Metal-Free Chiral Phosphoric Acid or Chiral Metal Phosphate as Active Catalyst in the Activation of *N*-Acyl Aldimines

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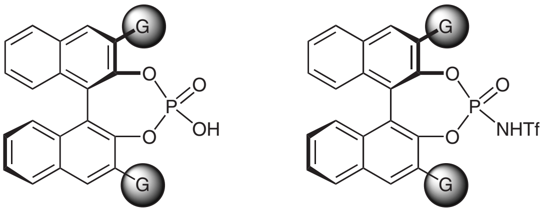
Abstract: Whether metal-free chiral phosphoric acid or chiral metal phosphate functions as an active catalyst was confirmed in three reactions. In the aza-Friedel–Crafts and aza-ene-type reactions, a metal-free chiral phosphoric acid, namely, a chiral Brønsted acid, was verified to be the active catalyst. In contrast, the substitution reaction of α-diazoacetate with aldimine was accelerated by a salt-containing chiral phosphoric acid and hence chiral metal phosphate presumably functioned as an active catalyst.

Key words: asymmetric catalysis, enantioselectivity, Friedel–Crafts reaction, organocatalysis, substitution

Chiral Brønsted acids have emerged as efficient catalysts for enantioselective transformations, and reactions using these chiral acid catalysts have become a rapidly growing area in asymmetric synthesis.[1] Among the acid catalysts, binaphthol-derived chiral phosphoric acids **1** independently reported by Akiyama and our group in 2004,[2] as well as amide analogues **2** developed by Yamamoto and Nakashima,[3] are some of the most efficient chiral Brønsted acid catalysts identified to date (Figure 1) and have been utilized as versatile enantioselective catalysts for numerous organic transformations.[4]



(*R*)-**1** (*R*)-**2**

Figure 1 Binaphthol-derived chiral phosphoric acids **1** and amide analogues **2** as chiral Brønsted acid catalysts

In recent years, several researchers have diverted their attention to chiral phosphoric acids contaminated with alkali or alkaline-earth metal salts. Ding and co-workers demonstrated that the treatment of chiral phosphoric acid with an acid dramatically improved the catalytic activity in the enantioselective Baeyer–Villiger oxidation,[5] although they did not clearly mention the reason for the improvement of the catalytic activity. Shortly thereafter, Rueping and co-workers reported the formation of the calcium salt of chiral phosphoramide **2a** (G = 4-MeOC$_6$H$_4$),[6] and treatment of the calcium salt with an acid resulted in the formation of metal-free, completely protonated, phosphoramide **2a** that functioned as a catalytically active species. Meanwhile, in early 2007, we reported the enantioselective Friedel–Crafts reaction of enecarbamates **3** with indoles **4** catalyzed by **1a** (Scheme 1).[7] During the course of this study, we also observed that the catalytic activity could be significantly improved by treatment of **1a** with an acid.[8] Until the report by Ishihara and co-workers in 2010,[9] it had been considered that metal contamination affected only the catalytic activity and not the enantioselectivity.[10] This is because it seems unlikely that alkali or alkaline-earth metal phosphates would function as an active catalyst for enantioselective transformations, although the catalytic activities of these metal salts have been little exploited[11,12] with the exception of the activation of trimethylsilyl cyanide.[13] However, in 2010, Ishihara and co-workers reported that not only metal-free chiral phosphoric acid but also calcium phosphate functioned as an efficient enantioselective catalyst for the direct Mannich-type reaction of *N*-Boc aldimines with a broad range of 1,3-dicarbonyl compounds.[9] They also pointed out that binaphthol-derived chiral phosphoric acids **1** readily capture adventitious metal impurities, alkali and alkaline-earth metal salts, during purification using silica gel to generate a salt-containing chiral phosphoric acid,[6b,10,14] and hence the acid treatment of silica gel purified chiral phosphoric acids **1** has a substantial influence on the catalytic performance. In fact, they clearly demonstrated differences in the catalytic performance between calcium phosphate and metal-free phosphoric acid, where a judicious choice of substituent G introduced at the 3,3′-positions of the binaphthyl backbone was required to achieve high enantioselectivities in the direct Mannich-type reaction. More importantly, these catalysts provided products with opposite absolute configuration even when catalysts having the same axial chirality were used. We therefore confirmed whether metal-free chiral phosphoric acid or chiral metal phosphate is the active catalyst in the reactions reported before 2006 by our group.[15–17] Herein we report the reaction outcomes using acid-washed, thus metal-free, chiral phosphoric acids **1** in three transformations of *N*-acyl aldimines, namely, the Friedel–Crafts reaction,[15] the substitution reaction of α-diazoacetates,[16] and the aza-ene-type reaction,[17] and compared the outcomes with the results obtained using silica gel purified **1**.

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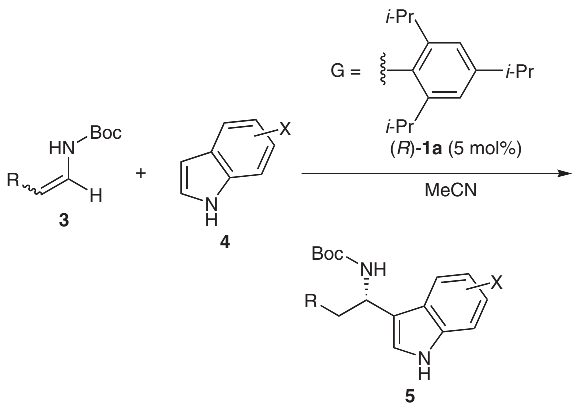
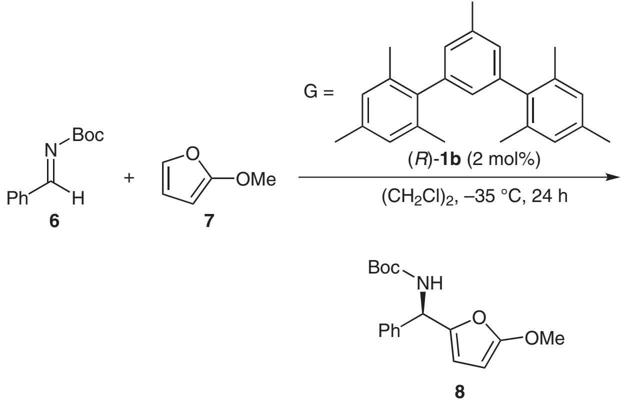


acid-washed **1a** (ref. 7):	~98%, ~96% ee
silica gel purified **1a**:	low reproducibility of yields but comparable enantioselectivities

Scheme 1 Friedel–Crafts reaction of enecarbamates **3** with indoles **4** catalyzed by acid-washed metal-free chiral phosphoric acid **1a**

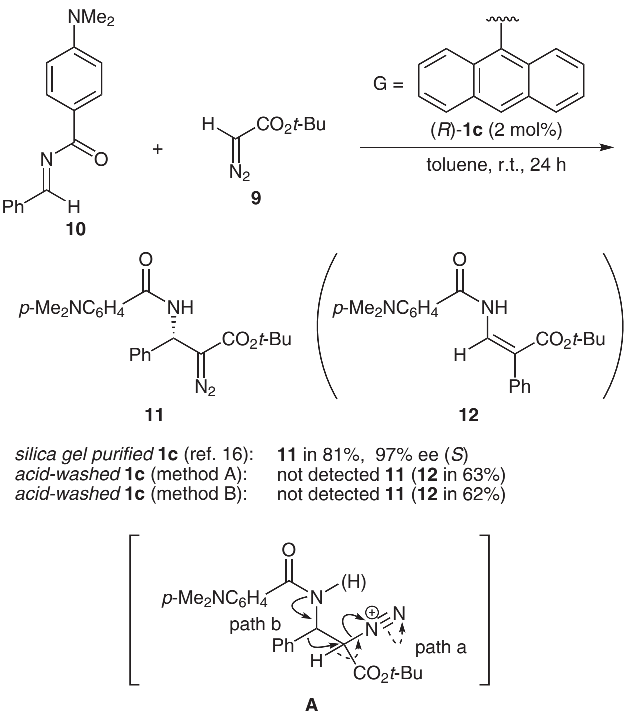
At the outset, we washed silica gel purified **1** with aqueous HCl solution (2 M) to prepare metal-free phosphoric acid, namely, acid-washed **1** (method A).[18] Then, in an effort to eliminate acid contaminants, acid-washed **1** (method A) was further subjected to short-path column chromatography using metal-free extra pure silica gel[19] to afford acid-washed **1** (method B). We initially investigated the catalytic performance of the three types of phosphoric acid **1b** (G = hexamethylterphenyl), namely, silica gel purified[15] and acid-washed (method A and B) phosphoric acids, in the aza-Friedel–Crafts reaction of *N*-Boc aldimines **6** with 2-methoxyfurane (**7**) (Scheme 2). All three catalysts **1b** exhibited similar catalytic performance to afford Friedel–Crafts products **8** with comparable enantioselectivities and the same absolute configuration albeit with a slight decrease in the chemical yield when the two metal-free acids, acid-washed **1b** (method A and B), were used. These results strongly suggest that metal-free chiral phosphoric acid is an active catalyst in the aza-Friedel–Crafts reaction.



silica gel purified **1b** (ref. 15):	87%, 97% ee (*R*)
acid-washed **1b** (method A):	76%, 93% ee (*R*)
acid-washed **1b** (method B):	78%, 95% ee (*R*)

Scheme 2 Aza-Friedel–Crafts reaction of *N*-Boc aldimines **6** with 2-methoxyfurane (**7**)

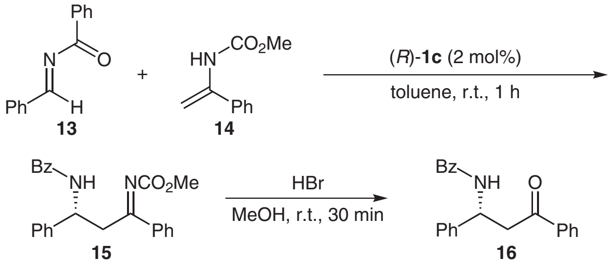
In 2005, we reported the substitution reaction of α-diazoacetates **9** with *N*-benzoyl aldimines **10** catalyzed by **1c** (G = 9-anthryl).[16] In the present study, we investigated the catalytic performance in the substitution reaction using three types of catalyst **1c** (Scheme 3). In the original paper, α-substituted product **11** was afforded as the sole structural isomer in the presence of silica gel purified **1c**.[16] In sharp contrast, the catalytic reaction using acid-washed **1c** (method A and B) yielded α,β-unsaturated ester **12** as the sole product, instead of **11**. These results imply that the carbon–carbon bond-forming reaction of α-diazoacetates **9** with aldimines **10** was accelerated by either salt-containing or metal-free chiral phosphoric acid to give intermediate **A**.[20,21] The subsequent reaction course was divided into two pathways depending upon the catalyst employed. Under the influence of silica gel purified **1c**, the salt-containing chiral phosphoric acid, the α-proton of intermediate **A** is deprotonated exclusively to give substitution product **11** through path a (indicated by dashed arrows). Although it is not known which metal species of the salt-containing chiral phosphoric acid functioned as the active catalyst for the substitution reaction,[22] metal-free acid is not the efficient catalyst for the substitution reaction and instead, intermediate **A** undergoes 1,2-migration of the phenyl group with concomitant elimination of a nitrogen molecule via path b (indicated by solid arrows) to yield **12**.[20,21a]



silica gel purified **1c** (ref. 16):	**11** in 81%, 97% ee (*S*)
acid-washed **1c** (method A):	not detected **11** (**12** in 63%)
acid-washed **1c** (method B):	not detected **11** (**12** in 62%)

Scheme 3 Reaction of α-diazoacetates **9** with *N*-benzoyl aldimines **10**

Finally, we examined the aza-ene-type reaction of *N*-benzoyl aldimines **13** with enecarbamates **14** using three types of chiral phosphoric acid **1c** (Scheme 4).[17] In the previous report, silica gel purified **1c** displayed marked catalytic efficiency, and the catalyst loading could be reduced to as low as 0.05 mol%. However, in the evaluation of the catalytic performance, we employed 2 mol% each of **1c** to exclude experimental errors. The reaction catalyzed by acid-washed **1c** (method A and B) proceeded smoothly. After the hydrolysis of imine products **15**, corresponding ketones **16** were obtained in nearly quantitative yields and hence the metal-free acids are catalytically more active than the salt-containing acid, silica gel purified **1c**. In addition, the absolute stereochemistry of ketones **16** was the same *R* configuration for all cases albeit a slight decrease in enantioselectivity. These results clearly reveal that the aza-ene-type reaction is efficiently catalyzed by metal-free chiral phosphoric acid, not by chiral metal phosphate.



silica gel purified **1c** (ref. 17): 85%, 95% ee (*R*)
acid-washed **1c** (method A): >99%, 93% ee (*R*)
acid-washed **1c** (method B): 98%, 93% ee (*R*)

Scheme 4 Aza-ene-type reaction of *N*-benzoyl aldimines **13** with enecarbamates **14**

In summary, we have documented whether metal-free chiral phosphoric acid or chiral metal phosphate functioned as an active catalyst in three reactions. In the aza-Friedel–Crafts and aza-ene-type reactions, a metal-free acid, namely, chiral Brønsted acid, was verified to be the active catalyst by comparing its reaction outcome with those of silica gel purified and acid-washed chiral phosphoric acids. In contrast, we ascertained that the substitution reaction of α-diazoacetate with aldimine is efficiently accelerated by the silica gel purified acid catalyst, where chiral metal phosphate presumably participates in the catalytic cycle.

As summarized above, either Brønsted acid or metal phosphate is catalytically active, although their activities are dependent on the type of reaction. In past experiments, our unintentional use of silica gel purified ‘salt-containing’ chiral phosphoric acids led to substantial confusion in the development of chiral Brønsted acid catalysis. We identified chiral phosphoric acids by HRMS, NMR, and IR spectroscopy, despite the fact that these analytical methods are not effective for the detection of the formation of metal salts. Our lack of detailed attention to structural identification is responsible for the erroneous full characterization of silica gel purified chiral phosphoric acids. Elemental analysis is clearly more important than HRMS for identifying elemental composition and determining the purity of a compound.[14] On the other hand, the accidental use of salt-containing chiral phosphoric acid has opened new avenues in the field of enantioselective catalysis. Indeed, after the report by Ishihara and co-workers,[9] a couple of excellent enantioselective catalyses have been accomplished by means of chiral calcium phosphates.[12] The derivatization of chiral phosphoric acids with alkali, alkaline-earth, and other metal salts has broadened the scope for the development of enantioselective catalysis by chiral phosphate salts.[11] Further studies along this line are in due course in our laboratory.

Acknowledgment

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(18) **For the Preparation of Acid-Washed 1b (Method A)**
Silica gel purified **1b** was dissolved in Et_2O. The resultant solution was washed with HCl aq solution (2 M) in a separatory funnel. The resultant ether layer was dried over Na_2SO_4 and evaporated to remove organic solvents. The resultant residue was dried under reduced pressure for more than 12 h to eliminate organic solvents completely.
For the Preparation of Acid-Washed 1c (Method A)
Silica gel purified **1c** was dissolved in MeOH. Then HCl aq solution (2 M) was added to the resultant MeOH solution to give a white suspension. The resultant suspension was extracted with CH_2Cl_2 (twice or more), and the combined organic layer was dried over Na_2SO_4. This was followed by the procedure as shown in the preparation of acid-washed **1b** (method A).

(19) Extra pure silica gel (Silica gel 60 extra pure for column chromatography: Catalogue No. 1.07754) was purchased from Merck KgaA. Short-path column chromatography was performed using CH_2Cl_2–MeOH (10:1) mixtures as eluent.

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