An Efficient HCl Promoted Petasis Reaction of 2-Pyridinecarbaldehydes, Amines and 1,2-Oxborol-2(5*H*)-ols

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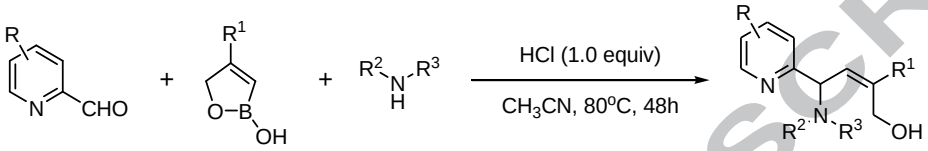

15 examples
***yield* : 36~98%**

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An Efficient HCl Promoted Petasis Reaction of 2-Pyridinecarbaldehydes, Amines and 1,2-Oxborol-2(5*H*)-ols

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ABSTRACT

A Petasis Reaction of 2-pyridinecarbaldehydes with various amines and 4-substituted 1, 2-oxaborol-2(5*H*)-ols was developed. In the presence of HCl, the reaction proceeded smoothly under very mild conditions and the corresponding desired products were obtained in medium to excellent yields. This method allows the access a wide range of highly functionalized allylic alcohols, which might be useful compounds in medicinal and material chemistry.

The Petasis borono-Mannich(PBM) reaction involves the condensation of amines, aldehydes and boronic acid nucleophiles[1]. This reaction has been proved to be a useful tool to prepare complex molecules in a single step from readily available materials[2]. Amino acids[1b,3], amino alcohols[1a,4], amino diols[5], 2*H*-chromenes[6], 2,5-dihydrofurans[7] and some other types of heterocycles[8] could be constructed from this versatile reaction.

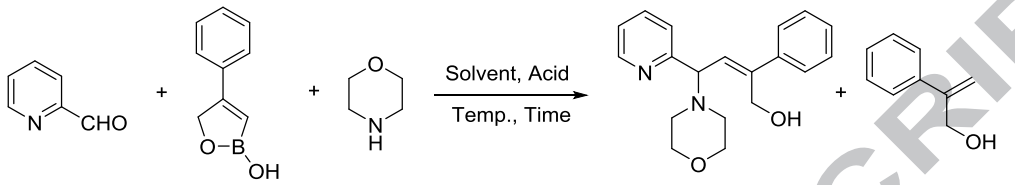
Organoboron compounds are stable, non-toxic and compatible of many functional groups[9]. In 2006, Fang reported the first preparation of 4-substituted 1,2-oxaborol-2(5*H*)-ols and their Suzuki-Miyaura cross-coupling reaction with aryl halides[10]. Indeed, substituted allyl alcohols are commonly encountered in natural products and their syntheses are tedious and usually led to mixtures of E and Z configurations[11]. Allylic alcohols are necessary intermediates for allylic substitution. Kobayashi etc. reported that the E and Z configurations of the olefin could switch the configuration of the products[12]. By involvement of 4-substituted 1,2-oxaborol-2(5*H*)-ols, (Z)-4-aryl-but-2-en-1-ols were prepared efficiently by Fang's method. A more delicate structure, furan, was designed based on the coupling reaction of oxaborol compounds and carboxylic anhydrides[13]. In 2013, we reported the first amine-promoted Petasis borono-Mannich reaction of 4-substituted 1,2-oxaborol-2(5*H*)-ols with salicylaldehydes[7]. This procedure combines a borono-Mannich reaction and an intramolecular SN_2 cyclization.

The borono-Mannich reaction was limited to salicylaldehydes in the early stage. This allows the activation of boronic acid as an 'ate' complex and resulted in the transfer of a vinyl or aryl group to the transient iminium species[14]. Later on, 2-pyridinecarbaldehydes[15], 2-sulfamidobenzaldehyde[6b] and aziridine-aldehyde dimers16 were reported to react successfully in the PBM reaction. To expand the reaction scope of the unique 1,2-oxabrol-2(5H)-ols, herein we reported the details of an efficient Petasis borono-Mannich reaction of 2-pyridinecarbaldehydes, amines and 4-substituted 1, 2-oxaborol-2(5H)-ols.

2-Pyridinecarbaldehyde, 4-benzyl-1, 2-oxaborol-2(5H)-ol and morphine was selected as model substrates for the Petasis reaction (Table 1). When using 1, 2-dichloroethane as solvent, the desired compound 4a was obtained in a low yield of 28% after stirring at 80°C for 48 hrs (Table 1, Entry 1). Reductive product 5a from 4-benzyl-1, 2-oxaborol-2(5H) was also observed in the reaction. An elevated temperature of 90°C led to 4a in a better yield of 54% (Table 1, Entry 2). Considering the acidic property of glyoxylic acid or salicyladehyde commonly used in the Petasis reaction, we anticipated that acid might accelerate the iminium formation step and benefit the Petasis reaction. At the beginning, some organic acids like acetic acid, benzoic acid and trifluoromethanesulfonic acid were tested, only acetic acid afforded 4a in 29% yield (Table 1, Entry 3). While benzoic acid and trifluoromethanesulfonic acid only led to messy mixtures and no further effort was given. Lowering the temperature was totally disfavored when using acetic acid as addictive (Table 1, Entry 4). Then we turn our attention to inorganic acids, which showed hydrochloride acid could promote the reaction well and afforded the desired product in yield of 75% determined by 1H NMR (Table 1, Entry 5). A reaction was carried out under Argon did not provide better yield (Table 1, Entry 6). When the reaction was proceed for a shorter time of 24 hrs, only 41% yield of the desired production was obtained. However prolonged reaction time provided 4a in 76% yield (Table 1, Entry 9). A little

decrease in yield was observed when utilizing a higher reaction temperature of 90°C (Table 1, Entry 10). Increasing in the amount of HCl affected the reaction dramatically and led to low yields. In the following experiments, several solvents were screened and acetonitrile was proved to be the best solvent and an excellent yield of 94% was obtained (Table 1, Entry 16). When 4 Å molecular sieves were added, yield of 4a was higher or just similar to conditions without it. But byproduct 5a was not detected (Table 1, Entry 7 & 17). A control experiment without acid was carried out in acetonitrile and the yield of desired product 4a was decreased (Table 1, Entry 18).

Table 1: Opitimization of Reaction Conditions[a]



1a **2a** **3a** **4a** **5a**

Entry	Solvent	Temp(°C)	Time(h)	Acid(equiv)	**4a**[b](%)	**5a**[b](%)
1	DCE	80	48	none	28	9
2	DCE	90	48	none	54	11
3	DCE	80	48	AcOH (1.0)	29	24
4	DCE	70	48	AcOH (1.0)	15	14
5	DCE	80	48	HCl (1.0)	75(59)[c]	8
6[d]	DCE	80	48	HCl (1.0)	75	7
7[e]	DCE	80	48	HCl (1.0)	80	0
8	DCE	80	24	HCl (1.0)	41	4
9	DCE	80	72	HCl (1.0)	76	7
10	DCE	90	48	HCl (1.0)	73	9
11	DCE	80	48	HCl (1.5)	35	45
12	DCE	80	48	HCl (2.0)	20	24
13	*i*-PrOH	80	48	HCl (1.0)	50	5
14	Toluene	80	48	HCl (1.0)	52	9
15	CH_3CN:H_2O(4 : 1)	80	48	HCl (1.0)	68	trace
16	CH_3CN	80	48	HCl (1.0)	94	5
17[e]	CH_3CN	80	48	HCl (1.0)	93	0
18	CH_3CN	80	48	none	86	16

[a] Reaction conditions: A mixture of **1a** (1.0 equiv), **2a** (1.5 equiv) and morpholine **3a** (1.0 equiv) was stirred in a sovlent at elevated temperature in a sealed tube.
[b] Determined by crude 1H-NMR (400 MHz, CDCl3) with adding 4'-nitro-acetophenon as internal standard. Reaction yield was based on **1a**.
[c] Isolated product yield (silica gel chromatography) was showed in parentheses.
[d] Reaction was carried out under Argon.
[e] With 4 Å molecular sieves.

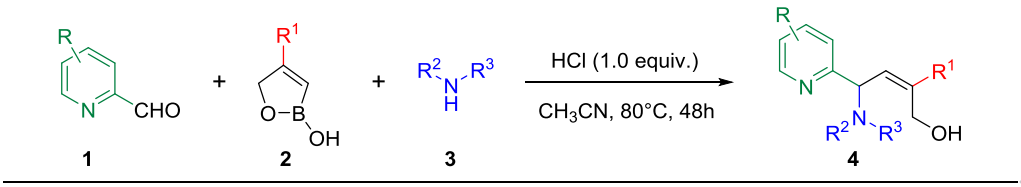
Next, the reaction scope was investigated under the optimized reaction conditions (Table 1, Entry 16). As we can see from Table 2, both aryl groups (**4a**-**4d**) and alkyl group (**4e**) on 4-substituted 1,2-oxaborol-2(5*H*)-ols could tolerate the reaction well and gave the corresponding Petasis products in good to excellent yields. A strong electron-donating group of methoxyl on benzyl ring led to a decreased yield (**4c**, 61%). However, a bulky group of naphthalene gave an excellent yield (**4d**). A yield of 75% was achieved when 4-phenylehthyl-1, 2-oxaborol-2(5*H*)-ol was utilized (**4e**).

Both cyclic and acyclic amines could be used in the Petasis reaction, affording the desired product in medium to excellent yields (**4f**-**4j**). Cyclic amines (**4f**&**4i**) led to better results than acyclic amines (**4g**&**4h**). While a steric-hindered amine, 8-oxa-3-aza-bicyclo [3.2.1] octane, only afforded the desired product in yield of 42% (**4j**).

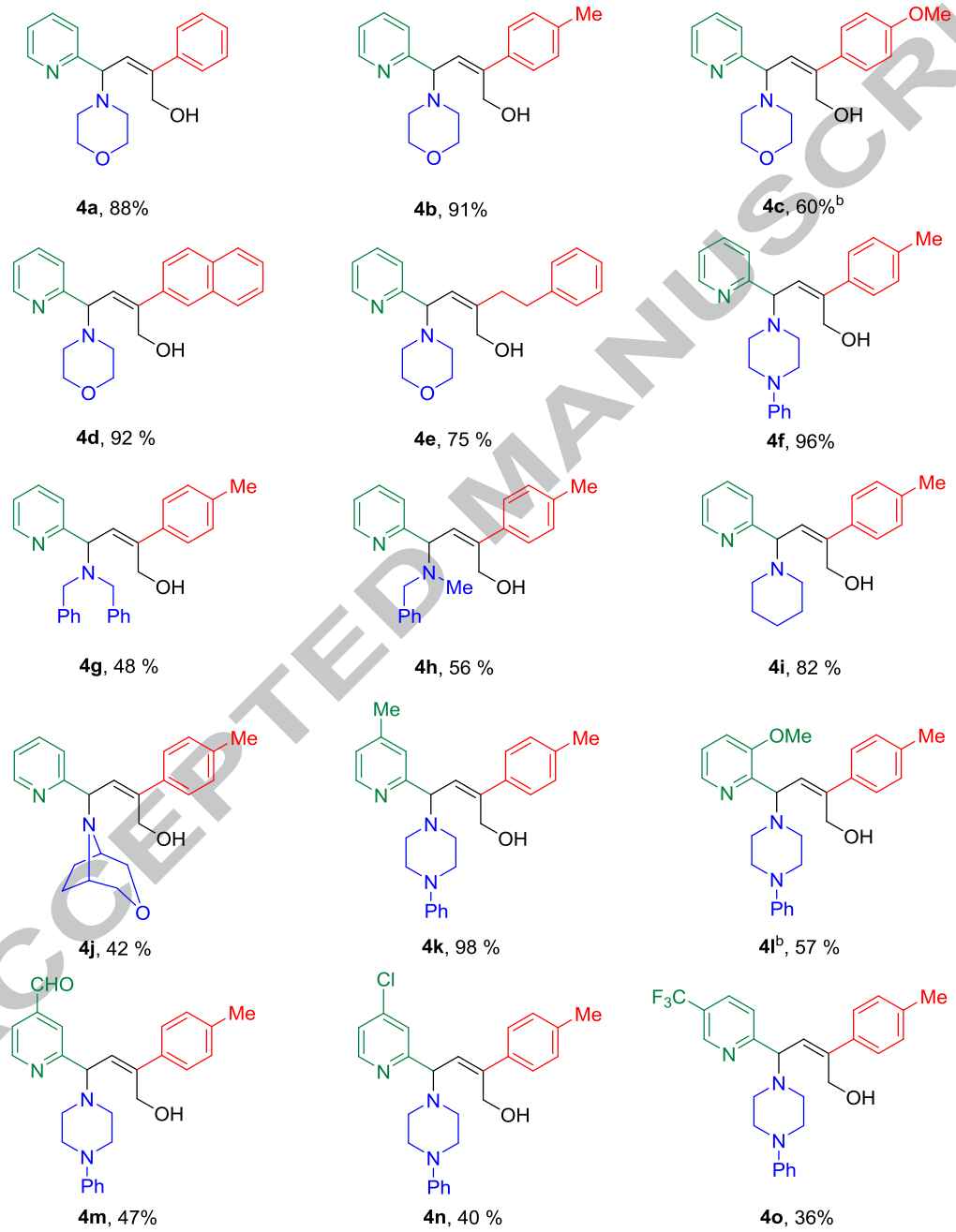
As regard for aldehyde components, both electronic and steric effects played important roles in the reaction (**4k**-**4o**). Electron-withdrawing groups on 2-pyridinecarbaldehyde could retard the reaction and only give the desired product in low to medium yields (**4m**-**4o**). It is worth mentioning that when two aldehydes present on pyridine, only aldehyde at *ortho*-position took place in this reaction and *para*-position aldehyde left intact (**4m**). A steric hindered 3-methoxyl-2-pyridinecarbaldehyde could react with 4-

p-methylphenyl-1, 2-oxaborol-2(5*H*)-ol and 1-phenylpiperazine and gave the desired product in a yield of 37% (**4o**). The structure of the Petasis reaction products was confirmed by the X-ray crystallographic analyses of **4a** (Figure 1).

Table 2. Substrate Scope for Petasis Reaction of 2-Pyridinecarbaldehydes, 1, 2-Oxaborol-2(5H)-ols, and Amines[a]



1 2 3 4



[a] Reaction conditions: A mixture of **1a** (0.5 mmol, 1.0 equiv), **2a** (0.75mmol, 1.5 equiv), **3a** (0.5 mmol, 1.0 equiv) and HCl (2.0 M in dioxane, 0.5 mmol, 1.0 equiv) in a sealed tube was stirred at 80°C for 48h.

[b] With side reaction. Reaction time was 24h.

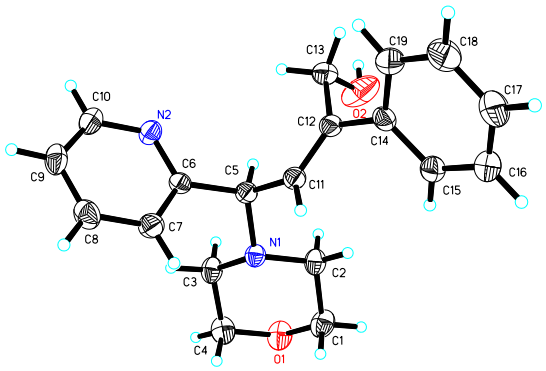
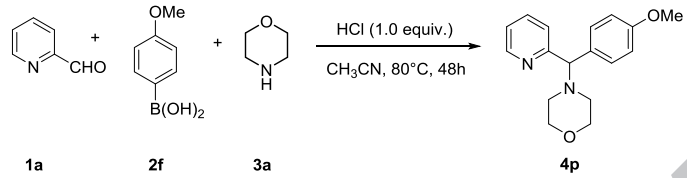


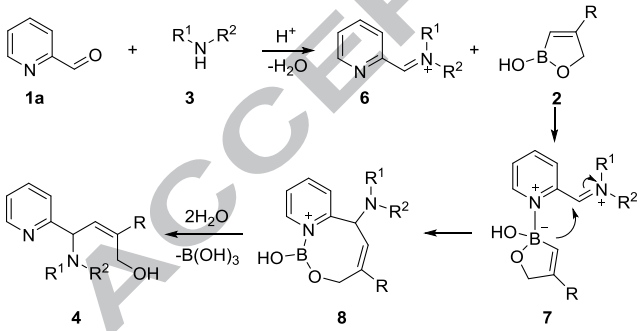
Figure 1 X-ray Structure of 4a

In order to test the generality of this method, a normal boronic acid, 4-methoxyphenylboronic acid was used to participate in this HCl promoted Petasis reaction and a good yield of 86% was achieved (Scheme 1).



Scheme 1 Boronic Acid in Petasis Reaction

A possible mechanism for the process was depicted in Scheme 2. Initially pyridinecarbaldehyde reacted with secondary amines and converted to iminium intermediate 6 under the aid of acid. Next, complexation of 4-substituted 1, 2-oxaborol-2(5H)-ol yielded an ate complex 7. Subsequent, a C-C bond was formed by the intermolecular transfer of the vinyl group to give intermediate 8. Finally hydrolysis of intermediate 8 gave the final product 4.



Scheme 2 Plausible Reaction Mechanism

In conclusion, we have developed a Petasis reaction of 2-pyridinecarbaldehydes with various amines and 4-substituted 1, 2-oxaborol-2(5H)-ols. In the presence of HCl, the reaction could proceed smoothly under very mild conditions and the corresponding desired products were obtained in medium to excellent yields. This method allows us to access a wide range of amines adjacent to heteroaromatic rings, which might be useful compounds in medicinal and material chemistry. Further exploration of this powerful strategy of Petasis reactions in establishing new C-N bond formation reactions is underway in our laboratory.

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