

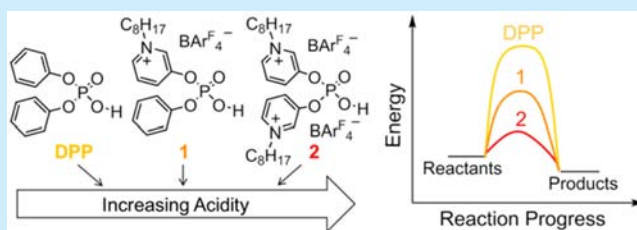
Electrostatically Enhanced Phosphoric Acids: A Tool in Brønsted Acid Catalysis

Jie Ma and Steven R. Kass*

Department of Chemistry, University of Minnesota, 207 Pleasant Street SE, Minneapolis, Minnesota 55455, United States

Supporting Information

ABSTRACT: A novel type of phosphoric acid catalyst with enhanced reactivity is reported. These compounds possess one or two positively charged centers which electrostatically activate them. This is illustrated in several bond-forming transformations including Friedel–Crafts and Diels–Alder reactions as well as a ring-opening polymerization. Rate accelerations corresponding to orders of magnitude are observed.



Brønsted acids are among the most commonly employed catalysts and are used to promote a wide variety of chemical transformations.^{1,2} They provide an excellent alternative to transition-metal-containing catalysts in that they tend to be tolerant of water and air and generally are environmentally friendlier.^{2,3} Substrate activation commonly takes place by proton transfer or hydrogen bonding, both of which lower the energy of the lowest unoccupied molecular orbital (LUMO) and facilitate nucleophilic attack.^{4,5} Different types of Brønsted acid catalysts with a wide range of acidities have been developed including thioureas,⁶ $\alpha,\alpha,\alpha,\alpha$ -tetraaryl-1,3-dioxolane-4,5-dimethanols (TADDOLs),⁷ 1,1'-bi-2-naphthol (BINOL) derivatives,⁸ and phosphoric acids,⁹ and their utility has been amply demonstrated. Of these compounds, phosphoric acids are inherently the strongest acids, and their structural flexibility enables them to be introduced into rigid organic frameworks. The presence of a phosphoryl oxygen also can serve as a hydrogen bond accepting site, enabling dual or bifunctional activation modes that increase their catalytic potential.^{1,9a,10}

Diphenyl phosphate [(PhO)₂P(O)OH, DPP] is widely used and can catalyze a variety of transformations such as Friedel–Crafts and Diels–Alder reactions^{11,12} and ring-opening polymerizations.¹³ Its reactivity is limited due to its modest acidity but can be enhanced by the presence of strong electron-withdrawing groups on the two aromatic rings.¹⁴ More acidic derivatives are of interest given Rueping et al.'s recent report demonstrating the relationship between catalyst acidity and activity.¹⁵ That is, more acidic catalysts led to faster rates of a Nazarov cyclization test reaction.

The incorporation of a positively charged center into phenols and thioureas recently was found to enhance their acidities and catalytic reactivities.^{16,17} We therefore decided to investigate charge-containing phosphoric acid derivatives of DPP (1 and 2, Figure 1) and report the results herein.

Two electrostatically enhanced phosphoric acids 1 and 2 were envisioned in which one or both of the phenyl groups in DPP are replaced by *N*-alkylated pyridinium ions.¹⁸ The

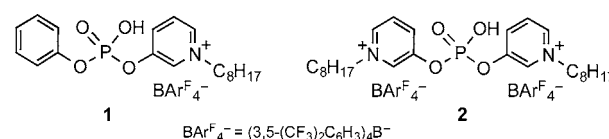


Figure 1. Charged phosphoric acids reported in this study.

positively charged substituents should act as powerful electron-withdrawing groups in low polarity media, but not in polar solvents, and the long-chain octyl groups were selected to enhance the solubility of these salts in solvents such as dichloromethane, chloroform, and toluene. A noncoordinating counteranion is required to avoid deactivating hydrogen bonds with the phosphoryl hydroxyl group, and tetrakis(3,5-bis(trifluoromethyl)phenyl)borate (BArF_4^-) was chosen for this purpose since it also has good solubility and reactivity characteristics.^{19–21}

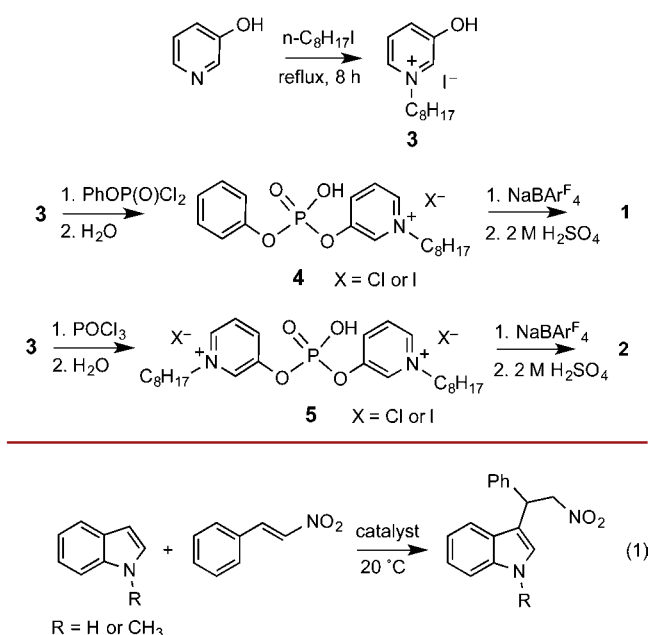
Both catalysts were synthesized as illustrated in Scheme 1 starting with commercially available 3-hydroxypyridine. Its *N*-alkylation with 1-iodooctane afforded the pyridinium iodide salt (3) in a reasonable yield (66%) as previously described.¹⁶ Upon reaction of 3 with phenyl dichlorophosphate or phosphorus oxychloride followed by an aqueous hydrolysis, the halide salts corresponding to 1 and 2 were produced (4 and 5). Ion exchange with NaBArF_4 in CH_2Cl_2 occurred readily since the sodium halide salts are not soluble and precipitate out of solution. A sulfuric acid wash was subsequently carried out to ensure that the target compounds were produced in their protonated form (HCl is not suitable; presumably, it leads to loss of the octyl group) and this was verified via titration.

To evaluate the catalytic reactivity of 1 and 2, the room-temperature Friedel–Crafts alkylation of indole and *N*-methylindole with β -nitrostyrene were examined at various catalyst loadings in dichloromethane and chloroform (eq 1).

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Scheme 1. Synthetic Route for Catalysts 1 and 2



These transformations were monitored by ¹H NMR, and the kinetic data displayed second-order behavior as expected. Rate constants, and background corrected half-lives and relative rates under the different conditions that were employed are summarized in Table 1. In the absence of a catalyst, neither indole or *N*-methylindole reacts with β -nitrostyrene in CD₂Cl₂ or CDCl₃ for all practical purposes. That is, the reaction half-lives were estimated to be 9 months or more (see Tables S1 and S2 for the kinetic data); a control experiment in which CH₂Cl₂ was washed with H₂SO₄ as done in the preparation of 1 and 2 had no impact on the background rate of the reaction with indole. These transformations are accelerated by 10 mol % of DPP, but it is an ineffective catalyst in that it takes between 3

and 48 weeks for half of the starting material to be converted to product depending upon the reaction conditions. Incorporation of an electron-withdrawing nitro group in DPP at the 3-position of both phenyl rings [(3-O₂NC₆H₄O)₂P(O)OH, DPP*] has a modest accelerating effect corresponding to a factor of 4.5. Monocharged phosphoric acid derivative 1, however, speeds up the reactions of indole and *N*-methylindole relative to DPP by factors of 12 and 210 in CD₂Cl₂ (entries 4 and 14) and 7.2 and 78 in CDCl₃ (entries 10 and 20). These differences can be enhanced by 1 order of magnitude if a second charged center is incorporated into the catalyst. That is, $k_2/k_{\text{DPP}} = 120$ and 2100 for indole and *N*-methylindole in CD₂Cl₂ (entries 5 and 15) and 38 and 870, respectively, in CDCl₃ (entries 11 and 21). As a result, the half-lives for these reactions are reduced to as little as 3.5 h.

Bifunctional activation brought about by phosphoric acid derivatives has been invoked previously^{1,9a,10,22} and would involve a N–H⋯O=P hydrogen bond when indole is used as the reactant (Scheme S1). With *N*-methylindole, this interaction is absent, and consequently, one might expect this latter transformation to proceed more slowly. This is the case for the DPP-catalyzed reactions where $k_{\text{indole}}/k_{\text{N-methylindole}} = 13\text{--}15$ in CD₂Cl₂ and CDCl₃. When 1 and 2 were used, $k_{\text{N-methylindole}}/k_{\text{indole}} = 1.4\text{--}1.5$ except for when the former catalyst is used in CDCl₃, then $k_{\text{indole}}/k_{\text{N-methylindole}} = 1.4$. These results are consistent with bifunctional activation being involved in the rate-determining step when DPP is used, but it is unclear if this is important with the charge-containing phosphoric acids. These species undoubtedly are more acidic than DPP, and thus, their N–H⋯O=P hydrogen bonds should be weaker. However, *N*-methylindole is more nucleophilic than indole, and this could counterbalance the loss of the hydrogen bond when 1 and 2 are used.

A small solvent effect (≤ 2) is observed for the Friedel–Crafts reactions when CD₂Cl₂ and CDCl₃ are used. If DPP is the catalyst, the background corrected rate constants are ~ 2

Table 1. Kinetic Data of Friedel–Crafts Reactions^a

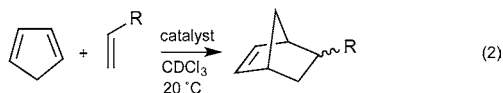
entry	solvent	R	cat.	mol %	k (M ⁻¹ h ⁻¹)	$t_{1/2}^b$ (h)	k_{rel}^b
1	CD ₂ Cl ₂	H			0.000544	19400	
2	CD ₂ Cl ₂	H	DPP	10	0.0185	587	1.0
3	CD ₂ Cl ₂	H	DPP*	10	0.0813	131	4.5
4	CD ₂ Cl ₂	H	1	10	0.215	49.2	12
5	CD ₂ Cl ₂	H	2	10	2.06	5.12	120
6	CD ₂ Cl ₂	H	2	5.0	0.904	11.7	100 ^c
7	CD ₂ Cl ₂	H	2	2.0	0.367	28.8	100 ^c
8	CDCl ₃	H			0.000396	26600	
9	CDCl ₃	H	DPP	5.0	0.0203	530	1.0
10	CDCl ₃	H	1	5.0	0.143	74.0	7.2
11	CDCl ₃	H	2	5.0	0.750	14.1	38
12	CD ₂ Cl ₂	Me			0.000324	32600	
13	CD ₂ Cl ₂	Me	DPP	10	0.00176	7350	1.0
14	CD ₂ Cl ₂	Me	1	10	0.297	35.6	210
15	CD ₂ Cl ₂	Me	2	10	3.06	3.45	2100
16	CD ₂ Cl ₂	Me	2	5.0	1.39	7.59	1900 ^c
17	CD ₂ Cl ₂	Me	2	2.5	0.771	13.7	2200 ^c
18	CDCl ₃	Me			0.00156	6760	
19	CDCl ₃	Me	DPP	5.0	0.00286	8110	1.0
20	CDCl ₃	Me	1	5.0	0.103	104	78
21	CDCl ₃	Me	2	5.0	1.13	9.35	870

^aBoth reactant concentrations were 94.8 mM. ^bBackground corrected half-lives and relative rates. ^cLinearly corrected for the amount of catalyst.

times larger in the latter solvent upon making a 2-fold linear correction for the catalyst loading (i.e., 5 vs 10 mol %). In contrast, this transformation takes place 1.2–1.5 times faster in the former medium when **1** and **2** are employed, except for when **1** is used in the reaction with indole and then $k_{\text{CDCl}_3}/k_{\text{CD}_2\text{Cl}_2} = 1.3$. Presumably the more polar solvent tends to lead to faster reactions with the charged catalysts, as observed with charged thioureas,¹⁷ because it stabilizes the polar transition state. Lack of solubility under the reaction conditions prevented toluene from being explored, but **2** was found to be unreactive in THF-*d*₈ since it is a hydrogen bond acceptor and a more polar solvent. Chlorobenzene is also a poorer solvent for this reaction than CD₂Cl₂ and CDCl₃ even though it is less polar by some measures.^{23,24}

Catalyst loading was examined with **2** in CD₂Cl₂ (entries 5–7 and 15–17), and smaller amounts of it led to slower transformations with both indole and *N*-methylindole. Linear relationships between the mol % of **2** and the background-corrected reaction rate constants are observed in both cases (Figure S1). This indicates that these Friedel–Crafts reactions are first order in catalyst, which contrasts with the second-order behavior reported for a charged thiourea.¹⁷

To examine the catalytic abilities of **1** and **2** further, Diels–Alder reactions between 1,3-cyclopentadiene and methyl vinyl ketone (MVK) or acrylonitrile (AN) were carried out (eq 2).



These reactions were monitored by ¹H NMR to obtain the reactant and product concentrations at different times (Table S3). Both transformations displayed second-order behavior, and the resulting data are summarized in Table 2. For the

Table 2. Kinetic Data of Diels–Alder Reactions^a

entry	R	cat.	mol %	k (M ⁻¹ h ⁻¹)	$t_{1/2}$ ^b (h)	endo/ exo	k_{rel} ^b
1	Ac			0.660	15.2	81:19	
2	Ac	DPP	1.0	0.823	61.3	81:19	1.0
3	Ac	DPP*	1.0	3.89	3.26	82:18	19
4	Ac	1	1.0	163	3.7 min	88:12	1000
5	Ac	2	1.0	412	1.5 min	88:12	2500
6	Ac	2	0.10	35.9	17 min	87:13	
7	CN			0.0698	143	65:35	
8	CN	DPP	1.0	0.0744	2170	65:35	1.0
9	CN	1	1.0	0.119	203	70:30	11
10	CN	2	1.0	0.302	43	75:25	50
11	CN	2	5.0	1.58	6.6	76:24	

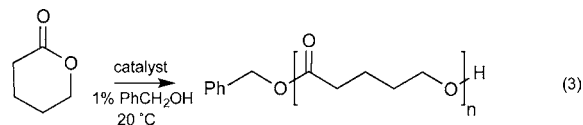
^aBoth reactant concentrations were 100 mM. ^bBackground corrected half-lives and relative rates.

reaction with MVK, 1.0 mol % of DPP was found to be a very poor catalyst as the rate constant is only 25% larger than for the noncatalyzed transformation (entries 1 and 2). DPP* is almost 20 times more reactive (entry 3), but the endo/exo selectivity for these three processes is the same. Our monocharged phosphoric acid, however, is 1000 times more active than DPP (entry 4) and reduces the reaction half-life to under 5 min. It also increases the endo/exo ratio from 81:19 to 88:12 as commonly observed with Lewis acids.²⁵ The doubly charged derivative is even better in that it is 2500 times more reactive

than DPP and $t_{1/2} = 1.5$ min without any loss in the diastereoselectivity relative to **1** (entry 5). Moreover, a reduced catalyst loading of 0.1 mol % still leads to a very efficient transformation (i.e., $t_{1/2} = 17$ min) without any falloff in the selectivity.

Similar results were obtained for the Diels–Alder reaction between 1,3-cyclopentadiene and acrylonitrile, but all three catalysts (DPP, **1** and **2**) are less effective. Diphenyl phosphate only enhances the reaction rate of the noncatalyzed process by 7% (entries 7 and 8), and this difference is well within the experimental uncertainties of the two measurements; we estimate the errors in the rate constants to be $\pm 10\%$. There is also no change in the observed endo/exo ratio of 65:35, and thus, 1 mol % of DPP has little, if any, effect on this reaction. An equivalent amount of **1** does speed up the transformation and improves the diastereoselectivity, but the reaction is still slow with an observed nonbackground corrected half-life of 84 h and an endo/exo ratio of 70:30 (entry 9). This kinetic acceleration, however, does correspond to a factor of 11 compared to DPP. A further improvement is found with the doubly charged catalyst **2** in terms of the rate ($k_2/k_{\text{DPP}} = 50$) and the product selectivity (endo/exo = 75:25, entry 10). The apparent half-life for this reaction is 33 h, but this is for a 1 mol % loading, and when 5 mol % is employed (entry 11) this decreases to 6.6 h.

A ring-opening polymerization of δ -valerolactone with benzyl alcohol as the initiator in four different solvents was examined (eq 3) since this is an important process in which DPP is



commonly used.^{13,26} The conversion of the monomer in these living polymerizations was followed by ¹H NMR (Table S4), and the data can be fit using a first-order kinetic model.^{13,27,28}

No conversion was observed over the course of one month in the absence of a catalyst, whereas the ring-opening polymerization is facile when 0.5 mol % of DPP or **2** is used. Rate constants for the propagation stage are provided along with reaction half-lives and relative rates in Table 3. In all four

Table 3. Kinetic Data of Polymerizations^a

entry	solvent	cat.	k (h ⁻¹)	$t_{1/2}$ (h)	k_{rel}
1	C ₆ D ₅ CD ₃	DPP	0.444	1.6	1.0
2	C ₆ D ₅ CD ₃	2	0.833	0.8	1.9
3	C ₆ D ₆	DPP	0.325	2.1	1.0
4	C ₆ D ₆	2	0.574	1.2	1.8
5	CD ₂ Cl ₂	DPP	0.0380	18	1.0
6	CD ₂ Cl ₂	2	0.0759	9.1	2.0
7	CDCl ₃	DPP	0.0460	15	1.0
8	CDCl ₃	2	0.108	6.4	2.3

^aExperiments performed with 0.5 M δ -valerolactone, 1.0 mol % of PhCH₂OH, and 0.5 mol % of the catalyst.

solvents, our doubly charged catalyst outperforms DPP by a factor of about two. The actual reaction rates vary by a factor of 12 regardless of the catalysts with the faster processes occurring in benzene-*d*₆ and toluene-*d*₈ and the slower ones taking place in CD₂Cl₂ and CDCl₃. When smaller concentrations of the monomer are used, the polymerization takes longer but k_{rel}

increases. This was also observed for the Friedel–Crafts and Diels–Alder reactions presumably because the reactants are more polar than the solvent and enhance the polarity of the medium.

The effects of the two catalysts on the number-average molecular weights ($M_{n,NMR}$) of the polymers at different conversions were also investigated by 1H NMR. In all four solvents, $M_{n,NMR}$ was found to be similar at equivalent conversions of the monomer regardless of the catalyst (Figure S2).

In summary, we successfully designed and synthesized two electrostatically enhanced phosphoric acid derivatives (**1** and **2**). To the best of our knowledge, these compounds are the first examples of phosphoric acids with positively charged centers incorporated to enhance their acidities and catalytic abilities in nonpolar media. This was evaluated by investigating a series of acid-catalyzed processes and comparing the catalytic efficiencies of **1** and **2** with diphenyl phosphate (DPP) and di(3-nitrophenyl) phosphate (DPP*), their noncharged analogues. Impressively, both charged phosphoric acid derivatives outperformed DPP and DPP* in all of the reactions that were examined, in some cases by more than 3 orders of magnitude. Extension of this strategy to other Brønsted acid catalysts such as chiral phosphoric acid derivatives is a promising research avenue and currently is the focus of ongoing efforts in our group.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: [10.1021/acs.orglett.6b02750](https://doi.org/10.1021/acs.orglett.6b02750).

Experimental procedures, NMR spectra, and reaction data (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: kass@umn.edu.

Notes

The authors declare no competing financial interest.

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