Chapter 2

Imidazolium-supported 2-Chloropyridinium Triflate: An Efficient Coupling Reagent for Amide Bond Formation

2.1 INTRODUCTION

Amide functional group is represented as one of the most important functional groups which links the building blocks *i.e.* amino acids in living organism. The amide link is undeniably present in numerous fascinating molecules such as peptides, pharmaceutical agents, polymers, naturally occurring molecules, proteins and alkaloids.[1-4] They have played a significant role in designing biodegradable polymers such as polyester amides (PEAs) polymers due to its ability to impose degradable character and worthy thermal and mechanical features. Importance of amide bond is not limited to biological system, indeed according to the Comprehensive Medicinal Chemistry (CMC) database its presence accounts in over 25% of commercial drugs. Amide bonds have been attributed for increasing the metabolic stability to synthetic drugs such as Lidocaine and Tocainide since these can be easily solubilise in human plasma. Representative examples of selective amides functional group containing drugs and polymer are shown in **Figure 2.1**. Consecutively, the construction of organic molecules having amide bond is an immensely interesting pursuit in organic synthesis.[5]

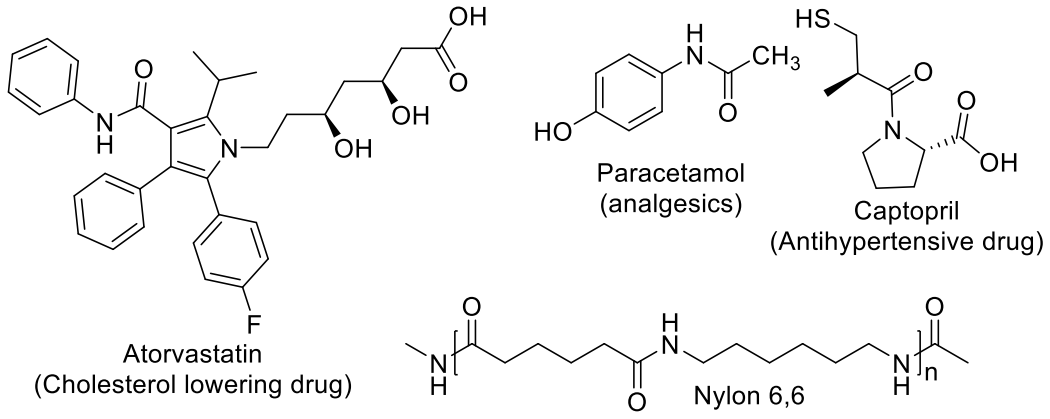


Figure 2.1 Representative examples of amide containing marketed drugs and polymers

In general, the synthesis of amide bond from amines and carboxylic acids appear as a simple condensation reaction with the expulsion of a water molecule. However, the formation of amide bond from carboxylic acids is not a spontaneous process at ambient temperature and requires higher temperature *i.e.* >200 °C which might be detrimental for substrates and coupled products. Thus, the most prevalent strategy for amide bond formation relies heavily upon the inter-conversion of activated carboxylic acid derivatives with an amine. Consequently, the activation of a carboxylic acid in which –OH group is changed to good leaving group like acyl halides, acyl

azides, acylimidazoles, anhydrides and esters is accomplished prior to reaction with amines. In this regard, the coupling agents and additives emerged as stand-alone reagents to generate activated carboxylic compounds. Most common used amide coupling reagents such as dicyclohexylcarbodiimide (DCC),[6] 1-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline (EEDQ),[7] and boron reagent,[8] have been described extensively in literature. Moreover, coupling reagents such as benzotriazolium based salts like HATU, HBTU BOP and PyBOP also have generated considerable interest among research community.[9-10]

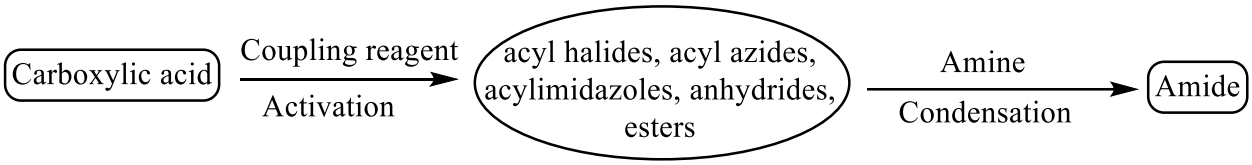
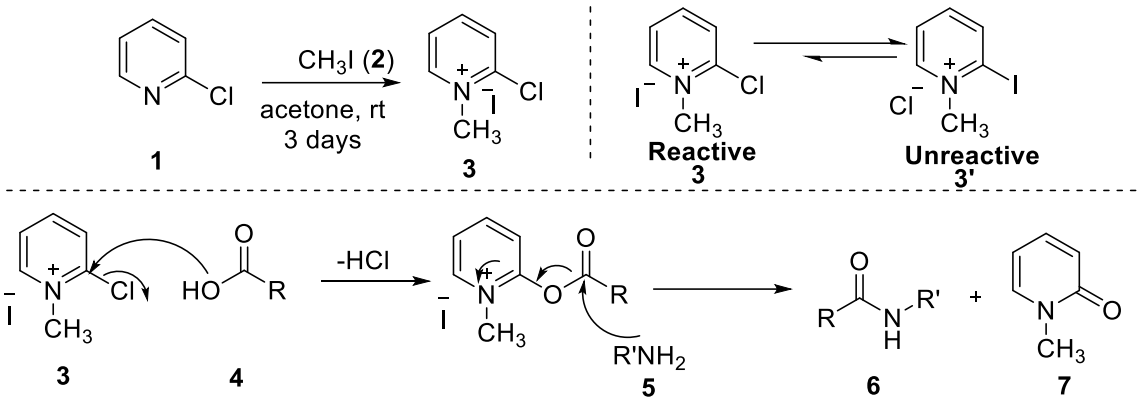


Figure 2.2 Schematic representation for amide bond formation *via* activation of carboxylic acid

2.1.1 *N*-Methyl-2-chloropyridinium Iodide (Mukaiyama Reagent)

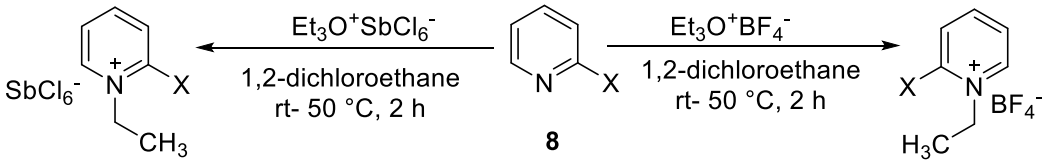
A highly explored pyridinium salt *i.e. N*-methyl-2-chloropyridinium iodide (**3**) commonly known as Mukaiyama reagent was first developed by T. Mukaiyama in 1975 as convenient reagent for synthesis of carboxylic esters.[11]. The reagent was obtained as yellow solid by the quaternization reaction of 2-chloropyridine (**1**) with methyl iodide (**2**) at room temperature for 3 days. Mukaiyama reagent have a unique ability to undergo stepwise transformations into *N*-alkylpyridones (**6**) by "withdrawing" the oxide ion from oxygen containing nucleophiles (mainly carboxylic acid) and donating their electrophilicity to the remaining species (**Scheme 2.1**). This is achieved in stepwise manners *i.e.* initially facile replacement of α-halogen in reagent by oxygen nucleophile and secondly, fast elimination of the stable *N*-alkyl-2-pyridone (**7**) residue. It is shown to be a good activating agent of hydroxyl group of carboxylic acid in the formation of esters[12-13] and carboxamides[14], ketenes[15], lactone[16] and lactam[17-18] derivatives. Over the time, the derivatives of 2-chloropyridinium salts have evolved as an important reagent for amide bond formation.[19-24]



Scheme 2.1 Synthesis of *N*-methyl-2-chloropyridinium iodide and application in amide bond formation

Despite its great success, this particular reagent suffers from disadvantages such as solubility and stability issues. The more nucleophilic iodide anion can substitute the chlorine in the pyridinium salts and the resulting *N*-Methyl-2-iodopyridinium chloride (**3′**) do not activate carboxylic acids (**4**) towards nucleophilic reactions. This non-reactivity can be attributed to poor leaving nature of iodine.

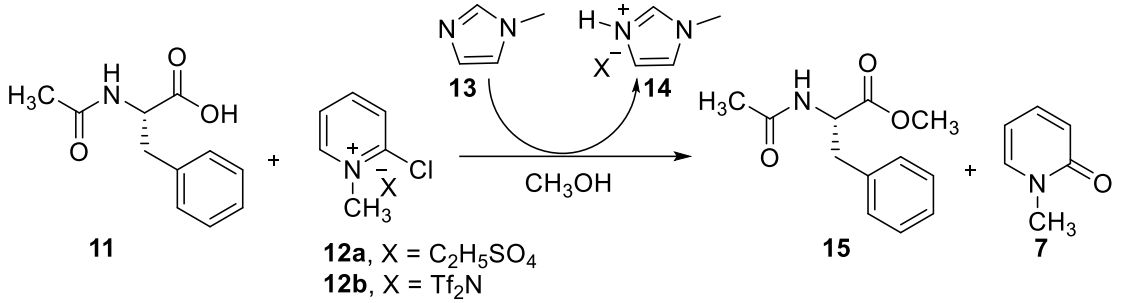
Xu *et al.* synthesized 4 examples of novel *N*-ethyl-2-halopyridinium tetrafluoroborate and *N*-ethyl-2-halopyridinium hexachloroantimonate by quaternization reaction of 2-halopyridine (**8**) and triethyloxonium tetrafluoroborate/hexachloroantimonate under inert atmosphere condition. The *N*-ethyl-2-bromopyridinium tetrafluoroborate (**10a**) was found to be stable and an excellent coupling reagent for peptide synthesis with high activity and a low level of racemization. [25]



Scheme 2.2 Synthesis of stable Mukaiyama reagent.

Mukaiyama reagent resembles an ionic liquid in structural aspect but the basic definition of ionic liquid to possess melting point less than 100 °C is not fulfilled. Zhao and group modified the original Mukaiyama reagent, 2-chloro-1-methylpyridinium iodide (**3**) (MP 200 °C), from ionic solid into liquids by replacing iodide with anions like PF_6, $EtSO_4$ and Tf_2N. The microwave-assisted esterification of *N*-acetyl-*L*-phenylalanine (**11**) was investigated as a model reaction. They

identified two modified Mukaiyama's compounds (*i.e*. hydrophilic [2-ClMePy][$EtSO_4$] (**12a**) and hydrophobic [2-ClMePy][Tf_2N] (**12b**)) as the best IL type coupling reagents.[26]



Scheme 2.3 Esterification using ionic liquid type Mukaiyama reagents

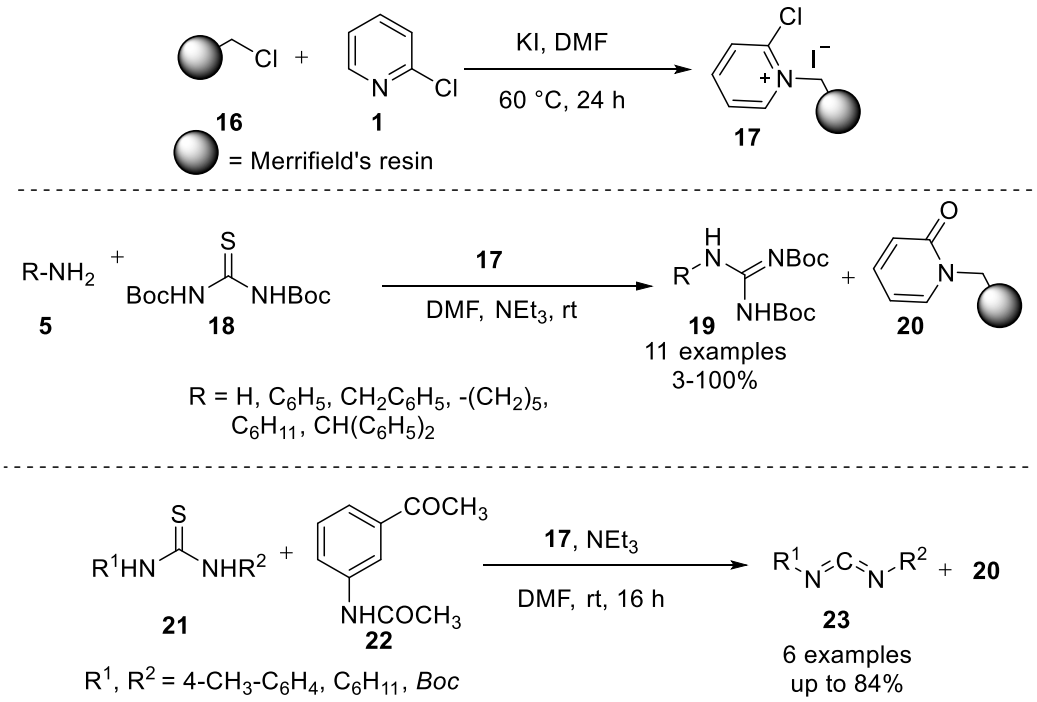
Even though, the modification solved the stability and solubility issues of reagent but additionally the need of cumbersome chromatographic separation was still mandatory to separate the product from byproduct *N*-alkylpyridone (**7**). To overcome this, many research groups introduced further modified Mukaiyama reagents by using polymers-support as well as fluorous-support.

2.1.2 Polymer-supported Mukaiyama Reagent

In 1963, the Nobel Laureate R. Bruce Merrifield reported the synthesis of polypeptides on solid support which embarked the beginning of new era in organic chemistry field *i.e*. solid phase synthesis.[27] Since then, the solid-support synthesis is most sought after process in peptide synthesis. The solid-phase synthesis is applied in two ways, by immobilizing one of the reactant with solid-support or, secondly by using immobilized reagents or catalyst. Over the time, various types of solid supports has been introduced like Wang resin, Merrifield resin, ROMPGel, polyglycerol, tentagel, macroporous, and silica gel. Reaction done using polymer-supported coupling agents follows the "capture and release" technique. In this technique, the polymer binds with one of the substrate or reagent that reacts in the reaction leading to the product formation and the "byproducts" or reagent remains attached to the polymer-support. The advantages associated with this method are no need for chromatographic purification of products, the reagent can be regenerated and reused.

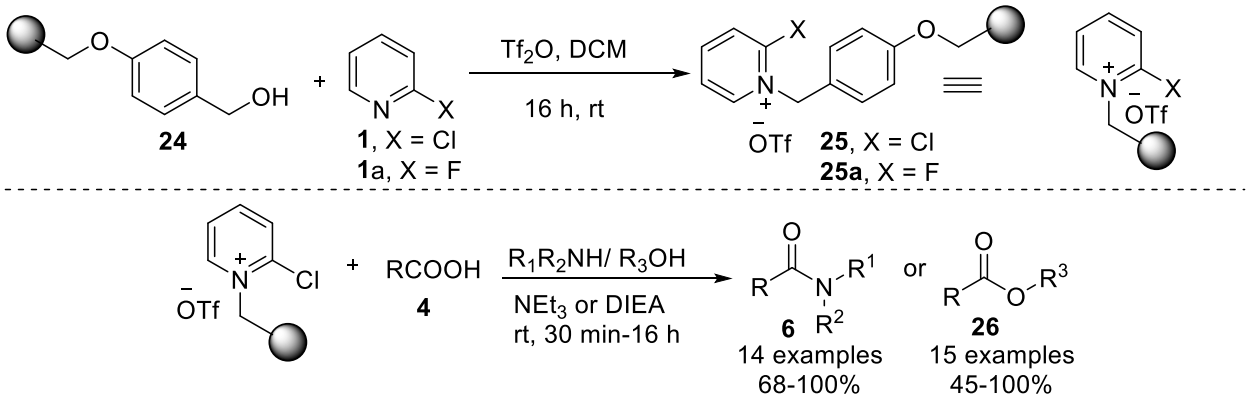
In 2004, Convers *et al.* reported the first synthesis of a polymer-supported (PS) Mukaiyama reagent (**17**) by reaction of chloro-functionalized Merrifield's resin (**16**) and 2-chloropyridine (**1**) in the presence of potassium iodide and DMF at 60 °C. The synthesized reagent was employed for

the guanylation of primary amines (**5**). Additionally, examples for the dehydration of thioureas (**21**) to carbodiimides (**23**) were also shown using PS-Mukaiyama reagent.[28]



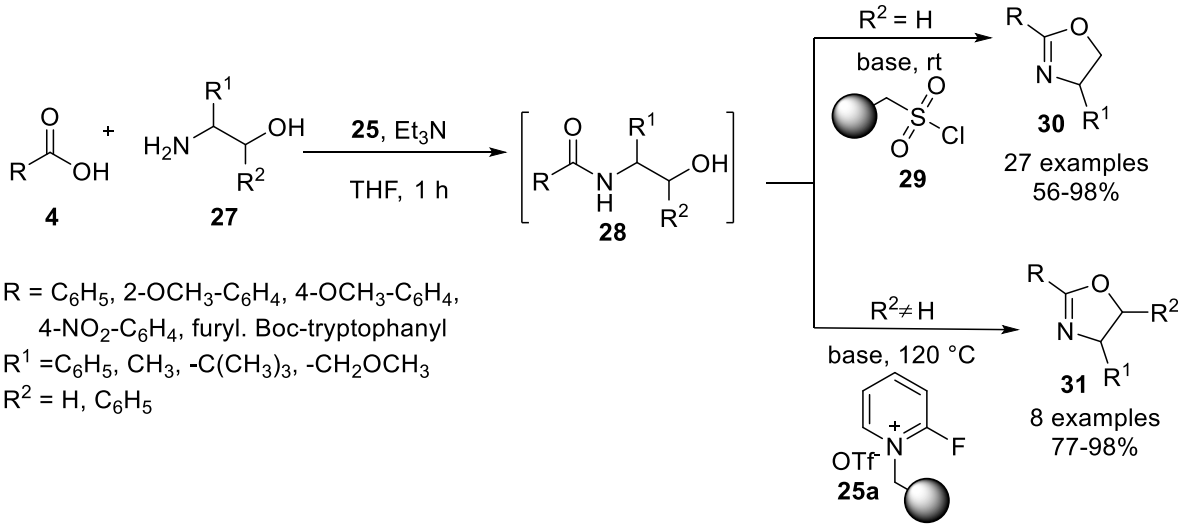
Scheme 2.4 Synthesis and application of Merrifield's resin-supported Mukaiyama reagent

Swinnen and group reported the one step synthesis of Wang resin-supported Mukaiyama reagent (**25** & **25a**) and efficiently used for the activation of carboxylic acid (**4**) in the construction of amide and ester bonds. The hydroxyl functionalized Wang resin **24** was subjected to the quaternization reaction with 2-chloropyridine (**1**) in presence of triflouromethane sulfonic acid anhydride in dichloromethane for 16 h. The synthesized reagent was applied for the formation of 14 examples of amides (**6**) and 15 examples of esters (**26**) in good to excellent yields.[29]



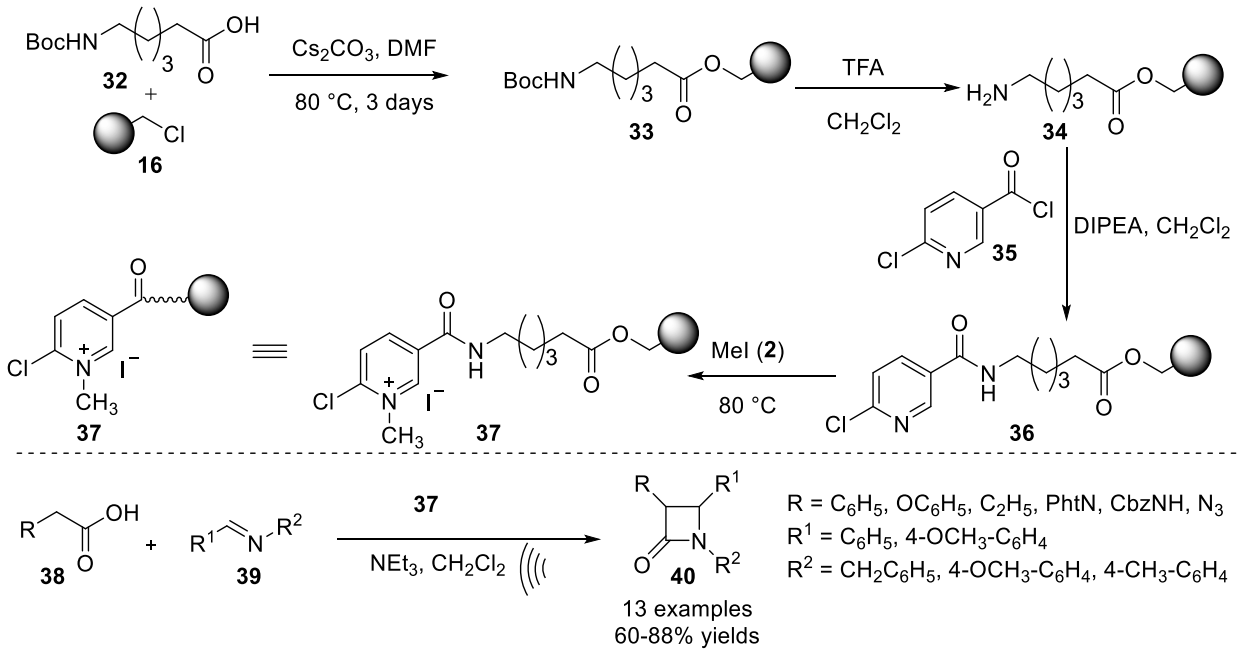
Scheme 2.5 Synthesis and application of Wang resin-supported Mukaiyama reagent

The polymer-supported Mukaiyama reagents (**25** & **25a**) were also utilized in the synthesis of 2-oxazolines (**30**) and 2,4,5-trisubstituted oxazolines (**31**). The reagent **25** promoted coupling reaction of a carboxylic acid (**4**) with an amino alcohol (**27**) to get α-hydroxyamide (**28**), which cyclized *in situ* to 2-oxazoline using either polymer-supported sulfonyl chloride (**29**) or polymer-supported 2-fluoropyridinium triflate (**25a**). While polymer-supported sulfonyl chloride failed to lead the 2,4,5-trisubstituted oxazolines (**31**), thus cyclization of α-hydroxyamide (**28**) was done using polymer-supported 2-fluoropyridinium triflate (**25a**).[30] The advantages of the protocol includes one-pot reaction, operationally simple and gives products in high yields and in diastereomerically pure state.



Scheme 2.6 Polymer-supported Mukaiyama reagent-assisted synthesis of oxazolines

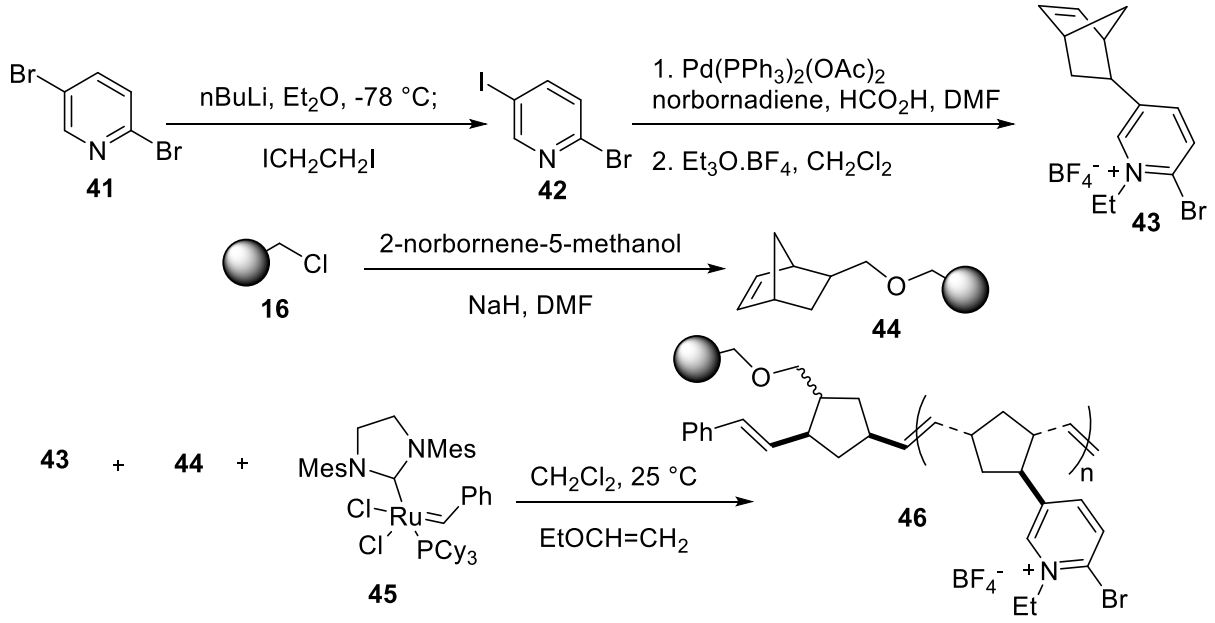
Taddei and group prepared polymer-supported Mukaiyama reagent and successfully applied for the synthesis of β-lactam. Initially, the group tried to synthesis reagent in a fashion reported by Convers's group and used for β-lactam synthesis but the reaction failed. The inability of the reagent to carry out β-lactam synthesis was attributed to the steric hindrance at the reactive site. Thus they coined a new method to synthesize sterically less hindered and more reactive Merrifield's resin-supported reagent by introducing a spacer group. First, *N*-Boc-6-aminocaproic acid **32** was linked to a Merrifield resin (**16**) under basic condition and the deprotection of amino group was done in acidic medium. The polymer linked caproic acid (**34**) was coupled with 6-chloronocotinoyl chloride (**35**) followed by methylation to afford the polymer-supported Mukaiyama reagent (**37**). The synthesized reagent afforded good to excellent yields of β-lactam (**40**) by the reaction of carboxylic acids (**38**) and imines (**39**) under basic medium. The reagent was suitable for the generation of ketenes for Staudinger cycloaddition with imines.[31]



Scheme 2.7 Synthesis of polymer-supported Mukaiyama reagent and its application

G. M. Barrett and group introduced ROMPsphere-supported 2-bromo-1-ethylpyridinium tetrafluoroborate (BEP) coupling reagent (**46**) and utilized in parallel synthesis of hindered peptides containing α, α-disubstituted amino acid residues in 80-97% yields. Firstly, a monomer norbornene pyridinium salt (**43**) was prepared by selective bromine-lithium exchange reaction of 2,5-dibromopyridine (**41**) with *n*-butyllithium at -78 °C and iodination using 1,2- diiodoethane

followed by palladium-catalyzed exo-hydroarylation and subsequently ethylation using triethyloxonium tetrafluoroborate. Secondly, Merrifield resin (**16**) was allowed to react with excess 2-norbornene-5-methanol in DMF under basic conditions for 24 h on reflux. Lastly, the reaction of Merrifield resin-supported 2-norbornene (**44**) was allowed to polymerize with Ru-catalyst (**45**) and norbornene pyridinium salt monomer (**43**) in DCM at 25 °C and subsequently, the polymerization reactions terminated with ethyl vinyl ether to afford ROMPsphere-supported 2-bromo-1-ethylpyridinium tetrafluoroborate (BEP) (**46**) coupling reagent. [32]



Scheme 2.8 Synthesis of ROMPsphere-supported 2-bromo-1-ethylpyridinium tetrafluoroborate (BEP) coupling reagent **46**

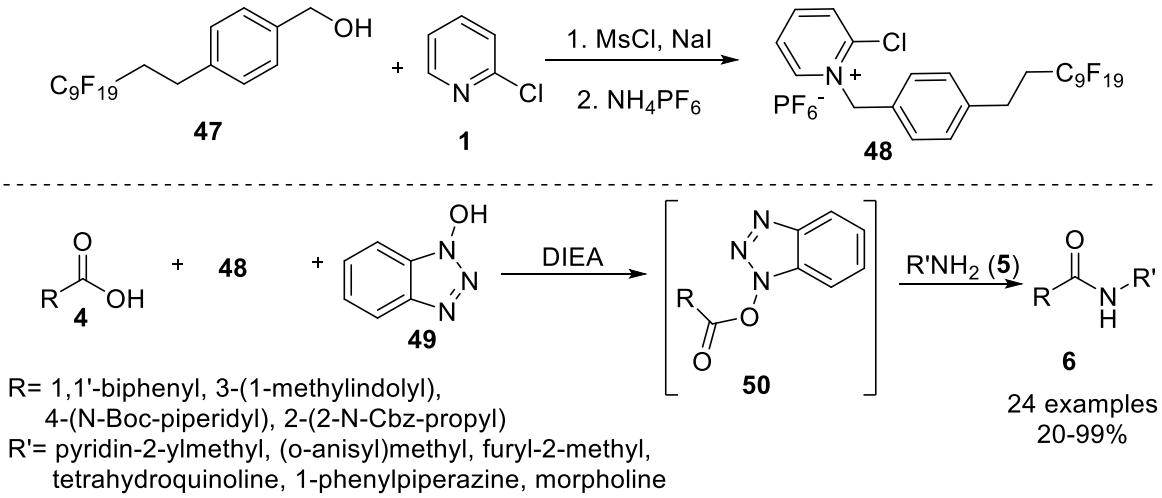
Although polymer-supported reagents have addressed some of the issues of 2-chloropyridinium salts, the low loading capacity, high cost and slower reaction rates and non-linear kinetics makes these approaches less attractive. Additionally, reaction could not be monitored by conventional analytical methods such as TLC, HPLC, and NMR.

2.1.3 Fluorous-supported Mukaiyama Reagent

In fluorous-supported synthesis, perfluoroalkyl chains are active "phase tags" and linked to reagents, catalyst or one of the reactants. The fluorous-supported synthesis exhibit many advantages of solution phase synthesis like ease of reaction monitoring and homogeneous reaction

conditions compared with solid-supported synthesis.[33] The loading capacity of this support is more as compared to solid-support.[34-35]

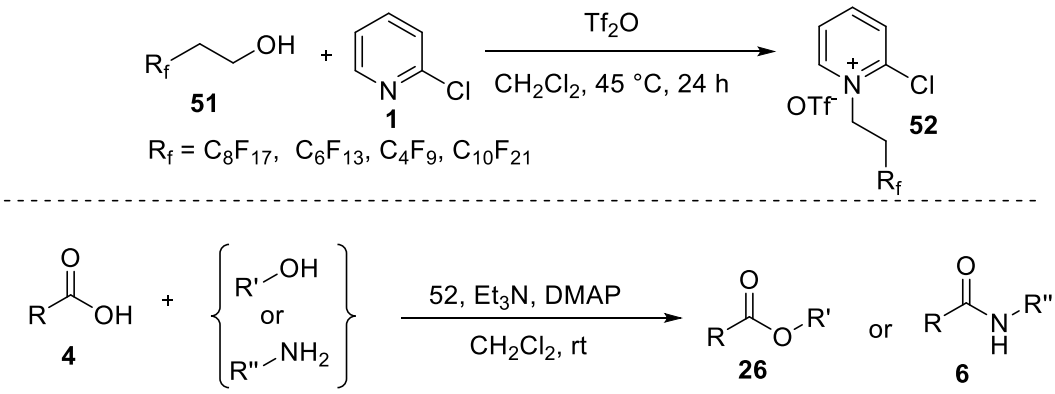
Nagashima and co-workers reported a first report of fluorous-supported 2-chloropyridinium hexafluorophosphate as modified Mukaiyama reagent and utilized for amide bond formation reaction. Fluorous tagged 2-chloropyridinium hexafluorophosphate was prepared from fluorous tagged benzyl alcohol (**46**). The mesylation of alcohol, followed by iodination and then quaternization of corresponding benzyl iodide with 2-chloropyridine (**1**) led to the formation of fluorous-tagged 2-chloropyridinum iodide. The anion metathesis reaction with ammonium hexafluorophosphate yielded fluorous-supported 2-chloropyridinium hexafluorophosphate as modified Mukaiyama reagent (**48**). The amide bond formation was carried out in two steps *viz* the activation of carboxylic acid (**6**) using fluorous-supported 2-chloropyridinium hexafluorophosphate (**48**), 1-hydroxybenzotriazole (**49**), and *N*,*N*-diisopropylethylamine (DIEA) as base and then the reaction with amines (**5**). The addition of **49** suppressed the formation of carboxylic anhydride in the reaction. The progress of the reaction was monitored by LC-MS analysis of reaction mixture. The fluorous-tagged byproduct i.e. 2-pyridone was removed by F-SPE and resin-tagged carbonate was employed to remove unreacted acids.[36]



Scheme 2.9 Synthesis and application of fluorous-supported 2-chloropyridinium hexafluorophosphate

Matsugi and group reported light fluorous 2-chloropyridinum triflate (**52**) as modified Mukaiyama reagent. The group synthesized different examples of light and medium sized fluorous 2-

chloropyridinum triflate by varing the fluorine contents and applied in amidation and esterification reaction. The reactivity of these reagents was found to be more than the reagent reported by Nagashima group.[37] A through study of these reagents revealed that the seperation of Mukaiyama coupling reagent bearing a medium fluorous tag, between 40% and 60% fluorine by weight does not require fluorous solid phase extraction. The separation could be achieved by increasing the water content of the crude reaction mixture and subsequent filtration.[38] Additionally, the comparison study of reactivity towards esterification reaction was carried out using ^{1}H NMR monitoring of reaction mixtures. The study revealed that the reactivity of fluorous-tagged Mukaiyama reagent showed increased reaction rate compared to untagged Mukaiyama reagent. The reactivity of reagent was found to be dependent on the length of the fluorous tag in molecule *i.e.* the longer the fluorous chain, the higher the activity of the Mukaiyama reagent.[39]

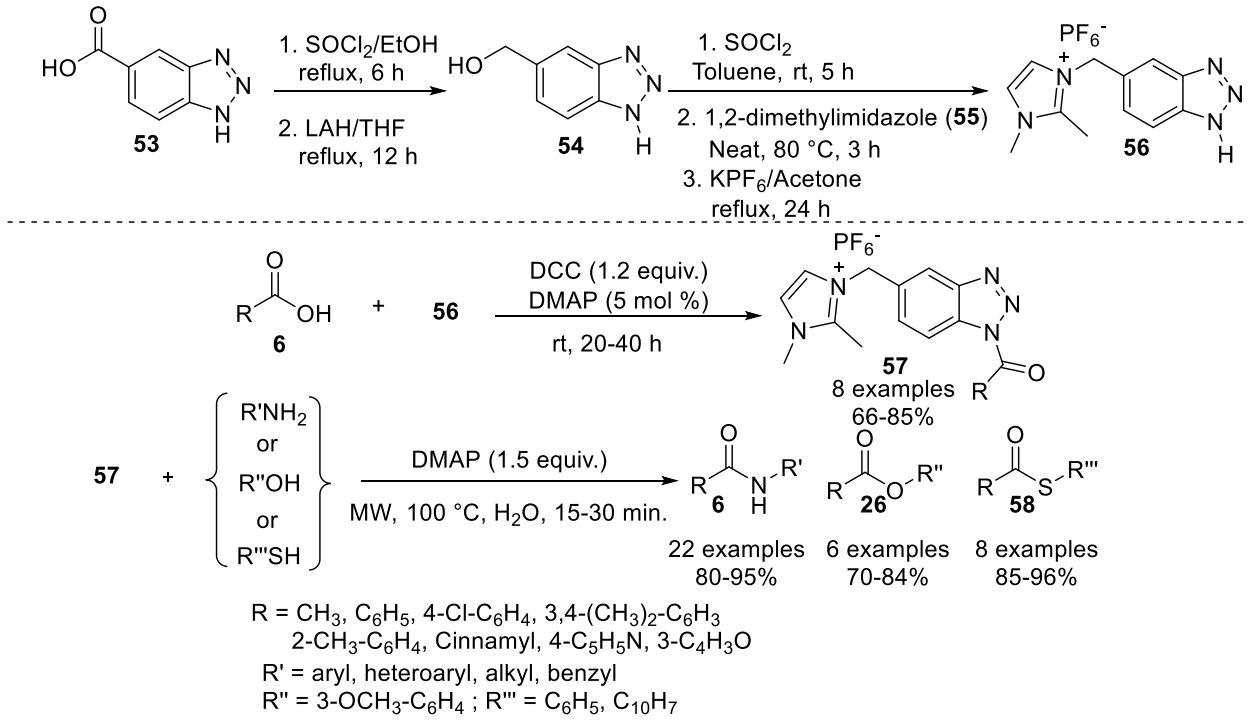


Scheme 2.10: Synthesis and application of medium fluorous-tagged Mukaiyama reagent

Even though, fluorous-supported reagent solved the issue raised in polymer-supported synthesis and was found to be more effective in amide and ester formation reaction, the special solvents requirement and cost are some serious concerns.[40-41]

A considerable attention has been given to the synthesis of imidazolium-supported reagents and catalyst for their application in solution-phase synthesis.[42] These reagents have gained considerable interest as promising alternative soluble support for reagents owing to their high loading capacity, tuneable solubility by altering anion or cation, homogeneity and easy monitoring of the reaction by various analytical techniques such as TLC, NMR and mass spectroscopy.[43] In view of their unique characteristics, imidazolium-supported reagents and catalyst have attracted great interest both from academia and industry.[44] In this respect, Sakhuja *et al.* reported the

imidazolium-supported benzotriazole reagent (**56**) as effective activating reagent for carboxylic acid in the synthesis of amides, esters and thioesters (**58**) (**Scheme 2.11**).[45]



Scheme 2.11 Synthesis and application of imidazolium-supported benzotrizole reagent

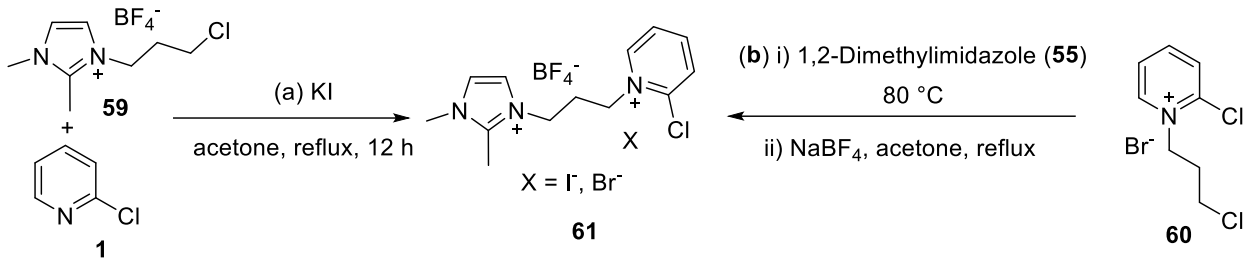
With our groups prior capable knowledge and interest in imidazolium-supported reagents in organic synthesis,[46-50] and growing objective of using pyridinium salt as coupling agent, herein this chapter we intend to report the synthesis of novel imidazolium-supported 2-chloropyridinium salt (Mukaiyama reagent) and its application in amide bond formation.

2.2 RESULTS AND DISCUSSION

2.2.1 Synthesis of Imidazolium-supported Mukaiyama Reagent

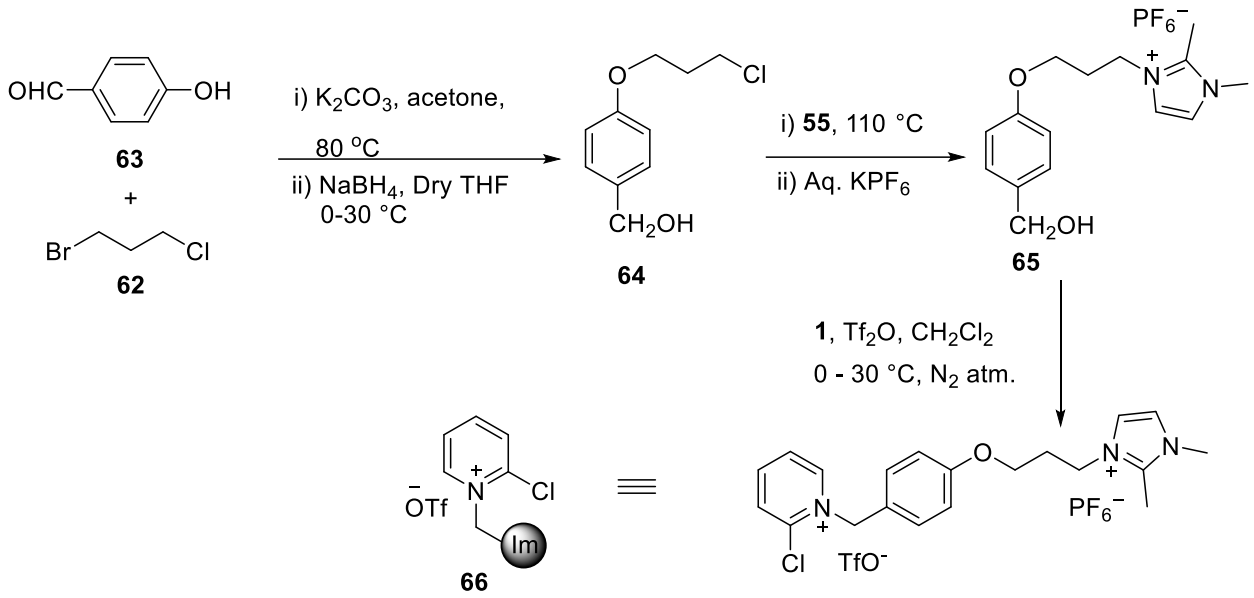
Our preliminary effort in this direction initiated with the efforts to synthesize suitable imidazolium-supported Mukaiyama reagent. The first investigation to develop imidazolium-supported Mukaiyama reagent led us to the reaction of 1-(3-chloropropyl)-2,3-dimethylimidazolium tetrafluoroborate (**59**) with 2-chloropyridine (**1**) in presence of KI under reflux condition, but failed to get substantial yield of product (**Scheme 2.12** (**a**)). Subsequently, we sought an alternative method by first *N*-alkylation of 2-chloropyridine (**1**) and then tagging it to imidazolium-support

(**Scheme 2.12** (**b**)). Unfortunately, longer reaction time (2-3 days) prompted us to explore new method.



Scheme 2.12 Failed attempts to synthesize imidazolium-supported 2-chloropyridinium salt **61**

We envisioned that the reaction of imidazolium-supported aryl alcohol with 2-chloropyridine and triflic anhydride will lead us to the desired imidazolium-supported Mukaiyama reagent. Imidazolium-supported arylalcohol was synthesized by following multi-step approach as shown in **Scheme 2.13**. Reaction of 4-hydroxybenzaldehyde (**63**) with 1-bromo-3-chloropropane (**62**) in the presence of potassium carbonate gave monoalkylated aldehyde, which on subsequent reduction resulted into monoalkylated benzylalcohol (**64)**. Reaction of **64** with 1,2-dimethylimidazole (**55**) at 110 °C gave the corresponding chloride salt. The anion exchange of chloride salt with aqueous KPF_6 resulted in corresponding ionic liquid-supported arylalcohol (**65**). Reaction of **(65**) and 2-chloropyridine (**1)** in presense of triflic anhydride under nitrogen atmosphere in dichloromethane for 10 h resulted in the imidazolium-supported Mukaiyama reagent **66** in good yield (55%). It is believed that sequential *in situ* formation of imidazolium-supported triflic acid ester followed by quaternization with 2-chloropyridine produced **66** (Im-supported Mukaiyama reagent). This reaction proved to be convenient and fast compared to our earlier attempts.



Scheme 2.13 Synthesis of imidazolium-supported Mukaiyama reagent

The structure of reagent **66** was confirmed by spectroscopic techniques like IR, ^{1}H NMR, ^{13}C NMR and HRMS. Presence of two singlet at δ 3.73 ppm (NCH_3) and δ 5.92 ppm ($PhCH_2$), two doublets at δ 7.60 ppm and δ 7.64 ppm for the imidazolium protons along with characteristic double doublet at δ 9.27 for the ortho-protons adjacent to nitrogen of pyridinium and other peaks in the ^{1}H NMR spectrum of **66** clearly indicated that the 2-chloropyridine has been tagged with imidazolium salt (**Figure 2.3**).

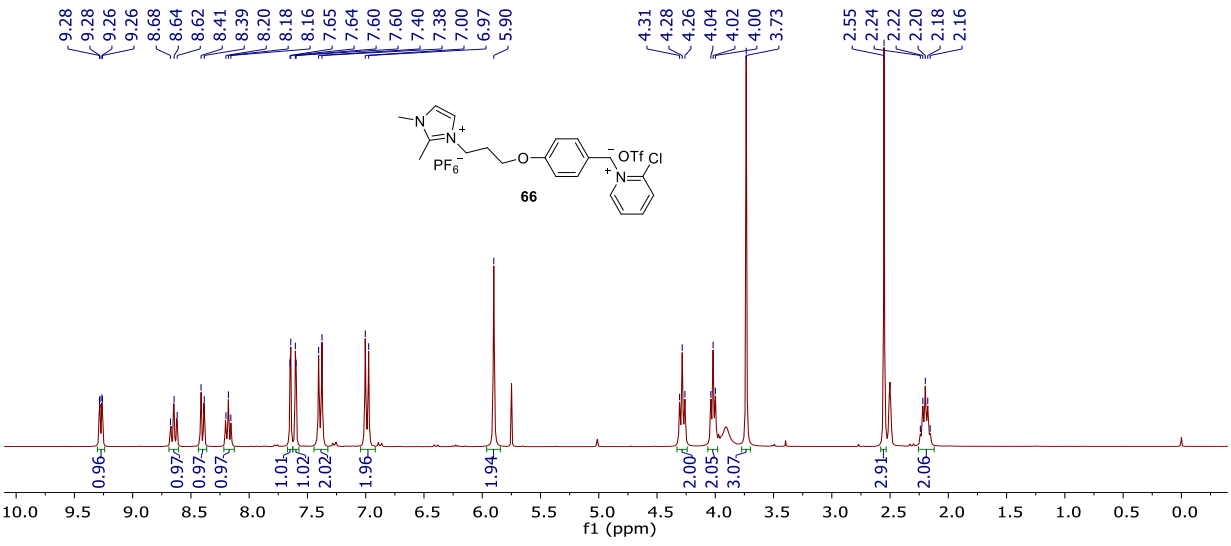


Figure 2.3 ^{1}H NMR spectrum of Im-Mukaiyama reagent **66**

Similarly, the ^{13}C NMR spectrum of **66** showed the peaks corresponding to aromatic carbons, 6 aliphatic carbons along with a benzylic carbon at δ 62 ppm to show that 2-chloropyridine was attached with imidazolium salt (**Figure 2.4**). Presence of the peaks at *m/z* 502.4 $[M\text{-}CF_3SO_3]^+$ and 506.3 $[M\text{-}PF_6]^+$ in the mass spectrum of **66** confirmed the formation of **66**.

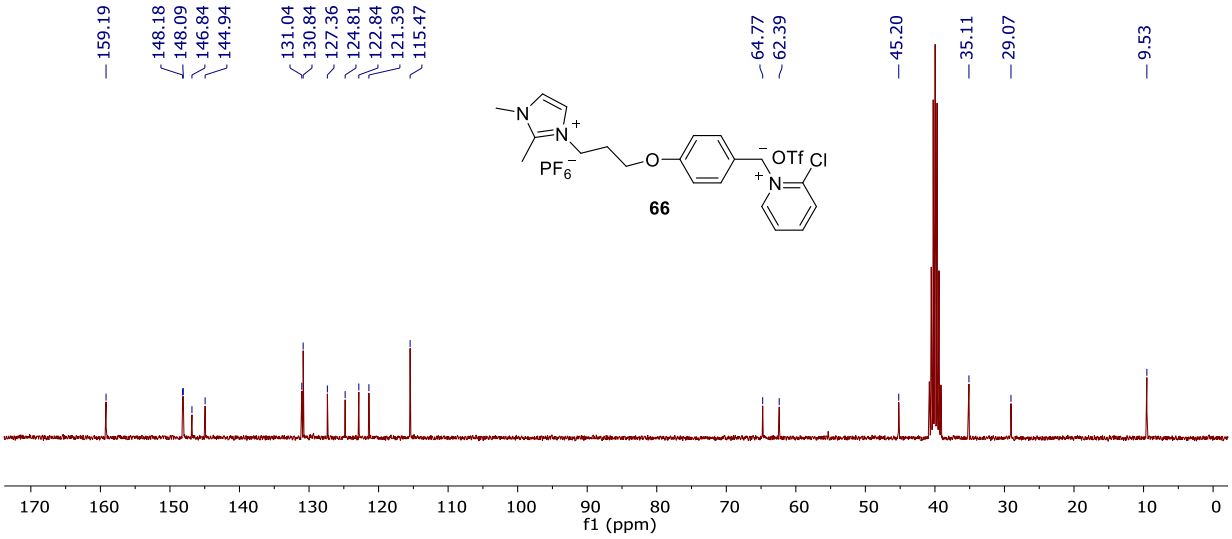
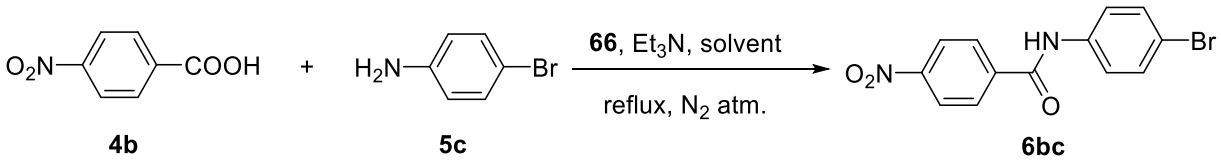


Figure 2.4 ^{13}C NMR spectrum of Im-Mukaiyama reagent **66**

2.2.2 Application of Imidazolium-supported Mukaiyama Reagent

In order to explore synthetic applicability of the reagent, coupling of suitable carboxylic acids and amines were studied and the results are summurised in **Table 2.1**. Initially, the coupling of 4-nitrobenzoic acid (**4b**) and 4-bromoaniline (**5c**) was performed without additive in DCM as a prototype reaction. DCM was the first solvent of choice and this proved to work efficiently showing completion of reaction within 2 h with 72% yield of **6bc** (**Table 2.1**, entry 1). However, the choice of DCM is not optimal, because many carboxylic acids are insoluble in it, while it is too volatile for parallel synthetic use. Thus, other solvents such as acetonitrile, methanol, water and THF were screened to circumvent the issue. Although the reagent was soluble in acetonitrile the yield of product was less even after longer reaction time (**Table 2.1**, entries 2-3). Among all the solvents evaluated for the reaction, THF was proved to be the best choice in terms of good yield (85%) and reaction time (**Table 2.1**, entry 4). In methanol, the yield of desired product was even poor probably due to neucleophilicity of methanol could also lead to the formation of ester as by-product (**Table 2.1**, entry 5).

Table 2.1 Optimization of reaction conditions for amide synthesis[a]



Entry	Solvent	Time (h)	Yield (%)
1	DCM	2	72 (62)[b]
2	CH_3CN	2	55
3	CH_3CN	4	65
4	**THF**	**2**	**85**
5	Methanol	2	43
6	H_2O	2	20 (53)[c]

[a]Reaction condition: acid (0.170 mmol), amine (0.170 mmol), triethylamine (0.430 mmol), reagent (0.210 mmol) refluxed for 2h in solvent under N_2 condition. [b] room temperature, [c] stirring for 5 h

The structure of amide **6bc** was confirmed by spectroscopic techniques like IR, ^{1}H NMR and ^{13}C NMR spectroscopy. In the ^{1}H NMR, the presence of singlet at δ 10. 68 ppm for N-H proton along with four doublets at δ 7.56 ppm, 7.76 ppm, 8.17 and 8.37 for the aromatic protons clearly indicated the formation of amide linked molecule with para subtitiution (**Figure 2.5**).

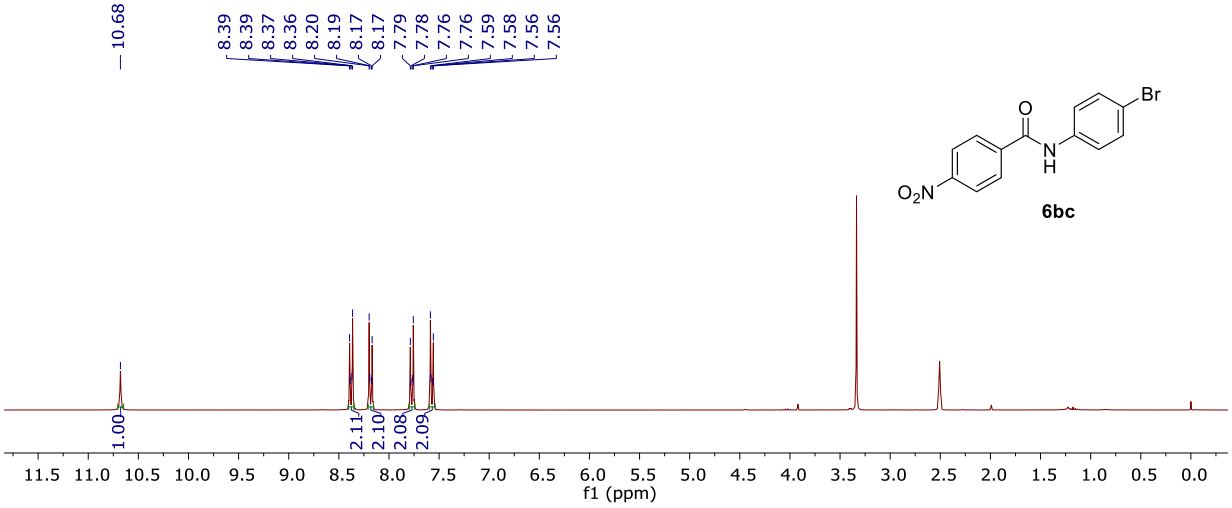


Figure 2.5 ^{1}H NMR spectrum of *N*-(4-bromophenyl)-4-nitrobenzamide (**6bc)**

Similarly, the appearance of amidic carbonyl carbon at δ 168 ppm along with other carbons peaks ^{13}C NMR spectrum of conformed the formation of desired product **6bc** (**Figure 2.6**).

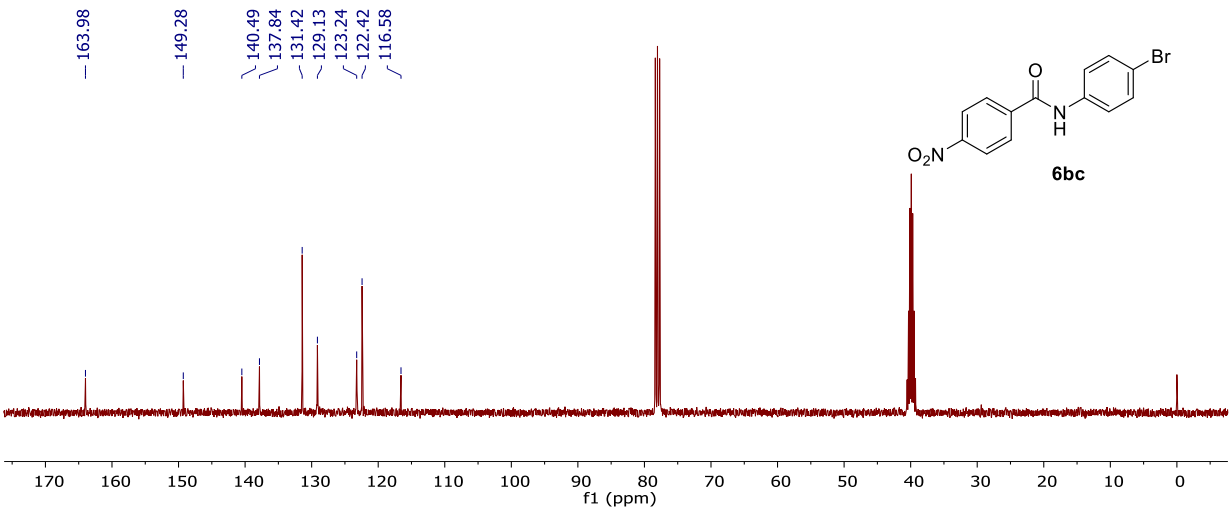
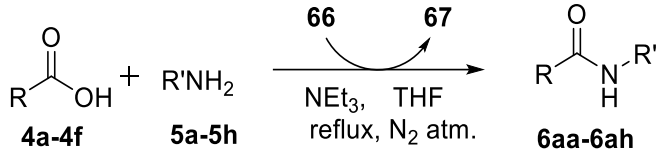


Figure 2.6 ^{13}C NMR spectrum of *N*-(4-bromophenyl)-4-nitrobenzamide (**6bc**)

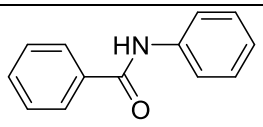
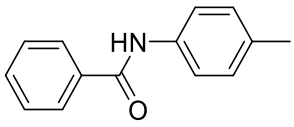
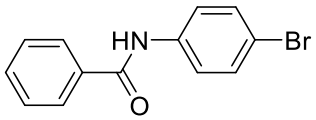
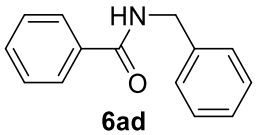
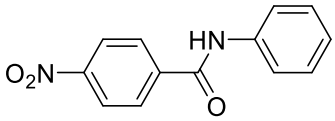
Having identified optimum reaction conditions, the scope of reagent for amide bond formation was examined by employing different substituted carboxylic acids and amines and results are summarized in **Table 2.2**. For the synthesis of amide, a mixture of benzoic acid (**4**), imidazolium-supported Mukaiyama reagent (**66**), triethylamine were suspended in THF and amine (**5**) was added to mixture. The reaction mixture was refluxed for optimum time. It was observed that aromatic amines having electron-donating substituents like methyl and methoxy group furnished better yield of products as compared to aniline with electron-withdrawing bromo substituents (**Table 2.2**, entries 1, 10, 2-3 & 6-7). On the other hand aromatic acid with electron donating as well as withdrawing groups showed excellent reactivity (**Table 2.2**, entries 5–9, entries 2 and 10). It is worth mentioning that highly electron-rich 3,4,5-trimethoxybenzoic acid gave poor yield even after longer reaction time (5 h) (**Table 2.2**, entry 12). This may be attributed to steric hindrence in attack of amine by three methoxy groups in transition state. Aliphatic acid, propionic acid also furnished low yield of corresponding *N*-phenylpropionamide (**Table 2.2**, entry 13). Butylamine also coupled with benzoic acid giving good yield of *N*-butylbenzamide (**Table 2.2**, entry 12). The heterocyclic amine such as 2-aminobenzothiazole and 6-aminoquinoline also coupled with benzoic acid to give desired amide in moderate to good yield (48–59%) in 4–6 h using **66** as coupling reagent (**Table 2.2**, entries 14, 16). Nicotinic acid also coupled with aniline affording good yield

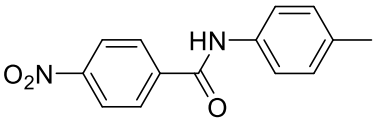
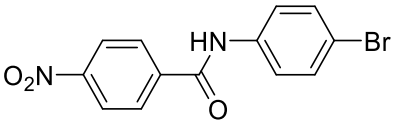
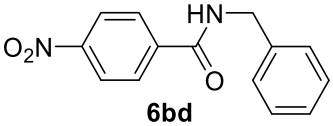
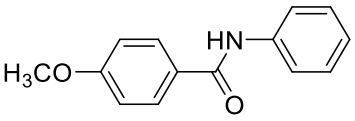
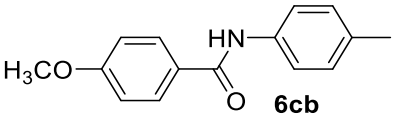
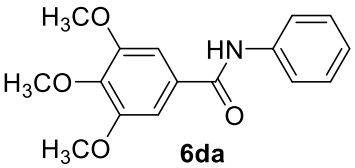
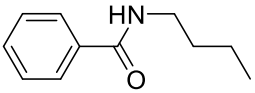
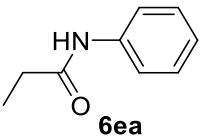
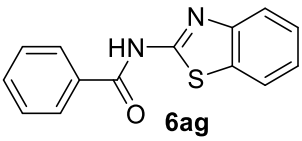
of the desired product in 4 h (**Table 2.2**, entry 15). The longer reaction time taken by heteroaromatic acids and amines is attributed to lesser reactivity of acid and lower nucleophilicity of heteroamines. All the amides were obtained in excellent purity after simple workup without additional chromatography. The melting point and NMR data for the synthesized amides were in agreement with the reported data in the literature.

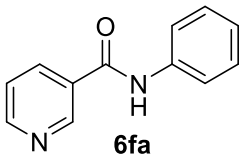
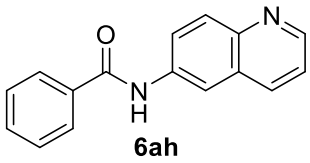
Table 2.2: Synthesis of amide derivatives[a]



4a-4f **5a-5h** **6aa-6ah**

Entry	R	R′	Product	Time (h)	Yield (%)
1.	C_6H_5	C_6H_5	 **6aa**	3	87
2.	C_6H_5	4-$CH_3C_6H_4$	 **6ab**	2	93
3.	C_6H_5	4-BrC_6H_4	 **6ac**	3	70
4.	C_6H_5	$C_6H_5CH_2$	 **6ad**	3	68
5.	4-$NO_2C_6H_4$	C_6H_5	 **6ba**	3	90

6.	4-$NO_2C_6H_4$	4-$CH_3C_6H_4$	 **6bb**	3	95
7.	4-$NO_2C_6H_4$	4-BrC_6H_4	 **6bc**	2	84
8.	4-$NO_2C_6H_4$	$C_6H_4CH_2$	 **6bd**	3	90
9.	4-$OCH_3C_6H_4$	C_6H_5	 **6ca**	3	92
10.	4-$OCH_3C_6H_4$	4-$CH_3OC_6H_4$	 **6cb**	3	95
11.	3,4,5-$(CH_3O)_3C_6H_4$	4-$CH_3C_6H_4$	 **6da**	5	60
12.	C_6H_5	C_4H_9	 **6af**	4	82
13.	C_2H_5	C_6H_5	 **6ea**	2.5	56
14	C_6H_5	C_7H_4NS	 **6ag**	4	48

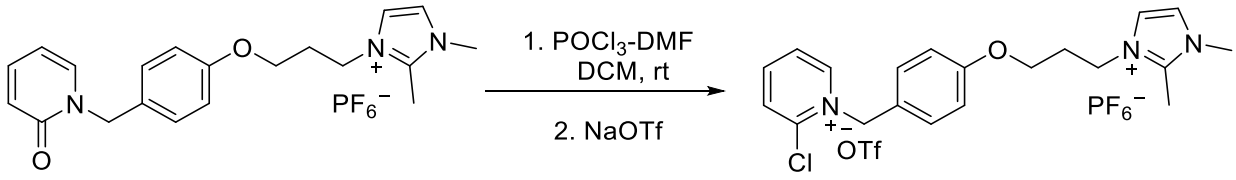
15.	C_5H_4N	C_6H_5	 **6fa**	4	63
16.	C_6H_5	C_9H_6N	 **6ah**	6	59

[a]Reaction condition: acid (0.170 mmol), amine (0.170 mmol), triethylamine (0.430 mmol), reagent (0.210 mmol) refluxed in THF under N_2 condition.

2.2.3 Recycling of Imidazolium-Supported Mukaiyama Reagent

After the completion of reaction, the desired product was removed from reaction mass by simple solvent extraction leaving behind the residue in the round bottom flask. The residue was thoroughly washed 2-3 times with diethyl ether to obtain the by-product imidazolium-supported pyridone **67**. The structure of imidazolium-supported pyridone **67** was confirmed by ^{1}H NMR, ^{13}C NMR and IR spectroscopy.

It is worth to mention that recovered imidazolium-supported pyridone (**67**) can be easily converted to reagent **66** by reacting with phosphorus oxychloride followed by anion metathesis with sodium trifluoromethanesulfonate (**Scheme 2.14**).



Scheme 2.14: Recycling of imidazolium-supported pyridone (**67**) to imidazolium-supported Mukaiyama reagent (**66**)

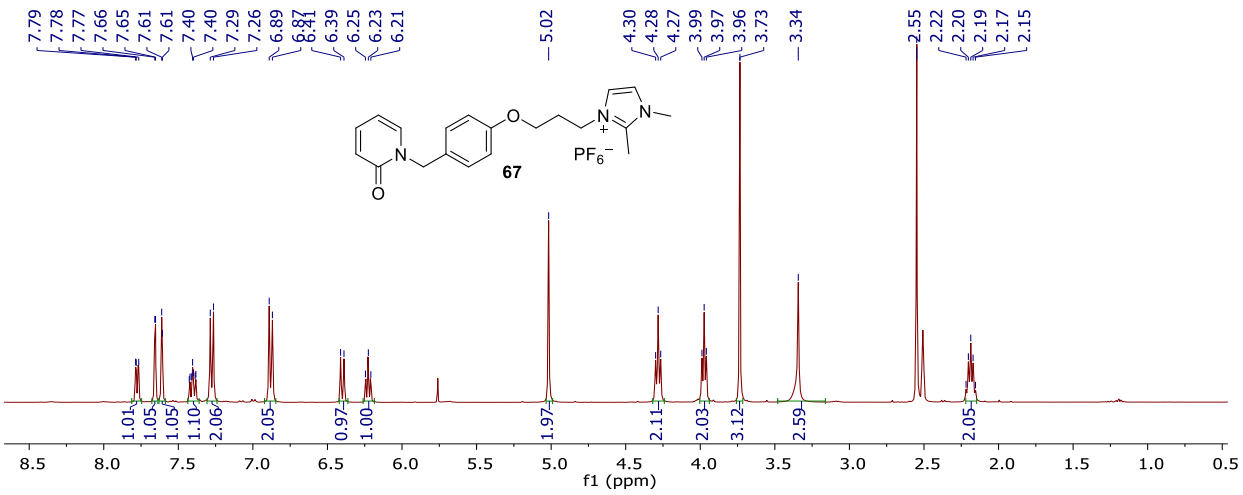


Figure 2.7 ^{1}H NMR spectrum of imidazolium-supported pyridone **67**

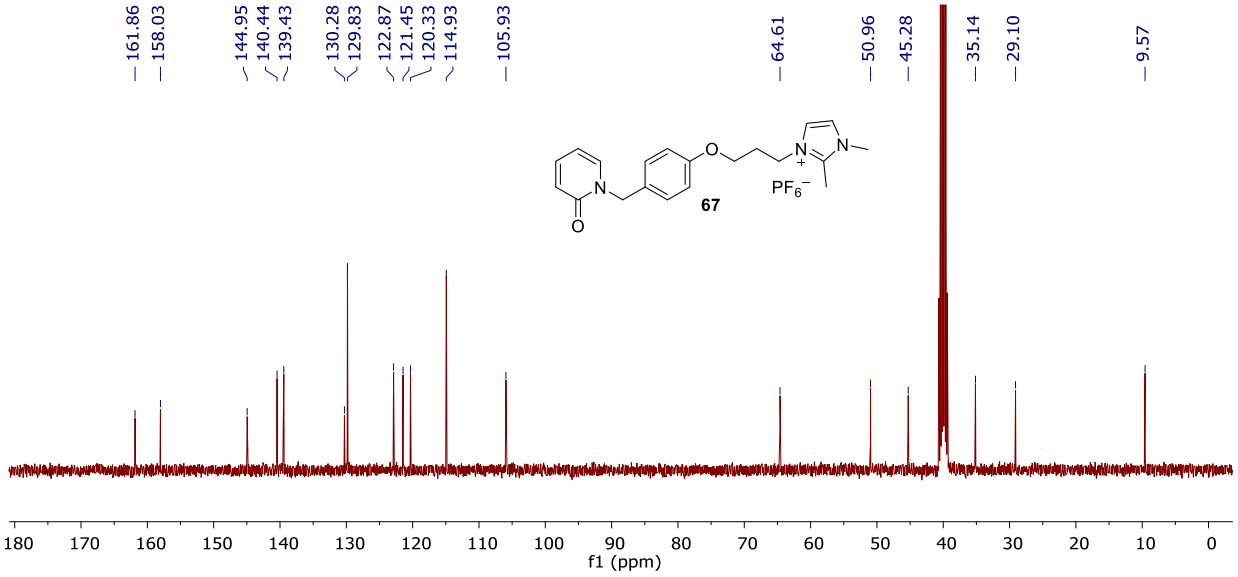
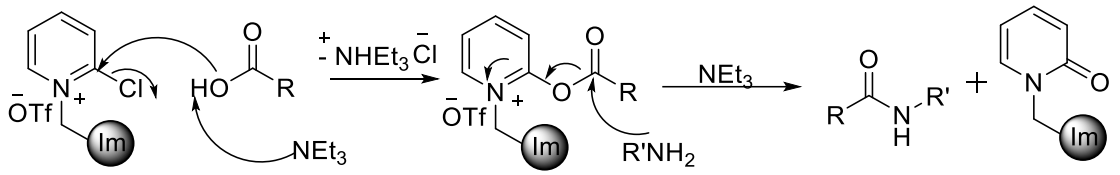


Figure 2.8 ^{13}C NMR spectrum of imidazolium-supported pyridone **67**

2.2.4 Plausible Mechanism

Based upon literature reports available, it is believed that the reaction proceeds through initial activation of carboxylic acid (**67**) by imidazolium-supported 2-chloropyridinium triflate to give intermediate ester (**71**) which on subsequent reaction with amine (**68**) by nucleophilic attack furnishes amide (**69**) as product and Im-supported pyridone (**70**) as by-product (**Scheme 2.15**).



Scheme 2.15: Plausible reaction mechanism

2.3 CONCLUSIONS

In conclusion, we have developed a shelf-stable and efficient imidazolium-supported Mukaiyama reagent. This reagent is utilized for amide bond formation between carboxylic acids and amines. The significance of this protocol is evading column chromatography, shorter reaction time and good to excellent yields of amides. The isolated byproduct imidazolium-supported pyridone (**67**) can be further utilized in regeneration of Mukaiyama reagent.

2.4 EXPERIMENTAL SECTION

2.4.1 Materials and Methods

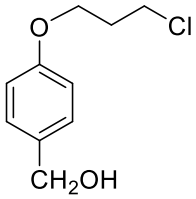
The ^{1}H and ^{13}C NMR spectra were recorded on 300 MHz and 400 MHz spectrometer in $CDCl_3$ and DMSO-d_6. The chemical shifts were expressed in parts per million (ppm) and coupling constants (*J*) in Hertz (Hz). The IR spectra were recorded on ABB Bomen MB3000 FTIR spectrophotometer. The progress of the reaction was determined on thin-layer chromatography (TLC) performed on Merck-precoated silica gel 60-F254 plates. Melting points were determined on open capillary tube on MPA-120G EZ-Melt automated melting point apparatus and are uncorrected. 1,2-Dimethylimidazole, 2-chloropyridine, trifluoromethanesulfonic acid and other reagents and solvents were purchased from commercial sources and used without further purification unless otherwise specified.

2.4.2 General Procedure for the Synthesis of (4-(3-Chloropropoxy) phenyl)methanol (64)

4-Hydroxybenzaldehyde (8.00 g, 65 mmol), 1-bromo-3- chloropropane (6.46 mL, 65 mmol) and potassium carbonate (9.05 g, 65 mmol) were taken in dry acetone (25 mL) in a 250 mL round bottom flask. The reaction mixture was refluxed for 12 h. After completion of reaction, acetone was evaporated and residue was washed with water (20 mL) and extracted by ethyl acetate (2 × 15

mL). The organic layer was dried with anhydrous sodium sulphate and evaporated under reduced pressure to get crude product. Crude product was purified by column chromatography on silica (60–120 mesh) using hexane and ethylacetate as eluent (9:1, *v/v*) to get 7.86 g of pure 4-(3-chloropropoxy) benzaldehyde. It was further dissolved in dry THF (15 mL) at 0 °C, then sodium borohydride (2.24 g, 59 mmol) was added in pinches. After addition the resulting mixture was stirred at room temperature for 3 h. On completion of reaction, methanol was evaporated and water (15 mL) was added to the viscous residue. The solution was neutralized to pH 7 by 2N HCl and extracted in ethyl acetate (2 × 15 mL). The organic layer was washed with brine water and dried with anhydrous sodium sulfate and concentrated under reduced pressure to get pure product as white solid.

***(4-(3-Chloropropoxy)phenyl)methanol* (64).**

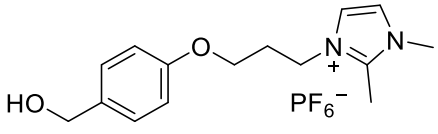


White solid (6.80 g, 86%); MP 53 – 55 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (d, J = 8.7 Hz, 2H), 6.92 (d, J = 8.7 Hz, 2H), 4.65 (d, J = 5.9 Hz, 2H), 4.14 (t, J = 5.8 Hz, 2H), 3.78 (t, J = 6.3 Hz, 2H), 2.31 – 2.20 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.4, 133.4, 128.7, 114.6, 65.0, 64.3, 41.5, 32.3.

2.4.3 General Procedure for the Synthesis of Imidazolium-supported Benzyl Alcohol (65)

A mixture of **64** (6.00 g, 30 mmol) and 1,2-dimethylimidazole (2.87 g, 30 mmol) was heated at 110 °C for 3 h to give thick viscous liquid. The viscous liquid was washed with ethyl acetate (3 × 20 mL) to remove unreacted starting materials to give pure chloride salt (8.56 g, 96%). Ion exchange of chloride was performed using (20 mL) aqueous potassium hexafluorophosphate (6.37 g, 35 mmol) solution at room temperature for 1 h. The resulting solid precipitate was filtered and washed with water and dried in vacuum to get pure **65**.

3-(3-(4-(hydroxymethyl)phenoxy)propyl)-1,2-dimethyl-1H-imidazol-3-ium hexafluoro phosphate (65).



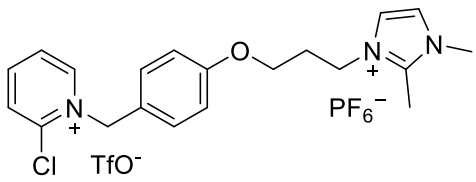
White solid (11.37 g, 97%); MP 115 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.65 (d, J = 2.0 Hz, 1H), 7.60 (d, J = 2.0 Hz, 1H), 7.23 (d, J = 8.5 Hz, 2H), 6.86 (d, J = 8.6 Hz, 2H), 5.05 (t, J = 5.6 Hz, 1H), 4.41 (d, J = 5.6 Hz, 2H), 4.29 (t, J = 6.8 Hz, 2H), 3.97 (t, J = 5.9 Hz, 2H), 3.73 (s,

3H), 2.55 (s, 3H), 2.19 (p, J = 6.4 Hz, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 157.4, 144.9, 135.3, 128.4, 122.9, 121.4, 114.4, 64.5, 62.9, 45.3, 35.1, 29.1, 9.5.

2.4.4 General Procedure for the Synthesis of Imidazolium-supported Mukaiyama Reagent (66)

A mixture of **14** (11.00 g, 27 mmol) and 2-chloropyridine (14.00 g, 135 mmol) was suspended in 20 mL DCM at 0 °C under N_2 atmosphere. Triflic anhydride (6.40 mL, 38 mmol) was added drop wise over 5 min. After complete addition, the resulting reaction mixture was allowed to stir at room temperature for 10 h. Reaction was monitored by TLC. On completion, the reaction mixture was filtered and washed with 20% DCM–methanol solution (20 mL) to furnish pure **66**.

2-Chloro-1-(4-(3-(1,2-dimethyl-1H-imidazol-3-ium-3-yl)propoxy)benzyl)pyridin-1-ium (66).

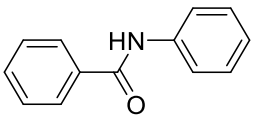


White solid (9.68 g, 55%); MP 120 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.27 (dd, J = 6.2, 1.3 Hz, 1H), 8.65 (td, J = 8.1, 1.5 Hz, 1H), 8.40 (dd, J = 8.2, 1.0 Hz, 1H), 8.21–8.14 (m, 1H), 7.65 (d, J = 2.0 Hz, 1H), 7.60 (d, J = 2.0 Hz, 1H), 7.39 (d, J = 8.7 Hz, 2H), 6.99 (d, J = 8.7 Hz, 2H), 5.90 (s, 2H), 4.28 (t, J = 6.9 Hz, 2H), 4.02 (t, J = 5.9 Hz, 2H), 3.73 (s, 3H), 2.55 (s, 3H), 2.20 (q, J = 6.3 Hz, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 159.2, 148.2, 148.1, 146.8, 144.9, 131.0, 130.8, 127.3, 124.8, 122.8, 121.4, 115.4, 64.7, 62.4, 45.2, 35.2, 29.0, 9.5; ESI-MS (m/z): 502.4 $[M\text{-}OTf]^+$ and 506.3 $[M\text{-}PF_6]^+$.

2.4.5 Representative Procedure for the Amide Bond Formation using 66

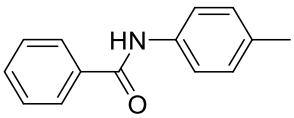
A mixture of 4-nitrobenzoic acid (0.030 g, 0.17 mmol) and imidazolium salt-supported Mukaiyama reagent **66** (0.1404 g, 0.21 mmol) was suspended in THF (5.0 mL) under nitrogen atmosphere. To this reaction mixture were added triethylamine (0.044 g, 0.43 mmol) and 4-bromoaniline (0.029 g, 0.17 mmol) in sequence. The resulting reaction mixture was allowed to reflux for 2 h. After completion of reaction, THF was evaporated to obtain viscous mixture. Product was extracted with 30% ethyl acetate–hexane (2 × 10 mL) from viscous mixture and washed with 2M HCl solution (3 × 5 mL) and saturated bicarbonate solution (3 × 5 mL) in order to remove any unreacted amine and by-products. The organic layer was washed with brine and dried over sodium sulphate and concentrated in vacuum to get pure amide **6bc** in 0.048 g (84%).

N-Phenylbenzamide (6aa).



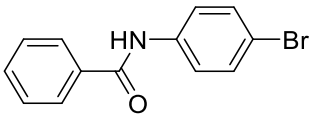
Pale yellow solid (0.042 g, 87%); MP 157 – 159 °C (lit.[51]162 – 164 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (d, J = 7.2 Hz, 2H), 7.84 (s, 1H), 7.67 (d, J = 7.7 Hz, 2H), 7.62 – 7.56 (m, 1H), 7.52 (t, J = 7.3 Hz, 2H), 7.41 (t, J =7.9 Hz, 2H), 7.19 (t, J = 7.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.7, 137.9, 135.0, 131.8, 129.1, 128.8, 127.0, 124.6, 120.2; IR (KBr, cm^{-1}): 3298, 3075, 1670, 1556, 1450, 728.

N-p-Tolylbenzamide (6ab).



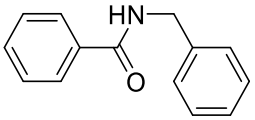
Crystalline solid (0.048 g, 93%); MP 158 – 160 °C (lit. [52] 158 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (s, 1H), 7.90 – 7.85 (m, 2H), 7.57 – 7.52 (m, 3H), 7.50 – 7.44 (m, 2H), 7.18 (d, J = 8.2 Hz, 2H), 2.36 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.8, 135.4, 135.0, 134.2, 131.7, 129.5, 128.7, 127.0, 120.4, 20.94; IR (KBr, cm^{-1}): 3319, 2910, 1649, 1580, 1521, 1404, 1315, 812.

N-(4-Bromophenyl)benzamide (6ac).



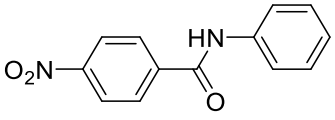
Off-white solid (0.047 g, 70%); MP 196 – 198 °C (lit. [53] 200 – 202 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (d, J = 8.4 Hz, 2H), 7.82 (s, 1H), 7.61 – 7.56 (m, 3H), 7.52 (dd, J = 12.2, 5.3 Hz, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.6, 137.0, 134.6, 132.1, 128.9, 127.0, 121.7, 117.1;); IR (KBr, cm^{-1}): 3322, 2935, 1644, 1588, 1530, 1360, 830.

N-Benzylbenzamide (6ad).



Yellow crystalline (0.035 g, 68%); MP 102 – 103 °C (lit. [54] 100 – 101 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.79 (d, J = 7.2 Hz, 2H), 7.53 – 7.46 (m, 1H), 7.41 (t, J = 7.3 Hz, 2H), 7.35 (d, J = 4.1 Hz, 2H), 7.32 – 7.28 (m, 4H), 6.49 (s, 1H), 4.64 (d, J = 5.6 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.3, 138.2, 134.4, 131.5, 128.8, 128.6, 127.9, 127.6, 126.9, 44.1; IR (KBr, cm^{-1}): 3325, 3055, 2924, 1643, 1551, 1319, 800, 694.

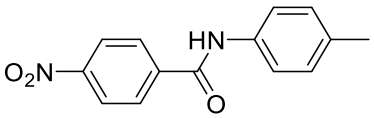
4-Nitro-N-phenylbenzamide (6ba).



Yellow solid (0.039 g, 90%); MP 210 – 212 °C (lit. [55] 211 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.38 (d, J = 8.6 Hz, 2H), 8.07 (d, J = 8.5

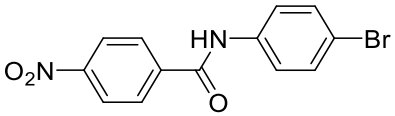
Hz, 2H), 7.84 (s, 1H), 7.67 (d, *J* = 8.0 Hz, 2H), 7.44 (t, *J* = 7.8 Hz, 2H), 7.24 (t, *J* = 7.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.0, 149.3, 140.8, 138.5, 129.1, 128.6, 124.4, 123.2, 120.9; IR (KBr, cm^{-1}): 3317, 3078, 2924, 1651, 1597, 1528, 1350, 1319, 856.

4-Nitro-N-p-tolylbenzamide (6bb).



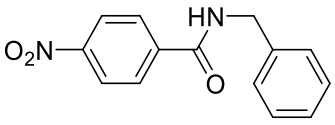
Yellow solid (0.044 g, 95%); MP 200 – 203 °C (lit. [56] 201 – 203 °C); ^{1}H NMR (300 MHz $CDCl_3$) δ 8.33 (d, *J* = 8.7 Hz, 2H), 8.03 (d, *J* = 8.6 Hz, 2H), 7.82 (s, 1H), 7.51 (d, *J* = 8.0 Hz, 2H), 7.20 (d, *J* = 8.2 Hz, 2H), 2.36 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.4, 149.7, 140.6, 135.1, 134.6, 129.7, 128.2, 124.0, 120.4, 20.9; IR (KBr, cm^{-1}): 3317, 2924, 2854, 1651, 1597, 1528, 1350, 1319, 849.

N-(4-Bromophenyl)-4-nitrobenzamide (6bc).



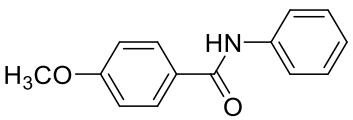
Yellow solid (0.048 g, 84%); MP 236 – 238 °C (lit. [56] 238 – 240 °C); ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.68 (s, 1H), 8.42 – 8.33 (m, 2H), 8.22 – 8.14 (m, 2H), 7.80 – 7.72 (m, 2H), 7.61 – 7.52 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.9, 149.2, 140.4, 137.8, 131.4, 129.1, 123.2, 122.4, 116.5; IR (KBr, cm^{-1}): 3296, 2839, 1659, 1597, 1529, 1389, 1342, 840, 825.

N-Benzyl-4-nitro benzamide (6bd).



Off-white solid (0.041 g, 90%); MP 137 – 138 °C (lit. [55]136 – 137 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.17 (d, *J* = 8.7 Hz, 2H), 7.86 (d, *J* = 8.7 Hz, 2H), 7.33 – 7.21 (m, 5H), 6.62 (s, 1H), 4.56 (d, *J* = 5.7 Hz, 2H), ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.3, 149.6, 139.9, 137.4, 128.9, 128.2, 127.9, 127.9, 123.8, 44.4; IR (KBr, cm^{-1}): 3279, 2924, 1628, 1597, 1535, 1342, 872.

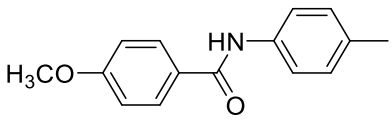
N-(4-Methoxyphenyl)benzamide (6ca).



Off-white solid (0.043 g, 95%); MP 154 – 157 °C (lit. [51] 156 – 157 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (dd, *J* = 7.0, 1.5 Hz, 2H), 7.74 (s, 1H), 7.59 – 7.54 (m, 3H), 7.53 – 7.48 (m, 2H), 6.97 – 6.88

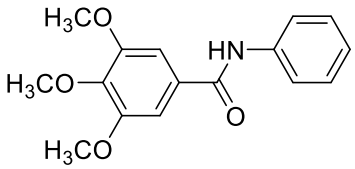
(m, 2H), 3.84 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.6, 156.6, 135.0, 131.7, 131.0, 128.7, 127.0, 122.1, 114.2, 55.5; IR (KBr, cm^{-1}): 3325, 3047, 2839, 1643, 1612, 1026, 825.

4-Methoxy-N-p-tolylbenzamide (6cb).



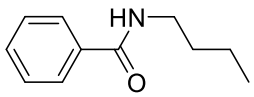
White solid (0.046 g, 97%); MP 186 – 188 °C (lit. [57] 169 – 170 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (d, J = 8.8 Hz, 2H), 7.80 (s, 1H), 7.53 (d, J = 8.4 Hz, 2H), 7.18 (d, J = 8.2 Hz, 2H), 6.97 (d, J = 8.8 Hz, 2H), 3.88 (s, 3H), 2.36 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.2, 162.4, 135.5, 133.9, 129.5, 128.8, 127.2, 120.3, 113.9, 55.4, 20.9; IR (KBr, cm^{-1}): 3340, 2916, 2839, 1651, 1605, 1520, 841, 818.

3,4,5-Trimethoxy-N-phenylbenzamide (6da).



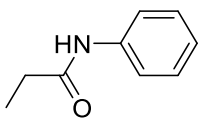
Yellow solid (0.024 g, 60%); MP 139 – 140 °C (lit.[58] 137 – 139 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (s, 1H), 7.68 – 7.63 (m, 2H), 7.41 – 7.35 (m, 2H), 7.17 – 7.15 (m, 1H), 7.08 (s, 2H), 3.91 (s, 3H), 3.90 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.6, 153.3, 141.2, 137.9, 130.4, 129.1, 124.6, 120.3, 107.9, 104.5, 60.9, 56.3; IR (KBr, cm^{-1}): 3249, 2924, 1682, 1643, 1589, 841, 756.

N-Butylbenzamide (6af).



Colourless liquid (0.036 g, 82%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 – 7.76 (m, 2H), 7.50 – 7.45 (m, 1H), 7.40 (dd, J = 8.6, 7.2 Hz, 2H), 6.48 (s, 1H), 3.44 (dd, J = 13.0, 7.2 Hz, 2H), 1.60 (dt, J = 14.9, 7.5 Hz, 2H), 1.40 (dq, J = 14.5, 7.3 Hz, 2H), 0.95 (t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.7, 134.8, 131.2, 128.4, 126.9, 39.8, 31.7, 20.1, 13.7.

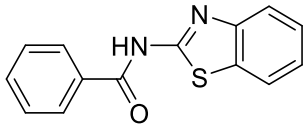
N-Ethylbenzamide (6ea).



Off-white solid (0.034 g, 56%); MP 110 – 114 °C (lit.[59] 106 – 108 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44 (d, J = 7.9 Hz, 2H), 7.23 (dd, J = 15.5, 7.4 Hz, 2H), 7.02 (t, J = 7.3 Hz, 1H), 2.32 (q, J = 7.5 Hz, 2H), 1.18 (dd, J = 9.0, 6.1 Hz, 3H);

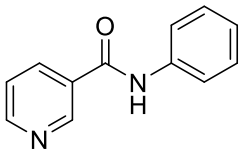
^{13}C NMR (75 MHz, $CDCl_3$) δ 172.0, 137.9, 128.9, 124.1, 119.7, 30.7, 29.7, 9.6; IR (KBr, cm^{-1}): 3294, 2978, 2932, 1666, 1605, 1551, 1260, 1080.

N-(Benzo[d]thiazol-2-yl)benzamide (6ag).



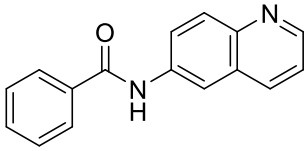
Off white solid (0.030 g, 48%); MP 188 – 191 °C (lit. [60] 188 – 190 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.66 (s, 1H), 8.22 (d, J = 6.4 Hz, 1H), 8.09 (d, J = 6.5 Hz, 1H), 7.85 (s, 1H), 7.57 (d, J = 7.2 Hz, 1H), 7.52 – 7.39 (m, 3H), 7.33 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.8, 147.4, 133.1, 131.9, 130.0, 128.9, 128.4, 128.0, 126.2, 124.0, 121.4, 120.4; IR (KBr, cm^{-1}): 3225, 3055, 2962, 1674, 1597, 1551, 1234, 1111, 756.

N-Phenylnicotinamide (6fa).



Off white solid (0.030 g, 63%); MP 112 – 115 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.06 (s, 1H), 8.91 (s, 1H), 8.67 (s, 1H), 8.17 (d, J = 7.7 Hz, 1H), 7.63 (d, J = 7.8 Hz, 2H), 7.33 (t, J = 7.7 Hz, 3H), 7.16 (t, J = 7.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.2, 152.1, 147.9, 137.6, 135.6, 130.9, 129.0, 125.0, 123.7, 120.7; IR (KBr, cm^{-1}): 3225, 3055, 2962, 1685, 1530, 1551 1257.

N-(Quinoline-6-yl)benzamide (6ah).



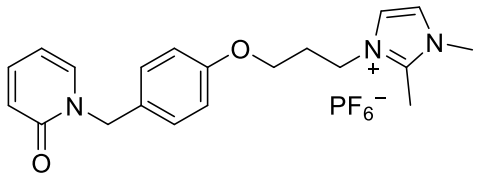
Yellow solid (0.036 g, 59%); MP 155 – 158 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.84 (d, J = 2.8 Hz, 1H), 8.50 (s, 1H), 8.47 (s, 1H), 8.12 – 8.05 (m, 2H), 7.94 (d, J = 7.4 Hz, 2H), 7.72 (dd, J = 8.9, 1.9 Hz, 1H), 7.56 (t, J = 7.2 Hz, 1H), 7.48 (t, J = 7.4 Hz, 2H), 7.38 (dd, J = 8.2, 4.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.1, 149.5, 145.6, 135.9, 134.6, 133.8, 132.0, 130.1, 128.8, 127.14, 123.5, 121.6, 116.6, 107.4.

2.4.6 Representative Procedure for the Regeneration of 66 from 70

A 10 mL clean oven dried round bottom flask was charged with Im-supported pyridone **70** (0.168 g, 0.347 mmol) and phosphorus oxychloride (95 mL, 1.04 mmol) was added drop-wise at room temperature. The reaction mixture was then heated at 80 °C for 8 h. After completion of the reaction, the volatile impurities were removed under reduced pressure. To the residue was added

dry acetonitrile (5 mL) and sodium trifluoromethansulfonate (0.080 g). The reaction mixture was again refluxed for 12 h. After complete anion metathesis, the reaction mixture was filtered through a thin pad of silica to remove solid impurity and the filtrate was concentrated to get viscous product. The viscous liquid on washing with ethyl acetate (3 × 5 mL) resulted into desired reagent **66**.

1,2-Dimethyl-3-(3-(4-((2-oxopyridin-1(2H)-yl)methyl)phenoxy)propyl)-1H-imidazol-3-ium hexafluorophosphate: **Im-supported pyridone (70).**



White solid; MP 70 – 72 °C; ^{1}H NMR (400MHz, DMSO-d_6) δ 7.80 – 7.75 (m, 1H), 7.66 (d, J = 2.0Hz, 1H), 7.61 (d, J = 2.0 Hz, 1H), 7.40 (m, 1H), 7.27 (d, J = 8.6 Hz, 2H), 6.88 (d, J = 8.6 Hz, 2H), 6.40 (d, J = 9.1 Hz, 1H), 6.23 (t, J = 7.2 Hz, 1H), 5.02 (s, 2H), 4.28 (t, J = 6.8 Hz, 2H), 3.97 (t, J = 5.9 Hz, 2H), 3.73 (s, 3H), 3.34 (s, 3H), 2.19 (p, J = 6.3 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 161.8, 158.0, 144.9, 140.4, 139.4, 130.2, 129.8, 122.8, 121.4, 120.3, 114.9, 105.9, 64.6, 50.9, 45.2, 35.1, 29.1, 9.5; IR (KBr, cm^{-1}): 3140, 2932, 1659, 1582, 1535, 1250, 841, 771.

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