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STUDIES ON THE PETASIS REACTION OF 2-PYRIDINECARBALDEHYDE DERIVATIVES AND ITS PRODUCTS

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Abstract – The Petasis reaction of various 2-pyridinecarbaldehydes with secondary amines and boronic acids in refluxed acetonitrile proceeded to afford desired products up to 96% yield. The reaction proceeded under mild conditions to afford wide range of amines adjacent to heteroaromatic rings. Interestingly, the aldehyde possessing a nucleophilic moiety, 4-(dimethylamino)-2-pyridinecarbaldehyde, with (*S*)-(-)-*N*-methyl-1-phenylethylamine and 2 equivalent of *trans*-2-phenylvinylboronic acid afforded unexpected product, (*E*)-*N*-benzyl-3-phenyl-1-(pyridin-2-yl)prop-2-en-1-amine, in high yield. This product might be formed through the direct alkylation of aldehyde by *trans*-2-phenylvinylboronic acid, followed by anion/enolate isomerization. Derivatization of the Petasis products were also employed and 2-alkyl substituted pyridine derivatives can be obtained through deamination of the Petasis products under the simple hydrogenation conditions.

INTRODUCTION

In synthetic organic chemistry, multicomponent reactions proceed with greater efficiency and atom economy.[1] They can be also used in constructing various compound libraries in medicinal chemistry. Many groups have reported on the Petasis borono–Mannich reaction, known as the Petasis reaction, during the last two decades.[2-5] Such reactions were widely studied for the construction of nitrogen-containing molecules (e.g., amino acid) by the condensation reaction of three substrates: aldehyde, amine, and boronic acid. In most cases, only a few aldehydes (e.g., glyoxylic acid[6-11] and

α-hydroxyaldehyde[12-14]) have been employed in these reactions, and successful examples of aromatic aldehydes have been limited to salicylaldehyde[15-20] (Figure 1).

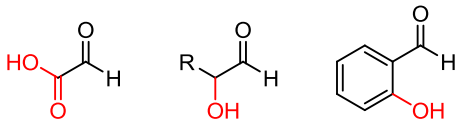


Figure 1. Aldehydes employed in Petasis reaction

These limitations are attributed to borate formation by the coordination of the hydroxy- or carboxyl-group in the iminium intermediate; followed by an intramolecular delivery of sp^2 carbon (R) from boronic acid to iminium carbon (Figure 2).[2] ^{11}B NMR study of the reaction mixture[21] and computational calculations[20,22] support these mechanisms.

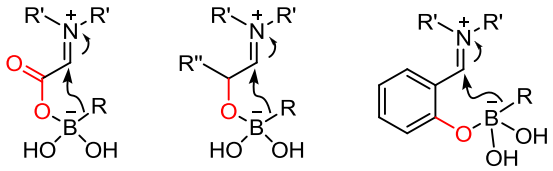
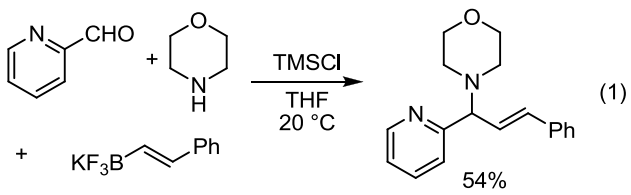


Figure 2. Borate formation in the Petasis reaction

In 2000, Bryce and Hansen reported the Petasis reaction other than those listed above. 2-Pyridinecarbaldehyde was reacted with morpholine and *trans*-2-phenylvinylboronic acid under catalyst-free conditions, affording the desired products in 10% yield.[23] In addition, they found that the use of more reactive potassium *trans*-2-phenylvinyltrifluoroborate and chlorotrimethylsilane, as an activator, improved the yield of the desired product up to 54% (Eq. 1). However, examples of heteroaromatic aldehydes in the Petasis reaction are still limited. Furthermore, 2-substituted pyridine compounds are attractive scaffolds for biologically active compounds.[24-26] In this study, we report in detail an improved method for the Petasis reaction of 2-pyridinecarbaldehydes with various amines and boronic acids.[27] The derivatization of the Petasis adducts were also explored.

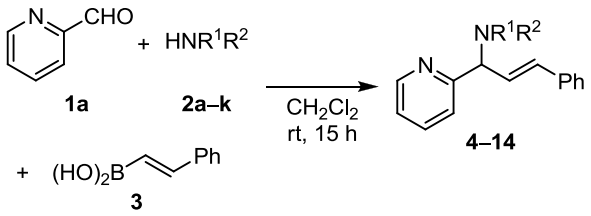


(1)

RESULTS AND DISCUSSION

Initially, we selected 2-pyridinecarbaldehyde **1a** as the model substrate and examined various amines **2a**–**k** (Table 1) in the Petasis reaction of **1a** with vinylboronic acid **3** in CH_2Cl_2, which is often utilized as a solvent in the Petasis reaction. Primary amines including chiral amine **2a**–**c** formed products in low conversions (entries 1–3). In all cases, unreacted imines in situ generated from aldehyde and amines were observed by ^{1}H NMR analysis of the unpurified reaction mixtures. Hence, we used secondary amines for the generation of more reactive iminium species. As predicted, the use of dibenzylamine (**2d**), *N*-benzyl *o*-anisidine (**2e**), and diallylamine (**2f**) afforded the desired product in 55%, 52%, and 42% conversions, respectively (entries 4–6). Further investigations showed that other secondary amines containing the bulkier amine **2g** and cyclic amines **2i**–**k** were ineffective amine sources compared to **2d** (entries 7–11 vs 4). Thus, **2d** as the amine component showed the best conversion under these conditions.

Table 1. The Petasis reaction of **1a** with various amines[a]



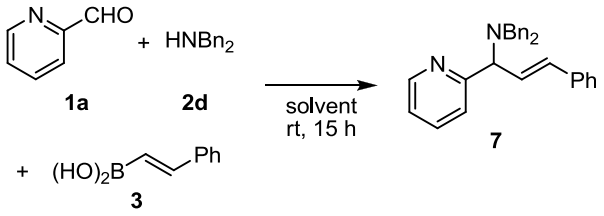
Entry	Amines **2**	Product	Conv. (%)[b]
1	benzylamine **a**	**4**	14
2	(*S*)-phenylglycinol **b**	**5**	<2
3	(*S*)-(-)-1-phenylethylamine **c**	**6**	<2
4	dibenzylamine **d**	**7**	55
5	*N*-benzyl-*o*-anisidine **e**	**8**	52
6	diallylamine **f**	**9**	42
7	diisopropylamine **g**	**10**	<10
8	*N*-methylbenzylamine **h**	**11**	<10
9	morpholine **i**	**12**	<10
10	piperidine **j**	**13**	<10
11	pyrrolidine **k**	**14**	38

[a]Reactions were performed under N_2 atmosphere with 1.0 equiv of aldehyde **1a** and amine **2** in the presence of 1.0 equiv of boronic acid **3** in CH_2Cl_2 at room temperature. [b]Conversions were determined by the analysis of ^{1}H NMR spectra of unpurified reaction mixtures and based on the consumption of **1a**.

Subsequently, we examined numerous solvents for the Petasis reaction of **1a** with **2d** and **3** at room temperature. As illustrated in Table 2, CH_2Cl_2, dichloroethane, MeCN, and hexafluoroisopropanol (HFIP)[8] underwent the Petasis reaction in 55–73% conversion. However, other solvents such as MeOH, H_2O, and 1-butyl-2,3-dimethylimidazolium tetrafluoroborate ([bdmim]BF_4),[2] which are often utilized in the Petasis reaction, resulted in <10% conversion. Although the effect of solvent is unclear, MeCN clearly

enhanced the reaction rate and was found to be an optimal solvent (entry 3).

Table 2. The Petasis reaction of **1a** with **2d** and **3** under various solvents[a]

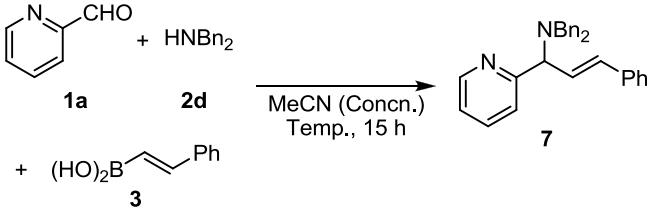


Entry	Solvent	Conv. (%)[b]
1	CH_2Cl_2	55
2	CH_2Cl_2	46
3	MeCN	73
4	HFIP	58
5	MeOH	<10
6	toluene	<10
7	THF	<2
8	Et_2O	<2
9	DMF	<10
10	H_2O	<10
11	[bdmin]BF_4	<2

[a]Reactions were performed under N_2 atmosphere with 1.0 equiv of aldehyde **1a** and amine **2d** in the presence of 1.0 equiv of boronic acid **3** at room temperature. [b]Conversions were determined by the analysis of ^{1}H NMR spectra of the unpurified reaction mixtures and based on the consumption of **1a**.

Then, to improve the conversion of the desired product **7**, we screened the substrate concentration and reaction temperature (Table 3). The reactions in 0.1 and 0.2 M gave a slightly better conversion than those in 0.5 M, which caused solubility issues of the vinylboronic acid **3** (entries 1–3). In addition, the reaction at the refluxed temperature in 0.2 M of MeCN formed the product in >98% conversion after 15 h (entry 5). Later, the TLC analysis of reaction mixture revealed that the full consumption of aldehyde was observed after 3 h, under the same conditions (entry 6). Accordingly, the Petasis reaction of 2-pyridinecarbaldehyde **1a** with dibenzylamine **2d** and vinylboronic acid **3** proceeded smoothly in MeCN at a refluxed temperature within 3 h, affording the Petasis adduct **7** in >98% conversion (96% isolated yield after silica gel column chromatography).

Table 3. Effect of substrate concentration and reaction temperature[a]



Entry	Concn. (M)	Temp. (°C)	Conv. (%)[b]
1	0.1	rt	73
2	0.2	rt	73
3	0.5	rt	59
4	0.2	50	84
5	0.2	reflux	>98 (96)[d]
6[c]	0.2	reflux	>98 (96)[d]

[a]Reactions were performed under N_2 atmosphere with 1.0 equiv of aldehyde **1a** and amine **2d** in the presence of 1.0 equiv of boronic acid **3** in MeCN. [b]Conversions were determined by the analysis of ^{1}H NMR spectra of unpurified reaction mixtures and based on the consumption of **1a**. [c]The reaction time was 3 h. [d]Isolated yields of the product after silica gel column chromatography.

Under the optimal conditions, various 2-substituted pyridines were synthesized by the Petasis reaction between amines, aldehydes, and boronic acids (Table 4). Both acyclic and cyclic amines could be used in the Petasis reaction, affording the desired products **7**, **9**, and **11**–**13** in 72–96% yield (entries 1–5). Although some amines were ineffective in the initial screening (Table 1), the optimal conditions (MeCN, reflux) enabled us to use less reactive amines **2h**–**j**. In contrast, the structure of an aldehyde greatly influenced the yield of products (entries 6–12). For example, the reactions of 6-methoxy- and 6-bromo-2-pyridinecarbaldehyde with **2d** and **3** significantly decreased the reaction efficiency under optimal conditions (16% for **14** and 11% for **15**, respectively; entries 6 and 8). Thus, the use of excess **3** (1.5 equiv) slightly increased the yield of products **14** and **15** (31% and 23%, respectively; entries 7 and 9). In all cases, the starting aldehydes, which may be derived from the hydrolysis of unreacted iminium species, could be observed by ^{1}H NMR of unpurified reaction mixtures. Whereas 5-bromo-2-pyridinecarbaldehyde with 1.0 equiv of **2d** and **3** reacted smoothly to deliver the Petasis adduct **16** in 91% yield (entry 10). These results clearly indicate that steric hindrance adjacent to pyridine nitrogen dominates the reaction efficiency of the Petasis reaction. It may be considered that an α-heteroatom moiety is important in bringing boronic acid close to the reaction site and/or in the intramolecular activation of boronic acid (e.g., borate formation by nitrogen atom). To judge the importance of the α-heteroatom in aldehyde component, we tested various heteroaromatic aldehydes in the Petasis reaction. As listed in Figure 3, the reaction of five-membered ring heteroaromatic aldehydes as well as pyridinecarbaldehyde, including 3- or 4-pyridinecarbaldehydes, resulted in the formation of a complex mixture or recovery of the aldehyde, suggesting that the structure of the aldehyde component is responsible for the reaction to proceed. The reaction of 4-chloro- and 4-dimethylamino-2-pyridinecarbaldehyde proceeded to afford the products **17** and **18** in 74% and 35% yields, respectively (entries 11 and 12). As a result, the Petasis reaction of various 2-pyridinecarbaldehyde derivatives occurred, and these phenomena were consistent with previous observations.[23] With regard to the boronic acid component, a variety of aromatic boronic acids can be used in these reactions, leading to

the formation of desired products **19**–**22** in 46–90% yields (entries 13–17). In some cases, 1.5 equiv of boronic acid was required to obtain a reasonable yield (entry 15 vs 16 and 18 vs 19). However, no desirable products **24** and **25** were obtained, when these reactions were carried out with phenylboronic acid and electron deficient 3,5-bis(trifluoromethyl)phenylboronic acid (entries 20 and 21). It seemed that the boronic acid component required enough nucleophilicity to react with the iminium intermediate.

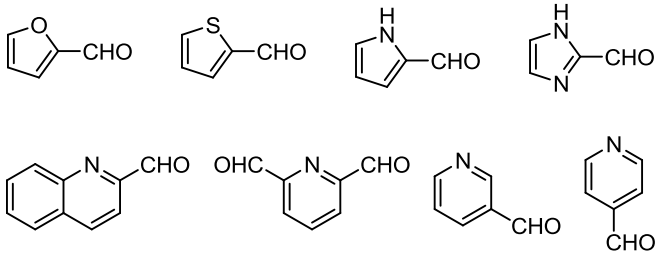
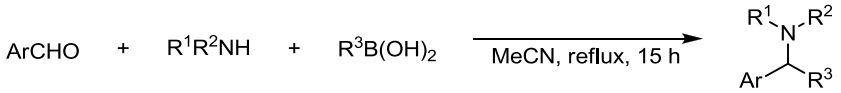
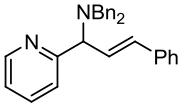
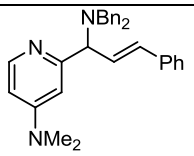
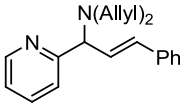
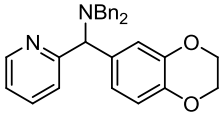
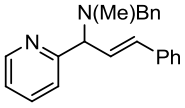
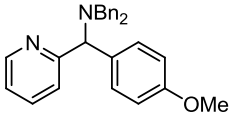
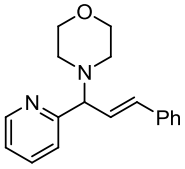
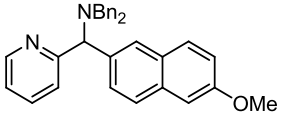
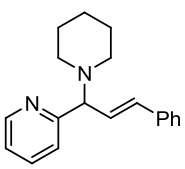
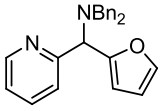
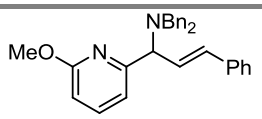
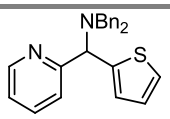
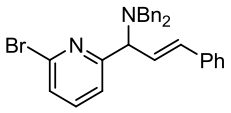
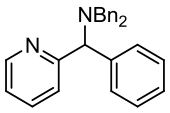
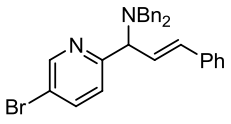
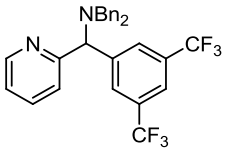
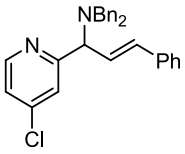


Figure 3. Ineffective aldehydes in the Petasis reaction

Table 4. Scope of the substrate in the Petasis reaction[a]



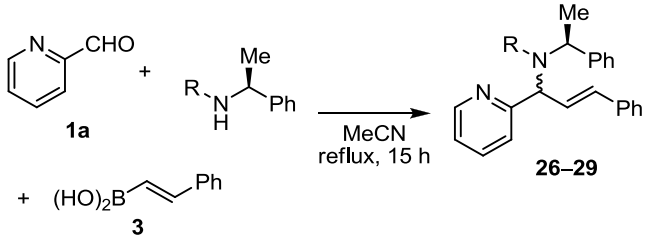
Entry		Product	Yield (%)[b]	Entry	Product	Yield (%)[b]
1[c]	**7**		96	12	**18** 	35
2[d]	**9**		72	13	**19** 	90
3	**11**		77	14	**20** 	70
4	**12**		95	15 16[e]	**21** 	27 46
5	**13**		75	17	**22** 	80

6	**14**		16	18	**23**		32
7[e]			31	19[e]			78
8	**15**		11	20	**24**		n.d.[f]
9[e]			23				
10	**16**		91	21	**25**		n.d.[f]
11	**17**		74				

[a]Reactions were performed under N_2 atmosphere with 1.0 equiv of aldehyde and amine in the presence of 1.0 equiv of boronic acid in refluxed MeCN. [b]Isolated yields of the product after silica gel column chromatography. [c]The reaction time was 3 h. [d]The reaction time was 12 h. [e]1.5 equiv of boronic acid was used. [f]Not detected

Subsequently, we examined the diastereoselective Petasis reaction of **1a** by using (*S*)-(-)-1-phenylethylamine-based secondary amines (Table 5). The reaction with (*S*)-(-)-*N*-benzyl-1-phenylethylamine, one stereogenic center added to dibenzylamine, became sluggish and led to a 1:1 mixture of diastereomer **26** in 64% yield (entry 1). (*S*)-(-)-*N*-Methyl-1-phenylethylamine gave 81% yield of **27** with no improvement of diastereoselectivity (50:50 d.r.; entry 2). In the case of (*S*)-(-)-*N*-allyl-1-phenylethylamine, both yield and diastereoselectivity slightly increased (87%; 56:44 d.r.; entry 3). The reactions at lower temperatures (from reflux to 50 °C and rt) were carried out with the same amine (entries 4 and 5), and resulted in 67% and 16% yields, respectively, with similar diastereomeric ratios. The diastereoselective reactions with chiral amines were challenging under current reaction conditions. Furthermore, neither the desired products were obtained nor recovered starting substrate when C_2-symmetric chiral amine, (*S*,*S*)-*N*,*N*-bis(1-phenylethyl)amine, was used, possibly due to the steric hindrance of the amine (<2% conv., entry 6).

Table 5. The Petasis reaction of **1a** with chiral amine and **3**[a]

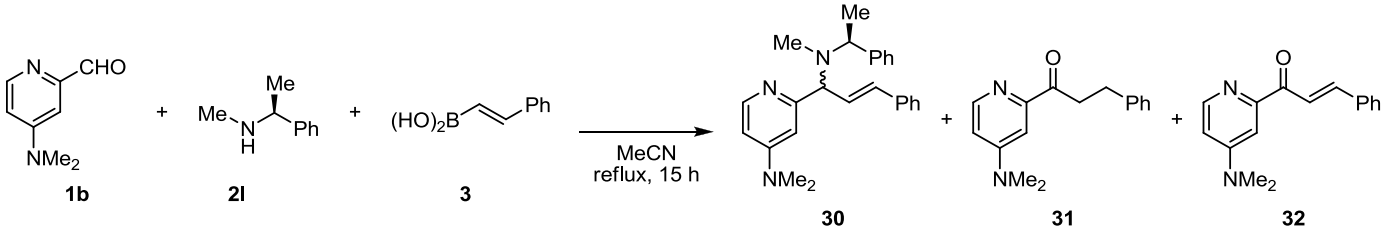


Entry	R	Product	Yield (%)[b]	d.r.
1	Bn	**26**	64	50:50
2	Me	**27**	81	50:50
3	Allyl	**28**	87	56:44
4[c]	Allyl	**28**	67	55:45
5[d]	Allyl	**28**	16	58.5:41.5
6		**29**	n.d.[e]	-

[a]Reactions were performed under N_2 atmosphere with 1.0 equiv of aldehyde **1a** and chiral amine in the presence of 1.0 equiv of boronic acid **3** in MeCN at refluxed temperature. [b]Isolated yields of the mixture of diastereomer after silica gel column chromatography. [c]The reaction temperature was 50 °C. [d]The reaction temperature was room temperature. [e]Not detected.

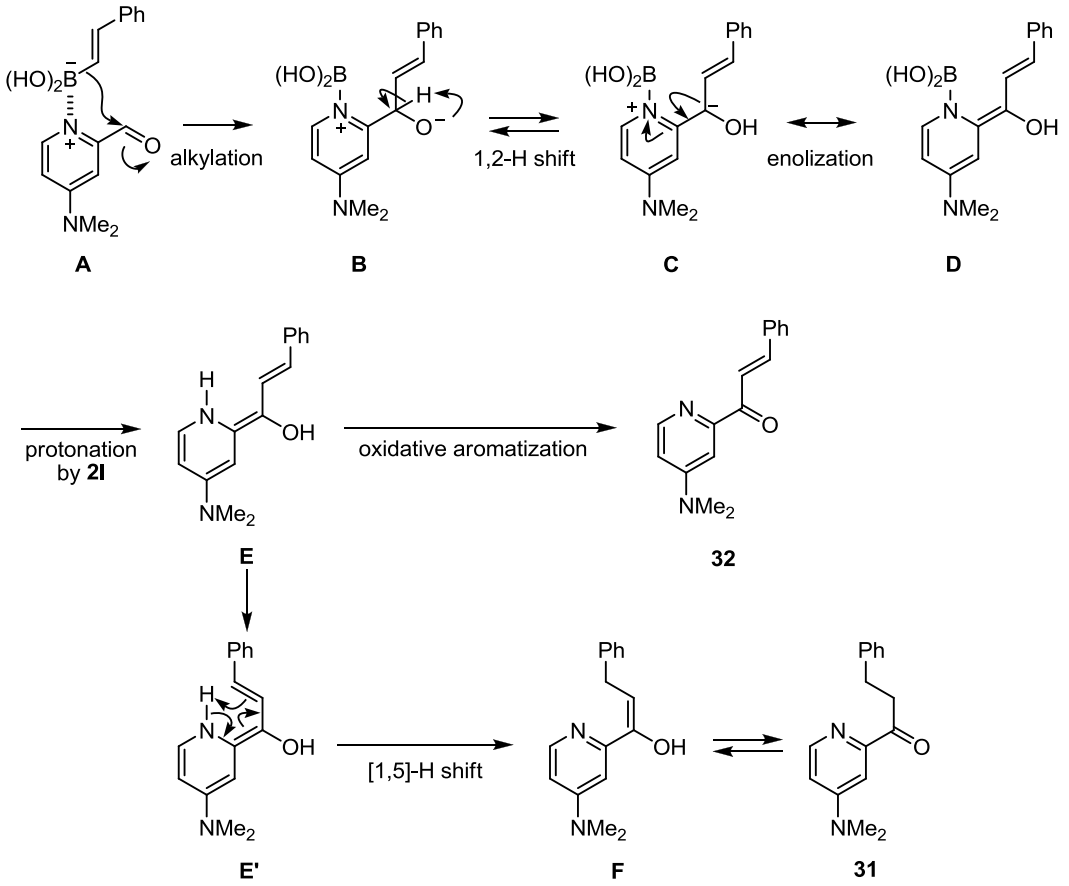
As shown in Table 6, unexpected compounds could be produced when 4-(dimethylamino)-2-pyridinecarbaldehyde **1b** was used as an aldehyde component. The reaction of **1b** with **2l** and **3** produced the desired the Petasis product **30** in 40% yield (59.5:40.5 d.r.) along with an inseparable mixture of byproducts **31** and **32** with a 80:20 ratio,[28] which did not contain an amine component (entry 1). Interestingly, using excess vinylboronic acid **3** (2 equiv) under the same reaction conditions only afforded compound **31** in a quantitative yield and did not produce the desired product **30** (entry 2). We speculated whether **31** and **32** could be generated in the absence of **2l**. However, trace amounts of byproducts could be obtained in the absence of **2l** (entries 3 and 4). According to these results, **2l** was essential for the formation of **31** and **32** (*vide infra*). Taking into account Giomi and Brandi's report regarding the thermal isomerization of allyl pyridyl alcohol,[29] the acceptable mechanism for the byproduct formation may involve direct alkenylation of **1b** by **3**, followed by anion/enolate isomerization (Scheme 1). That is, 4-(dimethylamino)pyridine moiety of **1b** interacted with **3** (**A**), and the intramolecular delivery of vinyl group afforded alkenylated intermediate **B**, which underwent 1,2-proton transfer (**B**→**C**), followed by the formation of fully conjugated enamine **D**. The final byproduct **32** was formed after oxidative aromatization of **E**.[30] In contrast, the formation of **31** may involve [1,5] sigmatropic hydrogen shift from *s-cis* conformer (**E′**→**F**) to afford ketone **31**. Although there is no direct evidence to support the above mechanism, Giomi and Brandi's mechanism could be relevant to the formation of **31** and **32**.

Table 6. The Petasis reaction of **1b** with **2l** and **3**[a]



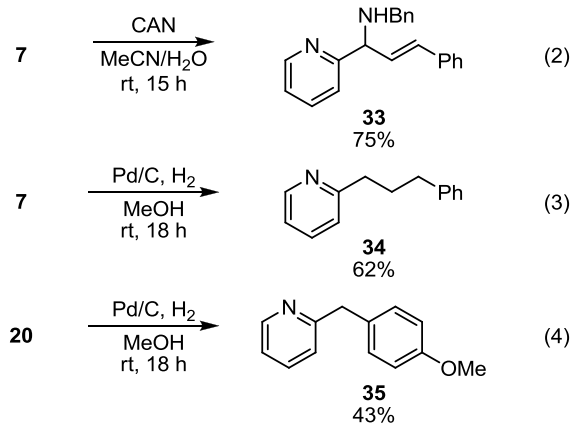
Entry	**1b** (mmol)	**2l** (mmol)	**3** (mmol)	Yield of **30** (%)[b]	d.r.	Yield of **31/32** (%)[c]	**31**:**32**
1	0.2	0.2	0.2	40	59.5:40.5	24	80:20
2	0.2	0.2	0.4	n.d.[d]	-	>98	100:0
3	0.2	-	0.2	-	-	trace	-
4	0.2	-	0.4	-	-	trace	-

[a]Reactions were performed under N_2 atmosphere in MeCN at refluxed temperature. [b]Isolated yields of the product after silica gel column chromatography. [c]Isolated yields of the mixture of byproducts after silica gel column chromatography. [d]Not detected.



Scheme 1. Plausible mechanism for the formation of byproducts **31** and **32**

The derivatization of the Petasis products was also employed to deliver various pyridine-containing compounds. For example, *N*-benzyl product **33**, which cannot be directly accessed by the Petasis reaction of **1a** with benzylamine **2a**, was obtained in 75% yield by the treatment of the Petasis product **7** with 2.5 equiv of CAN. Furthermore, the standard hydrogenation conditions (Pd/C, H_2) for the Petasis products **7** and **20** gave rise to the unexpected deamination products **34** and **35** (Eqs. 3 and 4). In general, 2-substituted pyridine derivatives were obtained by the transition metal-catalyzed cross-coupling reaction[31-35] or direct alkylation of 2-pyridinecarbaldehyde by Grignard reagent[36] or organozinc,[37] followed by the removal of hydroxy at the benzylic position. Herein, our method allowed the access of 2-substituted pyridine derivatives by the simple hydrogenation reaction.



In conclusion, we studied the Petasis reaction of 2-pyridinecarbaldehydes derivatives with various amines and boronic acids in the absence of a catalyst. The reaction proceeded under mild conditions to afford wide range of amines adjacent to heteroaromatic rings. Based on the detailed study of the utility of aldehydes, the aldehyde structure is essential for the Petasis reaction to proceed; suggesting that an α-heteroatom moiety of aldehyde plays an important role in bringing boronic acid close to the reaction site and/or in the intramolecular activation of boronic acid (e.g., ate complex formation by nitrogen atom). When the aldehyde **1b** possessing a nucleophilic moiety was used, direct alkylation products of **31** and **32** were obtained in an 80:20 ratio. The byproduct formation mechanism may involve the direct activation of vinylboronic acid **3** by the DMAP moiety of **1b** and the intramolecular alkylation of **1b**, followed by anion/enolate isomerization. Furthermore, the derivatization of the Petasis products led to the mono-protected amine, which cannot be accessed directly by the Petasis reaction. In addition, 2-alkyl substituted pyridine derivatives could be obtained from the Petasis product by simple hydrogenation. Our methods allow the simple synthesis of various pyridine-containing compounds, which may be useful in medicinal and material chemistry.

EXPERIMENTAL

Infrared (IR) spectra were recorded on a JASCO FT/IR-4100 spectrophotometer, Vmax in cm^{-1}. ^1H NMR spectra were recorded on a Varian 400 MR (400 MHz) spectrometer at the SC-NMR Laboratory of Okayama University. Chemical shifts were reported in ppm from tetramethylsilane with the solvent resonance resulting from incomplete deuteration as the internal standard ($CDCl_3$: 7.26 ppm). Data is reported as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), and coupling constants. ^{13}C NMR spectra were recorded on a Varian 400 MR (100 MHz) or a Varian 600 MR (150 MHz) with complete proton decoupling. The ^{13}C chemical shifts were reported in ppm from tetramethylsilane with the solvent resonance as the internal standard ($CDCl_3$: 77.00 ppm). High-resolution mass spectrometry was performed on a JEOL JMS-700 MStation

FAB-MS or EI-MS (positive mode) at the Mass Spectrometry Facility (Okayama University). Acetonitrile was distilled from P_2O_5 and then from CaH_2 and dried subsequently (molecular sieve 4A).

General procedure for the Petasis reaction

Under N_2 atmosphere, aldehyde **1a** (54.0 mg, 0.500 mmol), and amine **2d** (99.0 mg, 0.500 mmol) in MeCN (2.50 mL) were stirred for 5 min, and vinylboronic acid **3** (74.0 mg, 0.500 mmol) was successively added to this solution. The resulting mixture was stirred for 3 h at refluxed temperature. Then, the solution was cooled to room temperature and evaporated *in vacuo* to dryness. The resulting oil was purified by column chromatography on SiO_2 (hexane/EtOAc = 1/1, v/v) to afford desired product **7** (192 mg, 0.490 mmol, 96% yield). Analytical data for compounds **7**, **9**, **11–25** were previously reported.[27]

(*E*)-*N*-Benzyl-3-phenyl-*N*-((*S*)-1-phenylethyl)-1-(pyridin-2-yl)prop-2-en-1-amine (26). Pale yellow oil; for a mixture of two diastereomers: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.51-8.55 (m, 2H), 7.68-7.70 (m, 2H), 7.57-7.61 (m, 1H), 7.46-7.52 (m, 3H), 7.30-7.39 (m, 7H), 7.10-7.29 (m, 23H), 6.38-6.51 (m, 3H), 6.21 (dd, *J* = 9.2, 16 Hz, 1H), 4.68 (d, *J* = 9.2 Hz, 1H), 4.63 (d, *J* = 8.4 Hz, 1H), 4.14 (q, *J* = 6.4 Hz, 1H), 4.05 (q, *J* = 6.8 Hz, 1H), 3.95 (d, *J* = 15.6 Hz, 1H), 3.92 (d, *J* = 16 Hz, 1H), 3.76 (d, *J* = 15.6 Hz, 1H), 3.68 (d, *J* = 8.4 Hz, 1H), 1.51 (d, *J* = 7.2 Hz, 3H), 1.34 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.0, 162.5, 148.8, 148.7, 144.9, 142.8, 142.3, 136.9, 136.4, 136.3, 131.8, 131.4, 130.4, 129.7, 128.3, 128.2, 128.1, 128.0, 127.8, 127.3, 126.7, 126.7, 126.5, 126.1, 123.2, 123.0, 122.0, 121.9, 70.2, 69.9, 58.4, 56.8, 51.8, 50.7, 17.1; IR (neat) 3060, 3026, 2971, 1588, 1494, 1145, 968, 733 cm^{-1}; HRMS-FAB (*m*/*z*): $[M+H]^+$ calcd for $C_{29}H_{29}N_2$ 405.2331, found 405.2348.

(*E*)-*N*-Methyl-3-phenyl-*N*-((*S*)-1-phenylethyl)-1-(pyridin-2-yl)prop-2-en-1-amine (27). Pale yellow oil; for a mixture of two diastereomers: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.58-8.60 (m, 1H), 8.55-8.56 (m, 1H), 7.59-7.73 (m, 4H), 7.12-7.46 (m, 22H), 6.69 (d, *J* = 16 Hz, 1H), 6.56-6.58 (m, 2H), 6.43 (dd, *J* = 8.8, 15.6 Hz, 1H) 4.41-4.47 (m, 2H), 4.14 (q, *J* = 6.8 Hz, 1H), 3.91 (q, *J* = 6.8 Hz, 1H), 2.23 (s, 3H), 2.05 (s, 3H), 1.40-1.43 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.6, 162.5, 149.2, 149.0, 144.1, 142.7, 136.9, 136.8, 136.7, 136.5, 132.7, 131.5, 130.8, 129.3, 128.4, 128.2, 128.0, 127.9, 127.7, 127.4, 126.7, 126.6, 126.4, 122.7, 122.4, 122.0, 121.9, 72.2, 70.4, 58.8, 57.5, 33.5, 33.4, 16.5, 14.5; IR (neat) 3026, 2972, 2792, 1587, 1431, 1154, 969, 747 cm^{-1}; HRMS-FAB (*m*/*z*): $[M+H]^+$ calcd for $C_{23}H_{25}N_2$ 329.2018, found 329.2033.

(*E*)-*N*-Allyl-3-phenyl-*N*-((*S*)-1-phenylethyl)-1-(pyridin-2-yl)prop-2-en-1-amine (28). Pale yellow oil; for a mixture of two diastereomers: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.53-8.55 (m, 2H), 7.61-7.69 (m, 3H),

7.55-7.58 (m, 1H), 7.46-7.50 (m, 2H), 7.19-7.43 (m, 18H), 7.11-7.15 (m, 2H), 6.57-6.59 (m, 2H), 6.37-6.46 (m, 2H), 5.81-5.91 (m, 1H), 5.70-5.80 (m, 1H), 4.90-5.08 (m 4H), 4.64-4.71 (m, 2H), 4.21 (q, *J* = 6.8 Hz, 1H), 4.06 (q, *J* = 6.8 Hz, 1H), 3.19-3.42 (m, 4H), 1.45 (d, *J* = 6.8 Hz, 3H) 1.38 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.0, 162.7, 148.8, 145.2, 143.9, 139.1, 138.6, 137.0, 136.4, 136.2, 131.9, 131.5, 130.4, 129.7, 128.4, 128.3, 128.2, 127.9, 127.8, 127.6, 127.3, 126.5, 126.4, 123.2, 122.8, 121.9, 115.2, 115.1, 69.3, 69.2, 58.2, 56.7, 50.6, 49.9; IR (neat) 3026, 2973, 1587, 1493, 1372, 1148, 968, 748 cm^{-1}; HRMS-FAB (*m*/*z*): $[M+H]^+$ calcd for $C_{25}H_{27}N_2$ 355.2174, found 355.2198.

(*E*)-*N*-Methyl-3-phenyl-*N*-((*S*)-1-phenylethyl)-1-((4-(*N*,*N*-dimethylamino)pyridin-2-yl))prop-2-en-1-amine (30). Pale yellow oil; for a mixture of two diastereomers: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (d, *J* = 6.4 Hz, 1H), 8.18 (d, *J* = 6.0 Hz, 1H), 7.15-7.46 (m, 20H), 6.82-6.83 (m, 2H), 6.64 (d, *J* = 14.4 Hz, 1H), 6.60 (d, *J* = 16.0 Hz, 1H), 6.50 (dd, *J* = 8.8, 16 Hz, 1H), 6.36-6.42 (m, 3H), 4.29 (d, *J* = 8.0 Hz, 1H), 4.27 (d, *J* = 8.8 Hz, 1H), 4.12 (q, *J* = 6.8 Hz, 1H), 3.96 (q, *J* = 6.4 Hz, 1H), 3.03 (s, 6H), 3.01 (s, 6H), 2.21 (s, 3H), 2.07 (s, 3H), 1.40 (d, *J* = 6.8 Hz, 3H), 1.39 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.3, 155.1, 155.0, 149.2, 149.1, 144.3, 142.3, 137.2, 137.1, 132.0, 131.7, 131.1, 130.8, 128.4, 128.3, 128.1, 127.9, 127.8, 127.3, 126.6, 126.5, 105.6, 104.8, 104.7, 72.7, 71.6, 57.9, 57.4, 39.2, 39.1, 33.7, 33.4, 15.2, 14.7; IR (neat) 3026, 2972, 2187, 1603, 1542, 1507, 1374, 1225, 992, 733 cm^{-1}; HRMS-FAB (*m*/*z*): $[M + H]^+$ calcd for $C_{25}H_{30}N_3$ 372.2440, found 372.2439.

1-(4-(*N*,*N*-Dimethylamino)pyridin-2-yl)-3-phenylpropan-1-one (31). Colorless solid; mp 128-130 °C, ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 (d, *J* = 6.0 Hz, 1H), 7.27 (d, *J* = 2.8 Hz, 1H), 7.23-7.25 (m, 5H), 7.14-7.17 (m, 1H), 6.59 (dd, *J* = 2.8, 6.0 Hz, 1H), 3.51-3.55 (m, 2H), 3.02 (s, 6H), 3.01-3.06 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.0, 154.8, 153.6, 149.0, 141.6, 128.5, 128.3, 125.8, 109.2, 104.6, 39.5, 39.2, 29.9; IR (KBr) 2932, 1687, 1604, 1514, 1416, 1356, 1228, 1068, 984 cm^{-1}; HRMS-EI (70 eV, *m*/*z*): $[M]^+$ calcd for $C_{16}H_{18}N_2O$ 254.1419, found 254.1411.

Derivatization of the Petasis products

(*E*)-*N*-Benzyl-3-phenyl-1-(pyridin-2-yl)prop-2-en-1-amine (33). Under N_2 atmosphere, the Petasis product **7** (149.6 mg, 0.38 mmol) and CAN (525 mg, 0.96 mmol) in MeCN/H_2O (12 mL, v/v = 5/1) were stirred for 15 h at room temperature. Then, the reaction mixture was diluted with saturated aqueous Na_2CO_3 and EtOAc. The suspension was stirred for about 5 min. The aqueous layer was extracted with EtOAc (5 mL × 3). Subsequently, the organic solution was washed with brine. After drying ($MgSO_4$), the solvent was evaporated *in vacuo* to dryness. The resulting residue was purified by column chromatography on SiO_2 (hexane/EtOAc = 1/1) to afford desired product **33** (85.8 mg, 0.29 mmol, 75%

yield). Pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.58-8.60 (m, 1H), 7.64-7.68 (m, 1H), 7.16-7.43 (m, 12H), 6.64 (d, *J* = 16 Hz, 1H), 6.35 (dd, *J* = 7.6, 16 Hz, 1H), 4.52 (d, *J* = 7.6 Hz, 1H), 3.88 (d, *J* = 13 Hz, 1H), 3.79 (d, *J* = 13 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 161.6, 149.3, 140.2, 136.8, 136.6, 131.9, 131.1, 128.5, 128.4, 128.3, 127.6, 126.9, 126.5, 122.2, 122.0, 65.7, 51.3; IR (neat) 3316, 3025, 2839, 1589, 1433, 968 cm^{-1}; HRMS-FAB (*m*/*z*): $[M + H]^+$ calcd for $C_{21}H_{21}N_2$ 301.1705, found 301.1733.

2-(3-Phenylpropyl)pyridine (34).

The Petasis product **7** (136 mg, 0.35 mmol) and Pd/C (10 wt%, 50 mg) in MeOH were stirred for 18 h at room temperature under H_2 atmosphere. Then, the reaction mixture was filtered off through a pad of celite. The solution was evaporated *in vacuo* to dryness. The resulting residue was purified by column chromatography on SiO_2 (hexane/EtOAc = 5/1) to afford the desired product **35** (43.0 mg, 0.22 mmol, 62% yield). Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.53-8.54 (m, 1H), 7.55-7.59 (m, 1H), 7.21-7.30 (m, 2H), 7.08-7.21 (m, 5H), 2.81-2.85 (m, 2H), 2.67-2.71 (m, 2H), 2.04-2.12 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.0, 149.3, 142.1, 136.3, 128.5, 128.3, 125.8, 122.8, 121.0, 37.9, 35.6, 31.5 IR (neat) 3061, 2931, 1590, 1496, 1433, 1150, 749 cm^{-1}; HRMS-FAB (*m*/*z*): $[M + H]^+$ calcd for $C_{14}H_{16}N$ 198.1283, found 198.1297.

2-(4-Methoxybenzyl)pyridine (35).[32] Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.53-8.55 (m, 1H), 7.55-7.59 (m, 1H), 7.17-7.19 (m, 2H), 7.08-7.11 (m, 2H), 6.84-6.86 (m, 2H), 4.10 (s, 2H), 3.78 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.4, 158.1, 149.3, 136.5, 131.6, 130.0, 122.9, 121.1, 114.0, 55.2, 43.8; IR (neat) 3005, 2931, 2833, 1610, 1568, 1434, 1301, 1247, 1108 cm^{-1}.

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28. Two products **31** and **32** cannot be isolated in pure form by column chromatography on SiO_2. Since the treatment of the mixture of **31** and **32** with Pd/C under hydrogen atmosphere converged on the single compound **31** in >98% yield, we identified **32** as α,β-unsaturated ketone which shows two trans olefinic protons [^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 (d, J = 16.2 Hz, 1H), 7.90 (d, J = 16.2 Hz, 1H)].
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