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Microwave-Assisted Esterification of *N*-Acetyl-L-Phenylalanine Using Modified Mukaiyama's Reagents: A New Approach Involving Ionic Liquids

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Abstract: Inspired by the concept of ionic liquids (ILs), this study modified the original Mukaiyama's reagent, 2-chloro-1-methylpyridinium iodide (m.p. 200-dec), from ionic solid into liquids by changing its anion. The esterification of *N*-acetyl-L-phenylalanine was investigated as a model reaction. The microwave irradiation was more effective in esterifying *N*-acetyl-L-phenylalanine than the conventional reflux method. The original Mukaiyama's reagent was modified into ILs through manipulating its anion. However, only non-nucleophilic anions (such as $EtSO_4^-$ and Tf_2N^-) were favorable since nucleophilic ones (such as CF_3COO^- and CH_3COO^-) could exchange with chlorine resulting in non-reactive coupling reagents. Two modified Mukaiyama's compounds (i.e. hydrophilic [2-ClMePy][$EtSO_4$] and hydrophobic [2-ClMePy][Tf_2N]) have been identified as the best IL-type coupling reagents. The esterification reaction was greatly enhanced by using 1-methylimidazole as the base instead of conventional toxic tertiary amines, and by using excess amount of alcohols as solvents instead of dichloromethane. Overall, the method reported is effective and 'greener'.

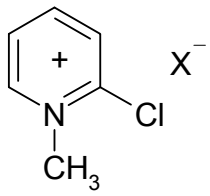
Keywords: amino acid, ionic liquid, Mukaiyama's reagent, microwave, esterification.

1. Introduction

Amino acid esters are versatile intermediates for many synthetic reactions including peptide synthesis [1-2]. Thus, they are of particular interests to chemical and pharmaceutical industry [3].

However, the esterification of amino acids is much more difficult than ordinary carboxylic acids mainly because of the zwitterionic structures. Conventional methods of esterifying amino acids include: (1) Acid-catalyzed reactions using concentrated acids (such as HCl or H_2SO_4) or solid acids (such as *p*-toulenesulfonic acid [4-5] or benzenesulfonic acid [6]). These reactions are equilibrium-driven and generate huge amounts of salts such as NaCl or Na_2SO_4 during large-scale productions [7]. An improvement made by Wegman et al. [7] was the utilization of acid form of ultrastable zeolite Y (H-USY) as a solid catalyst at 100-130 °C (15-20 bar). This process does not require the *N*-protection of amino acids. (2) Formation of acyl halides by reacting amino acids with thionyl chloride first [8-9], followed by the addition of alcohols. However, thionyl chloride is not environmentally friendly and is difficult to handle. (3) Esterification using cesium salts (Cs_2CO_3 or $CsHCO_3$) [10], cesium fluoride (CsF) or potassium fluoride (KF) [11-13].

Another effective esterification method is the use of coupling reagents, many of which have been summarized by Mukaiyama et al [14]. In particular, onium salts (such as 2-halogenated pyridinium, benzoxazolium, benzothiazolium and pyridinium salts), have been extensively studied as activating agents for carboxylic acids and alcohols, enabling a whole regime of synthetic reactions [15]. A simple onium salt, 2-chloro-1-methylpyridinium iodide ([2-ClMePy]I) **1a** (Scheme 1), and its derivatives (often referred as Mukaiyama's reagents) are effective coupling reagents in the synthesis of carboxylic esters [16-17]. In order to simplify the product purification, a recent trend in enhancing Mukaiyama's reagents is to immobilize them on the polymer support (such as Wang resin), and to conduct the heterogeneous reactions [18-21].

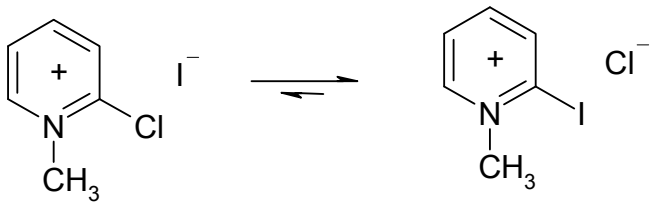


1a X = I,
1b X = CH_3COO,
1c X = CF_3COO,
1d X = BF_4,
1e X = $EtSO_4$,
1f X = Tf_2N [i.e. $(CF_3SO_2)_2N$]

Scheme 1. Structures of original Mukaiyama's reagent (**1a**) and its derivatives (**1b-1f**).

This paper was inspired by the resemblance of the original Mukaiyama's reagent **1a** with ionic liquids (ILs). As a brief background, ILs are ionic salts that are liquids at low temperatures (< 100 °C), many of which are room-temperature ionic liquids (RTILs). Typical ILs produce little vapor pressure; by this means, they are 'greener' solvents in contrast to traditional volatile organic compounds (VOCs). During the past ten years, ILs have attracted tremendous attention as solvents or co-catalysts in a variety of synthetic reactions [22-28]. The salt **1a** is not an IL because of its high melting point (200 °C-dec). However, if its anion (I^-) can be substituted by other anions (such as anions in **1b-1f** of Scheme 1, which appear in common RTILs), the melting point of this salt may be considerably lowered. Another advantage of such a modification is that the halogen exchange (Scheme 2) within the Mukaiyama's reagent **1a** results in a non-reactive form (*N*-methyl-2-iodopyridinium chloride, **2**); this non-reactive form is unable to activate the carboxylic acids [29]. Therefore, the use of non-nucleophilic anions may suppress such exchange [30].

Another improvement to be made is the heating method. Conventional esterification is usually achieved through several hours of conductive heating (such as reflux using hot-plates or heating mantles). As an alternate energy source, microwave irradiation (0.3–300 GHz) has become a routine and efficient heating method for chemical reactions [31]. Microwaves can increase the reaction rates through the thermal effect. Although many studies have realized the non-thermal (or specific microwave) effect of microwaves [32], it is still controversial whether such non-thermal effect exists. It was reported that microwave irradiation can shorten the esterification reaction time, and increase the conversions [33-34].



Scheme 2. Inactivation of Mukaiyama's reagent **1a**.

In this study, we carried out the esterification of *N*-acetyl-L-phenylalanine (**L-3**) as a model reaction in achieving the following objectives: (1) substituting conventional heating with microwave irradiation; (2) making the process 'greener' (such as using excess alcohol as solvent instead of dichloromethane, and using 1-methylimidazole as the base instead of toxic triethylamine or tributylamine); (3) modifying the original Mukaiyama's reagent into ILs.

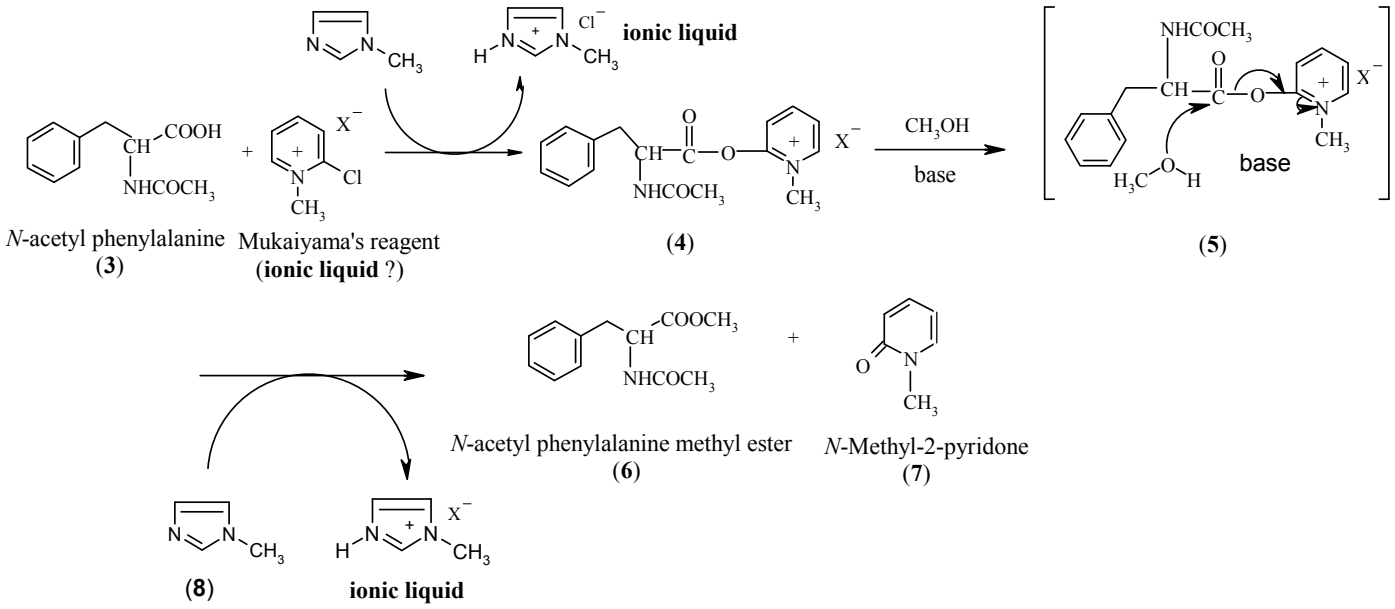
2. Results and Discussion

The esterification through Mukaiyama's reagent usually begins with *N*-protection of amino acids. Amino acids without *N*-protection are not soluble in organic solvents and are difficult to be esterified. In addition, amides may be produced in the absence of *N*-protection [15]. Therefore, in this study, we used *N*-acetyl-L-phenylalanine (L-**3**) as a model compound. As illustrated in Scheme 3, the Mukaiyama's reaction is generally considered as a two-step strategy [16-17]: (1) a nucleophilic aromatic substitution of halogen atom (Cl) in Mukaiyama's reagent by the carboxylate in L-**3** under a basic condition, resulting in pyridinium salt **4**; this is a fast step due to a facial displacement. (2) nucleophilic attack of methanol to give the key intermediate **5**, which is further converted into *N*-acetyl phenylalanine methyl ester (**6**) and *N*-methyl-2-pyridone (**7**). Since all reactant molecules are gathered in the vicinity of a central pyridinium salt, the condensation reaction is entropically driven [16].

2.1. Effect of solvents and bases

The commonly used bases in Mukaiyama's reaction are triethylamine (TEA) and tributylamine (TBA) [16-19], although other bases (such as 2,6-lutidine, α-picoline, pyridine and *N*,*N*-diethylaniline) have been considered (they usually produced lower yields than TEA or TBA) [17]. However, both TEA and TBA are quite toxic and corrosive; TEA is very flammable; and TBA is hydrophobic (difficult for work-up). On the other hand, 1-methylimidazole (MIM, **8**, in Scheme 3), is less toxic than

TEA and TBA, less flammable than TEA, and soluble in water (easy for work-up). In fact, MIM (**8**) has been used in the commercial process to scavenge acid by BASF AG (Ludwigshafen, Germany) since 2003; and the end product is 1-methylimidazolium chloride, a nonflammable, nonvolatile and stable IL (m.p. 75 °C) [35-36]. Inspired by these facts, we compared the esterification reaction using these bases (Table 1), and concluded that in addition to the 'green' features, MIM (**8**) also produced the highest yield (77%, entry 3 in Table 1) when compared to TEA (32%, entry 2) and TBA (14%, entry 1).



Scheme 3. Esterification of *N*-acetyl phenylalanine using Mukaiyama's reagents (where $X^- = I^-$, $EtSO_4^-$, BF_4^-, Tf_2N^-, CF_3COO^- or CH_3COO^-).

To explain the base effect on the esterification, the basicity is an important factor to be considered. The bascities of these bases (pKa of their conjugate acids) are: TEA (**10.71** in MeOH at 25 °C [37], and 10.75 in H_2O at 25 °C [38]), TBA (**9.12** in MeOH at 25 °C as determined by Atofina Chemicals, and 10.0 in H_2O at 25 °C based on Advanced Chemistry Development [ACD/Labs] calculations [39]), and MIM (**7.20** in H_2O at 25 °C [40]). Therefore, the order of basicity (TEA > TBA > MIM) is not consistent with the order of corresponding ester yields (TBA < TEA < MIM). The strongest base TEA did not produce the highest yield. Two other factors are quite important in this case: (1) the accessibility of lone-pair electrons on the nitrogen atoms of bases by amino acid **3** (Scheme 3) is in a decreasing order of MIM > TEA > TBA due to the increasing bulkiness of groups associated with nitrogen atoms, especially in the case of three bulky butyl groups in TBA; (2) strong bases (such as TEA and TBA) act as nucleophiles [41] to perform aminolysis of ester, resulting in low ester yields.

Table 1. Esterification of *N*-acetyl-L-phenylalanine under various conditions[1]

Entry	Mukaiyama's reagent (2.4 mmol)	Solvent (5.0 mL)	Alcohol (excess)	Base (4.8 mmol)	Yield (%) [3]
1	[2-ClMePy]I [2]	MeOH	MeOH	TBA [4]	14
2	[2-ClMePy]I	MeOH	MeOH	TEA [5]	32
3	[2-ClMePy]I	MeOH	MeOH	MIM [6]	77
4	[2-ClMePy]I	DCM [7]	MeOH (4.0 mmol)	MIM	12
5	[2-ClMePy]I	EtOH	EtOH	MIM	37
6	[2-ClMePy]I (3.6 mmol)	MeOH	MeOH	MIM	25

Note: [1] all reactions were carried out with 2.0 mmol amino acid, under microwave for 15 min at 80 °C; [2] [2-ClMePy]I = 2-chloro-1-methylpyridinium iodide; [3] yield was based on the isolated ester; [4] TBA = tributylamine; [5] TEA = triethylamine; [6] MIM = 1-methylimidazole; [7] DCM = dichloromethane (extra care should be practiced when performing microwave experiments in DCM!).

Many organic solvents have been investigated in the Mukaiyama's esterification, which include dichloromethane (DCM), toluene, tetrahydrofuran (THF), ethyl ether, 1,2-dimethoxyethane, acetonitrile, and pyridine [16-19]. The obvious disadvantages of using these solvents are their volatility and toxicity. Because many amino acid esters are usually the methyl- or ethyl- esters, we added an excess amount of methanol or ethanol as both the solvent and reagent. The advantage of this approach is the elimination of another organic solvent, and to increase the reactant (alcohol) concentration. Comparing entry 3 and 4 in Table 1, the ester yield was considerably improved when replacing DCM (12% yield) by methanol (77%). However, the use of ethanol only gave 37% yield although it is still higher than that in DCM (12%). The higher yield in methanol than in ethanol is likely due to methanol (smaller size) being a better nucleophile than ethanol.

In an attempt to further enhance the ester yield, we increased the amount of Mukaiyama's reagent (2.4 mmol → 3.6 mmol for 2 mmol amino acid) (entries 3 and 6 in Table 1). However, we observed a decreasing yield (77% → 25%). The adverse effect of excess Mukaiyama's reagent on the esterification could be caused by a pronounced halide exchange (Scheme 2) at a higher concentration.

2.2 Comparison of microwave and conventional heating

We conducted the esterification reactions under reflux or microwave heating at the same temperature (66 °C). As shown in Figure 1, when the reaction time was short (15 min), ester yields were comparable under both heating modes. There was no indication of non-thermal effect. However, with an extended reaction time (30 and 60 min), the difference between reflux and microwave heating became obvious. The microwave irradiation is more effective than the conventional heating.

In addition, the reflux method has a limitation on the reaction temperature. It can not go beyond the boiling point of the reaction mixture, which is a main reason of low yields (< 40%) at 66 °C even

under microwave irradiation (Figure 1). However, when we conducted the reaction at 80 °C in the microwave oven at about 2 atms (Figure 2), the ester yield considerably increased in the case of [2-ClMePy]I. The optimum reaction times for the two Mukaiyama's reagents [2-ClMePy]I and [2-ClMePy][$EtSO_4$] were 15 min (77% yield) and 20 min (56%) respectively.

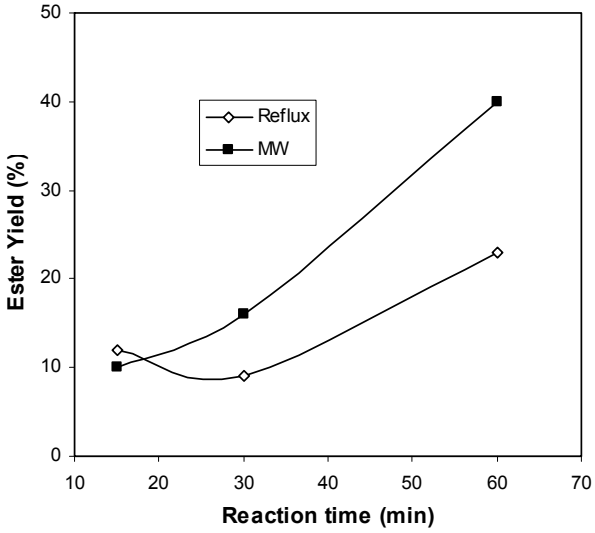


Figure 1. Comparison of reflux and microwave on the esterification of *N*-acetyl-L-phenylalanine (2.0 mmol amino acid, 5.0 mL methanol, 2.4 mmol [2-ClMePy]I, 4.8 mmol 1-methylimidazole, and all reactions at 66 °C).

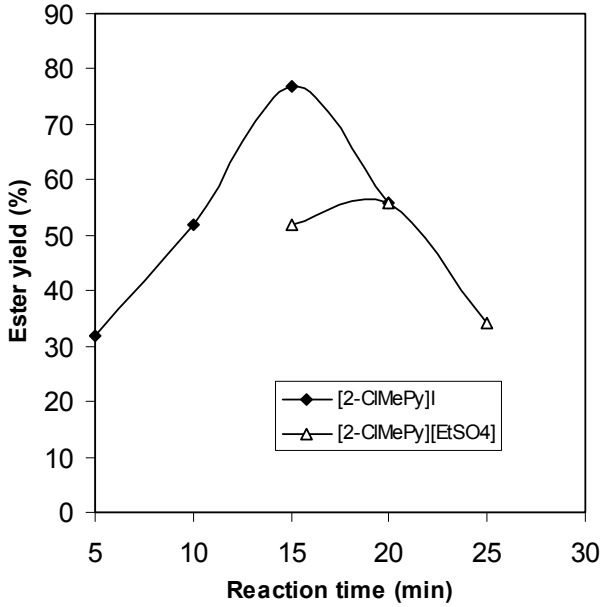


Figure 2. Effect of microwave irradiation time on the yield of *N*-acetyl-L-phenylalanine methyl ester (2.0 mmol amino acid, 5.0 mL methanol, 2.4 mmol [2-ClMePy]I, 4.8 mmol 1-methylimidazole, and all reactions at 80 °C).

2.3 Modification of Mukaiyama's reagent

Another objective of this study is to make the Mukaiyama's reagent [2-ClMePy]I (m.p. 200 °C - decomposition) ILs. We exchanged the anion (I^-) with five popular IL anions (Scheme 1). All modified Mukaiyama's reagents have m.p. below 100 °C, and three of them are room-temperature ILs (see Experimental and Table 2). Among these new ionic reagents, [2-ClMePy][$EtSO_4$] and [2-ClMePy][Tf_2N] gave the best yields (52% and 53%, respectively), while three others (based on BF_4^-, CF_3COO^- and CH_3COO^-) are relatively poor coupling reagents. The ^{1}H NMR data (see Experimental) suggested the exchange of chlorides with stronger nucleophiles CF_3COO^- and CH_3COO^- in [2-ClMePy][CF_3COO] and [2-ClMePy][CH_3COO] respectively, resulting in non-reactive salts towards carboxylate activation. On the other hand, no such exchange was observed in [2-ClMePy][$EtSO_4$], [2-ClMePy][Tf_2N] and [2-ClMePy][BF_4] because their anions are non-nucleophilic. The lower yield in [2-ClMePy][BF_4] might be related to the unstable and basic nature of BF_4^- anions.

Table 2. Esterification of *N*-acetyl-L-phenylalanine through different Mukaiyama's reagents [1]

Entry	Mukaiyama's reagent	m.p. (°C)	Yield (%)[2]
3	[2-ClMePy]I	200 (dec.)	77
7	[2-ClMePy][$EtSO_4$]	Liquid	52
8	[2-ClMePy][BF_4]	70-75	38
9	[2-ClMePy][CF_3COO]	Liquid	37
10	[2-ClMePy][CH_3COO]	Liquid	37
11	[2-ClMePy][Tf_2N]	74-76	53
12	[2-BrEtPy][BF_4]	102-104	60
13	[2-FMePy][OTs]	130-134	30

Note: [1] all reactions were carried out with 2.0 mmol amino acid, 2.4 mmol Mukaiyama's reagent, 5.0 mL MeOH, 4.8 mmol 1-methylimidazole, under microwave for 15 min at 80 °C; [2] yield was based on the isolated ester.

We also examined two other commercially available Mukaiyama's reagents ([2-BrEtPy][BF_4] and [2-FMePy][OTs]). Both of them have m.p. above 100 °C, and are not considered as ILs. The former coupling reagent produced a yield of 60% (Table 2) because bromide is a better leaving group than chloride. However, the latter coupling reagent ([2-FMePy][OTs]) gave a rather poor yield of 30% because 2-fluoro-onium is too reactive and is known to react with the alcohol directly (since it is also in excess) [42-43].

The fact that [2-ClMePy]I produced a higher yield (entry 3 in Table 1) than other IL-type coupling reagents, is probably due to its smaller anion size (I^-) than others (such as $EtSO_4^-$ and Tf_2N^-). Large anions may create a steric hindrance for substitutions on C-2 position of pyridinium in both steps of reactions (Scheme 3). However, in addition to having basic advantages of ILs, these modified reagents are more stable (non-nucleophilic anions) than [2-ClMePy]I (which is unstable in moisture), and can be designed as either hydrophilic or hydrophobic ones based on the needs of individual applications.

2.4 Racemization of amino acid ester

We examined the optical rotation of the *N*-acetyl phenylalanine methyl ester (entry 8 in Table 2), and calculated the specific rotation as $[\alpha]_D^{25}$ = + 11° (c=2, MeOH). The literature values of specific rotation $[\alpha]_D^{25}$ of *N*-acetyl-L-phenylalanine methyl ester are varied: +19.5° (*c* = 2, MeOH) [44], 17.8 ± 1.2° (*c* = 2, MeOH) [9], and 15.5° (c = 2.1, MeOH, at 24 °C) [§] [45]. Therefore, the enantiomeric excess of the product (eep) is in the range of 56-71% depending on the literature values used in the calculation. In either case, our measurement suggested a partial racemization of the amino acid ester. This is not surprising since amino acid esters can be racemized under heat [46].

3. Experimental Section

3.1 Materials

The following chemicals were purchased from Sigma-Aldrich (St Louis, MO, USA): 2-chloro-1-methylpyridinium iodide ([2-ClMePy]I, m.p. 200 °C-dec.), 2-fluoro-1-methylpyridinium *p*-toluenesulfonate ([2-FMePy][OTs], m.p. 130-134 °C), 2-bromo-1-ethyl-pyridinium tetrafluoroborate ([2-BrEtPy][BF_4], m.p. 102-104 °C), silver acetate, silver trifluoroacetate, silver tetrafluoroborate, bis(trifluoromethane)sulfonimide lithium salt (Li[Tf_2N]), anhydrous methanol, anhydrous ethanol, 1-methylimidazole (MIM), triethylamine (TEA), tributylamine (TBA), and *N*-acetyl-L-phenylalanine. Ethylsulfuric acid sodium salt was purchased from TCI America (Portland, OR, USA).

3.2 Synthesis of modified Mukaiyama's reagents (2-Chloro-1-methylpyridinium acetate ([2-ClMePy][CH_3COO]), 2-Chloro-1-methylpyridinium trifluoroacetate ([2-ClMePy][CF_3COO]), and 2-Chloro-1-methylpyridinium tetrafluoroborate ([2-ClMePy][BF_4]))

A solution of 15.0 g [2-ClMPy]I in 80 mL H_2O was added drop-wise into an equal molar amount of silver acetate (or silver trifluoroacetate, or silver tetrafluoroborate) suspended in 100 mL distilled water. The reaction container was wrapped by the aluminum film to prevent the photo-degradation of silver salts. The reaction mixture was stirred at room-temperature for 2 hrs. A small sample of the reaction solution was examined by 0.1 N $AgNO_3$ and 0.1 N HCl respectively to ensure the absence of I^- and Ag^+ ions. Once the reaction was completed, charcoal was added to the solution to remove color and other impurities. After filtering off the charcoal, water was removed from the solution by a rotary evaporator under vacuum at 60 °C.

[2-ClMePy][CH_3COO] weighs 5.40g, yield 49%, yellow liquid at room temperature, ^{1}H NMR (CD_3OD) δ: 2.05 (s, 3H, OAc^-), 3.73 (s, 3H, OAc on the ring), 4.48 (s, 3H, -NCH_3), 6.78 (d and t, 2H), 7.81 (t, 1H, J = 7.3), 7.91 (d, 1H, J = 7.3), 8.08 (t, 1H, J = 7.3), 8.30 (d, 1H, J = 8.0 Hz), 8.62 (t, 1H, J = 8.0 Hz), and 9.09 (d, 1H, J= 6.0 Hz).

[§] Calculated from the specific rotation of 15.4 with 99.1% ee at the same condition.

[2-ClMePy][CF_3COO] weighs 8.69g, yield 62%, yellow liquid at room temperature, ^{1}H NMR (CD_3OD) δ: 2.81 (s, 3H), 6.64 (s, 3H), 7.46 (s, 3H), 9.69 (t, 1H), 10.06 (d, 1H), 10.73 (t, 1H), 10.98 (t, 1H), 11.24 (d, 1H), 11.57 (t, 1H), 11.76 (d, 1H), and 12.29 (d, 1H).

[2-ClMePy][BF_4] weighs 7.24 g, yield 57%, white powder, m.p. 70-75 °C, and ^{1}H NMR (D_2O) δ: 4.41 (s, 3H, -NCH_3), 7.99 (t, 1H, J = 8.0 Hz), 8.21 (d, 1H, J = 8.0 Hz), 8.52 (t, 1H, 8.0 Hz), 8.90 (d, 1H, J = 8.0 Hz).

3.3 Synthesis of 2-Chloro-1-methylpyridinium ethyl sulfate ([2-ClMePy][$EtSO_4$])

[2-ClMePy][$EtSO_4$] was synthesized through an anion exchange method. About 100 mL of anion exchange resin (Amberlite® IRA-400 Cl) packed in a glass column was washed with methanol and distilled water thoroughly until no yellow color was observed in the eluting water, and no precipitate could be detected by 0.1 M $AgNO_3$ solution. After washing the resin with distilled water, a solution of 50 g sodium ethylsulfate ($NaEtSO_4$) in 200 mL H_2O was dripping through the column to replace Cl^- ions with $EtSO_4^-$ anions. The eluting solution was monitored by 0.1 M $AgNO_3$ solution until no white precipitate could be detected, which indicated the completeness of the anion exchange. A solution of 15.0 g [2-ClMPy]I in 100 mL H_2O was then dripping through the column. The eluting solution was collected and purified by charcoal. Water was further removed through a rotary evaporator under vacuum at 60 °C to give a slightly yellow liquid (12.07 g and yield 81%). ^{1}H NMR (D_2O) δ: 1.28 (t, 3H, -CH_3, J = 6.9 Hz), 4.07 (q, 2H, -CH_2-, J = 6.9 Hz), 4.42 (s, 3H, -NCH_3), 8.00 (t, 1H, Ar-H, J = 7.6 Hz), 8.21 (d, 1H, Ar-H, J = 7.6 Hz), 8.53 (t, 1H, Ar-H, J = 7.6 Hz) and 8.91 (d, 1H, Ar-H, J = 6.0 Hz).

3.4 Synthesis of 2-Chloro-1-methylpyridinium bis(trifluoromethane)sulfonimide ([2-ClMePy][Tf_2N])

A 80 mL solution of 15.0 g [2-ClMPy]I in H_2O was added drop wise into 1.2 molar equivalent bis(trifluoromethane)sulfonimide lithium salt (Li[Tf_2N]) in 100 mL H_2O. A precipitate was formed immediately. The reaction mixture was stirred at room temperature for 2 hrs. The precipitate was collected by filtration and washed with distilled water. The wet product was dried in an oven overnight at 100 °C. The slightly yellow product weighs 18.9 g, yield 79%, m.p. 74-76 °C, and ^{1}H NMR (CD_3OD) δ: 4.42 (s, 3H, -NCH_3), 8.02 (t, 1H, J = 7.6 Hz), 8.20 (d, 1H, J = 7.6 Hz), 8.53 (t, 1H, 7.6 Hz), 8.90 (d, 1H, J = 8.0 Hz).

3.5 General procedure for esterification of amino acid

The procedure is a modification of the Mukaiyama's method [16-17]: 2-chloro-1-methylpyridinium ethyl sulfate (0.609 g, 2.4 mmol) (or other molar-equivalent Mukaiyama's reagents) was fully dissolved in 5 mL anhydrous methanol (or dichloromethane) after a gentle stirring. Into the reaction mixture, *N*-acetyl-L-phenylalanine (0.414 g, 2.0 mmol) and 1-methylimidazole (0.394 g, 4.8 mmol) were added. A homogeneous solution was formed after a gentle stirring. The reaction mixture was sealed in a microwave glass reactor and then irradiated by a CEM Discover® LabMate single-mode microwave oven (CEM Corporation in Matthews, NC) at a constant temperature of 80 °C (monitored by a vertically-focused IR temperature sensor, and controlled by automated power adjustment based on

temperature feedback and air cooling) with continuous stirring (1 min ramp, 15 min reaction time). After the reaction was completed, the solvent was removed through a rotary evaporator, and the resulting residue was extracted by a biphasic system of 45 mL diethyl ether and 45 mL water (1-methyl-2-pyridone, 2-alkoxypyridinium salt, base and other salts are soluble in water [15, 42]; if tributylamine is used, vigorously washing the organic layer with 5% HCl to dissolve the base). After the layer separation, the ether layer was dried by anhydrous sodium sulfate, followed by an evaporation of ether. The resulting oil-like ester formed white crystals overnight with $[\alpha]_D^{25} = +11°$ (c=2, MeOH) as determined by a Rudolph Autopol III polarimeter. The ester structure was confirmed by a Shimadzu 8300 FT-IR (sample in NuJol, CaF_2 window) (C=O: 1720 cm^{-1}, C(O)-O-C: 1152 cm^{-1}, C-O-C: 1071 cm^{-1}), and ^1H NMR (CD_3OD) δ: 3.10 (1H, CH), 4.52 (2H, $-CH_2-$), 4.88 (1H, -NH-), 6.05 (6H, $-OCH_3$), 8.43 (5H, -Ar).

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