional methods.<sup>93</sup> The aza-Cope reaction is one such rearrangement that fits this description. It has been used by several groups successfully in the synthesis of complex targets, but until 2008, no asymmetric variant had been reported. Rueping was the first to investigate this reaction using homo allylic amines **102**.<sup>94</sup> Upon treatment with an aldehyde **103** and 10 mol % of catalyst [ $\text{H}_3$ ]-PA 6, the rearrangement occurred smoothly to give the enantioenriched allylic imines **104** in good yields and selectivity (Figure 53).

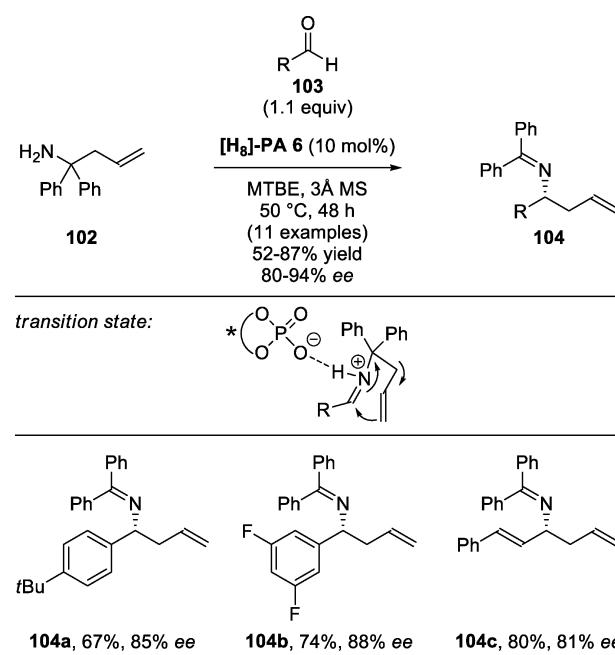


Figure 53. Aza-Cope rearrangement by Rueping (2008).

The reaction was found to function productively in a number of solvents, but MTBE proved to be superior in terms of enantioselectivity. The products were shown to be able to be further transformed including a deprotection of the imine to yield the allylic amine products, which are useful motifs in

synthesis. It is thought that the monocontact activation of the generated imine substrate leads to the stereoselective rearrangement observed.

**2.1.6. Multicomponent Transformations.** Multicomponent reactions resemble a powerful strategy to create complex molecules from simple starting materials.<sup>85</sup> The nature of the reaction also allows chemical space and molecular diversity to be explored in a modular fashion with relative ease. In 2009, Zhu and Wang reported on a multicomponent reaction sequence that involved the key step of the addition of an isocyanide (**105**) to an aldimine, which was generated from the corresponding aldehyde (**103**) and amine (**35**) (Figure 54).<sup>96</sup>

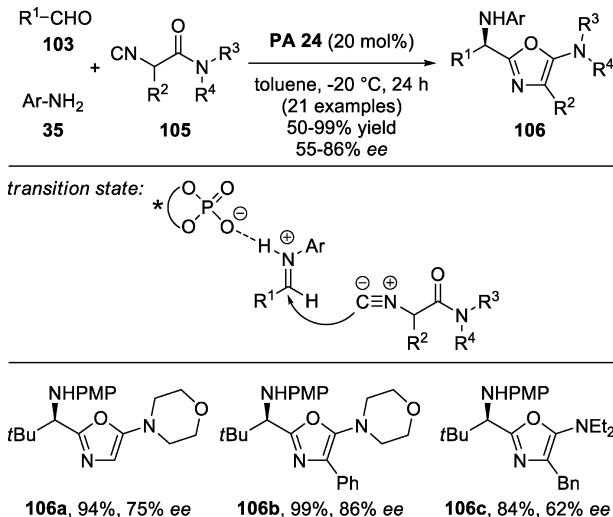


Figure 54. Multicomponent reaction using isocyanides by Zhu and Wang (2009).

The process utilized 20 mol % of catalyst **PA 24**, which promoted the reaction to give 2-(1-aminoalkyl)-5-amino-oxazoles **106** in good yields with moderate to high enantioselectivities. The oxazoles themselves were shown to be able to be opened to useful amide motifs. The key stereocenter is thought to be controlled by monoactivation of the generated aldimine by the catalyst.

In 2012, the scope of the transformation was extended to include a fourth component, an acid chloride.<sup>97</sup> Imino formation was again performed from the corresponding aldehyde **103** and amine **35**, and then reaction with isocyanide **107** gave the expected oxazole, which reacted further with the acid chloride to give pyridinones **108** (Figure 55).

In general, the yields ranged from modest to good, but the enantioselectivities were excellent. The mechanism is thought to follow a pathway similar to that shown in Figure 52. The addition of an isocyanide to an imine is a scarcely reported transformation, and this work should open many more possibilities.

**2.1.7. Miscellaneous Reactions.** In this section, we will aim to cover the literature that we believe follows a monoactivation pathway but does not fall into any of the major subdivisions usually due to being represented by a single example or report. The methodologies presented are still powerful strategies in organic synthesis and should not be overlooked.

In 2008, Rueping disclosed the asymmetric carbonyl-ene reaction of ethyl trifluoropyruvate **109** with a range of styrenes

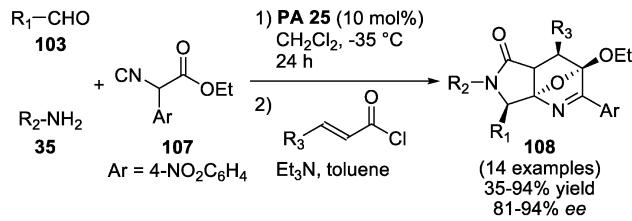


Figure 55. Ugi-type reaction by Zhu and Masson (2012).

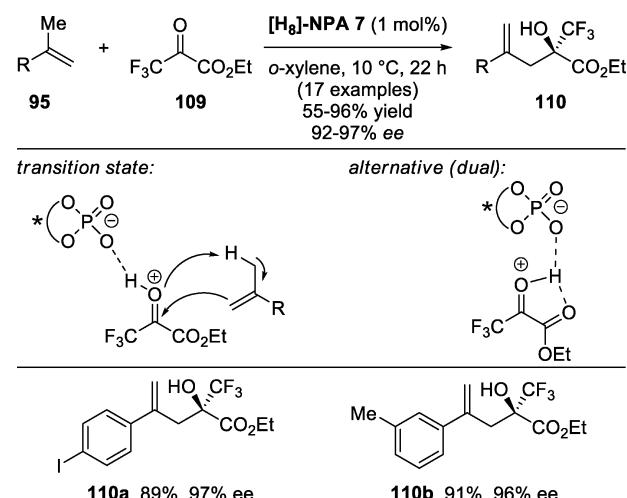


Figure 56. Carbonyl-ene reaction by Rueping (2008).

**95** (Figure 56).<sup>98</sup> The reaction was conducted with 1 mol % of catalyst **[H<sub>8</sub>]-NPA 7** to give hydroxy-trifluoromethyl esters **110** in good yields and high enantioselectivity.

During the catalyst screening, it was noticed that groups at the 4-position gave higher enantioselectivities, with the OMe group bearing the highest selectivity. The catalyst itself is stable to air, and overall the reaction is carried out under remarkably mild conditions. It is proposed that monoactivation of the carbonyl by the catalyst induces the selectivity observed. It is worth considering however that, although the adjacent ester is known to increase the basicity of the carbonyl group, it may also be involved in the activation step. This alternative dual activation mode for the substrate cannot be ruled out to be occurring.

Dynamic kinetic resolutions are one of the most powerful techniques known to obtain enantiopure compounds from racemic starting materials.<sup>99</sup> In 2011, Birman described a unique dynamic kinetic resolution of azlactones using 5 mol % of catalyst **PA 7**.<sup>100</sup> Azlactones **111** could be made to undergo ring opening with various alcohols to yield the corresponding  $\alpha$ -amino esters **112** in good yields and modest to good selectivity (Figure 57). The nature of both the C<sub>2</sub>-substituent and the alcohol was explored and found to have a big effect on the reaction in terms of both yield and enantioselectivity.

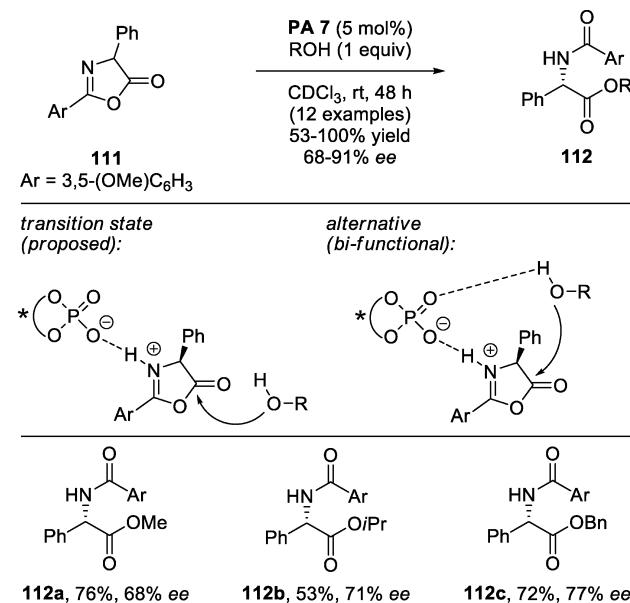


Figure 57. Dynamic kinetic resolution of azlactones by Birman (2011).

The consistency of the reaction was also found to be variable depending on the batch of catalyst they had been synthesized, and this led them to consider the role of impurities. It was thought that metal salts present in small amounts could affect the reaction. Indeed, when freshly purified catalyst that had been washed with acid was utilized, the reactivity and selectivity were far superior to unwashed catalyst. The mechanism proposed by the authors is that of monoactivation by a single contact with the protonated nitrogen. It can however be envisioned that an interaction between the catalyst and the alcohol nucleophilic does exist, and therefore the reaction may proceed via a bifunctional activation.

The deracemization of substrates is a powerful strategy employed in asymmetric synthesis. It allows you the flexibility to obtain enantio-enriched products starting from racemic starting materials. Recently, Du has developed a variant of this process, which involves the rearrangement of racemic epoxides catalyzed by a chiral Brønsted acid.<sup>101</sup> Taking epoxides 113 in the presence of N-SPA 1 resulted in a rearrangement to form an intermediate aldehyde species, which in the same pot could be reduced to give the alcohols 114 (Figure 58).

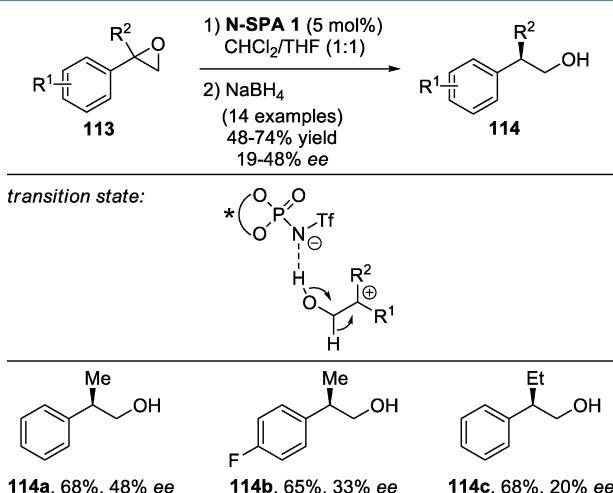


Figure 58. Rearrangement of racemic epoxides by Du (2013).

The transition state of the reaction is given in Figure 56. Activation of the epoxide occurs by the Brønsted acid, which leads to opening of the epoxide to reveal a planar cation at the chiral center that is then quenched by a asymmetric 1,2-hydride shift. Both the yields and the enantioselectivity of the reaction are modest, suggesting the catalyst has little influence on the stereogenic center being formed.

An interesting example of the use of Brønsted acids to carry out asymmetric transformations was shown by Xie in 2009, who employed 20 mol % of catalyst PA 1 in conjunction with 20 mol % of cinchona alkaloid 117 (Figure 59).<sup>102</sup> Using this

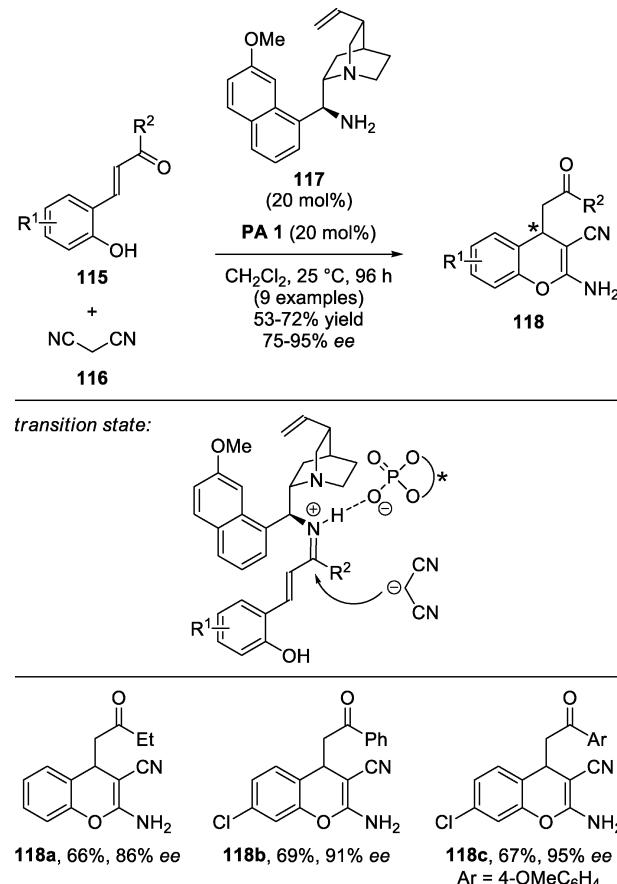
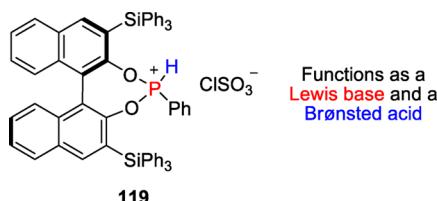


Figure 59. Cascade reaction for the synthesis of 2-chromenes by Xie (2009).

combination, 2-chromenes 118 could be formed from the corresponding phenols 115 and malononitrile 116 in good yields and selectivity.

A study was conducted to understand the synergistic effect of using both catalysts together, and first it was found that in the absence of 117 the yield and enantioselectivity suffered dramatically and in the absence of PA 1 no reaction took place. It is thought that the cinchona alkaloid 117 is needed to form an imine, which can be protonated by PA 1 that then undergoes subsequent reaction. This unique system has been taken up by Wang who has shown various enantioselective Michael reactions with isatins.<sup>103</sup> The processes all utilized a 2:1 ratio of acid to alkaloid with the optimal loadings being rather high at 40 and 20 mol %, respectively. The combination of a chiral phosphoric acid and a chiral amine has also been used by other groups.<sup>104</sup>

In 2011, Ishihara developed a novel catalyst, which could be generated *in situ* from a Lewis basic phosphorus(III)



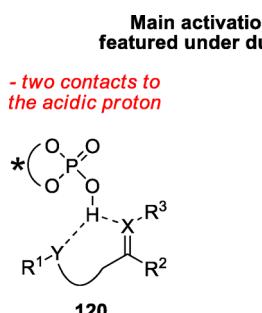
**Figure 60.** Chiral phosphonous acid by Ishihara (2011).

compound to give a chiral Lewis base-assisted Brønsted acid **119** (Figure 60).<sup>105</sup> In 2013, they extended the utility of this catalyst architecture to the kinetic resolution of unsaturated carboxylic acids.<sup>106</sup>

Finally, in an isolated example, a Mukaiyama aldol reaction could be controlled with a *N*-triflylthiophosphoramido catalyst to afford the aldol products in excellent yields and good to excellent enantioselectivities.<sup>107</sup>

## 2.2. Dual Activation

Dual activation of substrates is the smallest category among the various activation modes available to BINOL-derived Brønsted acids; however, it is still a very powerful method for achieving high enantioselectivities. In this Review, the term “dual activation” will involve all activations, which involve one reactive component making two specific contacts with the catalyst. The two main forms that are encountered are shown in Figure 61.



**Figure 61.** Examples of different modes covered by dual activation

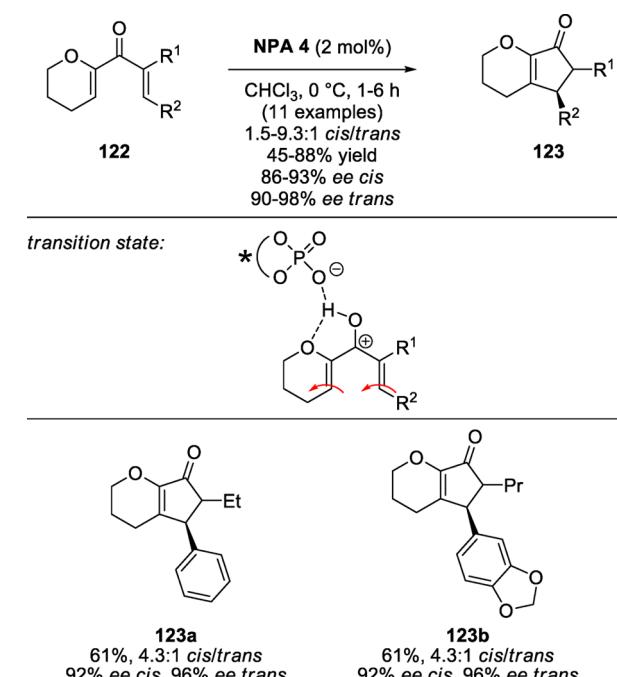
It should be mentioned that generally dual activation involves activations of electrophilic reacting partners. The first most common case involves two contacts to the acidic proton of the catalyst by the substrate (120). This usually occurs when the group being activated to undergo reaction contains a Lewis basic group in close proximity within the substrate. The second case involves the substrate making two contacts to the catalyst (121). This usually occurs when the substrate contains an acidic proton close to the reacting site. A tutorial review from the Rueping group discusses in detail the differences between these two modes.<sup>12</sup>

In this section, we will cover all examples that we believe to be proceeding by dual activation and where possible will aim to clarify the exact interactions thought to be involved during activation by the catalyst.

**2.2.1. Nazarov Cyclizations.** Electrocyclic reactions are powerful transformations that involve the rearrangement of orbitals to create new bonds, which are usually carbon–carbon bonds. The Nazarov cyclization is an important member of this category and is a  $4\pi$ -electron process that converts divinyl ketones into cyclopentenones.<sup>108</sup> It can be accelerated greatly by the presence of catalytic amounts of Lewis or Brønsted

acids. In 2007, Rueping was the first to recognize the possibility of utilizing a chiral Brønsted acid to access enantiomerically enriched products.<sup>109</sup>

Taking  $\alpha$ -alkoxy ketones **122** in the presence of 2 mol % of catalyst NPA **4** resulted in a smooth cyclization to yield optically active cyclopentenones **123** in good yields and excellent enantioselectivities (Figure 62). Key to the enantioselectivity of the



**Figure 62.** Nazarov cyclization by Rueping (2007).

reaction is the presence of the  $\alpha$ -alkoxy group. It is proposed that the acidic proton of the catalyst is involved in a bidentate interaction with both the  $\alpha$ -alkoxy group and the oxygen of the carbonyl group. This bidentate coordination is what is thought to be the reason that enables activation of the carbonyl group because normally chiral phosphoric acids struggle to effectively activate isolated carbonyl groups. Following activation, cyclization occurs followed by protonation of the enolate species to give the products and regenerate the catalyst. In 2012, the same group showed that the tetrahydrofuran ring could be substituted for an  $\alpha$ -alkoxy ether group to provide complementary products also with high enantioselectivities.<sup>110</sup> This strategy has recently been used by Flynn in the formal synthesis of (+)-roseophilin.<sup>111</sup>

In 2011, the Rueping group exploited the mechanism of the Nazarov reaction to facilitate a domino electrocyclization–halogenation sequence to access 5-bromocyclopentenones **125**. A selection of halogenating agents was tested, and 2,4,4,5-tetra-bromocyclohexa-2,5-dienone **124** was found to be optimal for the desired reaction with  $\alpha$ -alkoxy ketones **122** (Figure 63).<sup>112</sup>

The reaction at the time was the first example of an asymmetric Brønsted acid catalyzed Nazarov-bromination reaction. The reaction provides access to two chiral centers, one being a quaternary one. In general, the products **125** were obtained with high selectivity and modest to good yields. The mechanism of selectivity is thought to proceed in a fashion similar to that described in Figure 62.

**2.2.2. 1,3-Dipolar Cycloadditions.** The presence of both a Brønsted acidic site and a Lewis basic site on Brønsted acidic catalysts renders them to be suitable for the stabilization of

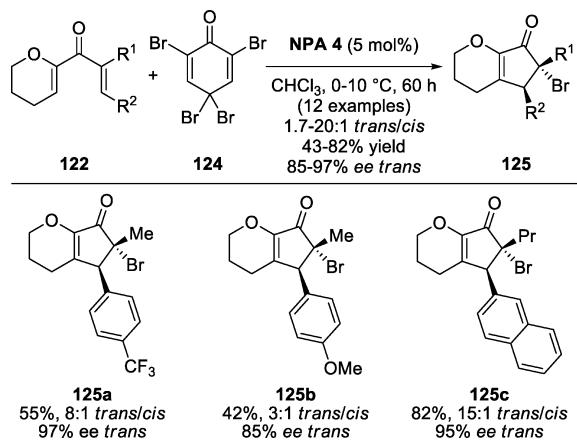


Figure 63. Domino electrocyclization–halogenation reaction by Rueping (2011).

both positive and negative charges in molecules. When both of these charges are contained in the same molecule and more specifically in a 1,3-relationship, then stabilization is known to be possible and can ultimately lead to further reactions when suitable coupling partners are present. This concept has been elegantly explored by the Gong group to great effect. In 2008, the first report described the reaction between aldehydes **103**, amines **35**, and electron-deficient alkene **126** (Figure 64).<sup>113</sup>

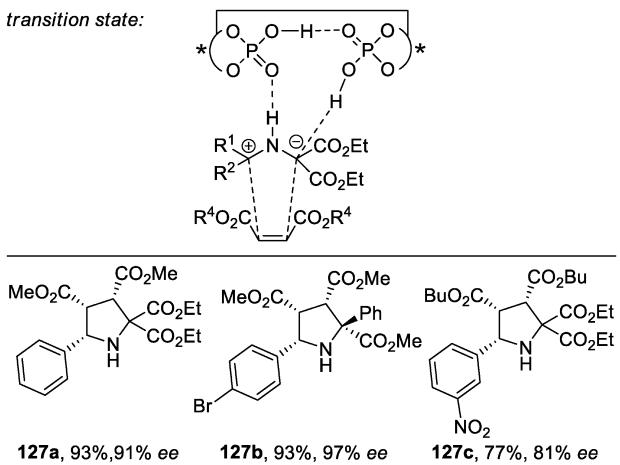
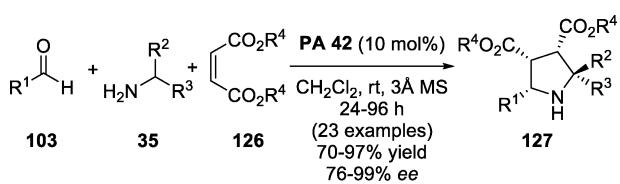


Figure 64. Three-component 1,3-dipolar cycloaddition by Gong (2008).

The first step in the reaction is condensation of **103** and **35** to give an imine intermediate. This imine intermediate can be considered as a precursor to an azomethine ylide, which can be generated in the presence of chiral diphosphoric acid **PA 42** and allowed to react with **126** in an enantioselectively controlled manner. The reaction generates multisubstituted pyrrolidines **127** in good yields and high selectivities. The use of diphosphoric acid **PA 42** is rather uncommon; however, studies with more popular acids provided low levels of control. Mechanistic

studies by the same group seem to suggest that the reaction is greatly facilitated by the presence of two phosphoric acid moieties (Figure 42).<sup>114</sup>

The presence of the diester substituent on amine **35** is thought to be crucial for the formation of the azomethine ylide. During formation of the 1,3-dipole, diphosphoric acid **PA 42** can stabilize both the positive and the negative charges associated with the reactive species (Figure 62), which allows it to undergo a stereoselective cyclization. Following the initial breakthrough, Gong and other research groups have published several variations to widen the scope of these cyclizations greatly.<sup>115</sup>

In 2008, Gong also demonstrated that alkenes were not the only coupling partner suitable for reaction with the generated azomethine ylides. Instead, it was shown that imines could also participate and furthermore could be generated in situ, removing the need to handle them directly. The reaction of **103**, **35b**, and **35** conducted in the presence of **PA 25** furnished chiral imidazolidines **128** (Figure 65).<sup>116</sup>

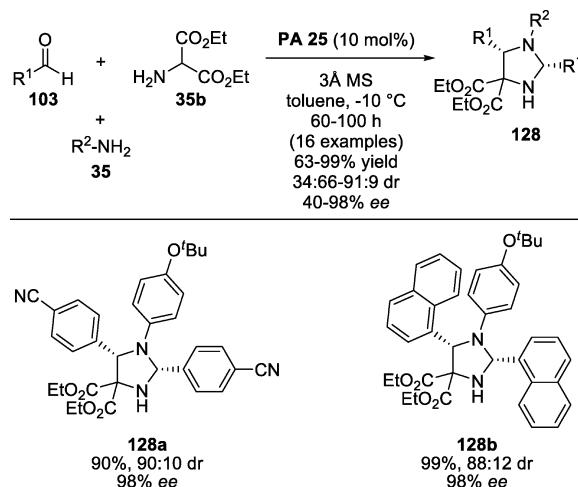
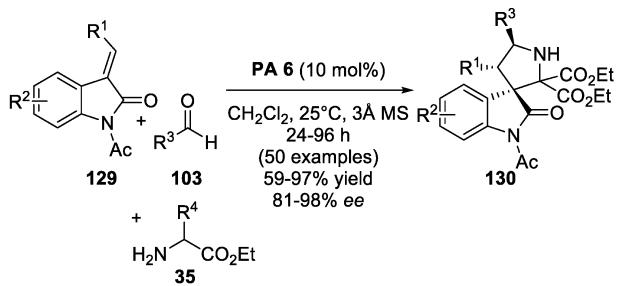


Figure 65. 1,3-Dipolar cycloadditions by Gong (2008).

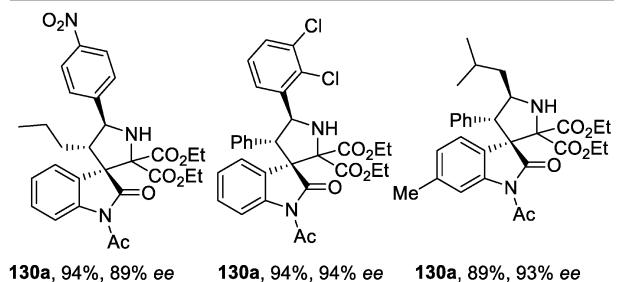
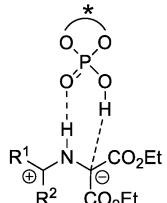
Although diphosphoric acid (**PA 42**) proved to be a highly active catalyst for the reaction, the group actually found **PA 25** to be also sufficiently active and versatile for a broad substrate scope. The group however did observe a nonlinear effect with regards to the catalyst loadings and has suggested the possibility that multiple molecules of the catalyst are involved in the transition state of the reaction.

A noteworthy variant of the 1,3-dipolar cycloaddition with azomethine ylides is that presented by Gong in 2009 which involved their reaction with unsaturated indoles to generate spirooxindoles. Reaction of **103** and **35** with 3-alkylideneindolin-2-ones **129** gave the spiro products **130** in good yields and selectivities (Figure 66).<sup>117</sup>

Interestingly, a more conventional phosphoric acid (**PA 6**) was shown as the optimal catalyst for the reaction, and a mechanism is proposed as previously described, which involves dual activation. The catalyst in this case using a single phosphoric acid unit makes two contacts to the reacting substrate. Closely related to this, an alternative route to spirooxindoles has been developed whereby isatins can be employed as ketone-based precursors for the azomethine intermediate.<sup>118</sup> Gong has also recently demonstrated a biomimetic 1,3-hydride shift process, which can be used to



transition state:



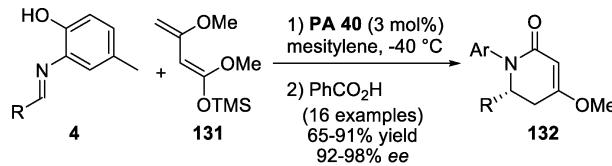
**Figure 66.** Synthesis of spiro[pyrrolidi-N-3,3'-oxindoles] by Gong (2009).

generate azomethine intermediates that can also participate in 1,3-dipolar cycloadditions.<sup>119</sup>

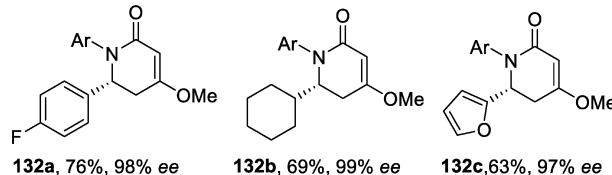
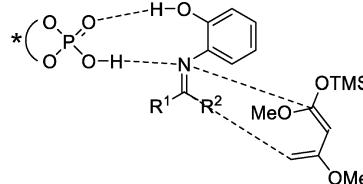
**2.2.3. Diels–Alder.** The Diels–Alder reaction is one of the most famous organic reactions known and has been the subject of numerous reviews.<sup>120</sup> The classic aza-Diels–Alder variant, when an imine is used as a dienophile, has become a useful extension to access piperidines.<sup>121</sup> In 2006, Akiyama developed an elegant aza-Diels–Alder reaction between 2-hydroxyphenyl imines **4** and Brassard's diene **131** to give enantioenriched lactams **132** (Figure 67).<sup>122</sup>

The reaction is carried out with 3 mol % of catalyst **PA 40**, which is a pyridine salt; however, the pyridine is not thought to contribute to the mechanism of the reaction but more to stabilize the diene. The mechanism of this reaction, which can be assumed rather general for all reactions involving 2-hydroxyphenyl imines, is one that involves dual activation. The presence of the hydroxyl group on the aniline has been shown to be an essential component for achieving high selectivities. Its role is proposed and calculated to provide an additional contact point for activation by the catalyst. The reaction generally works well and can be performed on a gram scale without a drop in yield or enantioselectivity. It should be noted that formally the reaction proceeds via two steps and requires the use of benzoic acid to complete the cyclization to furnish the cycloadduct products. In the same year, Akiyama also disclosed his results on the use of 2-hydroxyphenyl imines with Danishefsky's diene<sup>123</sup> and simple enol ethers<sup>124</sup> in an inverse electron demand aza-Diels–Alder reaction.

Although imine components constitute a large portion of substrates that can be activated by chiral Brønsted acids, the activation of carbonyl groups has also been shown to be successfully activated in many reports. One such publication

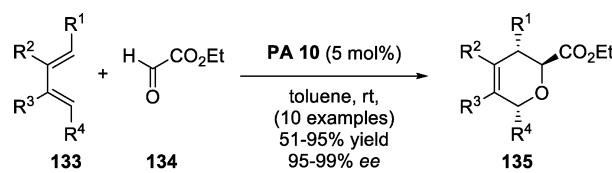


transition state:

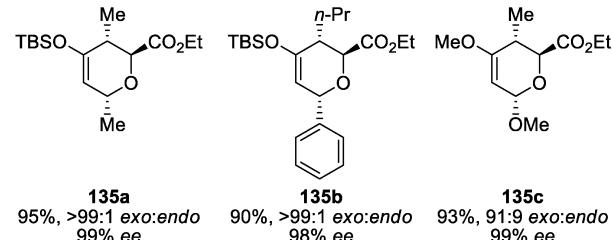
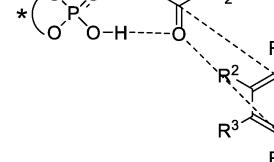


**Figure 67.** Aza-Diels–Alder reaction of Brassard's diene by Akiyama (2006).

was that from Terada in 2009, who showed that glyoxylate **134** can undergo a hetero-Diels–Alder reaction with dienes **133** to give dihydropyrans **135** (Figure 68).<sup>125</sup>



transition state:



**Figure 68.** Hetero-Diels–Alder reaction of glyoxylates by Terada (2009).

Interestingly, the reaction proceeds to give the products **135** where the major isomer results from the less frequently encountered *exo*-transition state. The reaction methodology has a wide scope and furnishes **135** in excellent enantioselectivities. It is proposed that glyoxylate aldehydes can participate in dual activation in a manner similar to that of 2-hydroxyphenyl imines. In the case, the aldehyde-proton is proposed to be acidic enough to be involved in an interaction with the Lewis basic site of the catalyst along with the interaction between the

oxygen atom of the aldehyde and the acidic proton on the catalyst.

**2.2.4. Mannich.** The dual activation Mannich reaction is one of the very first reactions disclosed to the synthetic community by Akiyama in 2004.<sup>15</sup> Since then, the chiral Brønsted acid-catalyzed Mannich reaction and the field of Brønsted acid catalysis have received a great deal of attention. In contrast to other modes of activation, the dual activation of imines has only been seldomly studied.

The majority of catalyst modifications observed in the literature for chiral phosphoric acids are aimed toward tuning the substituents at the 3,3'-positions. Akiyama's group is one of the few groups that have looked at modifications along the backbone of the binaphthyl rings. In 2008, Akiyama demonstrated the use of catalyst PA 30 containing iodine atoms at the 6,6'-positions toward an enantioselective vinylogous Mannich-type reaction.<sup>126</sup> 2-Hydroxyphenyl imines **4** were reacted with furan derivative **54b** to give the butenolides **136** (Figure 69).<sup>127</sup>

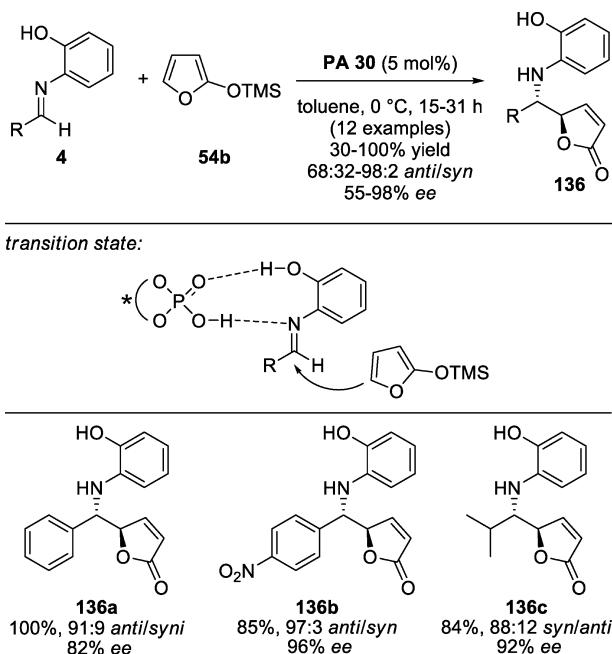


Figure 69. Vinylogous Mannich-type reaction by Akiyama (2008).

A comparative study between catalyst PA 30 and the related non-iodinated catalyst showed an increase of 8% ee (74% as compared to 82% ee); however, based on theoretical calculations, very little conformational change is predicted to be the cause of the higher selectivity. Instead, an electronic effect is considered to be more likely the reason for higher selectivity.

**2.2.5. Miscellaneous.** In this section, we will aim to cover unique examples of chiral Brønsted acid-catalyzed reactions, which are thought to involve either dual activation with one reacting partner. In 2008, Terada reported an aza-ene-type reaction of glyoxylate **134** and enecarbamates **137** in the presence of 5 mol % of catalyst PA 11 (Figure 70).<sup>128</sup>

The products **138** were generally obtained with high levels of enantioselectivity; however, (*Z*)-enecarbamates were found to give the corresponding products with lower selectivity. The proposed activation is that of dual activation of the glyoxylate aldehyde. DFT computational analysis calculated that two

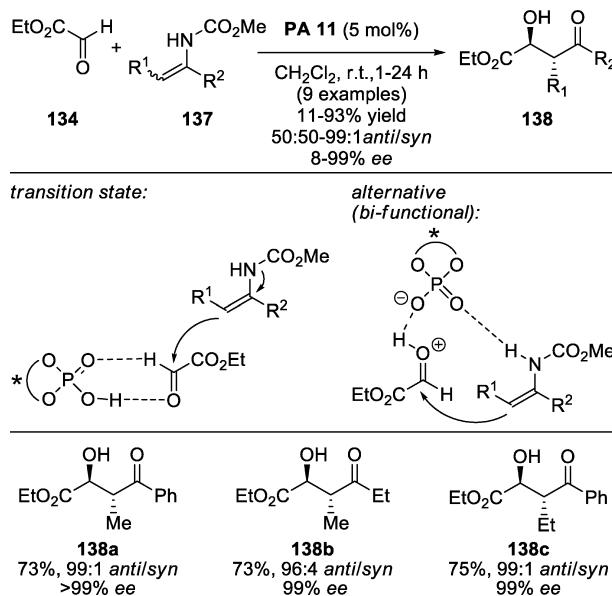


Figure 70. Aza-ene-type reaction by Terada (2008).

hydrogen bonds between the glyoxylate and the catalyst is the lowest energy transition state. It should be mentioned though that the enamine reacting partner contains an acidic proton and may be interacting with the catalyst in a bifunctional type mechanism.

A year later, Terada also published his findings on the direct Aldol reaction of azlactones **140** with various enol ethers **139** (Figure 71).<sup>129</sup> The reaction is promoted by catalyst PA 25 and following a basic hydrolysis yielded the  $\beta$ -hydroxy- $\alpha$ -amino acid derivatives **141** containing a quaternary stereocenter.

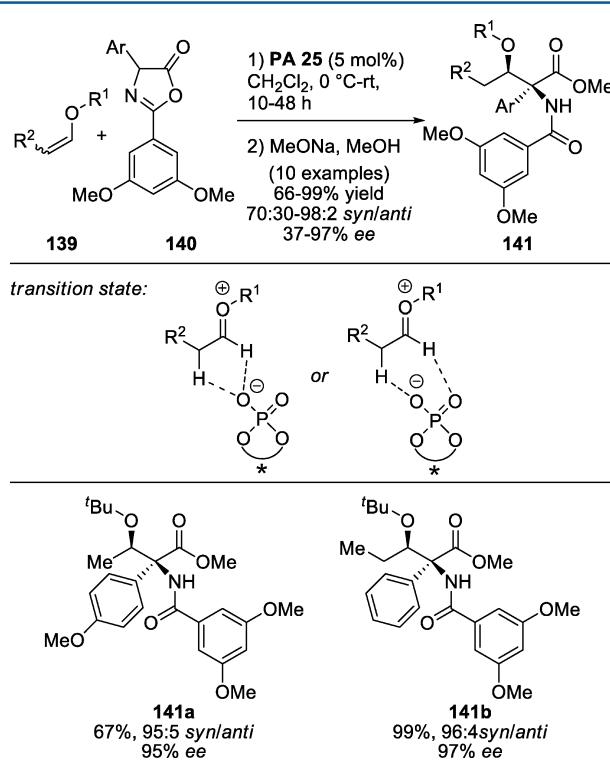


Figure 71. Direct Aldol-type reaction by Terada (2009).

The reaction is thought to proceed via a generated oxonium ion promoted by the acid catalyst. The authors propose that this intermediate contains two contact points with the catalyst, which can take one form from a possible of two. The first transition state involves the catalyst's negatively charged oxygen atom interacting with both the aldehyde proton and the  $\alpha$ -proton to the carbonyl. The second scenario is that where the negatively charged oxygen is bound to the site of protonation, while the Lewis basic site on the catalyst is coordinated to the aldehyde proton.

An Aldol reaction catalyzed by a chiral phosphoric acid has also been reported by Blanchet, who used cyclic ketones **142** with glyoxylate **134** in the presence of catalyst  $[\text{H}_8]\text{-PA 24}$  to access the aldol products **143** (Figure 72).<sup>130</sup>

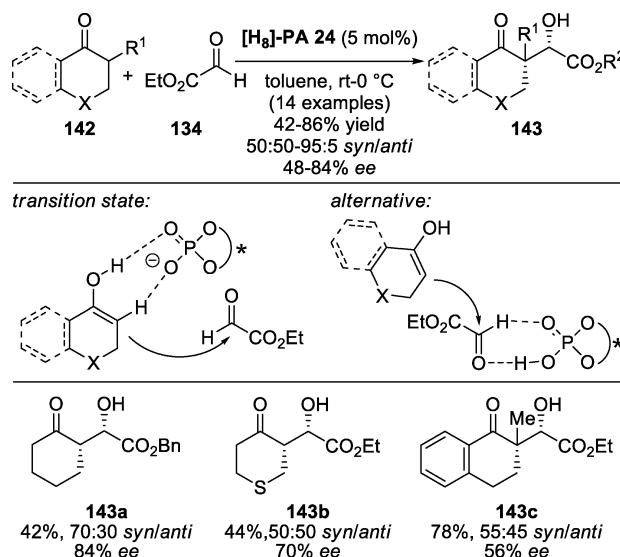


Figure 72. Aldol reaction by Blanchet (2010).

The Aldol products **143** are obtained mainly as the *syn*-isomer, which is complementary to approaches using conventional enamine catalysis. Commonly, the activation of glyoxylate aldehydes with chiral phosphoric acids is that of dual activation with two contacts made to the catalyst. Interestingly, the authors in this case propose that dual activation is occurring but of the nucleophile. Two contacts to the enol-proton and the  $\alpha$ -proton are thought to be responsible for the selectivity observed. One could also envision a more traditional dual activation of the glyoxylate. Further mechanistic studies are indeed needed to truly determine which pathway is occurring in this case. Blanchet has also shown the direct Aldol reaction with enone carbonyls to be catalyzed by chiral phosphoric acids.<sup>131</sup>

Optically active sulfoxides are important compounds and have been found to be useful in a wide variety of roles, for example, as chiral auxiliaries.<sup>132</sup> For this reason, many research groups have successfully developed routes to access enantioselectively pure sulfoxides; however, the majority relies on the use of metals to facilitate the process. In 2012, Wang reported the seminal publication on the use of a chiral phosphoric acid and aqueous  $\text{H}_2\text{O}_2$  to solely facilitate the oxidation process and was able to achieve modest selectivity (56–82% ee).<sup>133</sup> Later that year, List reported a much more improved process utilizing a new family of chiral phosphoric acids, which contain a confined chiral pocket (Figure 73). PA **43** is thought to contain a well-defined and narrow cavity, which restricts the number of possible trajectories for the  $\text{H}_2\text{O}_2$  and hence increases the selectivity of the oxidation.<sup>134</sup>

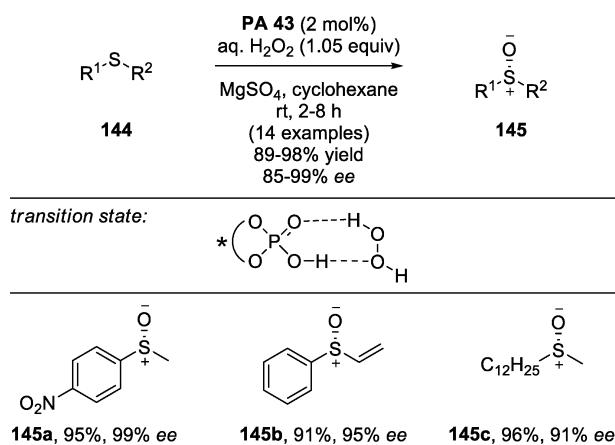


Figure 73. Sulfoxidation by List (2012).

The oxidation of sulfides **144** to sulfoxides **145** proceeded in excellent levels of enantiocontrol and utilized only 2 mol % of PA **43**. Naturally, the  $\text{H}_2\text{O}$  from the oxidant was detrimental to the reaction but could be controlled by the use of  $\text{MgSO}_4$  in the reaction flask. The enantioselectivities obtained are very comparable to the best results obtained with metal catalysts. The mechanism proposed is thought to be dual activation of the peroxide by the catalyst. Two contacts between the proton and the opposite oxygen atom are thought to be responsible for the enantioselectivity.

The enantioselective desymmetrization of chiral molecules is a powerful route to enantioenriched building blocks, which may be difficult to access by other methods due to the nature of the stereogenic center. The Fischer indole synthesis,<sup>135</sup> which was reported over 120 years ago, is a widely employed procedure both in academia and in industry, but until 2011 had evaded all attempts to be performed in an asymmetric manner using catalysis. List developed a powerful protocol to address this problem by utilizing a spirocyclic phosphoric acid (SPA **1**) to effectively desymmetrize 4-substituted cyclohexanones to then undergo the desired reaction (Figure 74).<sup>136</sup>

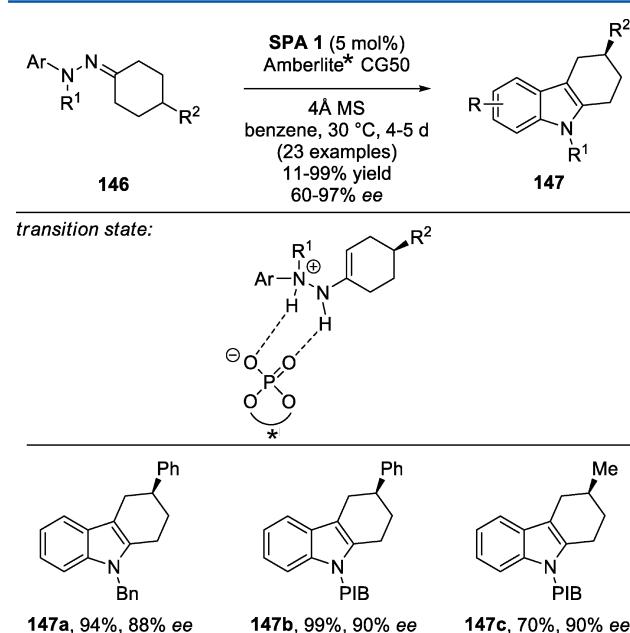
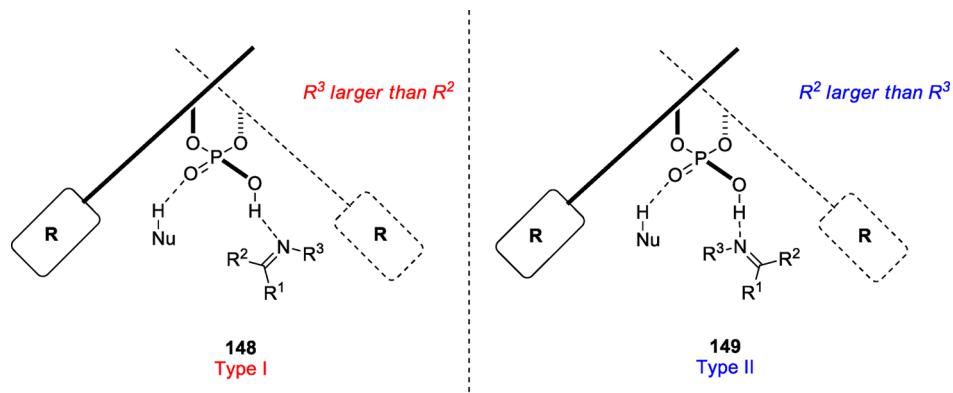


Figure 74. Fischer indole reaction by List (2011).



**Figure 75.** Models for bifunctional activation (Goodman).

Taking hydrazones **146** with 5 mol % catalyst SPA **1** and Amberlite CG50 allowed for a smooth desymmetrization reaction to occur to give the tetrahydrocarbazole products **147** in good yields and high selectivity. The mechanism proposed involves two hydrogen bonds from the substrate to the catalyst, and it is thought that only one diastereoisomeric pair undergoes an irreversible [3,3]-sigmatropic rearrangement. The use of Amberlite CG50 was needed to capture the released ammonia to prevent catalyst poisoning. The utility of the process was demonstrated with a formal synthesis of (*S*)-Ramatroban, a thromboxane receptor antagonist.

Recently, the Kurti group<sup>137</sup> and subsequently the List group<sup>138</sup> have reported on a catalytic benzidine rearrangement using chiral phosphoric acids. The reaction mechanism may follow a dual activation pathway; however, it is still unclear. The observance of nonlinear effects from the List group's study suggests that multiple instances of the catalyst are involved in the stereoselective transition state.

### 2.3. Bifunctional Activation

Bifunctional activation is perhaps the mechanistic pathway that covers the largest proportion of chiral BINOL-derived Brønsted acid-catalyzed procedures. Indeed, even early papers in the field proceeded via this pathway; however, due to the absence of mechanistic studies, the authors at the time opted to propose more simplified mechanisms. Although the mechanism of reactions can be highly dependent on the nature of the reactants, Goodman has studied the bifunctional model in great depth for BINOL-phosphoric acid-catalyzed reactions of imines.<sup>21</sup> In his study of over 40 different reaction types, he concluded on the basis of in-depth DFT calculations a model that consisted of two different types of transition states, which were involved in these reactions, that could also correctly explain the stereochemical outcome (Figure 75).

They were referred to respectively as Type I and Type II models and projected a view of the transition state whereby the phosphoric acid's oxygen atoms are in the plane while the bulky substituents are on different sides. Both models predict that when the nucleophile contains an acidic proton, it will be involved in H-bonding to the catalyst. The calculated lowest energy transition state is that of a Type I model **148** whereby the group on nitrogen ( $R^3$ ) is pointed into the empty space. A Type II model **149** is calculated to be higher in energy because now the imine substituent is pointing toward the catalyst's substituent and additional steric interactions will be involved. The prediction of whether a particular reaction follows either a

Type I or a Type II reaction involves the comparison of the steric impact of groups  $R^2$  and  $R^3$ . In general, most reactions follow a Type I model ( $R^3$  is bigger than  $R^2$ ); however, changes can occur especially when the nucleophile involved is not reacting with the atom bonded to the acidic hydrogen, for example, Friedel-Crafts reactions of indoles.

The absolute stereochemistry of a reaction also depends on the imine geometry. In general, acyclic aldimines are usually reacting in their *E*-configuration. However, ketimines have a smaller energy difference between the *E*- and *Z*-forms and so can react in both configurations. By the nature of their structure, cyclic imines are forced to react in a *Z*-configuration.

In this section, we will present and cite all of the reactions we believe to be occurring through a bifunctional mechanism. We will not try to classify all of the reactions in terms of Type I or II models, but it is important to know that all of the reactions in the section will involve activation of both the electrophile and the nucleophile by the catalyst. Also worth noting is that in some examples the electrophile and nucleophile are within the same molecule, but due to the catalyst activating two reacting components, it has been classified under bifunctional rather than dual activation.

**2.3.1. Addition of Nucleophiles to Iminium Ions.** The first use of enecarbamates as nucleophiles in asymmetric catalysis was first described by Kobayashi in 2004 with imines.<sup>139</sup> The reaction was catalyzed by chiral copper complexes and thought to proceed via an aza-ene-type pathway. Two years later, Terada reported a highly enantioselective aza-ene-type reaction of enecarbamates **137** with *N*-benzoylated imines **31** (Figure 76) using just 0.1 mol % of catalyst PA **7**.<sup>140</sup> The reaction proceeded in toluene at room temperature to furnish  $\beta$ -amino-imine derivatives **150**, which can be reduced to give 1,3-diamines in a straightforward manner.

The mechanism of the reaction is proposed by Terada to function by the catalyst electrophilically activating the imine by protonation while accepting a proton from the enecarbamate. This serves to keep a rigid network between the reactants and regenerates the catalyst following the addition. It is worth highlighting that the reaction uses a substrate to catalyst loading of 1000:1 and impressively can go as low as 2000:1 without any significant loss in yield or enantioselectivity. The reaction can be easily performed on a gram scale; for instance, 3.5 mg of catalyst was enough to produce 1.7 g of product. In 2009, Zhu and Masson demonstrated a multicomponent variant of the reaction by forming the reactive imine from the corresponding amine and aldehyde.<sup>141</sup>

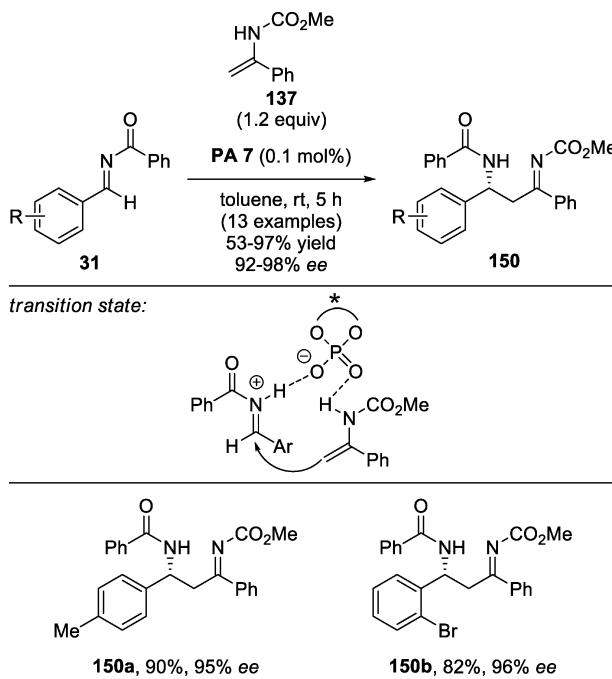
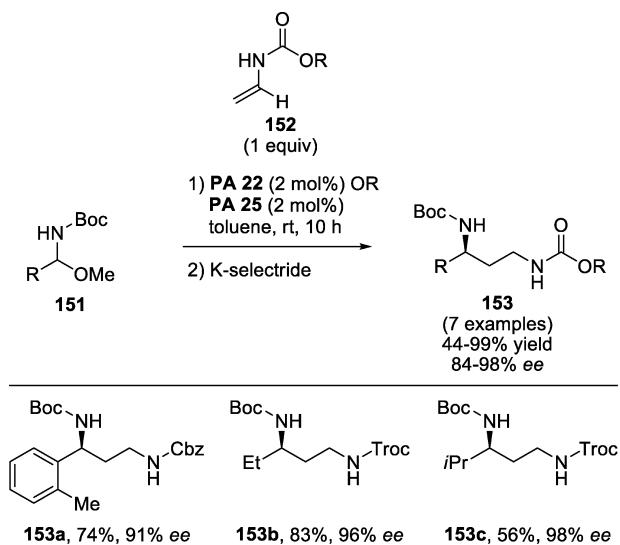


Figure 76. Aza-ene reaction by Terada (2006).

In 2009, Terada showed that ene-carbamates were efficient potent reaction partners to hemiaminals under chiral phosphoric acid catalysis.<sup>142</sup> Using 2 mol % of catalyst PA 22 or PA 25, reaction of hemiaminals 151 with ene-carbamates 152 gave the corresponding 1,3-diamine products 153 after subsequent reduction (Figure 77).

Figure 77. Enamine addition into *N,O*-acetals by Terada (2009).

The reaction functions well with both aromatic and aliphatic aminals to furnish useful chiral diamine products. The most common problem of using ene-carbamates is the over-reaction with the prospective products, which usually leads to lower yields. In this case, it is thought the MeOH released upon activation of hemiaminals 151 prevents over-reaction of the product prior to reduction by K-selectride. Mechanistically, the reaction follows a pathway similar to that described for the addition of enecarbamates to imines.

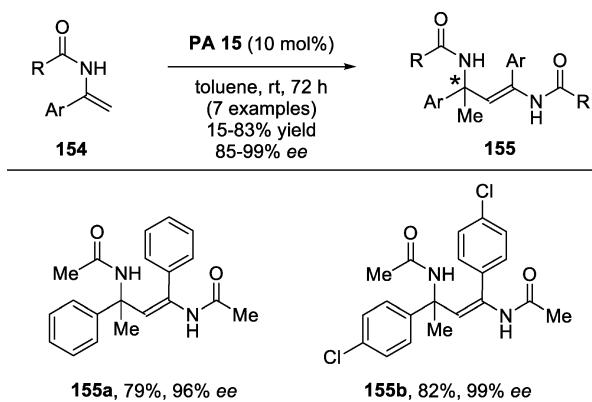


Figure 78. Self-coupling of enamides by Tsogoeva (2008).

The reactive nature of ene-carbamates was exploited by Tsogoeva in 2008 in which she reported the self-coupling reaction of substrates 154 (Figure 78).<sup>143</sup> For the first time, reaction conditions were developed to exploit this usually unwanted reactivity to yield useful amine products 155 bearing a quaternary chiral center. It should be noted that the generation of quaternary chiral centers is a difficult and scarcely reported reaction using chiral Brønsted acid catalysis.

The addition of an enamine intermediate to an imine is generally accepted to occur in the Friedländer condensation, and this process was developed into a desymmetrization process by Gong in 2011.<sup>144</sup> Taking aldehydes 156 with various 4-substituted cyclohexanones 157 and an achiral amine led to a smooth condensation reaction to yield quinolines 158 in high yields and excellent selectivities (Figure 79).

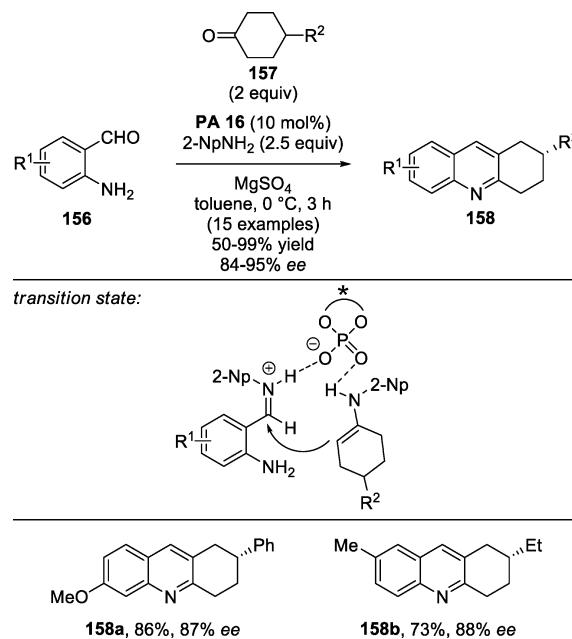


Figure 79. Friedländer condensation promoted by an achiral amine by Gong (2011).

The reaction has a broad scope and also encompasses electron-rich aldehydes 156, which were absent from the first enantioselective Friedländer condensations.<sup>145</sup> The role that the achiral amine plays was found to be rather crucial, and from optimization studies 2-NpNH<sub>2</sub> was found to be the optimal

balance for the best yield and selectivity. The authors propose a bifunctional role for the catalyst, which involves activation of the generated imine and enamine intermediates prior to formation of the stereocenter.

Cyclic aminals, in particular dihydroquinazolinones, are important stereogenic heterocycles that are present in molecules that display a broad range of pharmacological properties.<sup>146</sup> Simultaneously, the groups of List and Rueping realized the importance of a catalytic asymmetric process toward these useful motifs. List showed that by taking 2-amino amides **159** with aliphatic aldehydes, he could access the corresponding condensation products **160** in good yields and enantioselectivities (Figure 80).<sup>147</sup> The use of a highly sterically

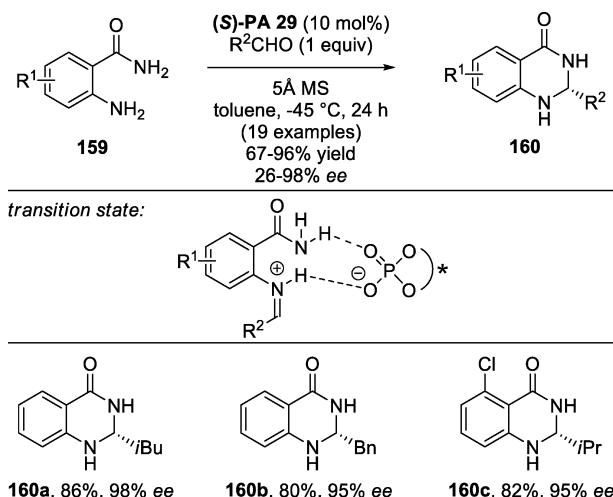


Figure 80. Addition to in situ formed imines from aliphatic aldehydes by List (2008).

hindered catalyst ((S)-PA 29) was essential to achieving high enantioselectivities.

Although not proposed by the authors, one can envision that the first step involves condensation of the aniline with the aldehyde to form an imine intermediate. This will be activated by the catalyst via protonation while simultaneously coordinating to the N–H from the amide. Cyclization thus leads to the product and regeneration of the catalyst. As mentioned earlier, this mode of activation has been classified under bifunctional rather than dual activation due to the catalyst activating both the nucleophile and the electrophile, albeit within the same molecule.

Rueping in his approach explored the scope of aromatic aldehydes and found these to work best in CHCl<sub>3</sub> at room temperature to yield the cyclic aminals **161** in good yields and good to excellent enantioselectivities (Figure 81).<sup>148</sup>

In their case, the best catalyst was shown to be PA 7. Lower temperatures did not affect the selectivity but did prolong the reaction times. In 2012, Tian was able to demonstrate a procedure using *N*-sulfonamide imines to access similar cyclic aminals.<sup>149</sup> Recently, Lin has shown SPINOL-phosphoric acids to be able to also catalyze this reaction.<sup>150</sup>

Mixed acetals containing nitrogen and oxygen are also highly useful molecules that have found commercial applications. In 2010, List extended his asymmetric methodology to *N,O*-acetals starting from 2-hydroxyamides **162** (Figure 82).<sup>151</sup> Interestingly, the commonly used chiral Brønsted acids failed to

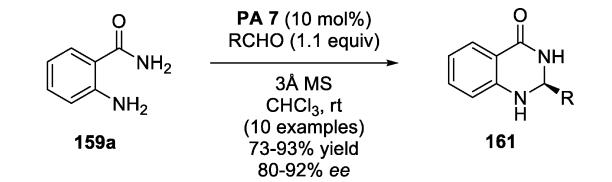


Figure 81. Addition to in situ formed imines from aromatic aldehydes by Rueping (2009).

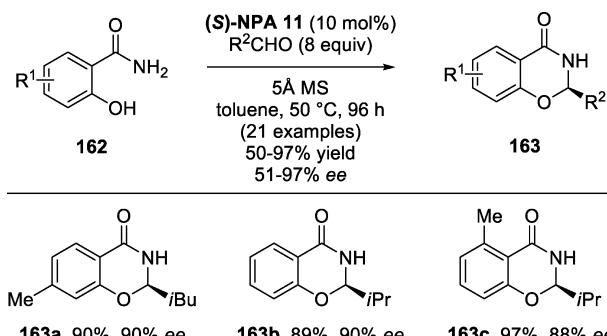


Figure 82. Addition of phenols to in situ formed imines by List (2010).

give any applicable selectivity, and so a new catalyst motif was designed for organocatalysis.

The group designed a range of *N*-phosphinyl phosphoramidate catalysts in the hope that the additional P=O bond would help to stabilize the unique transition state geometry and bring about higher selectivities. After some optimization, it was found that catalyst (S)-NPA 11 was able to deliver the desired reactivity and also provide **163** in high enantioselectivity. The proposed interaction between the catalyst and the reactive intermediate is shown in Figure 83.

Evidence for the intermediacy of the benzolimine was obtained by the treatment of an enamine precursor under the same reaction conditions, and it afforded the product in similar yields and the same enantioselectivity. Chiral *N,O*-aminals have also been studied by the group of Antilla. In 2008, Antilla reported the first asymmetric addition of alcohols to *N*-acyl imines **31** to give chiral *N,O*-aminals **164** (Figure 84).<sup>152</sup> Using 5 mol % of catalyst PA 7 under mild conditions yielded **164** in good yields and enantioselectivity.

Despite the use of a more simple BINOL-phosphoric acid, the mechanism of the reaction is thought to closely follow that proposed by List (Figure 83). In 2011, Antilla further extended the methodology to the addition of thiols under similar reaction conditions (Figure 85).<sup>153</sup> Addition of thiols to **31** using 2 mol % catalyst PA 25 gave the corresponding *N,S*-aminals **165** in good yields and excellent selectivities. A broad substrate scope was evaluated, and both aromatic and aliphatic thiols performed efficiently in the reaction. Although 2 mol % gave the optimal results, during their optimization study it was found that the use of as little as 0.005 mol % catalyst was able to yield enantiomeric excesses as high as 88%.

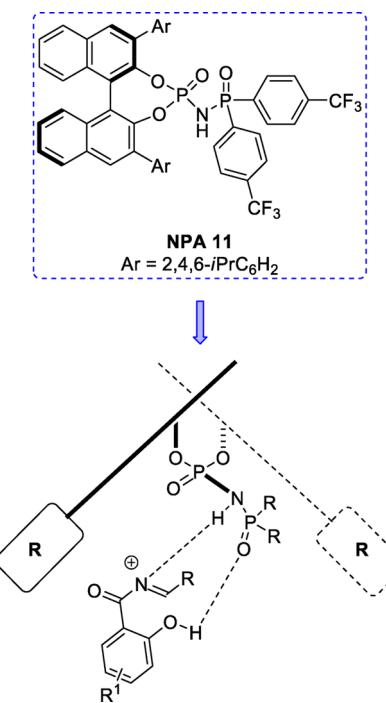


Figure 83. Proposed interaction of N-phosphinyl catalyst (List).

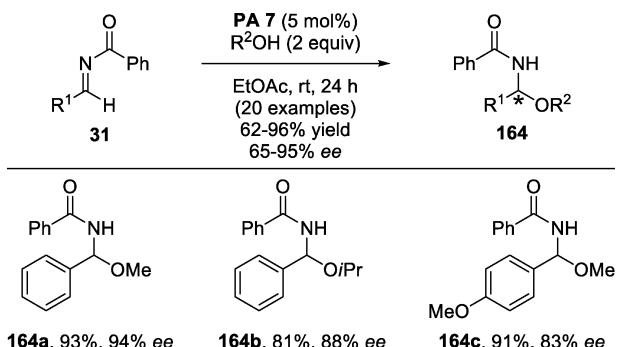


Figure 84. Addition of alcohols to imines by Antilla (2008).

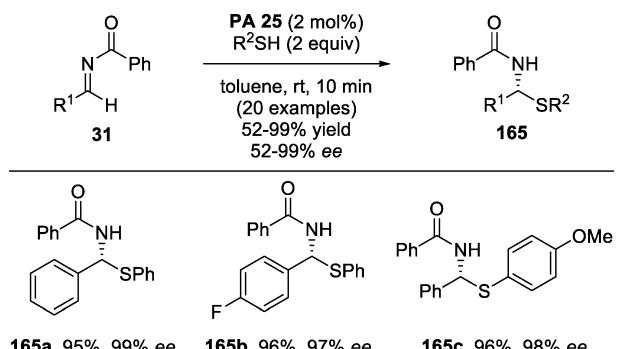


Figure 85. Addition of thiols to imines by Antilla (2011).

*N,N*-Aminals are present in a variety of important molecules and have been shown to be medicinally active in functions such as proteinase inhibitors. Antilla was the first to develop a protocol for the intermolecular addition of sulfonamides to *N*-acyl imines **166** to yield the corresponding protected aminals **167** (Figure 86).<sup>154</sup>

In their optimization study, they found that commonly used BINOL-derived catalysts gave modest to poor results, but

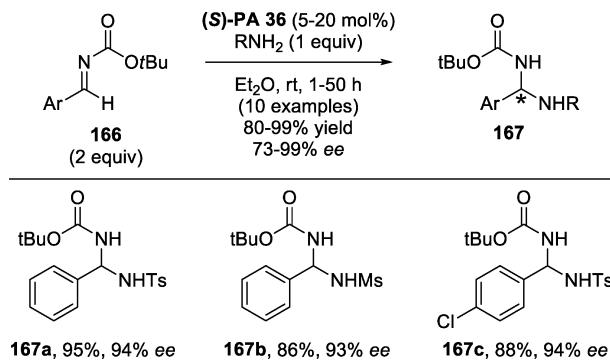


Figure 86. Addition of sulfonamides to imines by Antilla (2005).

(S)-PA 36, a catalyst derived from VAPOL, gave much higher selectivity. Once again, reaction conditions similar to those used for the formation of *N,O*- and *N,S*-aminals were used, and therefore we propose the reaction to be proceeding via bifunctional activation. In addition to being useful motifs, the products themselves were found to be quite stable with decomposition or racemization not being observed over several days.

In 2007, Antilla was able to extend this to include imide nucleophiles (Figure 87).<sup>155</sup> Under mild conditions and

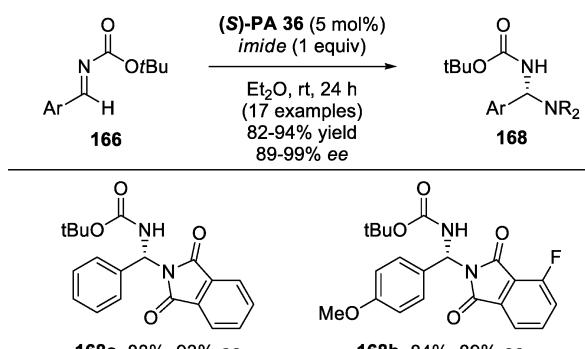


Figure 87. Addition of imides to imines by Antilla (2007).

utilizing once again (S)-PA 36 in 5 mol %, a variety of imides could be added into *N*-acyl imines **166** in good yields and high selectivities to yield the products **168**.

In 2011, the You group realized the potential of spiro iodolinones **169** toward generating electrophilic intermediates that could be intercepted by aromatic coupling partners (Figure 88).<sup>156</sup> Using catalyst (S)-PA 25, it was found that **169** undergoes Friedel-Crafts reactions with various indoles **60** to give the products **170** in high yields and enantioselectivities.

The reaction could also be conducted with N-H free pyrroles, with similar levels of selectivity being achieved. Our proposed mechanism involves H-bonding with the indole coupling partner with simultaneous coordination to the generated iminium ion.

In 2009, Antilla disclosed the opening of *meso*-aziridines **171** with aromatic thiols using 10 mol % of catalyst (S)-PA 36.<sup>157</sup> The opening preceded under mild reaction conditions and was operationally simple to yield non-racemic  $\beta$ -amino thioethers **172** in good yields and high enantioselectivities (Figure 89).

Once again, it was found that BINOL-derived catalysts failed to produce any significant enantioselectivity while VAPOL-derived (S)-PA 36 gave the optimal results. Interestingly, the

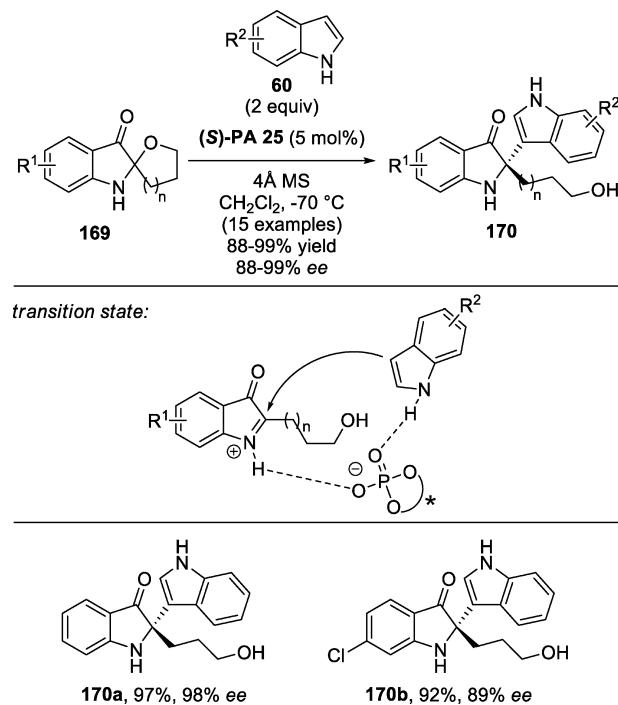


Figure 88. Friedel–Crafts reaction of racemic spiro-indolinones by You (2011).

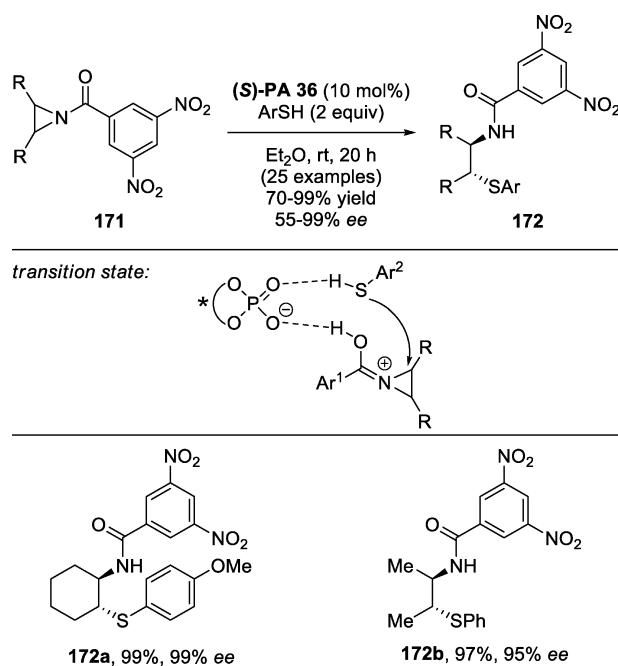


Figure 89. Addition of thiols into *meso*-aziridines by Antilla (2009).

reaction proceeds in the absence of a silylating agent, something that was not possible when conducting the opening using azides. The authors propose that a bifunctional activation of the aziridine *N*-acyl unit and the thiol is the most likely mode of activation.

The intermolecular addition of oxygen to imines and in particular peroxide addition is of high importance in chemical synthesis, but methods of performing this in an asymmetric manner are still limited. In 2010, Antilla reported the first example of a chiral phosphoric acid-catalyzed addition of

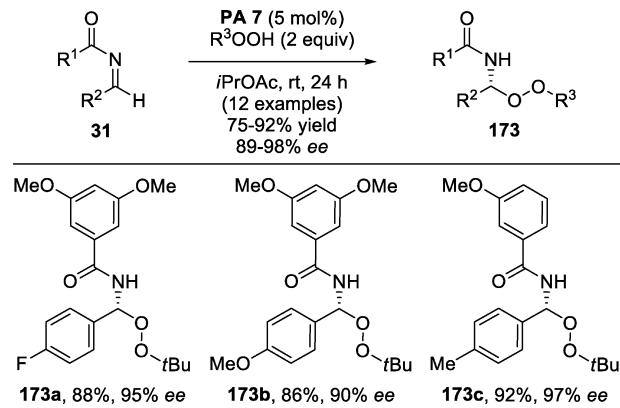


Figure 90. Addition of peroxides to imines by Antilla (2010).

hydroperoxides to imines that allowed access to non-racemic  $\alpha$ -amino peroxides (Figure 90).<sup>158</sup>

Taking *N*-acyl imines **31** with 2 equiv of hydroperoxide and 5 mol % of **PA 7** led to a smooth reaction in  $i\text{PrOAc}$  at room temperature to deliver the desired products **173** in good yields and good to high enantioselectivities. A bifunctional hydrogen-bonding interaction of the catalyst with both the peroxide and the imine is proposed for the high selectivities seen.

The aza-Henry reaction<sup>159</sup> represents a simple but effective method for the synthesis of adjacent nitrogen stereocenters in molecules, which can be used to create further highly useful molecules such as vicinal diamines. The first reported procedure came from Rueping in 2008, who reported the direct aza-Henry reaction of  $\alpha$ -imino esters **64b** with nitroalkanes **174** to give the desired products **175** in good yields, high diastereoselectivity, and high enantioselectivity (Figure 91).<sup>160</sup>

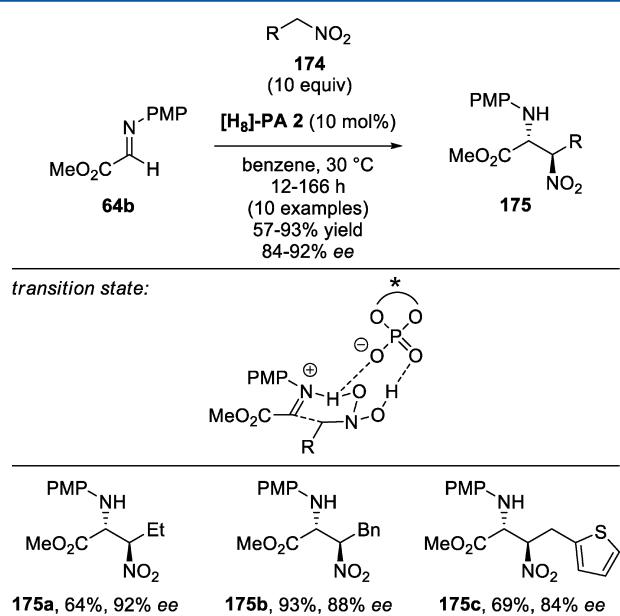


Figure 91. Addition of nitroalkanes to imines by Rueping (2008).

The use of 10 mol % of catalyst  $[\text{H}_3]\text{-PA 2}$  was found to be the optimal catalyst for obtaining high yields and improved the reaction rate substantially. Other catalysts tested led to poor reactivity and lower diastereoselectivity. A broad range of nitroalkanes were explored and generally gave good results.

The authors propose the reaction involves a six-membered transition state where the catalyst activates the imine and a proton attached to the oxygen atom of the nitro group.

A unique example of the addition of a nucleophile to an imine derivative was presented by Akiyama in 2006.<sup>161</sup> By taking diisopropyl phosphite **176a** and various imines **52** in the presence of 10 mol % **PA 20** at room temperature, an efficient reaction proceeded to give the  $\alpha$ -amino phosphonates **177** in good yields and selectivities (Figure 92).

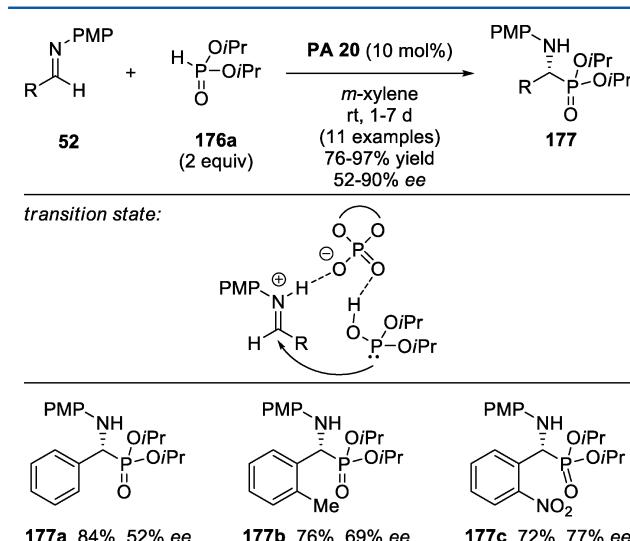


Figure 92. Hydrophosphonylation of imines by Akiyama (2005).

Phosphites are well-known to be able to tautomerize to a conformation that contains a lone pair on phosphorus and hence a nucleophilic phosphorus atom. A bifunctional mechanism is proposed that involves coordination by the catalyst to the imine and the reactive phosphite tautomer of **176a**. The importance of hydrogen bonding was highlighted when taking a trialkyl phosphite containing no acidic hydrogen atoms, which resulted in an almost racemic product. Further computational studies have also found good evidence for a bifunctional mechanism occurring.<sup>162</sup> The groups of Song and Lin have also studied this reaction with good success.<sup>163</sup>

**2.3.2. Addition of Nucleophiles to Oxonium Ions.** The allylation of aldehydes in an enantioselective fashion is a difficult challenge that faces organic chemistry. Accordingly, the problem has received a high amount of attention chiefly due to the products also being highly versatile intermediates in the synthesis of pharmaceuticals and natural products. In 2010, Antilla presented his solution to this problem by utilizing a chiral Brønsted acid catalyst to achieve a highly selective reaction.<sup>164</sup> Taking a range of aldehydes **103** with allyl boronic ester **178** in toluene with 5 mol % of **PA 25** allowed access to homoallylic alcohols **179** in high yields and excellent enantioselectivity (Figure 93).

Antilla proposes monoactivation of the boronate's equatorial oxygen atom; however, such a flexible transition state is thought to not be possible to account for the uniformly high enantiomeric excesses. The exact mechanism of the reaction has been expertly investigated by the groups of Goodman and Houk.<sup>165</sup> Both have concurred that the most likely mechanism occurring involves a six-membered transition state whereby the catalyst activates the pseudoaxial oxygen of the boronate along with the aldehyde proton (Figure 94). An equatorial transition

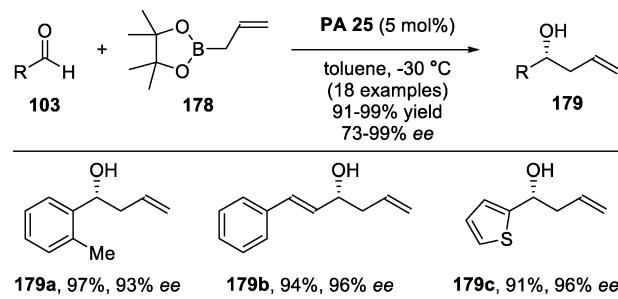


Figure 93. Allylation of aldehydes by Antilla (2010).

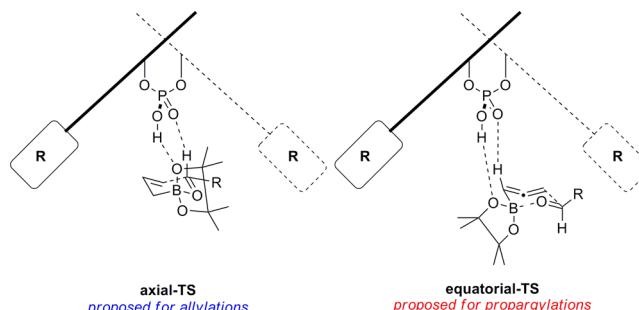


Figure 94. Proposed activation of boronates.

state is proposed by Houk for enantioselective propargylations of aldehydes (see Figure 96) but was calculated to be higher in energy in this case.

Two years later, Hu managed to develop a SPINOL-based catalyst, which was also shown to catalyze the reaction in a highly selective manner.<sup>166</sup> The substrate scope consisted of aromatic, alkenyl, alkynyl, and aliphatic aldehydes. Recently, Malkov has shown that chiral phosphoric acids can perform resolutions on racemic secondary boronates.<sup>167</sup>

A rather unique example of the use of phosphoric acids for asymmetric catalysis came from Antilla in 2011, where he reported the reduction of ketones **180** using catecholborane **181** (Figure 95).<sup>168</sup> A screen of various phosphoric acids actually led to poor enantioselectivity even though yields were uniformly high. At this point, they began by looking at the effects of various salts, formed in situ, as to whether or not they would be beneficial. From their studies, it was quickly realized this was the case and that DMAP was the optimal additive for improving the enantioselectivity.

The optimal conditions were found to be 5 mol % of **PA 7** with 5 mol % DMAP, and this led to very efficient reduction of aromatic ketones **180** to the secondary alcohols **182** also with high enantioselectivity. Preliminary mechanistic studies by Antilla led to the proposed transition state shown in Figure 93. When catecholborane is mixed with the catalyst, a gas is observed, which is thought to be  $\text{H}_2$ , and a boronate complex is formed. This complex is stabilized by the DMAP and can activate both the reagent and the ketone to undergo asymmetric reduction. Although the catalyst here is still bifunctional, the reaction could also be classified under counterion catalysis due to the absence of any hydrogen-bonding interactions.

In 2012, the addition of allenyl boronic ester **183** into a variety of aldehydes **103** was shown to also be able to be controlled by catalytic amounts of chiral phosphoric acid (Figure 96).<sup>169</sup> The reaction utilized 20 mol % of catalyst **PA**

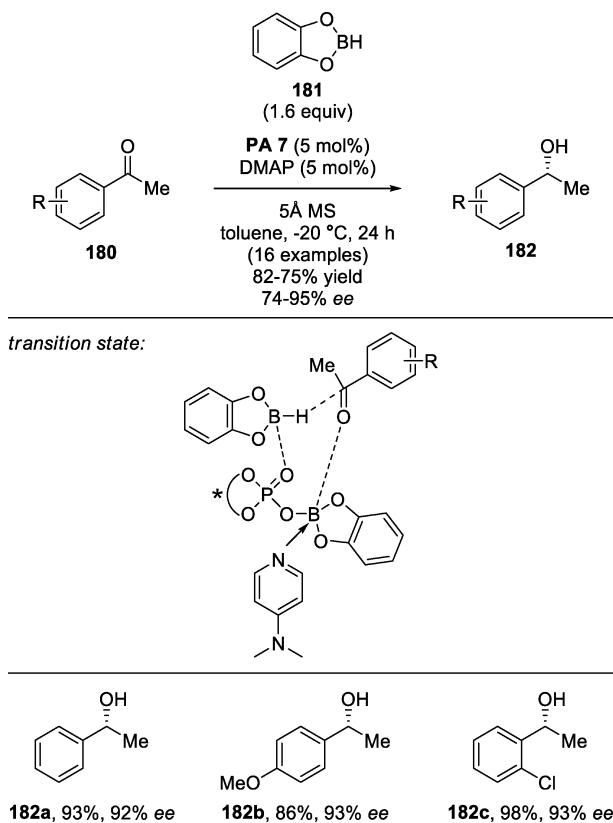


Figure 95. Reduction of ketones by Antilla (2011).

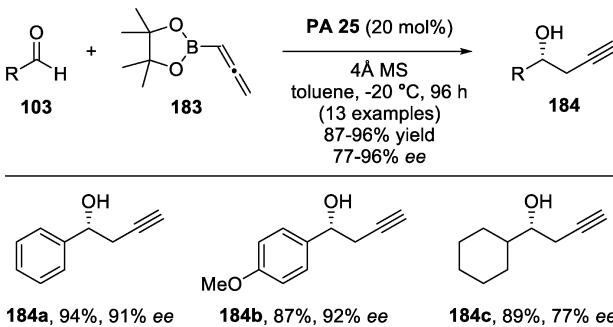


Figure 96. Propargylation of aldehydes by Antilla (2012).

25 and provided the corresponding propargylated products 184 in good yields and selectivity.

A computational study suggests that the transition state involves an interaction between the catalyst and the boronic ester nucleophile, which activates it for subsequent reaction. Houk has also proposed that an interaction with the boronate's equatorial oxygen atom occurs (cf., Figure 94). In 2013, Roush was able to show that racemic allenyl boronic esters could be used in the enantioselective synthesis of propargyl alcohols via a kinetic resolution facilitated by a chiral phosphoric acid.<sup>170</sup> Reddy has also studied a mechanistically related transformation involving the addition of propargyl boronates to aldehydes to give allenyl alcohols.<sup>171</sup>

The Baeyer–Villiger (BV) reaction has become one of the fundamental and perhaps most well-known transformations in organic chemistry since its discovery in 1899.<sup>172</sup> The classic oxidant for the reaction is typically aqueous hydrogen peroxide ( $H_2O_2$ ), but the use of this reagent with a catalyst is scarce. Inspired by a reported asymmetric BV reaction using

stoichiometric chiral hydroperoxides,<sup>173</sup> in 2008 Ding recognized the potential of Brønsted acids to facilitate the procedure in a catalytic fashion (Figure 97).<sup>174</sup>

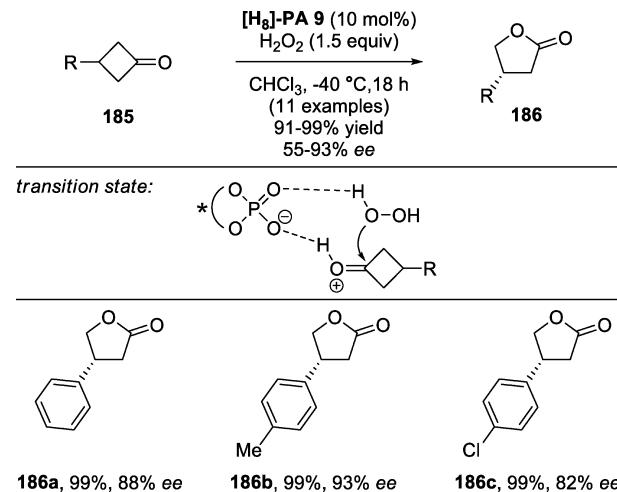


Figure 97. Baeyer–Villiger reaction by Ding (2008).

Taking a variety of 3-substituted cyclobutanones 185 with aqueous  $H_2O_2$  and 10 mol % of catalyst PA 9 gave rise to the BV reaction to yield  $\gamma$ -lactones 186 in excellent yields and moderate to high enantioselectivity. It is proposed that the typical Criegee intermediate is bound to the catalyst via hydrogen-bonding interactions, which results in the asymmetric induction observed. Mechanistic studies also suggested that only one molecule of the catalyst is involved in the induction due to the absence of any nonlinear effects. A more detailed mechanistic study was carried out by Ding in 2010 to elucidate the kinetics and chiral induction taking place.<sup>175</sup> A related desymmetrization of cyclic carbonates by ring opening with benzyl alcohol was recently published by Sano.<sup>176</sup>

Spiroethers are a challenging motif for synthetic chemists to synthesize, but their importance is of high value due to their presence in numerous natural products and pharmaceuticals.<sup>177</sup> One possible route to them is via a semipinacol rearrangement, but this has been difficult to incorporate in an asymmetric manner. In 2009, Tu demonstrated the potential of bifunctional phosphoric acids in aiding this transformation via simultaneous activation of the nucleophilic and electrophilic sites of reaction.<sup>178</sup> Taking allylic alcohols 187 in  $CCl_4$  with 10 mol % of catalyst PA 25 resulted in a smooth transformation to give spirocycles 188 in good yields and high selectivities (Figure 98).

The mechanism is proposed to involve the bifunctional activation of the alcohol and hydrogen-bonding activation of the enol-ether moiety. Alternatively, one could envision a counterion mechanism whereby the enol ether is initially protonated. Interestingly, the reaction could also be carried out using the Ag-salt of PA 25, and this pathway would strongly suggest the involvement of a chiral counterion effect rather than hydrogen bonding between the catalyst and substrates.

The desymmetrization of meso-compounds is a powerful tool in the synthesis of enantiomerically pure products. In particular, the distinguishing of meso-1,3-dicarbonyls provides useful synthetic intermediates. Typically, this can be carried out with proline catalysts under covalent bond control, but in 2009, Akiyama showed that phosphoric acids could also facilitate the reaction via multiple hydrogen-bonding interactions.<sup>179</sup> Taking

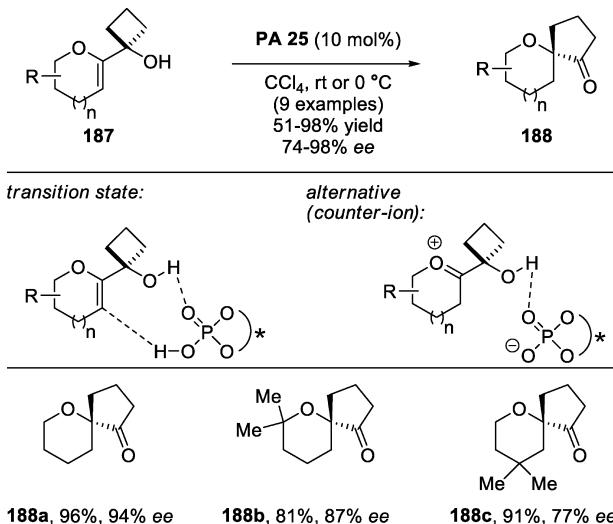


Figure 98. Semipinacol rearrangement by Tu (2009).

dicarbonyl compounds **189** and treating with 5 mol % of catalyst PA 25 resulted in a Robinson annulation to give chiral cyclohexanones **190** in good yields and enantioselectivities (Figure 99).

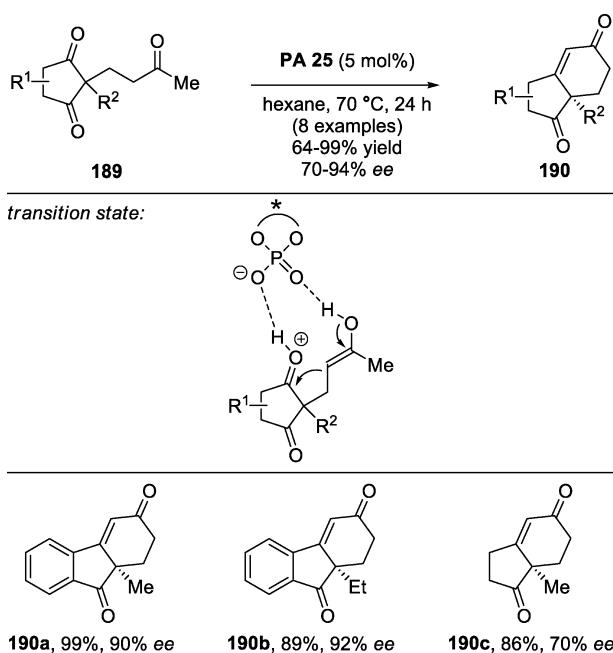


Figure 99. Desymmetrization using a Robinson annulation by Akiyama (2009).

ONIOM calculations revealed that the transition state is controlled by the phosphoric acid, which simultaneously activates the carbonyl and enol functions with its Brønsted acidic and Lewis basic sites. Steric repulsion between the phosphoric acid and the aromatic backbone is thought to be the reason for high selectivity. Its importance is highlighted with the fact that **190c** was formed with lower levels of selectivity, presumably due to the lack of an aromatic substituent.

1,3-Dicarbonyls **191** were also the substrate of choice for Zhang's approach to desymmetrization via an intramolecular Schmidt reaction.<sup>180</sup> They first noticed that an achiral acid was

able to promote the desired reaction and then extended the procedure by replacement with a chiral phosphoric acid in the hope it would produce enantioenriched products.

From extensive screenings, it was eventually found that using 1.5 equiv of catalyst NPA 9 resulted in modest yields and selectivities of **192** (Figure 100). A similar mechanism of

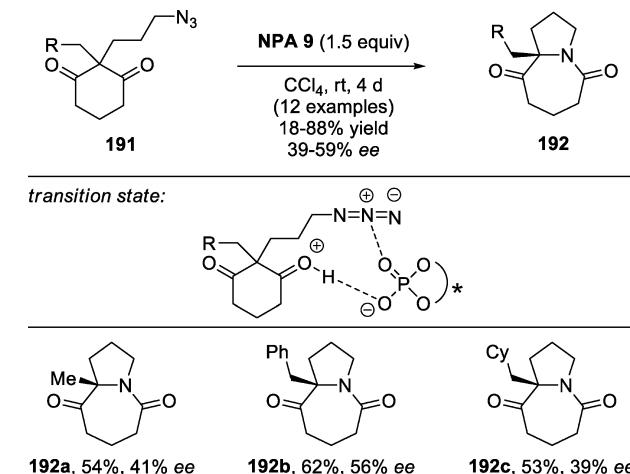


Figure 100. Desymmetrization using a Schmidt reaction by Zhang (2011).

desymmetrization is proposed as postulated by Akiyama.<sup>179</sup> In this case, the catalyst coordinates to one of the carbonyl groups while interacting with the azide group.

**2.3.3. Addition of Nucleophiles to Alkenes.** This section will deal with reactions that involve the formal addition of a nucleophile to a double bond that does not include activation (e.g.,  $\alpha,\beta$ -unsaturated carbonyls used in Michael additions). Reports on the enantioselective addition of nucleophiles to unactivated alkenes are scarce. The primary reason for this is the difficulty in activating a group that does not contain any natural sites for binding. In 2008, Ackermann showed a rather remarkable example of a hydroamination of unsaturated amine **193** (Figure 101).<sup>181</sup>

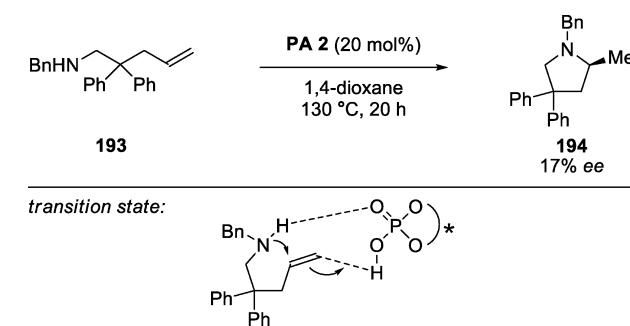


Figure 101. Hydroamination of an unactivated alkene by Ackermann (2008).

Treating **193** with 20 mol % of PA 2 at 130 °C overnight gave the pyrrolidine **194** in an unreported yield and 17% ee. Although rather low, this example constitutes the first activation of an isolated alkene under metal-free conditions. The transition state can be envisioned to involve coordination of the amine to the Lewis basic site and a weak interaction of the catalyst's proton to the alkene.

The activation of an unsaturated bond with an electrophilic halogen source is a common strategy employed, which allows the addition of nucleophiles to carbon centers. The halogenation of olefins is an effective approach to simultaneously form two C-heteroatom bonds in the same reaction. In 2011, Shi was able to show that the process could be catalyzed by a chiral phosphoric acid to form optically active tetrahydrofurans and pyrrolidines (Figure 102).<sup>182</sup>

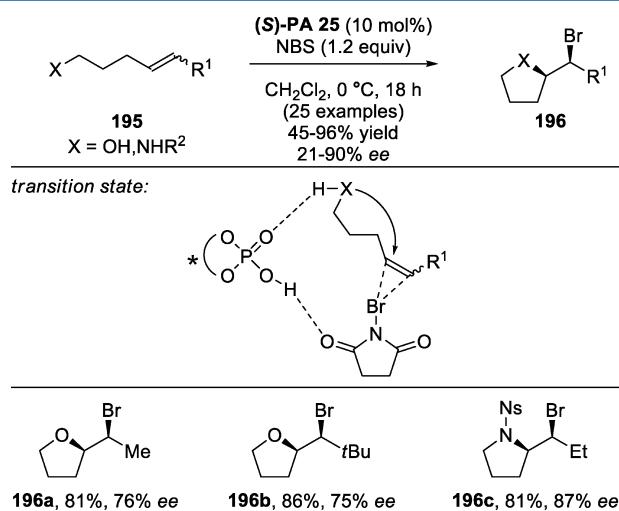


Figure 102. Bromocyclization using alkenes by Shi (2011).

Using NBS as a brominating agent, it was shown that unsaturated substrates **195** could be cyclized to give the corresponding five-membered brominated heterocycles **196** in good yields and modest to good enantioselectivities. The authors propose that NBS is coordinated to the Brønsted acidic site on the catalyst, which helps deliver the bromine to a single face of the alkene. In 2013, they extended the transformation to sulfaminations using an electrophilic sulfur source.<sup>183</sup> Recently, Gong has also shown that asymmetric selenofunctionalization using chiral phosphoric acids can be achieved with electrophilic selenium reagents similar in structure to NBS.<sup>184</sup> They also propose an interaction between the amide carbonyl of the reagent and the catalyst being responsible for delivering enantioselectivity.

**2.3.4. Transfer Hydrogenation.** The transfer hydrogenation<sup>185</sup> reaction is the single most popular reaction type that has been reported to be able to be catalyzed using chiral Brønsted acids.<sup>186</sup> The category largely contains imines or imine equivalents as substrates, but this has not limited the importance.<sup>187</sup> Hantzsch esters<sup>188</sup> have become incredibly popular as hydride sources, and many groups have studied the kinetics of their reactivity in reductive transformations.<sup>189</sup> The most commonly used Hantzsch esters are shown in Figure 103,

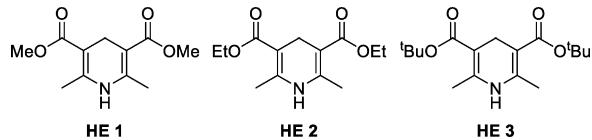


Figure 103. Commonly used Hantzsch ester variants.

and the abbreviations below will be used to simplify the schemes in this section.

The groups of Goodman<sup>190</sup> and Himo<sup>191</sup> have specifically investigated the mechanism and origin of enantiocontrol in the Hantzsch ester-mediated reduction of imines. Both groups have concluded that a bifunctional mechanism best explains the available theoretical and experimental data.

A generic transition state, which can be used to explain nearly all BINOL-phosphoric acid-catalyzed Hantzsch ester reductions of imines, is shown in Figure 104. As one would expect, activation of

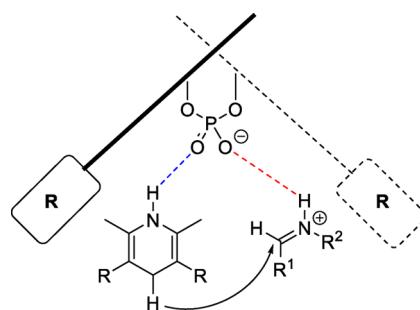


Figure 104. Generic transition state for Hantzsch ester-mediated reductions.

the imine occurs by protonation by the catalyst, and simultaneous activation of the hydride donor occurs via interaction with the acidic N–H moiety. From calculations, it was revealed that the imine prefers to adopt a Z-configuration. Unless otherwise stated, all reactions presented and cited under this section can be assumed to be following this generic mechanistic pathway.

**2.3.4.1. Using Imines as Substrates.** The enantioselective reduction of imines to amines represents a simple but incredibly useful procedure to access chiral amines. The reduction of imines using Hantzsch esters has in fact been known for over 20 years.<sup>192</sup> In 2005, the first phosphoric acid-catalyzed hydrogen transfer reaction of imines was reported by the Rueping group using a Hantzsch ester as the hydride source.<sup>193</sup> In 2005, the Rueping group was also the first to report a chiral phosphoric acid catalyzed procedure to perform the enantioselective variant.<sup>194</sup> Taking a range of ketimines **197** protected with an aromatic ring, 20 mol % catalyst **PA 20** and 1.4 equiv of **HE 2** the desired products **198** could be obtained in modest yields and selectivities (Figure 105).

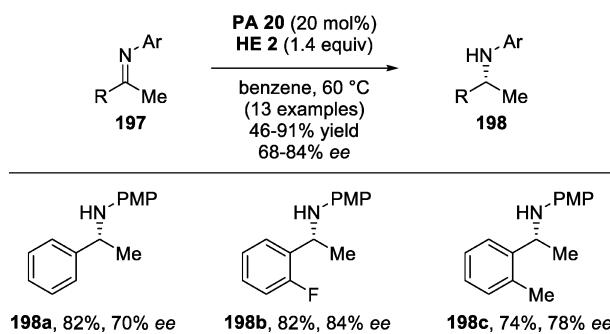


Figure 105. Seminal transfer hydrogenation of imines by Rueping (2005).

Almost at the same time, the List group published an identical transformation using 10 mol % (S)-PA 25 to obtain high enantioselectivities using toluene as the solvent.<sup>195</sup>

In 2007, Antilla disclosed the reduction of  $\alpha$ -imino esters using vaulted phosphoric acid catalyst (S)-PA 37.<sup>196</sup> Taking substrates **199** with 1 equiv of **HE 2** and 5 mol % of (S)-PA 37

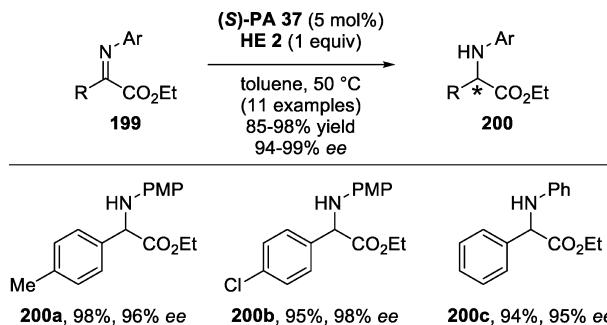


Figure 106. Transfer hydrogenation of  $\alpha$ -imino esters by Antilla (2007).

resulted in a smooth reduction to give **200** in excellent yields and selectivities (Figure 106).

Formation of the  $\alpha$ -imino esters **199** could be carried out *in situ* albeit with lower yields but identical ee's. In the same year, a similar protocol was published by You who also showed  $\alpha$ -imino amides can function as viable substrates for the hydrogenation reaction.<sup>197</sup> A year later, a subsequent publication demonstrated that  $\beta,\gamma$ -alkynyl  $\alpha$ -imino esters could be subjected to extremely mild reaction conditions to afford the *trans*-alkenyl  $\alpha$ -amino esters with good levels of selectivity.<sup>198</sup>

Nearly all of the transformations in this section are thought to go via a bifunctional mechanism involving coordination of both the imine and Hantzsch ester to the catalyst (see Figure 102). In 2010, however, a report by Wang seemed to suggest that this mechanism could be overridden by the use of *ortho*-hydroxyaryl imines **201** (Figure 107).<sup>199</sup>

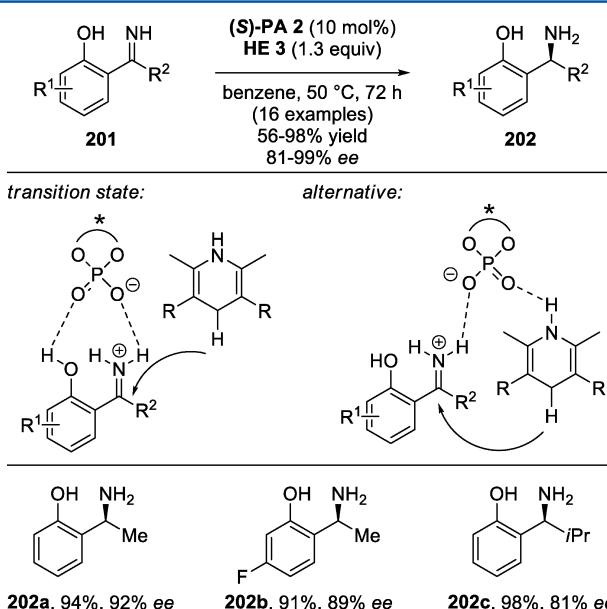


Figure 107. Transfer hydrogenation of *o*-hydroxyaryl imines by Wang (2010).

By reaction of **201** with HE 3 and in the presence of (S)-PA 2 the desired reduction took place to give secondary amines **202** in good yields and enantioselectivity. Mechanistic experiments by the group suggest that the presence of the free hydroxyl group on the aromatic ring switches the mechanism to a dual coordination mechanism that resembles that of

*2-hydroxyphenyl imines*. A clear shift in the  $^1\text{H}$  NMR of the compound when a chiral phosphoric acid is introduced can be observed. Although proposed to be dual activation, coordination of the Hantzsch ester to the catalyst cannot be ruled out, and therefore we have chosen to classify this transformation under this section. The initial scope was extended further in 2011 and used toward the formal synthesis of a histamine H1-antagonist.<sup>199c</sup>

**2.3.4.2. Generating Imines as Substrates.** In this subsection, we will cover the reduction of generated imines, which are not formally reductive aminations. Although imines represent the most widely used substrates for phosphoric acid catalysis, their relatively low stability can be a hindrance to their usage as synthetic intermediates. Therefore, the ability to generate imines *in situ* and subsequently carry out transformations is a powerful tool in organic synthesis. In 2009, Antilla showed that enamides could be utilized as useful precursors to imines that could be accordingly reduced.<sup>200</sup> Taking enamides **154** with a dual chiral–achiral catalytic system in the presence of Hantzsch ester HE 2 led to the corresponding amines **203** in generally good yields and high selectivity (Figure 108).

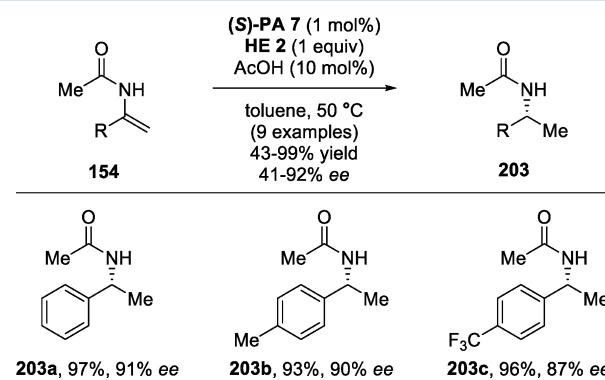


Figure 108. Transfer hydrogenation of enamines by Antilla (2009).

The dual catalytic system consisting of catalyst (S)-PA 7 and AcOH is thought to be purely for regeneration of the catalyst, and in fact in the absence of any phosphoric acid no reaction occurred. A similar system has been applied previously by the Rueping group in the synthesis of isoquinuclidines.<sup>201</sup>

An interesting precursor for imine generation was developed by Zhou, who showed that racemic 3-hydroxyisoindolinones could be used to generate an iminium intermediate by dehydration and then subsequently reduced. Treating substrates **204** with catalyst PA 37 and HE 3 at 35 °C led to the desired transformation to give the products **205** in modest yields and good selectivity (Figure 109).<sup>202</sup>

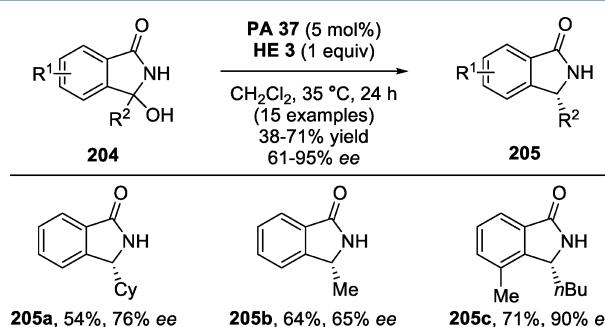


Figure 109. Transfer hydrogenation of *N,O*-acetals by Zhou (2012).

Interestingly, the use of molecular sieves failed to improve the enantioselectivities and also resulted in an unwanted by-product. The importance of the free N–H group was highlighted by the failed reaction of a methyl-protected substrate. A very similar reaction was shown by Jia who utilized a benzothiazoline as the hydride source.<sup>203</sup>

**2.3.4.3. Reductive Amination.** Reductive amination is one of the most practically used methods in the synthesis of amines. The combination of both a carbonyl and an amine in the presence of the reducing agent is a remarkably simple but powerful tool in organic synthesis. In 2006, MacMillan recognized that chiral phosphoric acids could provide a possible solution for catalyzing such an important transformation in an asymmetric manner. By taking aromatic amine **35a** and aromatic ketones **180** in the presence of **PA 2** and **HE 2**, the desired reaction was accomplished to yield the corresponding secondary amines **206** in good yields and excellent ee's (Figure 110).<sup>204</sup>

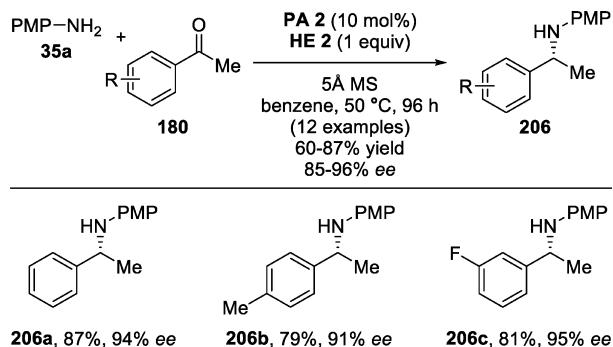


Figure 110. Reductive amination of aryl ketones by Macmillan (2006).

The reaction can also be carried out on alkyl ketones, but slightly lower enantioselectivities are obtained, suggesting some aromatic interactions with the catalyst. Remarkably, an 18:1 preference is seen for methyl aromatic ketones over ethyl ketones. In 2010, List was able to improve the practicality of this transformation by optimization of the reaction conditions to allow for a benzyl group on the amine.<sup>205</sup> A simple acidic workup followed by a mild hydrogenation was demonstrated as an effective method to obtain enantioenriched primary amines.

A rather unique example of an asymmetric reductive amination was presented by the List group in 2006 via a dynamic kinetic resolution of  $\alpha$ -branched aldehydes. By taking enolizable aldehydes **103** with aromatic amines **35**, catalyst **PA 25**, and 1.2 equiv of **HE 3**, an equilibrium could be set up and drained in preference for enantiomer **207** (Figure 111).<sup>206</sup>

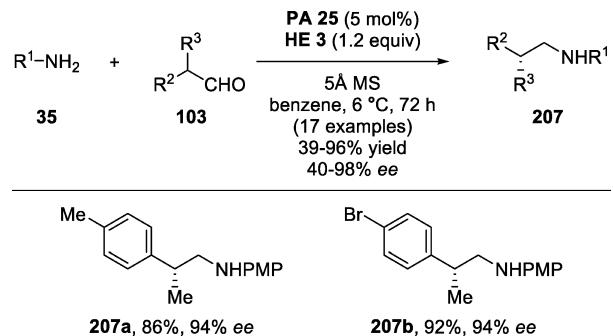


Figure 111. Dynamic kinetic resolution via reductive amination by List (2006).

In general, good yields and selectivities were obtained for electron-rich and electron-deficient aromatic substrates, but for alkyl aldehydes slightly lower values were obtained. The stereochemical outcome of the reaction has been studied by calculations by the Himo group.<sup>207</sup> A related strategy involving  $\alpha$ -branched ketones was presented by the same group in 2010 and applied to the formal synthesis of perindopril.<sup>208</sup>

**2.3.4.4. N-Heterocycles.** Within the field of transfer hydrogenation, the hydrogenation of *N*-heterocycles is by far the biggest area of focus among research groups. *N*-Heterocycles are found in many pharmacologically active molecules, and the ability to synthesize them in an enantioselective manner from the corresponding oxidized precursor is an incredibly efficient but difficult process.<sup>209</sup> This area of research began in 2006, when Rueping disclosed the first metal-free Brønsted acid-catalyzed hydrogenation of quinolines in racemic form.<sup>210</sup> In the same year, the Rueping group extended the process toward an enantioselective protocol by the use of chiral phosphoric acid catalyst **PA 8** (Figure 112).<sup>211</sup>

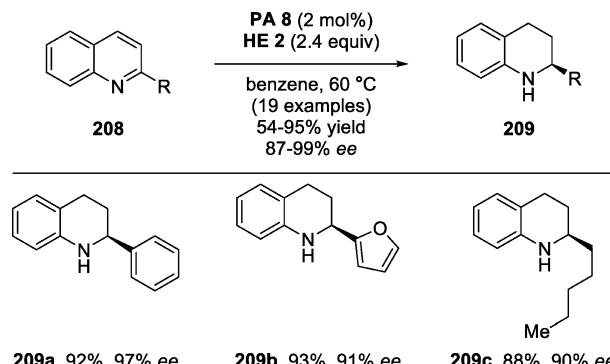


Figure 112. Transfer hydrogenation of quinolines by Rueping (2006).

**HE 2** was used in a slight excess to effect a double reduction of quinolines **208** substituted at the 2-position to give the tetrahydroquinolines **209** in modest to good yields and high enantioselectivities. Various natural products containing this core were also synthesized to demonstrate the potential of the described methodology. Several publications have followed since describing various modifications that can be tolerated. For example, in 2010 Rueping<sup>212</sup> disclosed conditions, which allow the reaction to function efficiently in  $H_2O$ , and in 2012 Blechert<sup>44</sup> showed that a heterogeneous microporous polymeric catalyst could be used and recycled without loss of selectivity. The Rueping group has also developed a procedure, which allows for the reaction to be conducted in flow.<sup>213</sup> In 2008, Du developed a double axially chiral phosphoric acid (**210**), which was also shown to facilitate the reduction of 2-substituted quinolines.<sup>214</sup> Recently, Marinetti has developed catalysts containing ferrocene-bridged frameworks (**211**) and achieved modest results in the enantioselective reduction of quinolines (Figure 113).<sup>215</sup>

In 2006, Rueping showed that benzoxazines and benzothiazines could also be reduced under transfer hydrogenation conditions in the presence of a chiral phosphoric acid.<sup>216</sup> Taking substrates **212** with catalyst **PA 8** and **HE 2** in  $CHCl_3$  at ambient temperature resulted in smooth reduction to the corresponding products **213** generally in good yields and high selectivity (Figure 114).

Rather remarkably, the catalyst loading could be dropped to as low as 0.1 mol % without any significant decrease in yields or

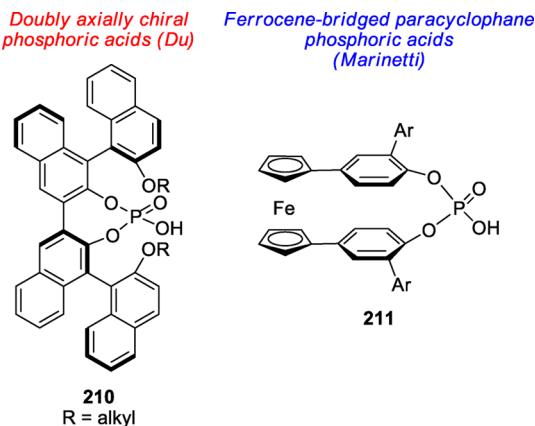


Figure 113. Specially designed catalysts for transfer hydrogenation.

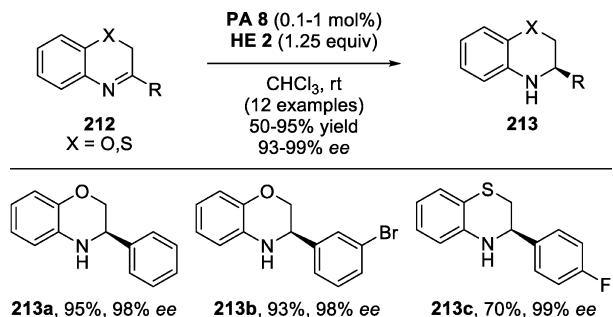


Figure 114. Transfer hydrogenation of benzoxazines and benzothiazines by Rueping (2006).

enantioselectivities. Particularly useful is that benzothiazines can be reduced under these conditions whereby under many metal-catalyzed procedures the sulfur atom is prone to poison the catalyst. This reaction has also been found to work with polymer-supported catalysts.<sup>217</sup>

A rather unique example was reported in 2007 by the Rueping group who discovered that transfer hydrogenation could be applied to pyridines.<sup>218</sup> Various pyridines **214** containing an electron-withdrawing group at the 5-position could be reacted in the presence of catalyst PA 7 and HE 2 to give the corresponding tetrahydropyridines **215** in good yields and good enantioselectivities (Figure 115).

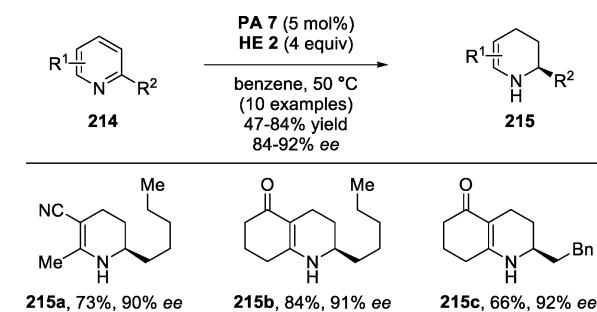


Figure 115. Transfer hydrogenation of pyridines by Rueping (2007).

This procedure opens a useful route to enantioenriched tetrahydropyridines, which form the core of various biologically active molecules.<sup>219</sup> Recently, You has used this reduction in a cascade process, which involves the trapping of the generated iminium ion with pyrroles.<sup>220</sup>

The asymmetric hydrogenation of heteroarenes represents a powerful route to access the core frameworks of many useful molecules.<sup>221</sup> Of the three presented heterocycle examples, many more reports exist that involve different substitution patterns or closely related heterocycles. Presented below is a concise summary of the most important heterocyclic moieties that can be accessed via phosphoric acid-catalyzed transfer hydrogenation (Figure 116). It should be mentioned that in most cases the catalyst loadings are between 5 and 10 mol %.

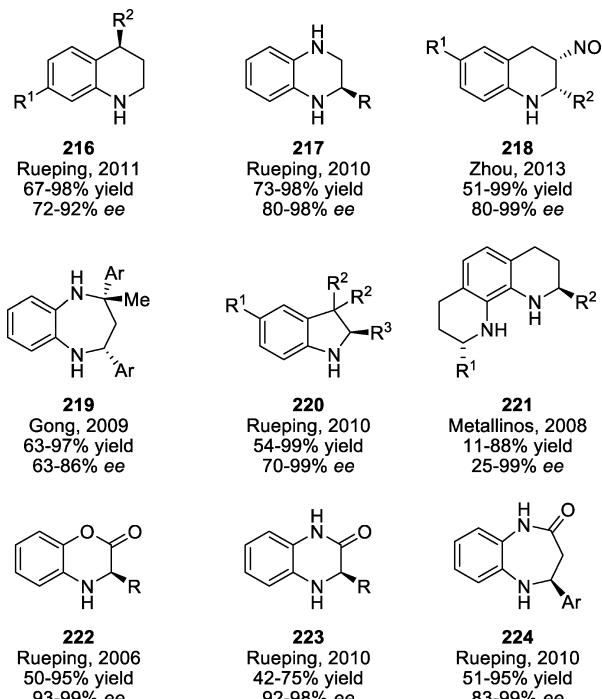


Figure 116. Transfer hydrogenation of other heterocycles.

The groups of Rueping (**216**)<sup>222</sup> and Zhou (**218**)<sup>223</sup> have shown that different or multiple substitutions on the quinoline core are well tolerated. In 2010, Rueping completed the synthesis of (*R*)-levofloxacin by utilizing an asymmetric transfer hydrogenation of a fluoroquinolone.<sup>224</sup> Quinoxalines (**217**),<sup>225</sup> quinoxalinones (**223**),<sup>226</sup> and benzoxazinones (**222**) have also all demonstrated good compatibility. In 2008, Metallinos has reported an interesting route to 1,10-phenanthrolines (**221**) albeit in low enantioselectivities.<sup>226</sup> Finally, seven-membered benzo[1,4]diazepines (**219**),<sup>227</sup> benzodiazepinones (**224**),<sup>228</sup> and five-membered indoles (**220**)<sup>229</sup> have proven to be suitable for asymmetric hydrogenation.

**2.3.4.5. Non-Hantzsch Ester Reductions.** Although the majority of the transfer hydrogenations catalyzed by phosphoric acids are with Hantzsch esters, there are a couple of distinct alternatives available that have been shown to work well too. One of the most commonly used is the benzothiazoline reducing agent,<sup>230</sup> and a mechanistic study by Yamanaka has calculated the profile of reduction to closely match that of Hantzsch ester reductions.<sup>231</sup> The kinetics of hydride transfer have also been studied by Mayr.<sup>232</sup>

In 2009, Akiyama was the first to introduce the benzothiazoline **225a** as an efficient reducing agent for imines **197** in the presence of a chiral phosphoric acid to generate enantioenriched amines **226** (Figure 117).<sup>233</sup>

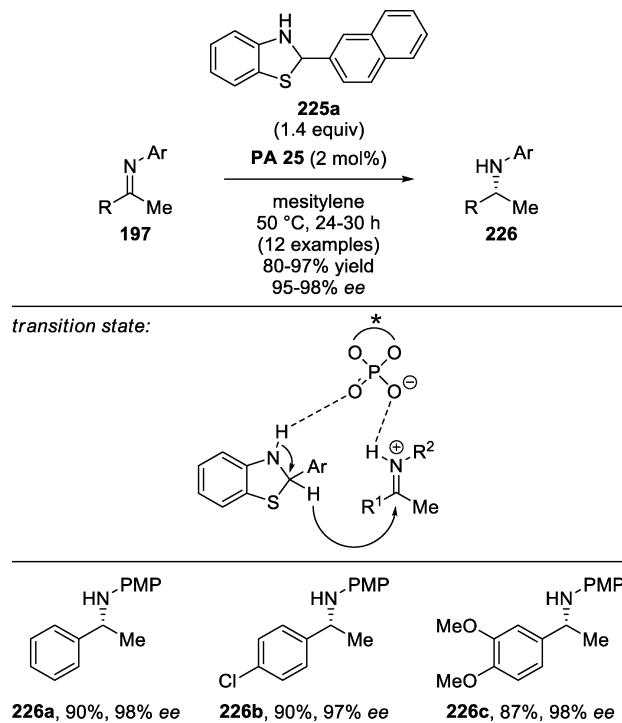


Figure 117. Transfer hydrogenation using benzothiazoline by Akiyama (2009).

Taking a naphthyl-substituted benzothiazoline with various imines **197** and 2 mol % of catalyst PA 25, the reduction to the corresponding amines **226** could be carried out in good yields and very high enantioselectivities. A bifunctional mechanism involving coordination of the benzothiazoline to the phosphoric acid's Lewis basic site is proposed by the authors. This methodology was extended by the same group to include  $\alpha$ -imino esters in 2010.<sup>234</sup> Akiyama has also shown that the transfer hydrogenation reaction can be applied to the synthesis of trifluoromethylated amines<sup>235</sup> and for the deuteration of ketimines.<sup>236</sup> A unique example has also been presented by the group of Enders who used a transfer hydrogenation using a benzothiazoline as the first step of a cascade process.<sup>237</sup>

In 2012, Akiyama further widened the scope of benzothiazoline-mediated reductions by including the possibility to preform aliphatic imines *in situ*. A series of aromatic amines **35** and aliphatic ketones **180** were shown to react with 5 mol % PA 25 in the presence of benzothiazoline **225b** to give secondary amines **227** in good yields and generally high selectivity (Figure 118).<sup>238</sup>

In this report, the authors compared the reactivity of benzothiazoline and a Hantzsch ester and found that, although a similar yield was obtained, a lower level of enantioselectivity was achieved. In 2013, Jia also utilized a benzothiazoline reductant in conjugation with a chiral phosphoric acid to reduce intramolecularly *in situ* formed imines.<sup>203</sup>

An isolated example of the use of catecholborane **181** in the presence of an *N*-triflyl phosphoramido catalyst has been reported by the Enders group in 2013. It was shown that a range of imines **228** could be reduced to the corresponding amines **229** using 5 mol % of NPA 9 as a catalyst (Figure 119).<sup>239</sup>

The reaction procedure is simple and mild, and the products (**229**) are obtained in good yields and modest enantioselectivities. The transition state for the reaction is proposed to be bifunctional, and it is thought that the boron atom can be coordinated by the Lewis basic oxygen on the catalyst.<sup>11B</sup>

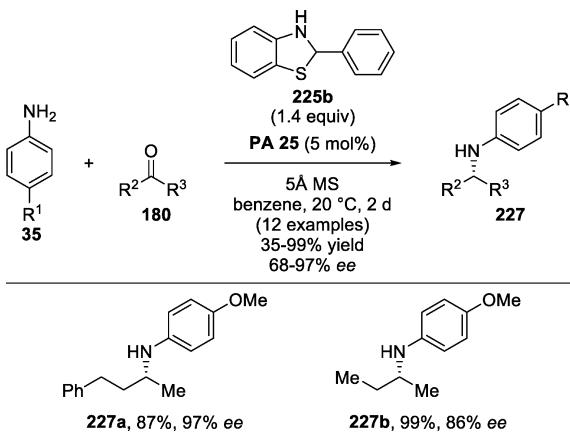


Figure 118. In situ imine formation and transfer hydrogenation using benzothiazoline by Akiyama (2012).

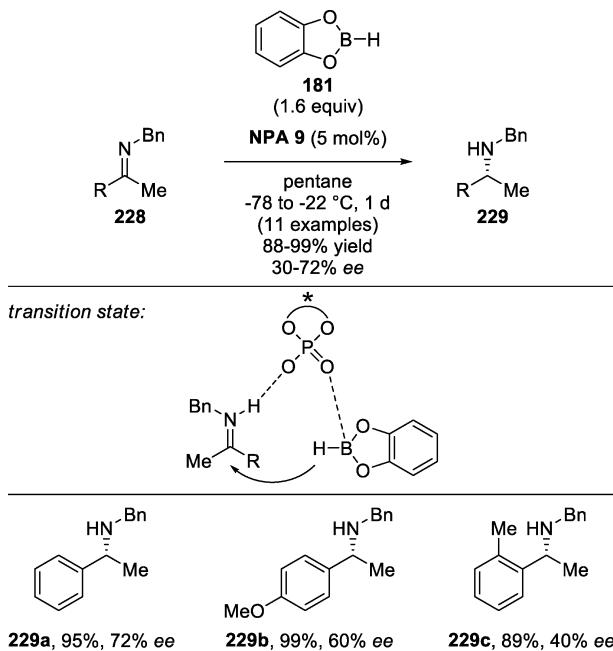
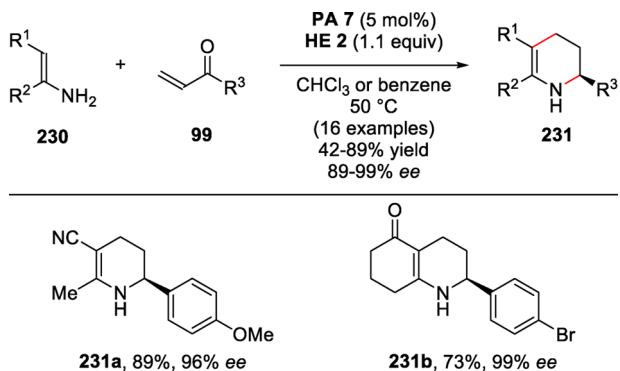


Figure 119. Transfer hydrogenation using catecholborane by Enders (2013).

NMR studies were also conducted to suggest that this could be occurring. Enders has also shown the use of this system to reduce  $\alpha$ -imino esters.<sup>240</sup>

**2.3.4.6. Cascades.** Because Brønsted acids are commonly used as catalysts for condensation reactions, which usually yields unsaturated molecules, the subsequent use of a Hantzsch ester to carry out an asymmetric reduction can be a powerful route to complex molecules starting from simple starting materials. In 2008, Rueping showed that various enamines **230** could be combined with  $\alpha,\beta$ -unsaturated ketones **99** in the presence of Hantzsch ester HE 2 to yield tetrahydropyridines **231** (Figure 120).<sup>241</sup>

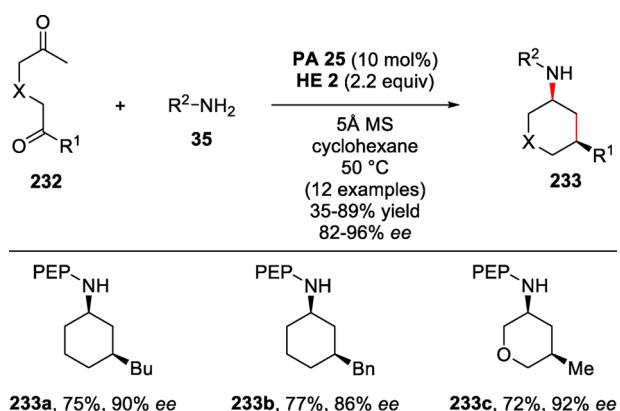
The sequence comprises of a Michael addition, isomerization, cyclization elimination, isomerization, and finally a transfer hydrogenation. All of the steps are thought to be catalyzed by the chiral phosphoric acid (PA 7) with the final step being the enantioselective step. A range of substrates were examined and were found to work efficiently with high levels of enantioselectivity being achieved. In 2011, the Rueping group



**Figure 120.** Cascade reaction involving a transfer hydrogenation by Rueping (2008).

also used a condensation/asymmetric reduction procedure to access chiral quinolizidines and indolizidines.<sup>242</sup> Recently, Shi has shown a one-pot cyclization/asymmetric hydrogenation sequence to access tetrahydroquinoxalines and dihydroquinoxalinones.<sup>243</sup>

A cascade sequence to access substituted cyclohexylamines, which also involves a transfer hydrogenation, was presented by List that employed the use of 1,5-dicarbonyls 232 and primary amines 35 (Figure 121).<sup>244</sup> The sequence exploits a combination of enamine and iminium catalysis.

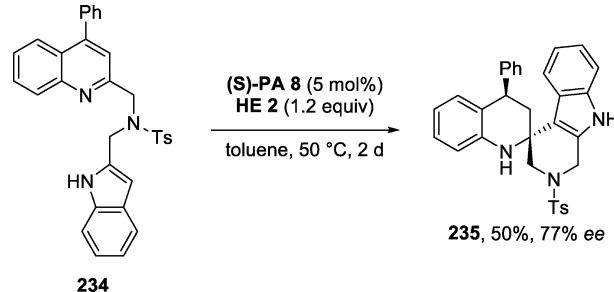


**Figure 121.** Cascade reaction involving a transfer hydrogenation of an imine by List (2007).

Using 10 mol % of catalyst PA 25 gave the products 233 in good yields and good selectivity. The phosphoric acid was found to be crucial in achieving the *cis*-selectivity as many other phosphoric acids gave the opposite diastereoisomer. The key intermediates have also been studied by mass spectrometry by the same group.<sup>245</sup>

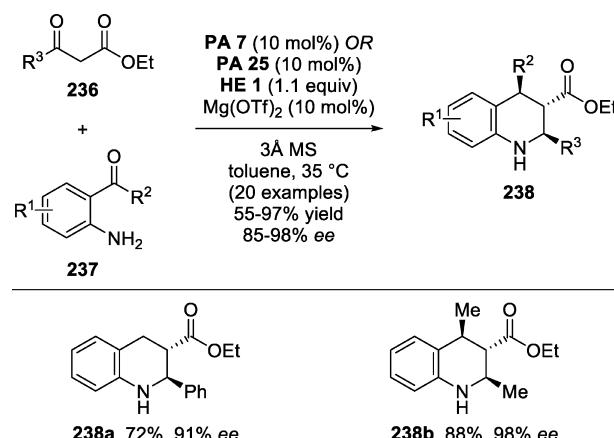
Recently, You reported a cascade process to access spiro-tetrahydroquinolines by using a hydrogenative dearomatization followed by a Friedel–Crafts alkylation reaction.<sup>246</sup> A range of achiral acids were initially studied, and phosphoric acids were found to be the optimal catalysts for promoting the desired reaction.

They next began to examine the use of chiral phosphoric acids to render the process enantioselective; however, initial attempts led to low selectivity. Inspired by a reported enantioselective reduction of 4-substituted quinolines,<sup>222</sup> You utilized similar conditions to transform 234 into enantio-enriched spiro product 235 albeit with a modest yield and



**Figure 122.** Cascade reaction involving a transfer hydrogenation of a quinoline by You (2013).

selectivity (Figure 122). In 2012, Gong presented a relay cascade reaction, which allows access to 1,2,3,4-tetrahydroquinolines (238) containing up to three stereocenters. The process first involves a Friedländer condensation followed by an asymmetric transfer hydrogenation of the resultant quinoline (Figure 123).<sup>247</sup>



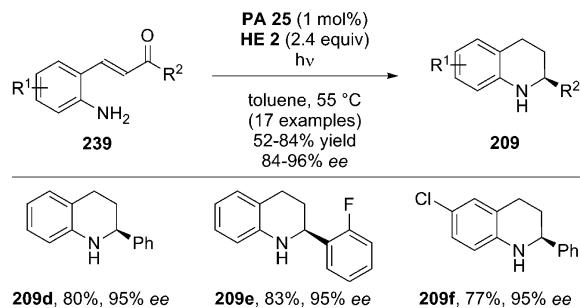
**Figure 123.** Friedländer condensation coupled with a transfer hydrogenation cascade by Gong (2012).

The reaction utilizes  $\beta$ -keto esters 236 and anilines 237 to give the tetrahydroquinoline products in good yields and high enantioselectivities. Interestingly, the combination of phosphoric acid and Mg(OTf)<sub>2</sub> is needed to catalyze the first step of the reaction, but the transfer hydrogenation can only be catalyzed by the phosphoric acid, which helps to prevent any racemic background reactivity.

Recently, the Rueping group has developed a one-pot cascade process, which involves the rare combination of light activation in conjunction with a chiral phosphoric acid. Taking aminochohalcones 239, a light-assisted cyclization to the corresponding quinolines occurs first that can then be reduced by HE 2 in the presence of catalyst PA 25 to give the products 209 (Figure 124).<sup>248</sup>

The reaction shows an impressive scope and provides a more simplified route to 1,2,3,4-tetrahydroquinolines by connecting the light-assisted step in the same pot. It was also shown that the reaction could be carried out in flow using a glass microreactor and was found to experience a dramatic rate acceleration postulated to be due to better absorption of light in the narrow microchannels of the microreactor.

**2.3.5. Friedel–Crafts Reaction.** The Friedel–Crafts reaction is an important reaction that has received a great deal of attention, especially in conjunction with chiral Brønsted



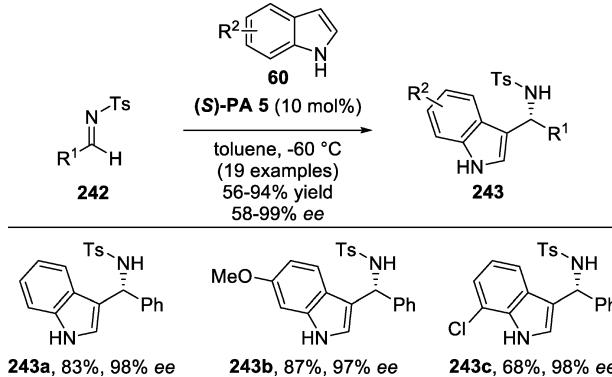
**Figure 124.** Photocyclization-reduction cascade in the synthesis of tetrahydroquinolines by Rueping (2013).

acids being used as catalysts for the process. Because imines are well recognized as substrates for phosphoric acid catalysis, it is no surprise that it has received the largest efforts with regards to undergoing the Friedel–Crafts reactions. Detailed mechanistic studies from Goodman have shown that when imines are used with unprotected indoles, a bifunctional mechanism is at play.<sup>249</sup> The absolute stereochemistry however can depend on the nature of the protecting group on the imine.

Goodman was able to compare the differing reactivity of *N*-acetyl and *N*-tosyl protected imines. It was found that although they both function via a bifunctional activation by the catalyst, the imine substrates orient themselves differently (Figure 125). For example, acetyl-protected imines prefer the *s-cis* acyl *E*-imine (**240**) with the indole placed over the acyl group, while tosyl-protected imines (**241**) prefer the opposite geometry. In this section, we will not aim to classify which orientation the imine is reacting through. It can be assumed if not otherwise stated that the transition state shown above is occurring for the reactions presented in this section, which involve imines, generated imines, and carbonyls.

**2.3.5.1. Using Imines as Substrates.** In 2007, You was the first to use tosyl imines **242** as electrophiles for unprotected indoles **60** to give the corresponding products **243** alkylated at the 3-position (Figure 126).<sup>250</sup>

The reaction generally proceeds to completion within a few hours and gives the products **243** in high yields and excellent selectivity. Aromatic imines perform the best, with aliphatic imines providing both lower yields and enantioselectivities. The reaction can also be easily scaled up to a 10 mmol scale without any loss in yield or enantiopurity of the products. In 2008, Hiemstra developed a similar reaction, which employed benzenesulfonyl protected glyoxylate imines to synthesize (*S*)-indolylglycine.<sup>251</sup> The groups of You<sup>252</sup> and Hu<sup>253</sup> have also shown glyoxylate imines to be suitable substrates for the enantioselective Friedel–Crafts reaction catalyzed by chiral



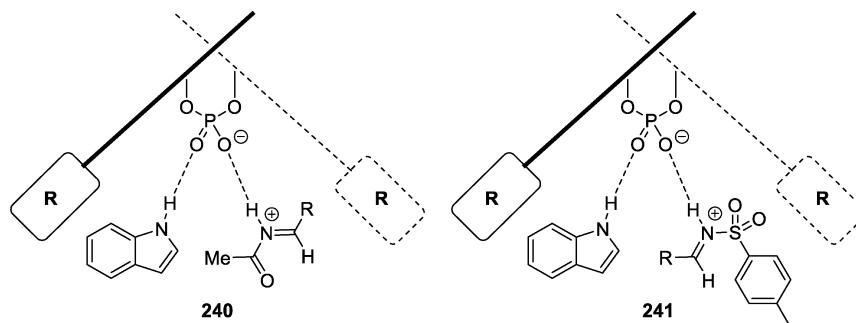
**Figure 126.** Friedel–Crafts reaction of *N*-sulfonylimines by You (2007).

phosphoric acids. Following these reports, spirocyclic phosphoric acids were shown by the groups of Wang<sup>254</sup> and Hu<sup>255</sup> to be efficient catalysts for the same reaction with imines. Notably, Hu's procedure employed just 2 mol % of catalyst to achieve very high enantioselectivities (97–99% ee). Recently, Zhang has shown a new catalyst architecture containing a chiral bisphorylimide to be able to catalyze the reaction with very high levels of enantioselectivity.<sup>42a</sup>

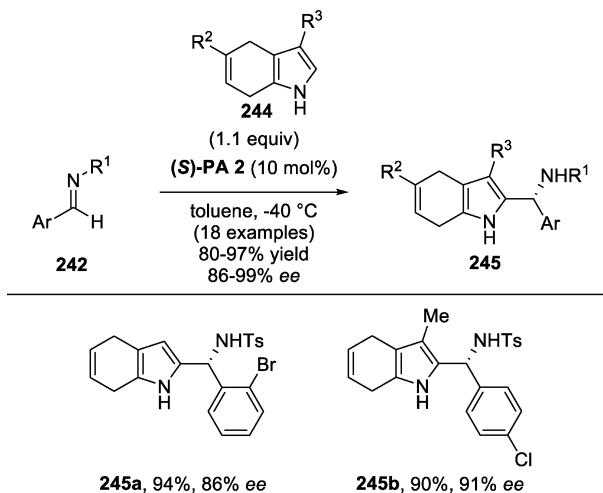
Nearly all studies that use indoles as coupling partners in Friedel–Crafts reactions lead to 3-substituted indoles as this position is inherently more nucleophilic. In 2008, You recognized an elegant solution to circumvent the expected reactivity to allow for substitution at the 2-position. By taking 4,7-dihydroindole **244** with various aromatic imines **242** and 10 mol % of catalyst (*S*)-PA **2**, the desired reaction took place smoothly to give the products **245** in high yields and excellent enantioselectivities (Figure 127).<sup>256</sup>

It is worth noting that in the majority of cases the reaction was complete in less than 20 min. It was also shown that the 4,7-dihydroindole products **245** could be easily oxidized to the corresponding indoles in one pot without any deterioration of enantiopurity. A year later, a similar reaction was shown by Nakamura with pyrroles to also give substitution at the 2-position.<sup>257</sup> *N*-Sulfonylimines were also shown recently by Pericas to be able to be used in flow with a polymer-supported phosphoric acid catalyst.<sup>258</sup>

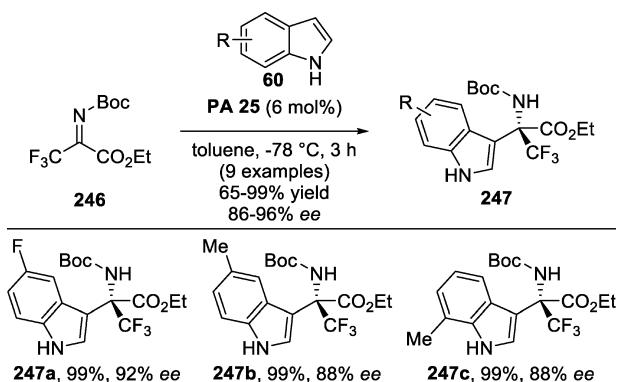
Synthetic methods to introduce fluorinated building blocks into molecules are highly desirable processes given the importance of fluorine in a wide variety of applications.<sup>259</sup> In 2011, Bolm and Rueping were able to construct quaternary  $\alpha$ -amino acids bearing a  $-CF_3$  motif by applying a highly enantioselective Friedel–Crafts reaction of imines **246** (Figure 128).<sup>260</sup>



**Figure 125.** Different imine orientations for Friedel–Crafts reactions with indole.



**Figure 127.** Friedel–Crafts reaction of *N*-sulfonylimines with dihydroindoless by You (2008).



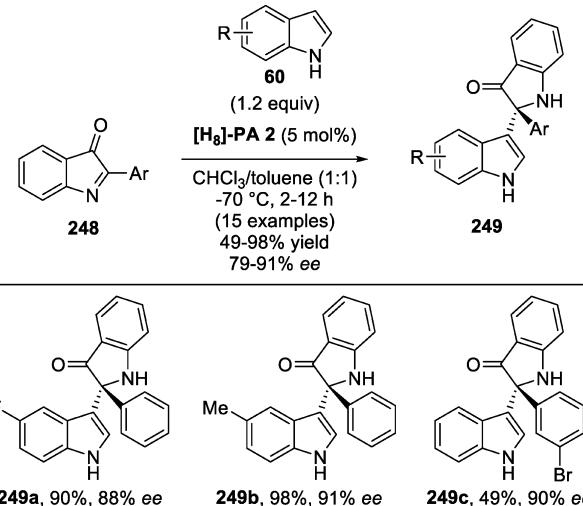
**Figure 128.** Friedel–Crafts reaction of CF<sub>3</sub>-N-Boc imines by Bolm and Rueping (2011).

By taking **246** with various N–H free indoles **60** and 6 mol % **PA 25**, a smooth reaction took place at -78 °C to give the corresponding products **247** in good yields and high selectivity. The importance of having a free N–H was highlighted by examination of a methyl-protected indole, which gave almost racemic products under identical reaction conditions. Recently, Ma has developed a similar reaction with cyclic imines containing a CF<sub>3</sub> group.<sup>261</sup>

The use of acyclic imines is very common under phosphoric acid catalysis, but the alternative cyclic imine counterparts are rarely seen. In 2011, Rueping developed the use of cyclic imines with indoles **60** in a Friedel–Crafts reaction. By taking cyclic imines **248** with 5 mol % of catalyst [H<sub>8</sub>]-PA **2** and various indoles, an efficient reaction occurred to give the products bearing a chiral quaternary center **249** in good yields and selectivity (Figure 129).<sup>262</sup>

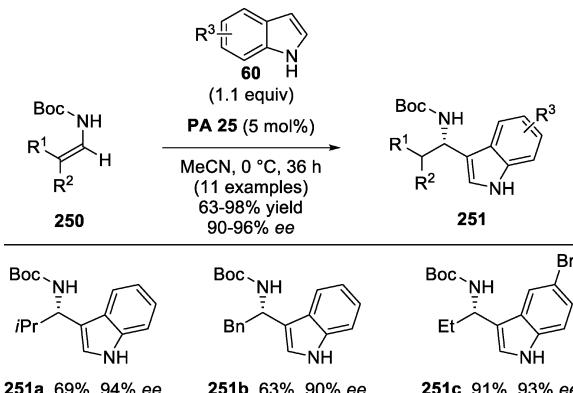
A broad scope was explored for both components, and in general the reaction performed well. The products contain both an indole and an indolinone motif, which are suitable for further synthetic transformations. Maruoka has also recently shown nonaromatic cyclic imines to be suitable substrates for the enantioselective Friedel–Crafts reaction.<sup>263</sup>

**2.3.5.2. Using Imine Precursors as Substrates.** Although imines are commonly used substrates for activation by chiral phosphoric acids, they can also be difficult to handle. This is particularly so for aliphatic imines. In 2007, Terada recognized



**Figure 129.** Friedel–Crafts reaction of cyclic imines by Rueping (2011).

that enecarbamates could serve as stable precursors of aliphatic imines and could be activated by phosphoric acids to undergo a Friedel–Crafts reaction by *in situ* tautomerization. Boc-protected enecarbamates **250** were shown to undergo reaction with indoles **60** in the presence of catalyst **PA 25** to give the adducts **251** (Figure 130).<sup>264</sup>



**Figure 130.** Friedel–Crafts reaction of enamines by Terada (2007).

The scope explored was broad, and the selectivities of the products **251** were uniformly high. It is worth noting that the reaction is run in the highly polar and protophobic acetonitrile. The authors suggest that the protonation of **250** to give an imine intermediate is the rate-determining step of the reaction. The polar solvent is required to support the ionic charges that subsequently develop. A few months later, the group of Zhou published a similar protocol using  $\alpha$ -aryl enamides and propose a bifunctional mechanism.<sup>265</sup>

Another class of substrates that can act as imine precursors are 3-hydroxyisoindolinones. In 2011, Wang showed that they efficiently undergo Friedel–Crafts reactions with indoles. Taking **252** in the presence of 5 mol % [H<sub>8</sub>]-PA **6** effects a dehydration to form an iminium ion, which subsequently proceeds to give the products **253** (Figure 131).<sup>266</sup>

An interesting observation is that the use of molecular sieves was detrimental to the reaction and resulted in lower yields and enantioselectivities. The importance of hydrogen-bonding was

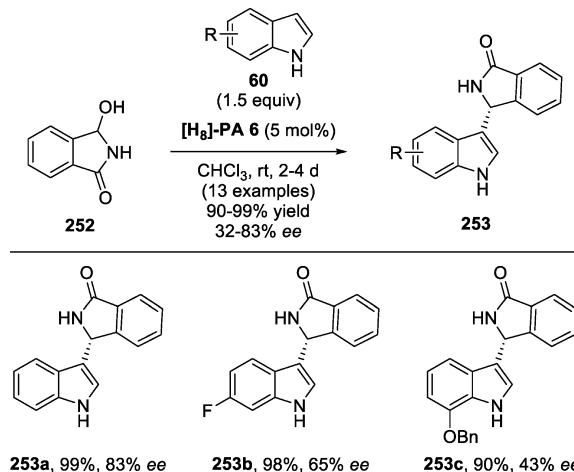


Figure 131. Friedel–Crafts reaction of hydroxy-isoindolinones by Zhou (2011).

highlighted by using an *N*-methyl protected variant of **252**, which resulted in an almost racemic reaction. By changing to a different catalyst (**PA 2**), substituted 3-hydroxyisoindolinones could be used to generate quaternary chiral centers.<sup>267</sup>

**2.3.5.3. Using Carbonyls as Substrates.** The use of carbonyls as potential substrates for activation by chiral phosphoric acids is usually a challenge that is beyond the reach of its acidity. In some cases, however, this limitation can be overcome by making the carbonyl more reactive. This strategy was employed to great effect by Ma in 2009, who showed that trifluoromethyl ketones **254** could undergo an asymmetric Friedel–Crafts reaction with various indoles **60** (Figure 132).<sup>268</sup>

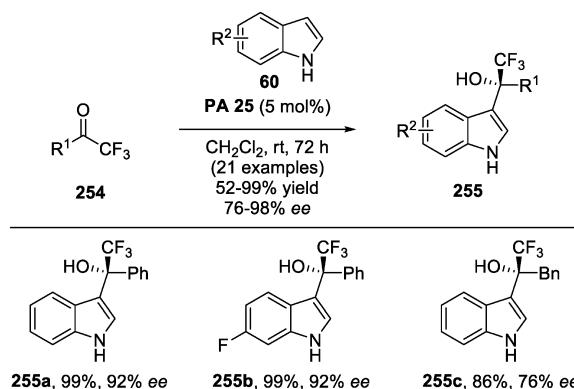


Figure 132. Friedel–Crafts reaction of  $\text{CF}_3$ -ketones by Ma (2009).

By employing 5 mol % of catalyst **PA 25**, it was shown that **254** would be sufficiently activated to react at the 3-position of various indoles to give the corresponding products **255** in excellent yields and high selectivities. The protocol could also be performed with similar yields and selectivity on difluoro- and perfluoroalkyl ketones. In 2010, Akiyama also showed a similar reaction using an  $[H_8]$ -phosphoric acid, which was performed with pyrroles and furans.<sup>269</sup> In the same year, Ma was able to show that 4,7-dihydroindoless react at the 2-position with trifluoromethyl ketones under phosphoric acid catalysis.<sup>270</sup>

In 2009, Ma was able to show that  $\beta\text{-CF}_3$ -ketoesters were suitable substrates for phosphoric acid activation and subsequent reaction with various indoles **60** (Figure 133).<sup>271</sup>

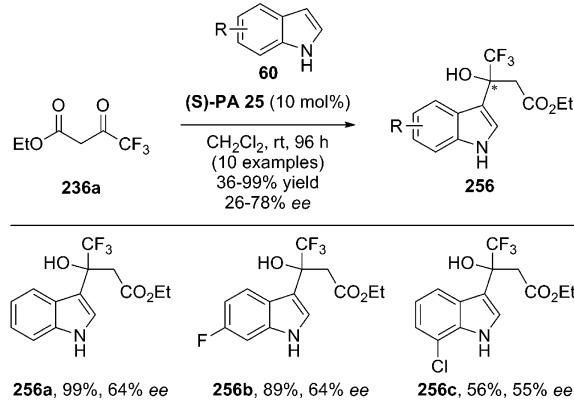


Figure 133. Friedel–Crafts reaction of  $\beta\text{-CF}_3$ -ketoesters by Ma (2009).

Taking 10 mol % of catalyst (**S**)-**PA 25** with ethyl trifluoropyruvate **236a** at room temperature for 96 h gave the corresponding Friedel–Crafts products **256** in good yields and modest enantioselectivity.

It was also extended to  $\alpha\text{-CF}_3$ -ketoesters, and although the yields were uniformly high, the selectivity was generally modest (<60% ee).

**2.3.5.4. Using Activated Alkenes as Substrates.** Examples of the use of alkenes as motifs for phosphoric acid catalysis are scarcely reported. For unfunctionalized alkenes, the lack of polarity results in a poor interaction between itself and the acid component. In contrast, polarized alkenes, in particular electron-poor substrates, have been shown to be sufficiently reactive enough to be activated. In 2008, Akiyama was the first to show that nitroalkenes **257** could be activated with 10 mol % **PA 2** to react with various indoles **60** in a Friedel–Crafts reaction to give adducts **258** with high enantioselectivities (Figure 134).<sup>272</sup>

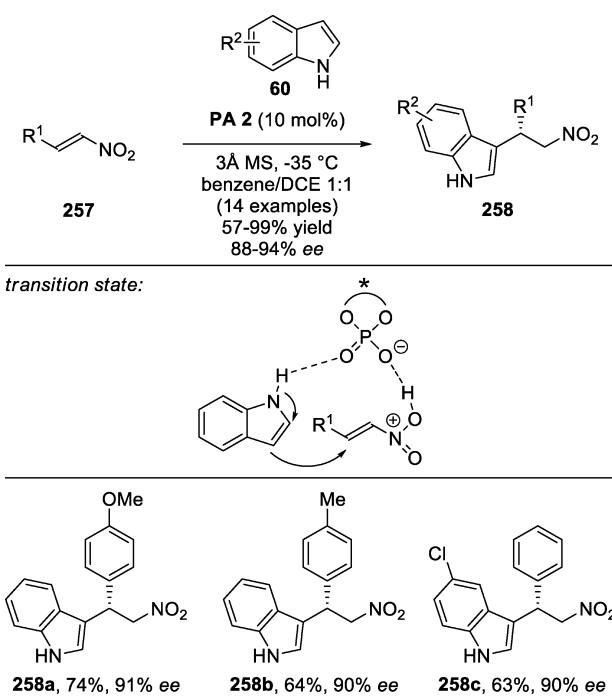


Figure 134. Friedel–Crafts reaction of nitroalkenes by Akiyama (2008).

The use of molecular sieves was found to be crucial as dramatic reductions in yields and selectivity were noticed in their absence. The products were shown to be useful synthetic intermediates for further transformations. DFT studies by Yamanaka and You both concluded that a bifunctional mechanism is most likely the course of the reaction.<sup>273</sup> The catalyst activates the indole N–H in the usual manner and uses its acidic proton to activate the nitro-group so that the conjugated alkene can undergo the desired reaction. In 2009, You was able to show that nitroalkenes could be used with 4,7-dihydroindoless, which react at the 2-position to give the corresponding products with high enantioselectivities using just 0.5 mol % catalyst.<sup>274</sup> The asymmetric Friedel–Crafts reaction with fluorinated nitroalkenes has been studied by Xiao in combination with chiral phosphoric acids.<sup>275</sup> Zhang has also studied this reaction with a [H<sub>8</sub>]-BINOL-based catalyst with moderate success.<sup>276</sup>

In 2009, You also published the reaction of nitrostyrenes **257** with pyrrole derivatives **259**. Reaction occurred at the 2-position using 5 mol % of catalyst (S)-PA **7** at room temperature (Figure 135).<sup>277</sup> The reaction required molecular sieves

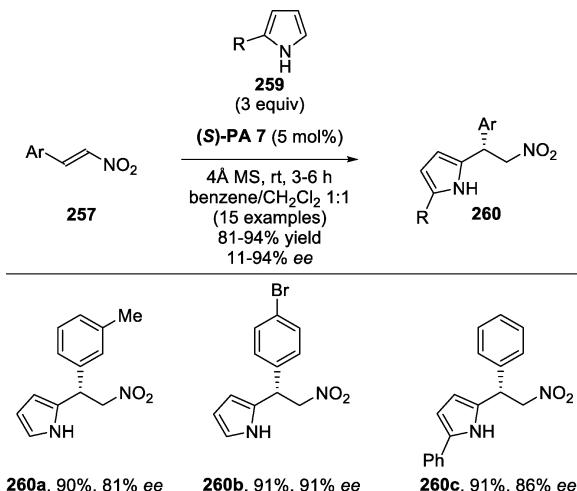


Figure 135. Friedel–Crafts reaction of nitrostyrenes with pyrroles by You (2009).

and the slow addition of **257** to ensure high yields and selectivity of **260**.

The authors propose a bifunctional mechanism, which involves the interaction of the nitro group and the N–H of the pyrrole to be coordinated to the phosphoric acid catalyst. When N-methyl pyrrole is used, a lower yield is obtained, but interestingly an almost racemic product is formed. This strongly suggests that the acidic N–H of the pyrrole group is involved in coordination to the catalyst during the transition state of the reaction.

Another distinctive class of alkenes that have shown to be suitable for activation by phosphoric acids are  $\alpha,\beta$ -unsaturated carbonyls. In 2008, Zhou was able to demonstrate that enones **261** could be activated toward a Friedel–Crafts reaction with 2-substituted indoles **60** using just 2 mol % of [H<sub>8</sub>]-PA **13** (Figure 136).<sup>278</sup>

During the optimizations, it was actually found that the more bulky substituents lowered the enantioselectivity. The products **262** were obtained in good yields but only modest selectivity while using [H<sub>8</sub>]-PA **13**. The mechanism can be assumed to be proceeding via a transition state similar to that described for the

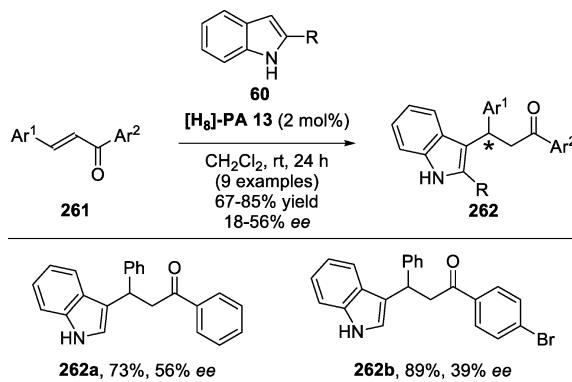


Figure 136. Friedel–Crafts reaction of enones by Zhou (2008).

$\alpha,\beta$ -unsaturated nitro alkenes. A similar protocol was published by the Acocella and Ma groups with modest enantioselectivity being achieved.<sup>279</sup> The Toy group demonstrated the potential of an easily recoverable phosphonium ion tagged phosphoric acid catalyst (**263**, Figure 137) to facilitate a similar Friedel–Crafts reaction of alkenes.<sup>43</sup>

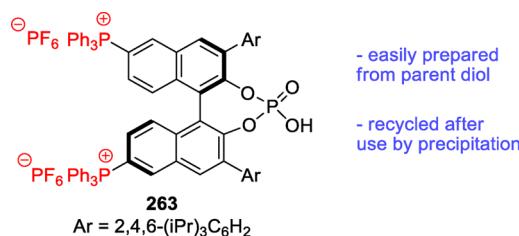


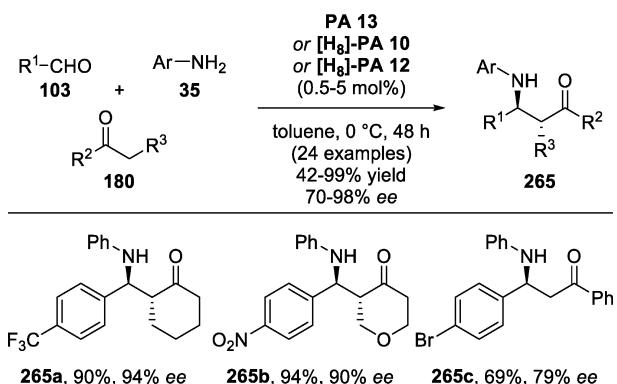
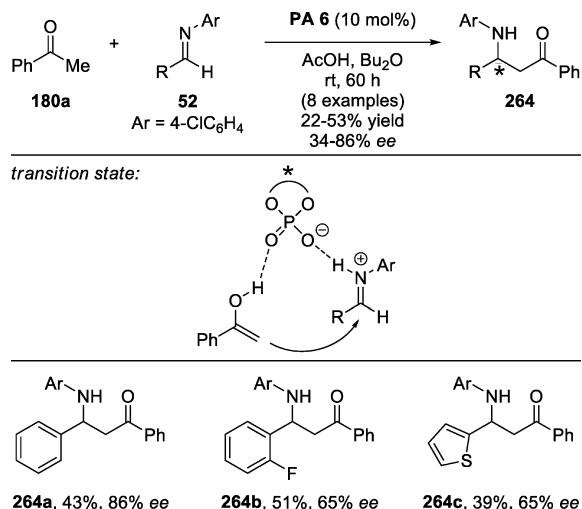
Figure 137. Easily recoverable catalyst by Toy (2011).

In 2010, Akiyama published the Friedel–Crafts reaction with 4,7-dihydroindoless and after oxidation was able to access 2-substituted indoles in good yields and high enantioselectivities (<87% ee).<sup>280</sup> Akiyama has also shown  $\alpha,\beta$ -unsaturated acyl phosphonates as viable substrates for activation by chiral phosphoric acids.<sup>281</sup>

**2.3.6. Mannich.** The Mannich reaction was the reaction that kick-started the field of asymmetric Brønsted acid catalysis using BINOL-phosphoric acids. The bifunctional activation mode of the catalysts was used by Terada in his seminal paper.<sup>19</sup> These results have been earlier described in the Introduction and will not be repeated here. In 2010, the group of Ishihara studied the Mannich reaction in great detail and found that the method of purification used to isolate the catalyst can have dramatic effects on both the yields and the selectivity of the reaction.<sup>35a</sup> In 2007, Rueping extended the direct Mannich reaction to the use of acetophenone **180a** with *N*-aryl imines **52** catalyzed with 10 mol % of PA **6** (Figure 138).<sup>282</sup>

It is worth noting that the achiral acetic acid is used in the reaction to tautomerize **180a** to its enol form, but more importantly it is not able to activate the imine for subsequent reaction. The products **264** were obtained in modest yields and enantiomeric excesses.

In 2007, Gong demonstrated a multicomponent variant for the direct Mannich reaction by *in situ* generation of the imine component.<sup>283</sup> Condensing aldehydes **103** with aromatic amines **35** formed the imine component *in situ*, which could react with various ketones **180** to give the Mannich products **265** in high selectivity as the anti-diastereoisomers (Figure 139).

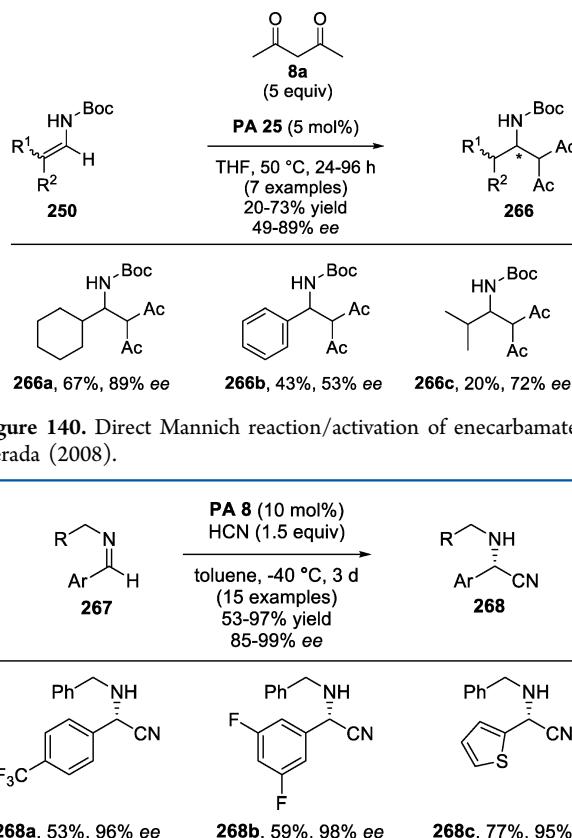


A choice of three catalysts was found to be suitable for the reaction and could be employed with as little as 0.5 mol %. It was also found that cyclic ketones performed better than acyclic counterparts. A three-component Mannich reaction has also been applied with a doubly axially chiral bis-phosphorylimide catalyst developed by Zhang.<sup>42b</sup>

Similar to his study on the Friedel–Crafts reaction with enecarbamates,<sup>264</sup> Terada also recognized that they could serve as stable precursors of imines that would undergo a direct Mannich reaction. Treating enecarbamates **250** with 5 mol % of catalyst **PA 25** and acetyl acetone **8a** gave the Mannich products **266** in modest yields and enantioselectivities (Figure 140).<sup>284</sup>

It was found that both the (*E*)- and the (*Z*)-isomers reacted in a similar fashion and gave identical enantioselectivities. A limitation of the reaction was found to be disubstitution, and this caused a dramatic reduction in the yield of the product (**266c**). Recently, Maruoka has also published a Mannich reaction of  $\beta$ -keto esters using imines generated from aminals.<sup>285</sup>

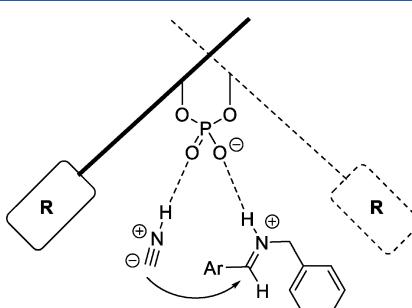
**2.3.7. Strecker.** The addition of hydrogen cyanide (or an equivalent) to an imine or preformed imine is known as the Strecker reaction and is one of the most practical and useful methods to synthesize both natural and unnatural  $\alpha$ -amino acid derivatives.<sup>286</sup> Various methods have been shown to be able to catalyze this transformation, including Lewis acids and chiral metals complexes.<sup>287</sup> In 2006, Rueping showed that the reaction could be catalyzed effectively with a chiral phosphoric acid for the first time (Figure 141).<sup>288</sup>



**Figure 141.** Strecker reaction by Rueping (2006).

Using 10 mol % of catalyst **PA 8**, various benzyl protected imines **267** could be reacted in the presence of HCN to give the Strecker products **268** in good yields and high enantioselectivities. The choice of protecting group and solvent was found to be crucial components to the reaction, with benzyl and toluene, respectively, being the optimal choices. Conversion of the products to amino acids and diamines was shown to be facile through simple synthetic procedures without any loss of enantiopurity. Later that year, the extension to include ketimines using the same catalyst was also shown.<sup>289</sup> The reaction was still as efficient but with slightly lower enantioselectivities.

Detailed mechanistic studies on the reaction have been carried out by Goodman.<sup>290</sup> From his calculations, a bifunctional mechanism was postulated to be occurring, and for benzaldehyde derived imines the lowest energy transition state was calculated to be the imine in its *E*-configuration (Figure 142). In addition, the benzyl group prefers to occupy the most open site during the enantioselective addition step.



**Figure 142.** Calculated transition state for the Strecker reaction (Goodman).

**2.3.8. Pictet–Spengler.** The Pictet–Spengler reaction is a powerful transformation for the synthesis of tetrahydro- $\beta$ -carbolines and tetrahydroisoquinolines. The alkaloid products form the skeletons of many naturally occurring compounds with useful biological activity. Despite its importance, small-molecule catalysis of the direct reaction is scarce.<sup>291</sup> In 2006, List disclosed a procedure for the asymmetric Pictet–Spengler catalyzed by a chiral phosphoric acid (Figure 143).<sup>292</sup>

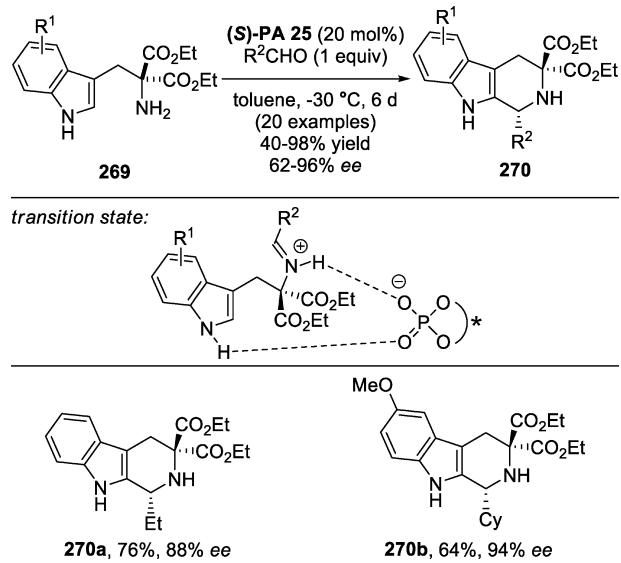


Figure 143. Pictet–Spengler reaction by List (2006).

Taking various tryptamine derivatives **269** with 1 equiv of an aldehyde and a modest catalyst loading of 20 mol % of (S)-PA **25** gave the corresponding alkaloid products **270** in good yields and with good selectivity. The geminal disubstitution on the tryptamines was thought to be needed for promoting the cyclization via a Thorpe–Ingold effect.<sup>293</sup> It was shown however that diastereoselective functionalization of this group was possible. Although a mechanism was not proposed, we believe that a bifunctional mode of activation is occurring whereby coordination to the protonated imine and the N–H of the indole by the catalyst is occurring. In 2012, Belder developed an on-chip method for carrying out a Pictet–Spengler reaction and monitoring the reaction progress by time-resolved fluorescence.<sup>294</sup>

In 2011, Bencivenni extended the utility of the phosphoric acid-catalyzed Pictet–Spengler to incorporate isatins **272** as electrophilic partners to various tryptamines **271** to access spirooxindoles **273** (Figure 144).<sup>295</sup>

During the optimization, it was found that a range of solvents gave good conversion but DMF proved optimal for selectivity. This result is rather impressive considering that DMF can act

as a hydrogen-bond acceptor and would be expected to disrupt the interactions between the catalyst and the reactive intermediates. A bifunctional mechanism for the catalyst is proposed by the authors. A related reaction of isatins was also disclosed by Franz who also showed that DMF could be employed with successfully high enantioselectivities.<sup>296</sup>

**2.3.9. Michael Reaction.** The Michael reaction is one of the fundamental reactions in synthetic organic chemistry and is also considered as one of the mildest methods for the formation of C–C bonds. For this reason, the reaction has received a great deal of attention especially regarding asymmetric variants.<sup>297</sup> In 2009, Akiyama demonstrated the potential of the reaction as a route to carrying out Robinson annulations.<sup>298</sup>

Taking  $\beta$ -ketoesters **274** with methyl vinyl ketone **99b** and 10 mol % of catalyst [H<sub>8</sub>]-PA **20** gave the Michael addition products **275** in good yields and enantioselectivity (Figure 145).

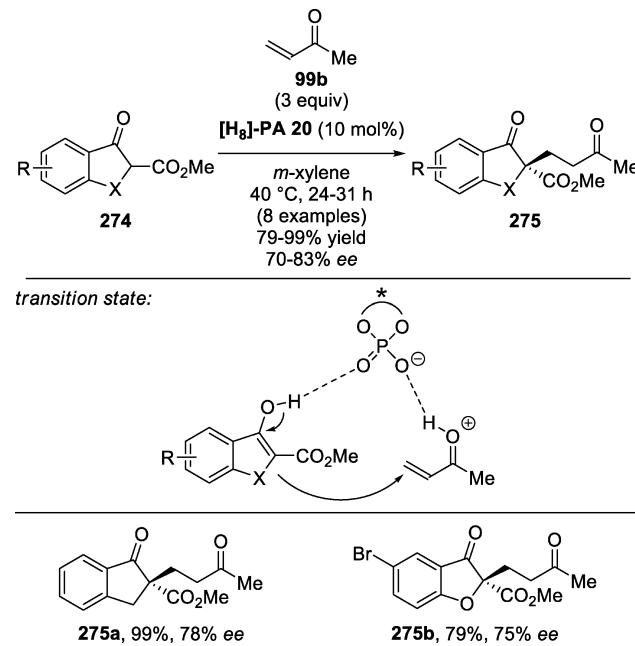


Figure 145. Michael reaction of methyl vinyl ketone by Akiyama (2009).

It was noticed however that the racemic products could also be persuaded to undergo a Robinson annulation in the presence of the phosphoric acid and in doing so would also undergo a kinetic resolution. This strategy was used in a one-pot procedure to achieve excellent selectivity for the Robinson annulations products. The mechanism proposed by the authors involves interactions between the catalyst and the enol tautomer of **274** with simultaneous protonation of the carbonyl.

In 2010, the intramolecular aza-Michael reaction of indoles was disclosed by You.<sup>299</sup> The reaction involved taking unsaturated

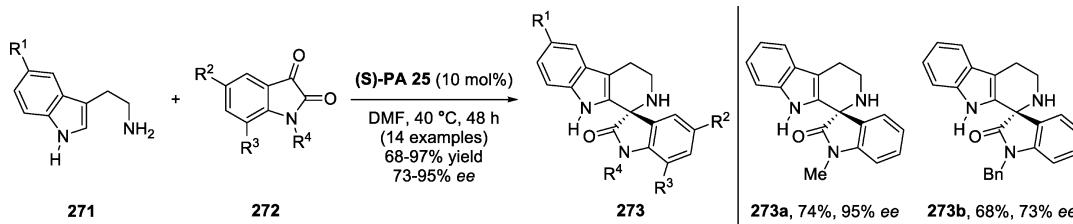


Figure 144. Pictet–Spengler reaction of isatins by Bencivenni (2011).

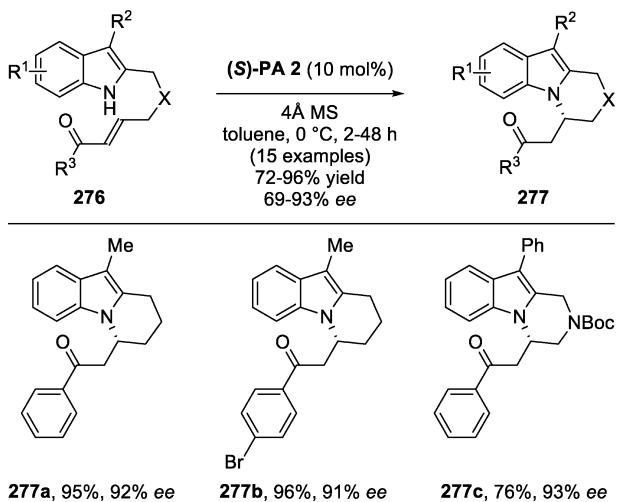


Figure 146. Aza-Michael reaction of indoles by You (2010).

indoles 276 and treating them with 10 mol % of catalyst (S)-PA 2 in toluene at 0 °C (Figure 146).

The polycyclic indole products 277 were obtained in excellent yields and generally high enantioselectivities. A one-pot procedure for the generation of  $\alpha,\beta$ -unsaturated carbonyls from the corresponding terminal alkenes and subsequent reaction was also developed. In this procedure, a rhodium catalyst was used to carry out olefin metathesis prior to subsequent reaction. The mechanism can be assumed to be similar to that proposed in Figure 145, but instead of coordination to the enol in this case coordination to the indole N–H occurs.

Also in 2010, the same group published their work on the oxo-Michael reaction as a method for the desymmetrization of cyclohexadienones.<sup>300</sup> Taking meso-alcohols 278 and treating them with 10 mol % of (S)-PA 28 promoted the reaction to give enantioenriched enones 279 in good yields and generally high selectivity (Figure 147).

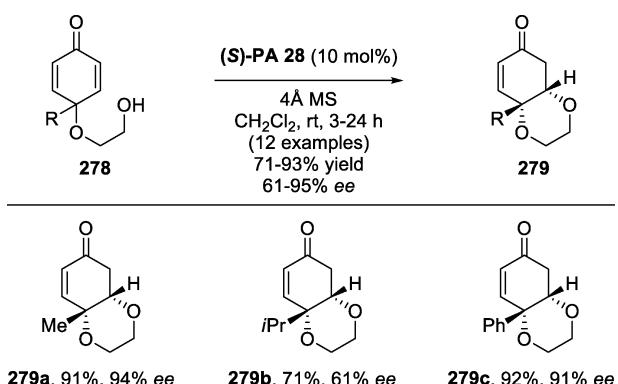


Figure 147. Oxo-Michael reaction of cyclohexadienones by You (2010).

The proposed mechanism of enantioinduction is a bifunctional activation of the alcohol nucleophile and the carbonyl group by the catalyst. In general, the more bulky was the catalyst the better was the selectivity obtained. The products were shown to be highly versatile intermediates and also used in the synthesis of a family of natural products known as cleroidicins. Rovis has also demonstrated a similar reaction

catalyzed by a spiro-phosphoric acid catalyst in the synthesis of 1,2,4-trioxane anticancer agents.<sup>301</sup>

**2.3.10. Multicomponent Reactions.** The attraction of multicomponent reactions has certainly grown in recent years as atom economy is usually high, and the sequential reaction of components in the same reaction pot makes for a highly desirable process for synthetic chemists. Because of the reaction-media containing multiple components, developing the process to be enantioselective with a small-molecule catalyst can be a difficult task. The classic Biginelli reaction reported over a hundred years ago is today still a useful synthetic procedure to synthesize dihydropyrimidinones.<sup>302</sup> This field has received a major contribution from the Gong group.<sup>303</sup> In 2008, Gong reported an exquisite variant on this reaction to access enantioenriched dihydropyridines (Figure 148).<sup>304</sup>

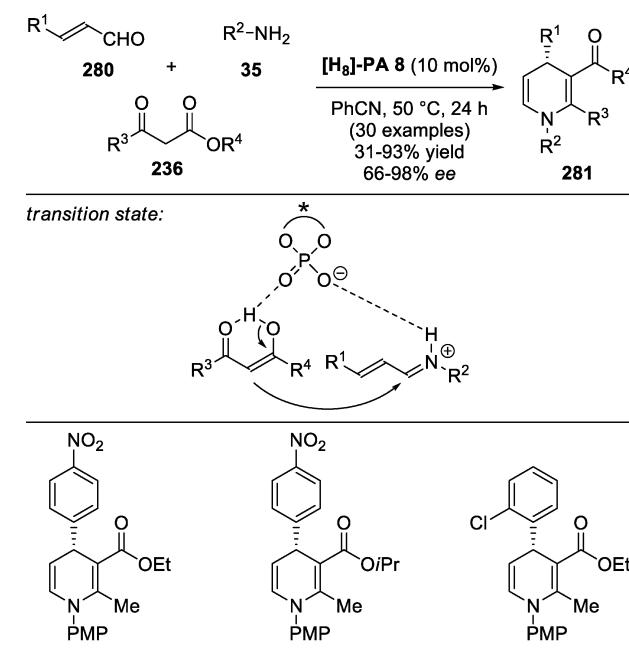
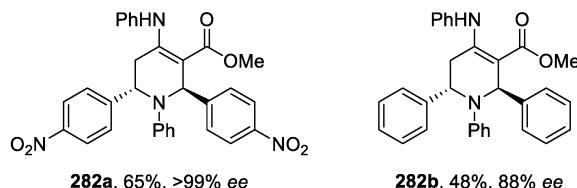
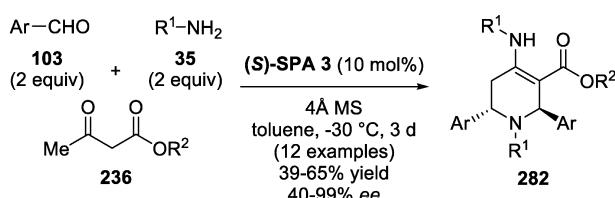


Figure 148. Three-component cyclization to form dihydropyridines by Gong (2008).

Treating unsaturated aldehydes 280, amines 35, and  $\beta$ -keto esters 236 in PhCN at 50 °C for 24 h in the presence of 10 mol % of catalyst [H<sub>8</sub>]-PA 8 gave the condensed products 281 in modest to good yields and high selectivity. The authors propose a monoactivation of the generated iminium species by the chiral phosphoric acid, but hydrogen bonding to the incoming enol by the Lewis basic site on the catalyst is most likely occurring here to obtain the high selectivities observed. A year later, Gong was able to extend the scope of this multicomponent reaction to include azlactones in place of 236 to give 3,4-dihydropyridines.<sup>305</sup> Zhang has synthesized a family of multiple chiral axis catalysts (cf., PA 43) that can catalyze the Biginelli reaction with high enantioselectivities.<sup>306</sup> Cheng has also shown a similar multicomponent reaction to access dihydro-pyrrol-2-ones using chiral phosphoric acids as catalysts.<sup>307</sup>

A multicomponent reaction is formally described as more than two reactants combining together to give the corresponding product. Three components are typically the most common amount of reactants seen in the literature; however, research

groups have been trying to push this boundary further. In 2013, Lin disclosed the first five-component reaction, which was shown to be catalyzed by a chiral spirocyclic phosphoric acid (Figure 149).<sup>308</sup>



**Figure 149.** Five-component cyclization to form tetrahydropyridines by Lin (2013).

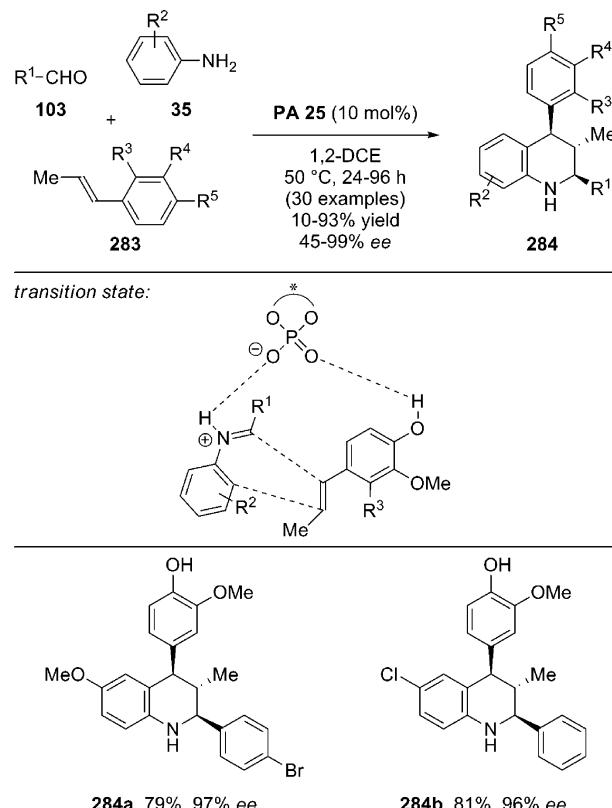
The condensation was formally an  $\text{AB}_2\text{C}_2$  type, which consisted of  $\beta$ -keto esters **236**, 2 equiv of aryl aldehydes **103**, and 2 equiv of primary amines **35** to give tetrahydropyridines **282** in modest yields but generally high selectivity. The reaction uses just 10 mol % of catalyst (S)-SPA 3, which was shown to be the superior catalyst against simpler BINOL-derived acids. It is worth noting that the reaction is an impressive display of atom economy, and the products can also be selectively reduced to give enantioenriched piperidines. More recently, a similar five-component approach has also been published by Tu who was able to use a BINOL-phosphoric acid to catalyze the process giving the products in modest yields and enantioselectivity.<sup>309</sup>

In 2012, Masson disclosed an inverse electron-demand aza-Diels–Alder reaction (IEDDA reaction) by the use of three components, aldehydes **103**, amines **35**, and styrenes **283** (Figure 150).<sup>310</sup> The styrenes were chosen to be isoeugenol derivatives as they provided much higher selectivity than simple styrenes.

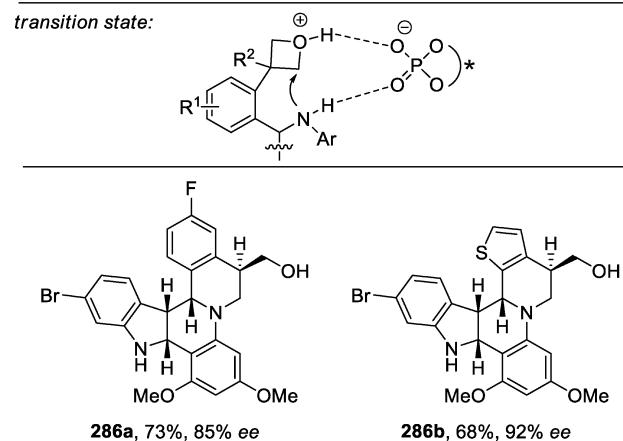
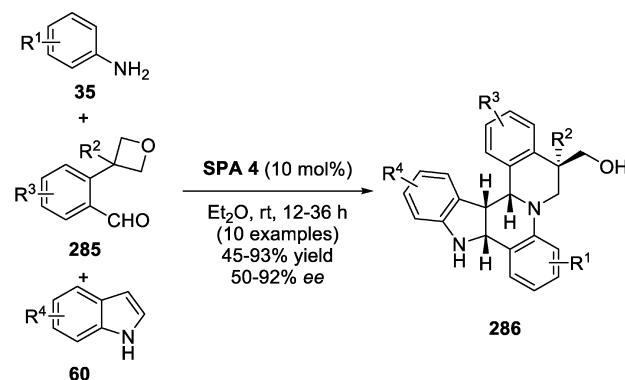
The tetrahydroquinoline products **284** were fully substituted and were obtained in good to high yields with excellent selectivities. The authors propose a bifunctional mechanism between the catalyst and both reaction components. They believe that the hydroxyl group on the isoeugenol styrenes can coordinate to the catalyst while the diene is also being activated by protonation of the imine.

In 2013, Sun demonstrated the importance of coordination by utilizing an oxetane as a directing group for a multi-component aza-Diels–Alder reaction (Figure 151).<sup>311</sup> The idea of a directing group resulted by initial attempts at the reaction giving poor yields and multiple byproducts. Introduction of ether residues at the 2-position of the aldehydes instantly improved the yields, but selectivity remained poor. Further optimization revealed that the oxetane group in the 2-position resulted in extremely high levels of control. The reaction takes places with anilines **35**, aldehydes **285**, and indoles **60** to give polycyclic, highly complex products **286** generally in modest to good yields and good to high selectivity.

Spiro-cyclic phosphoric acid **SPA 4** is used in 10 mol %, and although the authors propose a bifunctional activation of the



**Figure 150.** Three-component aza-Diels–Alder reaction by Masson (2012).



**Figure 151.** Three-component aza-Diels–Alder reaction to form complex polycycles by Sun (2013).

reactive intermediates, the exact role of the catalyst appears to be complex. The authors suggest that protonation of the oxetane and simultaneous activation of the nucleophile result in the stereoselectivity observed. However, during their studies, they observed positive nonlinear effects but propose that this may be due to higher-order interactions that are not involved in the catalytic step. The methodology was also shown to be useful in the formal synthesis of (+)-(8*S*,13*R*)-cycloelabenzine.<sup>312</sup>

The Biginelli reaction in recent years has received an increased amount of attention due to the dihydropyrimidinone scaffold being recognized as a highly important motif that has been shown to possess a variety of pharmacological properties. The first organocatalytic variant of this reaction was reported by Gong in 2006 using a chiral phosphoric acid (Figure 152).<sup>313</sup>

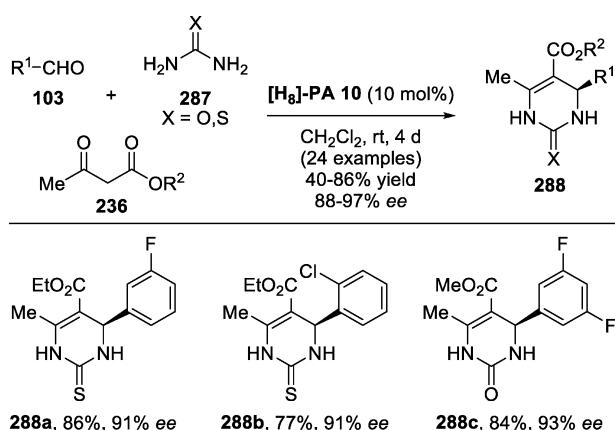


Figure 152. Three-component Biginelli reaction by Gong (2006).

The condensation of aldehydes **103**,  $\beta$ -ketoesters **236**, and urea derivatives **287** led to the formation of the products **288** in good yields and high selectivity. Interestingly, the use of bulky substituents on the catalyst (at the 3- and 3'-positions) resulted in low reactivity and only modest selectivity. It was found that  $[H_8]\text{-PA 10}$  was the optimal catalyst for the reaction. In 2010, Gong found an interesting positive nonlinear effect, which was thought to be due to the solubility of the catalyst.<sup>314</sup> A very similar reaction was also found to be efficiently catalyzed by SPINOL-phosphoric acids by Wang and Lin in 2012.<sup>315</sup> The nature of the selectivity was the subject of a more detailed investigation by Gong.<sup>316</sup>

The detailed study revealed that the 3- and 3'-substituents could effectively be tuned to give the desired stereochemistry of choice. As a representative example, it was shown that combining aldehyde **103a** with **236b** and **287a** gave (*S*)-**289** when 10 mol % of PA **2** was used as a catalyst. Alternatively, when  $[H_8]\text{-PA 10}$  was used in  $\text{CH}_2\text{Cl}_2$ , the corresponding (*R*)-**289** was obtained (Figure 153). The authors propose through DFT calculations that in each case a bifunctional mechanism is thought to be occurring; however, the facial selectivity is determined by the strength of the hydrogen-bonding interaction between the catalyst and the nucleophile **236b**. The bigger are the substituents, the weaker is the interaction and thus the opposite enantiomers are obtained.

In 2008, Ma reported a three-component Friedel–Crafts reaction involving imines generated from acetals **290** and the corresponding amines **35** (Figure 154).<sup>317</sup> Reaction with a variety of substituted N–H free indoles **60** gave the products **291** in good yields and excellent enantioselectivities.

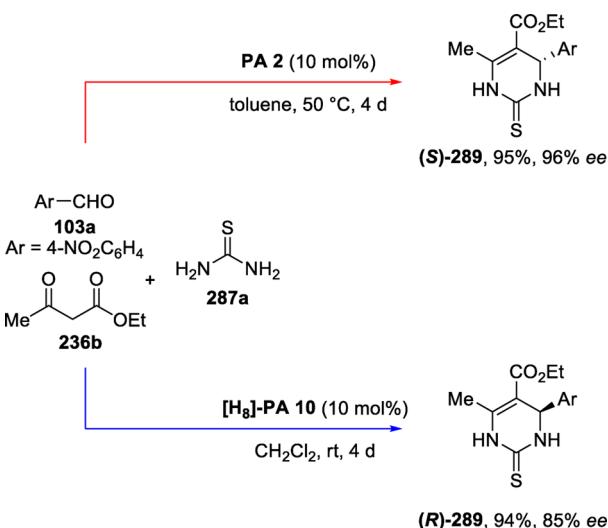


Figure 153. Reversal of absolute stereochemistry with different catalysts by Gong (2009).

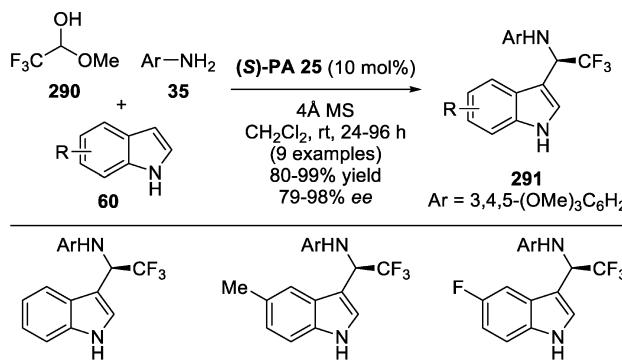
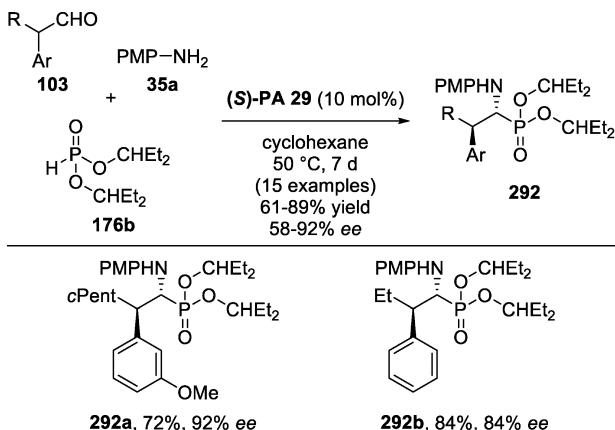


Figure 154. Three-component coupling reaction involving acetals by Ma (2008).

The procedure provides a very useful method for the introduction of a  $\text{CF}_3$  group due to the acetal **290** being commercially available and easy to handle. The deprotection of the aromatic group on the amine was also shown to be facile without loss of enantioselectivity.

The three-component coupling of a carbonyl compound, an amine, and a hydrophosphoryl compound is known as the Kabachnik–Fields reaction and is a method to synthesize  $\alpha$ -aminophosphonates. The structural moiety is a useful and versatile pharmacological motif due to the broad spectrum of biological activity exhibited by compounds bearing this structural unit. In 2008, List developed a direct asymmetric Kabachnik–Fields reaction using aldehydes **103**, aryl amine **35a**, and phosphite **176b**, which gave the corresponding products **292** in good yields and selectivity (Figure 155).<sup>318</sup>

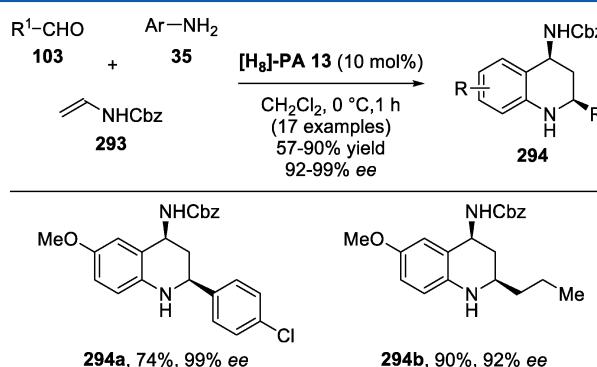
During the catalyst optimization, it was found that an extremely sterically hindered catalyst (*S*)-PA **29** was optimal for achieving good selectivity. Generally, the reaction worked well and yields were independent of the nature of substituents. It was however noticed that *o*- or *m*-substitution on the aromatic ring of aldehydes **103** led to slightly lower enantioselectivities. As described earlier, the mechanism most likely involves bifunctional activation of the phosphite and protonation of the imine generated from the aldehyde and amine.



**Figure 155.** Three-component Kabachnik–Fields reaction by List (2008).

**2.3.11. Povarov.** The Povarov reaction is defined by the cycloaddition of aromatic imines with electron-rich alkenes.<sup>319</sup> In some cases, the generation of the imine is performed in situ, thus rendering the reaction multicomponent. It can also be classified as an inverse electron-demand aza-Diels–Alder. It is a very useful way of building up substituted tetrahydroquinolines, which have been shown to possess various biological activities.

As described earlier, Akiyama was the first to demonstrate the reaction could be catalyzed by a chiral phosphoric acid going via a dual activation mode.<sup>124</sup> In 2009, Zhu and Masson reported the first Povarov reaction that proceeded through a bifunctional transition state (Figure 156).<sup>320</sup> The mechanism proposed closely resembles that depicted in Figure 147.

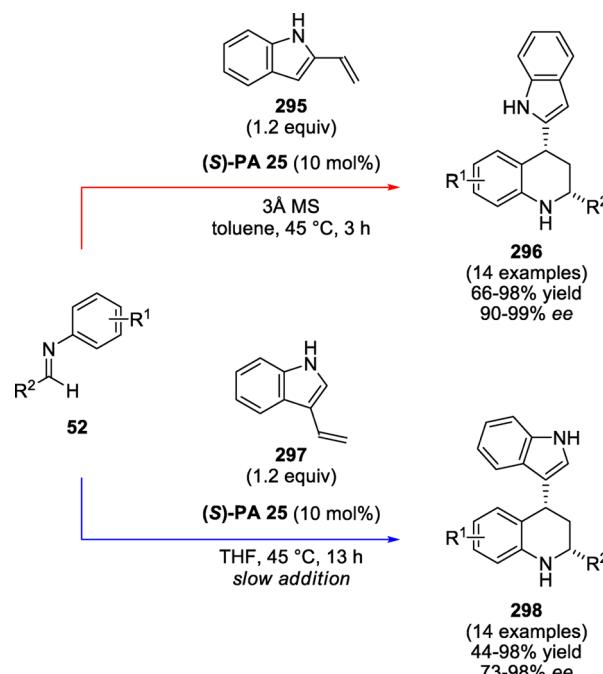


**Figure 156.** Povarov reaction by Zhu and Masson (2009).

Combining aldehydes 103 with aryl amines 35 and enamine 293 gave in the presence of 10 mol % of catalyst [H<sub>8</sub>]-PA 13 the corresponding tetrahydroquinolines 294 in good yields and excellent selectivities. A short synthesis of Torcetrapib, a phase three drug candidate, was also shown to be possible using this methodology. It was later shown by the same group that their methodology was suitable for the extension to substituted<sup>321</sup> and cyclic enamines<sup>322</sup> under similar reaction conditions. As a further extension, Liu has shown that CF<sub>3</sub>- or CF<sub>2</sub>-substituted imines also work well in the desired reaction.<sup>323</sup> Gong has also studied the Povarov reaction with 2-hydroxystryrenes catalyzed by a chiral phosphoric acid.<sup>324</sup> Recently, the Lin group and the Huang group have also published their efforts on the reaction to good effect.<sup>325</sup>

In 2010, Ricci was able to show that the Povarov reaction is not just limited to simple enamines but in fact vinyl indoles

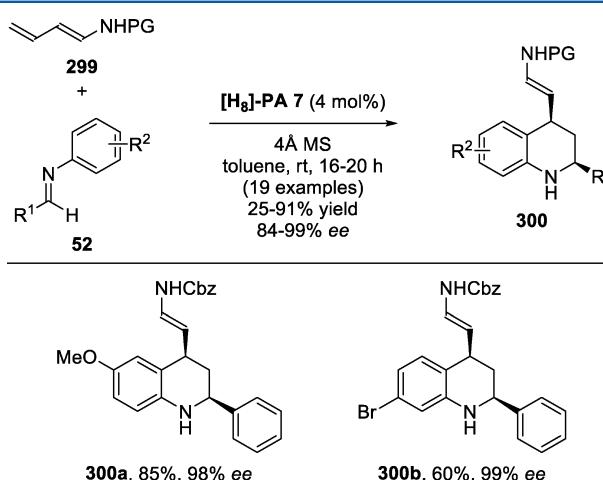
could be used under phosphoric acid catalysis.<sup>326</sup> Taking imines 52 and reacting with 2-vinyl indole 295 or 3-vinyl indole 297 gave the respective products 296 and 298 in good yields and high selectivity (Figure 157).



**Figure 157.** Povarov reaction with vinyl indoles by Ricci (2010).

The scope was broad with a range of aromatic and alkyl imines performing well under the standard reaction conditions. Mechanistic studies suggested that the reaction may follow a stepwise approach. Evidence for this was found by the trapping of a reactive-intermediate on the reaction profile with an external nucleophile.

Recently, Bernardi has shown that the Povarov reaction can be carried out in a vinylogous fashion using unsaturated enamines 299 as the alkene component with aromatic imines 52 (Figure 158).<sup>327</sup> Reaction with 4 mol % of [H<sub>8</sub>]-PA 7 gave the corresponding products 300 in good yields and high selectivities.



**Figure 158.** Vinylogous Povarov reaction by Bernardi (2013).

During the optimization process, it was shown that as little as 0.3 mol % of catalyst could still furnish high selectivity albeit with lower yields. The advantage of the vinylogous reaction is that the products **300** contain a synthetic handle for further transformations.

**2.3.12. Oxidations.** Asymmetric oxidations mediated by chiral Brønsted acids is a field of research that has seen relatively few reports presumably due to the difficulty in controlling the process. In 2009, Zhong reported the first  $\beta$ -hydroxylation of  $\beta$ -dicarbonyl compounds by utilizing nitroso compounds as the source of oxygen (Figure 159).<sup>328</sup>

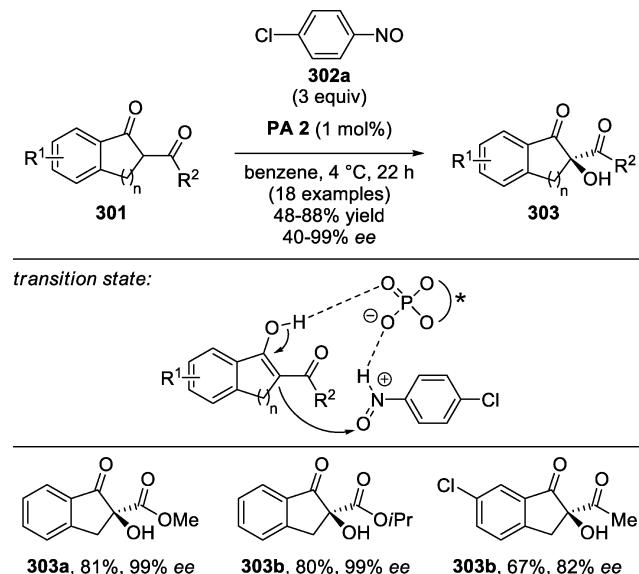


Figure 159. Hydroxylation of dicarbonyl compounds by Zhong (2009).

A variety of  $\beta$ -dicarbonyls **301** could be oxidized to the  $\alpha$ -hydroxy products **303** in good yields and generally high selectivity. In addition, only 1 mol % of catalyst PA 2 was required. The role of the phosphoric acid is proposed to be bifunctional, by simultaneously activating **301** in its enol form and the nitroso compound **302a**. It is also thought that by specifically hydrogen bonding to the nitrogen atom of the nitroso compound, the phosphoric acid prevents the attack of **301** onto the nitrogen atom.

A year later, the group expanded the scope of the reaction toward using enamines as nucleophiles with nitroso compounds (Figure 160).<sup>329</sup> Reaction of enecarbamates **137** with nitroso

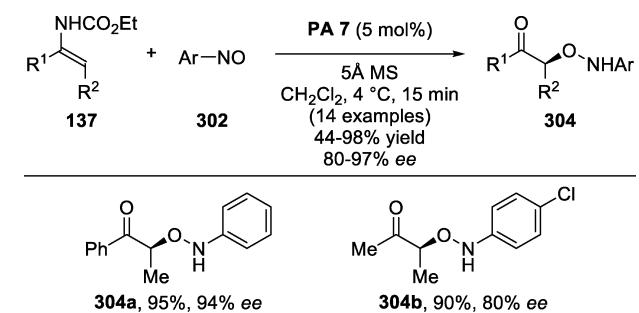


Figure 160. Hydroxylation of enecarbamates by Zhong (2010).

compounds **302** gave after a few minutes the  $\alpha$ -aminoxylated products **304** in good yields and high enantioselectivities.

The carbonyl products **304** were obtained after an acidic workup; however, it was also shown that the intermediate imine could be reduced using DIBAL-H to give the corresponding amine. This product could be converted into an enantioenriched oxazolidinone, thus demonstrating the synthetic potential of this reaction.

**2.3.13. Kinetic Resolution.** The kinetic resolution of racemic products can sometimes provide an efficient and alternative route to accessing stereochemically enriched compounds.<sup>330</sup> The benefits of this strategy over asymmetric synthesis can include such factors as the cost of synthesis, the efficiency of the reaction, and ease of isolation. The biaryl skeleton is a motif found not only in catalysis but also in biologically active molecules. In 2013, Akiyama demonstrated a two-step desymmetrization followed by kinetic resolution of substituted biaryls **307** (Figure 161).<sup>331</sup>

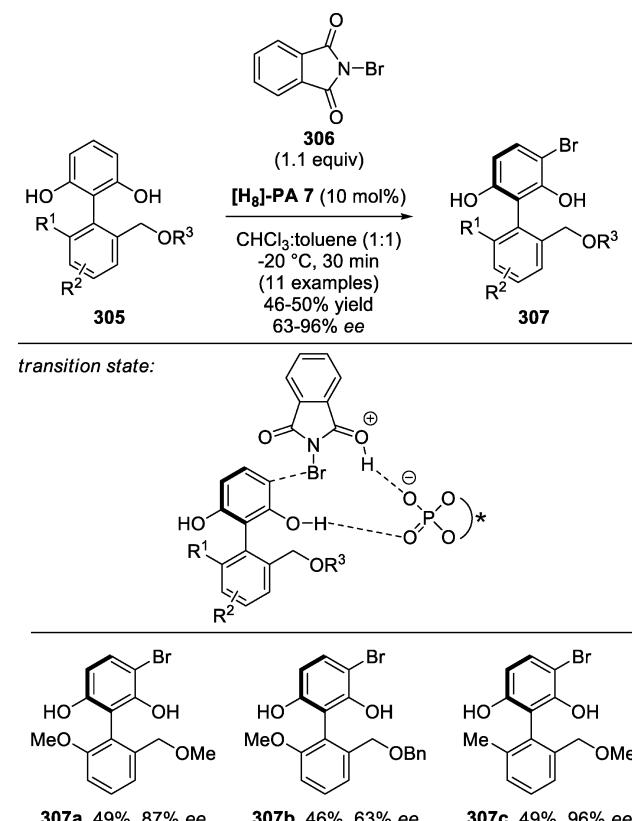


Figure 161. Resolution of biaryls by Akiyama (2013).

Treatment of **305** with N-bromophthalimide **306** in the presence of 10 mol % [H<sub>8</sub>]-PA 7 initiated a desymmetrization followed by resolution bromination reaction to give enantioenriched biaryls **307** in good overall yields and high enantioselectivities. DFT calculations appear to suggest a bifunctional mode of reactivity whereby N-bromophthalimide and the alcohol group on the aromatic are hydrogen bonded to the catalyst. The importance of the alcohol group was confirmed by reactivity of the corresponding methyl ether, which gave much lower selectivity and a low overall yield. Later in 2013, Akiyama developed a <sup>1</sup>H NMR method, which allows the user to screen for the correct catalyst and predict the enantioselectivity.<sup>332</sup>

The most common hybridized state for carbon for the addition of nucleophiles under chiral phosphoric acid catalysis

is typically  $sp^2$ -hybridized. The attack of nucleophiles on  $sp^3$ -hybridized carbons under phosphoric acid conditions is relatively scarce. In 2013, List proposed that phosphoric acids may be able to bridge the trigonal bipyramidal transition state required for a  $S_N2$  reaction on a secondary carbon center (Figure 162).<sup>333</sup>

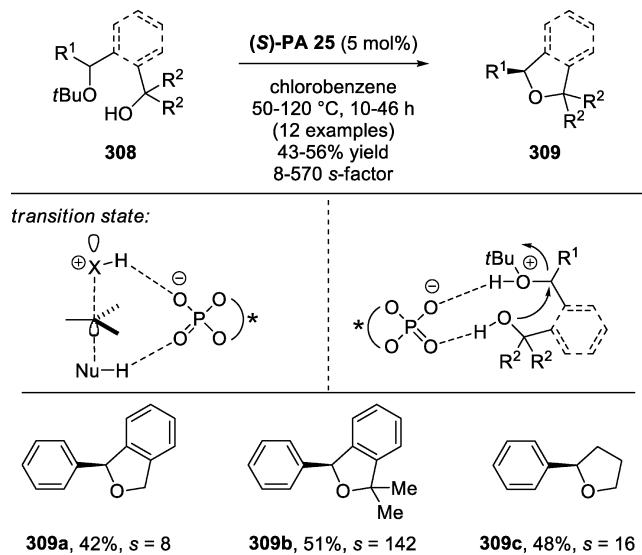


Figure 162. Resolution with  $S_N2$ -type O-alkylations by List (2013).

They decided to use benzylic ethers **308** as their test substrate with a pendant alcohol group to act as the nucleophile. Treating **308** with 5 mol % of catalyst (S)-PA **25** resulted in a resolution cyclization to give enantioenriched tetrahydrofurans **309** in good yields and with high *s*-factors. A bifunctional mechanism is proposed to be occurring as depicted in Figure 159. The catalyst is involved in activating the nucleophile and the leaving group so that a substitution reaction involving nucleophilic attack at the  $\sigma^*$  orbital of a  $sp^3$ -hybridized carbon atom occurs. To confirm that an  $S_N2$  reaction was indeed taking place, treatment of enantioenriched substrates resulted in inversion of the stereocenter with no loss of optical purity. Recently, a resolution of  $\alpha$ -substituted esters by selective lactonization using a chiral Brønsted acid has been shown by Petersen.<sup>334</sup>

In 2010, You demonstrated the potential of chiral phosphoric acids to catalyze a kinetic resolution of *N*-benzylic sulfonamides by using an indole as a nucleophile.<sup>72</sup> Although only a modest selectivity was achieved, it inspired Tian to improve this process by switching to a thiol nucleophile.<sup>335</sup> Using 10 mol % of catalyst PA **15**, it was shown that benzylic sulfonamides **310** would undergo a kinetic resolution via selective nucleophilic displacement by BnSH (Figure 163).

The products **(−)-310** were obtained in good yields with high levels of enantiopurity. It is thought that the thiol nucleophile is better at capturing the carbocation and preventing any unwanted recombination of the sulfonamide group once it has been eliminated. Measurement of the kinetics revealed it to be a  $S_N1$  reaction, indicating it to be first order in sulfonamide and phosphoric acid but zero order in thiol.

Recently, Takasu has demonstrated the kinetic resolution of secondary alcohols using chiral phosphoric acids. He was able to show a remarkably mild and simple procedure for the resolution of racemic alcohols  $(\pm)$ -**311** using an electronically tuned catalyst

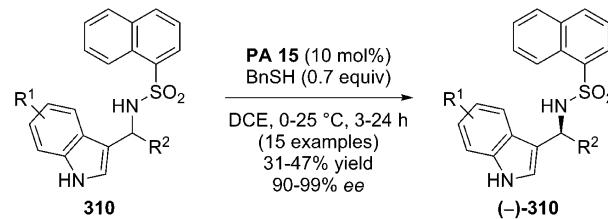


Figure 163. Resolution of *N*-sulfonamides by Tian (2012).

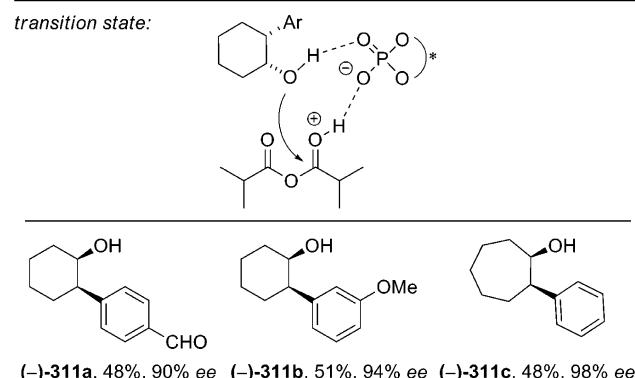
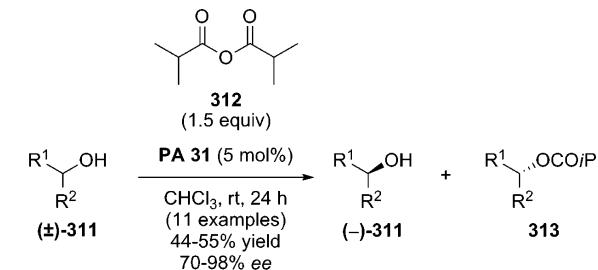


Figure 164. Kinetic resolution of secondary alcohols by Takasu (2013).

(PA **31**). In the presence of anhydride **312**, a clear preference for one enantiomer to react was shown (Figure 164).<sup>336</sup>

The products **(−)-311** and **313** were generally obtained in close to the theoretical yield of 50% and also with high levels of selectivity. Calculations by the group suggest a bifunctional mechanism involving coordination of one alcohol enantiomer and protonation of the anhydride.

In 2012, Akiyama was able to demonstrate the kinetic resolution of diketones **306** using 10 mol % of chiral phosphoric acid PA **25** (Figure 165).<sup>337</sup> The resolution occurred by

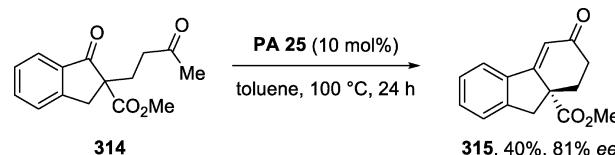
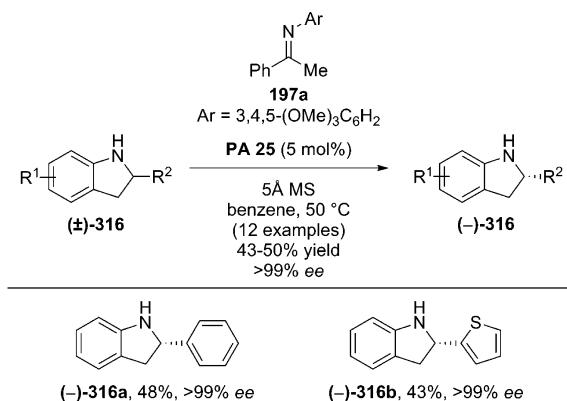


Figure 165. Resolution via an aldol-dehydration by Akiyama (2012).

a Robinson-type annulation, which was able to distinguish between the two enantiomers of **314**.

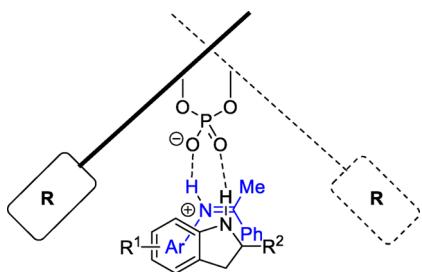
The aldol-dehydration product **315** was obtained in good yield and modest selectivity. Theoretical calculations suggested that a bifunctional coordination is responsible for the resolution process.

In 2013, Akiyama published the first efficient oxidative kinetic resolution of indolines using chiral phosphoric acids to mediate a transfer hydrogenation reaction. It was shown that *rac*-indolines ( $\pm$ )-**316** could be discriminated by catalyst **PA 25** so that one enantiomer would preferentially be resolved by reaction of the opposite enantiomer. The opposite enantiomer was removed by effectively being oxidized by transfer hydrogenation to aryl imine **197a**. The remaining enantiomer ( $-$ )-**316** was left untouched and isolated in extremely high enantiomeric excess (Figure 166).<sup>338</sup>



**Figure 166.** Kinetic resolution of indolines using an oxidative kinetic resolution by Akiyama (2013).

Preliminary mechanistic experiments suggest that the high selectivity arises from the repulsions between the bulky aryl group on the imine and the substituents on the catalyst. The calculated transition state for hydride transfer is predicted to be where the imine is oriented in an *s-cis* form while the lower energy indoline enantiomer delivers a hydride to it (Figure 167).

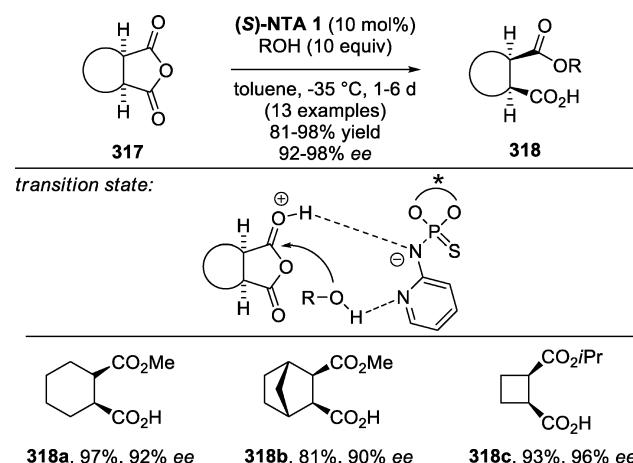


**Figure 167.** Calculated transition state for the kinetic resolution of indolines.

**2.3.14. Desymmetrization.** The bifunctionality of commonly used BINOL-based Brønsted acids can be a powerful tool in catalyzing reactions with high degrees of selectivity. Aside from modifying the substituents at the 3- and 3'-positions, there are a number of other variables that can be changed to improve the catalyst to perform a particular reaction in mind. Most of that attention has been paid to the Brønsted acidic site, but very few have looked at altering the Lewis basic site. In

2010, List decided to incorporate a more basic site into the catalyst while retaining the acid functionality.<sup>339</sup> The aim was to perform a desymmetrization of meso cyclic anhydrides **317**.

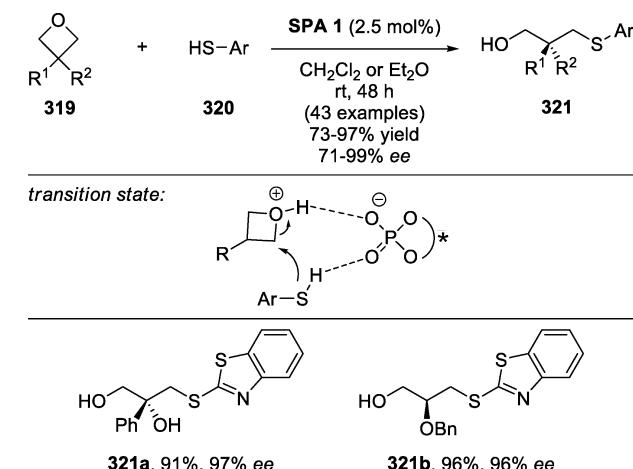
After some optimization, it was found that (*S*)-NTA **1** could be utilized in 10 mol % in conjunction with simple alcohols to effect the desymmetrization of **317** by ring opening to give the products **318** in good yields and high enantioselectivities (Figure 168). It is thought that acidic activation of the carbonyl



**Figure 168.** Desymmetrization using a bifunctional catalyst by List (2010).

occurs as expected, but now the attached pyridine motif can act as a much stronger activator of nucleophiles by coordination to the acidic proton. The synthetic utility of the process was demonstrated with a formal synthesis of (+)-grandisol.

In 2013, Sun recognized the potential of ring opening prochiral oxetanes to build up useful chiral building blocks. His strategy involved taking 3-substituted oxetanes **319** and opening them with various aromatic thiols **320** (Figure 169).<sup>340</sup> Although



**Figure 169.** Desymmetrization of oxetanes by Sun (2013).

BINOL-based phosphoric acids gave poor levels of selectivity, it was found that spirocyclic catalyst **SPA 1** could be employed in as little as 2.5 mol % to effect high levels of enantioselectivity.

The three carbon unit products **321** were obtained in good to high yields with high levels of selectivity. The mechanism is proposed to be bifunctional with coordination of the oxetane and the thiol to the catalyst. Evidence of the interaction

between the catalyst and the oxetane was seen by  $^1\text{H}$  NMR. When the catalyst is introduced to the oxetane, the chemical shifts of the protons change and become more complex, suggesting an interaction that is creating a chiral environment around the oxetane. Recently, a desymmetrization of *meso*-epoxides by thiols using a chiral phosphoric acid has also been shown by Sun.<sup>341</sup>

**2.3.15. Cascades.** The construction of complex molecules is a challenge in organic chemistry that has received a large amount of attention. The systematic approach is undoubtedly a useful tool for chemists but usually involves multiple steps, which can be lengthy and wasteful. The use of cascade (or domino) reactions has emerged as a more powerful technique to construct complex targets in a rapid and direct fashion.<sup>342</sup> The use of imines as substrates for chiral phosphoric acid-catalyzed transformations is well-known, but the extension to cascade reactions is less well studied perhaps due to the difficulty in achieving high levels of control both on the process and on the selectivity. In this section, the reactions can be all considered to be functioning by bifunctional activation by the catalyst. In each case, the enantioselective step is produced via reactions already discussed. For that reason, the mechanisms in this section will not be discussed in detail.

In 2007, Terada published a one-pot entry to enantioenriched piperidines using a cascade process that involved 2 equiv of enamine **293** along with various Boc-protected imines **7** (Figure 170).<sup>343</sup>

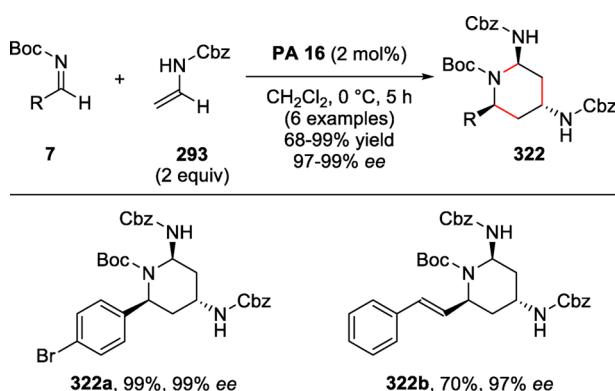


Figure 170. Cascade reaction involving an aza-ene/cyclization by Terada (2007).

The process formally involves two successive aza-ene reactions followed by a cyclization to form the piperidine ring system. The reaction works well to deliver piperidines **322** in good yields with very high enantioselectivity.

The challenge of catalyzing cascade reactions involving multiple steps is to find a suitable catalyst that either promotes all of the steps or does not adversely affect any of the steps, and this can sometimes be difficult. In 2006, Rueping reported a rare example of the use of two Brønsted acids (one chiral and one achiral) to perform a cascade sequence comprised of a Mannich reaction followed by an aza-Michael reaction (Figure 171).<sup>201</sup>

They recognized that for the process to occur efficiently an acid of higher  $\text{pK}_a$  than typical BINOL phosphates was needed. After examination of a range of stronger achiral acids, AcOH was found to be the optimal catalyst for achieving high enantioselectivities. By taking a range of imines **52** with cyclohexanone **323** in the presence of 10 mol % of PA **6** and 20 mol % of AcOH, the cascade process was performed to give isoquinuclidines **324** in good yields and good selectivity. In the same year, Gong also

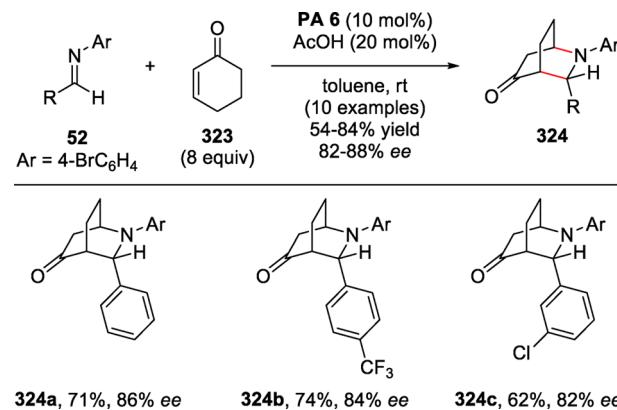


Figure 171. Cascade reaction involving a Mannich–Michael reaction by Rueping (2006).

published a similar protocol and found that a H<sub>8</sub>–BINOL catalyst on its own could catalyze the reaction to give the products in fairly good yields and enantioselectivities.<sup>344</sup>

In 2012, You published a cascade reaction of tryptamines **325** with  $\alpha,\beta$ -unsaturated carbonyls **99** to give pyrroloindolines **326** in an enantioselective manner (Figure 172).<sup>345</sup> The reaction utilized

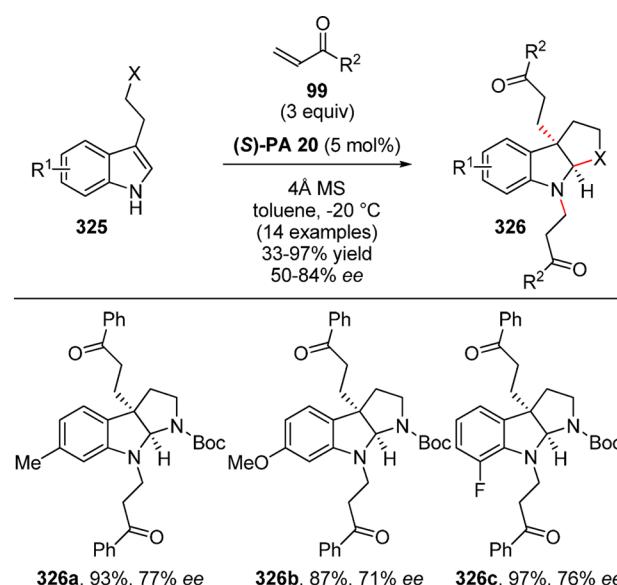
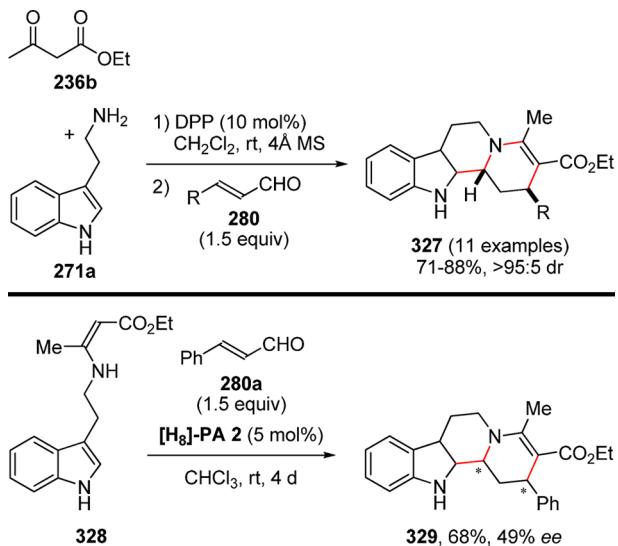


Figure 172. Cascade reaction involving a Michael-cyclization reaction by You (2012).

5 mol % of PA **20** in combination with 4 Å MS to give the optimal enantioselectivity.

The reaction consists of a Michael addition followed by cyclization of the pendant nucleophile (X = Nu–H). The reaction works best with aromatic ketones and nitrogen nucleophiles. In general, the reaction gives good yields and modest to high selectivity.

A rather exquisite example of a cascade reaction was presented by Rueping in 2011, which involved a one-pot operation to access indolo[2,3-*a*]quinolizidine skeletons starting simply from tryptamine. Initially, an achiral procedure was developed, which involved taking **271a** with  $\beta$ -keto ester **236b** and subsequent treatment with DPP followed by a series of  $\alpha,\beta$ -unsaturated aldehydes (**280**) to yield the polycyclic products **327** (Figure 173).<sup>346</sup> Formally, the process involves an initial



condensation between **271a** and **236b** followed by a Michael reaction, condensation, and then a Pictet–Spengler reaction. In general, good yields were obtained, and exceptional diastereoselectivity was observed in all cases.

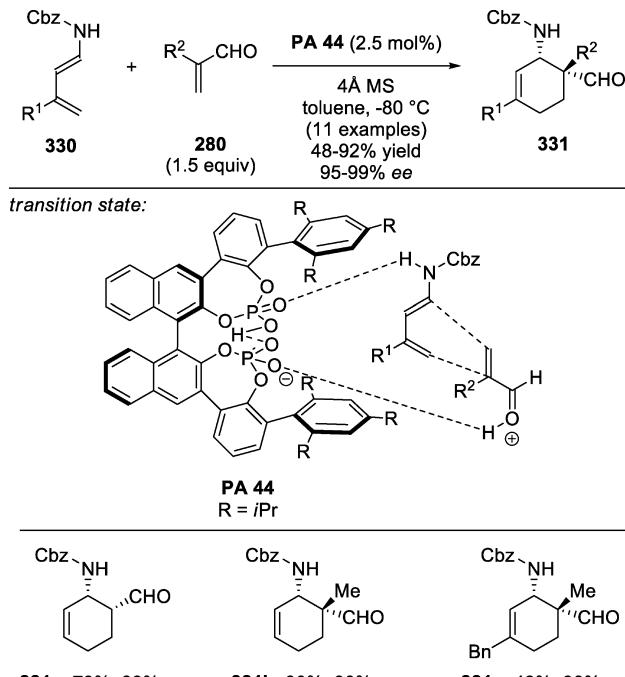
Extension toward an asymmetric variant involved taking tryptamine **328** with 5 mol %  $[H_8]$ -PA **2** and cinnamaldehyde **280a** to give the polycyclic product **329** in 68% yield and 49% ee. Although modest selectivity was achieved, it should be noted that the complexity of the transformation redeems this value.

**2.3.16. Miscellaneous Reactions.** Common strategies for influencing both the reactivity and the selectivity of BINOL-derived Brønsted acids are to vary the substituents at the 3- and 3'-positions and to increase the acidity of the catalyst. The introduction of alternative groups can sometimes be fruitful, and various examples have been presented already in this Review. In 2011, Terada introduced a new catalyst motif, which consisted of a diphosphoric acid possessing three points of axial chirality.<sup>347</sup> To assess the success of this catalyst, he applied it to the enantioselective Diels–Alder reaction between diene **330** and dienophile **280** (Figure 174).

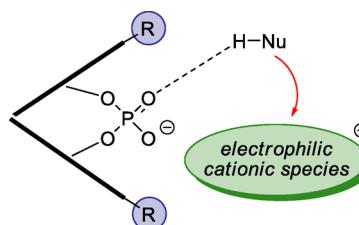
Using just 2.5 mol % of **PA 44**, a smooth reaction occurred to yield various cyclohexenes **331** in good yields and very high enantioselectivities. In comparison, when more commonly used monophosphoric acids were used, both the yield and the selectivity dropped even with increased loadings of catalyst. It is thought that through intramolecular hydrogen bonding between the acidic moieties of the catalyst, the acidity of one of the phosphoric acid units can be increased, allowing it to potentially activate less-basic substrates such as aldehydes in this case. This increased acidity of bis-phosphoric acids as catalysts has also been exploited by Hong to carry out enantioselective 1,3-dipolar cycloadditions.<sup>348</sup> The closely relatedaza-Diels–Alder reaction has also recently been disclosed by Masson who employs unsaturated imines with enamines in the presence of **PA 25**.<sup>349</sup>

#### 2.4. Counterion Catalysis

Most, if not all, of the reactions presented so far have involved the use of charged intermediates, but they have all been generated by protonation or hydrogen bonding by the phosphoric



acid catalyst. This leads to ambiguity when it comes to whether discrete ion-pairs are involved or a somewhat intermediate species where the proton is covalently between the catalyst and the substrate.<sup>45</sup> Recently, there has been an exponential growth in harnessing strict ion-pairings of charged intermediates with chiral counterions.<sup>350</sup> Chiral phosphoric acids have shown their versatility by demonstrating that their conjugate bases can be used as powerful chiral anions for highly enantioselective processes (Figure 175).



**Figure 175.** A generic schematic for chiral phosphate catalysis.

A generic schematic would involve the ion-pairing of a chiral phosphate anion with a cationic species that can react with a nucleophile in an asymmetric manner. Because of the presence of the Lewis basic site on the catalyst, there is also the possibility of hydrogen bonding available to any nucleophile containing acidic protons to help control the transition state further. It should be noted that counterion procedures occasionally employ discrete phosphate catalysts (usually as a metal salt), but in many cases the parent acid is also used. Generation of the phosphate occurs *in situ* usually by loss of a molecule (e.g., H<sub>2</sub>O). As one might expect, this can lead to users being innocently deceived about the true role of the catalyst.

In this section, we will aim to cover transformations where the enantioselective step of the reaction is controlled by a chiral

phosphate anion binding to a cationic species. Where possible, we will use our experienced opinion to clarify the role of the catalyst.

**2.4.1. Addition of Nucleophiles to Iminium Ions.** The List group was one of the first groups who started the field of using phosphate salts as chiral counterions in asymmetric transformations. They along with only a select few have been pioneering the use of phosphate amine salts as catalysts for asymmetric counteranion-directed catalysis (ACDC).<sup>29b</sup> One such catalyst salt popularized by the group has been **PA 41** (Figure 176).

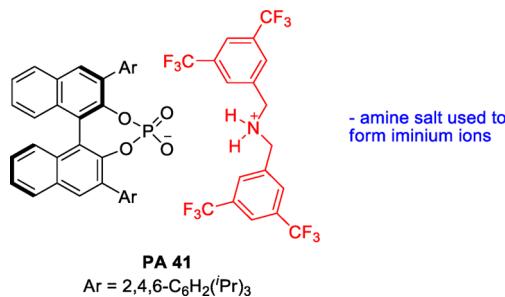


Figure 176. Phosphoric acid salt used by List.

The amine is specifically chosen as the counterion as it can be used to form cationic iminium ions with the substrate and hence allow for the chiral phosphate anion to control its selectivity upon reaction. In 2008, List used **PA 41** to perform an asymmetric epoxidation of enals with high levels of diastereo- and enantioselectivity being achieved. By taking enals **280** with <sup>t</sup>BuOOH and 10 mol % **PA 41**, the desired oxidation to the epoxides **332** was performed (Figure 177).<sup>351</sup>

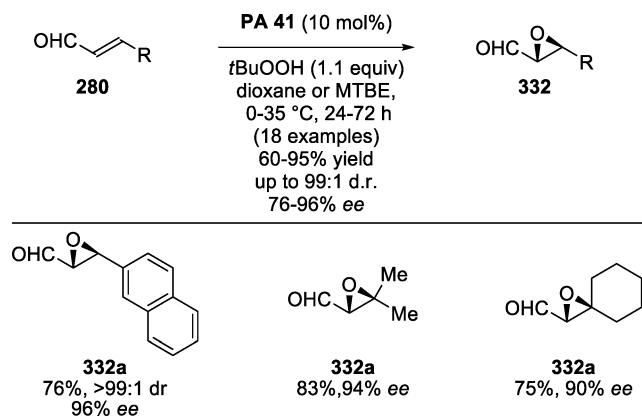


Figure 177. ACDC epoxidation by List (2008).

The role of the amine is very clear in that it has been included to form a cationic iminium species **333** by condensation with the aldehyde moiety. This allows the chiral phosphate to form an ion pairing and thus create a chiral environment for the subsequent attack by the peroxide to give intermediate **334**. Attack by the generated enamine then gives epoxide **335**, which can be hydrolyzed by H<sub>2</sub>O to give the products and regenerate the amine catalyst (Figure 178).

Both mono- and disubstituted enals could be epoxidized with good levels of control and in high yields. Interestingly, when equally disubstituted enals were used, the initial attack by peroxide generates no stereochemistry; however, the subse-

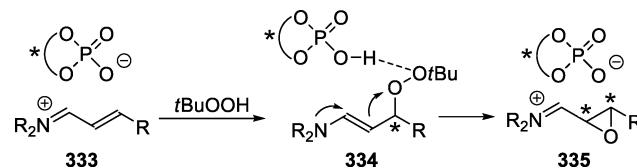


Figure 178. Mechanism for epoxidation (List).

quent attack by the enamine yields products with high enantioselectivity. This suggests that both steps in the mechanism may be controlled by the catalyst. The reaction has been extended to cyclic enones with high selectivities obtained by using a chiral amine salt of (*S*)-**PA 25**.<sup>351b</sup> The List group has also had major successes in using this strategy for the hydrogenation of unsaturated carbonyls.<sup>351c</sup>

The two most common ways for the generation of iminium ions are from two distinct functional groups: carbonyls and acetals. The latter category is less commonly utilized but is still a powerful method for generating these reactive intermediates. In 2010, Rueping showed this concept by taking hydroxylactams as *N*-acyliminium precursors<sup>352</sup> for participation in Friedel–Crafts reactions. Taking indole **60a** with lactam **336** and 5 mol % of [H<sub>8</sub>]-NPA **1**, the reaction proceeded smoothly to give the corresponding products **337** (Figure 179).<sup>353</sup>

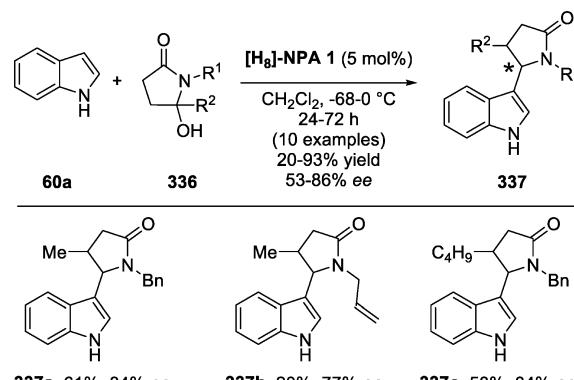


Figure 179. Addition to chiral *N*-acyliminium ions by Rueping (2010).

In this case, the free acid is being used to promote the loss of H<sub>2</sub>O from the starting material to generate iminium species **338** containing the bound phosphate anion. Stereoselective nucleophilic attack then leads to the product **339** (Figure 180).

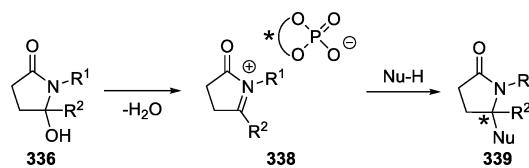


Figure 180. Generic mechanism for iminium formation and reaction.

This concept has also been explored by other groups in different situations.<sup>354</sup> One class of compounds that are relatively unknown to behave as *N*-acyl iminium precursors are unsaturated  $\gamma$ -lactams; however, in the presence of a Brønsted acid, they can be easily converted to the desired reactive species. Huang has been able to demonstrate this idea in 2011 with the enantioselective N–H functionalization of indoles. Taking lactam **340** with indoles **60**, the desired reaction

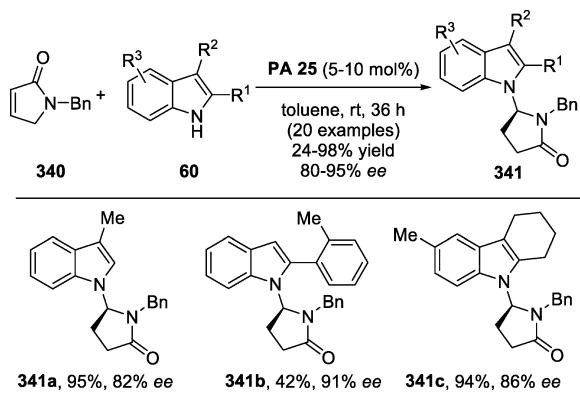
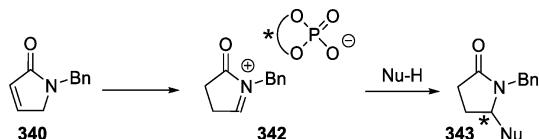


Figure 181. N–H functionalization of indoles by Huang (2011).

proceeded with phosphoric acid catalyst PA 25 to give the products 341 (Figure 181).<sup>355</sup>

The group also performed detailed mechanistic studies into the reaction mechanism using deuterium labeling experiments along with IR and HRMS techniques. They were able to obtain strong proof that N-acyl iminium species 342 was being formed under their reaction conditions (Figure 182).

Figure 182. Generic N-acyl iminium ions generated from unsaturated  $\gamma$ -lactams.

This species (342) goes on to react with the indole nucleophile to ultimately give the products 343. Deuterium labeling experiments also showed that extensive deuteration can occur by just stirring 340 for 5 h with a  $\text{DCO}_2\text{D}$ .

An interesting enantioselective example was presented by Bach in 2011, where he showed the use of a secondary *ortho*-hydroxybenzylic alcohol in a Friedel–Crafts reaction. The reaction of alcohol 344 and indole 60a in the presence of PA 10 gave the Friedel–Crafts product 345 in low yield and with modest selectivity (Figure 183).<sup>356</sup>

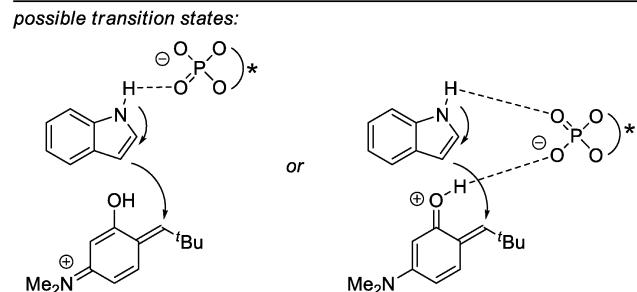
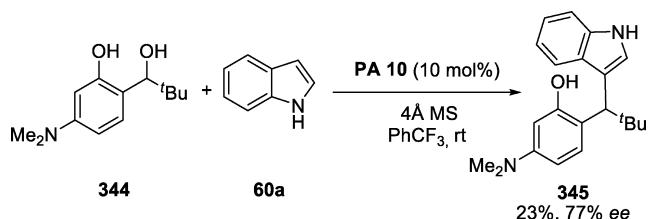


Figure 183. Friedel–Crafts reaction by Bach (2011).

The presence of an electron-donating group on the aromatic ring system was crucial, and dehydration to form a cationic species may be promoted by either the  $-\text{NMe}_2$  group or the  $-\text{OH}$  group to form a iminium or oxonium-like species, which can be intercepted by the indole. An equally modest kinetic resolution was also observed, but this was proved to not be the reason for obtaining enantiomerically enriched products.

The addition of nucleophiles to indolyl alcohols has also been studied by a few research groups with some success. One of the first reports was in 2009 by Gong who reported an enantioselective alkylation of enamides. Taking alcohol 346 with enamide 154 and catalyst  $[\text{H}_8]\text{-PA 10}$ , the reaction proceeded smoothly to give after an aqueous workup the alkylated products 347 (Figure 184).<sup>357</sup>

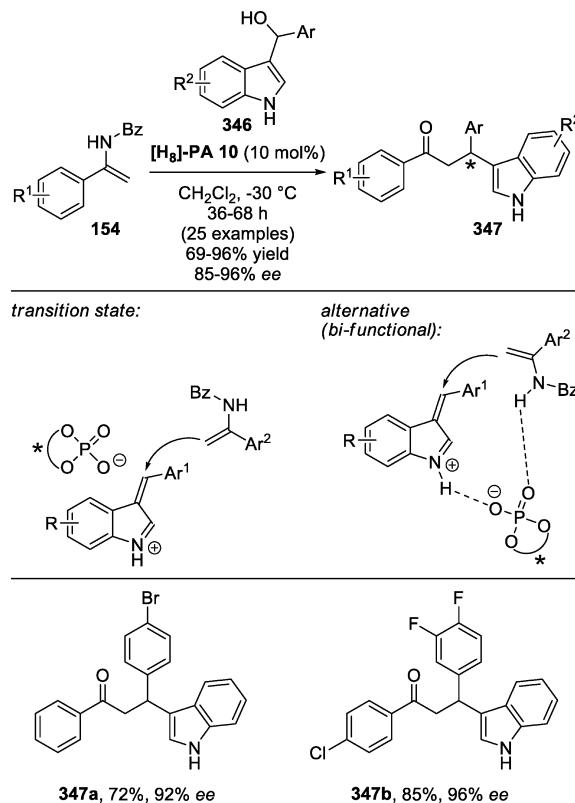


Figure 184. Alkylation reaction of enamides by Gong (2009).

The reaction boasts a broad scope and generally provides high selectivities of the products. The authors postulate a counterion role for the phosphoric acid catalyst for the generated iminium species upon elimination of  $\text{H}_2\text{O}$ . A similar intermediate has been described earlier by the Rueping group (cf., 71). It can however be envisioned that a bifunctional mechanism may be occurring whereby the catalyst coordinates to both the indole N–H and the enamine. This general concept has been extended to include different nucleophiles by the You<sup>358</sup> group and the Peng<sup>359</sup> group. The Guo group has also reported on this concept and used it toward a multistep one-pot synthesis of enantioenriched cyclopentaindoles.<sup>360</sup>

In 2011, Terada demonstrated the activation of an alkene conjugated to an indole skeleton to access enantioenriched tryptophan derivatives (Figure 185).<sup>361</sup> The method provides a highly complementary approach to the more typical displacement of a leaving group at the same position.

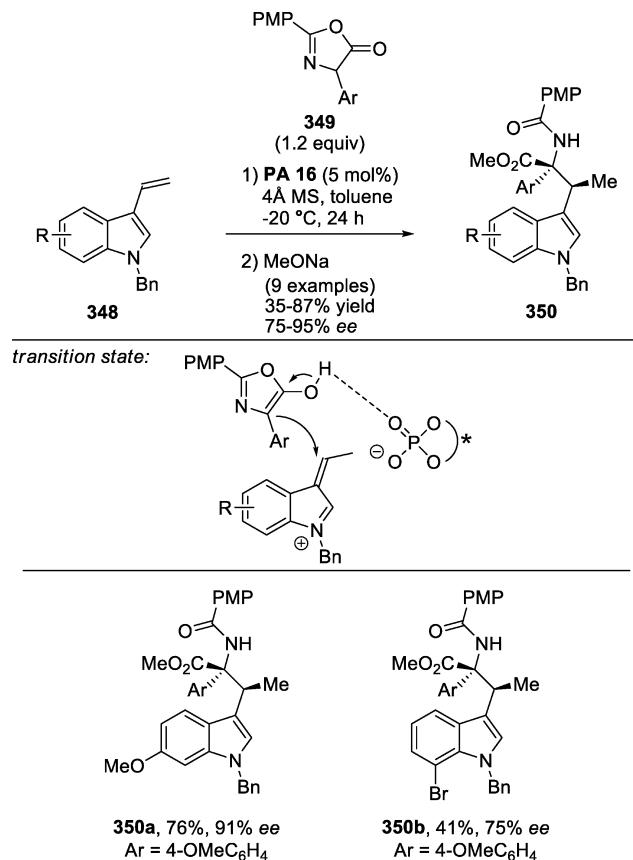


Figure 185. Additions to vinyl indoles by Terada (2011).

Terada demonstrated the concept by using aza-lactones 349 as nucleophiles that could react with vinyl indoles 348 in the presence of 5 mol % of catalyst PA 16. The corresponding product was hydrolyzed with MeONa to yield the tryptophan derivatives 350 in good yields and selectivity. Substituents on the alkene could be tolerated, but the products were obtained with lower selectivity. In addition, the geometry of the alkene was shown to have a large impact on the enantioselectivity with the (*E*)-isomer being favored. Mechanistically, we propose that initial protonation of 348 results in an iminium-species where the chiral phosphate can control the facial selectivity of attack from the aza-lactone possibly via coordination to the enol-tautomer.

In 2010, Antilla reported an interesting example, which also utilized in principle the same concept of carbocation generation from indolyl alcohols to perform a phosphate anion controlled Pinacol rearrangement. Taking diol 351 with [H<sub>8</sub>]-PA 5 performed the desired transformation to give the products 352 in high yields and high levels of selectivity (Figure 186).<sup>362</sup>

Once again, the reactive intermediate can be thought of as an iminium ion with the chiral phosphate controlling the selectivity and a possible hydrogen bond to the hydroxyl group.

In recent time, C–H activation has gained a tremendous amount of attention from research groups; however, the use of chiral phosphoric acids to facilitate the process in an enantioselective manner has rarely been exploited. In 2009, the Seidel group demonstrated that the *tert*-amino effect could be accelerated by the presence of a Brønsted acid catalyst.<sup>363</sup> Two years later, this process was shown by Akiyama, which allowed for the selective activation of C(sp<sup>3</sup>)–hydrogen atoms using a phosphoric acid catalyst. Taking compounds 353, it was

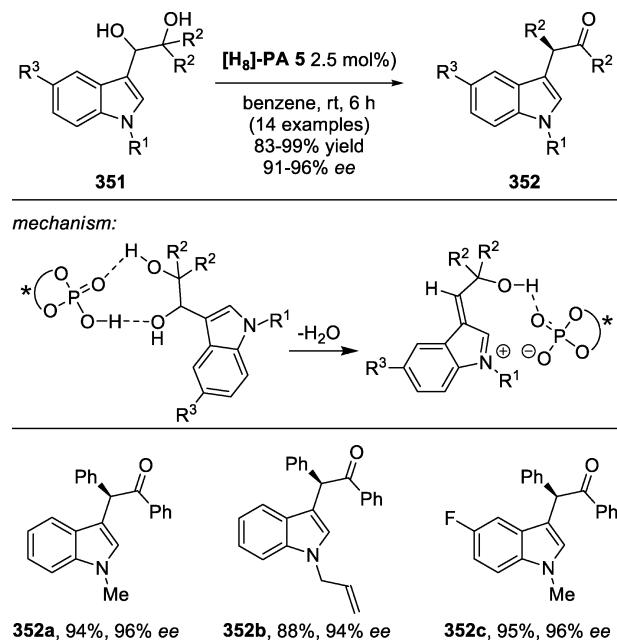


Figure 186. Pinacol rearrangement by Antilla (2010).

shown that a 1,5-hydride shift could be catalyzed by PA 34 to generate an iminium ion with a closely bound phosphate anion, which could be intercepted by the malonate to form tetrahydroquinolines 354 with high levels of selectivity (Figure 187).<sup>364</sup>

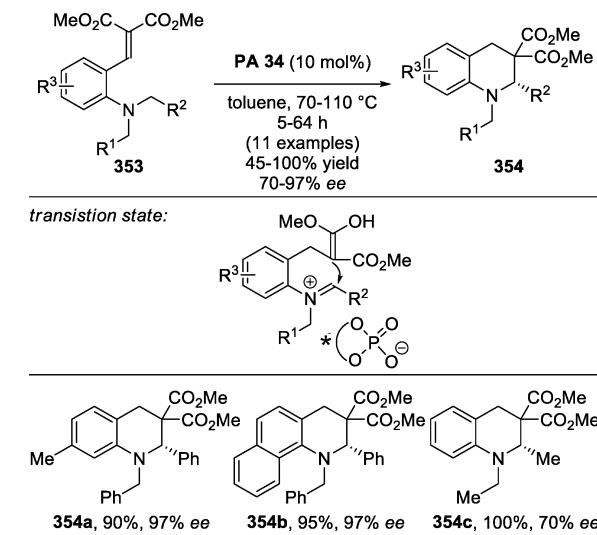


Figure 187. Activation of enantiotopic C(sp<sup>3</sup>)–hydrogen atoms by Akiyama (2011).

Preliminary mechanistic studies revealed that when enantio-merically pure starting materials are used (355) with an achiral catalyst, enantiopurity is mostly retained in the product 356 (Figure 188). This suggests that the hydride transfer may be the cause of the enantioselectivity rather than ring closure on to the iminium ion. Detailed calculations have been performed by Luo, which support this theory.<sup>365</sup>

A rather special example was presented by the Toste group recently on the generation of iminium ions by an *in situ* oxidant containing a chiral phosphoric acid anion. They found that by taking oxoammonium salt 358 with catalyst PA 39, they would undergo anion metathesis, which upon oxidation of the tetrahydroquinoline

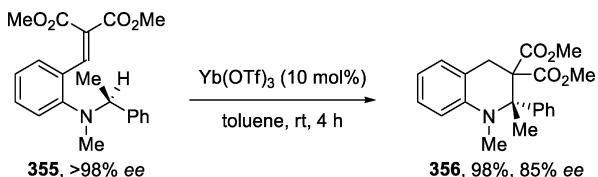


Figure 188. Retention of enantioselectivity from enantiopure starting materials.

would generate an iminium ion with a closely bound chiral phosphate ion. They designed tetrahydroquinolines **357** as candidates for the reaction, containing a pendant amide group that would intercept the iminium ion once formed (Figure 189).<sup>366</sup>

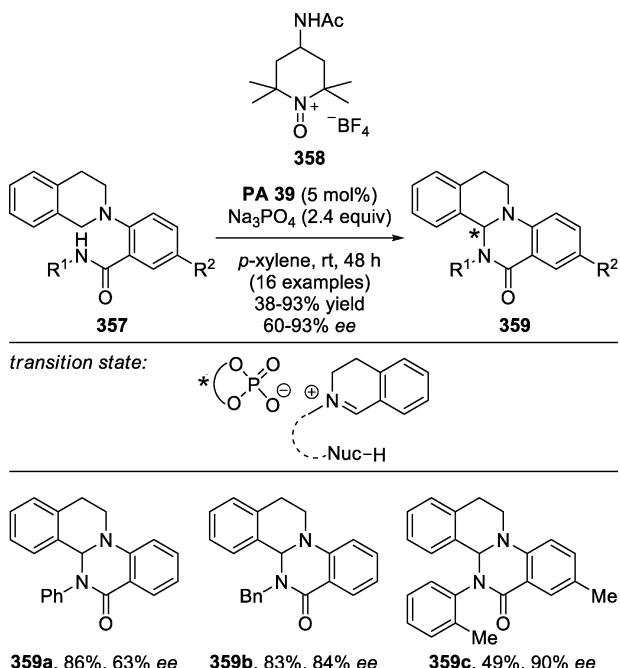


Figure 189. Asymmetric cross-dehydrogenative coupling by Toste (2013).

The reactions works fairly well to give the *N,N*-acetal products **359** in good to high yields and modest to high enantioselectivities. A survey of the commonly used phosphoric acids actually failed to give acceptable levels of selectivity. Instead, the group decided to develop triazole-containing catalysts, which are thought to aid in coordination to the nucleophile and improve the selectivity.

**2.4.2. Addition of Nucleophiles to Oxonium Ions.** The generation of oxonium ions and the ability to control the stereoselective nucleophilic addition toward them is a difficult process. The analogous process with imines is much more widespread, but reports with oxonium ions are scarce. A few groups have however reported the use of chiral phosphoric acid catalysts for diastereoselective glycosylation and protection reactions.<sup>367</sup>

Chiral acetals are a highly important motif found in natural molecules and include highly abundant compounds such as carbohydrates. In addition, chiral acetals are also found in pharmaceuticals, and so their importance is very clear. Despite this, methods to make acetals in an asymmetric manner are very limited. In 2010, List published the first catalytic enantioselective transacetalization reaction in an intramolecular manner

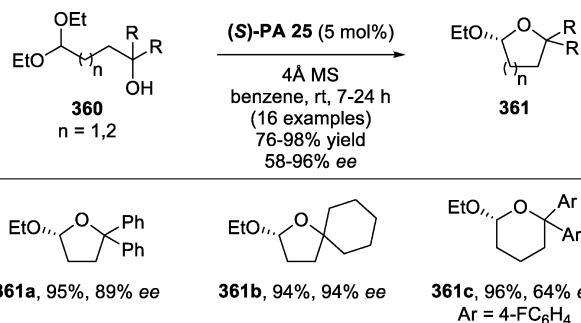


Figure 190. Transacetalization by List (2010).

(Figure 190).<sup>368</sup> Treating alcohols **360** in benzene with 5 mol % of catalyst (S)-PA 25 caused a cyclization–addition reaction to form cyclic acetal products **361** in good yields and high enantioselectivities.

Although the mechanism of the process is unclear, the authors clearly indicate the bifunctional nature of the catalyst is crucial and may well be involved in multiple hydrogen-bonding interactions with the substrate. It could be envisioned that activation of the acetal occurs by H-bonding with the catalyst while simultaneously interacting with the pendant hydroxyl group (Figure 191, **362**). Loss of EtOH would lead to an

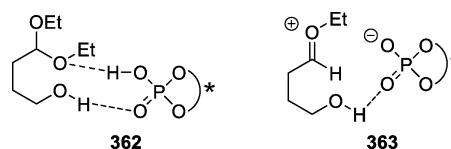


Figure 191. Possible interactions involved in the transacetalization reaction.

oxonium species (Figure 191, **363**), which contains a bound phosphate ion to facilitate the asymmetric cyclization step. It could however be also possible that an S<sub>N</sub>2-like mechanism is occurring with selective activation of one OEt group of the acetal.

The same group also published the kinetic resolution of secondary and tertiary racemic alcohols in the same year.<sup>369</sup> A related transformation has also recently been disclosed by Sun.<sup>370</sup>

In 2012, List designed a novel confined chiral Brønsted acid based on a C<sub>2</sub>-symmetric imidodiphosphoric acid, which enabled the catalytic synthesis of spiroacetals **365** (Figure 192).<sup>371</sup>

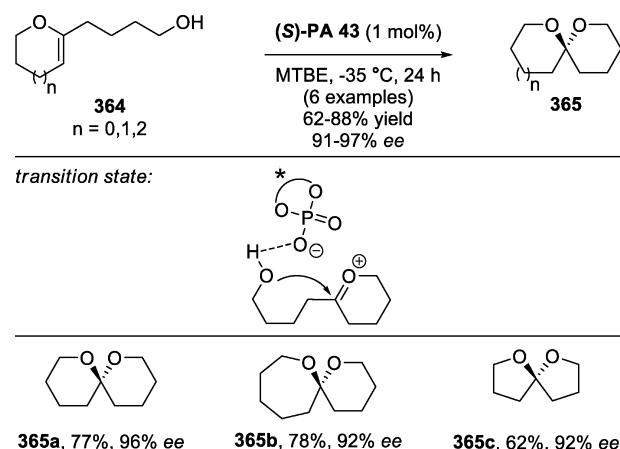
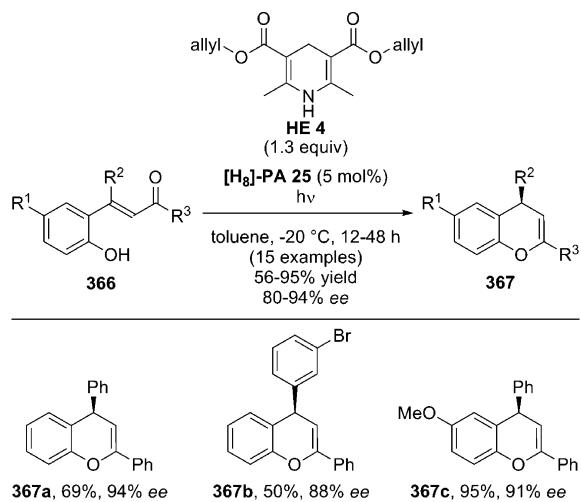


Figure 192. Spiroacetalization by List (2012).

Treating simple unfunctionalized alcohols **364** with just 1 mol % of catalyst (*S*)-PA **43** resulted in acetylation of the *in situ* generated oxonium ion.

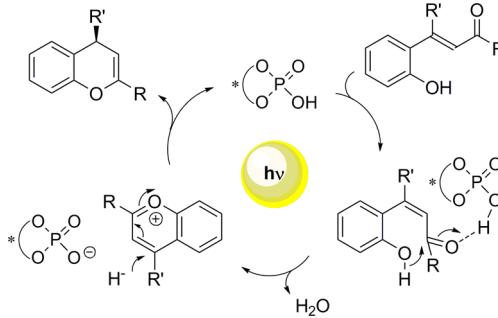
The rational for the new design was based on the observation that the commonly seen and previously used chiral acid catalysts tended to contain a highly open site, which involved the use of either highly sterically hindered substituents on the catalyst or highly bulky protecting groups on the substrate, both of which can be undesirable. The idea was to confine the substrate<sup>372</sup> by constraining the active site, which could be achieved with catalyst (*S*)-PA **43**. The imidodiphosphoric acids represent an exciting new class of catalysts and are easily accessible via one additional step when compared to the traditional phosphoric acid catalysts. They may also be able to overcome the need for high catalyst loadings that are featured in many of the processes using the more common catalysts. Also in 2012, Nagorny showed that the more commonly used phosphoric acid PA **25** could be used in 5 mol % loadings to carry out spiroketalizations.<sup>373</sup> In 2013, List reported a breakthrough in this area by describing an asymmetric acetalization reaction in an intermolecular fashion between diols and aldehydes.<sup>374</sup> Recently, Floreancig has also used chiral phosphates to control the addition of cyanide to *in situ* generated oxonium ions.<sup>375</sup>

Benzopyrylium ions are readily generated species due to their aromatic electron configuration, but their use in enantioselective procedures has been scarce. Recently, however, the first reports of their usage with chiral phosphoric acids have been developed. The first came from the Rueping group who disclosed a cascade process involving a light-mediated cyclization of phenols **366** followed by a Brønsted acid promoted hydrogenation to yield enantioenriched chromenes **367** (Figure 193).<sup>376</sup>



**Figure 193.** Hydrogenation of benzopyrylium ions by Rueping (2013).

The mechanism of the reaction is shown in Figure 194. It is thought that light-mediated cyclization occurs first to yield initially a chromen-2-ol and in the presence of the acid dehydrates to give the desired benzopyrylium ion with the chiral phosphate counterion. This is followed by a hydride transfer from the Hantzsch ester **HE 4**, which may also be guided toward the substrate via hydrogen-bonding interactions with the phosphate ion.

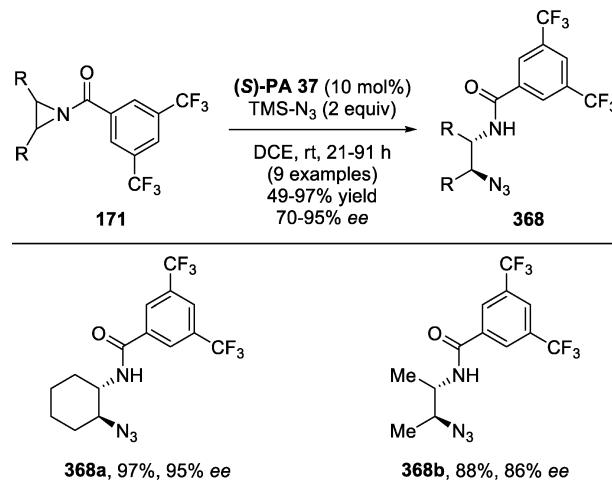


**Figure 194.** Mechanism of light-assisted hydrogenation of benzopyrylium ions.

Detailed mechanistic experiments revealed that the Brønsted acid was unable to catalyze the initial cyclization and the light was unable to promote the reduction, indicating both components were indeed needed for the reaction. More interestingly, a synergistic effect was observed in terms of a rate enhancement of both the cyclization and the reduction steps when both components were present; however, the cause of this remains uncertain. Also, very recently, Terada has also published his results on a related transformation that involves the hydrogenation of benzopyrylium ions generated from chromen-2-ols.<sup>377</sup>

#### 2.4.3. Addition of Nucleophiles to Silylated Aziridines.

Although the reactivity of imine substrates with nucleophiles has been shown to be readily possible with chiral phosphoric acids, aziridines have proven to be more difficult to activate toward nucleophilic attack. In fact, only a select few examples exist by which chiral phosphoric acids have been utilized for their ring opening. In 2007, Antilla disclosed the first of these publications on the desymmetrization of *meso*-aziridines (Figure 195).<sup>378</sup> Using 10 mol % of VAPOL-derived catalyst



**Figure 195.** Addition of TMS-N<sub>3</sub> into *meso*-aziridines by Antilla (2007).

(*S*)-PA **37**, it was shown that TMS-N<sub>3</sub> could be used as a nucleophile to open *meso*-aziridines **171** to give amides **368**.

The choice of the nitrogen protecting group was found to be critical for the success of the reaction. More traditional groups such as Boc or Cbz gave poor yields and racemic products. It was eventually found that the 3,5-di(trifluoromethyl)benzoyl group was the optimal protecting group to yield the products in

good yields and high enantiomeric excesses. Preliminary studies by the group into the mechanism suggest that activation of the aziridine starts by initial silylation of the amide group (**369**). This can be thought to occur directly from the reagent ( $\text{TMN}_3$ ) or from the prior formation of a silylated catalyst. This cationic intermediate then forms an adduct with the chiral phosphate derived from the catalyst (Figure 196). Intermediate **369** now under a

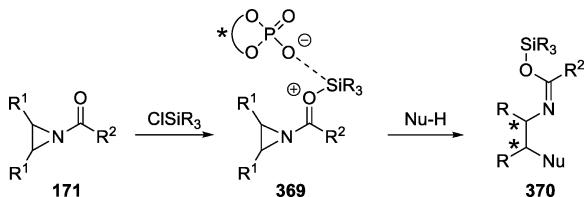


Figure 196. Proposed generic activation of aziridines.

chiral environment can react with the nucleophile stereoselectively to give **370**, which can be hydrolyzed to give the products.

When  $\text{TMN}_3$  is replaced for  $\text{HN}_3$ , no reaction is observed, but in the presence of trimethylsilyl chloride, the reaction is seen to proceed again. The Della Sala group has also published results on the desymmetrization of *meso*-aziridines with silylated sulfur<sup>379</sup> and selenium<sup>380</sup> nucleophiles. In 2013, they published their detailed studies into the mechanism of this process and found that metal impurities may be playing a role in the mechanism.<sup>381</sup> They propose that magnesium and calcium impurities function as Lewis acids; however, a phosphate anion is still involved and along with the aziridine coordinates to the metal center during the transition state.

**2.4.4. Addition of Nucleophiles to Carbocations.** The addition of nucleophiles to  $\text{sp}^2$  centers either by Brønsted acid activation or through a close contact ion-pairing with phosphoric acid catalysts has received a great deal of attention; however, the corresponding addition to  $\text{sp}^3$  centers, in particular to carbocations in an asymmetric manner, has been sparsely reported on. This may be a reflection of the increased difficulty in successfully activating carbocation systems as a close ion-pairing is required to create a strongly chiral environment. The first example of the use of chiral phosphates in cation pairing was reported by the Rueping group in 2011 in an asymmetric allylic substitution reaction. It was shown that phenols **371** in the presence of  $[\text{H}_8]\text{-NPA}$  **6** effected the dehydrative cyclization reaction to yield 2*H*-chromenes **372** (Figure 197).<sup>382</sup>

The mechanism of the reaction was explored and when enantiomerically enriched starting materials were used in conjugation with an achiral catalyst, all stereochemical information

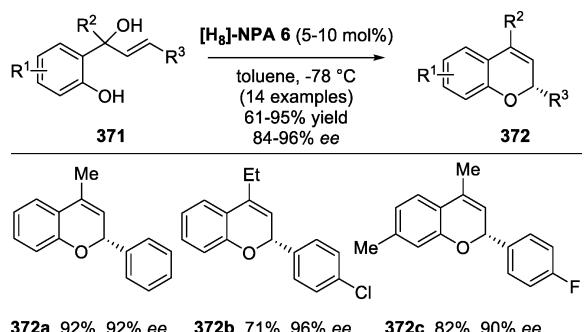


Figure 197. Contact ion pair allylic substitution by Rueping (2011).

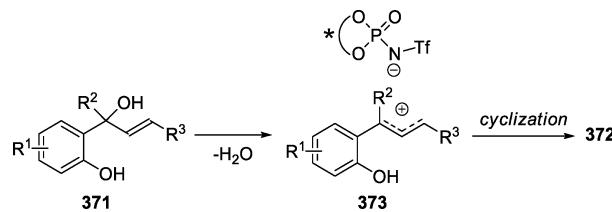
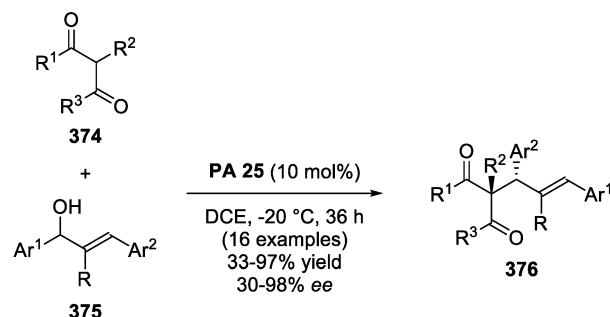


Figure 198. Allylic substitution mechanism (Rueping).

was lost, suggesting that the reaction proceeds via an initial dehydration to yield allylic cationic intermediate **373** (Figure 198). Subsequent cyclization of the alcohol group that may be involved in hydrogen-bonding interactions with the catalyst yields the desired product.

Recently, the Gong group has utilized this concept in an intermolecular fashion. He was able to show that 1,3-dicarbonyls **374** could be used as nucleophiles to react with carbocations generated from allylic alcohols **375** in the presence of chiral phosphoric acid **PA 25**.<sup>383</sup> The products **376** were obtained generally in good yields and with high enantiomeric excess (Figure 199).



application:

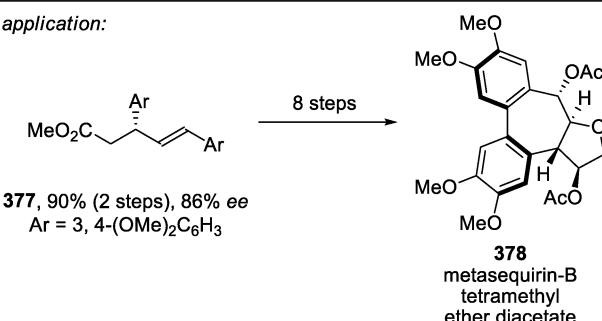


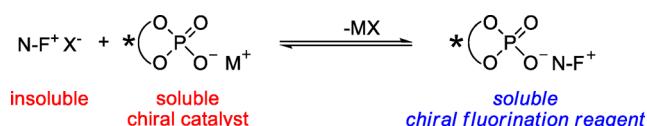
Figure 199. Allylic alkylation and application to natural product synthesis by Gong (2014).

The methodology was also shown to be applicable to the total synthesis of two members of the metasequirin family. Using the developed methodology followed by a decarboxylation, intermediate **377** could be prepared in 90% yield and 86% ee. A further six steps was required for the first family member in the series, and an additional two was all that was needed to complete the synthesis of **378**.

**2.4.5. Phase-Transfer Catalysis.** Phase-transfer technology has been known to the chemistry community for a long time, and it has found many uses in industrial applications. There are many advantages of performing any given process under phase-transfer, for example, faster reaction rates or fewer by-products. The development of asymmetric phase-transfer technology has also received a great deal of attention and has

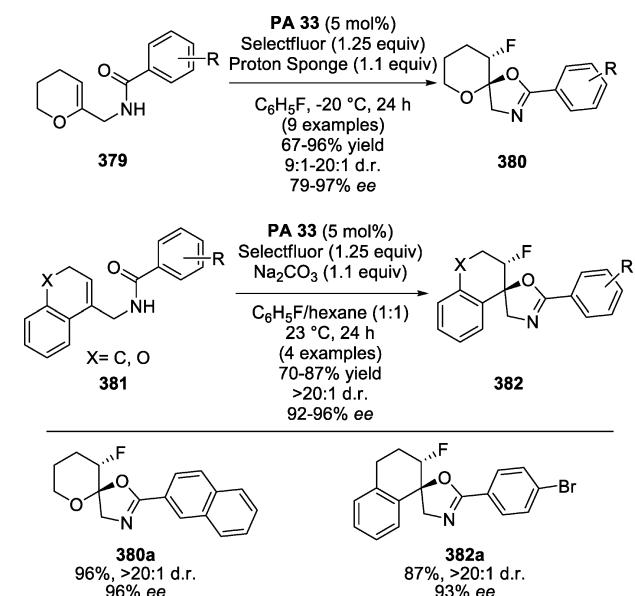
been immensely successful. Within this framework, the classic reaction would involve the pairing up of a chiral cation salt with an anionic reactant/reagent, which is soluble in the reaction medium of choice to undergo reaction. Quite surprisingly, the opposite technology of using a chiral anion with a cationic reactant/reagent has received less attention.

In 2011, Toste published the concept of utilizing chiral phosphates with a cationic reagent to effect an asymmetric fluorination under phase-transfer conditions. Although organocatalytic enantioselective methods<sup>384</sup> exist for fluorinations, before this report it had not been disclosed under phase-transfer conditions using chiral anions.<sup>385</sup> The reagent of choice was chosen to be the highly insoluble electrophilic fluorinating agent Selectfluor. By combining the insoluble reagent with a soluble phosphate catalyst, the group aimed to form a soluble chiral fluorination reagent (Figure 200).



**Figure 200.** Phase-transfer concept using phosphoric acids.

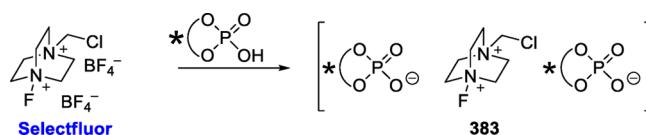
After some optimization of the solvent options, they found that C<sub>6</sub>H<sub>5</sub>F or a mixture with hexane were both suitable for ensuring that the Selectfluor reagent could only be solubilized when paired up with the chiral phosphate anion. With this system they initially reported the enantioselective fluoro-cyclizations of enol ethers 379 and aromatic alkenes 381 (Figure 201).<sup>386</sup>



**Figure 201.** Electrophilic fluorination using phase-transfer by Toste (2011).

The oxazoline products **380** and **382** were obtained in good yields and high enantioselectivities. Another benefit of the phase-transfer system was that substrates that were incompatible with a homogeneous system were shown to work better under phase-transfer conditions possibly due to the low concentration of the active fluorinating agent present at any given point during the reaction. Toste also carried out some preliminary mechanistic experiments on the process.

By analysis of the effect on enantioselectivity from varying purities of the catalyst, a nonlinear relationship was found. From this it was proposed that 2 equiv of chiral phosphate undergoes metathesis with the 2  $\text{BF}_4^-$  counterions contained within Selectfluor to generate intermediate 383 (Figure 202).

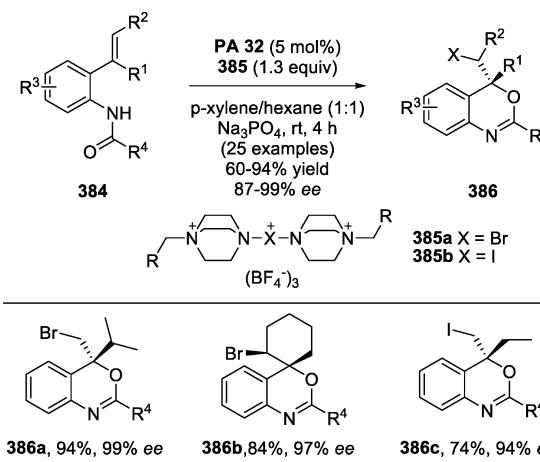


**Figure 202.** Generated species in solution

This intermediate can go on to fluorinate the alkene, and subsequent cyclization of the pendant amide group yields the products. The phosphate catalyst is regenerated by the inorganic base  $\text{Na}_2\text{CO}_3$  and can then participate in the catalytic cycle again. The Toste group has vastly explored this state-of-the-art concept and utilized the phase-transfer system toward a wide range of enantioselective processes.<sup>387</sup> The displacement of anionic counterions with chiral phosphates has also been used by Suga to perform kinetic resolutions of secondary alcohols.<sup>388</sup>

In further studies on their phase-transfer system, Toste also investigated the phase-transfer of alternative electrophilic reagents that could be used toward carrying out enantioselective transformations. To that extent, they looked into electrophilic halogen reagents based around the Selectfluor structure and were able to synthesize **385a** and **385b** through relatively straightforward procedures.<sup>389</sup>

Taking 385 with catalyst PA 32 in a *p*-xylene/hexane mixture afforded a soluble chiral halogenating agent, which could be used to react with unsaturated amides 384 to effect a halogenation–cyclization reaction to give 386 (Figure 203). In



**Figure 203.** Halocyclization by Toste (2012).

general, the yields of **386** were good and the enantioselectivities high. The phase-transfer system allows the catalyst loading to be dropped to as low as 0.1 mol % while similar selectivities could still be achieved.

An exquisite example of this phase-transfer system being used in a practical application has been demonstrated by Xie, Lai, and Ma.<sup>390</sup> The groups initially developed an asymmetric bromo-cyclization of tryptophans 387 using DABCO-derived bromine salt 388 (Figure 204). The reaction was extremely

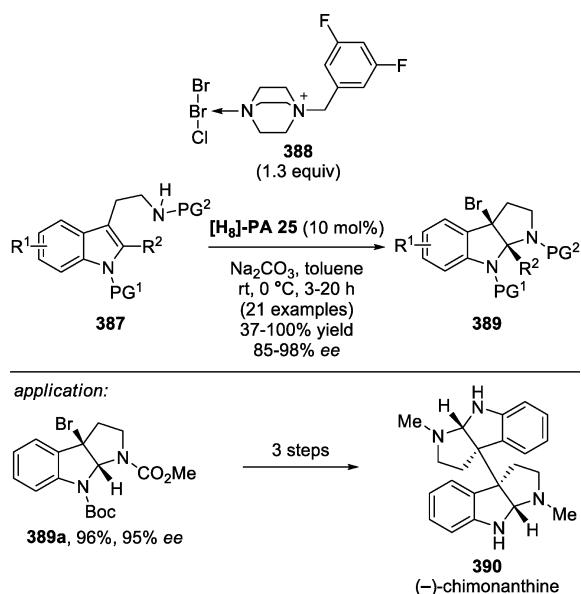


Figure 204. Bromo-cyclization of indoles and application to natural product synthesis by Xie, Lai, and Ma (2013).

efficient and generally gave both excellent yields and enantiomeric excesses of the products 389.

For application, the groups initially prepared pyrroloindoline 389a on a gram scale in 96% yield and 95% ee albeit with a prolonged reaction time of 3 days. This was then elaborated to the natural product 390 in three straightforward steps. The bromo-cyclization was also recently shown to proceed well with oxygen nucleophiles, and in this case the catalyst loading could be dropped to just 5 mol %.<sup>39b</sup>

The Toste group has also realized the potential of their phase-transfer system to carry out deracemizations, which can only be achieved due to efficient phase separations. They proposed a triphasic system as described in Figure 205.<sup>391</sup>

The system aims to keep the oxidant and reductant well separated so that unwanted quenching of their reactivity is

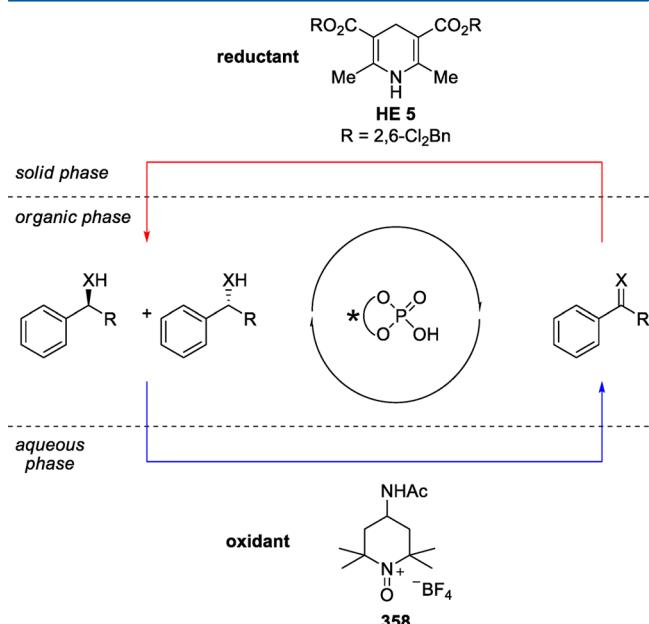


Figure 205. Phase separation model for the deracemization reaction.

minimized. The system aims to function by first taking a racemic compound and to perform an oxidation using oxopiperidinium 358 to yield an achiral molecule. This then can undergo a reduction by reacting with Hantzsch ester HE 5. The phosphoric acid aims to act as both the phase-transfer agent and the catalyst for performing an enantioselective reduction. They attempted to use this system toward the deracemization of indolines. Taking a range of indolines 391 with catalyst (*S*)-PA 25 with both oxidant 358 and reductant HE 5 in a triphasic system, they could afford the enantioenriched products (*S*)-391 (Figure 206).

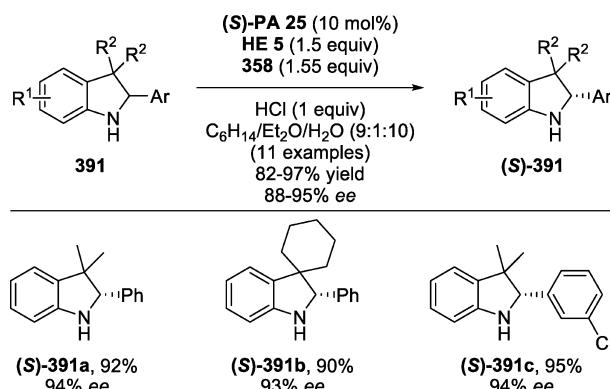


Figure 206. Deracemization of indolines by Toste (2013).

All results of the one-pot procedure were compared to that of a simple oxidation-reduction two-step procedure and were found to be identical in the majority of cases. When enantioERICALLY enriched starting material of the (*R*)-enantiomer was subjected to the reaction conditions, complete racemization to the (*S*)-enantiomer occurred.

So far the work presented in this category has involved the phosphoric acid acting solely as a chiral counterion to a cationic reagent to transfer it into the bulk reaction medium to react. Recently, Toste has exploited the structural feature of these acids to use them not only as a phase-transfer agent but also as a hydrogen-bond acceptor to direct reactivity in a molecule. By taking a range of alkenes 392 possessing a pendant secondary amide group, fluorination could be directed onto the alkene to give the corresponding products 393 (Figure 207).<sup>392</sup>

The setup in 392 is very similar to previous systems involving amide cyclizations, but mechanistic investigations revealed that a different mechanism is operating for the fluorination reaction (Figure 201). A stepwise process involving a latent carbocation is thought to be unrealistic due to the low polarity but instead a concerted process that involves coordination of the phosphate anion to the amide group, which facilitates the deprotonation and fluorination at the same time. The concept of coordination occurring along with phase-transfer catalysis with chiral phosphoric acids has also been recently shown by Alexakis in a Wagner-Meerwein rearrangement.<sup>393</sup>

The Toste group has recently pushed the boundaries of their fluorine phase-transfer system by combining it with classical enamine catalysis to asymmetrically fluorinate 2-substituted cyclohexanones.<sup>394</sup> A screen of various amino acids revealed hydrochloride salt 395 to be the best matched pairing for catalyst [*H*<sub>8</sub>]-PA 25. Crucial to the success and reproducibility of the reaction was the amount of H<sub>2</sub>O present in the inorganic base. After several optimizations, commercially available Na<sub>2</sub>CO<sub>3</sub>·H<sub>2</sub>O was found to be optimal for the desired reaction

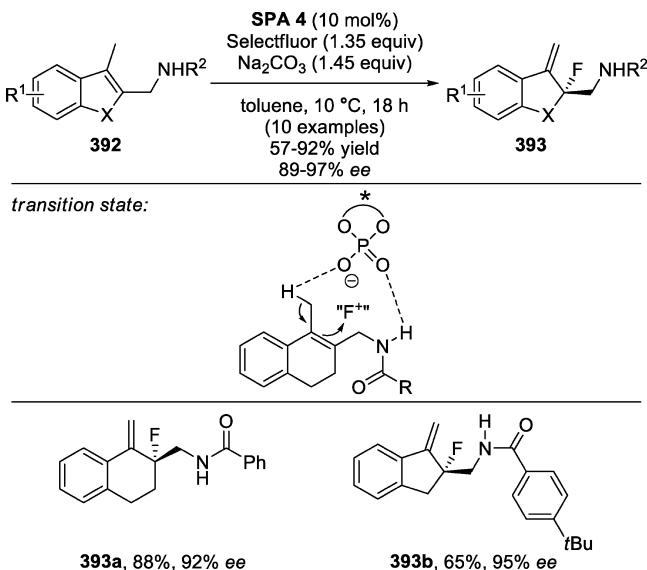


Figure 207. Combining direction groups and phase-transfer by Toste (2013).

and used as received. Treatment of *rac*-394 under the fully optimized conditions resulted in fluorination at the 2-position to give the products 396 in good yields and high enantiomeric excesses (Figure 208).

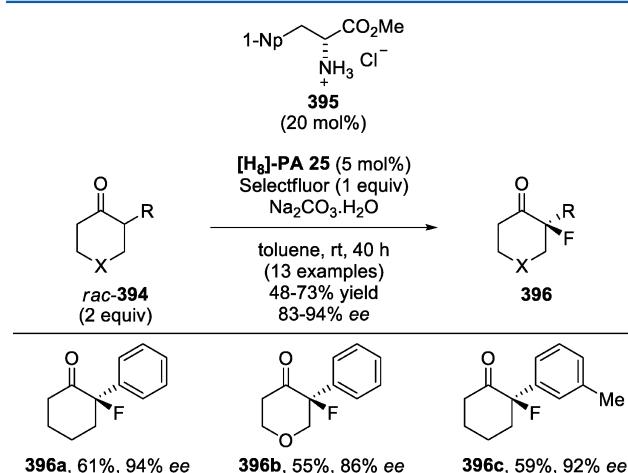


Figure 208. Combining direction groups and phase-transfer by Toste (2014).

Preliminary investigations into the mechanism of the reaction revealed that both the amino acid and the phosphoric acid catalysts work in tandem. The absence of either component resulted in a sharp decline of enantiomeric excess (<10% ee). In addition, when the opposite enantiomer of the amino acid catalyst is used, a drop in enantiomeric excess is also seen and suggests that a mismatched system is operating in this case.

**2.4.6. Cascades.** A major advantage of using chiral Brønsted acids as catalysts for asymmetric transformations is that they can also assist in accelerating other steps in the same pot that can be naturally catalyzed by acids. This opens a real opportunity in performing multiple processes in the same reaction pot using a single catalyst. The traditional Pictet–Spengler reaction has received attention from a couple of groups and has also been used in total synthesis.<sup>395</sup> The Dixon

group has been exploring this concept to a powerful degree over the past few years. In 2009, they reported an exquisite cascade reaction between tryptamines 271 and enol lactones 397 in the presence of catalyst [H<sub>8</sub>]-PA 2 (Figure 209).<sup>396</sup>

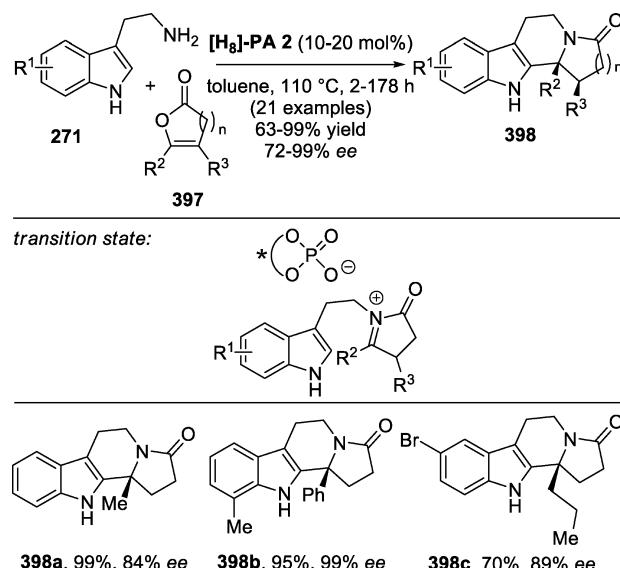


Figure 209. N-Acyliminium cyclization cascades by Dixon (2009).

The reaction is thought to proceed by initial acylation of the primary amine by 397 followed by condensation of the newly formed ketone with the secondary amine to yield an iminium ion (Figure 209). The iminium ion will contain the bound chiral phosphate ion, which helps to ensure that the correct enantiomer undergoes the final ring closure step to give the products 398. It is proposed that this intermediate can reversibly undergo epimerization via an enamine intermediate. This cascade process has been explored successfully by the Dixon group to include alternative acylating agents and a novel size exclusion phenomenon between PS-BEMP and sterically bulky phosphoric acids.<sup>397</sup>

**2.4.7. Miscellaneous.** Chiral phosphates have been shown to form close ion-pairs with a wide variety of positively charged species. Iminium ions and carbocations have received a great deal of attention, and more recently phase-transfer technology of cationic fluorinated agents has been pioneered by the Toste group. However, asymmetric reactions with more simple electrophilic halogenating agents have largely remained unexplored.<sup>398</sup> In 2012, Denmark published a rare example of the use of a chiral phosphoric acid to mediate an asymmetric halogenation reaction under normal reaction conditions. He showed that by taking unsaturated alcohols 195 with catalyst (S)-PA 25, NBS, and Ph<sub>3</sub>P=S as a Lewis base, an enantioselective cyclization could be accomplished (Figure 210).<sup>399</sup>

The reaction proceeds to give the products 196 in modest yields and selectivity, while the configuration of the brominated center is dependent on the starting geometry of the alkene in 195. The role of the Lewis base is to initially form a complex with the electrophilic bromine atom from NBS. This intermediate complex is thought to be able to be broken down by the chiral phosphate in the reaction medium (Figure 211).

This releases the Lewis base to go on to further extract Br from NBS and forms a chiral phosphate brominating agent. Upon contact with the alkene, a halonium ion is formed with a closely bound phosphate ion 399 and upon cyclization of the

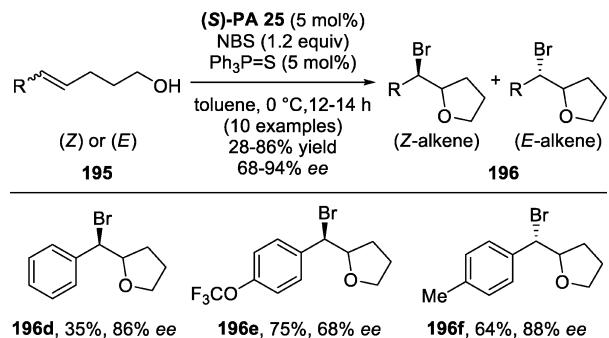


Figure 210. Bromocycloetherification by Denmark (2012).

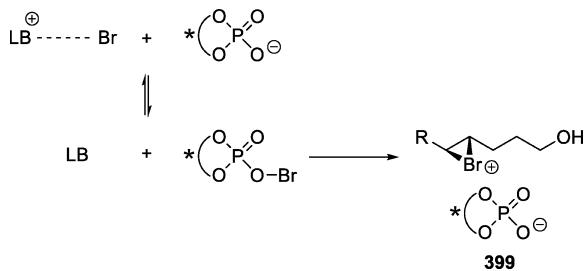


Figure 211. Possible mechanism for bromocyclization.

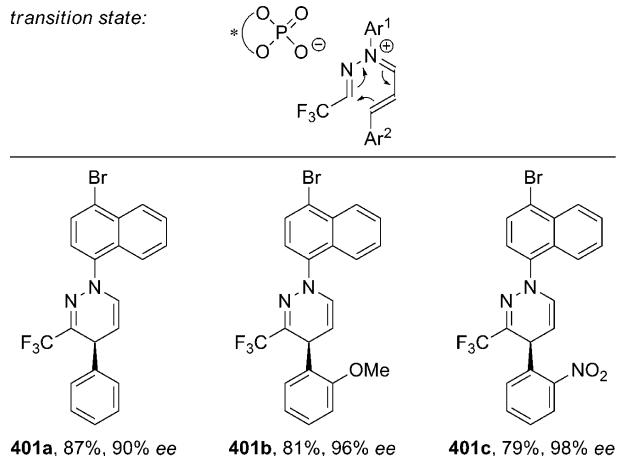
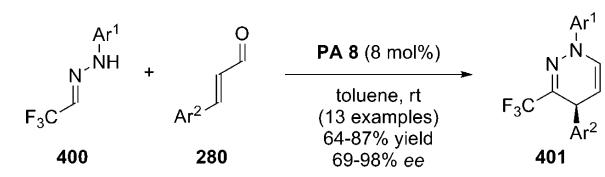
alcohol yields the products. Control experiments revealed that the reaction still proceeds in the absence of the Lewis base but at a much slower rate. It is worth noting that Shi has developed a very similar protocol, which is proposed to go via a bifunctional pathway (see Figure 102). Hennecke has also published a similar reaction by utilization of a chiral phosphate to control the selectivity of the ring opening of *meso*-halonium ions.<sup>400</sup> In 2012, Tang was also able to intercept *meso*-halonium ions with carboxylic acids in an intermolecular fashion catalyzed by a chiral Brønsted acid.<sup>401</sup>

Electrocyclizations are powerful processes, but very commonly they require high temperatures that can inhibit the ability to perform them in an asymmetric manner. As earlier described, List was able to develop the cycloisomerization of hydrazones whereby the catalyst activates the substrate by protonation.<sup>88</sup> The Rueping group decided to tackle a  $6\pi$  electrocyclization by forming a chiral contact ion pair with the substrate via a condensation reaction. They were able to show that **400** and **280** could react together in the presence of catalyst PA 8 to give 1,4-dihdropyridazines **401** in good yields and enantioselectivity (Figure 212).

The condensation of **400** and **280** leads to an iminium ion intermediate containing a closely bound chiral phosphate counterion. This is followed by a  $6\pi$  disrotatory cyclization whereby the phosphate controls the facial selectivity of the process. The formation of the iminium ion could be confirmed by ESI-MS measurements.

## 2.5. Enantioselective Protonations

Enantioselective protonations are attractive routes to enantioenriched compounds due to the pure simplicity of the transformation.<sup>403</sup> They are, however, quite difficult to perform and obtain high levels of selectivity. The largest problem facing successful enantioselective protonations is that they tend to occur too rapidly to be able to be controlled with high degrees of selectivity. Another common obstacle is that the newly formed center is usually prone to unwanted racemization. An additional aspect to consider for catalytic variants is the nature

Figure 212.  $6\pi$  electrocyclizations by Rueping (2013).

of the stoichiometric achiral proton source as this can also have a large effect on the reaction.

Chiral phosphoric acids are recognized as highly efficient activators of a variety of substrates through protonations; however, a large proportion of these substrates consists of basic nitrogen-containing electrophiles. Generally, the acidity of BINOL phosphoric acids is not sufficient enough to activate less basic substrates such as carbonyls. In 2008, Yamamoto was the first to develop a catalytic system, which could perform the enantioselective protonations of silyl enol ethers. First, a more acidic *N*-triflyl thiophosphoramido ((*S*)-NTA **3**) was synthesized from the starting BINOL precursors, and optimizations on the most suitable achiral proton source found phenol to perform best. With these conditions, it was shown that **402** could be asymmetrically protonated to yield **403** in high yields and generally high selectivity (Figure 213).

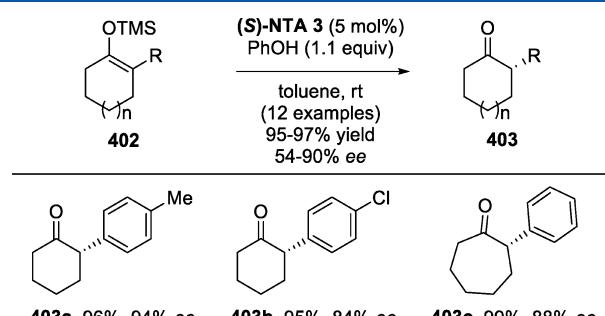


Figure 213. Protonation of silyl enol ethers by Yamamoto (2008).

It is intriguing to suggest a mechanism for the selectivity because no obvious points of interaction to the catalyst can be imagined. The Lewis basic site on the catalyst may be involved in coordination to the silicon group prior to protonation occurring. The catalyst loading could be lowered to as low as 0.05 mol % without any significant drop in enantioselectivity. Following this report, Rueping has shown that an *N*-triflyl

phosphoramidate catalyst can be used to facilitate Nazarov cyclizations and protonate the achiral intermediate with good levels of enantioselectivity.<sup>405</sup> Gong has also used an asymmetric protonation reaction using a chiral phosphoric acid to perform a dynamic kinetic resolution of azlactones.<sup>100b</sup>

The transfer hydrogenation of quinolines using chiral Brønsted acids is a well-established route to chiral 1,2,3,4-tetrahydroquinolines. Typically a Hantzsch ester is used as a hydride source to generate stereocenters, most commonly at the 2-position and in selected cases also at the 4-position. Substituents purely at the 3-position can also generate stereochemistry but do so by a protonation reaction (Figure 214).

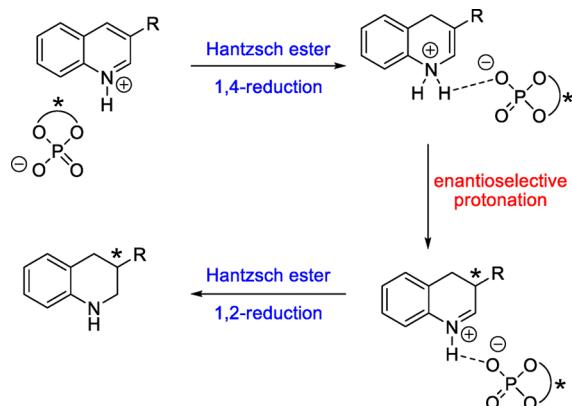


Figure 214. Generic mechanism for the reduction of 3-substituted quinolines.

In 2008, Rueping recognized the potential of using a chiral acid to control the protonation step occurring during the reductions and found that catalyst  $[H_8]$ -PA 2 gave the highest selectivities for the products **405** formed from **404** (Figure 215).<sup>406</sup>

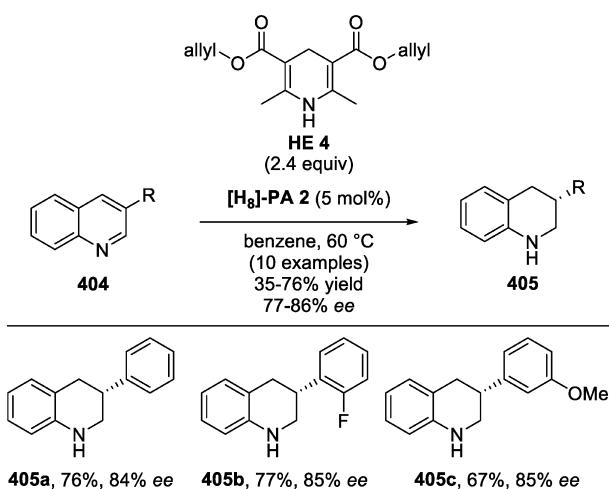


Figure 215. Reduction of 3-substituted quinolines by Rueping (2008).

During the optimizations, bulky aromatic-based substituents at the 3,3'-positions of the catalyst actually gave rather low selectivities; however, silicon-containing catalysts albeit also bulky ones performed well.

Silyl ketene imines (SKIs) are nucleophilic species that can be thought of as nitrile equivalents of ester (or amide)-derived silyl ketene acetals.<sup>407</sup> They are easily synthesized by deprotonation of the parent nitrile compound followed by selective

*N*-silylation with electrophilic silylating reagents. In 2013, List recognized that these compounds could be protonated to give access to enantioenriched  $\alpha$ -branched nitriles (Figure 216).<sup>408</sup>

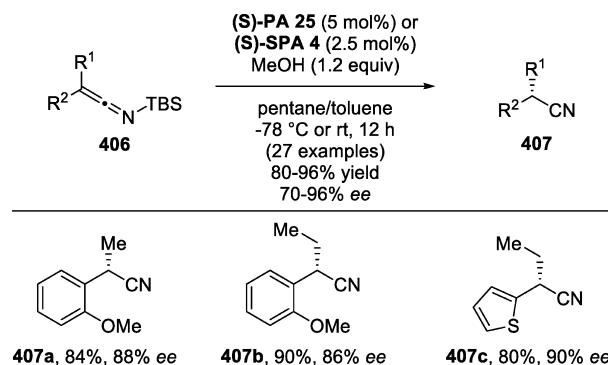


Figure 216. Protonation of silyl ketene imines by List (2012).

Taking SKIs **406** in the presence of **(S)-PA 25** or **(S)-SPA 4** and MeOH as the stoichiometric proton source, it was shown to give **407** in good yields and generally very high enantioselectivity. The silyl group was shown to have an influence on the selectivity of the reaction, and a mechanism is proposed in Figure 217.

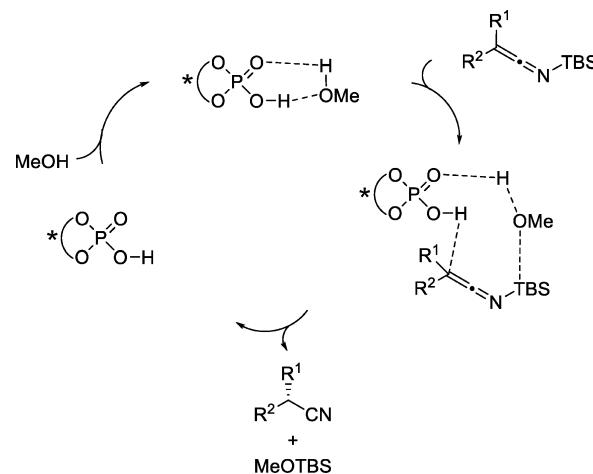


Figure 217. Protonation of silyl ketene imines by List (2012).

The mechanism proposed by the authors involves the initial formation of a complex between the methanol and the phosphoric acid, which as shown in the transition state can enantioselectively protonate the SKI and remove the silyl group. This results in silyl transfer to the methanol and simultaneous regeneration of the catalyst. A similar mechanism may be operating in the case of Yamamoto's protonation of silyl enol ethers.<sup>404</sup>

List has also shown the protonation of ketene dithioacetals via a catalytic protonation–cyclization sequence. Treating **408** with either **PA 20** or **PA 21** in cyclohexane resulted in the desired asymmetric sequence to yield **409** in high yields and excellent selectivities (Figure 218).<sup>409</sup>

The starting materials **408** were prepared from racemic  $\alpha$ -aryl hydrocoumarins, and so formally the process can be considered as a deracemization. The intramolecular cyclization of the phenol circumvents the need for a stoichiometric proton source in this case.

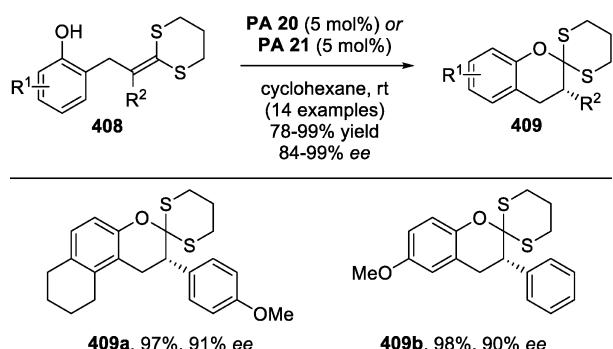


Figure 218. Protonation of ketene dithioacetals by List (2012).

## 2.6. Applications toward Natural Product Synthesis

As compared to the wealth of published literature involving chiral phosphoric acid-catalyzed methodology, the number of natural product syntheses utilizing such steps is relatively low. We have already mentioned numerous total and formal syntheses within the text of this Review where the actual methodology presented has been the greater focus.<sup>111</sup> In this section, we aim to highlight a few examples to demonstrate the potential of using chiral phosphoric acid catalysis with a clear synthetic purpose.

In 2012, Gong developed the asymmetric substitution of 3-hydroxyoxindoles with enamines to give the alkylated products containing a quaternary center in excellent enantioselectivities. To show the power of his methodology, he used it toward the synthesis of (+)-folicanthine.<sup>410</sup> Taking 3-hydroxyoxindole **410** with 10 mol % of (*S*)-**PA 6** and an enamine, the corresponding product **411** was obtained in 82% yield and 90% ee (Figure 219).

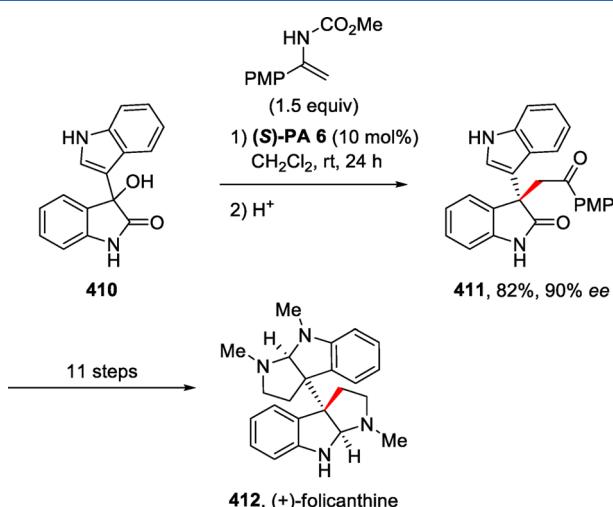


Figure 219. Asymmetric alkylation used in the synthesis of (+)-folicanthine by Gong (2012).

Following a further 11 steps, the total synthesis of **412** was completed. The mechanism is thought to involve a bifunctional mechanism with interactions between the catalyst and both the oxindole and the enamine being proposed. A similar asymmetric alkylation strategy was also demonstrated in the total synthesis of (+)-gliocladin.<sup>411</sup>

The group of Hiemstra has been involved in the development of several routes to chiral polycyclic molecules using the Pictet–Spengler reaction catalyzed by BINOL phosphoric

acids.<sup>395a,c</sup> In 2009, they showed the power of this methodology in the total synthesis of (−)-arboricine.<sup>395d</sup> In 2011, Hiemstra sought to build on his developed enantioselective Pictet–Spengler reaction to access the corynanthe alkaloids.<sup>412</sup> Taking indole **413** with aldehyde **414** and 2 mol % of catalyst [ $\text{H}_8$ ]-**PA 2**, a Pictet–Spengler reaction was performed to access the polycyclic motif **415** in 82% yield and 86% ee (Figure 220).

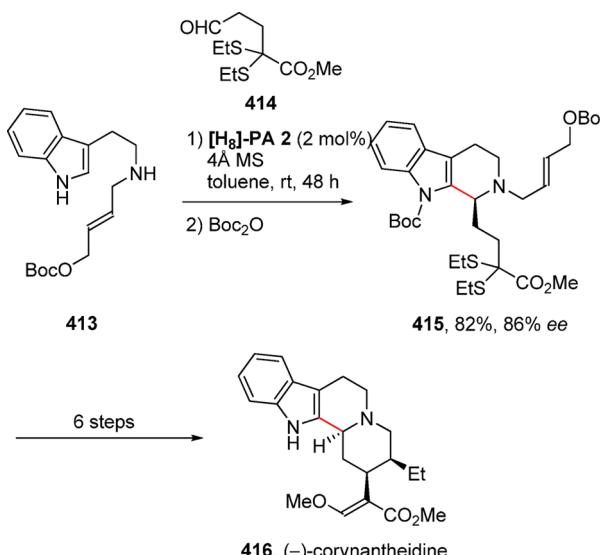


Figure 220. Total synthesis of (−)-corynantheidine by Hiemstra (2011).

After a further six steps, the total synthesis of (−)-corynantheidine **416** was completed. Access to other related structures that contained this core was also shown.

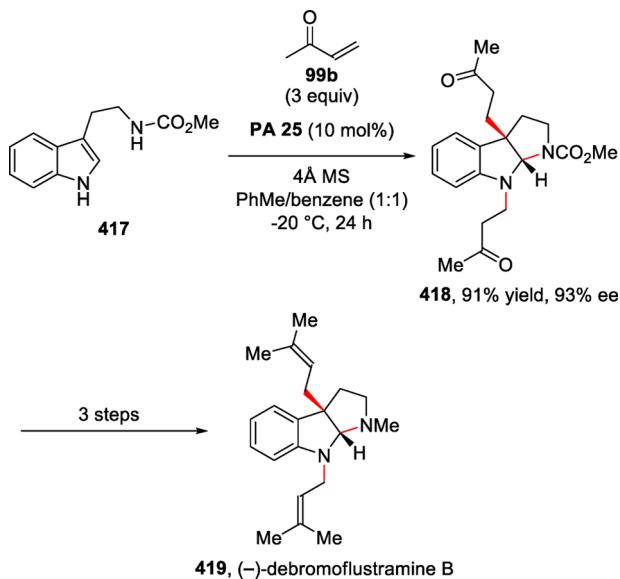
The formation of the C–N bond of a pyrroloindoline using catalytic asymmetric methodology has proved to be a difficult goal to achieve. In 2012, Antilla reported the first example of this using chiral phosphoric acids to accomplish the enantioselective synthesis of (−)-debromoflustramine B.<sup>413</sup> Taking tryptamine **417** with methyl vinyl ketone **99b** and 10 mol % of catalyst **PA 25** resulted in a remarkable cascade, which involves a double Michael addition with 2 equiv of methyl vinyl ketone and cyclization of the amine group to form the pyrroloindoline **418** (Figure 221).

Following a further three straightforward transformations, the total synthesis of (−)-debromoflustramine B **419** was completed. The importance of a free N–H on the indole moiety was briefly investigated and found to be crucial for achieving high enantioselectivities, strongly suggesting a bifunctional mechanistic course for the reaction.

Recently, Snyder has shown the use of a VAPOL derived phosphoric acid in stoichiometric amounts to achieve a diastereoselective Pinacol rearrangement.<sup>414</sup> It was used on route to the total synthesis of hopeanol and hopeahainol A.

## 3. REACTIONS IN THE PRESENCE OF METALS

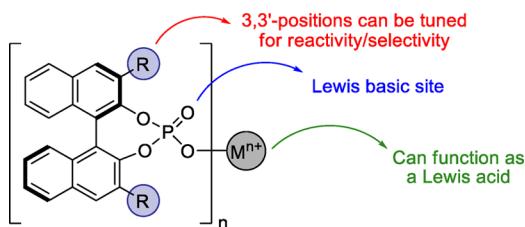
The use of metals, most commonly the transition metals with organic catalysts, has been attracting increasing amounts of attention over the past few years.<sup>415</sup> Researchers have found that unique catalytic properties can be created by combining metal catalysis with organocatalysis.<sup>416</sup> Within this category, asymmetric transformations using chiral organic catalysts have seen immense developments over the past few decades. The



**Figure 221.** Enantioselective construction of pyrroloindolines used in the synthesis of (−)-debromoflustramine B by Antilla (2012).

classical strategy involved during these processes is to include a chiral ligand that binds to the metal and creates a “chiral space” around the molecule of interest to perform the desired asymmetric reaction. Having the correct ligand–metal combination is vital and can in many cases be difficult to predict considering the vast number of possible permutations that exist.<sup>417</sup> The development of an efficient system usually requires many rounds of optimizations and in many cases may still rely on a little serendipity.

Chiral phosphoric acids typically activate their substrates through hydrogen-bonding interactions or ion-pair complexes. On the other hand, transition metals can often provide unique reactivity and selectivity through very distinct modes of coordinative interactions between itself and the substrate. The unification of the two can potentially provide a powerful combination for carrying out asymmetric transformations.<sup>418</sup> For example, on the chiral phosphoric acid, one can tune the substituents at the 3,3'-positions, which is well-known to have dramatic effects on reactions. When acting as a phosphate anion to the metal, the phosphoric acid still retains its Lewis basic site, while the metal can behave as a Lewis acid (Figure 222).



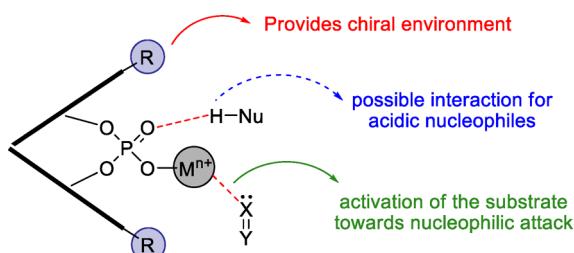
**Figure 222.** Potential of chiral phosphoric acid–metal complexes.

The combination of chiral phosphoric acids with metal catalysts has been the subject of previous reviews.<sup>419</sup> An area of on-going debate is the actual role of the phosphoric acid with regards to the metal center. Surveying the literature available fails to conclude a definite role for the phosphoric acid, but the two most commonly encountered forms involve the phosphate anion acting as either a ligand or a counterion for the metal.

Because of the mechanistic uncertainty involved, we have decided to order this section of this Review based on the role of the metal rather than the phosphoric acid to avoid confusion. The metal roles have been divided into three sections and are discussed in more detail below.

### 3.1. Lewis Acid Behavior

The ability of metal centers to accept electron density allows them to function very effectively as Lewis acids for the activation of substrates possessing a reactive lone pair. Furthermore, metal centers commonly possess multiple coordination sites, and this opens the possibility of using a chiral phosphate to control the chiral space around the metal. As mentioned previously, the role of the phosphoric acid can be unclear and will usually depend on the individual reaction conditions. Nevertheless, a generic model of the type of reactions being covered in this section is given in Figure 223.



**Figure 223.** A generic model for Lewis acid activations using metal phosphates.

First, the central theme in all of the reactions will revolve around the activation of a substrate through the interaction of its lone pair with the Lewis acidic metal. This will make it susceptible to nucleophilic attack, and if the nucleophile contains acidic hydrogens it may be involved in a hydrogen-bonding interaction with the phosphoric acid. Finally, the chiral environment will be created by the substituents at the 3,3'-positions of the BINOL framework.

**3.1.1. Additions to Imines.** Imine substrates are without a doubt the most easily activated functionalities for participation in phosphoric acid-catalyzed reactions. The tendency of a Brønsted acid to protonate an imine to form a highly electrophilic intermediate is a very well-established route of reactivity. Imines can however be also activated by Lewis acids, in particular electrophilic metal centers.

In 2010, Ishihara published his results on a very interesting observation he had found with regards to the varying performance of a catalyst depending on the method of purification used. He confirmed that catalysts purified solely over silica gel had a strong tendency to become contaminated with metal salts. These salts had the possibility in certain cases to alter yields, enantioselectivity, and even absolute stereo-configuration. The Rueping group has also observed these effects in their studies.<sup>35c</sup> Despite this, Ishihara found that these salts could in fact be advantageous when used in their pure form. He studied the Mannich reaction with catalyst  $\text{Ca}[\text{PA 6}]_2$  (Figure 224).<sup>35a</sup>

He found that imines **7** would react smoothly with 1,3-dicarbonyls **420** to give the Mannich products **421** in good yields and excellent enantioselectivities. In contrast, the free acids tested performed with only moderate selectivities. It is thought that the calcium phosphate activates the imine by acting as a Lewis acid, while the bound phosphate coordinates

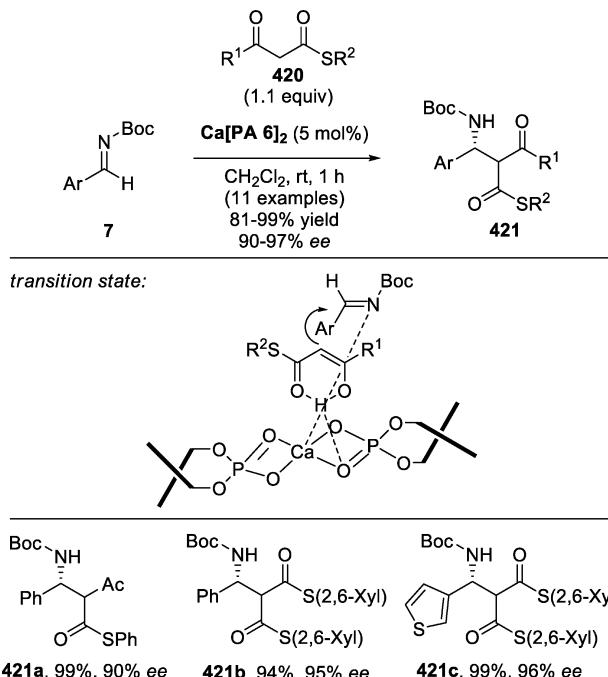


Figure 224. Mannich reaction using a calcium salt by Ishihara (2010).

to the 1,3-carbonyl substrate to facilitate the enantioselective reaction to occur. Subsequently, Ishihara has gone on to examine the Mannich reaction using various other chiral phosphate salts.<sup>420</sup> The Rueping group has also looked at using calcium salts toward catalyzing the Mannich reaction of cyclic 1,3-carbonyls.<sup>421</sup> Lewis acid activation of imines using metal phosphates toward attack by alternative carbonyl-based nucleophiles has also been successfully studied.<sup>422</sup>

The simple strategy of using a chiral phosphate salt to effect Lewis activation of an imine and attack by an incoming nucleophile stereoselectively has been shown to occur with various other nucleophiles. For example, Feng has shown sodium salts to be able to catalyze an asymmetric Strecker reaction between imines and TMS-CN.<sup>423</sup> In 2011, Antilla was able to show the addition of phosphine oxides stereoselectively into imines using a magnesium salt of a chiral phosphoric acid. Imines **267** when treated with  $\text{Ph}_2\text{P}(\text{O})\text{H}$  **422** in the presence of  $\text{Mg}[\text{PA 7}]_2$  gave the corresponding products of addition **423** in modest selectivity (Figure 225).<sup>424</sup>

It is proposed that the metal acts as a Lewis acid and the phosphate group activates the nucleophile for attack onto the imine. Alternatively, the metal center can activate the nucleophile while the phosphate ligand induces the stereoselectivity. It is also thought the dibenzocycloheptene group (cf., **423b** and **423c**) interacts with the catalyst through  $\text{CH}-\pi$  and  $\pi-\pi$  stacking to provide higher enantioselectivities.

Over the past decade, gold catalysis has been increasingly popular within the synthetic community, but the combination with organic catalysts is a relatively new concept within the field.<sup>425</sup> An interesting example of Lewis acidic behavior was reported by Gong for the reduction of quinolines using a Hantzsch ester in the presence of a gold-phosphate complex generated *in situ* from the free acid. Gong used various quinolines **208**, which upon reduction using Hantzsch ester **HE 2** and  $\text{PA 25}/[\text{IMesAuMe}]$  liberated tetrahydroquinolines **209** with good levels of enantioselectivity (Figure 226).<sup>426</sup>

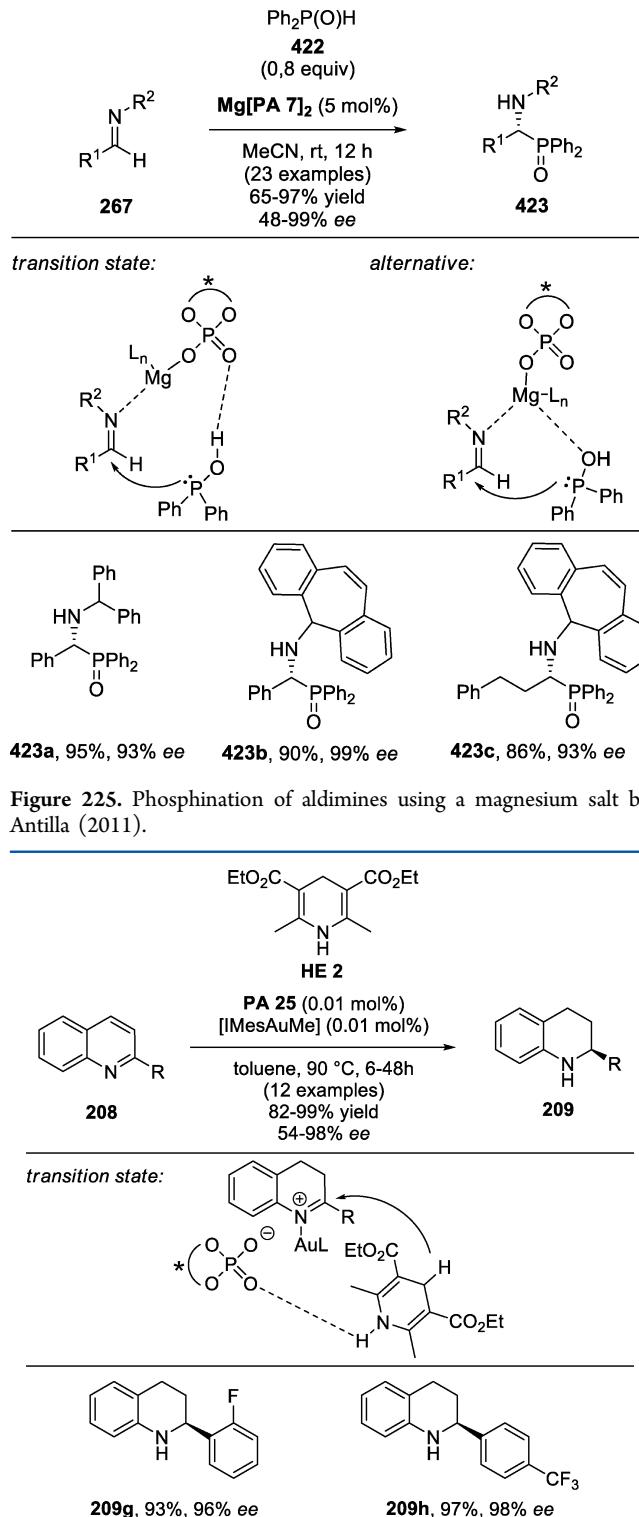


Figure 225. Phosphination of aldimines using a magnesium salt by Antilla (2011).

The mechanism is also intriguing; while the authors suggest it may be a gold phosphate responsible for the asymmetry during the reaction, it may also be due to a chiral anion effect that has been seen in other cases. A related example but using a silver phosphate was demonstrated in 2012 by You that involved *in situ* cyclization of alkynyl imines followed by a Friedel–Crafts reaction with indoles. Taking **56** or **60** with **424**

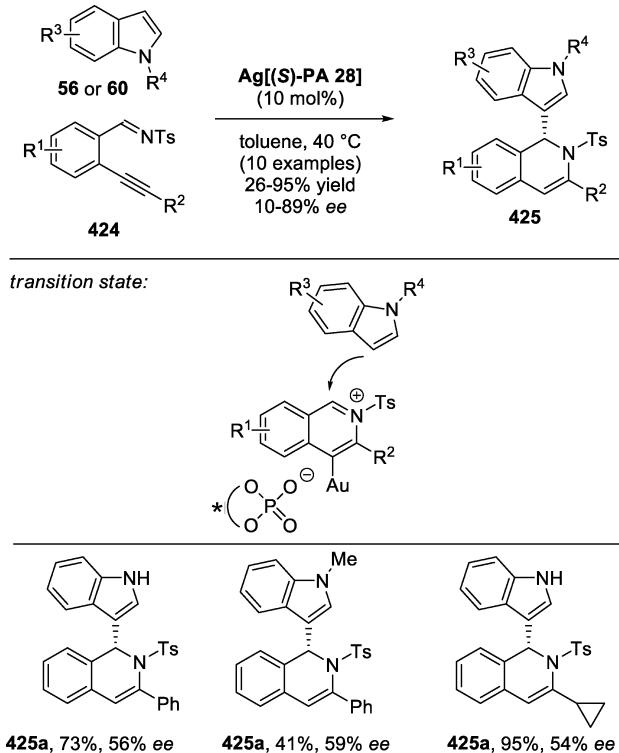


Figure 227. Synthesis of 1,2-dihydroquinolines using a gold phosphate by You (2012).

resulted in a smooth reaction to give the adduct products 425 in moderate enantioselectivity (Figure 227).<sup>427</sup>

Optimizations studies revealed that generation of the silver phosphate in situ resulted in modest reactivity and poor selectivity. Interestingly, highly enantioenriched products could be obtained by exploiting a difference in solubility between the enantiopure and racemic forms, which could also be done so on silica gel. The exact nature of the silver phosphate (an ion-pairing or a ligand) has not been determined.

**3.1.2. Additions to Carbonyls.** Analogous to the free-acid section on the activation of carbonyls, the use of metals for activation is scarcely reported. Reports are usually restricted to aldehydes or activated carbonyls substrates. An early report from Ishihara showed the potential of chiral phosphate lithium salts to catalyze an enantioselective cyanosilylation of aromatic ketones.<sup>428</sup> However, only modest enantioselectivities could be achieved. A Passerini-type reaction was reported a year later by Zhu and Wang, which involved the enantioselective addition of isocyanides 426 to aldehydes 103 (Figure 228).

The reaction generally worked well and gave modest enantioselectivity for the oxazole products 427. The free-acid catalyst (PA 13) is insoluble in toluene; however, upon addition of Et<sub>2</sub>AlCl the solution becomes clear, and it is thought the aluminum phosphate is formed. The authors propose that the catalyst's structure may exist as a mixture of three possible conformers (Figure 229).

They expect a 2:1 phosphate:aluminum complex to be formed during the reaction and suggest that the different conformers may possess different catalytic properties, thus affecting the overall enantioselectivity of the reaction.

In 2012, the Rueping group reported the activation of a ketone substrate toward undergoing a carbonyl-ene reaction. They found that CF<sub>3</sub>-containing ketones 109 and various alkenes in the presence of Ca[[H<sub>8</sub>]-PA 14]<sub>2</sub> reacted to give the

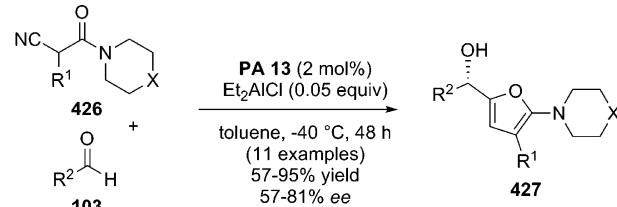


Figure 228. Addition of isocyanides to aldehydes using an aluminum phosphate by Zhu and Wang (2009).

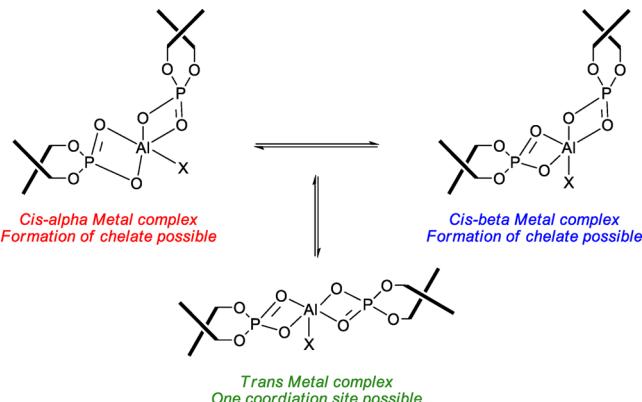


Figure 229. Possible conformers of aluminum phosphate catalysts.

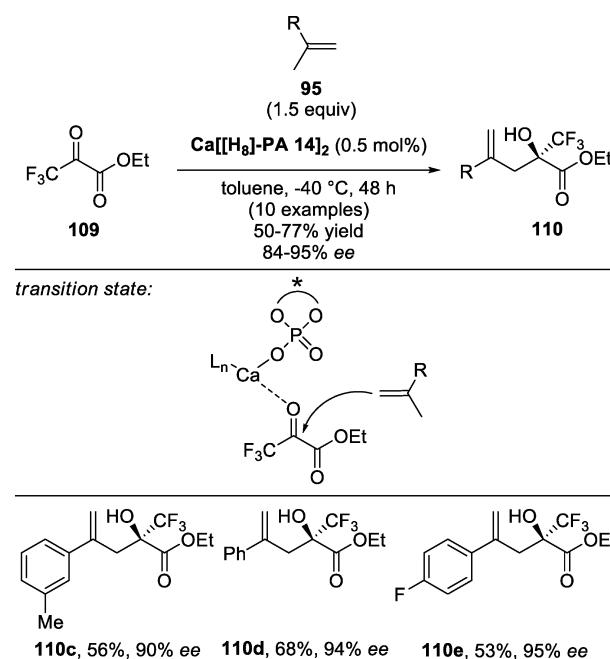


Figure 230. Carbonyl-ene reaction using a calcium salt by Rueping (2011).

adduct products 110 in moderate yields and high selectivity (Figure 230).<sup>430</sup>

The procedure provides a mild synthesis of quaternary  $\alpha$ -hydroxy esters containing a CF<sub>3</sub> group. Aside from being

biologically active, the  $\text{CF}_3$  group is a strong activator toward the carbonyl group, allowing it to be activated sufficiently for reaction. Earlier optimization studies with Brønsted acidic catalysts (see Figure S6) showed lower levels of reactivity and selectivity. Therefore, we propose that the calcium ion is most likely involved in Lewis acidic activation, but the true structure of the catalyst is not known. The group was also able to utilize these carbonyls toward undergoing a Friedel–Crafts reaction with indoles.

**3.1.3. Additions to Activated Alkenes.** The activation of unfunctionalized alkenes is difficult to achieve using phosphoric acids, and examples of truly unfunctionalized alkene activation are scarce.<sup>181</sup> This limitation has not deterred research though, and the most common strategy employed to overcome this is by employing activated alkenes such as  $\alpha,\beta$ -unsaturated carbonyls as the carbonyl group provides a nucleophilic site for Lewis or Brønsted acid coordination. In 2002, an early use of BINOL phosphates was reported by Inanaga where he showed the use of a chiral scandium phosphate catalyst being able to catalyze the 1,4-addition of an amine into an enone.<sup>431</sup> Some years later, Chen disclosed the addition of TMSCN using chiral sodium phosphate  $\text{Na}[\text{PA } 4]$  (Figure 231).<sup>432</sup>

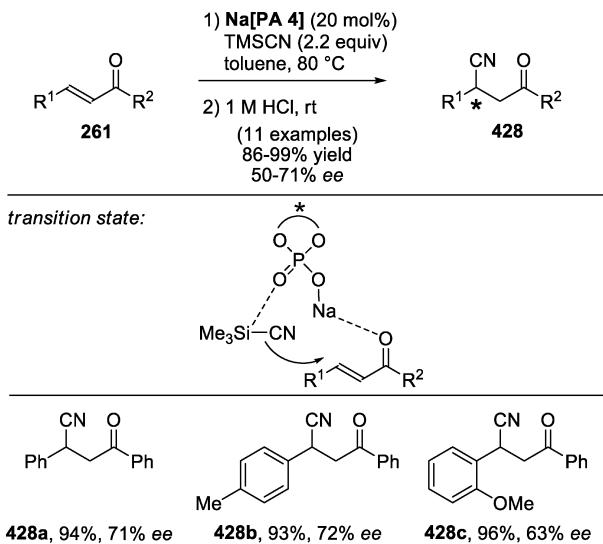


Figure 231. 1,4-Addition of TMSCN using a sodium salt by Chen (2010).

TMSCN was shown to efficiently add to enones **261** to give the corresponding products **428** albeit in modest enantioselectivity. The presence of the silicon may alter the mechanism from that of a simple chiral Lewis activation system. It could be thought to be interacting with the Lewis basic site of the catalyst while the sodium activates the carbonyl. Recently, Chen has published his full studies on the reaction and could perform the reaction with *in situ* generated HCN.<sup>433</sup>

The use of activated alkenes has also been exploited by research groups toward undergoing Friedel–Crafts reactions. One of the first reports using a chiral metal phosphate catalyst was reported by Luo in 2010, who used *(S)*-PA **16** with  $\text{MgF}_2$  to react enones **68** with phenol derivatives **429** to give **430** (Figure 232).<sup>434</sup>

The reaction generally works well and gives good yields and selectivity for the products. The reaction is thought to proceed via a magnesium phosphate that is generated *in situ*; however, using preformed phosphate salts with  $\text{MgF}_2$  results in no

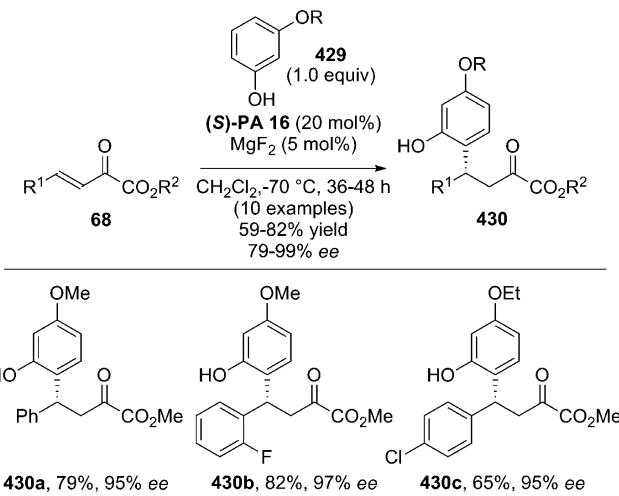


Figure 232. Friedel–Crafts reactions of unsaturated ketoesters using a magnesium salt by Luo (2010).

reactivity, suggesting that the acidic proton may play a role in the mechanism. The reaction also fails to function in the absence of  $\text{MgF}_2$ , and therefore a synergistic effect is achieved only when both PA **16** and  $\text{MgF}_2$  are included together. They could also show that the Friedel–Crafts reaction functioned well with indoles using this catalyst. This has subsequently been shown to be catalyzed by chiral iron and indium phosphates too.<sup>435</sup>

**3.1.4. Intramolecular Cyclizations.** The papers in this section will deal with the activation of double/triple bonds toward attack by internal nucleophiles. Although in the previous section we discussed the difficulty of activating alkenes toward external nucleophiles, it appears the intramolecular variant has received more success so far. In 2007, Toste published a landmark report on the use of chiral counterions with transition metals to effect asymmetric transformations. The use of neutrally charged chiral ligands on gold is well-known, but up to that point the use of anionic ligands with cationic gold complexes that relay stereochemical information through a close ion-pairing was unheard of. Toste showed that by combining  $\text{Ag}[\text{PA } 25]$  with a gold complex *in situ* he could perform asymmetric cyclizations of allenic substrates **431** possessing either an oxygen or a nitrogen nucleophile (Figure 233).<sup>436</sup>

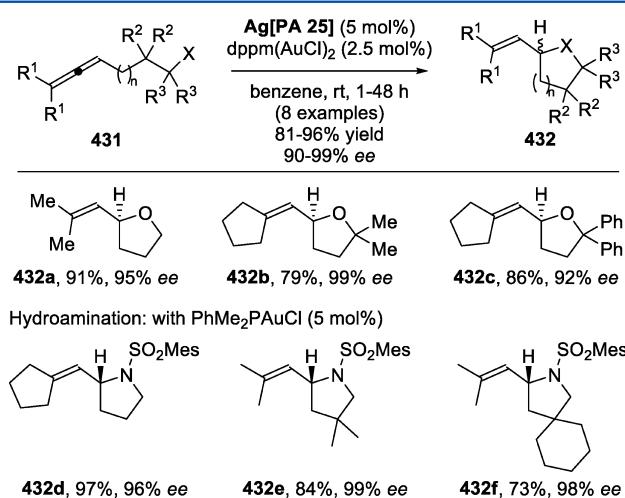


Figure 233. Hydroalkoxylation and hydroamination using chiral anions by Toste (2007).

The reaction furnished tetrahydrofurans (**432a–c**) and pyrrolidines (**432d–f**) in good yields and with high enantioselectivity. Evidence for the ion-pairing was noticed; when polar solvents were used the enantioselectivities dropped. The concept described here was predicted to be of high utility for not just gold complexes but also a wide variety of other metal-catalyzed reactions. The nature of the active catalyst has been studied in detail by Nguyen who proposes from calculations that the chiral phosphate should be thought of as a strongly bound ligand to the gold center.<sup>437</sup> A similar system has also been studied by Mikami (Figure 234).<sup>438</sup>

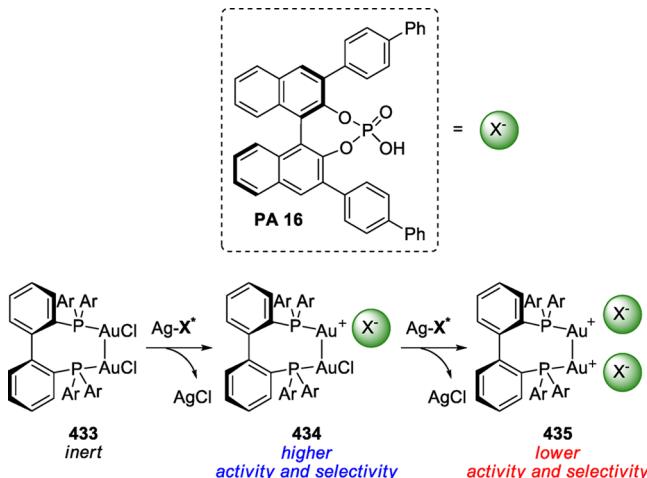


Figure 234. Comparison of gold complexes by Mikami (2010).

Interestingly, he found that a special synergy existed when a 1:1 ratio between the gold complex and chiral phosphate was used (**434**). This complex was catalytically superior and provided the highest enantioselectivity. The initial gold complex **433** was found to be inert, and the complex formed from 2 equiv of chiral phosphate **435** was able to catalyze the reaction but with lower yields and selectivity.

Also in 2010, Toste expanded the scope of his gold–chiral phosphate system to the cyclizations of N-Boc hydroxyl compounds **436** (Figure 235).<sup>439</sup>

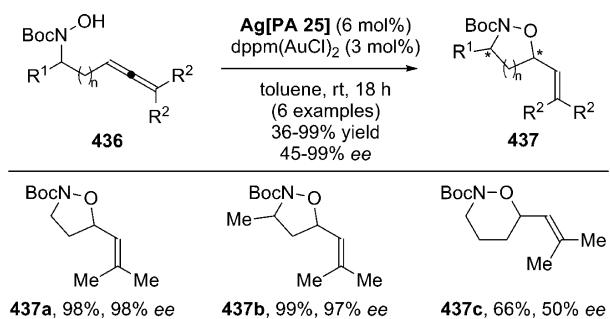


Figure 235. Synthesis of isoxazolidines using a chiral gold phosphate by Toste (2010).

The reaction proceeds well and generally gives good yields and selectivity of the products **437**. It could also be used to cyclize hydrazines to give pyrazolidines.

Terminal alkynes are difficult substrates to activate with gold complexes due to the linear geometry they adopt and the large distance between the chirality on the ligand and the

stereocenter being formed. In 2010, Czekelius introduced chiral phosphates to be used to control an enantioselective desymmetrization. With 1,4-diyneamides **438** and a gold complex containing PA **25**, the substrate undergoes an asymmetric desymmetrization to afford **439** with good enantioselectivities (Figure 236).<sup>440</sup>

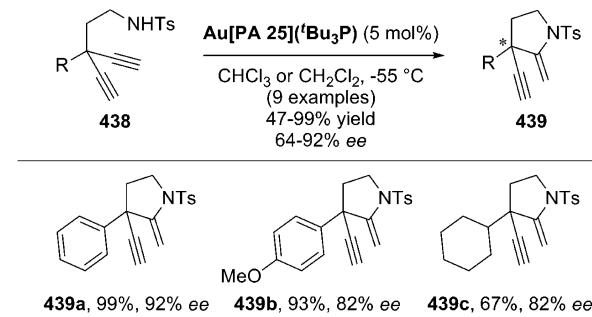


Figure 236. Diyneamide desymmetrization using a gold phosphate by Czekelius (2012).

As with previously described methodology, not all gold complexes performed equally with PA **25**. In the end, a synergistic system was found that involved the use of 'BuP as an additional ligand for the gold complex. The true nature of the structure for the chiral catalyst responsible for the selectivity is not proposed.

**3.1.5. Diels–Alder.** The asymmetric Diels–Alder reaction is a powerful reaction to construct six-membered ring systems and can be commonly found to be catalyzed by Lewis acids. Asymmetric catalysis with chiral lanthanide complexes is also a well-recognized branch of organic synthesis.<sup>441</sup> The group of Inanaga's has been one of the pioneers in utilizing chiral phosphates in asymmetric transformations. In 1997, they looked at using ytterbium phosphates to catalyze a hetero-Diels–Alder between aldehydes **103** and Danishefsky's diene **440** (Figure 237).<sup>442</sup>

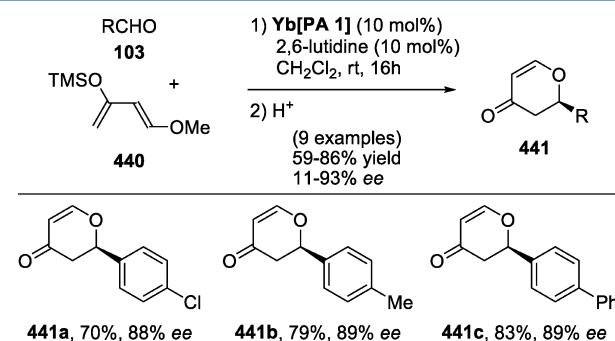


Figure 237. Hetero-Diels–Alder reaction using a ytterbium salt by Inanaga (1997).

The reaction leads to pyrans **441** generally in good yields and good enantioselectivity. The group also found that the choice of additive (2,6-lutidine) was crucial to the yield and enantioselectivity of the reaction. Its precise role is unknown, but it may be involved in stabilizing the diene. The group has also studied the reaction with a range of other chiral earth phosphates.<sup>443</sup> Inspired by this report, Antilla published a hetero-Diels–Alder reaction using Danishefsky's diene and unsaturated oxindoles using chiral magnesium phosphates.<sup>444</sup> Recently, Zhu has

reported the hetero-Diels–Alder reaction of unsaturated indolines with enol ethers to construct dihydropyrans.<sup>445</sup>

In 2012, Luo reported an interesting example of remote stereocontrol modulated by the fluorine atoms on the catalyst. Luo was studying the Diels–Alder reaction between cyclopentadienes **442** and unsaturated keto-esters **68** (Figure 238).<sup>446</sup>

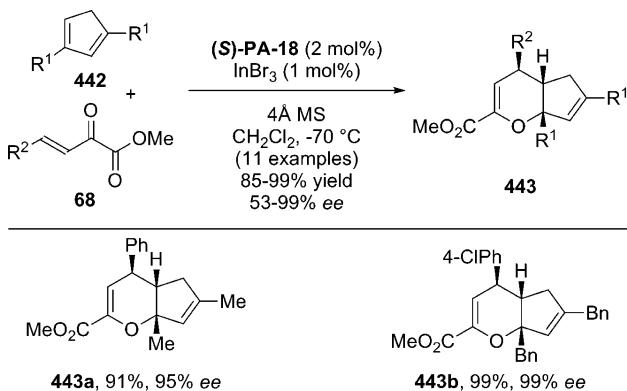


Figure 238. Hetero-Diels–Alder reaction by indium salts by Luo (2012).

He found that InBr<sub>3</sub> combined with highly fluorinated catalyst PA 18 gave the optimal yield and selectivity for the adduct products **443**. The reason for selectivity was thought to not solely rely on sterics, as more sterically hindered catalysts gave poor results. The transition state proposed by the authors is shown in Figure 239.

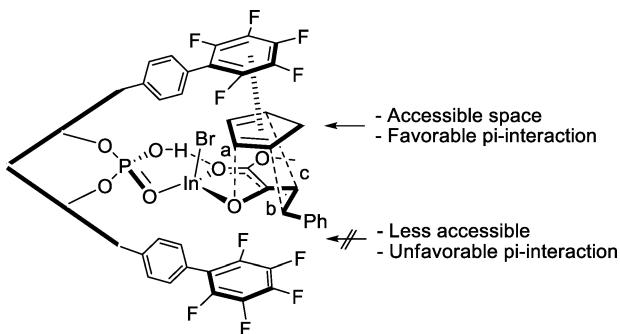
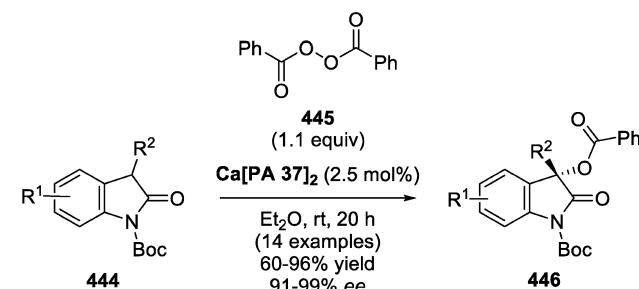


Figure 239. Proposed transition state.

It is thought that the fluorinated aromatic ring takes part in  $\pi$ - $\pi$  stacking interactions with the cyclopentadiene, which favors attack from the upper face of the unsaturated keto-ester that is bound to the indium metal center. It was also noted that a single fluorine atom on the catalyst's 3,3'-substituents was also able to achieve high enantioselectivities. A similar mechanism has been proposed by Luo to be occurring during his studies on the cycloadditions of unsaturated keto-esters with simple olefins.<sup>447</sup> Wang and Xu have recently published a hetero-Diels–Alder reaction of enamines using chiral yttrium phosphates.<sup>448</sup>

**3.1.6. Miscellaneous.** Thus far, we have generally described the use of chiral phosphates combining with metal centers to activate groups toward nucleophilic attack, but the activation of nucleophiles is also a well-established strategy with chiral Lewis acids. Within this class, chiral metal enolates are a dominant feature and once activated allow for reactivity with a variety of electrophiles in a stereoselective manner. An early

example of this concept using chiral phosphates was shown by Inanaga who used a scandium metal center to perform an asymmetric fluorination of  $\beta$ -keto esters.<sup>449</sup> Using a pyridinium salt as the fluorine source, he was able to achieve modest selectivities. This concept remained largely unexplored until 2011 when Antilla described the benzyloxylation of 3-aryl indoles. He was able to react indoles **444** with benzoyl peroxide **445** in the presence of Ca[PA 37]<sub>2</sub> to give the oxygenated products **446** in good yields and high enantioselectivities (Figure 240).<sup>450</sup>



transition state:

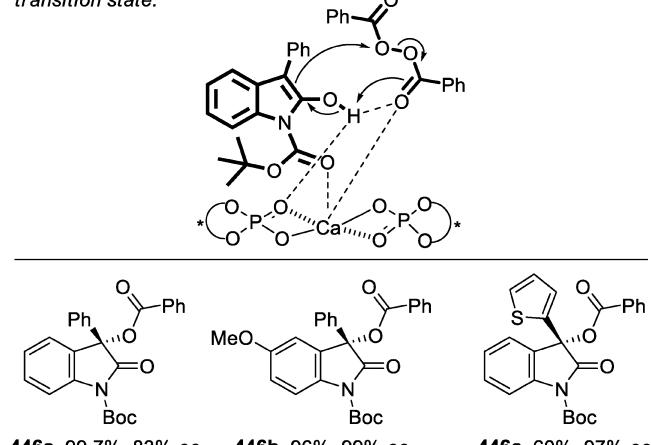
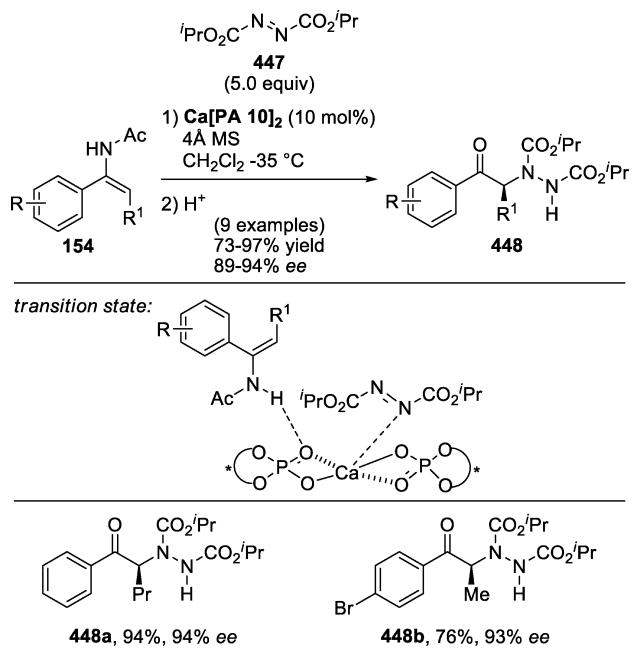


Figure 240. Production of oxindoles using a calcium salt by Antilla (2011).

Optimization studies conducted by the group revealed that simple free-acid catalysts performed poorly and those purified solely on silica gel gave variable results. This led them to conclude that the presence of metals may be beneficial to the reaction course, and subsequently a calcium center was found to be optimal. The transition state of the reaction is proposed in Figure 233. It is thought that the calcium center will form multiple contacts with the chiral phosphate, adjacent Boc group carbonyl, and the carbonyl of the peroxide reactant. The bifunctional nature of the phosphoric acid will also allow for coordination to occur between itself and the hydroxyl group of the enol tautomer. The combined consequence of all of these interactions results in a highly ordered transition state, which provides high enantioselectivities. The concept has also been extended to include Michael additions and chlorinations of 3-substituted oxindoles.<sup>451</sup>

Calcium has been shown to be a versatile metal for activation of a variety of substrates and in conjunction with chiral phosphoric acids can be a powerful combination. Zhu and Masson have studied the use of calcium phosphates for the amination reaction of enamides **154** using diazene **447**. The reaction was found to be efficiently catalyzed by Ca[PA 10]<sub>2</sub>



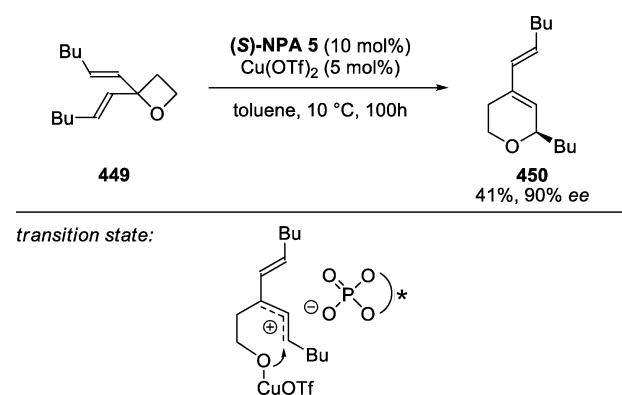
**Figure 241.** Amination of enamides using a calcium phosphate by Zhu and Masson (2011).

and gave the products **448** in good to high enantioselectivities (Figure 241).<sup>452</sup>

The mechanism is thought to involve activation of the azo-dicarboxylate by the calcium center and coordination of the enamide by the calcium-bound phosphate anion. The nature of the catalyst is unknown, but the authors suggest that it may be an oligomeric complex. Masson was also able to extend this work to include the asymmetric bromination of enecarbonates.<sup>453</sup>

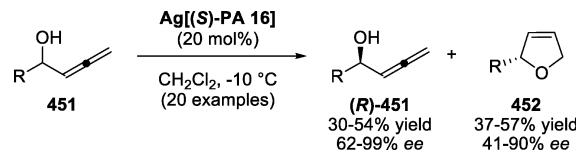
Lewis acids are well-known for their ability to facilitate intramolecular rearrangements when the appropriate functionality is set up within a molecule. In 2012, Njardarson was examining the ring expansion of oxetanes with copper salts and found Cu(OTf)<sub>2</sub> to be a highly efficient catalyst for the racemic rearrangement.<sup>454</sup>

He then examined chiral phosphoric acids as chiral anions for the transformation. The addition of (S)-NPA **5** under reaction conditions very similar to those previously found resulted in desymmetrization of **449** to give **450** in 41% yield and 90% ee (Figure 242). The exact mechanism is unclear, but it is thought



**Figure 242.** Ring expansion of a vinyl oxetane using copper by Njardarson (2012).

to first proceed by a Lewis acid-mediated ring opening to reveal an allylic cation, which can be recaptured by the oxygen atom by attack onto the alkene to form the less strained six-membered products. The role of the phosphoric acid may be as a chiral counterion. Also in 2012, the cycloisomerization of allenic alcohols was studied by Hong using silver phosphates. He found that he could perform an efficient kinetic resolution of alcohols **451** using Ag[(S)-PA **16**] as a catalyst (Figure 243).<sup>455</sup>

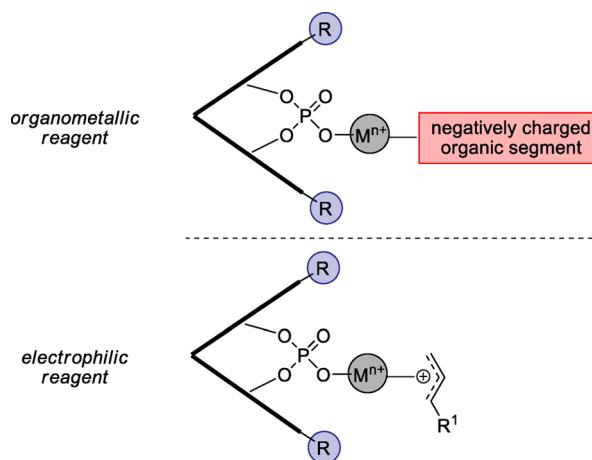


**Figure 243.** Kinetic resolution of allenic alcohols using a silver phosphate by Hong (2012).

The reaction results in the formation of non-racemic alcohols **(R)-451** along with non-racemic cyclized products **452**. The active catalyst was shown to be the silver phosphate rather than the free acid. It is thought that the silver catalyst promotes the cyclization by using the steric bulk of the chiral phosphate to prevent effective coordination of one enantiomer over the other. A semipinacol rearrangement has also been studied by Tu using chiral silver phosphates.<sup>178</sup>

### 3.2. Non-Lewis Acid Behavior

In this section, we are aiming to address the metal-catalyzed processes that involve the metal to be functioning in a role that is not purely Lewis acidic. Because of the nature of transition metals being Lewis acidic, it would be difficult to find examples where some acidic behavior was not being exhibited; however, the transformations in this section will feature reactions that usually cannot be carried out by generic Lewis acids. Such examples may include oxidation state changes or where the metal is somehow attached to either the nucleophilic or the electrophilic reactant formally through a σ-bond (Figure 244).



**Figure 244.** Examples of reactive non-Lewis acid intermediates.

As we saw in the Lewis-acid section on metal phosphate reagents, this section also has to deal with the uncertainty of the role of the phosphoric acid. Some groups utilize the free acid form, while others purposely employ phosphate salts. We believe that the exact role of the phosphoric acid will depend on

the individual reaction conditions; however, we also believe that the reactions in this section all involve some interaction between the metal and the acid, be it as a ligand or as a counterion.

**3.2.1. Additions to Carbonyls.** The activation of carbonyl systems is notoriously difficult using chiral phosphoric acids; however, some selective examples do exist. One strategy to overcome this is to use a metal center as a Lewis acid as discussed in the previous section. However, an alternative strategy can be to transform the nucleophilic reagent into a chiral reagent by the use of a metal and a chiral phosphate bound to the center. Recently, an example of this was shown by Murakami who used a cationic iridium complex with catalyst **PA 25** and an alkenyl boronate **453** to allylate aldehydes **103** to give *anti*-homoallylic alcohols **454** (Figure 245).<sup>456</sup>

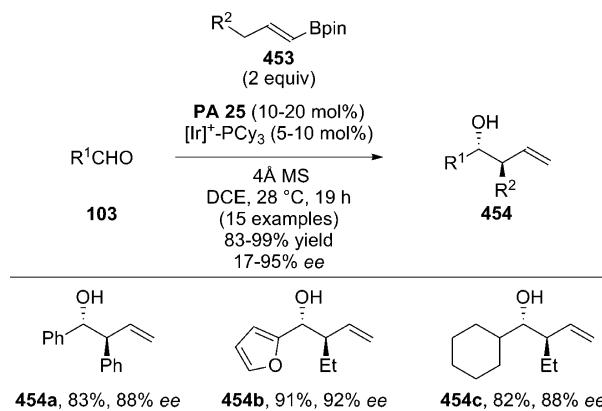


Figure 245. Synthesis of *anti*-homoallylic alcohols using iridium by Murakami (2013).

The exact mechanism for the process is not proposed by the authors but can be assumed to be going via activation of the boron species by the iridium complex, while the bound phosphate ion controls the stereoselectivity of its addition into the aldehyde.

The asymmetric allylation of aldehydes **103** to give the products **456** has also been shown by Faber who has used an *in situ* generated organozinc reagent from **455** and catalyst **PA 25** (Figure 246).<sup>457</sup>

Faber has also conducted a DFT study to elucidate the mechanism in more detail, which reveals a six-membered transition state that involves the zinc metal center activating the aldehyde, while the phosphoric acid provides both a chiral environment and a hydrogen bond to the aldehyde. A short total synthesis of a natural product was also shown to be possible with this methodology.

**3.2.2. Additions to Alkenes/Alkynes.** Carbocyclizations involving alkenes are a powerful method to build up complex molecular architecture. Commonly, these processes are catalyzed by transition metals, and asymmetric variants utilize chiral ligands as coordinating partners to the metal center. This strategy has also been studied by groups who have found chiral phosphates to be highly efficient counterions to facilitate asymmetric reactions. One such example was shown in 2011 by Fensterbank, who found that a silver phosphate ( $\text{Ag}[(S)\text{-PA 25}]$ ) when mixed with  $\text{IrCl}(\text{CO})(\text{PPh}_3)_2$  could function as a highly active catalyst for the asymmetric cyclizations of 1,6-enynes **457** (Figure 247).<sup>458</sup>

The products **458** obtained were isolated in good yields and with modest to high selectivity. Mechanistic studies involving

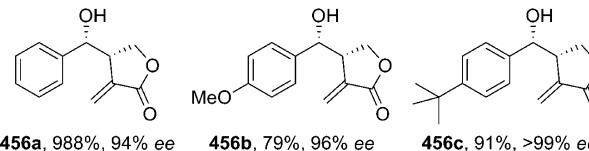
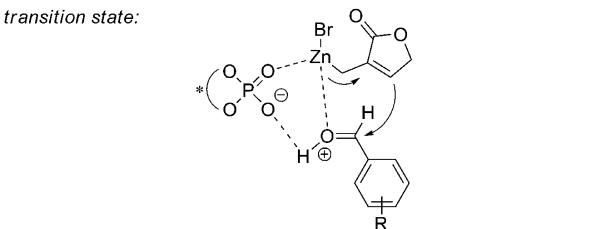
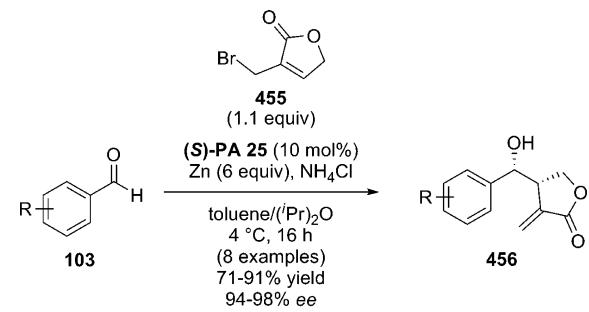


Figure 246. Synthesis of  $\beta$ -substituted  $\alpha$ -methylenebutyrolactones using zinc by Faber (2013).

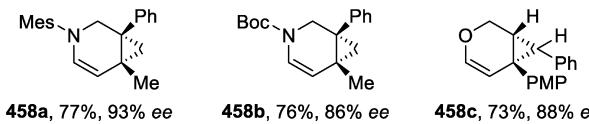
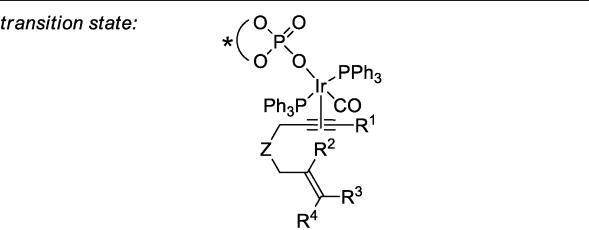
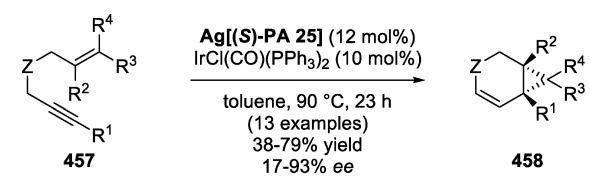


Figure 247. Carbocyclization of 1,6-enynes using an iridium phosphate by Gandon (2011).

<sup>31</sup>P NMR and IR spectroscopy revealed the formation of cationic iridium species that contains a bound chiral phosphate as an ion-pair, which is thought to control the stereoselectivity during the reaction.

Copper is a versatile transition metal and has been used in many asymmetric catalytic processes in the literature. Perhaps the most famous category of ligands used in conjunction with copper are the box ligands<sup>459</sup> as well as chiral phosphines. In 2009, Shi reported an interesting example of the use of a chiral copper phosphate for performing asymmetric diaminations. The catalyst could be prepared *in situ*; however, he also found that a straightforward synthesis of the copper species was possible.

Taking PA 1 with copper(I)-mesityl 459 in benzene at room temperature with overnight stirring gave the desired copper species Cu[PA 1] in 69% yield as a white solid (Figure 248).

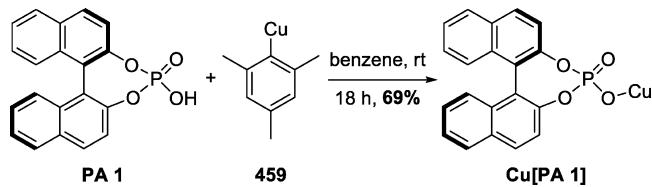


Figure 248. Synthesis of copper phosphates by Shi (2009).

The isolated salt is easy to handle, gave results similar to those of the in situ formed species, and could be stored in the freezer for 3 months without any decomposition. Taking the copper salt with a phosphine ligand, it could be shown that dienes 460 would react efficiently with aziridinone 461 to give the corresponding products 462 in good yields and modest enantioselectivity (Figure 249).<sup>460</sup>

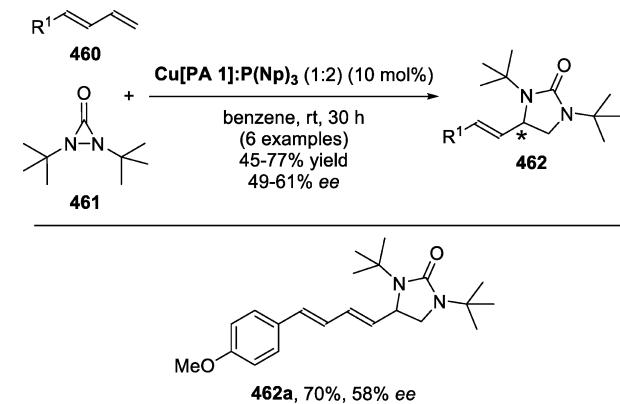


Figure 249. Diamination of conjugate olefins using a copper phosphate by Shi (2009).

The group came across the idea of using phosphate catalysts when they noticed a very strong dependence on the counterion of the catalytic copper species. In addition, a variety of alternative ligands were tested but failed to give any enantioselectivity.

Copper mesityl 459 has proven to be a convenient source of the metal for further complexation with chiral phosphate anions. Shibasaki has shown that 459 can be used with (S)-PA 25 and a chiral phosphine ligand 465 to perform 1,4-additions of alkynes 464 into electron-deficient alkenes 463 (Figure 250).<sup>461</sup>

The reaction generally functions well and affords the products 466 with modest to good enantioselectivity. The reaction mechanism however is rather complex. First, a lithium alkoxide is needed to deprotonate the parent acid (PA 25) to form the lithium phosphate catalyst in situ. The phosphine ligand provides a significant stereocontrol effect, but it was also shown that the presence of the chiral phosphate enhanced the level of selectivity. The authors propose that the chiral anion reinforces the stereocontrol effect exerted by the chiral ligand.

In 2011, Toste has demonstrated the use of copper(II) phosphates to catalyze the cycloisomerization-indole addition to synthesize functionalized furans. By taking alkynes 467 and treating with Cu[(S)-PA 25]<sub>2</sub>, a cycloisomerization reaction occurred, and the corresponding carbocation generated was

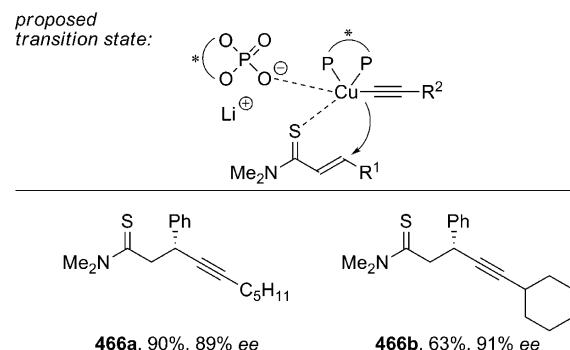
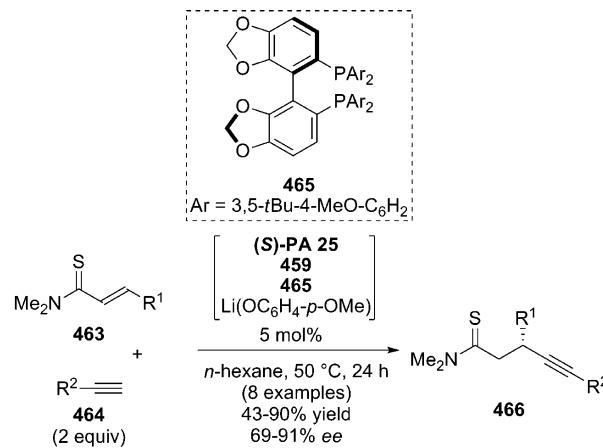


Figure 250. Conjugate addition of terminal alkynes to  $\alpha,\beta$ -unsaturated thioamides by Shibasaki (2010).

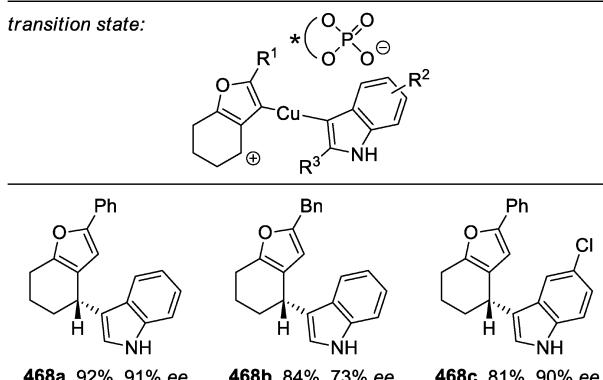
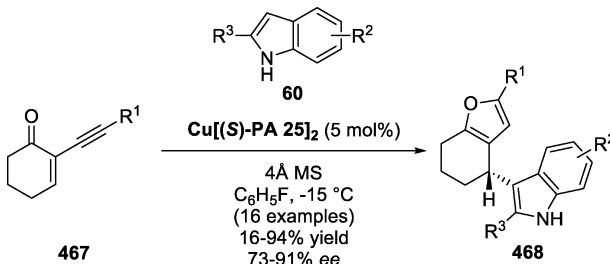


Figure 251. Cycloisomerization-indole addition using a copper phosphate by Toste (2011).

captured by various indole derivatives 60 to give the products 468 in high yields and selectivity (Figure 251).<sup>462</sup>

The exact nature of the mechanism is unclear; however, the authors suggest that a catalytic formation of a copper(II)-indole species occurs, while an ion pairing between the copper and the

phosphate anion controls the facial selectivity of the nucleophilic attack. A chiral copper(II)-phosphate was also proposed by Akiyama in his studies on the asymmetric transfer hydrogenation of carbonyl ylides.<sup>463</sup> A similar transformation has been shown by Terada using a chiral silver phosphate as the active catalyst.<sup>464</sup> Recently, Yao has shown that palladium can be used to cyclize 2-alkynyl aldehydes, which can be intercepted by 2-alkenyl phenols in a cascade process.<sup>465</sup>

**3.2.3.  $\pi$ -Allyl Species.** The utilization of  $\pi$ -allyl species is ubiquitous with transition metals and in particular palladium catalysts.<sup>466</sup> The asymmetric allylation reaction is an important transformation in organic chemistry because the allyl group is an incredibly versatile group for further transformations. In 2007, List was able to utilize his newly developed ACDC concept toward an asymmetric Tsuji–Trost<sup>467</sup> type  $\alpha$ -allylation of aldehydes catalyzed by a chiral phosphinate anion. Aldehydes **103** and an allylic amine **469** were treated with  $\text{Pd}(\text{PPh}_3)_4$  and catalyst (*S*)-PA **25**, and after an acidic workup gave the allylated products **470** in high selectivity (Figure 252).<sup>468</sup>

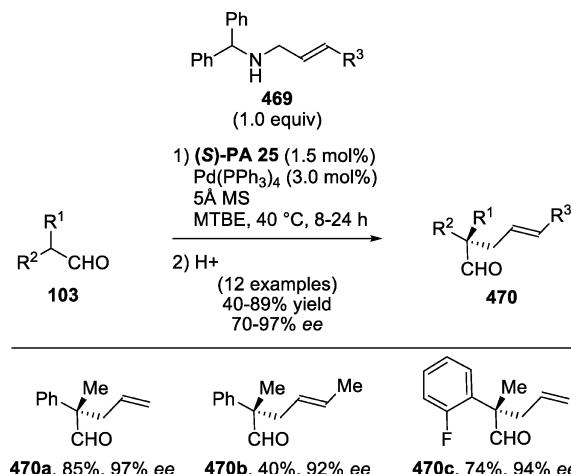


Figure 252.  $\alpha$ -Allylation of aldehydes using a palladium phosphate by List (2007).

The reaction represents a breakthrough for the field because prior to this the asymmetric process was known to primarily only be catalyzed by chiral phosphine ligands. The proposed mechanism is given in Figure 253.

It is thought that the phosphoric acid plays a dual role in the mechanism. First, it protonates the allylic amine, which aids in the formation of the key  $\pi$ -allyl species, and second it acts as a chiral counterion to the palladium during the key C–C bond forming step. In 2011, List extended the scope of the reaction to include allylic alcohols as precursors for the formation of  $\pi$ -allyl species under similar reaction conditions.<sup>468b</sup> A mechanistically related transformation, the Overman rearrangement, was also shown by the List group to be efficiently catalyzed by this system; however, in this case, the choice of ligand on palladium had an influence on the reactivity.<sup>469</sup>

The active catalyst is thought to be **472**, which contains a bridged dimer structure between two molecules of palladium catalyst **471** and (*S*)-PA **25** (Figure 254). The structure proposed (based on X-ray analysis of a derivative) suggests that rather than an ion-pairing between the palladium and phosphate, the phosphate acts as a charged ligand. Gong has also studied this reaction with a palladium catalyst and a chiral phosphoric acid, and he combines this system with a chiral

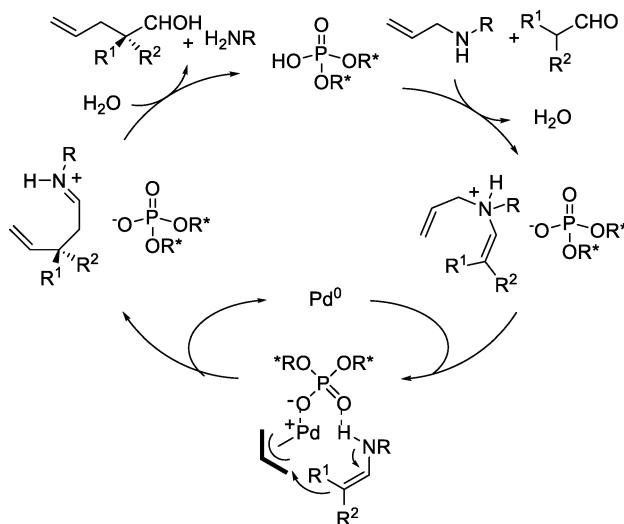


Figure 253. Mechanism of  $\alpha$ -allylation of aldehydes.

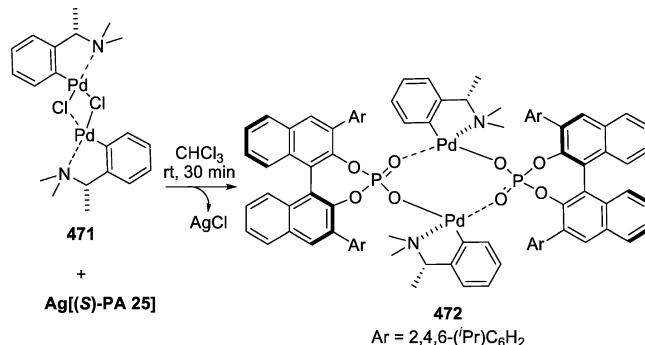


Figure 254. Synthesis of the active catalyst.

phosphoramidite ligand, and so the source of chiral induction may not come solely from the phosphate ion.<sup>470</sup>

In 2013, Hartwig realized the potential of phosphate counterions for the asymmetric allylation of azlactones.<sup>471</sup> In his report, he used a chiral ligand to control the stereoselectivity, while the use of an achiral phosphoric acid was thought to control the high diastereoselectivity observed. A few months later, Ooi developed a similar asymmetric allylation of benzofuran-2(3*H*)-ones using a palladium catalyst and a chiral phosphoric acid–amine salt for the activation of allylic carbonates **474**. Reaction of **473** proceeds to give the allylated products **475** in high yields and excellent enantiomeric excesses (Figure 255).<sup>472</sup>

The sense of stereoinduction in this case is rather unique by the use of an amine salt containing a phosphine. The phosphine is thought to act as a ligand for the palladium center while forming a strong ion-pairing with the chiral phosphate anion to control the absolute stereochemistry of the process. Ooi has also recently demonstrated that by tuning the nature of the substituents on the phosphoric acid, he can achieve a highly *E*-selective allylation of 1,2-disubstituted allylic carbonates.

A rather interesting example was presented by Rainey in 2012, which utilized a  $\pi$ -allyl species to effect a semipinacol rearrangement of spirocyclic alcohols. It was found that when alcohols **476** were treated with (*S*)-PA **25**, benzoquinone (BQ), and  $\text{Pd}(\text{OAc})_2$ , they underwent a stereoselective rearrangement to yield the ketone products **477** (Figure 256).<sup>473</sup>

The mechanism is proposed to be similar to previously discussed reports on  $\pi$ -allyl generation. Also in line with previous

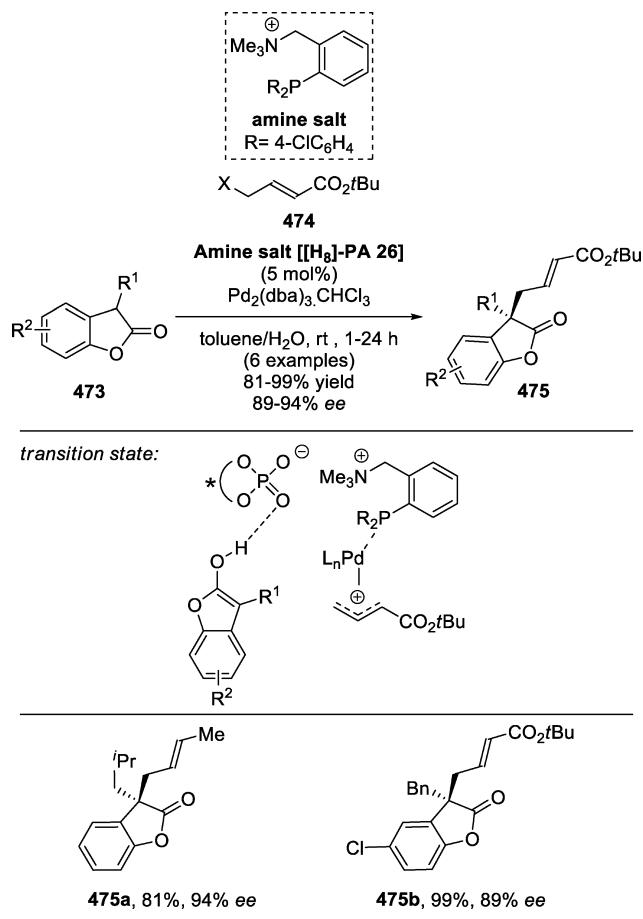


Figure 255. Allylation of benzofuran-2(3H)-ones using a palladium phosphate by Ooi (2013).

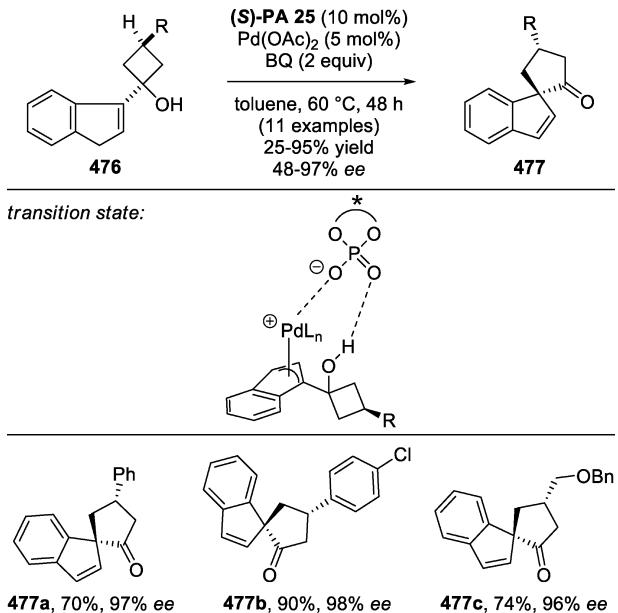


Figure 256. Semipinacol rearrangement using palladium phosphates by Rainey (2012).

reports, the enantioselectivity is thought to arise from the ion-pairing/ligand association between the palladium center and the chiral phosphate anion.

**3.2.4. Oxygen/Hydrogen Transfer Reaction.** Transition metal catalysts are known, among other qualities, to possess the ability to activate hydrogen and oxygen atoms through heterolytic bond dissociation.<sup>474</sup> This allows reagents in combination with the metal to be used in reactions that would not normally be possible. For example, in 2008 Xiao has shown that iridium in the presence of hydrogen gas can form a metal hydride complex, and when mixed with a chiral phosphoric acid<sup>475</sup> can perform the asymmetric hydrogenation of acyclic imines **52** to the products **479** (Figure 257).<sup>476</sup>

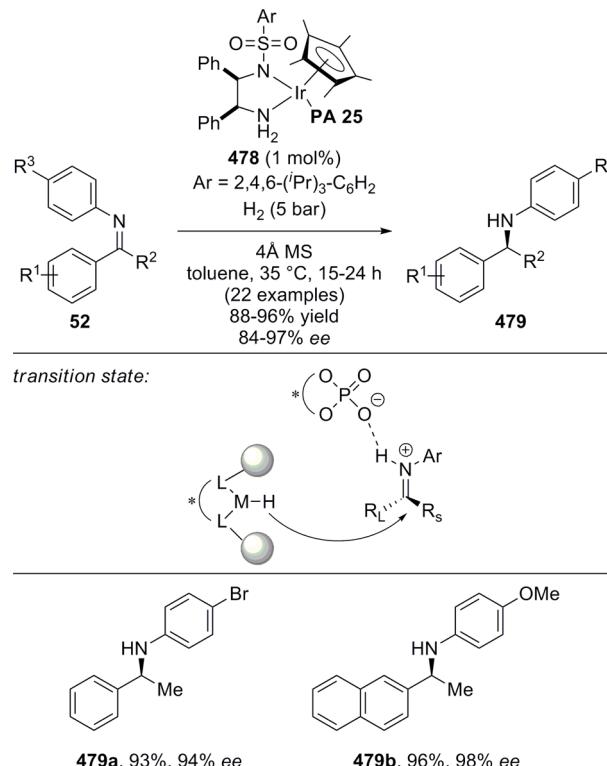
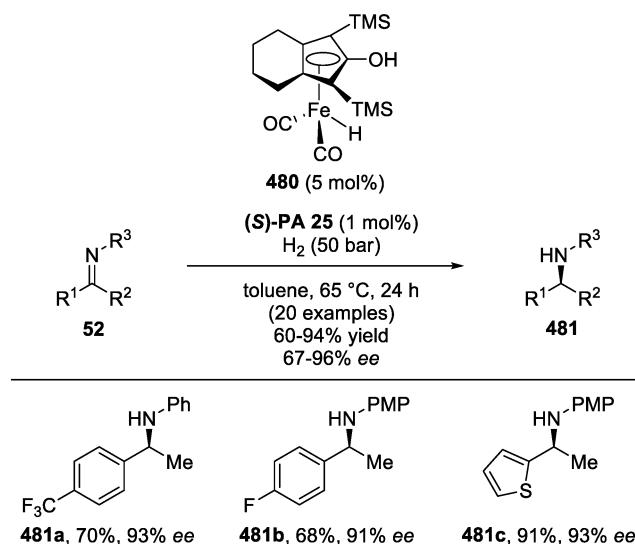


Figure 257. Hydrogenation of *N*-aryl imines using an iridium complex by Xiao (2008).

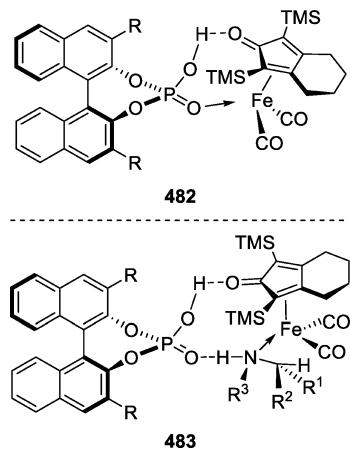
Iridium complex **478** containing a bound phosphate derived from **PA 25** was found to be the best promoter of enantioselectivity. It was also shown that the active complex could be prepared *in situ*, and similar results could be obtained. It is proposed by the authors that the chirality of the diamine ligand on iridium needs to function cooperatively with the chirality on the phosphoric acid for the reaction to produce the high selectivities seen. The phosphate acts as a chiral counterion to the protonated imine while a hydride is transferred from the metal center. A year later, Xiao was able to extend the procedure to *in situ* formed imines and thus perform an asymmetric reductive amination.<sup>476b</sup> Xiao has also studied the interplay between the metal and the phosphoric acid and found that noncovalent interactions are responsible for the catalytic activity and the enantioselectivity obtained during the reaction.<sup>476c</sup> Recently, Zhao has found that the enantioselective amination of alcohols can be carried out using a catalytic amount of a chiral iridium complex combined with a chiral phosphoric acid.<sup>477</sup> Ding has also shown catalytic rhodium hydride complexes in the presence of a chiral phosphoric acid to be suitable for the enantioselective reduction of CF<sub>3</sub>-substituted alkenes.<sup>478</sup>

The use of metal hydride species in conjunction with chiral phosphoric acids to asymmetrically reduce imines has additionally been studied by the Beller group.<sup>479</sup> In 2011, Beller showed that Knölker's complex **480** could be combined with (*S*)-PA **25** under a pressure of hydrogen to reduce imines **52** to the corresponding amines **481** generally with high selectivities (Figure 258).<sup>479a</sup>



**Figure 258.** Hydrogenation of *N*-aryl imines using an iron complex by Beller (2011).

Beller carried out a <sup>31</sup>P NMR study in an attempt to determine the active intermediates during the reaction. The results from these experiments suggest that coordinated species **482** may form when iron complex **480** is mixed with a phosphoric acid (Figure 259). Upon addition of the imine, it is

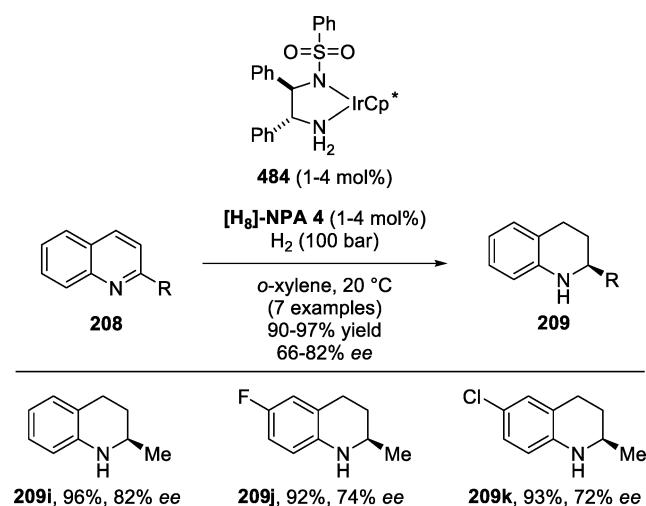


**Figure 259.** Possible reaction intermediates.

thought that complex **483** is formed, which contains the amine bound to the iron center.

Beller has since extended the utility of the iron system to include the reduction of quinoxalines and benzoxazines.<sup>479b</sup> He has also shown the reduction of *in situ* generated imines from the corresponding amine and an alkyne.<sup>479c</sup> The imine formation in this case is catalyzed by a gold catalyst in the same pot.

The majority of examples of chiral phosphoric acid–metal combinations usually involve the less acidic BINOL-based phosphoric acids, but in 2011 Rueping described a rather unique procedure for the reduction of quinolines **208** using an *N*-triflylphosphoramide catalyst [H<sub>8</sub>]-NPA **4** in combination with an iridium complex **484** (Figure 260).<sup>480</sup>



**Figure 260.** Reduction of quinolines using an iridium complex by Rueping (2011).

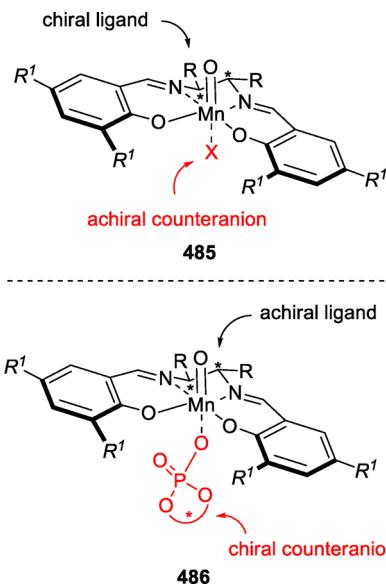
During the optimization studies for the reaction, it was found that the correct choice of chirality on the *N*-triflylphosphoramide and on the diamine complex was necessary for high levels of reactivity and selectivity; however, racemic diamine complex could also be used to achieve modest levels of selectivity for the products **209**.

In 2010, List published a chiral anion approach to enantioselective epoxidations of alkenes using manganese(III) salen complexes. These types of complexes are normally used with chiral diamine derived ligands (cf., **485**) such as in the Jacobsen–Katsuki epoxidation.<sup>481</sup> List however decided to use an achiral ligand and a chiral phosphate counteranion (cf., **486**) in the hope that a chiral environment around the metal center would be created (Figure 261).

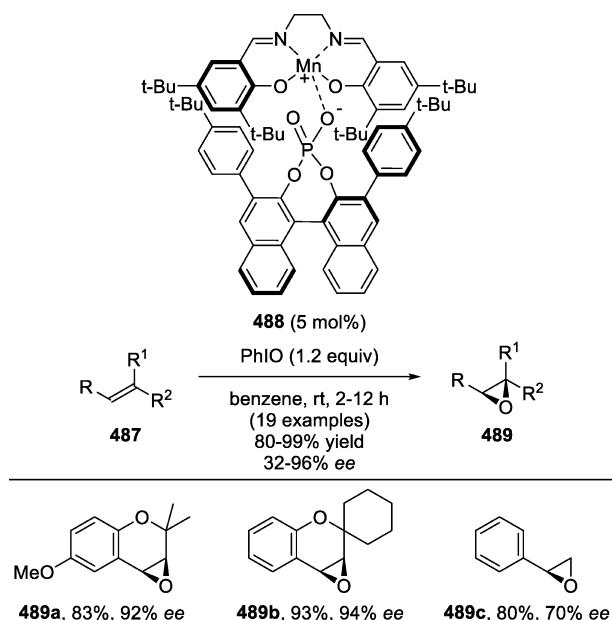
After some optimization, it was found that manganese complex **488** performed as the best catalyst for the enantioselective epoxidation of **487** to give epoxides **489** (Figure 262).<sup>482</sup>

The catalyst is easily prepared from the parent manganese complex and PA **11** by stirring in aqueous NaOH. Iodosobenzene was found to be suitable as the oxygen source for the reaction. It is thought the close ion-pairing between the metal center and the phosphate results in a highly ordered conformation of the catalyst upon delivery of oxygen to the substrate. A very similar system has also been applied by List for the enantioselective sulfoxidation reaction.<sup>483</sup>

**3.2.5. Ruthenium-Mediated C–C Couplings.** Carbon–carbon bond formations are one of the most useful transformations known in synthetic chemistry and are used in almost every type of synthetic application. Recently, efforts have been focused by various research groups on the use of transition metal catalysts to facilitate these types of couplings. One of the pioneers in this field has been the Krische group who has made huge strides toward atom economy and the use of simple feedstock chemicals that are produced on a ton scale from industry. In 2006, they were the first group to introduce a



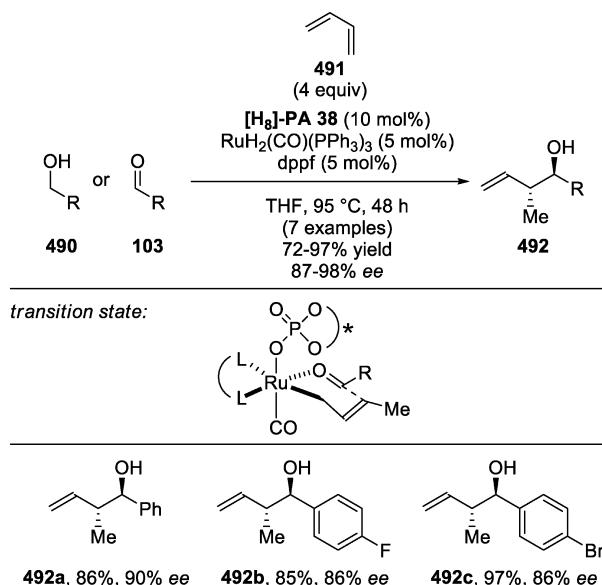
**Figure 261.** Comparison of classical and chiral phosphate strategies for asymmetric induction using manganese complex.



**Figure 262.** Epoxidation of alkenes with a manganese(III) salen phosphate complex by List (2010).

single example on the concept of combining a transition metal catalyst with a chiral acid as a method for performing enantioselective C–C couplings.<sup>484</sup> The concept was only revisited in full in 2012 when Krische reported on an enantioselective crotylation of primary alcohols using a ruthenium catalyst and  $[\text{H}_8]\text{-PA 38}$  (Figure 263).<sup>485</sup>

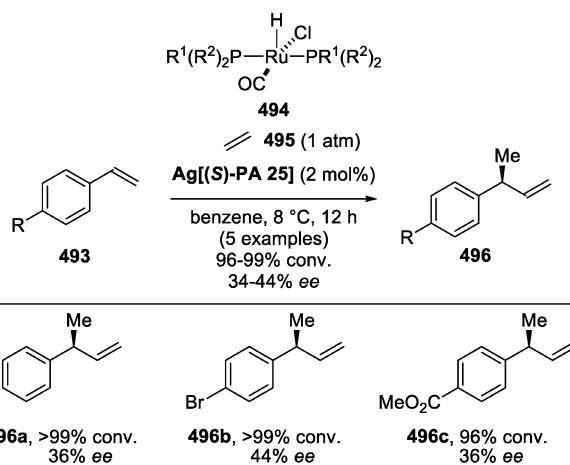
The reaction uses butadiene 491 with either the alcohol 490 or the aldehyde 103 oxidation states to give the corresponding products 492 with excellent stereoselectivities. The catalytic system is comprised of  $\text{RuH}_2(\text{CO})(\text{PPh}_3)_3$ , a diphosphine ligand, and  $[\text{H}_8]\text{-PA 38}$ . It is thought that the acid provides a chiral counterion to the cationic ruthenium center to induce the selectivity observed during the formation of the C–C bond. It is also proposed that it selectively controls the reactivity to go through the (*E*)-isomer of the crotyl group rather than the



**Figure 263.** C–H crotylation of primary alcohols using butadiene and a ruthenium catalyst by Krische (2012).

(*Z*)-isomer. It is interesting to note that  $[\text{H}_8]\text{-PA 38}$  is a rare example of a chiral phosphoric acid that contains non-identical groups at the 3- and 3'-positions. Krische has also been able to obtain a crystal structure of a ruthenium catalyst with a bound TADDOL-derived counterion.<sup>486</sup>

A similar concept has also been explored by List who has applied the system to the hydrovinylation of styrene derivatives 493. Using catalyst 494 with silver phosphate  $\text{Ag}[\text{Pa 25}]$  under an atmosphere of ethylene 495 gave the atom economical products 496 in excellent conversion but in low enantioselectivity (Figure 264).<sup>487</sup>



**Figure 264.** Hydrovinylation of styrene derivatives using a ruthenium catalyst by List (2011).

It is thought that the active catalyst is a chiral phosphate bound to the ruthenium center as Ag abstracts the chloride on catalyst 494. Although only low selectivity was achieved, this is the first example of an asymmetric hydrovinylation salt using a chiral phosphoric acid to control the process and opens the field for further development.

**3.2.6. Miscellaneous.** One of the very first uses of BINOL phosphates in asymmetric synthesis was reported in 1992 by

McKervey and McCann who reported on chiral rhodium phosphates as catalysts for reactions involving diazocarbonyl compounds. The group prepared catalyst **497** in a straightforward manner from (*S*)-PA **1** (Figure 265).<sup>488</sup>

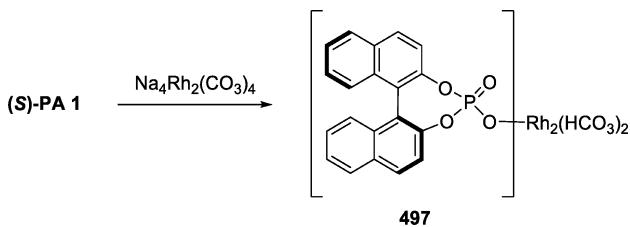


Figure 265. Synthesis of a chiral rhodium phosphate.

Taking (*S*)-PA **1** and stirring with  $\text{Na}_4\text{Rh}_2(\text{CO}_3)_4$  gave the complex **497** in a low yield. Nevertheless, the group showed the catalytic activity of this complex to be very strong. For example, just 0.5 mol % was needed for the 2,3-sigmatropic rearrangement of **498** to give **499** in 92% yield albeit with 32% ee (Figure 266).<sup>488</sup>

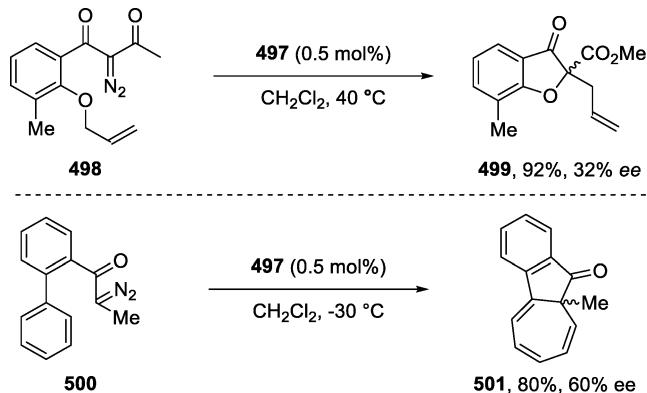


Figure 266. Reaction of diazocarbonyls using a chiral rhodium phosphate by McKervey (1992).

Complex **497** was also shown to be catalytically active in performing an aromatic cycloaddition of **500** to give **501** in 80% yield and a much improved 60% ee. Cycloadditions in an intermolecular fashion were also studied at the same time by Pirrung.<sup>489</sup> It can be assumed in both cases that the selectivity arises from the chiral environment created by the bound phosphate to the rhodium center.

In a previous section, we discussed the use of chiral phosphates with organozinc species, which could be enantioselectively reacted with aldehydes.<sup>457</sup> An earlier report of this concept was actually used by Charette to perform enantioselective Simons–Smith type cyclopropanations of styrenes **502** using a mixture of  $\text{Et}_2\text{Zn}$ ,  $\text{CH}_2\text{I}_2$ , and a stoichiometric amount of PA **19** (Figure 267).<sup>490</sup>

The reaction proceeds with modest yields and good levels of enantioselectivity for the products **503**. The problem was identified to be a strong background reaction that occurs in the absence of the phosphoric acid, which prevents higher levels of control being achieved. It was however shown that by using an appropriate zinc salt, a catalytic amount of PA **19** could be used, and high levels of enantioselectivity could still be achieved. It is proposed that coordination of the phosphoric acid to the cationic zinc center during the addition step is

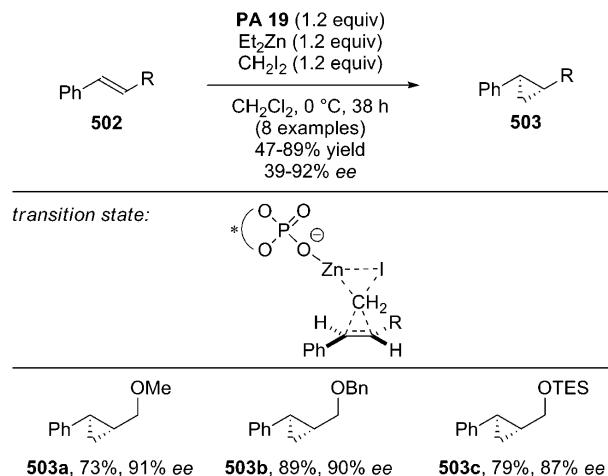


Figure 267. Cyclopropanation of alkenes using zinc metal by Charette (2005).

responsible for the enantioselectivity observed. Charette has also shown TADDOL phosphates to be suitable for performing enantioselective cyclopropanations.<sup>490b</sup>

A unique example of chiral metal phosphates being used to perform enantioselective processes was recently shown by Ollivier who reported a [2+2+2] cycloaddition using an in situ generated rhodium phosphate catalyst. First,  $[\text{Rh}(\text{cod})\text{Cl}]_2$ , a phosphine ligand, and Ag[*(S*)-PA **25**] were combined at 80 °C for 15 min to generate the active catalyst, which was shown to promote the reaction between **504** and **505** to give **506** as a mixture of atropisomers (Figure 268).<sup>491</sup>

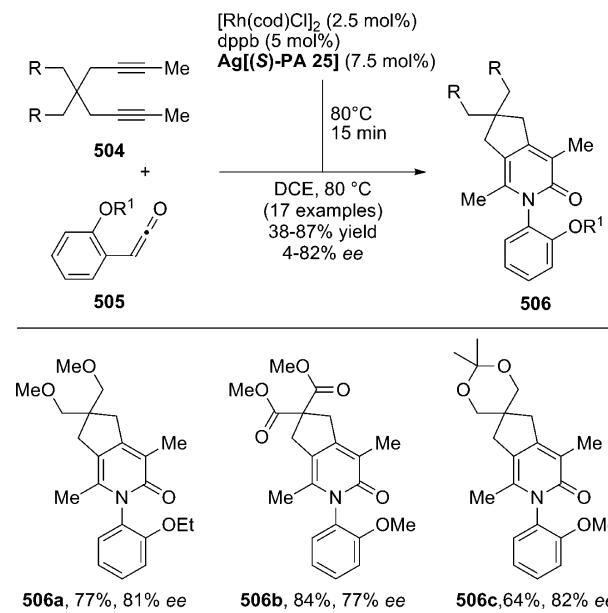


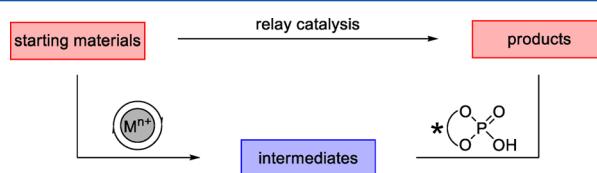
Figure 268. Atropselective [2+2+2] cycloadditions using a rhodium phosphate by Ollivier (2013).

The reaction provides the products **506** in modest yields and enantioselectivity; however, it represents a rare example of when a chiral phosphoric acid can be used to transfer axial chirality from itself to the products. In this case, it also provides an alternative to L-type ligands, which are commonly used with rhodium to induce enantioselectivity. The nature of the

selectivity is proposed to be due to a chiral counterion effect for the rhodium center.

### 3.3. Independent Relay Processes

In this section, we aim to cover cascade reactions whereby the metal catalyst performs the first process, and this is then followed by a phosphoric acid catalyzed step, or vice versa. It is worth noting that in some cases the enantioselective step may involve both the metal and the phosphoric acid at the same time, but we believe the phosphoric acid is not involved directly with the metal center. These so-called relay processes are incredibly powerful as simple molecular architecture can rapidly be transformed into complexity in a single pot.<sup>492</sup> The challenge in developing these processes is to find a system whereby the catalytic cycles of the metal and the phosphoric acid are fully compatible with one another in addition to all of the starting materials, products, and intermediates generated during the reaction (Figure 269).

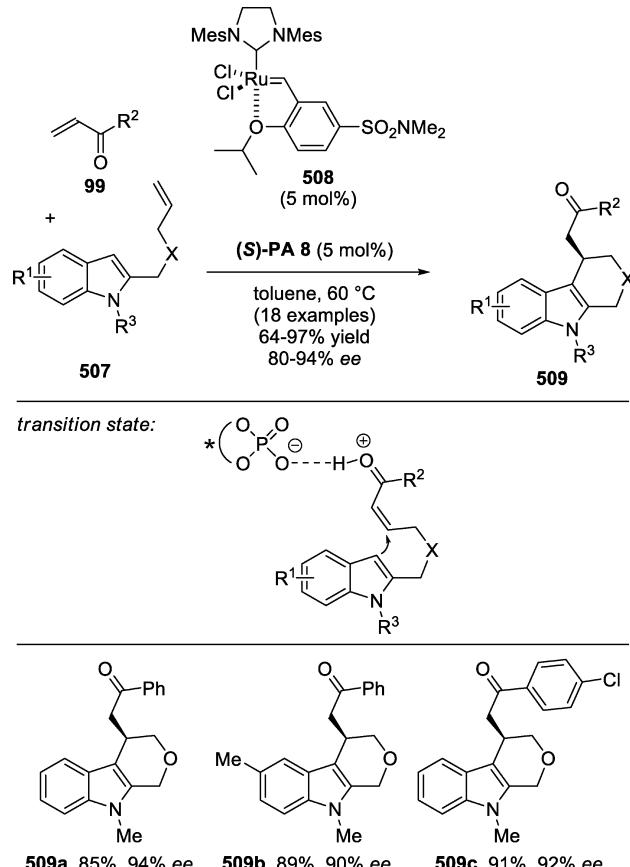


**Figure 269.** Generic overview of a relay process involving a metal and a phosphoric acid.

The role of phosphoric acid in these processes is relatively clearer than in the previous metal sections. In general, it behaves as a Brønsted acid toward the substrate(s) in question, and activation is carried out using one of the modes described earlier within this Review. Because many of the processes seen in this section only involve the metal, we will not discuss the metal-mediated transformation in detail but focus on the phosphoric acid's role.

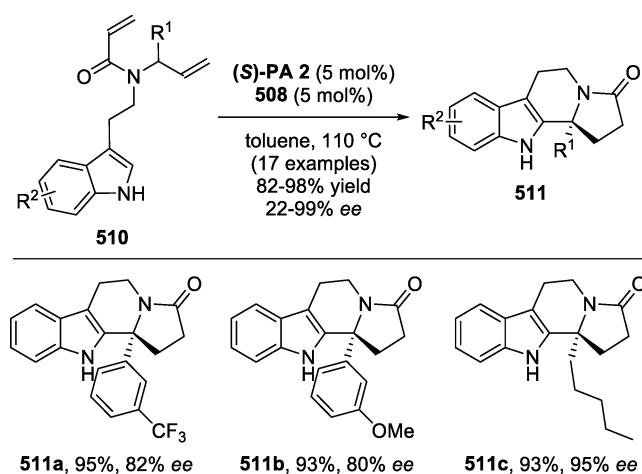
**3.3.1. Ring-Closing/Cross-Metathesis.** Within the field of metal-catalyzed reactions, ring-closing and cross-metathesis have become incredibly popular within the synthetic community.<sup>493</sup> The easily handled catalysts and commercial availability have helped in making this transformation a valuable tool that can be used by everyone. Cross-metathesis has the ability to transform seemingly unreactive terminal alkenes into functionalized alkenes for further transformations. As described in previous sections, alkenes and in particular functionalized alkenes are highly reactive groups for being activated by chiral phosphoric acids. The combination of a one-pot process would overcome the burden of tedious starting material synthesis, but the success would hinge on the compatibility of the metathesis catalyst in the presence of the acid. In 2009, You recognized the potential of combining a cross-metathesis process of terminal alkenes followed by a subsequent reaction of the newly formed alkene in a Friedel–Crafts-type reaction of indoles 507 (Figure 270).<sup>494</sup>

It is proposed that cross-metathesis of various enones 99 facilitated by the ruthenium catalyst 508 occurs first, and then the newly formed enone can be activated by (S)-PA 8 to undergo the Friedel–Crafts reaction to yield the products 509. Both catalytic cycles are thought to proceed independently but are compatible to be running in parallel to each other in one pot. A similar process has been described by You recently, which involves a chiral phosphoric acid-catalyzed oxo-Michael reaction following the initial cross-metathesis.<sup>495</sup>



**Figure 270.** Cross-metathesis/Friedel–Crafts cascade reaction by You (2009).

A related procedure involving the combination of a metathesis catalyst and a chiral phosphoric acid was published by the You group in 2012, which produced an exquisite cascade sequence to access tetrahydro-β-carbolines 511. Ruthenium catalyst 508 was used once again but to effect a ring-closing metathesis in substrates 510 (Figure 271).<sup>496</sup>



**Figure 271.** Ring-closing metathesis/isomerization/Pictet–Spengler cascade reaction by You (2012).

The proposed mechanism for the reaction is shown in Figure 272. Following the ring-closing metathesis, a double bond isomerization mediated by the phosphoric acid occurs,

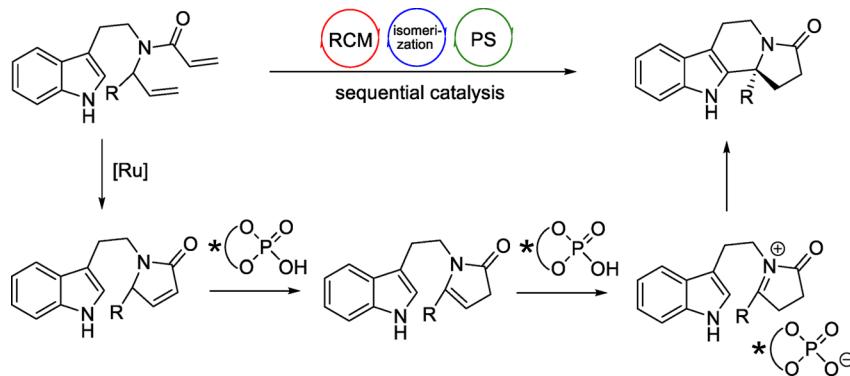


Figure 272. Mechanism of cascade process.

and subsequent activation of the resultant enamine intermediate enables the Pictet–Spengler reaction to proceed.

The products **511** are generally formed in high yields and enantioselectivities. Interestingly, the optimal catalyst was found to be the same as what the Dixon group<sup>396,397</sup> used in their studies on the Pictet–Spengler reaction of similar compounds and therefore suggests that the phosphoric acid process is independent of the metal-catalyzed process. The You group has also recently shown that the Hoveyda–Grubbs II catalyst can be used to isomerize allyl amines to enamines, which in the same pot can be activated by a chiral phosphoric acid to undergo a Pictet–Spengler reaction.<sup>497</sup> Metal-catalyzed double bond isomerization of allylic ethers to generate enol intermediates that can go on to react stereoselectively has also been shown by the groups of Terada and Scheidt.<sup>498</sup> A relay process involving a phosphoric acid-catalyzed allylation followed by ring-closing metathesis as the second step has also been studied by Fustero.<sup>499</sup>

**3.3.2. Hydroamination of Alkynes.** Hydroamination reactions are a useful tool to synthesize amines in an atom economic fashion.<sup>500</sup> The addition of an amine is usually carried out on alkynes because they are more reactive and can be activated sufficiently using transition metal catalysts. The initial product of a classic hydroamination of an alkyne is an enamine, and these are well-known precursors for chiral phosphoric acid catalysis, so therefore the opportunity for cascade process may be viable with the appropriate systems. The Gong group has been very interested in this concept and was one of the first to demonstrate the idea with a cascade reaction involving unsaturated anilines **512**. By taking a gold(I) catalyst in the presence of **PA 8** and **HE 2**, they showed that tetrahydroquinolines **209** could be prepared in good yields and with high levels of enantioselectivity (Figure 273).<sup>501</sup>

A general mechanism for the process is shown in Figure 274. The gold catalyst is first thought to activate the alkyne for a 6-*endo*-dig cyclization by the amine to yield a cyclic enamine. This enamine is then passed over for activation to the Brønsted acid and by combining with a Hantzsch ester can be reduced asymmetrically to give the desired enantioenriched products.

The relay catalytic system is remarkably compatible and shows a wide substrate scope. Because a vast number of enamine/imine reactions exist mediated by chiral phosphoric acids, it comes as no surprise that this generic concept has been used by Gong and other research groups for a wide range of related reactions all involving anilines.<sup>502</sup> Gong has recently also reported on a cascade process involving a hydroamination and then 1,5-hydrogen shift to synthesize cyclic aminals, which, however, needs to use an excess of chiral phosphoric acid to

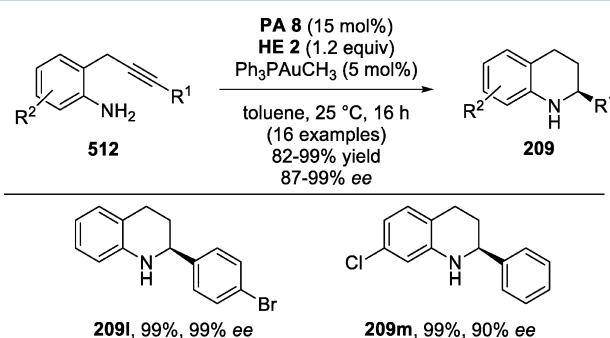


Figure 273. Relay catalysis by a gold complex/chiral Brønsted acid binary system by Gong.

achieve high enantioselectivities.<sup>503</sup> Because the phosphoric acid-catalyzed step(s) of the cascade processes cited here have been covered in previous sections, we will not discuss them again here.

Recently, the Dixon group has reported on an exquisite cascade process of the Pictet–Spengler type cyclization of *N*-sulfonyliminium species generated *in situ* from an initial hydroamination catalyzed by gold complex **514** (Figure 275).<sup>504</sup>

Indoles **513** were found to undergo the cyclization step, which is mediated by **PA 2** to give the polycyclic products **515** in good to high yields and high levels of enantioselectivity. Mechanistic studies from the group revealed that a careful choice of catalyst was required to prevent the key enantioselective cyclization step being catalyzed by the gold and thus providing lower selectivity. The catalyst in this case is acting as a chiral counterion to the generated iminium species.

**3.3.3. Cyclization of Alkynols.** The alcohol variant of the hydroamination reaction of alkynes also has the potential for relay catalysis because the initial products formed are enol ethers. Although the activation of carbonyl derivatives is notoriously more difficult than imine equivalents, there have been many cases of successful activation, and so the possibility of linking these processes with a metal-catalyzed procedure may be fruitful. An early example was shown by Gong of this concept where he has combined an alkynol cyclization catalyzed by a gold complex and intercepted the generated enol ether with a chiral phosphoric acid.<sup>505</sup> Tautomerization generated an oxonium ion, which could undergo reaction with azlactones with low enantioselectivities (<40% ee). In 2012, the concept was extended to a much more successful application of reacting silanols **517** with gold catalyst **514** to generate 1,3-silyloxydienes, which were shown to undergo an asymmetric Diels–Alder reaction with **518** to yield **518** (Figure 276).<sup>506</sup>

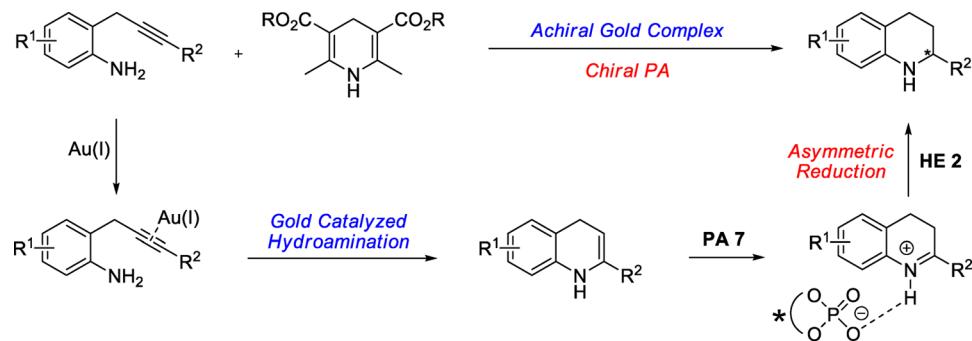


Figure 274. Mechanism of hydroamination/reduction cascade.

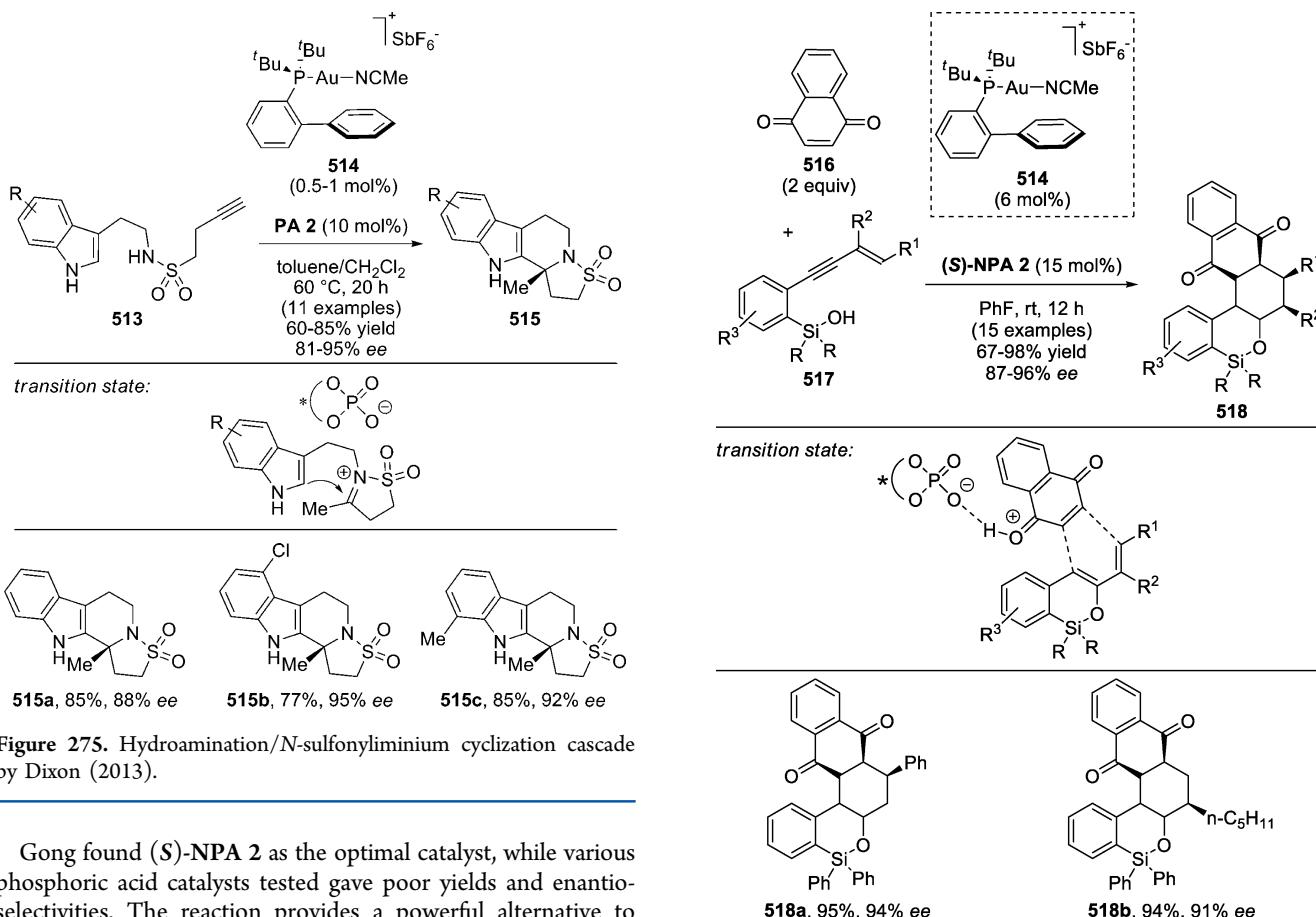


Figure 275. Hydroamination/N-sulfonyliminium cyclization cascade by Dixon (2013).

Gong found (S)-NPA 2 as the optimal catalyst, while various phosphoric acid catalysts tested gave poor yields and enantioselectivities. The reaction provides a powerful alternative to the classical Diels–Alder reaction of 1,3-silyloxydienes. The extension to alkyl enyne alcohols resulted in low enantioselectivities when BINOL-based phosphoric acids and phosphoramides were used.<sup>507</sup> Various research groups have also recently shown that the enol ether intermediates formed from gold catalyzed cyclizations of alkynols can be used as nucleophiles for the addition into imines.<sup>508</sup> Yao has also demonstrated a similar cascade process using palladium starting from 2-alkynyl aldehydes.<sup>465</sup> Zhang has shown that nitrones can also be used to generate enol derivatives that can add to internal imines activated by a chiral phosphoric acid.<sup>509</sup>

**3.3.4. Hydrogenation.** The transfer hydrogenation of unsaturated *N*-heterocycles is one of the most studied reactions in the library of phosphoric acid-mediated transformations. Typically the procedure involves the use of Hantzsch esters as the reducing agent but in some cases is needed in super stoichiometric amounts to achieve high conversions. In 2011, to overcome the need for this, Zhou developed a biomimetic-like

approach to regenerate the reducing agent using hydrogen gas and a transition metal catalyst. The combination of a dimeric ruthenium catalyst and hydrogen gas was shown to be an effective combination to reduce Hantzsch ester pyridines back to the parent Hantzsch esters. Using these conditions with 10 mol % of HE 2, it was shown that 519 could be reduced to give 222 in good yields and excellent stereoselectivity (Figure 277).<sup>510</sup>

The process is incredibly efficient, and the results obtained are identical to the stoichiometric variant of the reaction. The mechanism of the process is shown in Figure 278.

To achieve high stereoselectivity relies on the background reduction of the substrate to be slower than the phosphoric acid-catalyzed pathway. The Zhou group has also developed conditions for the reduction of various other *N*-heterocycles by using a self-transfer hydrogenation mediated by the substrate

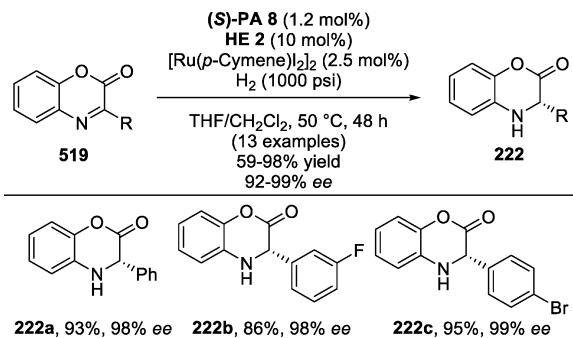


Figure 277. Hydrogenation of benzoxazinone by in situ generation of Hantzsch esters by Zhou (2011).

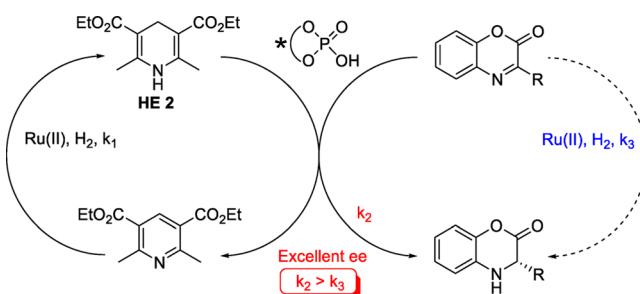


Figure 278. Catalytic hydrogenation of benzoxazinones by Zhou.

and a ruthenium catalyst/hydrogen gas system to regenerate the active reductant.<sup>511</sup>

**3.3.5. Reactions of Diazo-Compounds.** The reactions of diazo-compounds have previously been discussed within this Review to be useful substrates for chiral phosphoric acid catalysis. They are also very commonly decomposed by transition metals to yield metal carbenoids capable of doing a wide range of reactions. Within the field of diazo-compounds,  $\alpha$ -diazo carbonyls have received a great deal of attention and have been found to be particular good substrates for donor-acceptor type reactions.<sup>512</sup> Because electrophiles can be activated by chiral phosphoric acids, the possibility of combining both processes in an enantioselective manner should be viable. In 2008, Gong and Hu showed this concept with the three-component coupling reaction of diazo-carbonyls **520**, alcohol **521**, and imines **52** (Figure 279).<sup>513</sup>

The mechanism is thought to be decomposition of **520** with the rhodium catalyst to give a metal carbenoid, which can be attacked by the alcohol **521** to give a rhodium-enolate species that goes on to react with the imine that has been activated by PA 8. From a mechanistic point of view, the phosphoric acid is not thought to interact with the metal center, but bifunctional coordination to both the imine and the enolate-like species is postulated to be occurring. The Hu group has extended this concept to include a range of alternative nucleophiles and electrophiles to great effect.<sup>514</sup>

Gong has also utilized this concept toward aldehyde substrates, which are usually harder to activate with chiral phosphoric acids. By taking diazo-compound **523** with various anilines **35** and ethyl glyoxylate **134**, it was shown that with a rhodium catalyst it could react smoothly to give **524** in good yields and generally excellent enantioselectivities (Figure 280).<sup>515</sup>

Most phosphoric acids screened gave poor results, but PA 25 was found to be suitable, in particular in nonpolar solvents. Generally, electron-withdrawing substituents on the aniline

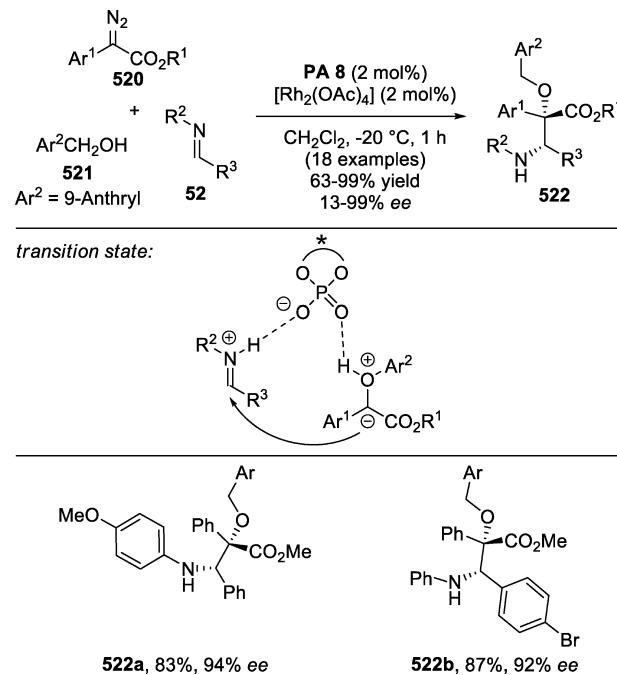


Figure 279. Three-component reactions of diazo compounds with alcohols and imines by Gong and Hu (2008).

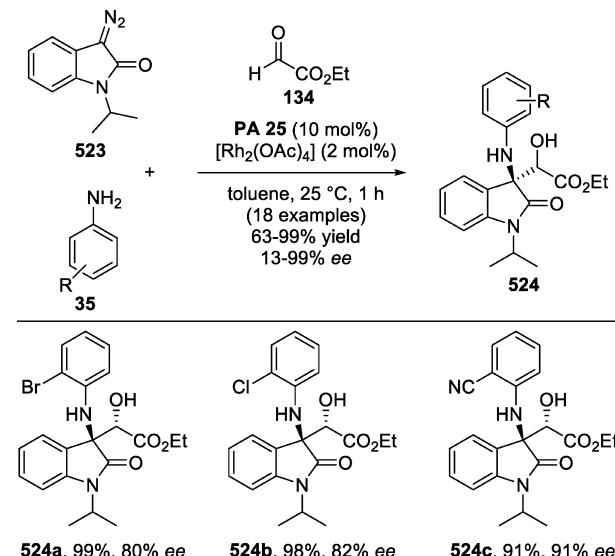


Figure 280. Catalytic cooperative asymmetric three-component Aldol-type reaction by Gong (2013).

were tolerated well except for nitro groups. The mechanism will closely follow that depicted in Figure 279.

In 2011, Zhou developed one of the classic reactions of metal carbenoids into an enantioselective process by using a spirocyclic chiral phosphoric acid, the insertion into N–H bonds. In the classical sense, the process is thought to occur in an intramolecular fashion, and so the control of stereochemistry is difficult. Zhou decided to use a phosphoric acid to assist the proton transfer and ultimately render it stereoselective. By taking compounds **520** with Boc-NH<sub>2</sub> **35b** in the presence of a rhodium catalyst and SPA 2, it was shown that the desired transformation to give **525** was possible in generally high enantioselectivities (Figure 281).<sup>516</sup>

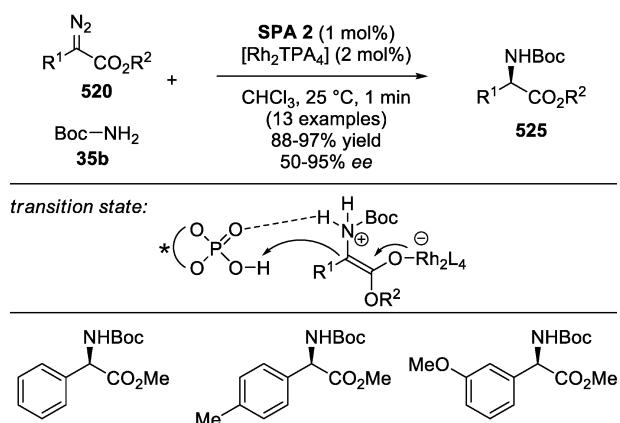


Figure 281. Asymmetric N–H insertion by Zhou (2011).

The group performed a series of mechanistic experiments to attempt to understand the mechanism and origin of stereo-selectivity. First,  $^{31}\text{P}$  NMR remained unchanged when the catalyst was mixed with the rhodium salt, suggesting no rhodium phosphate species is forming. Additionally, when the sodium salt of SPA 2 is used, the reaction still functions, but the products are obtained in low selectivity (<8% ee). This seems to suggest that an asymmetric protonation of a rhodium enolate-like species is occurring.

In 2012, Terada disclosed a relay process involving the decomposition of a diazo-compound using a rhodium catalyst followed by an asymmetric reduction mediated by a chiral phosphoric acid and a Hantzsch ester. Specially designed compounds **526** were found to undergo the desired transformation in the presence of 10 mol % PA 8 to give isochromenes **527** following a protection step (Figure 282).<sup>517</sup>

The reaction is believed to proceed via a phosphoric acid activated isobenzopyrylium ion intermediate, which can be reduced by the Hantzsch ester. The exact role of the phosphoric acid is unclear as in its absence, the reaction proceeds to give racemic products. The authors propose the catalyst may act as a chiral counterion for the rhodium center.

**3.3.6. Miscellaneous.** One of the first reports of combining a metal catalyst and a phosphoric acid catalyst in the same pot to carry out relay processes was reported by the Rueping group in 2007. They were able to show silver acetylides generated in situ from **464** could be stereoselectively reacted with imine **64b** to give the products **528** (Figure 283).<sup>518</sup>

Given the wide plethora of imine activation reactions involving phosphoric acids, it is thought that in this case the role of PA 8 is simply to activate the imine toward attack by the silver acetylides. An alternative mechanism involving a chiral silver phosphate counterion can also be considered.

Chiral phosphates<sup>488,489,519</sup> have been known to be able to control the stereochemistry of a variety of reactions, and the Toste group is well recognized for their important contributions relating to the exploitation of chiral phosphates in the field of asymmetric catalysis. In 2008, they reported a powerful strategy for the opening of *meso*-aziridinium ions with alcohol nucleophiles. Treatment of racemic chloroamine **529** with Ag[*(S*)-PA 25] resulted in chloride abstraction and concomitant cyclization of nitrogen to form *meso*-aziridinium ion **530** containing the bound chiral phosphate. This subsequently can be opened stereoselectively with a variety of alcohol nucleophiles to yield **531** (Figure 284).<sup>520</sup>

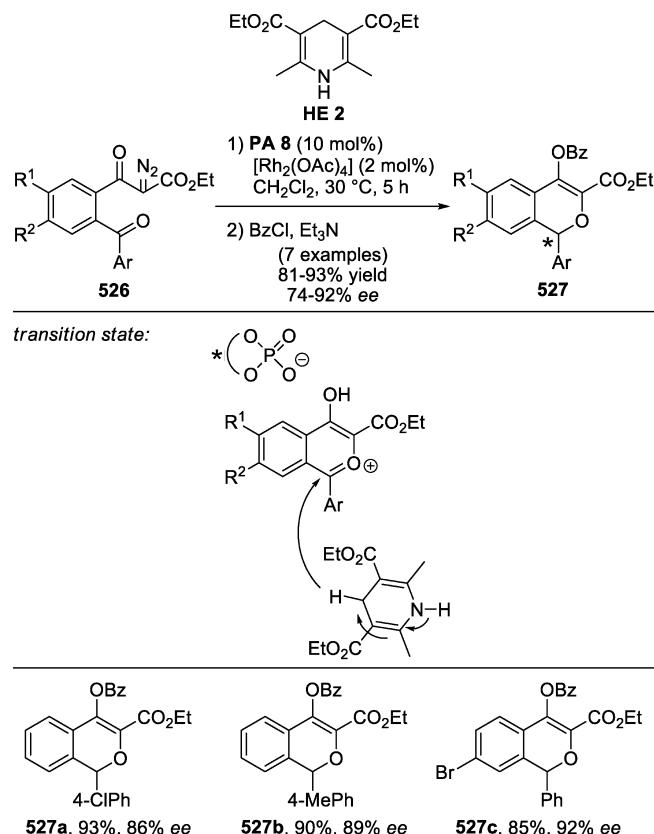


Figure 282. Enantioselective reductions using a rhodium catalyst by Terada (2012).

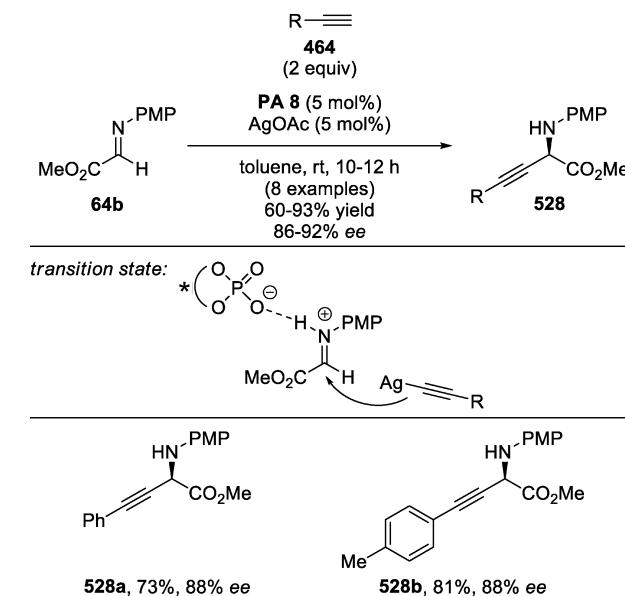


Figure 283. Alkylation of imines by Rueping (2007).

The biggest challenge for the reaction is the reforming of the Ag[PA 25] following the catalytic cycle. The group found that a rather insoluble silver salt,  $\text{Ag}_2\text{CO}_3$ , could facilitate this reforming without interference to the asymmetric process. Because of its insolubility, the achiral silver salt is kept away from the substrate in what can be thought of as a chiral-anion phase-transfer process. The group was also able to extend this process to the opening of episulfonium ions too.

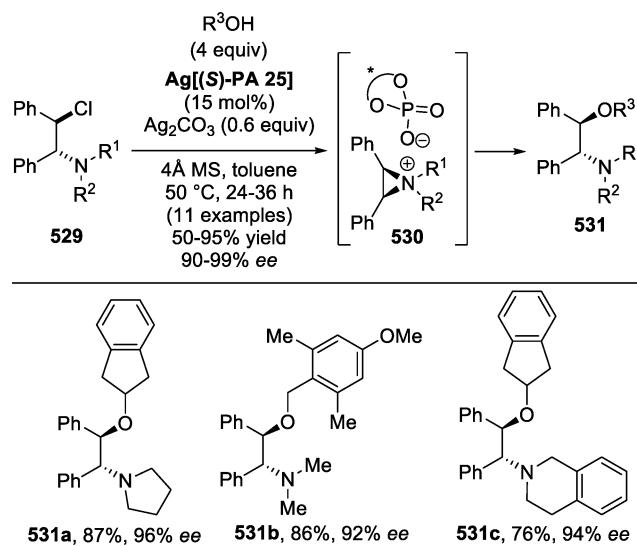
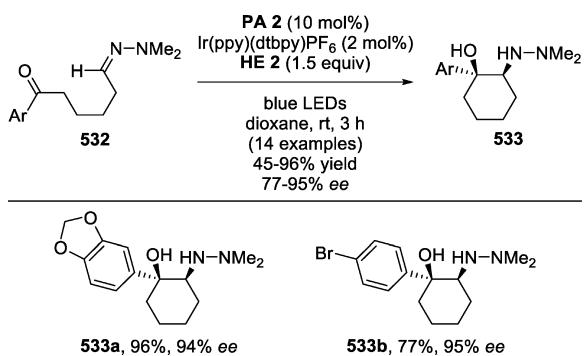
Figure 284. Ring opening of *meso*-aziridinium by Toste (2008).

Figure 285. Photoredox aza-Pinacol reaction by Knowles (2013).

In general, asymmetric radical reactions are scarcely found to be able to be catalyzed by chiral phosphoric acids. On the whole, asymmetric radical reactions still remain a difficult challenge to control asymmetrically. Recent work by Knowles has made some progress on the use of chiral Brønsted acids on controlling the cyclization of ketyl radicals. He showed that by taking aromatic ketones 532 and irradiating with blue LEDs in the presence of  $\text{Ir}(\text{ppy})(\text{dtbpy})\text{PF}_6$  (2 mol %) and Hantzsch ester, the aza-Pinacol reaction could be performed to yield 1,2-amino alcohols 533 (Figure 285).<sup>521</sup>

The Hantzsch ester plays a crucial role in the cycle as it is needed as a stoichiometric reductant and to act as an acid to regenerate the phosphoric acid so that it can enter the catalytic cycle again. The proposed mechanism for the reaction is shown in Figure 286.

The reaction starts by initial reduction of Ir(III) to Ir(II) mediated by light and the Hantzsch ester. Activation of the ketone by hydrogen bonding and electron transfer forms a neutral ketyl radical still H-bonded to the catalyst. This process is formally known as a proton-coupled electron transfer (PCET). Subsequent cyclization and further reduction by the Hantzsch ester yields the product. Further electron- and proton-transfers regenerate both the iridium and the phosphoric acid catalyst to enter the cycle again. The group was also able to carry out DFT evaluations of the relative strengths of various hydrogen bonds derived from ketyls. Rather surprisingly, it was found that the ketyl-radical H-bond was stronger than a variety of other H-bonds including that of neutral alcohols and carboxylic acids.

#### 4. CONCLUSIONS AND OUTLOOK

Brønsted acid catalysis is one of the wide-ranging disciplines to exist in organic chemistry. The asymmetric division within this field has received a tremendous amount of attention from research groups all around the world, and now it can truly be

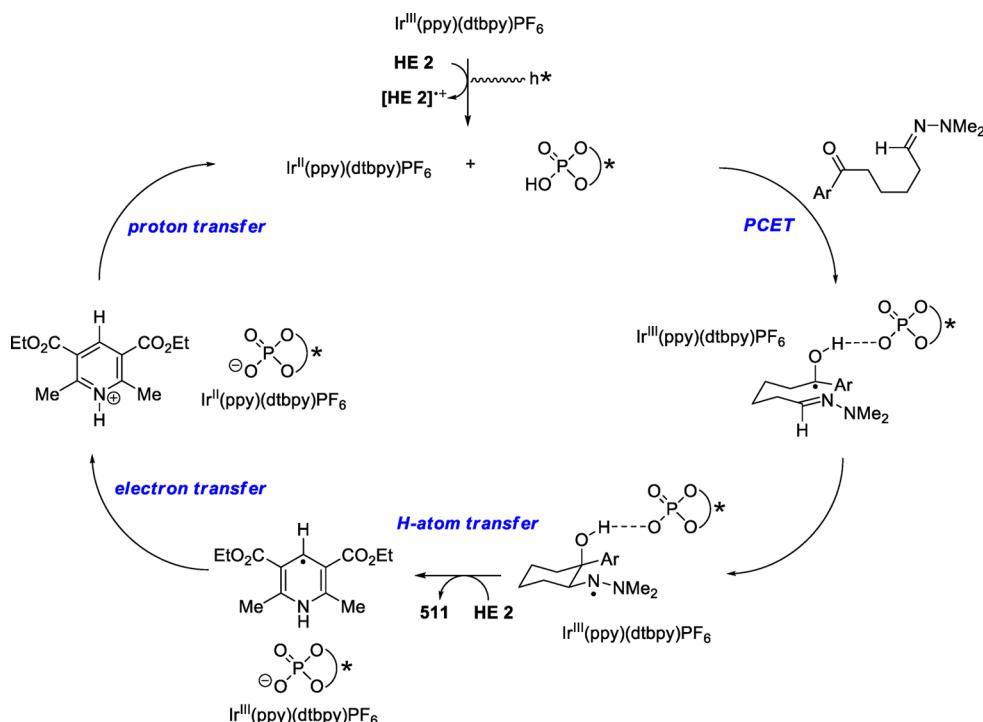


Figure 286. Aza-pinacol mechanism (Knowles).

Table 2. Classification by Reaction Type

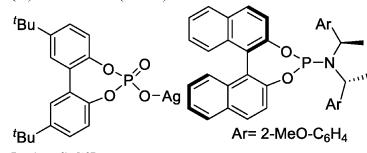
Reaction	Figure	Catalyst	Reference
Acetalization	82	PA 43 (S)-NPA 11	374 151
Addition of <i>alcohols to imines</i>	84	PA 7	152
<i>alkynes to <math>\alpha,\beta</math>-unsaturated aldehydes</i>	250	(S)-PA 25/phosphine ligand/mesitylcopper/Li(OC <sub>6</sub> H <sub>4</sub> -p-OMe)	461
<i>azlactones to vinyl indoles</i>	185	PA 16	361
<i>enamine to N,O-acetals</i>	77	PA 22 or PA 25	142
<i>enol ethers to imines</i>	25	PA 25	53
<i>imides to imines</i>	87	(S)-PA 36	155
<i>peroxides to imines</i>	90	PA 7	158
<i>sulfonamides to imines</i>	86	(S)-PA 36	154
<i>thiols to imines</i>	85	PA 25	153
Amination of			
<i>alcohols</i>	241	PA 25/ Ca[PA 10] <sub>2</sub>	477 452
<i>enamides</i>			
Aldol reaction	70	PA 25	129
	72	[H8]-PA 24	130
		[H8]-PA 24	131
	280	PA 25/[Rh <sub>2</sub> (OAc) <sub>4</sub> ]	515
Alkylation - S <sub>N</sub> 2-type	162	(S)-PA 25	333
Alkylation of <i>enamides</i>	184	[H8]-PA 10	357
<i>ketones</i>		PA 14	359
Alkynylation	283	PA 8/ AgOAc	518
Allenylation		PA 25	171
Allylation	93	PA 25	164
		SPA 4	166
	245	PA 25/[Ir] <sup>t</sup> -PCy <sub>3</sub>	456
	246	(S)-PA 25/Zn	457
	252	(S)-PA 25/Pd(PPh <sub>3</sub> ) <sub>4</sub>	468
<i>Benz-2-(3<i>H</i>)-ones</i>			471
		[Ir(cod)Cl] <sub>2</sub>	
		amine salt[[H8]-PA 25]/Pd <sub>2</sub> (dba) <sub>3</sub>	472
Allylic alkylation		(S)-PA 25	383
		PA 1/Ligand/Pd(dba) <sub>2</sub>	470
Allylic substitution	197	[H8]-NPA 6	382
Amidoalkylation		PA 20; PA 25	354a; 354b
$\alpha$ -Aminoxylation	160	PA 7	329
Aza-Cope rearrangement	53	[H8]-PA 6	94
Aza-Darzens	22	PA 3 Mg[PA-37]	50 422a
Aza-Ene	70	PA 11	128
	76	PA 7	140

Table 2. continued

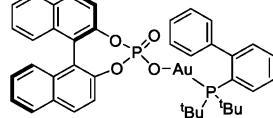
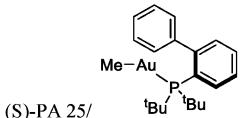
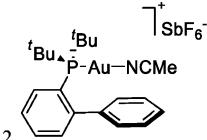
Reaction	Figure	Catalyst	Reference
Aza-Henry	91	[H8]-PA 2	160
Aza-Pinacol	285	PA 2/Ir(ppy)(dtbpy)PF <sub>6</sub>	521
Aziridination	23 24	PA 7 (S)-NPA 6	51 52
Baeyer-Villiger	97	[H8]-PA 9	174; 175
Benzidine rearrangement		PA 20	137; 138
Benzoyloxylation	240	Ca[PA 37] <sub>2</sub>	450
Biginelli	152	PA 43 [H8]-PA 10 PA 2 (S)-SPA (Ar: 1-naphthyl) PA or [H8]-PA	306 313 314 315 316
Bromination	161	[H8]-PA 7 [H8]-PA 7 PA 25 or Ca[PA 25] <sub>2</sub>	331 332 452
Bromocycloetherification	210	(S)-PA 25	399
Bromocyclization	102	(S)-PA 25	182
Bromoesterification		PA 8	401
Carbocyclization	247	Ag[(S)-PA 25]/IrCl(CO)(PPh <sub>3</sub> ) <sub>2</sub>	458
Carbonyl-Ene	56 230	[H8]-NPA 7 Ca[[H8]-PA 14] <sub>2</sub>	98 430
<hr/>			
Cascade			
<i>aza-ene/cyclization</i>	170	PA 16	343
<i>condensation/amine addition</i>	80	(S)-PA 29	147
	81	PA 7	148
		PA 7	149
		(S)-SPA 1	150
<i>condensation/cyclization</i>	209	[H8]-PA 2	396
		PA 2	397
<i>condensation/hydroamination</i>		(S)-PA 7/Ph <sub>3</sub> PAuMe	502b
<i>condensation/reduction</i>	123	PA 7 or PA 25	247
		PA 8	242
<i>cycloaddition/intramolecular hydroamination</i>			502a
<i>cyclization/Friedel-Crafts</i>	227	Ag[(S)-PA 28]	427
<i>cyclization/reduction</i>		PA 25	243
	121	PA 25	244; 245
	122	(S)-PA 8	246
		[H8]-PA 2/Cu(OTf) <sub>2</sub> /AgNO <sub>3</sub>	463
		Ag[PA 18]	464
		PA 7/(tBu) <sub>2</sub> (o-diphenyl)PAu(CH <sub>3</sub> CN)SbF <sub>6</sub>	502c
			502d
<i>hydroalkoxylation/isomerization/[4 + 2]</i>		(S)-PA 10/ Ph <sub>3</sub> PAuCl	507
<i>cycloaddition</i>			
<i>hydroamination/cyclization</i>	274	PA 2	504
<i>hydroamination/redox</i>		PA 25/PPh <sub>3</sub> AuNTf <sub>2</sub>	503

Table 2. continued

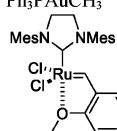
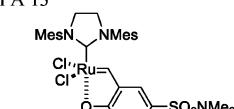
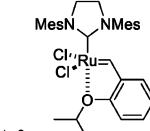
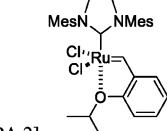
Reaction	Figure	Catalyst	Reference
hydroamination/reduction	273	PA 8 / Ph <sub>3</sub> P AuCH <sub>3</sub>	501
			
isomerization/Pictet-Spengler Mannich/Michael	171	SPA 1 PA 6 [H8]-PA 13	497 201 344
			
metathesis/Friedel-Crafts	270	(S)-PA 8	494
			
metathesis/isomerization/Pictet-Spengler	271	(S)-PA 2	496
			
metathesis/ oxo-Michael Michael/cyclization	59	[(S)-PA 2]	495
	172	PA 1	102
	173	(S)-PA 20	345
Michael/Pictet Spengler photocyclization/reduction	173	[H8]-PA 2	346
reductive amination/aza-Michael	124	PA 25	248
	120	PA 25	237
redox-pinacol-Mannich		PA 7	241
		PA 7/[AuCl(JohnPhos)]/AgSbF <sub>6</sub>	509
Chlorination		Ca[PA 37] <sub>2</sub>	451
C-H activation	187	PA 34	364
C-N bond forming	189	PA 39	366
Cyanosilylation		PA 10/n-Buli	428
Cycloisomerization	251	Cu[(S)-PA 25] <sub>2</sub>	462
Cyclopropanation	267	PA 19/Et <sub>2</sub> Zn	490
1,3-Dipolar cycloadditions	47	NPA 10	84
	48	PA 19	85
	49	PA 19	86
	50	[H8]-NPA 9	87
	64	PA 42	113; 114
		PA 42	115a; 115c; 115e;
			118a; 119
		PA 7	115b; 115d; 115f;
	65	PA 25	115g; 118b
	66	PA 6	116
		PA 44	117
			348
[2+2+2] cycloaddition	268	Ag[(S)-PA 25]/ [Rh(cod)Cl] <sub>2</sub> /dppb	491
Deracemization of <i>α</i> -aryl hydrocoumarins 3 <i>H</i> -indolines	218	PA 20 or PA 21	409
	206	(S)-PA 25	390
Desymmetrization	89	(S)-PA 36	157
	99	PA 25	179
	100	NPA 9	180
	147	(S)-PA 28	300
	161	[H8]-PA 7	331
	168	(S)-NTA 1	339

Table 2. continued

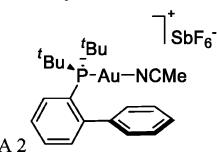
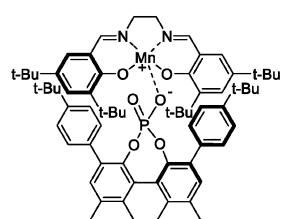
Reaction	Figure	Catalyst	Reference
	169	SPA 1	340
		PA 25	341
		(S)-SPA 4	370
	195	(S)-PA 37	378
		PA 37	379–381
	230	Au[PA 25]( <sup>t</sup> Bu <sub>3</sub> P)	440
	242	(S)-NPA 5/Cu(OTf) <sub>2</sub>	454
	284	Ag[(S)-PA 25]	520
DFT calculations			
DFT - allylboration			165c
DFT- C-H activation			365
DFT - Friedel Crafts	125		249 273
DFT - hydrophosphonylation			162
DFT - imine reactions	73		21
DFT - propargylation			165a; 165b
DFT - Strecker			290
Diamination	249	Cu[PA 1]:P(Np) <sub>3</sub>	460
Diels-Alder	52	(S)-NPA 9	41; 92
	67	PA 40	122
		PA 25	123
		PA 7	124
	68	PA 10	125
	150	PA 25	310
	151	SPA 4	311
	174	PA 44	347
		PA 25	349
	237	Yb[PA 1] Mg[PA 8] <sub>2</sub> Ca[PA 25] <sub>2</sub>	442; 443
	238	(S)-PA 18/InBr <sub>3</sub>	4446
	276		506
6π - Electrocyclization	51	(S)-PA 7	88; 89
	212	PA 8	402
Epoxidation of			
alkenes	262		482
enals	177	PA 41	351
Fischer-Indole	74	SPA 1	136
Fluorination	201	PA 33	386
	207	SPA 4	392
		PA (Ar: 2,4,6-(C <sub>5</sub> H <sub>10</sub> ) <sub>3</sub> -C <sub>6</sub> H <sub>2</sub> )	393a
	208	[H8]-PA25	394
Friedel-Crafts	30	PA 23	62
	31	PA 2	63
	32	PA 22	64
	33	NPA 8	65
	34	(S)-PA2	66
	35	NPA 9	68
	36	PA 16	69
	37	[H8]-NPA 1	70
	39	(S)-PA 17	72
	40	(S)-NPA 9	73
	41	(S)-NPA 3	74

Table 2. continued

Reaction	Figure	Catalyst	Reference
	88	(S)-PA 25	156
		PA 25	67
		SPA 4	220
	126	(S)-PA 5	250
		PA 2	251
		(S)-PA 25	252
		(S)-PA 8	253
		(S)-SPA 2	254
		SPA 2	255
		PA 43	42a
	127	(S)-PA 2	256
		PA 2	257
		PA 17 (Polymer)	258
	128	PA 25	260
		(S)-PA 25	261
	129	[H8]-PA 2	262
		(S)-PA 24	263
	130	PA 25	264
		(S)-PA 25	265
	131	[H8]-PA 6	266
		(S)-PA 2	267
	132	PA 25	268
		[H8]-PA 5	269
		(S)-PA (Ar= 4-Ad-2,6-(iPr) <sub>2</sub> C <sub>6</sub> H <sub>2</sub> )	270
	133	(S)-PA 25	271
	134	PA 2	272
		(S)-PA 7	274
		[H8]-PA 2	275
		[H8]-PA	276
	135	(S)-PA 7	277
	136	[H8]-PA 13	278
		PA 15; (S)-PA 7	279
			43
		<b>255</b>	
		Ar = 2,4,6-(iPr) <sub>3</sub> C <sub>6</sub> H <sub>2</sub>	
		PA 17	280
		PA 29	281
	179	[H8]-NPA 1	352
		PA 8	354c
	183	PA 10	356
		(S)-PA 5	358
		PA 1	360
	227	Ag[(S)-PA 28]	427
		Ca[[H8]-PA 14] <sub>2</sub>	430
	232	(S)-PA 16/MgF <sub>2</sub>	434
		PA 8/FeCl <sub>3</sub>	435
		(S)-PA 16/In ((3,5-(CF <sub>3</sub> ) <sub>2</sub> C <sub>6</sub> H <sub>3</sub> ) <sub>4</sub> B) <sub>3</sub>	447
		Ag[PA 1]/Yb(OTf) <sub>3</sub>	448
Friedländer condensation	79	PA 16	144
	123	PA 7 or PA 25	247
Glycoxylation		PA 17	367
Halocyclization	203	PA 32	389
	204	[H8]-PA 25	390
Haloetherification		Na[(S)-[H8]-PA 2]	400
Hydrocyanation of vinyl ether		PA 25	375
enone	231	Na[PA 4]	432
chalcone		(S)-PA (X: Ad)/NaNH <sub>2</sub>	
Hydroalkoxylation	233	Ag[PA 25]	436
		Ag[(S)-PA 16]	438
	235	Ag[PA 25]	439
	263	[H8]-PA 38/RuH <sub>2</sub> (CO)(PPh <sub>3</sub> ) <sub>3</sub>	485; 486
Hydroamination	101	PA 2	181

Table 2. continued

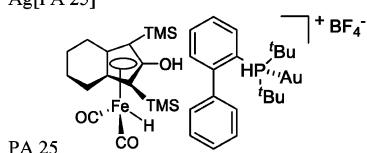
Reaction	Figure	Catalyst	Reference
223		Ag[PA 25]	436
235		Ag[PA 25]	439
			479c
Hydrophosphonylation	92	PA 20 SPA (Ar: 4-biphenyl)	161 163
$\alpha$ -Hydroxylation	159	PA 2	328
Hydrovinylation	264	$\text{R}^1(\text{R}^2)_2\text{P}-\overset{\text{H}}{\underset{\text{Cl}}{\text{Ru}}}(\text{OC})-\text{PR}^1(\text{R}^2)_2$ Ag[(S)-PA 25]/	487
Iodination		[H8]-PA 25	393b
Kabachnik-Fields reaction	155	(S)-PA 29	318
Kinetic resolution of			
alcohols	243	Ag[(S)-PA 16]	455
	164	PA 31	336
		(S)-PA 25	388
allenyl boronates		PA 25	170
allyl boronates		PA 25	167
azlactones	161	[H8]-PA 7	331
benzylic sulfonamides	57	PA 7	100
carboxylic acids	163	PA 15	335
cyclohexenones	60	113	105; 106
homoaldols	165	PA 25	337
hydroxy esters		(S)-SPA 4	369
indolines	166	(S)-PA 25	334
		PA 25	338
Mannich	5	PA 15	15
	6	PA 19	19
		PA 7 or Ca[PA 6] <sub>2</sub>	35a
	43	(S)-PA 35	76
	44	PA 24	77
		PA 24	78 - 81
	45	PA-2	82
	46	[H8]-NPA 4	83
	69	PA 30	127
	138	PA 6	282
	139	PA 13 or [H8]-PA 10 or [H8]-PA 12	283
	140	PA 25	284
		(S)-PA (Ar: 3,5-(4-F-C <sub>6</sub> H <sub>4</sub> ) <sub>2</sub> -C <sub>6</sub> H <sub>3</sub> )	285
		Ca[PA-25] <sub>2</sub>	421
		Ag[PA 2]	422b
Michael	145	[H8]-PA 20	298
	146	(S)-PA 2	299
	147	(S)-PA 28	300
		RE[PA] <sub>3</sub>	431
		Ca[PA 37] <sub>2</sub>	451
Multi-component	54	PA 24	96
	55	PA 25	97
	139	PA 13 or [H8]-PA 110 or [H8]-PA 12	283
		PA 43	42b
	148	(S)-[H8]-PA 8	304
		PA 2	305
		PA 43	306
		(S)-PA 25	307
	149	(S)-SPA 3	308
		PA 13	309
	150	PA 25	310
	151	SPA 4	311
		(S)-SPA 4	312

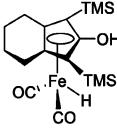
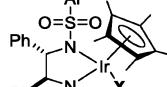
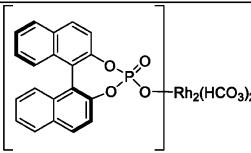
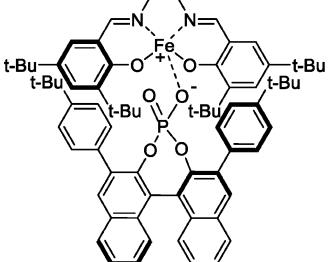
Table 2. continued

Reaction	Figure	Catalyst	Reference
	152	[H8]-PA 10	313
		PA 2	314
		(S)-SPA (Ar: 1-naphthyl)	315
		PA or [H8]-PA	316
	154	(S)-PA 25	317
	155	(S)-PA 29	318
	156	[H8]-PA 13	320
		[H8]-PA 13	321; 322
		[H8]-PA 7	325
	157	(S)-PA 25	326
	279	PA 8/[Rh <sub>2</sub> (OAc) <sub>4</sub> ]	513
	280	PA 25/[Rh <sub>2</sub> (OAc) <sub>4</sub> ]	515
		PA 2/PPh <sub>3</sub> AuMe	508a
		PA 7/(JohnPhos)AuMe	508b
		PA 25/(JohnPhos)AuMe	508c
		PA 8/[Rh <sub>2</sub> (OAc) <sub>4</sub> ]	514a
Natural products			
(+)-Folicanthine	219	(S)-PA 6	410
(+)-Gliocladin C		(S)-PA 7	411
(-)-Arboricine		[H8]-PA 2	395d
(-)-Corynantheidine	220	[H8]-PA 2	412
(-)-Debromoflustramine B	221	PA 25	413
Hopeanol and Hopeahainol A		PA 36	414
(S)-(−)-Hydroxymatairesinol	246	(S)-PA 25/Zn	457
Nazarov cyclizations	62; 63	NPA 4	109; 112; 110
		NPA 3	111
		NPA 4	405
N-H functionalization of indoles	181	PA 25	355
N-H insertion	281	SPA 2/[Rh <sub>2</sub> TPA <sub>4</sub> ]	516
Overman rearrangement			469
Passerini	228	PA 13/Et <sub>2</sub> AlCl	429
Phosphination	225	Mg[PA 7] <sub>2</sub>	424
Pictet-Spengler	143	(S)-PA 25	292
	144	(S)-PA 25	295
		PA 20	395a
		PA 2	395c
		[H8]-PA 2	395d
Pinacol rearrangement	186	[H8]-PA 5	362
Povarov	156	[H8]-PA 13	320
		[H8]-PA 13	321; 322
		PA 6	323
		PA 2	324
		[H8]-PA 7	325
	157	(S)-PA 25	326
	158	[H8]-PA 7	327
Propargylation	96	PA 25	169
		PA 25	170
Protonation of			
ketene dithioacetals	218	PA 20 or PA 21	409
silyl enol ethers	213	(S)-NTA 3	404
silyl ketene imines	216	(S) PA 25 or (S) SPA 4	408

Table 2. continued

Reaction	Figure	Catalyst	Reference
Rearrangement of epoxides	58	N-SPA 1	101
Reduction of			
benzodiazepines (with HEH)		[H8]-PA 10	227
benzodiazepinones (with HEH)		[H8]-PA 6	228
benzopyrylium ion (with HEH)	193	[H8]-PA 25	376
benzoxazines (with HEH)	114	PA 8 PA 8 (Polymer) PA (Polymer) [H8]-PA 2	216 217a 217b 224
benzoxazines (with H <sub>2</sub> )		PA 7/ PA 8	479b 216
benzoxazinone (with HEH)	277	(S)-PA 8/[Ru(p-Cymene)I <sub>2</sub> ]/H <sub>2</sub>	510
benzthiazines (with HEH)	114	PA 8	217
carbonyl ylides (with HEH)	282	PA 8/[Rh <sub>2</sub> (OAc) <sub>4</sub> ]	517
CF <sub>3</sub> -ketimines (with benzothiazolines)		PA 17	235
α-CF <sub>3</sub> -substituted acrylic acids		(S)-PA (R= ethyl)/[Rd(cod) <sub>2</sub> PF <sub>6</sub> ]	478
enamines (with HEH)	108	(S)-PA 7	200
hydroxyl imines (with HEH)	107	(S)-PA 2	199
hydroxylactams (with HEH)		(S)-PA 2	354d
imines (with HEH)	105	PA 20 (S)-PA 25	194 195
imines (with benzothiazoline)	117; 118	PA 25	233; 236; 237; 238
imines (with catecholborane)	119	NPA 9	239
imines (with H <sub>2</sub> )	257	PA 25	476a
α-imino esters (with HEH)	258	(S)-PA 25	479a; 479c
α-imino esters (with benzothiazoline)	106	(S)-PA 37 (S)-PA 7 PA 25	196 197; 198 234
α-imino esters (with catecholborane)		PA 25	240
3H-indoles (with HEH)		PA 7	229
N,O-acetals (with HEH)	109	PA 37	202
ketones (with catecholborane)	95	PA 7	168
phenanthrolines (with HEH)		PA 6 or PA 8	226
pyridines (with HEH)	115	PA 7 SPA 4	218 220
quinolines (with HEH)	112	PA 8 PA 8 PA 7 (Polymer) PA 8 (Polymer)	211 212 44 217a
		PA 8 PA 42 PA based on Fe-bridged Paracyclophane frameworks [H8]-PA 2 (S)-[H8]-PA 14 [H8]-PA 2	213 214 215 222 223
	215	[H8]-PA 2	224
	226	[H8]-PA 2 PA 25/[MesAuMe]	406 426
quinolines (with H <sub>2</sub> )	260	[H8]-NPA 4/	480

Table 2. continued

Reaction	Figure	Catalyst	Reference
quinoxalines (with $H_2$ )		(S)-PA 7/[Ru( <i>p</i> -cymene) $I_2$ ] <sub>2</sub>	511
			
quinoxalines (with HEH)	PA 7/ PA 7		479b 225
	PA 25		243
quinoxalinones (with HEH)	PA 7 PA 25		225 243
Reductive amination with HEH with benzothiazolines	110 PA 2 PA 17		204 235
with $H_2$	PA 25		476b
Robinson annulations	145 165	[H8]-PA 20 PA 25	298 337
Self-coupling of enamides	78	PA 15	143
Semipinacol rearrangement	98 256	PA 25 (S)-PA 25/Pd(OAc) <sub>2</sub> /benzoquinone	178 473
2,3-Sigmatropic rearrangement	266		488
Spiroketalization	190	(S)-PA 43 (S)-PA 25	371 373
Strecker	27 141	PA 15 (S)-PA 8 PA 8 Na[PA 1]	56 57 288; 289 423
Sulfoxidation			483
	PA5 PA 43		133 134
Transacetalization	190	(S)-PA 25 (S)-SPA 4	368 369
Wagner-Meerwein rearrangement		PA (Ar: 2,4,6-(C <sub>5</sub> H <sub>10</sub> ) <sub>3</sub> -C <sub>6</sub> H <sub>2</sub> ) [H8]-PA 25	393a 393c

considered as an essential tool for any organic chemist. Currently, the choice of chiral Brønsted acids in the literature is vast and varied; however, one of the most powerful and prominent class of catalysts that are utilized are the BINOL-derived phosphoric acids and their related family members. Originally, the catalysts were used as simple resolving agents for chiral amines and then later in 1992 were seen as promoters for

enantioselective cyclizations of rhodium carbenes formed from diazo-compounds. Only in 2004, over 10 years later were they fully introduced to the synthetic community as organocatalysts. Since then though, they have gone on to reach levels of fame that could never have been imagined over the past decade.

Chiral BINOL-derived Brønsted acids have shown themselves to be highly efficient catalysts for a huge plethora of

transformations and allow the end user to form C–C, C–H, and a variety of C–X bonds in a highly enantioselective fashion (Table 2). Although within this category phosphoric acids are strongly known for activating imine substrates, stronger acids in the form of *N*-triflyl phosphoramides have bridged the gap somewhat to accessing previously thought out-of-reach substrates. Their utility in synthesis however is not solely limited to their acidic character, and more recently they have become extremely powerful chiral counterions for an increasing list of reactions. Furthermore, they can be combined with metal catalysts to create a synergistic effect, which has opened new reaction modes previously not possible with the individual catalysts themselves.

Improved understanding of the mechanisms and interactions associated between the catalyst and the substrates has allowed research groups to develop highly powerful methodologies. Unfortunately, our understanding is still far from complete, and currently we have a crude understanding of how the catalysts function, but detailed experimental and computational studies are still required for further progress in the field. Our knowledge on the exact nature of enantioselectivity is also lacking, and hence for a large selection of reactions we are unable to predict the absolute stereochemistry prior to measurement. On a critical note, it is still common to find methodologies that utilize high catalyst loadings, and this may be a parameter that can be improved with better understanding. Having said that, since their introduction as organocatalysts, research groups have provided a rich wealth of methodologies that can be catalyzed by BINOL-derived Brønsted acids. They have covered a wide range of topics and have continued to push the boundaries of what can be achieved. We anticipate that the ability and scope of these catalysts will grow in the future, and we envision that the following decade will be equally exciting for the synthetic organic community.

## AUTHOR INFORMATION

### Corresponding Author

\*E-mail: magnus.rueping@rwth-aachen.de.

### Notes

The authors declare no competing financial interest.

### Biographies



Dixit Parmar obtained his M.Chem. degree in Chemistry with first class honors from the University of Manchester in 2008. He stayed there further to conduct his Ph.D. with Prof. David Procter on the development of reductive lactone cyclization cascades mediated by  $\text{SmI}_2\text{-H}_2\text{O}$ . In 2012, he moved to RWTH Aachen University as a

postdoctoral researcher in the group of Prof. Magnus Rueping. Currently he is an Alexander von Humboldt fellow, and his research interests include organocatalysis and asymmetric fluoro-cyclizations. Dixit has been the recipient of several awards including the prestigious winner of the 2011 Reaxys Ph.D. Prize.



Erli Sugiono studied chemistry at the Johannes Gutenberg University of Mainz, and obtained her diploma and Ph.D. degrees in organic chemistry under the supervision of HD Dr. Heiner Detert within the group of Prof. Herbert Meier. She then joined the group of Prof. Dr. Hans Wolfgang Spiess at Max Planck Institute of Polymer Research (Mainz) as a postdoctoral fellow working with PD Dr. Ingo Schnell studying the orientation of phospholipid bilayers within polymer matrixes in magnetic fields. In 2005, after a two and half year stay at the Max Planck Institute, she joined Prof. Rueping's group and was appointed to the position of senior scientist in 2009. Her research interests include the development of new methodologies for asymmetric catalytic transformations and catalytic flow reactions.



Sadiya Raja was born in Frankfurt, Germany in 1983. She received her Master's degree in Chemistry from the Goethe University, Frankfurt in 2009. Thereafter she started her Ph.D. at the RWTH Aachen University under the supervision of Prof. Dr. Magnus Rueping, where she worked on the development of enantioselective Brønsted acid-catalyzed pericyclic reactions and the synthesis of chiral N-heterocycles. She completed her Ph.D. in December 2012 and is currently a lab head at Bachem, Switzerland.



Magnus Rueping studied at the Technical University of Berlin, Trinity College Dublin, and ETH Zürich. He conducted doctoral studies with Professor Dieter Seebach and obtained his Ph.D. in 2002 from ETH Zürich. He then moved to Harvard University to work with Professor David A. Evans. In August 2004, he was directly appointed to a associate professorship, the Degussa Endowed Professorship of Synthetic Organic Chemistry, at the Goethe University Frankfurt. After four years in Frankfurt, he accepted a Chair and Full Professorship of Organic Chemistry at RWTH Aachen University. His group's research activities are directed toward the development and simplification of synthetic catalytic methodology and technology and their application in the rapid synthesis of diverse functional molecules.

## ACKNOWLEDGMENTS

M.R. expresses his deepest thanks to the graduate students and postdoctoral co-workers whose enthusiastic work has led to the results of our research efforts described in this review. M.R. acknowledges the many colleagues, in particular those at the University of Frankfurt and Degussa including Professors Göbel, Quinkert, and Schwalbe, as well as Professors Drauz and Dröscher, for their support and encouragement at the outset of our research in this area. Furthermore, thanks go to Degussa for supplying materials as well as support throughout. Financial support by the Deutsche Forschungsgemeinschaft and the European Research Council is gratefully acknowledged. D.P. would like to thank the Alexander von Humboldt Foundation for the Humboldt Research Fellowship Award for Postdoctoral Researchers.

## ABBREVIATIONS

Ac	acetyl
Ad	adamantine
Å	angstroms
Ar	aromatic substituent
BINOL	1,10-bi-2-naphthol
Bn	benzyl
Boc	tert-butyloxycarbonyl
BQ	benzoquinone
tBu	tert-butyl
BV	Baeyer–Villiger
cat	catalytic
Cbz	benzyloxycarbonyl
Cy	cyclohexyl
DBU	1,5-diazabicyclo[1.4.0]undec-5-ene
DCE	1,2-dichloroethane
DFT	density functional theory
DMAP	4-dimethylaminopyridine

DPP	diphenyl phosphate
dppb	1,4-bis(diphenylphosphino)butane
dr	diasteriomic ratio
ee	enantiomeric excess
equiv	equivalent(s)
ESI-MS	electrospray ionization–mass spectrometry
Et	ethyl
h	hour(s)
HRMS	high-resolution mass spectrometry
IR	infrared
M	metal
Me	methyl
min	minute(s)
MS	molecular sieves
MTBE	methyl <i>tert</i> -butyl ether
N-SPA	spiro N-phosphoramide
NTA	N-thiophosphoramide
Np	naphthyl
NPA	N-phosphoramide
NuH	nucleophile
p	para
PA	phosphoric acid
cPent	cyclo-pentyl
Ph	phenyl
PMP	<i>para</i> -methoxyphenyl
PPA	polyphosphoric acid
iPr	isopropyl
R	generic organic substituent
rac	racemic
rt	room temperature
s-factor	selectivity factor
SPA	spiro phosphoric acid
SKI	silyl ketene imines
TADDOL	$\alpha,\alpha,\alpha,\alpha$ -tetraaryl-1,3-dioxolane-4,5-dimethanols
TBS	<i>tert</i> -butyldimethylsilyl
tert	tertiary
Tf	trifluoromethanesulfonyl
TIPS	triisopropylsilyl
TMS	trimethylsilyl
Ts	tosyl
TTMSSH	tris(trimethylsilyl)silane
VAPOL	4,4'-dihydroxy-2,2'-diphenyl-3,3'-biphenanthryl
UV	ultraviolet
vis	visible

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