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Metal-free Brønsted acids catalyzed synthesis of functional 1,4-dihydropyridines

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Abstract—Brønsted acids catalyze the addition of β-enaminoacrylates to α,β-unsaturated aldehydes leading to substituted dihydropyridines in moderate to good yields under mild conditions. The first example of an enantioselective synthesis of a dihydropyridine is also reported.

Current literature reveals that 1,4-dihydropyridines exhibit interesting pharmacological and biological properties. Thus, they have been used as calcium channel modulators for the treatment of cardiovascular disorders.[1] They also present vasodilating activity,[2] and are NADH mimics.[3] The best known procedure for the preparation of symmetrical 1,4-dihydropyridines is the classical Hantzch synthesis: a multicomponent condensation involving two molecules of β-ketoesters, one molecule of aldehyde and one molecule of ammonia.[4] Due to the importance of this class of heterocyclic compounds, many efforts have been devoted to the preparation of such 1,4-dihydropyridines (Fig. 1).[5]

The N-substituted non-symmetrical 1,4-dihydropyridines are also of particular interest for a systematic study of their biological activities and from a synthetic point of view (Scheme 1). However, no general syntheses were disclosed in the literature[6]and the development of new efficient routes to these derivatives is of great importance. Due to the high synthetic potential of β-enaminoketones or esters, which combine nucleophilicity of the enamine[7,8] and electrophilicity of the

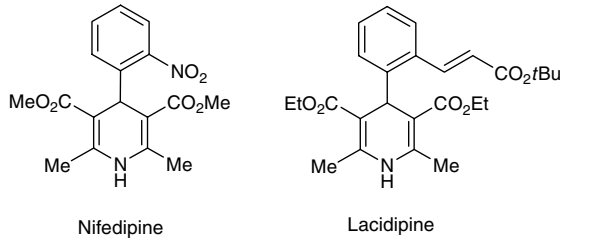
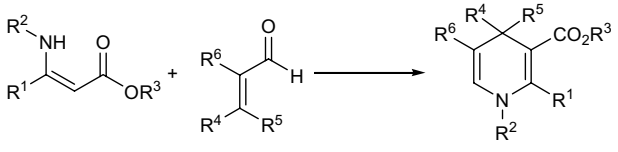


Figure 1.



Scheme 1. Synthesis of non-symmetrically substituted dihydropyridines.

Keywords: Phosphoric acid; Organocatalysis; Nitrogen heterocycles; 1,4-Dihydropyridines.
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enone moiety,[8] one route to compound **1** might be a domino-cascade involving a 1,4-Michael addition of β-enaminoketones or esters to α,β-unsaturated aldehydes, followed by an enamine formation (Scheme 1).[9]

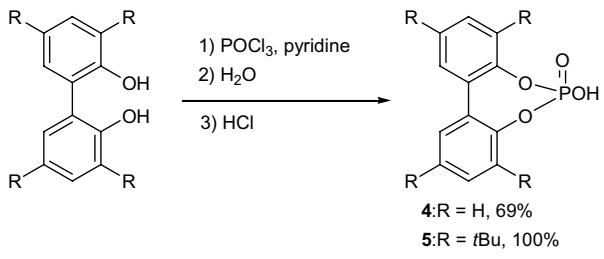
Electrophilic activation by small-molecule chiral H-bond donors has emerged as an important tool for enantioselective catalysis, with new applications and developments appearing at a rapidly increasing pace.[10] These organocatalysts do not contain any metals and, then, are advantageous for environmental perspectives. Compared to Lewis acid, they are less expensive, stable and moisture insensitive. Among the known carbonyl activators, Brønsted acids have recently demonstrated their potential to serve as active catalysts for a variety of synthetically useful reactions in organic chemistry.[10–12]

As Lewis acids demonstrate their potential as catalysts for the synthesis of non-symmetrical 1,4-dihydropyridines from β-enaminocarbonyl derivatives **2** and conjugated enals **3**,[13] we envisioned to develop a synthesis of such biologically interesting heterocyclic compounds via the Brønsted acid catalysis. For this purpose, we prepared the phosphoric acids **4** and **5**, according to known procedures (Scheme 2).[14,15]

To demonstrate the efficiency of our catalysts, a blank reaction was carried out at room temperature in dichloromethane from ethyl *N*-benzylaminobut-2-enoate **2a** and 3-methylbut-2-enal **3a**, in the absence of Brønsted catalyst. After a 16 h stirring and classical work-up, only the starting compounds were isolated.

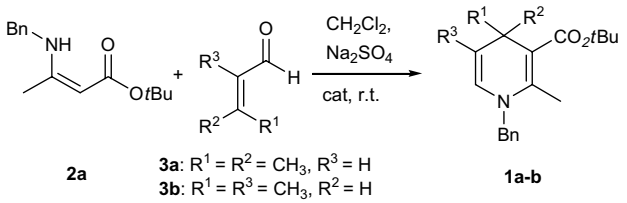
To determine which phosphoric acid (**4** or **5**) is the most efficient, 3-*N*-benzylaminobut-2-enoate **2a** was used as the starting material for the preparation of a set of 1,4-dihydropyridines (Table 1).

The reaction of 0.5 mmol of **2a** with 0.75 mmol of 3-methyl but-2-enal **3a** or 2-methyl but-2-enal **3b** in the presence of **4** or **5** and 1.05 mmol of sodium sulfate in dichloromethane led to the desired dihydropyridines **1a**,**b** in good yields (Table 1). Nevertheless, it has to be noticed that catalyst **5** provided higher yields than **4** in both reactions (89% vs 79% and 70% vs 64%, respectively), and that in both cases phosphoric acids led to better results than PTSA (Table 1).[16]



Scheme 2. Preparation of **4** and **5**.

Table 1. Synthesis of dihydropyridines **1a**,**b**



2a — **3a**: $R^1 = R^2 = CH_3$, $R^3 = H$; **3b**: $R^1 = R^3 = CH_3$, $R^2 = H$ — **1a-b**

Aldehyde	Catalyst	Temperature	Yield[c] (%)
3a[a]	**4**	Reflux	79
3a[a]	**5**	Reflux	89
3a[b]	PTSA	Reflux	39
3b[b]	**4**	rt	64
3b[b]	**5**	rt	70
3b[b]	PTSA	rt	55

[a] 0.75 mmol of aldehyde **3a** or **3b**, 0.5 mmol of β-enaminoester **2a**, 5 mol % of Brønsted acid in 5 mL of CH_2Cl_2, 150 mg of Na_2SO_4 (1.05 mmol).

[b] 10 mol % of Brønsted acid was used.

[c] All new compounds were characterized by ^1H and ^{13}C NMR, mass analysis.

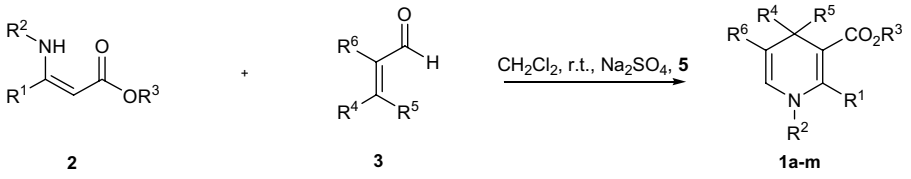
Using the best reaction conditions, we extended this process to the condensation of various enaminoesters with α,β-unsaturated aldehydes (Table 2). Thus, *N*-benzyl β-aminobutenoate (**2a**) and *N*-benzyl β-aminophenylacrylate (**2c**) reacted with cinnamaldehyde **3c** to give dihydropyridines **1c** and **1k** in high yields (Table 2, entries 3 and 11). More substituted enals, such as **3a** and **3b**, were also reactive and the corresponding dihydropyridines (**1a**,**b**,**i**) were isolated in 89%, 70% and 71% yield, respectively (Table 2, entries 1, 2 and 9).

More functionalized cinnamaldehydes such as **3e**–**g** have been then involved in this reaction with *N*-benzyl β-aminobutenoate (**2a**) leading to the corresponding derivatives (**1e**–**g**) (Fig. 2) in moderate to high yields (39%, 66% and 84%, Table 2, entries 5–7).

We therefore investigated some chiral binol-derived phosphoric acid derivatives, which were recently introduced as efficient catalysts for a number of reactions.[10b,e,17] Our preliminary results demonstrated that phosphoric acid derivatives **6** were able to promote the first enantioselective synthesis of dihydropyridine **1a** in up to 50% enantiomeric excess at 0 °C in dichloromethane (Scheme 3).[18,19]

In conclusion, we have demonstrated that Brønsted acids are efficient catalysts for the transformation of enaminoesters with conjugated enals to give functional dihydropyridine derivatives via cascade reactions. We also reported the first example of a chiral Brønsted acid-catalyzed enantioselective synthesis of a dihydropyridine. A tremendous advantage of these acids lies in the fact that they are stable, moisture insensitive and not expensive compared to Lewis acids. Further efforts will be devoted to extend the scope of the asymmetric version of these transformations.

Table 2. Synthesis of 1,4-dihydropyridines catalyzed by **5**[a]



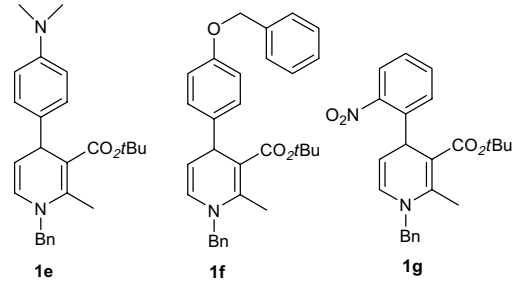
2 **3** **1a-m**

2a: $R^1 = CH_3$, R^2 = Bn, R^3 = *t*Bu
2b: $R^1 = CH_3$, R^2 = Bn, R^3 = Et
2c: R^1 = Ph, R^2 = Bn, R^3 = Et
2d: $R^1 = CH_3$, R^2 = Ph, R^3 = *t*Bu

3a: $R^4 = R^5 = CH_3$, R^6 = H
3b: $R^4 = R^6 = CH_3$, R^5 = H
3c: $R^5 = R^6$ = H, R^4= Ph
3d: $R^5 = R^6$ = H, R^4= 4-NO_2-C_6H_4

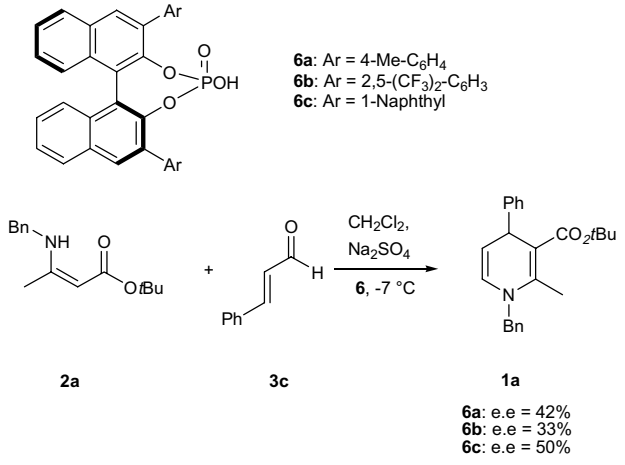
Entry	Enaminoester	Aldehyde	Compound	Yield[c] (%)
1	**2a**	**3a**	**1a**	89
2	**2a**	**3b**	**1b**	70
3[b]	**2a**	**3c**	**1c**	89
4[b]	**2a**	**3d**	**1d**	79
5	**2a**	**3e**	**1e**	39
6	**2a**	**3f**	**1f**	66
7	**2a**	**3g**	**1g**	84
8[b]	**2b**	**3c**	**1h**	54
9	**2c**	**3a**	**1i**	71
10[b]	**2c**	**3d**	**1j**	71
11[b]	**2c**	**3c**	**1k**	77
12	**2d**	**3a**	**1l**	31
13	**2d**	**3b**	**1m**	32

[a] 0.75 mmol of aldehyde **3**, 0.5 mmol of β-enaminoester **2**, 0.025 mmol of Brønsted acid **5** in 5 mL of CH_2Cl_2, 150 mg of Na_2SO_4 (1.05 mmol).
[b] 10 mol % of catalyst was used.
[c] All new compounds were characterized by ^1H- and ^{13}C NMR, mass analysis.



1e **1f** **1g**

Figure 2. More functionalized 1,4-dihydropyridines.



2a **3c** **1a**

Scheme 3. Enantioselective synthesis of DHP-**1a**.

Acknowledgement

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