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Phosphoric acid mediated tautomerism of imines: addition of a secondary enamine intermediate to aldehydes

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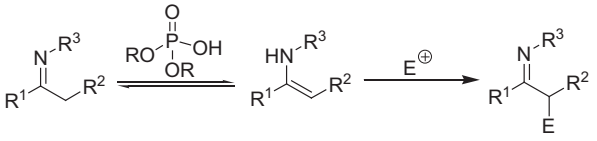
ABSTRACT

A phosphoric acid derivative has been shown to promote the addition between an imine and several aldehyde substrates through an enamine intermediate to give cross-aldol condensation products. The reaction scope and preliminary mechanistic investigations will be presented.

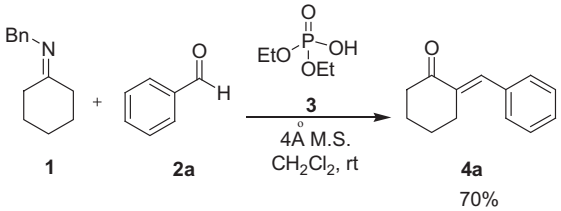
Organocatalysis has become a rapidly growing area of research in organic chemistry, as it provides mild reaction conditions that are operationally simple and environmentally-benign.[1,2] In particular, phosphoric acid derivatives have been used extensively to activate electrophiles containing imine and carbonyl moieties through hydrogen-bonding interactions or protonation resulting in an ion-pair.[3–5] Because phosphoric acid derivatives have both a Brønsted acid and a Brønsted basic site, many proposed transition states include a catalyst, nucleophile, and electrophile, although the primary role of the catalyst has largely remained electrophilic activation.[6] In an effort to extend the synthetic utility of phosphoric acid catalysis, we set out to investigate the role of a phosphoric acid derivative by activation of a nucleophile through tautomerism. Previous work in our lab has shown that hydrazones tautomerize under phosphoric acid conditions.[7] Rueping and Antonchick have reported a chiral phosphoric acid catalyzed aza-Henry reaction that requires the catalyst to accelerate isomerization of a nitroalkane to a nitronate.[8] In addition, phosphoric acids have been employed in the tautomerism between enecarbamates and imines or ketimines to generate Friedel–Crafts[9] or self-coupling products,[10] respectively. Based on these reports, we propose that secondary enamines can be generated in situ from imines under phosphoric acid conditions, with subsequent addition to electrophiles (Scheme 1).

Screening a cyclohexanone-derived imine (**1**) with benzaldehyde (**2a**) under phosphoric acid conditions (0.5 equiv of diethyl phosphate,[11] 0.5 M in CH_2Cl_2, 25 °C, 18 h, 4 Å molecular sieves) resulted in the formation of an α,β-unsaturated ketone **4a** (70% yield) as the major product (Scheme 2).

Notably, no reaction was observed between benzaldehyde and cyclohexanone under the same reaction conditions, highlighting the need of the imine component.[11,12] The enone product, likely resulting from an addition/elimination sequence, is similar to that of an aldol-condensation product. The aldol condensation is a



Scheme 1. Proposed formation of a secondary enamine followed by addition to an electrophile.



Scheme 2. Aldol-like reaction between an imine and aldehyde to form an enone.

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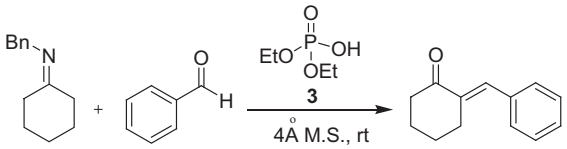
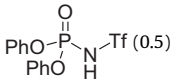
Table 1
Screening of organic acids



1 **2a** **4a**

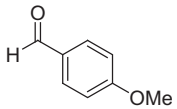
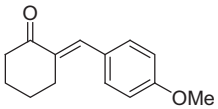
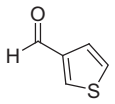
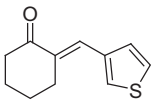
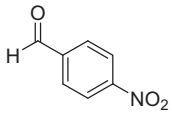
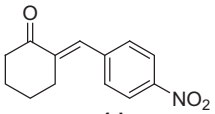
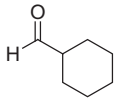
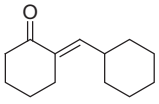
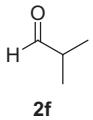
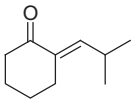
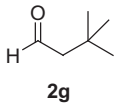
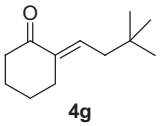
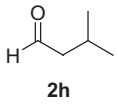
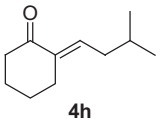
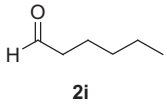
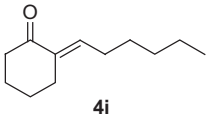
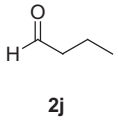
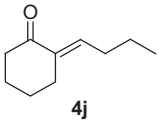
Entry	Ratio of **1**:**2a**	Additive (equiv)	*t* (h)	Solvent[a]	Yield **4a** (%)
Organic acids					
1	1:1	0	18	CH_2Cl_2	38
2[b]	1:1	H_3PO_4 (0.5)	18	CH_2Cl_2	Trace
3	1:1	CF_3COOH (0.5)	18	CH_2Cl_2	34
4	1:1		18	CH_2Cl_2	29
5[c]	1:1	Diethyl phosphate (0.5)	18	CH_2Cl_2	70
Reactant ratios					
6	1:1	Diethyl phosphate (0.1)	18	CH_2Cl_2	52
7	1:1	Diethyl phosphate (1)	18	CH_2Cl_2	63
Solvent					
8	1:1	Diethyl phosphate (0.5)	18	Toluene	63
9	1:1	Diethyl phosphate (0.5)	18	Acetonitrile	52

[a] All reactions were run on 1 mmol scale (0.5 M) with respect to **1** at room temperature with 4 Å molecular sieves.
[b] Crystalline H_3PO_4 was used.
[c] Diethyl phosphate was synthesized according to the literature procedure 21.

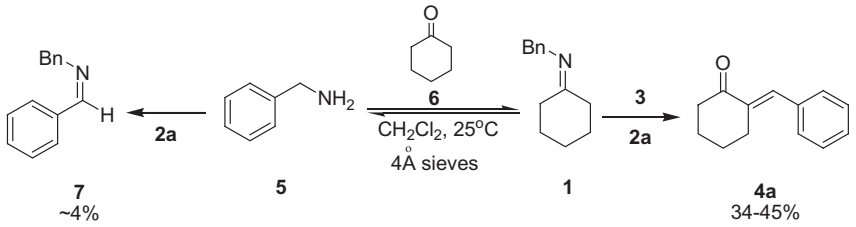
powerful carbon—carbon bond-forming reaction in organic chemistry.[13–15] Despite the synthetic utility of the aldol reaction, simple aliphatic aldehydes have been particularly challenging substrates because these aldehydes can act as both the nucleophilic and electrophilic component of the aldol reaction, resulting in homodimerization.[16,17] Several methods[18,19] have been developed to circumvent the problem of chemoselectivity including a report of a cobalt-catalyzed addition between an imine and an aldehyde.[20] This approach is intriguing because it allows for the designation of the nucleophilic component prior to the aldol condensation avoiding the possibility of homodimerization. However, it requires a two-step process and the scope of this reaction is limited to only a few aldehydes. Given our initial results and the need for a more general chemoselective aldol reaction with aliphatic aldehydes, we chose to explore this reaction in terms of reaction optimization and substrate scope.

Optimization of the reaction conditions for the addition of **1** and **2a** included the screening of organic acids, reactant ratios, and solvents (Table 1).

Table 2
Scope of the reaction[a]

Entry	Aldehyde	Product[b]	*t* (h)	Yield **4** (%)
1	 **2b**	 **4b**	18	66
2	 **2c**	 **4c**	18	63
3	 **2d**	 **4d**	24	49
4	 **2e**	 **4e**	18	48
5	 **2f**	 **4f**	19	40
6	 **2g**	 **4g**	18	46
7	 **2h**	 **4h**	19	42
8	 **2i**	 **4i**	19	33
9	 **2j**	 **4j**	19	10

[a] All reactions were run at room temperature on 1 mmol scale (0.5 M) with a 1:1 mol ratio of aldehyde to imine. Half of an equivalent of **3** was used.
[b] All products were characterized by ^1H NMR and ^{13}C NMR spectroscopy and determined to be the *E*-isomer only when compared to literature data. See Supplementary data for full details.



7 ~4% **5** **1** **4a** 34-45%

Scheme 3. One-pot reaction to form enone 4a from benzylamine (**5**) and cyclohexanone (**6**). A competing side reaction formed minor product **7**.

Acids such as phosphoric acid and trifluoroacetic acid were unable to promote the reaction more than the thermal reaction (compare Table 1, entries 2–3 to entry 1). In addition, the phosphoramidic acid diphenyl ester was found to be an unsuitable catalyst for this reaction compared to diethyl phosphate (Table 1, entries 4 and 5).[22] These results not only highlight the importance of diethyl phosphate, but also demonstrate the unique function of the phosphoric acid catalyst.

Interestingly, using 0.1 equiv of diethyl phosphate gave a moderate yield (Table 1, entry 6),[23] and a full equivalent did not increase the yield of the enone (Table 1, entry 7). Lastly, several solvents were screened. Toluene and acetonitrile gave inferior reaction yields compared to those in dichloromethane (Table 1, entries 8 and 9). Notably, during the course of the optimization studies, suspected reaction intermediates were not detected.

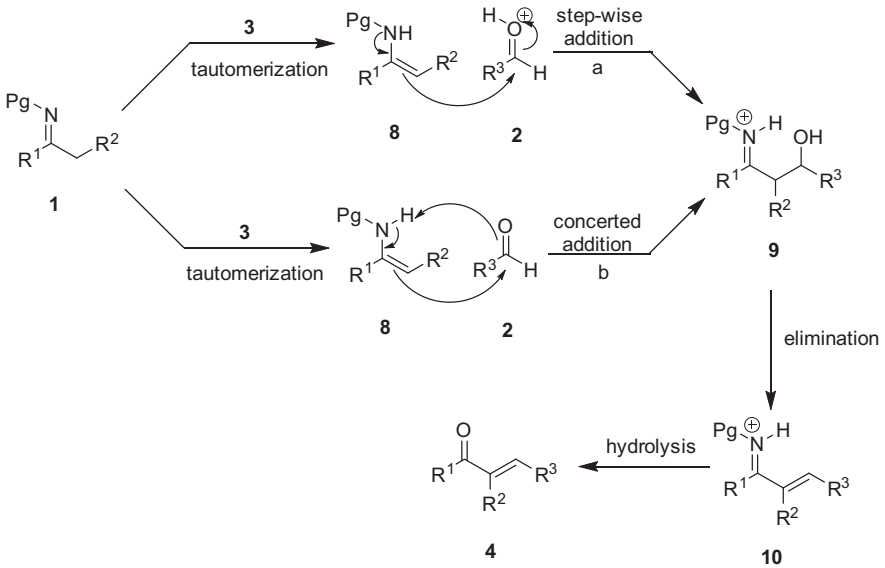
We attempted the synthesis of enone **4a** in a one-pot reaction from benzylamine (**5**) and cyclohexanone (**6**), presumably through the formation of imine **1** in situ. Compounds **5** and **6** were allowed to stir in solution between 0 and 4 h before the acid catalyst **3** and the aldehyde **2a** were added to the reaction flask (see Supplementary data). We were pleased to find that the reaction product was isolated in moderate yield (up to 45%), but the optimized reaction conditions for the one-pot reaction resulted in a significantly lower yield of **4a** compared to the optimized conditions reported above (see Table 1, entry 5). Upon further investigation, we discovered the imine was reacting in the presence of diethyl phosphate and aldehyde **2a** to give hydrolysis products and a newly formed aldimine **7** (Scheme 3).[24] Despite our attempt to limit the presence of water through the use of activated molecular sieves or performing the reaction under nitrogen, some hydrolysis inevitably occurred.

The scope of the addition reaction was investigated with respect to the aldehyde-component using the optimized reaction conditions (see Table 1, entry 5). Aldehydes bearing aromatic groups proceeded with good yield (Table 2, entries 1–3). Aldehyde **2d**, bearing an electron-withdrawing group (NO_2), is more activated than the other aromatic aldehydes employed and would therefore be expected to result in a higher yield of enone when coupled with **1**. As observed during the optimization of the reaction conditions with aldehyde **2a**, the hydrolysis of imine **1** allows for multiple reaction pathways. Considering this possibility and the increased reactivity of aldehyde **2d**, the lower yield of enone **4d** likely results from competing side reactions between hydrolysis products and aldehyde **2d** (Table 2, entry 3).

Less activated, branched aliphatic aldehydes proceeded with moderate yield in the addition reaction (Table 2, entries 4 and 5). α-Unsubstituted aldehydes (**2g**–**2j**) are a particularly challenging class of substrates because they contain enolizable hydrogens which can lead to the homodimerization of aldehydes. We were pleased to find that α-unsubstituted branched aldehydes (**2g** and **2h**) proceeded with moderate yield (Table 2, entries 6 and 7). Although one might anticipate homodimerization, these products were not detected. The coupling of hexanal (**2i**), a straight-chained aliphatic aldehyde, with **1** resulted in a comparable yield to the branched substrates (Table 2, entry 8), however a significant decrease in yield was noted with the substrate butanal (**2j**) (Table 2, entry 9). Degradation of **2j** was observed,[25] likely leading to the low-yielding reaction.

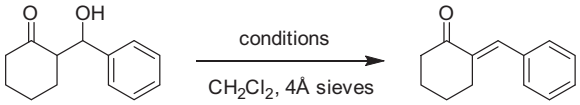
The formation of enones **4a-j** can be explained by two different mechanisms: (1) a multi-step aldol-like reaction (Scheme 4a), and (2) a concerted, aza-ene-type mechanism (Scheme 4b). The literature supports the possibility for both mechanisms. Babler and co-workers suggested a step-wise mechanism in their report of a cobalt(II) chloride catalyzed addition reaction between an *N-tert*-alkyl imine derivative and several aldehydes, while Terada's report of a phosphoric acid catalyzed addition reaction of enecarbamates to imines and aldehydes suggests a concerted manner.[26,27] Attempts to elucidate the correct reaction mechanism using ^{1}H NMR titrations were not productive. The elimination step of the reaction has also been further investigated. Our presumption is that under truly anhydrous conditions, the elimination step occurs before hydrolysis. A solution of β-hydroxy alcohol **11**[28] in dichloromethane was stirred under a variety of reaction conditions (Table 3). Interestingly, the aldol-condensation product **4a** was not observed under either acidic or basic conditions (Table 3, entries 1 and 2), and instead starting material was recovered in both cases. Only when both compounds **3** and **5** were present was enone **4a** isolated (Table 3, entry 3), suggesting that dehydration occurs through the imine; that is, elimination precedes hydrolysis. We are currently investigating additional methods to rigorously exclude water from the reaction mixture in an attempt to prevent hydrolysis and isolate the imine.

In conclusion, we have reported an addition reaction between imines and aldehydes through a phosphoric acid catalyzed



Scheme 4. Proposed potential mechanisms for the formation of enone **4** through either (a) a step-wise addition, or (b) a concerted addition.

Table 3
Elimination of β-hydroxy alcohol **11**



11 **4a**

Entry[a]	Additive (equiv)	*t* (h)	Recovery **11** (%)	Yield **4a** (%)
1	3	18	66	0
2	5	18	75	0
3	**3** (0.5) and **5** (0.5)	18	33	30

[a] All reactions were run on a 1 mmol scale (0.5 M) with respect to **1** at room temperature with 4 Å molecular sieves.

tautomerism of the imine component. Not only does this report expand the utility of phosphoric acid derivatives, it provides a chemoselective strategy for the cross-aldol condensation using aliphatic aldehydes as substrates. Efforts are in progress to fully understand the mechanism of the reaction and to expand the scope of the reaction to include other imine substrates.

Acknowledgements

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.04.002.

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23. Stirring this reaction for 48 hours did not result in an increase in product yield.
24. Compounds 6 and 7 were stirred in dichloromethane (0.5M) with diethyl phosphate (0.5 equiv.) for 18 hours. Enone 4a was isolated as the sole product (49% yield), presumably through the elimination of the Mannich base. GC/MS and NMR of the crude reaction mixture did not show any of the corresponding Mannich base.
25. Aldehyde 2j was stirred in a solution of diethyl phosphate (0.5 equiv) in dichloromethane (0.5 M). The aldehyde was completely degraded after 2 hours as indicated by TLC and NMR.
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