Functionalized Ionic Liquid-Supported Organic Synthesis

by

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Table of Contents

Abstracts I

Réseme III

Acknowledgements V

List of Schemes VI

List of Figures XI

List of Tables XIII

List of Abbreviation XIV

Chapter 1. Synthesis and Application of Functionalized (or Task-Specific) Ionic Liquids 1

1. 1. Introduction 1

1. 2. Chiral ionic liquids 3

1. 2. 1. Synthesis of chiral ionic liquids 3

1. 2. 1. 1. Chiral anion-based ionic liquids 3

1. 2. 1. 2. Chiral imidazolium-based ionic liquids 5

1. 2. 1. 3. Chiral oxazolinium-based ionic liquids 12

1. 2. 1. 4. Chiral quaternary ammonium-based ionic liquids 13

1. 2. 1. 5. Chiral pyridinium-based ionic liquids 14

1. 2. 1. 6. Chiral thiazolinium-based ionic liquids 16

1. 2. 2. Application of chiral ionic liquids 18

1. 3. Immobilization of ionic liquids on solid phase 22

1. 4. Organic synthesis and catalysis using ionic liquids as soluble supports 34

1. 4. 1. Ionic liquid-supported synthesis of small molecules 35

1. 4. 2. Ionic liquid-supported catalyst systems 36

1. 4. 3. Ionic liquid-supported reagents 45

1. 4. 4. Ionic liquid-supported synthesis of biopolymers 46

1. 5. Ionic liquid-stabilized metal nanoparticles and catalysis 49

1. 5. 1. Ionic liquid-assisted preparation of metal nanoparticle–based catalytic systems 50

1. 5. 2. Synthesis of metal nanoparticles using thiol-funtionalized ionic liquids as capping reagents 58

1. 5. 3. Preparation of metal nanoparticles in ionic liquids 61

1. 6. Summary and outlook 64

References 66

Chapter 2. New Non-Volatile and Odorless Organosulfur Compounds Anchored on Ionic Liquids. Recyclable Reagents for Swern Oxidation. 82

2. 1. Introduction 82

2. 2. Results and discussion 82

2. 3. Conclusions 88

2. 4. Experimental section 89

References and notes 95

Chapter 3. Ionic Liquid-Supported Oligosaccharide Synthesis 98

3. 1. Introduction 98

3. 2. Results and discussion 100

3. 3. Conclusions 104

3. 4. Experimental section 105

References 121

Chapter 4. Synthesis of Structure-Defined Imidazolium Salt Oligomers 124

4. 1. Introduction 124

4. 2. Results and discussion 127

4. 2. 1. Synthesis 127

4. 2. 2. Physical properties 131

4. 2. 3. Thermal stability 132

4. 3. Conclusion 135

4. 4. Experimental section 136

References 144

Chapter 5. Peptide Synthesis Using Imidazolium Oligomers as Soluble Supports 147

5. 1. Introduction 147

5. 2. Results and discussion 149

5. 2. 1. Synthesis and thermal stability of imidazolium salts with 149

hydroxyalkyl linkers
5. 2. 2. Peptide synthesis 151
5. 2. 3. Peptide block coupling 156
5. 2. 4. Cleavage of peptides from supports 159
5. 3. Conclusion 162
5. 4. Experimental section 163
References 192

Chapter 6. Summary and Conclusions 194

Appendix: Supporting Information 197

Abstract

Ionic liquid-supported synthesis is a new concept in organic chemistry. This concept has been well demonstrated in this thesis including ionic-liquid-supported Swern oxidation, oligosaccharide synthesis, imidazolium oligomer synthesis and peptide synthesis.

Ionic liquid-supported Swern oxidation provided a new odorless approach to oxidize primary and secondary alcohols into aldehydes and ketones as compared to the conventional method where DMSO was used as an oxidant and the toxic and volatile compound dimethylsulfide was generated quantitatively. The new ionic liquid-supported organosulfur reagents were thermally stable, nonvolatile and odorless, which were recoverable and recyclable after Swern oxidation.

Chapter 3 of this thesis described the first example in the research field of ionic liquid-supported oligosaccharide synthesis. This new approach possesses the advantages of both conventional solution phase synthesis and solid phase-supported synthesis. It made possible the chemical assembling of glycals and the cleavage of oligosacharide from the support without need of chromatography to purify the products.

Ionic liquid-type oligomers were designed to solve the problems involved in the one-ionic-unit ionic liquid-supported biopolymer synthesis because these compounds could have stronger ionic effects on support-bound molecules, which made easier the chemical assembling and purifications of large biopolymers than one-ionic-unit ionic liquid-supported organic synthesis. The thermogravimetric analysis (TGA) showed that these

imidazolium oligomers have very good thermal stability. They also have great potential application in the electrochemistry.

Imidazolium oligomer-supported peptide synthesis provided a new approach to prepare peptides in a straightforward way. The amino acid coupling reactions were conducted in homogeneous solution phase, which did not require largely excess of reagents to push the reaction to completion and the purification could be performed in a simple way such as centrifugation, decantation and washing without need of special solvents. Moreover, the cleavage of the peptide from the imidazolium oligomer support was done by hydrolysis under basic conditions and the product was obtained in NMR and MS purity. Importantly, imidazolium oligomer–supported peptide block coupling proceeded very well, which provided an approach to convergently synthesize peptides. This approach is very useful for the peptide synthesis in industry especially for the synthesis of peptides with less than 20 amino acids.

Résumé

La synthèse sur support liquide ionique est un nouveau concept en chimie organique. Cette thèse en illustre plusieurs applications, notament l'oxydation de Swern, la synthèse d'oligosaccharide, la synthèse d'oligomères d'imidazolium ainsi que la synthèse peptidique.

L'oxydation de Swern sur support liquide ionique fournit une approche novatrice, sans odeur, pour oxyder des alcools primaires et secondaires en aldéhydes et en cétones alors que la méthode traditionnelle, utilisant le DMSO comme oxydant, génère du diméthylsulfide en quantités non négligeables, un composé toxique et volatile. Les réactifs organo-sulfurés utilisés sur support liquide ionique se sont révélés être thermiquement stables, non-volatiles et sans odeur, en plus de pouvoir être récupérés et recyclés après l'oxydation de Swern.

Le troisième chapitre décrit le premier exemple d'une synthèse d'oligosaccharide sur support liquide ionique. Cette approche retient aussi bien les avantages de la synthèse traditionnelle en solution que de la synthèse en phase solide. En effet, l'assemblage chimique des glycals et la séparation de l'oligosaccharide du support a été possible sans même avoir recours à la chromatographie pour séparer les produits.

Les supports contenant une seule unité ionique pouvant avoir de forts effets ioniques sur les molécules qui leur sont associées, des oligomères de type liquide ionique ont été conçus en vue de la synthèse de biopolymères, rendant l'assemblage chimique et la purification de larges biopolymères plus facile. Une analyse thermogravimétrique (TGA)

a démontré que ces oligomères d'imidazolium possèdent une grande stabilité thermique. Ils ont également un grand potentiel d'application en électrochimie.

La synthèse peptidique sur support oligomérique d'imidazolium constitue une autre approche simple pour préparer des peptides. Les réactions de couplage avec les acides aminés ont été réalisées dans des solutions homogènes. Cette manière de procéder ne requiert pas l'utilisation d'un excès de réactif. La purification s'effectue de manière simple, par centrifugation, décantation et rinçage, sans qu'aucun solvant particulier ne soit requis. De plus, la séparation finale du support oligomérique d'ions imidazole s'effectue par hydrolyse en condition basique. La pureté du produit a d'ailleurs été confirmée par RMN et SM. Il convient de souligner que le couplage de groupes peptidiques sur support oligomérique d'ions imidazole est efficace, ce qui permet de synthétiser des peptides de manière convergente. Cette approche s'avère être très utile en industrie, particulièrement lorsque le peptide voulu contient moins de 20 acides aminés.

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List of Schemes

Chapter 1. Synthesis and Application of Functionalized (or Task-Specific) Ionic Liquids. 1

Scheme. 1. Synthesis of "double" chiral ionic liquid. 5

Scheme 2. Synthesis of imidazolium Ils with planar chirality. 7

Scheme 3. Synthesis of chiral ionic liquids from natural amino acids. 7

Scheme 4. 2-Alkylimidazolium ILs from 1-phenylethylamine. 8

Scheme 5. Imidazolinium ILs from (S)-valine. 9

Scheme 6. Synthesis of chiral ILs from histidine. 9

Scheme 7. Synthesis of chiral ILs and precursors by nucleophilic substitution and Mitsunobu reaction. 10

Scheme 8. Synthesis of spiro chiral ILs. 11

Scheme 9. Synthesis of functionalized chiral ionic liquids. 12

Scheme 10. Oxazolinium chiral ILs from (S)-valine. 12

Scheme 11. Synthesis of chiral ILs from ephedrine. 13

Scheme 12. Synthesis of chiral IL from chiral amine. 13

Scheme 13. Synthesis of chiral ILs from (1R, 2S, 5R)-(-)-menthol. 14

Scheme 14. Pyridinium ILs from an epoxides. 15

Scheme 15. Synthesis of pyridinium ILs with axial chirality. 16

Scheme 16. Synthesis of chiral thiazolinium-based ILs. 17

Scheme 17. Asymmetric Baylis–Hillman reaction in the presence of chiral ILs as reaction media. 19

Scheme 18. Photoisomerization of dibenzobicyclo[2,2,2]octatrienes in chiral ionic liquids. 19

Scheme 19. Copper-catalyzed 1,4-addition of diethylzinc to enone in chiral ionic liquids. 20

Scheme 20. Enantioselective Michael addition in chiral ionic liquids. 20

Scheme 21. Chiral ionic liquid catalyzed asymmetric Michael addition. 21

Scheme 22. Immobilization of chloroaluminate-based ionic liquid via impregnation. 24

Scheme 23. Immobilization of chloroaluminate-based ionic liquid by grafting imidazolium chloride to silica surface and then treatment with $AlCl_3$. 25

Scheme 24. Immobilization of Lewis acid $SnCl_4$ on silica gel via functionalized ionic liquid linkers. 25

Scheme 25. Immobilization of N-heterocyclic carbene palladium complex/ionic liquid matrix on silica. 26

Scheme 26. Supported ionic liquid asymmetric catalysis. 29

Scheme 27. Mizoroki-Heck reactions catalyzed by ionic liquid immobilized $Pd(OAc)_2$ on amorphous silica. 31

Scheme 28. Peroxotungstate immobilized on ionic liquid-modified silica as a heterogeneous catalyst with hydrogen peroxide. 32

Scheme 29. Preparation of the polymer-supported imidazolium salts PS[hmim][BF_4] and PS[hmim][OTf]. 33

Scheme 30. Ionic liquid-supported synthesis of small organic molecules. 35

Scheme 31. Suzuki coupling reaction using ionic liquid as a soluble support. 36

Scheme 32. Preparation of Ru carbene complex. 37

Scheme 33. Synthesis of ionic liquid-supported Rh-complex catalyst. 38

Scheme 34. Synthesis of ionic liquid-supported Ru-complex catalyst precursors. 40

Scheme 35. Synthesis of palladium complexes with nitrile-functionalized ionic liquids. 41

Scheme 36. Vanadyl salen complexes covalently anchored to an imidazolium ion as catalyst for cyanosilylation of aldehydes in ionic liquids. 42

Scheme 37. Ionic liquid-supported quinuclidine-catalyzed Baylis-Hillman reaction. 43

Scheme 38. Ionic liquid-supported NHPI and catalyzed reactions. 43

Scheme 39. Selective oxidation of alcohols to carbonyl compounds by IL-TEMPO. 44

Scheme 40. Selective oxidation of alcohols to carbonyl compounds by ionic liquid-supported iodine (III) reagent. 46

Scheme 41. Ionic liquid-supported oligopeptide synthesis. 48

Scheme 42. Preparation of ionic liquid-stabilized Pd(0) nanoparticles 53

Scheme 43. Synthesis of poly[(N-vinyl-2-pyrrolidone)-*co*-(1-vinyl-3-alkylimidazolium halide)] copolymers. 55

Scheme 44. Synthesis of gold nanoparticels using functionalized ionic 59 liquid.

Chapter 2. New Non-Volatile and Odorless Organosulfur Compounds Anchored on Ionic Liquids. Recyclable Reagents for Swern Oxidation. 82

Scheme 1. Preparation of ionic liquid-grafted sulfides and sulfoxides. 83

Scheme 2. Recycle of ionic liquid-supported sulfides and sulfoxides in Swern oxidation. 86

Chapter 3. Ionic Liquid-Supported Oligosaccharide Synthesis. 98

Scheme 1. 100

Scheme 2. 102

Chapter 4. Synthesis of Structure-Defined Imidazolium Salt Oligomers. 124

Scheme 1. Route 1 to synthesize imidazolium salt oligomers. 127

Scheme 2. Route 2 to synthesize imidazolium salt oligomers. 130

Chapter 5. Peptide Synthesis Using Imidazolium Oligomers as Soluble Supports. 147

Scheme 1. Synthesis of imidazolium salts with hydroxyalkyl linkers. 150

Scheme 2. Ionic liquid-type monomer, dimer and oligomer-supported peptide synthesis. 152

Scheme 3. Tris-imidazolium oligomer-supported peptide synthesis in homogenous solution phase without dilution. 156

Scheme 4. Imidazolium oligomer-supported peptide block coupling reactions. 158

Scheme 5. Cleavage of peptides from imidazolium supports. 160

List of Figures

Chapter 1. Synthesis and Application of Functionalized (or Task-Specific) Ionic Liquids. 1

Figure 1. Structures of the cations of four classic ionic liquids. 2

Figure 2. Chiral ionic liquids derived from (*S*)-10-camphorsulfonate and (*R*)-1,1'-binaphtyl-2, 2'-diyl phosphate. 5

Figure 3. Chiral ILs from terpene and nicotine. 14

Figure 4. Concept demonstration of supported ionic liquid catalysis used in the hydroformylation reaction of hexene-1 to form n, *i*-heptanal. 28

Figure 5. Molecular structures of Sulfoxantphos and [bmim][n-$C_8H_{17}OSO_3$]. 30

Figure 6. Ionic liquid–supported synthesis of biopolymers. 48

Figure 7. Immobilization of Pd nanoparticles on the surface of molecular sieves with ionic liquid layer. 56

Figure 8. Gold nanoparticels stabilized by zwitterionic imidazolium sulfonate-terminated thiols. 60

Figure 9. The molecular structures of multiple thiol-fuctionalized ionic liquids. 61

Chapter 3. Ionic Liquid-Supported Oligosaccharide Synthesis. 98

Figure 1. Ionic liquid supported synthesis. 100

Chapter 4. Synthesis of Structure-Defined Imidazolium Salt Oligomers. 124

Figure 1. Imidazolium-based polymers. 126

Figure 2. Thermogravimetric analysis (TGA) measurements of imidazolium salt oligomers without bromopropyl chain at the end of molecules. 132

Figure 3. Thermogravimetric analysis (TGA) measurements of imidazolium salt oligomers with bromopropyl chain at the end of molecules. 132

Chapter 5. Peptide Synthesis Using Imidazolium Oligomers as Soluble Supports 147

Figure 1. Thermogravimetric analysis (TGA) measurements of imidazolium salts as the synthetic support linker. 151

Figure 2. Product purification procedures of imidazolium oligomer-supported peptide synthesis. 154

Figure 3. HPLC analysis of compounds. 162

List of Tables

Chapter 1. Synthesis and Application of Functionalized (or Task-Specific) Ionic Liquids. 1

Table 1. Thermal properties and ionic conductivity (δ) of 20 amino acid-derived ionic liquids. 4

Chapter 2. New Non-Volatile and Odorless Organosulfur Compounds Anchored on Ionic Liquids. Recyclable Reagents for Swern Oxidation. 82

Table 1. Swern oxidation using ionic liquid-supported sulfoxides. 87

Table 2. Recycle of ionic liquid-supported sulfide **10b** in Swern oxidation of benzhydrol to bnzophenone. 88

Chapter 4. Synthesis of Structure-Defined Imidazolium Salt Oligomers. 124

Table 1. Decomposing temperatures (onset) and residue percentages of the samples according to TGA measurements. 134

Chapter 5. Peptide Synthesis Using Imidazolium Oligomers as Soluble Supports. 147

Table 1. Decomposing temperatures (onset) and residue percentages of samples according to TGA measurements. 151

List of Abbreviations

Ionic liquid	IL
Functionalized ionic liquid	FIL
Chiral Ionic liquid	CIL
3-*n*-Butyl-1-methylimidazolium	bmim
Ionic liquid supported synthesis	ILSS
3-Ethyl-1-methylimidazolium	emim
3-*n*-Butyl-1-*n*-butylimidazolium	bbim
3-*n*-Decyl-1-*n*-butylimidazolium	C_{10}mim
Nuclear magnetic resonance	NMR
Magic angle spin nuclear magnetic resonance	MAS NMR
Infra-red spectroscopy	IR
High-resolution mass spectroscopy	HRMS
Thermal gravimetric analysis	TGA
Glass transition temperature	T_g
Differential scanning calorimetric	DSC
X-ray diffraction	XRD
Trifluoromethane sulfonate or triflate	TfO^-
Transmission electron microscopy	TEM
Inductively coupled plasma	ICP
Methanesulfonyl	Ms
Lithium aluminum hydride	LAH

Excess enantiomer	e.e.
Pyridine	Py
Tetrahydrofuran	THF
Dimethylsulfoxide	DMSO
N, N-dimethylformamide	DMF
Hetero multiple quantum correlation	HMQC
Homonuclear correlation spectroscopy	COSY
m-Chloroperoxybenzoic acid	mCPBA
Coupling constant	*J*
Broad	br
Multiplet	m
Singlet	s
Chemical shift (ppm)	δ
doublet	d
Benzyl	Bn or Bzl
Butyl	Bu
Concentration (10mg/ml)	c
Isopopyl	*i*-Pr
Acetyl	Ac
Polyethylene glycol	PEG
1,3-Dicyclohexylcarbodimide	DCC
4-Dimethylaminopyridine	DMAP
Trifluoroacetic acid	TFA

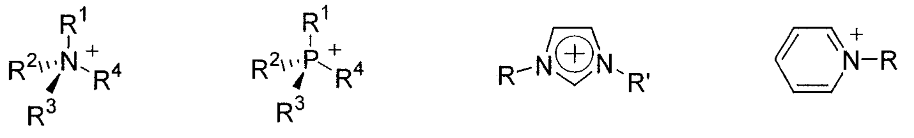
1-Hydroxybenzotriazole	HOBt
O-(benzotriazol-1-yl)-N, N, N’, N’-tetramethyluroniumhexafluorophosphate	HBTU
(Benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate	PyBOP
N, N-diisopropylethylamine	DIPEA
Melting point	M. P.
Calculated	Calcd
Angstrom	Å

Chapter 1. Synthesis and Application of Functionalized (or Task-Specific) Ionic Liquids

1. 1. Introduction

Ionic liquids are generally defined as organic salts that consist of only ions and have melting points of less than 100 °C. This definition provides clear criteria to distinguish ionic liquids from other organic or inorganic molten salts that have higher melting points and multiple compositions. The first example involving ionic liquids was described at the beginning of last century,[1] where, ethylammonium nitrate, which is a liquid at room temperature but usually contains 200-600 ppm water, was synthesized. The history of evolution and development of ionic liquids was well reviewed by Wilkes[2a] and Wasserscheid.[2b] It is worthy to mention here that the contributions from Wilkes' group[3]and Seddon's group[4] are of significant importance for ionic liquids to become more popular to academic community and industry. The most attractive properties of ionic liquids to people as compared to common organic solvents are that they have good thermal and chemical stability, non-flammability, no measurable vapor pressure and, most importantly, their physical and chemical behaviors are able to be tuned by choosing different anions and cations. Thus, people called them environmentally benign solvents or "green solvents" in the early research stage. In the latest years, it has been found that ionic liquids are not totally "green" to the environment[5] and they are not always innocent in some reaction cases[6] and especially they can be distilled under some certain conditions.[7] Therefore, it is better to call ionic liquids as "designer solvents" rather than as "green solvents". However, those blemishes cannot mitigate people's tremendous interests in these lovely solvents. Ionic liquids have been extensively used not only as reaction solvents,[8] catalyst-immobilizing reagents[9] and soluble supports[10] for organic catalysis and synthesis,[11] but also as ion sources to make electronic materials[12] for fuel cells[13] and lithium battery,[14] photoelectrochemical materials[15] for solar cells[16], piezoelectric sensing materials for gas sensors[17], and also as other starting materials for the preparation of ionic liquid-cellulose composites,[18] supported ionic membrane,[19] nanoparticle stabilizing ligands,[20] CO_2 absorbents,[21] and as well as analytical materials[22] for chromatography,[23] mass spectrometry[22] and ion exchange absorbents.[24]

Functionalized ionic liquids, sometimes called as task-specific ionic liquids, have no clear definition in the chemical literature so far. This nomenclature appeared five years ago,[25] which was used to distinguish the ionic liquids with special functional groups or structures for special tasks from the conventional ionic liquids such as tetraalkylammonium salts, tetraalkylphosphonium salts, alkylpyridinium salts and dialkylimidazolium salts (Figure 1). This review will describe recent research advances on the synthesis and applications of functionalized ionic liquids, which mainly include the preparations and applications of chiral ionic liquids, immobilization of ionic liquids on solid supports and related applications, ionic liquid-supported synthesis and ionic liquids-stabilized transition-metal nanoparticles and their applications in organic catalysis.



Ammonium ion Phosphonium ion Imidazolium ion Pyridinium ion

Figure 1. Structures of the cations of four classic ionic liquids.

1. 2. Chiral ionic liquids

Chiral ionic liquids, as a special concept, appeared in the literatures just a few years ago.[26] This is an interesting research extension of the synthesis and application of classic ionic liquids. This research field has started to attract significant attention from scientists due to its potential application to the chiral discrimination in the asymmetric synthesis and optical resolution of racemates. So far, more than one hundred chiral ionic liquids have been prepared in the chemistry labs.[27] Most of them were directly derived from chiral resources or "chiral pool". Some of them have been used as chrial solvents in the enantioselective reactions or as chiral stationary phases in the separation techniques.[28] Since most of ionic liquids consist of an organic cation and an inorganic anion and chemists have paid much more attention on the modification of cations than anions to design new family of ionic liquids, most of the chiral ionic liquids are derived from chrial cations. There are only several papers that have described the preparation of chiral ionic liquid with a chiral anion. The following review on the synthesis of chiral ionic liquids will be categorized according to their characteristic molecular structures.

1. 2. 1. Synthesis of chiral ionic liquids

1. 2. 1. 1. Chiral anion-based ionic liquids

The first example of chiral ionic liquid with a chiral anion was reported by Seddon and coworkers in 1999, in which [bmim][lactate] was prepared by anion exchange between [bmim][Cl] and sodium lactate in acetone.[29] Recently, Ohno and coworkers reported the synthesis and properties of chiral room-temperature ionic liquids that were derived from 20 natural amino acids.[30] Those chiral ionic liquids were prepared by neutralizing imidazolium hydroxide with amino acids to avoid using metal salts that could result in inorganic salt contamination in the final products. Differential scanning calorimetric (DSC) and thermal gravimetric analysis (TGA) showed that those chiral ionic liquids have no melting point, but a glass transition temperature (T_g) ranging from –65 °C to 6 °C (Table 1) and all ionic liquids are stable from room temperature up to 200 °C except [emim][Cys] which decomposes at 173 °C. In addition, those ionic liquids are transparent and miscible with many organic solvents and can dissolve natural amino acids, indicating their potential applications as chiral or biodegradable solvents in special fields.

Table 1. Thermal properties and ionic conductivity (δ) of 20 amino acid-derived ionic liquids.

Chiral Ionic liquids	T_g (°C)	δ (S/cm) at 25 °C	Chiral Ionic liquids	T_g (°C)	δ (S/cm) at 25 °C
[emim][Gly]	-65	5.7×10^{-4}	[emim][Trp]	-31	9.1×10^{-9}
[emim][Ala]	-57	6.4×10^{-4}	[emim][His]	-24	1.0×10^{-7}
[emim][Met]	-57	2.4×10^{-4}	[emim][Tyr]	-23	4.0×10^{-8}
[emim][Val]	-52	8.8×10^{-5}	[emim][Cys]	-19	3.5×10^{-5}
[emim][Ile]	-52	6.9×10^{-5}	[emim][Arg]	-18	9.0×10^{-7}
[emim][Leu]	-51	8.1×10^{-5}	[emim][Asn]	-16	1.1×10^{-6}
[emim][Ser]	-49	6.5×10^{-4}	[emim][Gln]	-12	1.7×10^{-7}
[emim][Lys]	-47	7.8×10^{-5}	[emim][Asp]	5	1.7×10^{-9}
[emim][Thr]	-40	1.0×10^{-4}	[emim][Glu]	6	5.0×10^{-7}
[emim][Phe]	-36	6.0×10^{-5}	[emim][Pro]	-48	1.6×10^{-4}

Other enantiopure compounds such as β-pinene and (*S*)-camphorsulfonate have also been used as anion chiral pool to prepare chiral ionic liquids.[31] Those chiral ionic liquids were prepared in a multigram scale by conventional methods in which anion exchanges between imidazolium chloride and potassium salts of (*S*)-10-camphorsulfonate and (*R*)-1,1'-binaphtyl-2, 2'-diyl phosphate were employed.

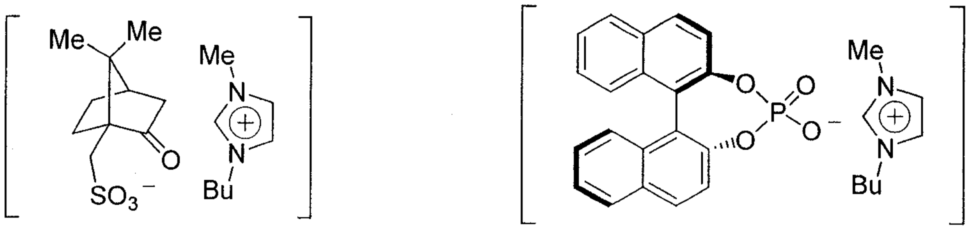
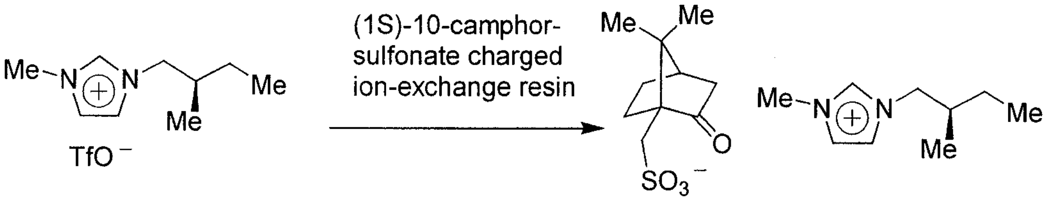


Figure 2. Chiral ionic liquids derived from (*S*)-10-camphorsulfonate and (*R*)-1,1'-binaphtyl-2, 2'-diyl phosphate.

It is worthy to mention that the first "double" chiral ionic liquid that consists of a chiral cation and a chiral anion was prepared through passing the solution of a "single chiral" ionic liquid through (1S)-10-camphorsulfonate-charged ion-exchange resin (Scheme 1).[31]



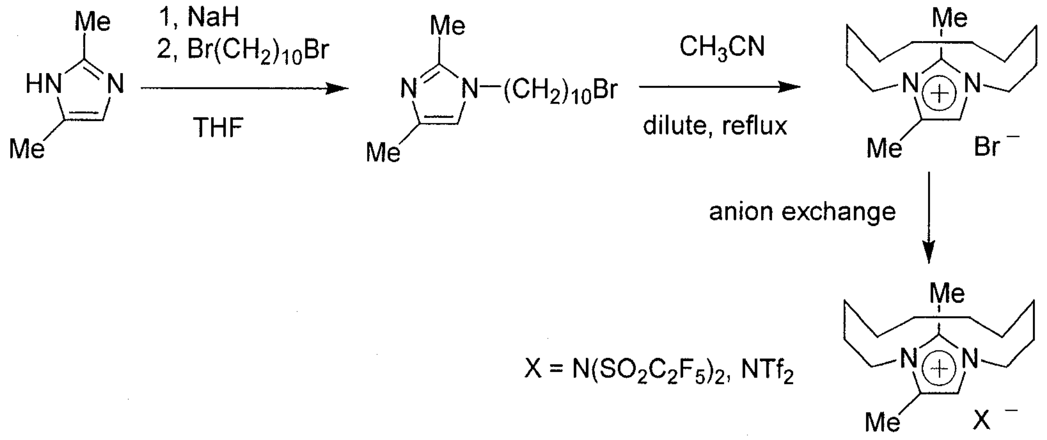
Scheme. 1. Synthesis of "double" chiral ionic liquid.

1. 2. 1. 2. Chiral imidazolium-based ionic liquids

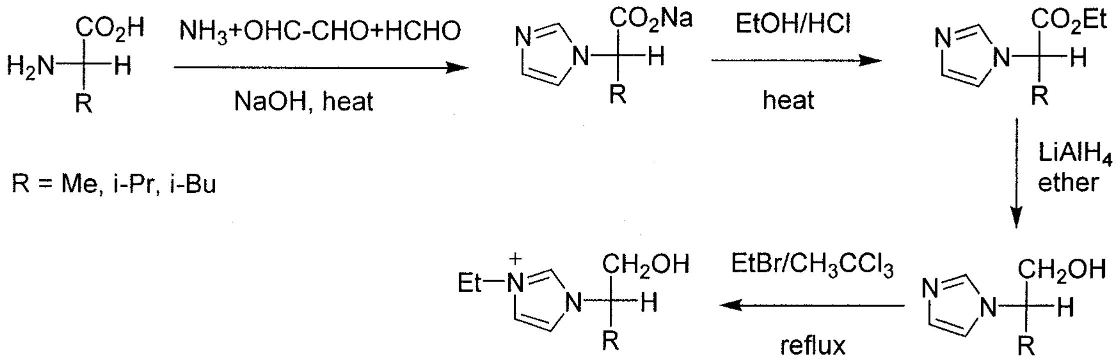
The first ionic liquid with a chiral imidazolium cation was reported by Howarth in 1997.[32] The homochiral N, N-di(2'S-2'-methylbutane)imidazolium bromide was prepared by heating the easily available compound (S)-(+)-1-bromo-2-methylbutane with TMS-imidazolium at refluxing temperature.

The first example of planar chiral ionic liquids, a cyclophane-type imidazolium salt was synthesized by Saigo and coworkers.[33] Treatment of imidazole, 2-methylimidazole or 2,4-dimethylimidazole with NaH and then with 1,10-dibromodecane in THF gave the corresponding 1-(10-bromodecyl)imidazoles, which were then highly diluted in acetonitrile and refluxed for several hours to generate the expected product cyclophane-type imidazolium bromide and undesired oligomer salts due to intermolecular coupling (Scheme 2). The purification of product was done by column chromatography. The obtained product imidazolium bromide can be converted into other type of salts via anion exchange. DSC measurement showed its analogous compounds like imidazolium bis(trifluoromethanesulfonyl)imide and 2-methylimidazolium bis(trifluoromethanesulfonyl)imide have melting points at 86 °C and 98 °C respectively, but the chiral compound 2,4-dimethylimidazolium bis(trifluoromethanesulfonyl)imide has a much lower metling point at 42-45 °C, possibly due to the asymmetric structure of the molecule. The chirality of this type of ionic liquids, which results from ring flipping suppression, was further confirmed by treatment with silver (1*S*)-(+)-10-camphorsulfonate to give clear diastereomeric splitting in NMR spectra. However, since the cyclization was conducted in highly diluted condition, the total yield was low. This procedure is difficult to be done in large scale, which may highly limit its applications.

The similar chiral imidazolium-based ionic liquids, which used tris(oxoethylene) chain instead of decylene chain to limit the flip of imidazolium ring to generate planar chirality, were reported by the same group.[34] XRD patterns and NMR spectra showed no interaction between oxygen lone pair electrons and the imidazolium ring in an intra/intermolecular manner. The diastereomeric interaction of the ionic liquids obtained with enantiopure europium complexes was also investigated, which showed good discrimination on the chirality of europium complexes.



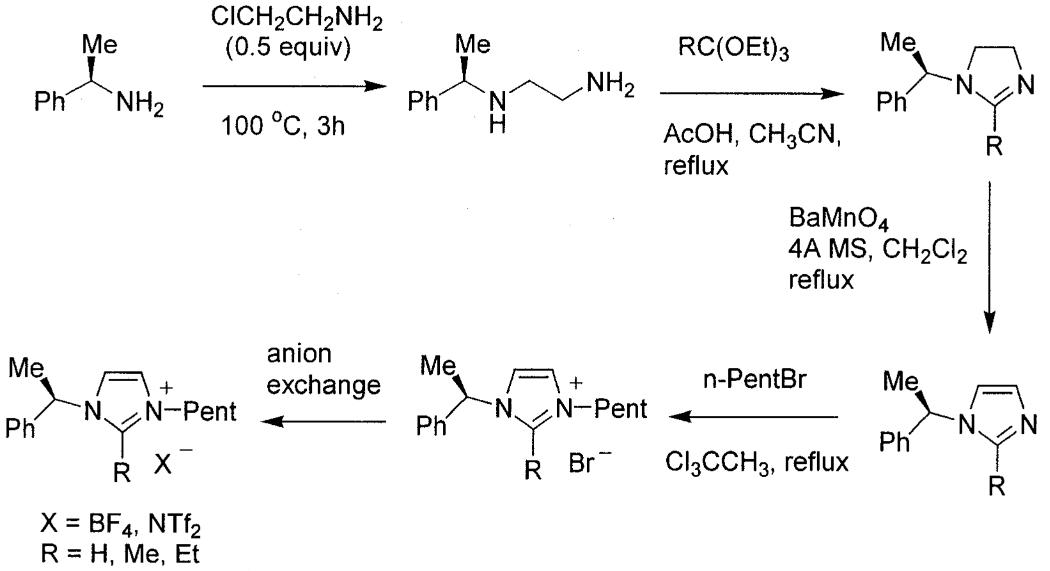
Scheme 2. Synthesis of imidazolium ILs with planar chirality.



Scheme 3. Synthesis of chiral ionic liquids from natural amino acids.

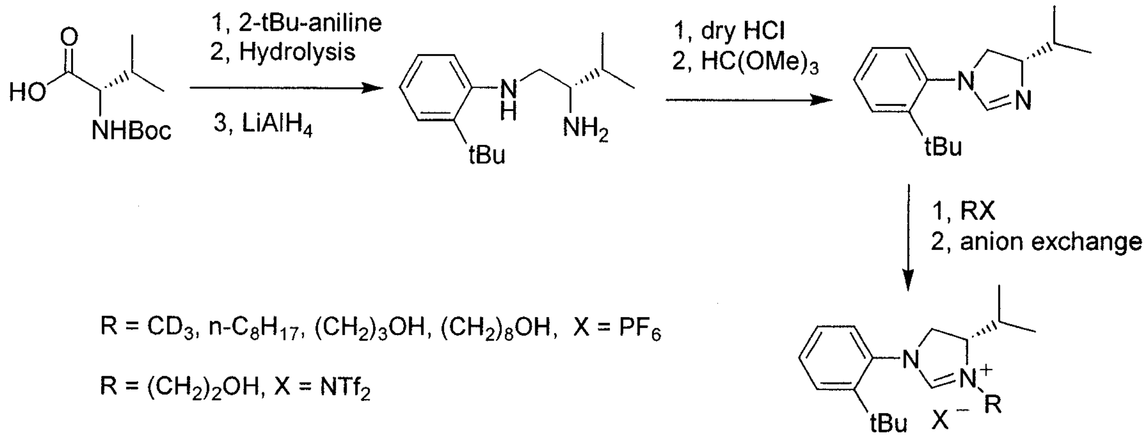
The synthesis of chiral imidazolium ionic liquids from natural amino acids was described by Bao and coworkers as shown in Scheme 3.[35] The imidazolium ring was prepared in one pot, which contained amino acid, formaldehyde, glyoxal, aqueous ammonia, and a certain amount of NaOH to regulate the pH value of the reactant mixtures. This was followed by esterification, reduction and alkylation to generate the final products of chiral imidazolium ionic liquids with a free OH group and one chiral center in 30-33% overall yield. The chiral ionic liquids obtained are miscible with water, methanol, acetone and other strongly polar organic solvents. They are immiscible with ether, 1,1,1-trichloroethane and other weekly polar organic solvent. These chiral ionic liquids are liquids at room temperature with melting points between 5-16 °C and are thermally stable up to 180 °C.

Another approach to construct imidazolium ring in the synthesis of chiral ionic liquids was reported by Génisson and coworkers.[36] 4,5-Dihydroimidazole ring was prepared in good yield via the treatment of 1,2-diamine with orthoester, followed by oxidative aromatization of the heterocyclic core with $BaMnO_4$ in dichloromethane (Scheme 4). This protocol makes C-2 substituted imidazolium chiral ionic liquids available, which have good thermal stability and low melting points. The capability of the imidazolium species to act as reaction medium and/or phase-transfer catalyst in the Michael addition of dimethyl malonate to chalcone was also assessed, 74% yield of the desired product was obtained.

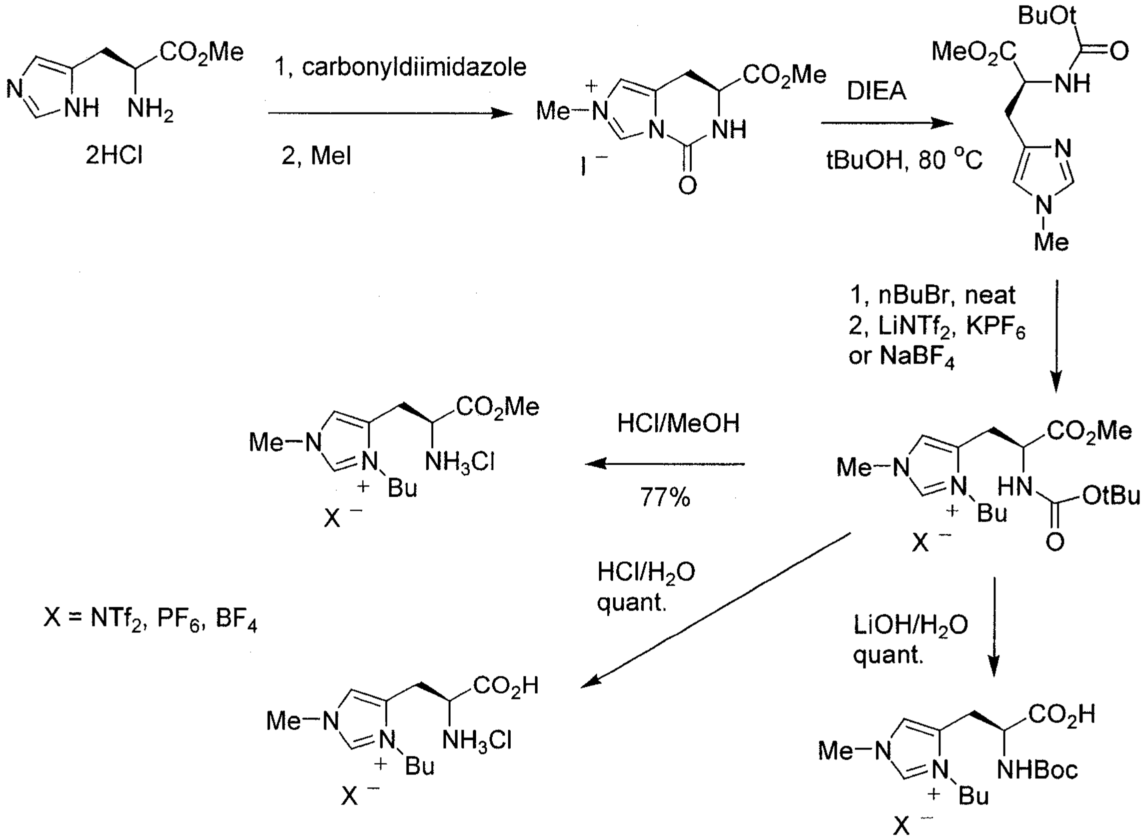


Scheme 4. 2-Alkylimidazolium ILs from (R)-1-phenylethylamine.

A similar protocol to construct imidazolinium ring derived from (S)-valine was reported by Guillemin and coworkers in 2004.[37] This approach makes it possible that the chiral center is located at C-4 of the imidazolinium ring (Scheme 5).



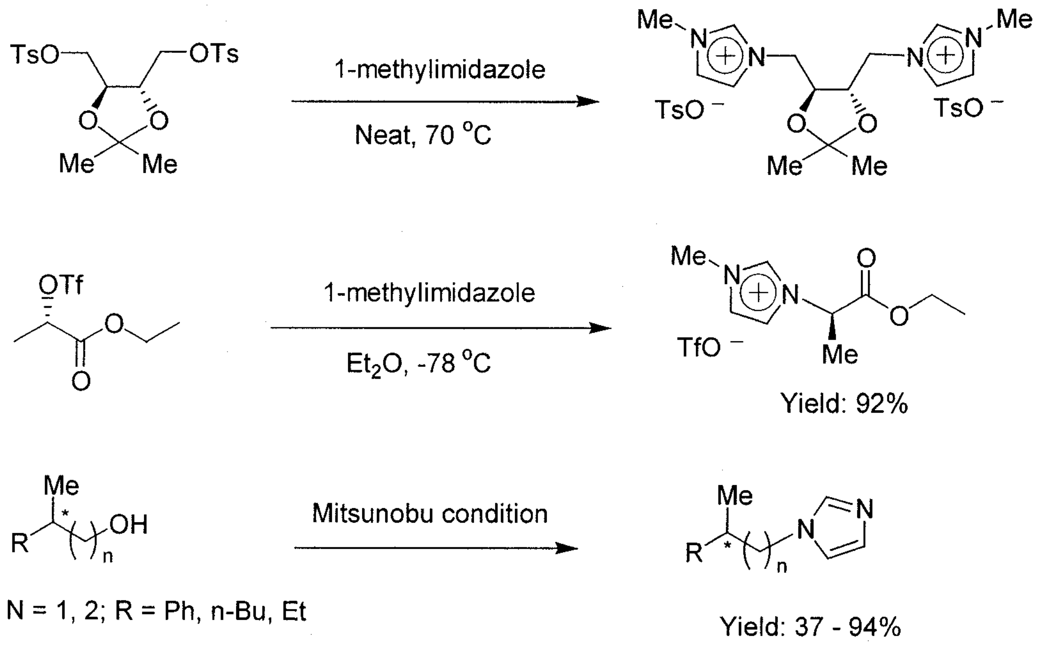
Scheme 5. Imidazolinium ILs prepared from (S)-Valine.



Scheme 6. Synthesis of chiral ILs from histidine.

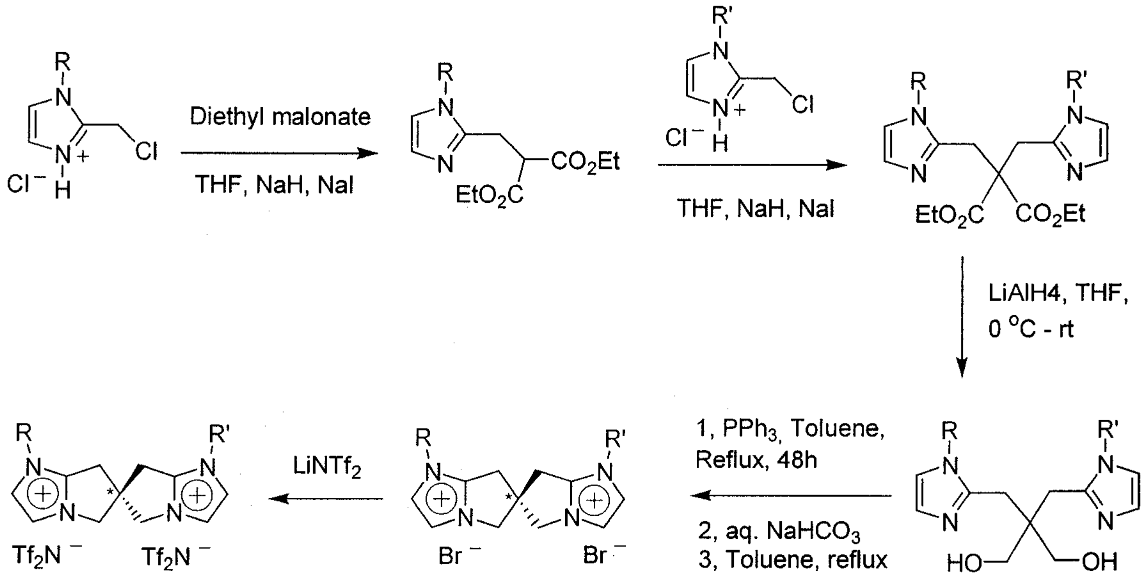
Since the natural amino acid histidine possesses imidazole ring, it is a good precursor for the construction of imidazolium-based chiral ionic liquids in which chiral bifunctional moiety, i.e. acid and primary amine, remains unchanged, which can be used as building blocks for the synthesis of peptidic ionic liquids (Scheme 6).[38]

However, the simplest way to prepare imidazolium-based chiral ionic liquids is one–pot nucleophilic substitution reaction between monoalkylimidazole and chiral reagents using halide,[32] triflate[39] or tosylate[40] as the leaving group. Mitsunobu alkylation is also a straightforward way to connect imidazole with chiral alcohols[41] as shown in Scheme 7.



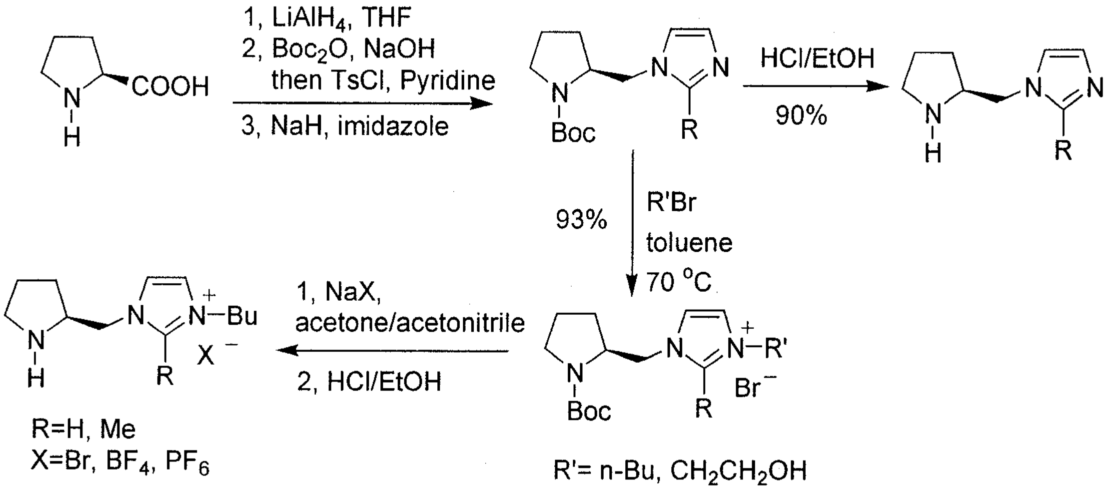
Scheme 7. Synthesis of chiral ILs and precursors by nucleophilic substitution and Mitsunobu reaction.

Sasai and coworkers reported the synthesis of spiro chiral imidazolium salts as shown in Scheme 8.[42] The preparation procedures started from the monoalkylation of diethyl malonate with an N-protonated 1-alkyl-2-chloromethylimidazole to produce an alkylimidazole-grafted diethyl malonate. This was followed by the second alkylation of the malonate ester with a differently alkyl substituted imidazolium salt to yield a disubstituted ester. Reduction of this diester with lithium aluminum hydride (LAH), followed by treatment with PBr_3 and N-alkylation, produced the desired unsymmetrical spiro bis(imidazolium) bromides. The counteranion exchange of these spiro imidazolium bromides gave bis(trifluoromethanesulfonyl)imide derivatives.



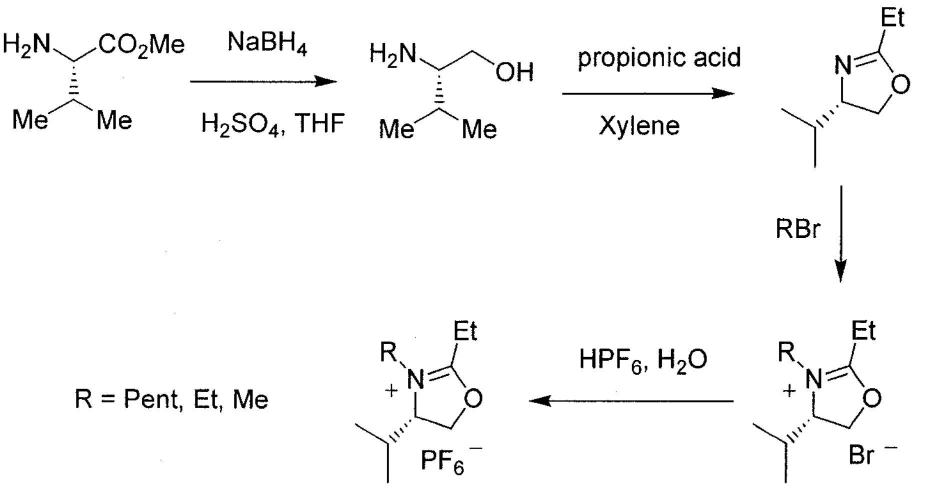
Scheme 8. Synthesis of spiro chiral ILs.

Recently, Luo, Cheng and coworkers have developed a novel asymmetric catalytic system with functionalized chiral ionic liquids.[43] The synthetic procedures are quite straightforward as shown in Scheme 9, starting from the reduction of (L)-proline to generate proline alcohol, followed by functional group protection of amine by Boc group and then tosylation of alcohol. Imidazole was introduced to the molecule by neucleophilic substitution of tosyl group. The fuctionalized chiral ionic liquids were made by further alkylation of the resulting monoalkylimidazole and anion exchange. The total yield of this synthetic route was 45%. All chiral ionic liquids obtained are viscous liquid at room temperature and soluble in moderately polar solvents such as chloroform, dichloromethane and methanol, but insoluble in less polar solvents such as diethyl ether, ethyl acetate and hexane.



Scheme 9. Synthesis of functionalized chiral ionic liquids from (L)-proline.

1. 2. 1. 3. Chiral oxazolinium-based ionic liquids

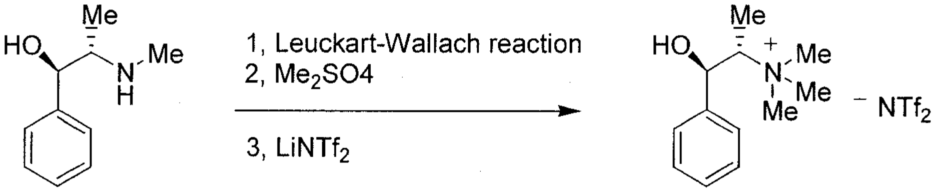


Scheme 10. Oxazolinium chiral ILs from (S)-valine.

The first example of chrial oxazolinium-based ionic liquids was reported by Wasserscheid and coworkers in 2002.[26] Those molecules were prepared in four steps, starting from (S)-valine methyl ester (Scheme 10). After reduction with $NaBH_4$-H_2SO_4 in THF,[44] the product (S)-valinol reacted with aliphatic acid to generated oxazoline[45] followed by alkylation with alkyl bromide and anion exchange. The enantiopurity of the final product was confirmed by ^{19}F-NMR spectroscopy after hydrolysis and reaction with (S)-Mosher's acid chloride. However, oxazolinium cations were found to be unstable under acidic condition in which ring-opening reaction could occur.

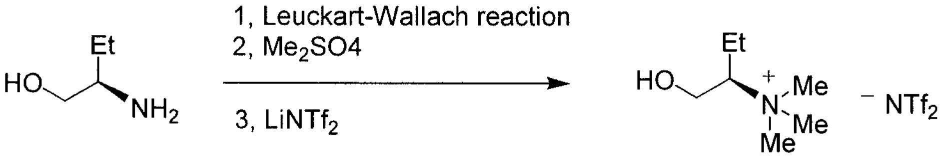
1. 2. 1. 4. Chiral quaternary ammonium-based ionic liquids

Chiral ionic liquid with an ephedrinium cation was prepared from the alkaloid ephedrine in three steps including a Leuckart-Wallach reaction, alkylation with Me_2SO_4 and anion exchange (Scheme 11).[26] This compound is stable up to 150 °C under high vacuum conditions (10^{-3} mbar) and has a melting point of 54 °C. This family of compounds can also be prepared from enantiopure ephedrine in one step under the conditions of solvent-free and microwave activation.[46]



Scheme 11. Synthesis of chiral ILs from ephedrine.

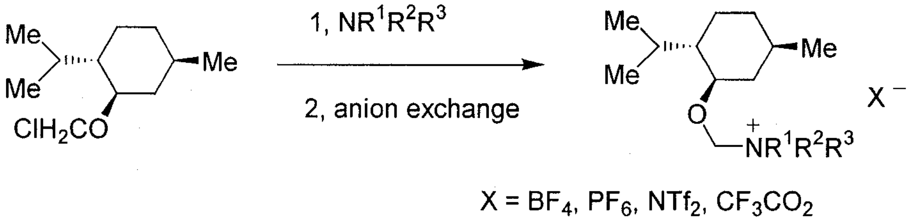
The same methodology was used to prepare other type of chiral ionic liquids with quaternary ammonium cation (Scheme 12).[26] This compound is a liquid at room temperature. It has a low temperature of melting point at –18 °C, and very low viscosity of 0.155 Pa at 20 °C. It also shows a good thermal stability up to 150 °C under high vacuum conditions (10^{-3} mbar).



Scheme 12. Synthesis of chiral IL from chiral amine.

Kou and coworkers reported a simple method to prepare chiral ionic liquids through one-step acidification of amino acids and amino acid esters.[47] Most of the ionic liquids obtained have melting points lower than 100 °C. But this type of ionic liquids cannot be used under basic conditions because they are just some protonated ammonium salts which can be easily deprononated under basic conditions.

Chiral ammonium-based ionic liquids containing the 1R,2S,5R-(-)-menthyl group can be easily and efficiently prepared via Menschutkin reaction with various tertiary amines under ambient conditions (Scheme 13).[48] The compounds are air and moisture stable and some of them are in liquid state at room temperature. They also showed strong antimicrobial and high antielectrostatic activities.



Scheme 13. Synthesis of chiral ILs from (1R, 2S, 5R)-(-)-menthol.

Other quaternary ammonium-based chiral ionic liquids from terpene[49] or (S)-nicotine[50] have also been reported or patented, respectively. (Figure 3)

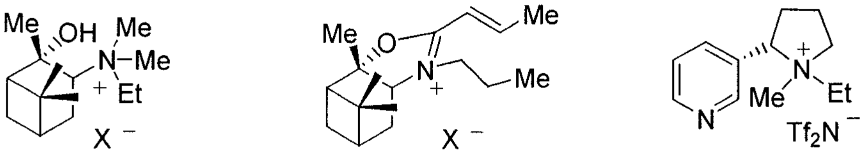
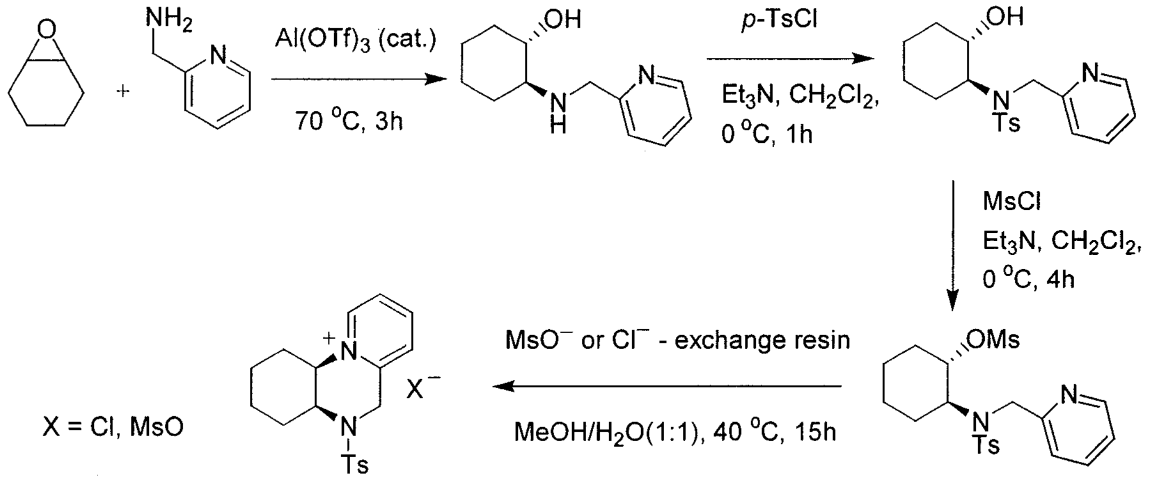


Figure 3. Chiral ILs from terpene and nicotine.

1. 2. 1. 5. Chiral pyridinium-based ionic liquids

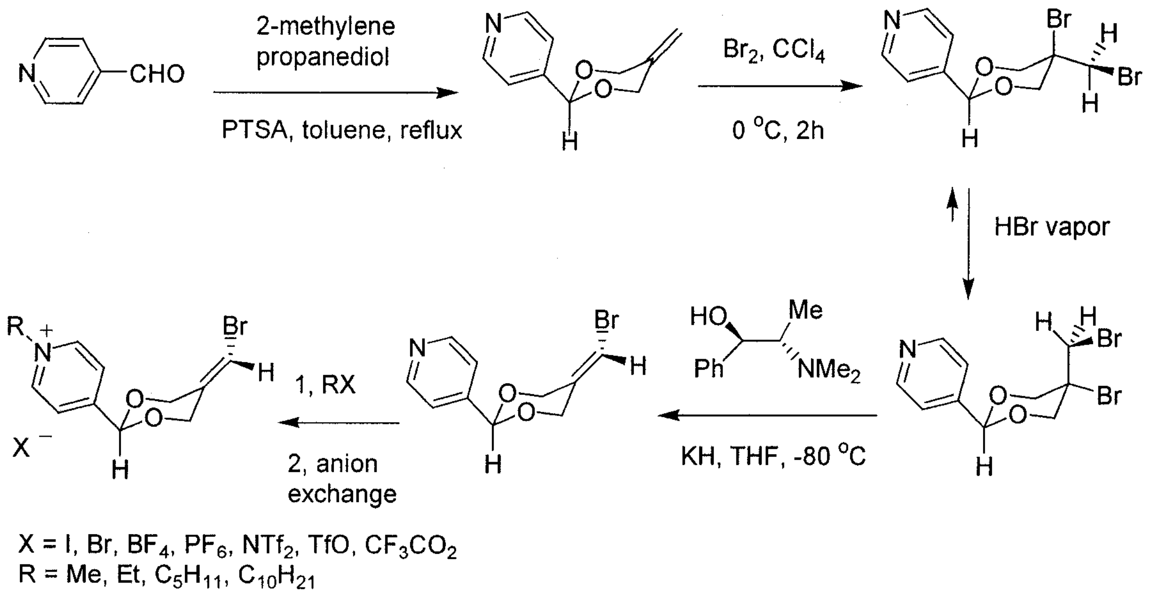
Normally, chiral pyridinium-based ionic liquids can be prepared through the reaction between pyridine and appropriate chiral reagents such as chiral halides,[51] or reaction between chiral primary amines and pyridines derivative such as Zincke's salt.[52]

In 2004, Pizzo, Vaccaro and coworkers reported the synthesis of a new family of chiral multicyclic pyridinium-based ionic liquids using epoxides as starting material as shown in Scheme 14.[53] The final compound *cis*-5-[(4'-methylphenyl)sulfonyl]-1,2,3,4,4a,5,6,11a-octahydropyrido [1,2-a]quinoxalin-11-ium methanesulfonate and its chloride derivative were synthesized through aminolysis of cyclohexane oxide with 2-picolylamine under the catalysis of $Al(OTf)_3$ and methanesulfonation of resulting compound in dichloromethane, followed by intramolecular cyclization of the resulting 2-[(pyridin-2'-yl)methylamino]cyclohexanol. The cyclization went smoothly by treating the precursor with MsO^- or Cl^--exchange resin at 40 °C in the mixed solvent of methanol and water. But it works slowly under normal heating condition.



Scheme 14. Pyridinium ILs from an epoxide.

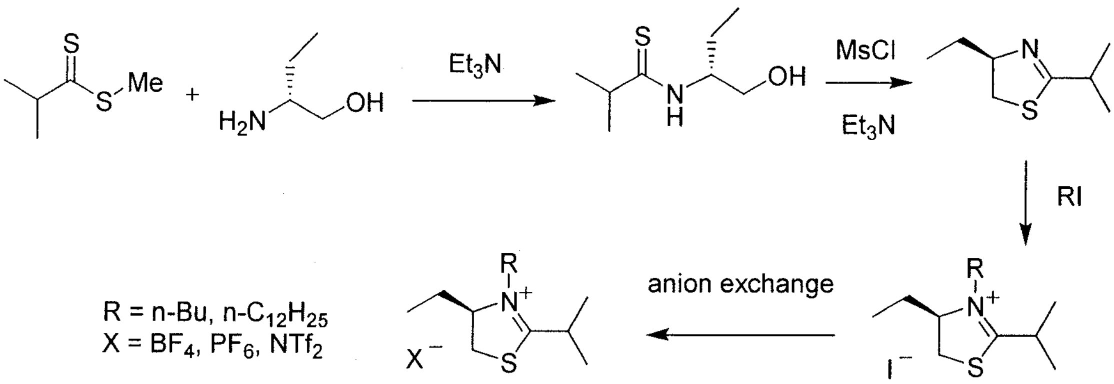
Pyridinium-based chiral ionic liquids with axial chirality were described by Judeinstein, Plaquevent and coworkers.[54] The preparation started from the acetalization of pyridine-4-carboxaldehyde, followed by stereospecific bromination to yield exclusively the 1,4-cis bromide. Treatment of the resulting compound with HBr vapor isomerized it to the trans-stereoisomer. After dehydrobromination with an excess of potassium chiral alkoxide derived from N-methylephedine and KH and purification by recrystallization, optically pure compound with vinylic bromide substituent was obtained. This compound was used as a precursor to make a new family of ionic liquids via alkylation with alkyl halides, which might be further modified with other substituents. It is worthy to mention that most of the compounds are liquids at room temperature and some of them are liquid crystals (Scheme 15).



Scheme 15. Synthesis of pyridinium ILs with axial chirality.

1. 2. 1. 6. Chiral thiazolinium-based ionic liquids

The first example of the synthesis of chiral ionic liquids with thiazolinium cations was reported by Gaumont and coworkers.[55] Those compounds were prepared in three steps starting from enantiopure amino alcohols. The commercially available (*R*)-2-aminobutanol reacted with dithioester in basic condition to generate a thioamide, which was then treated with mesyl chloride and triethyl amine in CH_2Cl_2 to give the chiral thiazoline. Alkylation of the thiazoline resulted in thiazolinium halides that underwent anion exchange to afford a series of chiral ionic liquids, which can be used as chiral recognition reagents or chiral solvents (Scheme 16).

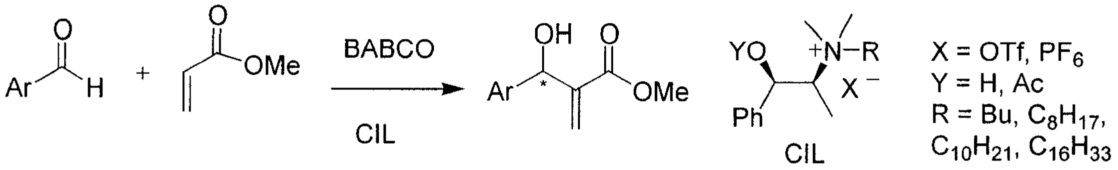


Scheme 16. Synthesis of chiral thiazolinium-based ILs.

The 1-butyl thiazolinium hexafluorophosphate, tetrafluoroborate and bis(trifluoromethanesulfonyl)imide in the Scheme 16 were soluble in dichloromethane, chloroform, acetonitrile and strongly polar solvents such as water, slightly soluble in ether, toluene and other weakly polar solvents. All of the thiazolinium salts showed good chemical stability under aqueous, basic and acidic conditions. This is in contrast to oxazolinium derivatives that are unstable under an acidic condition.[26] Thiazolinium salts also exhibited good thermal stability up to at least 170 °C as shown by TGA measurements. The effect of thiazolinium counterions on melting points of salts was examined by DSC, which showed thiazolinium salts having iodide, hexafluorophosphate or tetrafluoroborate as counterion displayed high melting points of 137, 136 and 111 °C, respectively. But bis(trifluoromethanesulfonyl) imide derivative is a liquid at room temperature with glass transition temperature at –68 °C. However, the melting points of those salts can be tuned by using long chain alkyl such as dodecyl instead of n-butyl to reduce them to less than 50 °C.

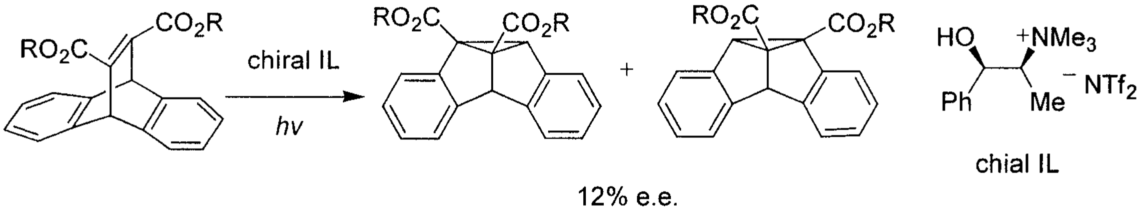
1. 2. 2. Application of chiral ionic liquids

The application of chrial ionic liquids is still in the infancy. They have been used as special regents in the chiral molecular recognition[34] and NMR shift investigation.[37, 26] In 1997, Howarth reported the use of chiral ionic liquid, N, N-di(2'S-2'-metthylbutane)imidazolium bromide, as a catalyst in asymmetric Diels-Alder reaction, no enantioselective excess (less than 5% e.e.) was observed by chiral GC.[32] The first attempt to use chiral ionic liquids as solvents to induce stereoselectivity in the reaction was reported by Seddon and coworkers, where [bmim][lactate] was used as solvent in Diels-Alder reaction, but no enantioselectivity was observed neither in the reactions.[29] The first successful example of the use of chiral ionic liquids as reaction media in asymmetric Baylis-Hillman reaction was described by Vo-Thanh and coworkers,[56] where good yields (30%-78%) and moderate enantiomeric excesses (20%-44%) were obtained (Scheme 17). The transfer of chirality of ephedrinium-based chiral solvents in the asymmetric transformation was demonstrated in several aspects. Firstly, the excess of chiral ionic liquids led to a noticeable enhancement in enantioselectivity. Secondly, the chiral ionic liquids with different alkyl chain length had no effect on the enantioselectivity. Finally, when (-)-N-methylephedrine was used as chiral catalyst for this study, a poor e.e. (only 9%) was obtained in the similar reaction condition. In addition, the chiral ionic liquids could be recovered and reused without loss of efficiency.



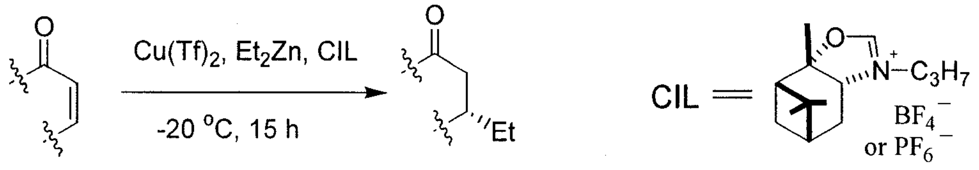
Scheme 17. Asymmetric Baylis–Hillman reaction in the presence of chiral ILs as reaction medium.

Armstrong and coworkers reported the use of chiral ionic liquids for the induction of optical activity in the photoisomerization of dibenzobicyclo[2,2,2]octatrienes.[57] Four chiral ionic liquids were investigated as chiral sources to induce the chirality in the reactions. The enantioselective induction in the products was not observed for the diester starting materials but was observed for the diacid starting molecules (Scheme 18) because the diacid can form ion pairs with the chiral ionic liquids. The control experiments, which were carried out in common organic solvents and resulted in no enantioselectivity, confirmed the chirality transfer from the chiral solvents. Even though the reactions gave low enantioselectivity, the importance of this example is that the chiral induction is kinetically driven in a reaction with low activation barrier due to photochemical nature as compared to above-mentioned asymmetric Baylis–Hillman reaction.



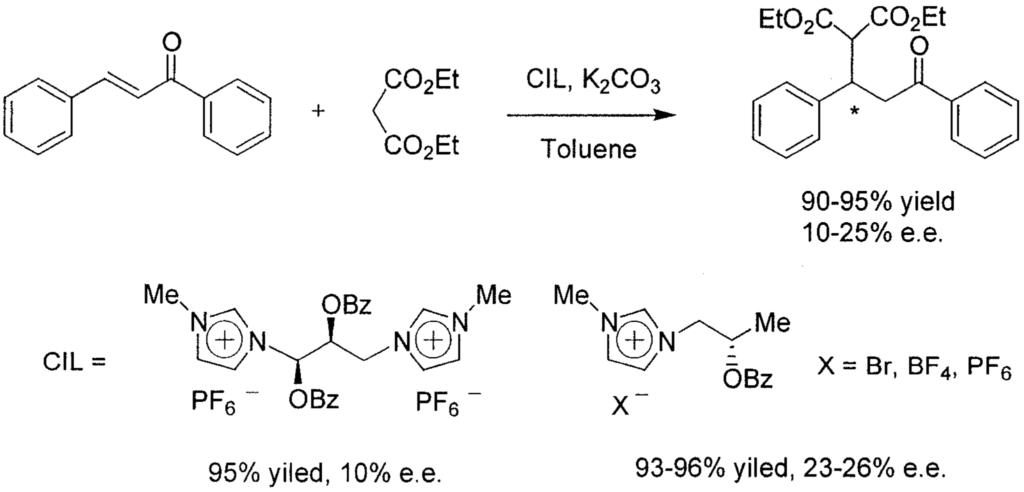
Scheme 18. Photoisomerization of dibenzobicyclo[2,2,2]octatrienes in chiral ionic liquids.

The application of chiral ionic liquids as a co-solvent in copper (II) triflate-catalyzed enantioselective 1,4-addition of diethylzinc to enones was reported by Malhotra and coworker (Scheme 19).[58] It was found that the molar concentration of chiral ionic liquids had a significant effect on the enantioselctivity of the reactions. For example, when the amount of chiral ionic liquid was increased from 3% to 35%, the e.e. of product was increased from 17% to 76%. The results obtained was better than the earlier reports in which conjugate addition to chalcone in an ionic liquid using a chiral phase transfer reagent as a catalyst.[59]



Scheme 19. Copper-catalyzed 1,4-addition of diethylzinc to enone in chiral ionic liquids.

Bao and coworkers reported the application of chiral ionic liquids as main solvents for the enantioselective Michael addition of diethyl malonate to 1,3-diphenyl-prop-2-en-1-one.[60] Good yield (90-96%) and moderate enantioselective excess (10-24%) were obtained. This report added one more example to the chirality induction from chiral ionic liquid molecules to asymmetric reactions (Scheme 20).



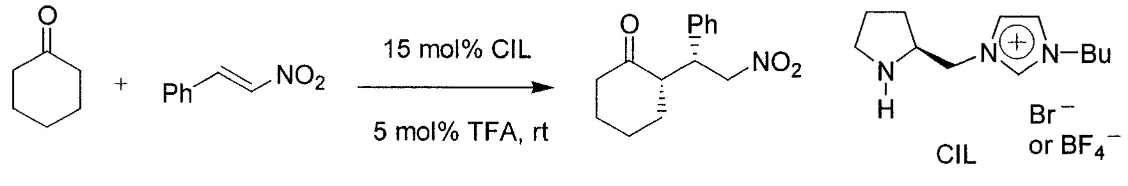
90-95% yield
10-25% e.e.

95% yiled, 10% e.e.

93-96% yiled, 23-26% e.e.

Scheme 20. Enantioselective Michael addition in chiral ionic liquids.

An elegant example on asymmetric Michael addition to nitroolefins catalyzed by functionalized chiral ionic liquids was described by Luo, Cheng and coworkers and is shown in Scheme 21.[61] The synthetic route of the chiral ionic liquids has been showed previously in Scheme 9. This family of catalysts are comprised of a chiral pyrrolidine moiety and an imidazolium unit. The pyrrolidine part is expected to serve as catalytic site, while the imidazolium part acts as a phase tag and a chiral induction group. It was found that the catalytic and enantioselective activities of these catalysts varied significantly with the ionic liquid moiety, such as compounds with imidazolium unit showed higher asymmetric activity than their 2-methyl counterparts. And the imidazolium ring with ethanol chains provided less catalytic activity and enantioselectivity. The anion of the ionic liquid part also influences the catalyst's properties. Bromide and tetrafluoroboronate gave catalysts with slightly enhanced activity than hexafluorophosphate counterpart and the exchange of Br^- for PF_6^- have a detrimental effect on catalytic activity and enantioselectivity. However, most of the cases gave excellent yield (more than 90%) and stereoselectivity (more than 95% ratio of *syn* to *anti*, 70-99% e.e.). The cocatalyst, 5% TFA, was found to be necessary for the catalyst system to have high activity. Moreover, these functionalized ionic liquids can be easily recovered and recycled to be reused in the next run, which still gave excellent yield and acceptable stereoselectivity in the reactions.



Scheme 21. Chiral ionic liquid catalyzed asymmetric Michael addition.

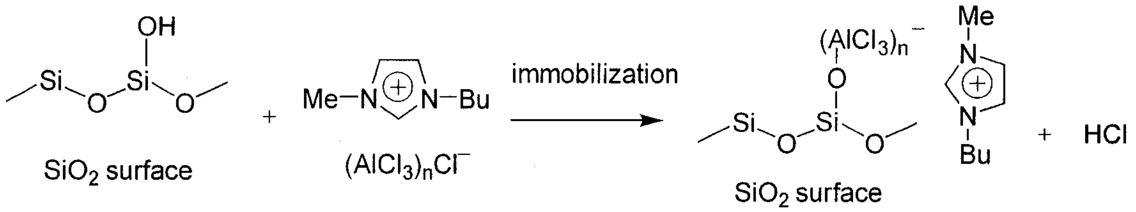
In addition to the above-mentioned, chiral ionic liquids have also used as chiral solvents in the stereoselective polymerization[62] and used as stationary phase for the resolution of organic compounds in gas chromatography.[63] The details on those cases are beyond this review.

In summary, the use of chiral ionic liquids as a stereoselectivity inducer is becoming an important strategy in asymmetric organic reactions, especially their being used as chiral catalysts. The successful applications have received growing attention recently due to those molecules possess some wonderful properties such as tunable physical and chemical properties, easy recovery and recycle. However, the high cost of chiral compounds may limit the extensive use of chiral ionic liquids as solvents in large-scale reactions.

1. 3. Immobilization of ionic liquids on solid phase

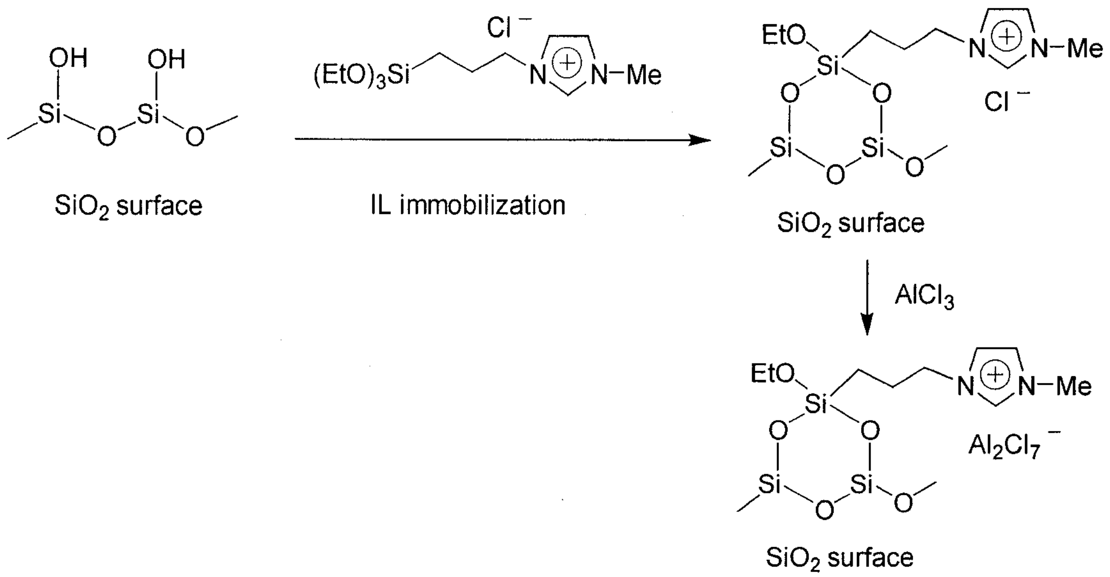
Although the first example of using ionic liquid as solvent for catalytic reactions can date back to more than 30 years ago,[64] this area has experienced a dramatic growth only in the last decade mainly due to the fact that ionic liquids can be used as metal complex catalyst-immobilizing solvents in organic catalysis.[9] For such catalytic system, one approach is to conduct the reaction in one single phase, and the workup through a two-phase separation. For illustration, both the catalyst and the reactants are dissolved in the ionic liquid. The reaction is conducted under normal conditions. When the reaction is completed, organic solvents are added to the reaction mixture to extract the products, while catalysts still stay in the ionic liquid phase for the next run. The other approach is to conduct the reaction in a two-phase system followed by a workup through a two-phase separation. In this approach, organic phase with reactants is added to the ionic liquid phase with catalysts. The reaction then proceeds on the interface of the two phases, when the reaction is completed, the organic phase with the products can be separated from the ionic liquid phase by simple decantation and the catalysts are still remaining in the ionic liquid phase, which can be recovered and reused for the next run. This strategy is also called as liquid-liquid biphasic catalysis. Since the chemical and physical properties of ionic liquids can be designed by choosing appropriate cations or anions, a large number of experiments have been done to reach the ideal condition of liquid-liquid biphasic catalyst systems[2b, 8, 65] involving ionic liquids, in which the active species of catalysts are well soluble, while substrates and products are partially miscible with it. Also catalyst leaching has to be prevented in the phase separation of the workup procedures, especially when expensive noble transition metal complex are used as catalysts in the system. The implementation of these strategies in industrial processes is hampered by the fact that the biphasic methodologies rely on relatively large amount of ionic liquids that are more expensive than traditional solvents. In many cases, the reaction occurs mainly on the interface or in the diffusion layer of ionic liquid catalyst phase rather than in the bulk solvent because the relative high viscosity of ionic liquids slows down mass transfer and the concentration of the reactants in the bulk ionic liquid is reduced significantly. An alternative to this approach is to modify a solid phase surface such as silica gel with ionic liquids, which can change the polarity of solid phase surface.[66] The modified solid phase can be used as compatible support in the heterogeneous catalyst system or directly used as reagents in the reactions. This idea is motivated by the advantages of easy phase separation and the ability to use fixed bed reactors, which are preferred in industry.

In the early examples of supported ionic liquid catalysts, Lewis acidic ionic liquids were anchored onto solid phase. The most popular one was aluminum chloride-derived ionic liquids, which were largely used for Friedel-Crafts reactions (Scheme 22).[67]

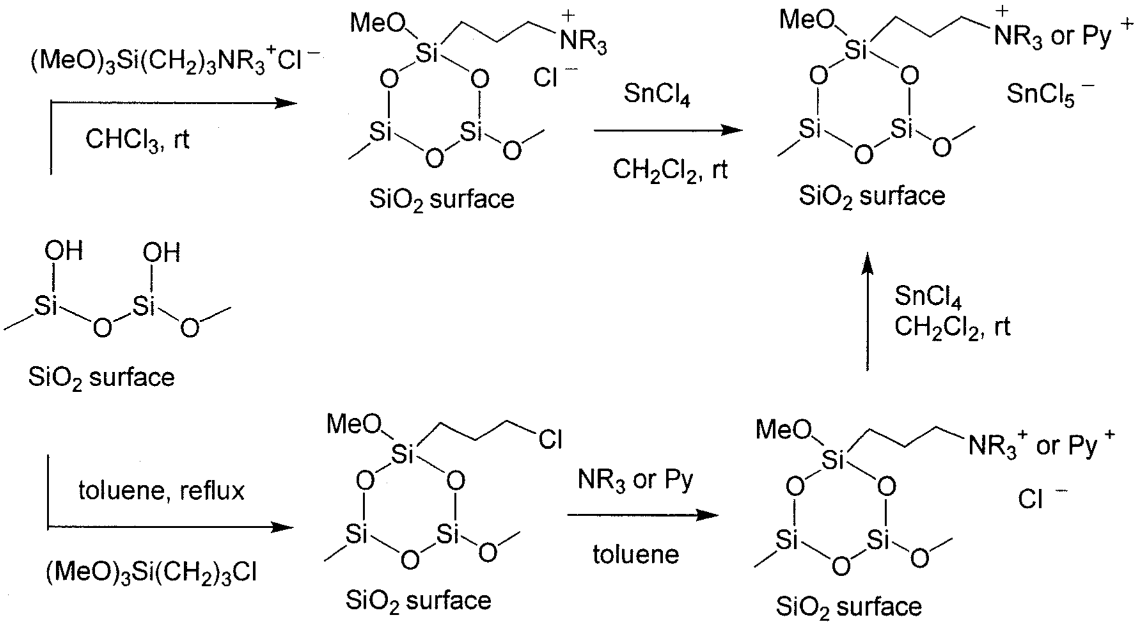


Scheme 22. Immobilization of chloroaluminate-based ionic liquid via impregnation.

The active species of chloroaluminate anions, which react with the hydroxyl groups on the surface of silica gel, are covalently anchored onto its surface. The formation of covalent bond between aluminum atom and OH group was confirmed by detailed material surface science analysis and extensive comparison studies of aluminum chloride bound on silica gel.[68] However, the problem of this approach was the generation of HCl during the reaction processes, which could crack the surface of the pores of inorganic solid materials. The decrease of pore surface area can negatively influence loading level and catalytic ability of active species. To circumvent the formation of hydrochloric acid, an alternative immobilization route was reported by Valkenberg and coworkers.[69] In this approach, the aluminate anions were formed as counterions in the second step after the imidazolium cations had been connected to silica gel surface via condensation between triethoxysilane of ionic liquid and the OH groups on the surface of silica gel (Scheme 23).

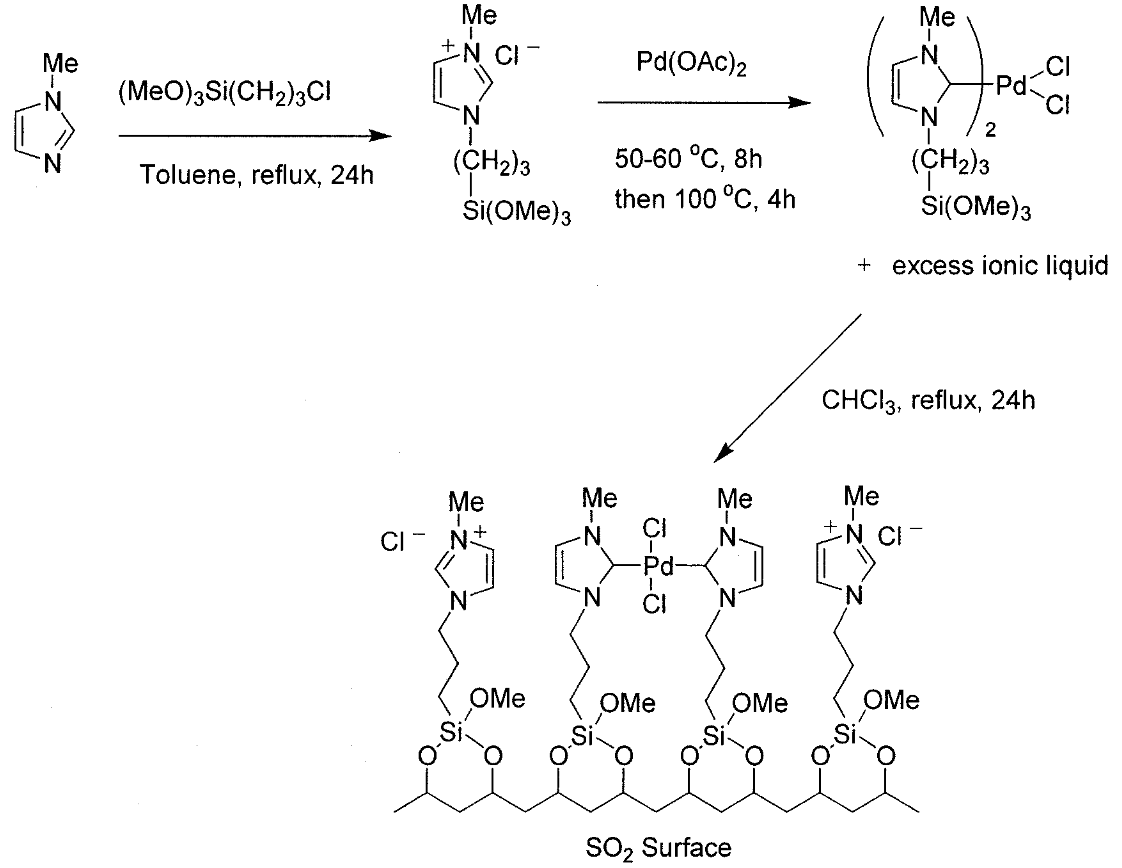


Scheme 23. Immobilization of chloroaluminate-based ionic liquid by grafting imidazolium chloride to silica surface and then treatment with $AlCl_3$.



Scheme 24. Immobilization of Lewis acid $SnCl_4$ on silica gel via functionalized ionic liquid linkers.

Another related example was reported by Landau and coworkers in 2001,[70] which demonstrated a tin Lewis acid catalyst anchored on silica gel via grafting it with quaternary alkylammonium chloride (Scheme 24). The active species was [NR_4^+] [$SnCl_5^-$], which is connected to silica gel via methoxysilane linker. This catalyst showed high selectivity in the synthesis of 3-methyl-3-butene-1-ol by Prins condensation of isobutene and formaldehyde.



Scheme 25. Immobilization of N-heterocyclic carbene palladium complex/ionic liquid matrix on silica.

Recently, Karimi and Enders reported the simultaneous covalent immobilization of methylimidazolium-derived carbene palladium complex and ionic liquid matrix on silica surface as shown in Scheme 25.[71] The treatment of $Pd(OAc)_2$ with excess ionic liquids resulted in a clear, pale green-yellow solution, which then reacted with silica gel in dry chloroform under refluxing condition to give the immobilized catalyst system. This heterogeneous catalyst system was effectively applied to Heck coupling reaction between a wide variety of iodo-and bromoarenes and acrylates in the solvent of N-methylpyrolidinone (NMP) with good yields obtained. Also, the supported catalyst system can be easily recovered and reused for four times with an average of 91.5% product yield even if the catalyst loading level was very low, just 0.01mol %. Further transmission electron microscopy (TEM) and energy-dispersion X-ray (EDX) analysis showed the formation of Pd nanoparticles within the immobilized ionic liquid layer during cross coupling reaction procedures, consistent with the observation addressed by Dupont and coworkers.[72]

In 2002, Mehnert and coworkers reported a different concept to immobilize a homogeneous catalyst system, which was used for the hydroformylation reaction[73] and hydrogenation reaction.[74] The silica gel surface, modified by imidazolium ionic liquid, provided a solid support for additional free ionic liquids and catalysts. This modified silica surface is supposed to have a better affinity for ionic liquids than unmodified one. The free ionic liquid layer served as reaction phase in which the homogeneous catalyst was dissolved as shown in Figure 4. The analysis of surface coverage revealed an average of 0.4 ionic liquid fragments per nm^2, which corresponds to approximately 17% of all the hydroxyl groups based on a hydroxyl content of 2.4 per nm^2 for the pretreated silica gel. The studies on the model transformation of 1-hexene and syngas (CO/H_2 ratio of 1:1) to n, i-heptanal revealed that modified silica supported system gave a slightly higher activity (TOF = 65 min^{-1}) with comparable selectivity than the common biphasic ionic liquid system (TOF = 23 min^{-1}), but much lower than the conventional homogeneous catalyst in toluene (TOF = 400 min^{-1}). Those results may be due to the higher concentration of active rhodium species in the reaction phase of supported ionic liquid system and larger interface area of the silica support as compared to biphasic ionic liquid system.

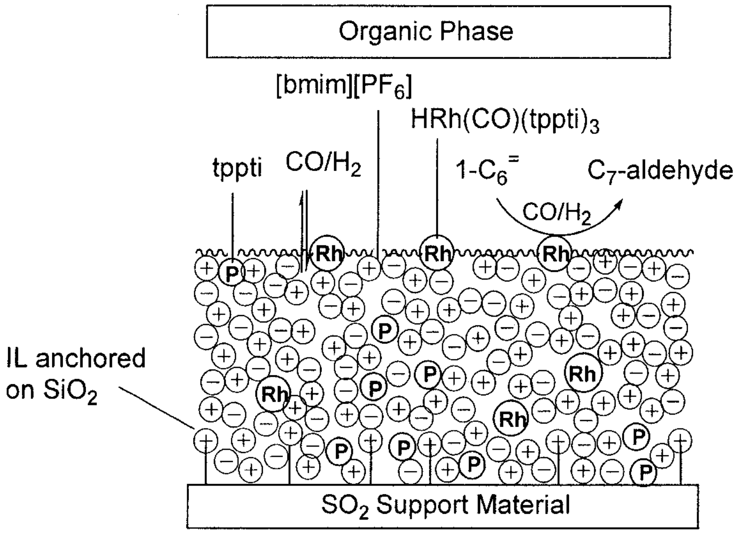
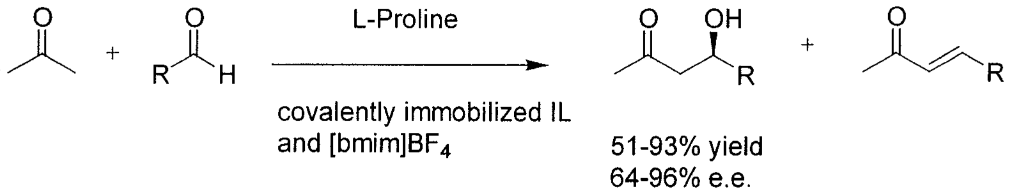


Figure 4. Concept demonstration of supported ionic liquid catalysis used in the hydroformylation reaction of hexene-1 to form n, *i*-heptanal.

However, more interesting results were obtained when this concept was used in the hydrogenation reaction, where alkene was transformed into alkane via using $[Rh(NBD)(PPh_3)_2]PF_6$ (NBD = norbornadiene) as catalyst. Enhanced activity for the supported ionic liquid system was observed as compared to both the homogeneous and the biphasic reaction system. The homogeneous case, where acetone was used as the solvent, showed that the initial rate constant K_h for the appearance of hydrogenation product was 0.4 min^{-1} at a reaction temperature of 50 °C, while the supported ionic liquid case gave a K_h of 11.2 min^{-1} at a reaction temperature of 30 °C. The biphasic ionic liquid system afforded a TOF of 4 min^{-1}, which is much lower than the supported ionic liquid system, giving a TOF of 447 min^{-1}. The enhanced activity can also be attributed to the increasing concentration of active species in the reaction phase of supported ionic liquid system.

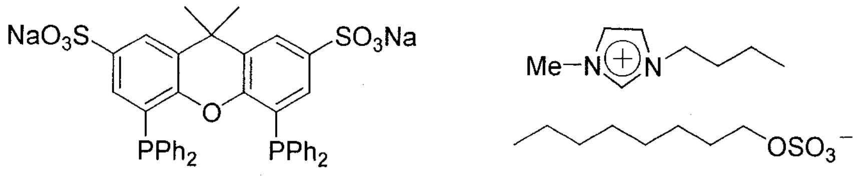
The same concept of supported ionic liquid reaction system was also used to L-proline involved asymmetric aldol reaction by Gruttadauria and coworkers as shown in Scheme 26.[75] The experimental results showed that the supported ionic liquid system gave good yield (51%) and enantioselectivity (64% e.e.) as compared with the homogeneous condition (L-proline in DMSO), which gave 62% yield and 60% e.e., and biphasic condition (L-proline in ionic liquid without modified SiO_2 support), which gave 55% yield and 76% e.e.. However, the simple mixture of unmodified silica gel, ionic liquid and proline gave obvious decrease in yield (38%) and enantioselectivity (12% e.e.). Further experiments showed that the ionic liquid-modified SiO_2/free ionic liquid/proline system could be recovered and recycled for three times without obvious decrease of yields and enantioselectivity of products.



R = Ph, *p*-$NO_2C_6H_4$, *p*-BrC_6H_4, *p*-$MeOC_6H_4$, *i*-Pr

Scheme 26. Supported ionic liquid asymmetric catalysis.

In the meantime, Riisager, Wasserscheid and coworkers reported a different heterogenized system of supported ionic liquid-phase catalysis. The catalytic phase was composed of a transition-metal complex that had been dissolved in a thin layer of the ionic liquid phase [bmim][n-$C_8H_{17}OSO_3$] (Figure 5), which was further held on a porous solid support such as silica gel with high surface area by physical adsorption, tethering or covalent anchoring.[76] This strategy was used in the continuous-flow fixed-bed hydroformylation of propene. The silica gel needed pre-treatment through heating at 500 °C in air for 15 hours to dehydroxylate SiO_2 surface because it negatively influenced the catalyst's activity and lifetime. Also, a large excess of phosphine ligand sulfoxantphos (Figure 5) was necessary for the catalytic system to have high activity, selectivity and stability. For example, when the ratio of ligand and rhodium was 10, the initial catalytic performance of catalyst could be kept at least 60 hours (TOF = 44 h^{-1}, TON = 2600, and n/iso-product > 20); when the ratio of ligand and rhodium was 3 or 5, the catalyst was deactivated relatively quickly in 24 hours. The turnover frequency (TOF) dropped to 4-5 h^{-1} and the selectivity of n/iso product fell to 1-1.3. This is due to the fact that the ligand can react with the support, most possibly with the hydroxyl group on the surface of silica gel, which results in the degradation of catalyst complex system. It was also found that a certain amount of ionic liquid solvent was necessary for the catalyst to keep high selectivity and stability during continuous processes because the ionic liquid could prevent phosphine ligand from fast surface-bonding to the support surface so that a homogeneous catalysis could occur in the supported ionic liquid layer.

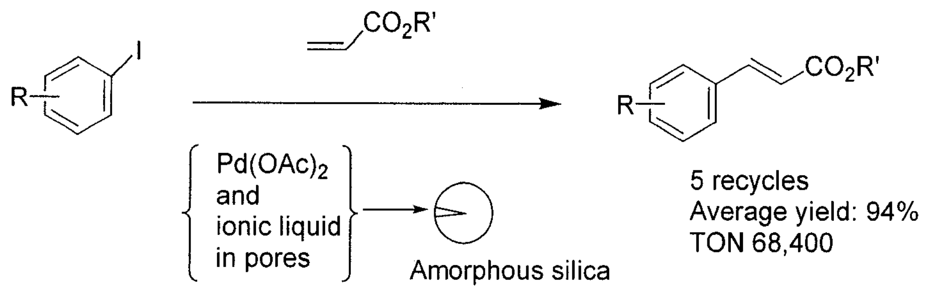


Sulfoxantphos

[bmim][n-$C_8H_{17}OSO_3$]

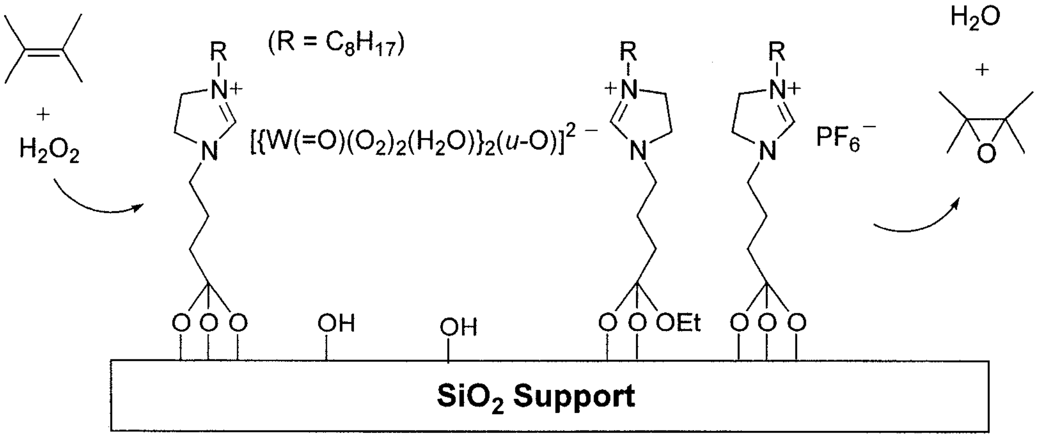
Figure 5. Molecular structures of Sulfoxantphos and [bmim][n-$C_8H_{17}OSO_3$].

The solid supported ionic liquid phase catalysis has also been applied to palladium catalyzed Mizoroki-Heck reaction[77] and transition metal catalyzed hydroamination.[78] The immobilized catalyst was highly efficient in promoting Mizoroki-Heck reaction without ligands in *n*-dodecane for at least six reuses, affording 89-98% yields. The TON and TOF reached 68400 and 8000 h^{-1}, respectively (Scheme 27).

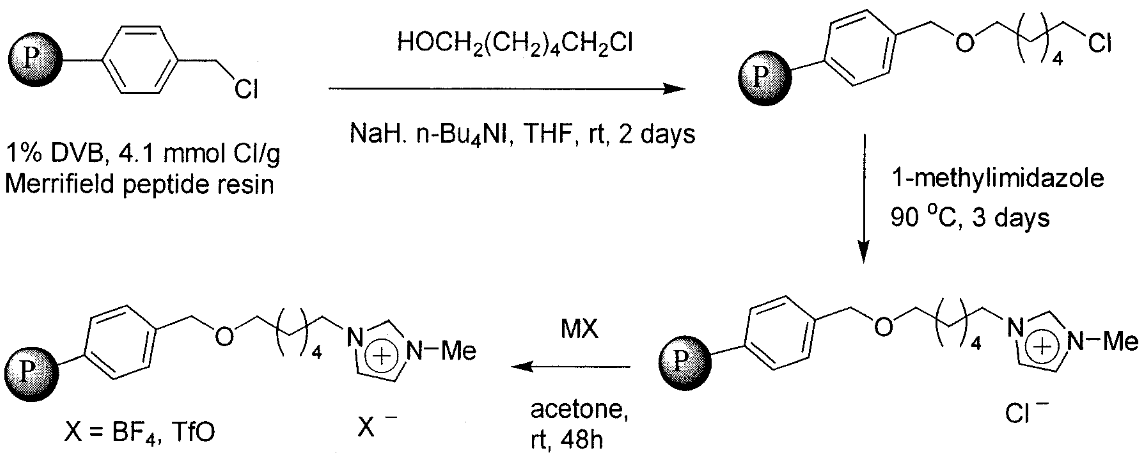


Scheme 27. Mizoroki-Heck reactions catalyzed by ionic liquid immobilized $Pd(OAc)_2$ on amorphous silica.

In the above systems, the catalyst was impregnated in the system via dissolving it in the ionic liquid reaction phase. There is no obvious chemical bonding connection between the catalyst and the support system. So the catalyst easily leached out into the organic solvent during the product extraction process. Another approach is to load the catalyst to the modified support system by ion exchange. Since ionic liquid consists of anion and cation, the anion or cation can exchange with active species of catalyst if the catalyst is also a salt. A recent example, which was reported by Mizuno and coworkers, demonstrates how to immobilize peroxotungstate onto ionic liquid-modified silica as a heterogenous epoxidation catalyst with hydrogen peroxide (Scheme 28).[79] The ionic liquid moiety was covalently anchored to silica gel through the condensation between OH groups on the silica surface and 1-octyl-3-(3-triethoxysilylpropyl)-4,5-dihydroimidazolium hexafluorophosphate. This was followed by anion exchange with potassium salt of peroxotungstate in aqueous solution at room temperature. The elemental analysis and ^{31}P MAS NMR spectroscopy showed that K^+ was not incorporated into the ionic liquid modified silica gel and PF_6^- had been replaced during the treatment. This result was further confirmed by Raman, IR, ^{13}C and ^{29}Si MAS NMR spectroscopic analysis, and consistent with BET surface analysis, which showed the surface area of silica gel decreased from 259 $m^2 \cdot g^{-1}$ to 203 $m^2 \cdot g^{-1}$. The loading level of hexaphosphate anion was 105 $\mu mol \cdot g^{-1}$. The resulting catalyst was applied to the epoxidation of various olefins using H_2O_2 as an oxidant. It was interesting to find that the stereochemistry of olefins could be retained after oxidation, suggesting that free radical intermediates were not involved in the reaction. The regioselective epoxidation of geraniol took place at the 2, 3-allylic double bond to afford 2,3-epoxy alcohol in high yield. The epoxidation of the secondary β,β–disubstituted allylic alcohol, 4-methyl-3-penten-2-ol, proceeded diaseteroselectively to form the threo-epoxy alcohol (threo/erythro=90/10). The catalyst was recovered and recycled for three times without loss of activity and selectivity. No leaching of catalyst was observed according to ICP-AES analysis of the filtrate and epoxidation could be completely stopped by removing catalyst. The parallel experiment using $[n\text{-}C_{12}H_{25}N(CH_3)_3]_2\text{-}[\{W(=O)(O_2)_2(H_2O)\}_2(\mu\text{-}O)$ as homogeneous catalyst gave similar results on the same conditions, which indicated that the homogeneous catalyst could be heterogenized with the retention of catalyst performance via anchoring it on to silica solid phase through ionic liquid chain.



Scheme 28. Peroxotungstate immobilized on ionic liquid-modified silica as a heterogeneous catalyst with hydrogen peroxide.



Scheme 29. Preparation of the polymer-supported imidazolium salts PS[hmim][BF_4] and PS[hmim][OTf]. DVB=divinylbenzene; hmim = 1-n-hexyl-3-methylimidazolium cation; MX = $NaBF_4$, KOTf; PS = polymer support.

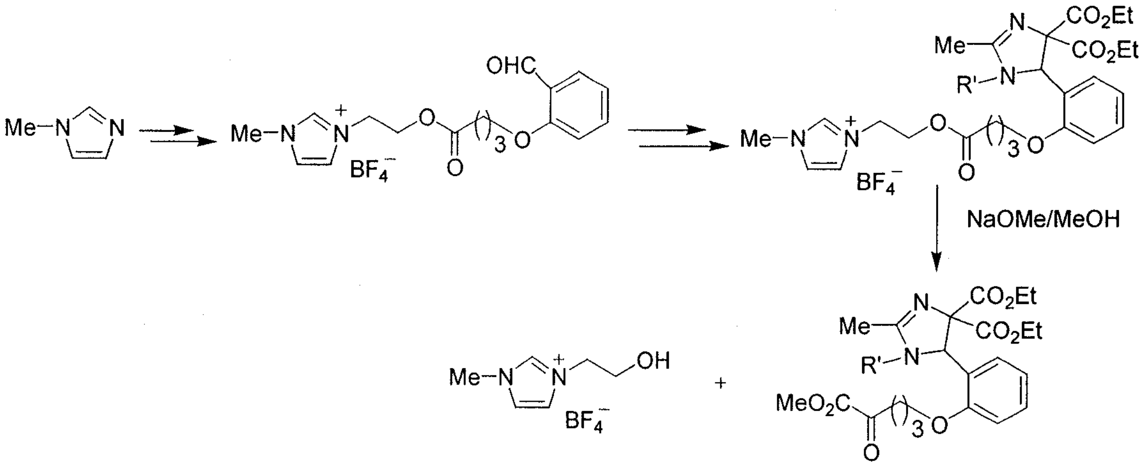
In addition, ionic liquid can also be connected to polymer resins to prepare polymer supported ionic liquid reagents.[80] This type of reagents were used as catalysts in the nucleophilic substitution reactions especially in fluorination of mesylates. The catalyst was prepared through three steps including linker connection, imidazolium salt generation and anion exchange as shown in Scheme 29. The loading level of imidazolium was as high as 2.2mmol of ionic liquid per gram of polymer-supported product. Experimental results showed fluorination of model compound 2-(3-methanesulfonyloxypropyl)naphthalene with 3 equivalents of CsF in acetonitrile at 100 °C gave a trace amount of fluoride after 2 hours, while the same reaction in the presence of 1.1 equivalents of polymer supported ionic liquid catalyst gave the product with 98% yield in two hours. And also, the reaction proceeded much faster than the parallel reaction using the same amount of free ionic liquid as phase-transfer catalyst or using 18-crown-6 ether as an additive. Those results indicated that the polymer-supported ionic liquid was a good catalyst in the fluorination reaction. This reaction was also expanded to other nucleophilic substitutions together with various potassium salts as additives such as chlorides, bromides, iodides, acetates and cyanides. Since the ionic liquid part was attached to polymer support through covalent bond, the catalyst could be recovered very easily after the reaction, just by filtering and washing. The recovered catalyst was reused without the loss of catalytic activity. However, for this polymer-supported catalyst, the reasons to significantly enhance the reactivity of those alkali-metal salts in the nucleophilic substitutions are not clear.

1. 4. Organic synthesis and catalysis using ionic liquids as soluble supports

Grafting technology is an important strategy widely used in nature and biology.[81] It is long time ago when people knew how to graft one kind of plant onto another one to cultivate a new species that could inherit the merits of both the two parent plants. When this technology is used in the organic synthesis, the chemical bonding formation via coupling may be taken as functional group grafting. This is especially important in the research and development of new drugs because a lot of drugs have a molecular core that determines its bioactivity and other functional groups grafted to this molecule mainly act as solubility-tuning groups. Since ionic liquids possess a number of intriguing physical and chemical properties such as tunable solubility in common solvents, high thermal and chemical stability, negligible vapor pressure, non-flammability and so on, those merits can be transferred into other molecules, which may tremendously simplify product purification procedures if ionic liquid species has been grafted onto them. Ionic liquid-supported synthesis is one of the successful applications of this concept. The following review will describe the use of ionic liquids as soluble supports in the synthesis of small molecules and biopolymers as well as catalyst supports for recyclable catalytic systems.

1. 4. 1. Ionic liquid-supported synthesis of small molecules

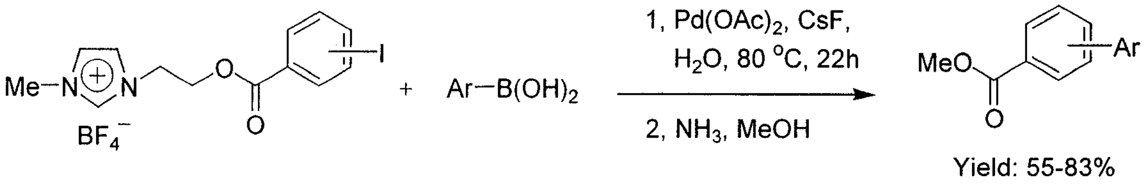
In 2001, Bazureau and coworkers reported the first example of ionic liquid-supported synthesis of small organic molecules.[82] The molecular precursor salicylaldehyde was attached to imidazolium salt via bromobutyrate linker. After Knoevenagel reaction and dipolar cycloaddition under solvent free condition associated with focused microwave irradiation, the final products were efficiently cleaved from the ionic liquid phase tag without need of silica gel chromatography in the product purification procedures. (Scheme 30)



Scheme 30. Ionic liquid-supported synthesis of small organic molecules.

This idea was also used in the one-pot three-component coupling of 4-thiazolidinones,[83] solution-phase synthesis of 2-thioxotetrahydropyrimidine-4-(1H)-ones,[84] Hantzsch 1,4-dihydropyridines and Biginelli 3,4-dihydropyrimidin-2(1H)-ones by the same group.[85] Another example was added by Song and coworkers in the synthesis of methyl-6-amino-5-cyano-4-aryl-2-methyl-4H-pyran-3-carboxylate, which demonstrated the merits of ionic liquid-supported synthesis of small molecules including high loading capacity, simple product purification and easy recovery and recycle of the supports.[86]

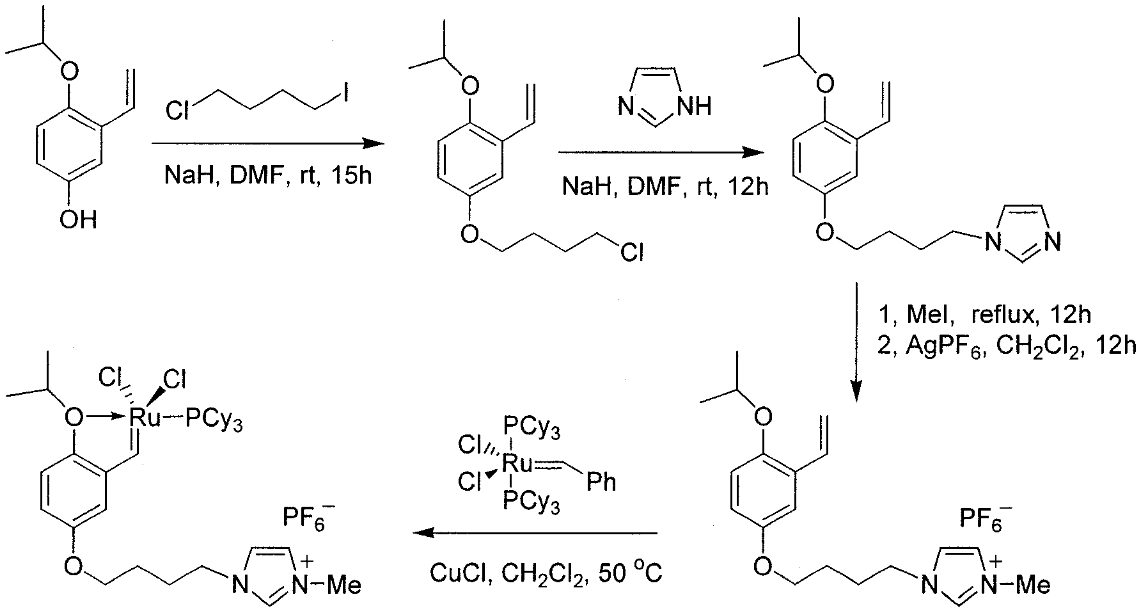
In 2003, our group for the fist time demonstrated the advantages of ionic liquid-supported synthesis over conventional liquid-phase synthesis with Suzuki coupling reaction (Scheme 31),[10c] in which the convenient phase separation and product purification without chromatography were described in detail and put forward that ionic liquids can be used as a soluble support in organic synthesis. The experimental results showed that ionic liquid-supported Suzuki coupling reactions in aqueous media gave higher yields than non-supported ones under the same reaction conditions, possibly due to better solubility of ionic liquid-supported substrates in aqueous media or enhancing effects of imidazolium moiety on the reactions. The advent of this type of support will offer organic chemists a new choice in the support chemistry such as polymer and fluorous phase-supported synthesis.



Scheme 31. Suzuki coupling reaction using ionic liquid as a soluble support.

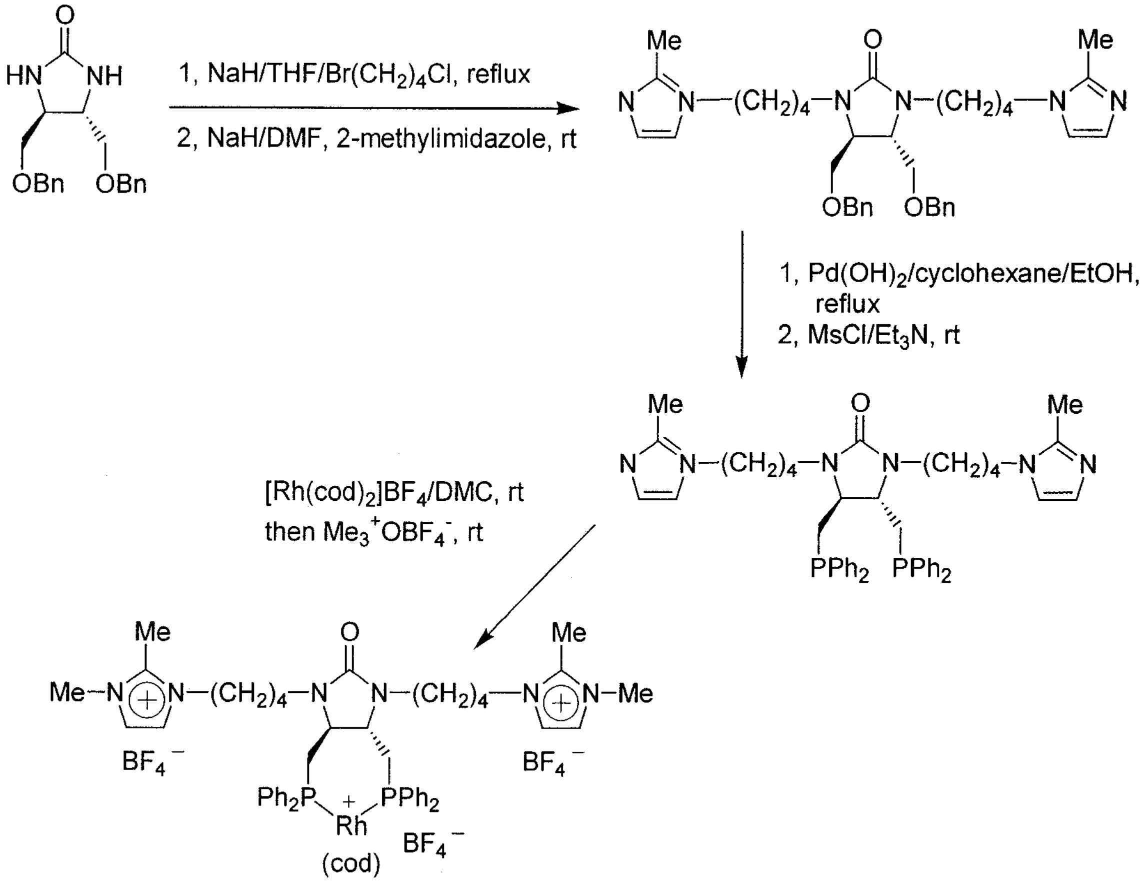
1. 4. 2. Ionic liquid-supported catalyst systems

The development of recoverable and recyclable catalysts has become an important research theme in the contemporary synthetic chemistry due to the environmental concerns and economical demands, especially for the noble transition metal catalyst systems.[87, 88] Grubb's ruthenium-based catalysts provide one of the most powerful and useful methods to generate cyclic molecules via ring-closing metathesis of olefins.[89] It was reported that Grubb's ruthenium catalyst and analogues did effectively catalyze olefin metathesis in room-temperature ionic liquids, but their catalytic activity vanished quickly in the subsequent recycling runs due to the slow decomposition of catalytic systems or catalyst leaching into the organic phase during product extraction procedures.[90] This problem had been solved when the ruthenium carbene complex was grafted to the ionic liquid phase tag.[91] The ionic liquid-supported catalysts can be prepared in several steps through common organic reactions as shown in the Scheme 32.



Scheme 32. Preparation of Ru carbene complex.

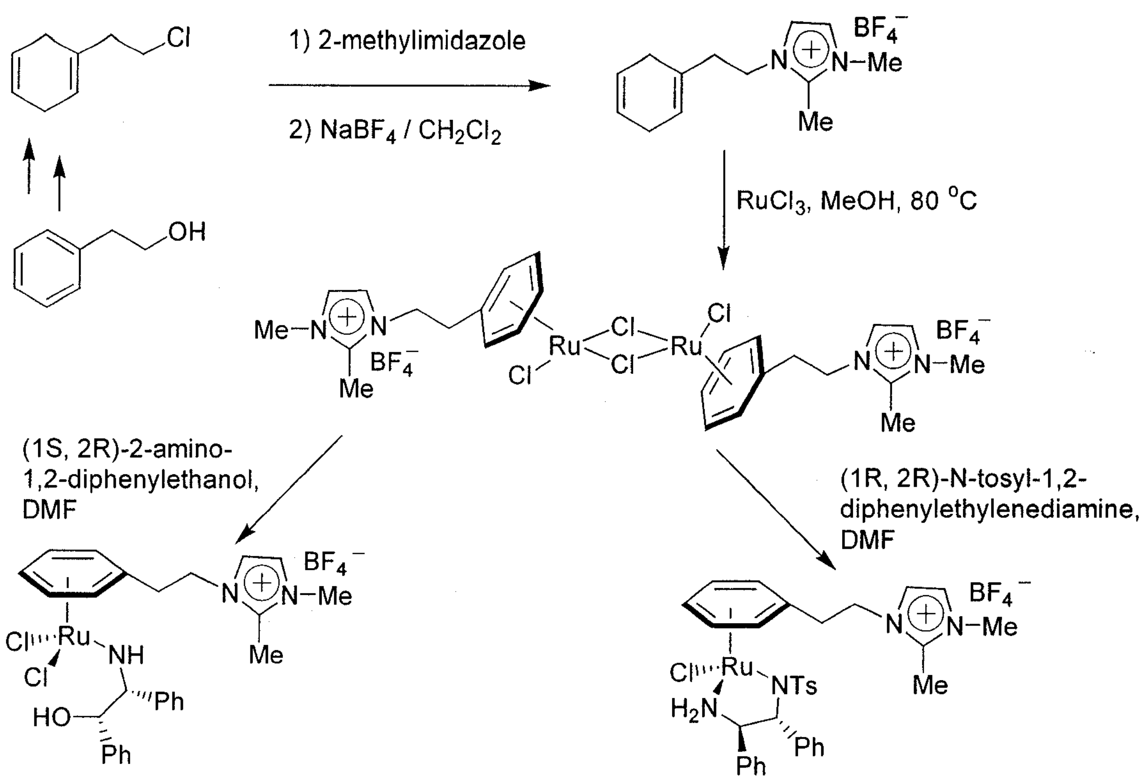
Thus, this methodology greatly improved the solubility of catalysts in the room-temperature ionic liquid such as [BMIM][PF_6], which was used as a sole solvent or mixed solvents with dichloromethane, and recyclability of the catalysts after each run. The experimental results showed that ionic liquid-grafted ruthenium catalysts were still very active after ten recycling runs, giving more than 90% conversion in the ring-closing metathesis of model dienes, while the similar catalyst without being bound to ionic liquid tag lost their catalytic activity after two or three recycling runs under the same reaction conditions.



Scheme 33. Synthesis of ionic liquid-supported Rh-complex catalyst.

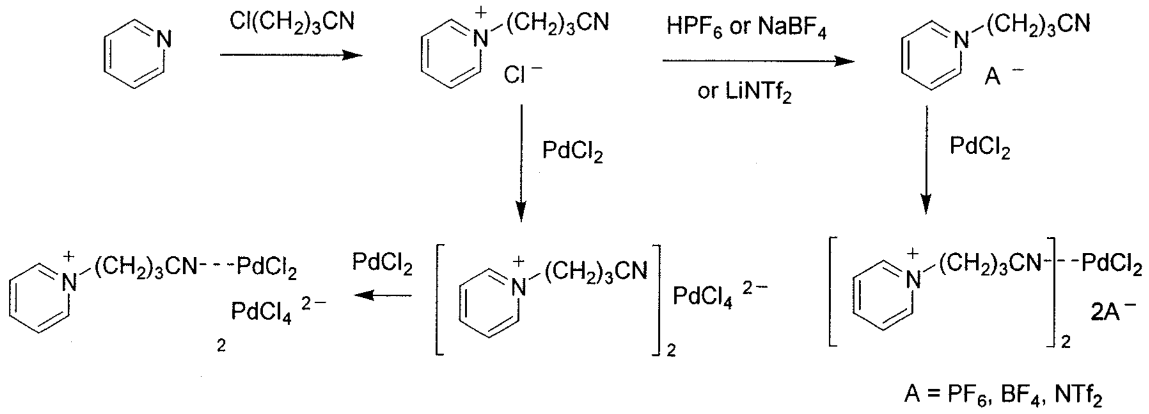
Meanwhile, the ionic tag strategy has also been used in the transition-metal complex-catalyzed asymmetric hydrogenation. Lee and coworkers reported that Rh-complex of chiral 1, 4-bisphosphine had been bound to two imidazolium salt tags.[92] The resulting catalyst system, after immobilized in an ionic liquid like [bmim][SbF_6], was used in the asymmetric hydrogenation of enamides for four times without significant loss of its catalytic efficiency. The model reaction was performed in two-phase system of [bmim][SbF_6]/*i*-PrOH, which showed that the introduction of imidazolium ionic tag to the ligand backbone not only avoided the catalyst leaching from ionic liquid layer but also increased the catalyst stability as compared with the control reaction. The preparation of the catalyst complex is shown in Scheme 33. The starting material was prepared from tartaric acid as described previously.[93]

In 2004, Geldbach and Dyson reported the development of new ionic liquid-supported ruthenium catalyst systems and their performance in ionic liquid biphasic transfer hydrogenation using 2-propanol or formic acid as the proton source.[94] The synthetic procedures of the catalyst precursors started from phenylethanol as shown in Scheme 34. After Birch reduction and subsequent chlorination, the product chloroethyl cyclohexadiene obtained was treated with imidazole, followed by anion exchange in dichloromethane. The resulting ionic liquid-bound cyclohexadiene was oxidized by $RuCl_3$ in methanol at 80 °C to generate a dinuclear complex. This compound was then treated with chiral ligand such as diamine and amino alcohol to give the ruthenium catalyst precursors because the active catalyst is a neutral 16-electron complex, which is usually formed *in situ* from the precursor. The experimental results showed that the catalyst precursors made from diamine gave much higher enantioselectivity than the precursor from chiral amino alcohols for the asymmetric transfer hydrogenation of acetophenone in isopropanol (including 2% mol KOH) with or even without the ionic liquid phase tag. The catalyst loss was ten times lower for the precursor with ionic tag than without the tag. However, ionic liquid-supported catalyst system was slightly less active and the catalytic activity was lost significantly after two runs while its counterpart without imidazolium tag could be used repeatedly for five times without decrease in activity.



Scheme 34. Synthesis of ionic liquid-supported Ru-complex catalyst precursors.

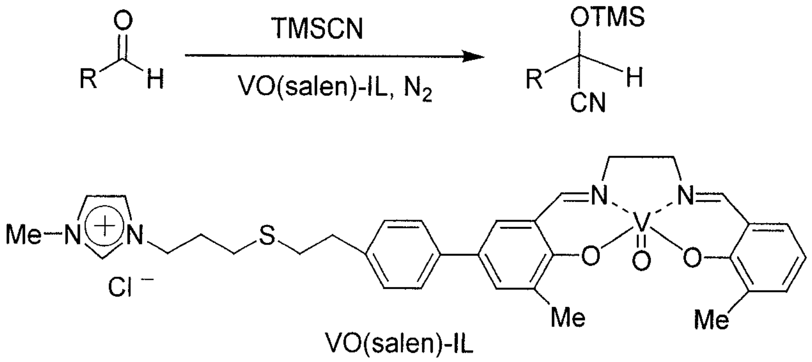
The palladium catalyst precursors, coordinated to nitrile-functionalized pyridinium ionic liquids as shown in Scheme 35, were successfully applied to Suzuki and Stille coupling reactions by the same group.[95] The single crystal structures obtained from the supported catalyst complexes showed pyridinium cations and palladium inorganic anions are held in place by extensive C-H···Cl interactions. The ionic liquid-supported catalysts had good solubility in the same nitrile-functionalized pyridinium ionic liquids such as [C_3CNPy][NTf_2] and the catalytic system could be recycled for nine times without obvious decrease in activity, while, when the same catalytic system was applied to non-nitrile-fuctionalized ionic liquid such as [C_4Py][NTf_2], the catalyst solution rapidly lost its activity after a couple of recycling runs. Those results could be explained by the metal analysis from inductive coupled plasma spectroscopy (ICP) in Suzuki reaction which showed less than 5 ppm of palladium was lost from the nitrile-functionalized ionic liquid solvent system while 28 ppm of palladium was lost from [C_4Py][NTf_2].



Scheme 35. Synthesis of palladium complexes with nitrile-functionalized ionic liquids.

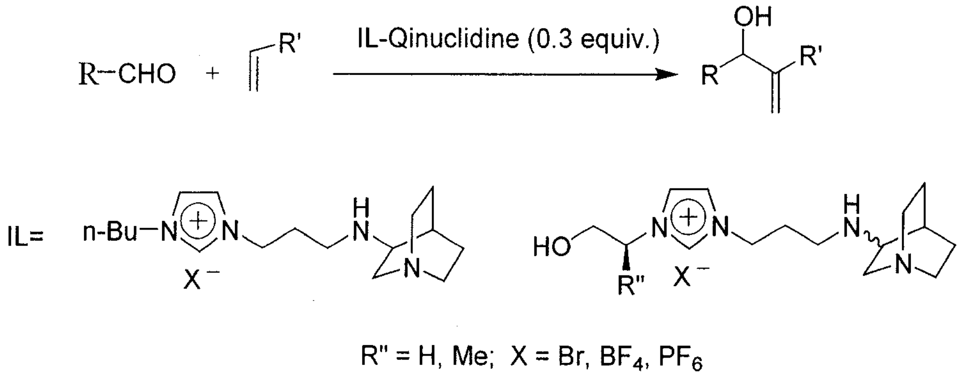
This also indicates that the nitrile-functionalized ionic liquids can stabilize the catalyst complex. Meanwhile, similar results were obtained from Stille reactions except palladium nanoparticles were generated in both solvent conditions. But the nanoparticles obtained from [C_4Py][NTf_2] were aggregated, while those from [C_3CNPy][NTf_2] were evenly distributed.

Garcia and coworkers reported the covalent immobilization of vanadyl salen complexes to imidazolium salt phase tag (VO(salen)-IL) (Scheme 36) and their application as catalysts to cyanosilylation of aldehydes in ionic liquids.[96] The resulting catalytic system showed good miscibility with ionic liquids such as [bmim][PF_6] and gave high conversion to the reactions. The catalyst was easily recycled and reused for six times with good recovery yield of the catalyst in each run. However, it was also found that the supported catalysts gave lower enantioselectivity than the unsupported counterpart catalyst and the counteranion of the solvent ionic liquid influenced the enantioselectivity as well.



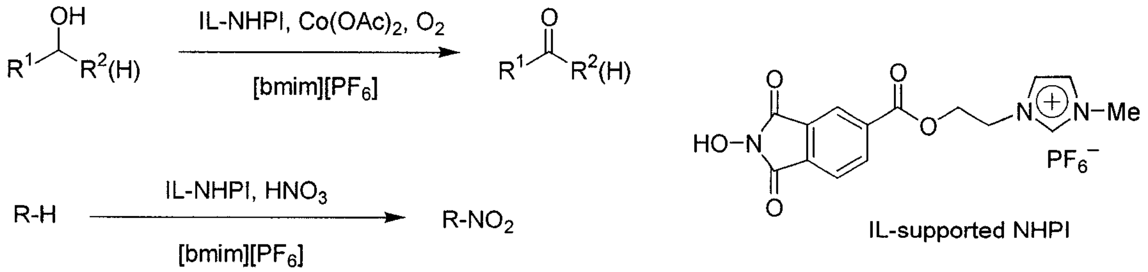
Scheme 36. Vanadyl salen complexes covalently anchored to an imidazolium ion as catalyst for cyanosilylation of aldehydes in ionic liquids.

In addition to the above mentioned ionic liquid-supported transition-metal catalyst systems, organocatalysts can also be grafted to ionic liquid phase tag to take advantage of the merits of ionic liquids. In 2005, Cheng and coworkers reported imidazolium salt-bound Quinuclidine-catalyzed Baylis-Hillman reaction[97] as shown in Scheme 37 because this reaction is one of the most versatile carbon-carbon bond formation reactions in organic chemistry with a new chiral center being generated during the procedures.[98] The ionic liquid-supported Qinuclidine was working well not only for common substrates such as acrylates but also for poor substrates such as acrylonitriles and cyclic enones. And also, the catalyst was recycled and reused for six times without significant loss of activity, and the recovering procedures were very easy, just by phase extraction and separation with diethyl ether. Due to the fact that ionic liquid-supported catalyst showed higher catalytic efficiency in protic solvents such as alcohols than in aprotic solvents such as dichloromethane and THF as well as in the sole solvent of ionic liquid, hydroxyl ionic liquid-immobilized Quinuclidine was designed and synthesized.[99] This catalyst showed higher catalytic activity than its non-hydroxyl-bearing counterpart in all solvents tested and the best results were given under solvent-free conditions, indicating the hydroxyl group on the catalyst provides proton donor in the reaction. However, the enantioselectivity of the reaction was reported to be quite poor, less than 10% e.e..



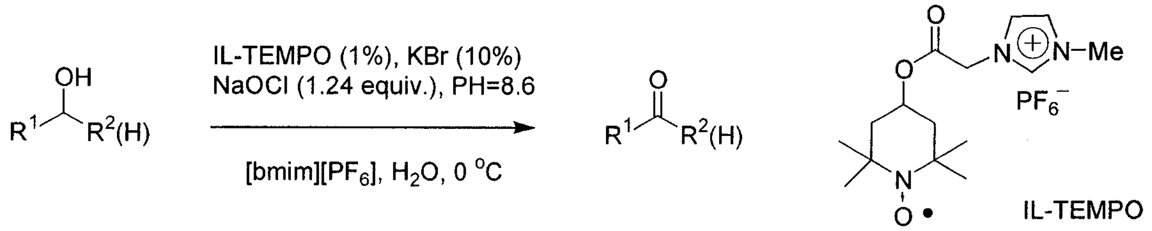
Scheme 37. Ionic liquid-supported quinuclidine-catalyzed Baylis-Hillman reaction.

Another example on ionic liquid-supported organocatalyst was described by Kitazume and Koguchi, where imidazolium salt-supported N-hydroxyphthalimide (NHPI) complex was used as a catalyst in room-temperature ionic liquid solvent for the transformation of alcohols into ketones or aldehydes (Scheme 38).[100] The ionic liquid-supported NHPI can readily recycled and reused for 5 times without any loss of the activity (96%-99% yield), while the non-supported NHPI was recycled for only three times with the product yield dropped from 93% to 26%. This catalytic system with HNO_3 was also applied to the nitration of alkanes into nitro-compounds.



Scheme 38. Ionic liquid-supported NHPI and catalyzed reactions.

2,2,6,6-Tetramethylpiperidin-1-oxyl (TEMPO) with a terminal oxidant is an important combination used extensively for selective and efficient oxidation of alcohols to carbonyl compounds under mild conditions.[101] In the reaction, TEMPO serves as a catalyst. So far, many different terminal oxidants have been developed for this reaction such as sodium hypochlorite,[102a] [bis(acetoxy)iodo]benzene,[102b] m-CPBA,[102c] sodium bromite,[102d] trichloroisocyanuric acid,[102e,f,g] oxone,[102h] iodine,[102i] and oxygen with CuCl,[102j,k] or $NaNO_2$.[102l] The problem for this oxidant system is that the separation of products from TEMPO requires tedious workup procedures especially for the large-scale reactions. However, it can be solved via anchoring TEMPO to the ionic liquid phase tag. Gao and coworkers reported the first example of imdazolium salt-bound TEMPO (Scheme 39), which showed good catalytic activity according to Anelli's protocol,[103] in the oxidation of primary and secondary alcohols to aldehydes and ketones without overoxidation to carboxylic acids.[104] The supported TEMPO showed similar catalytic behaviors to non-supported counterpart, but easier recovery of the catalyst in the supported case. Bao and coworkers reported another example, which used similar imidazolium salt-supported TEMPO catalyst and different terminal oxidants.[105]



Scheme 39. Selective oxidation of alcohols to carbonyl compounds by IL-TEMPO.

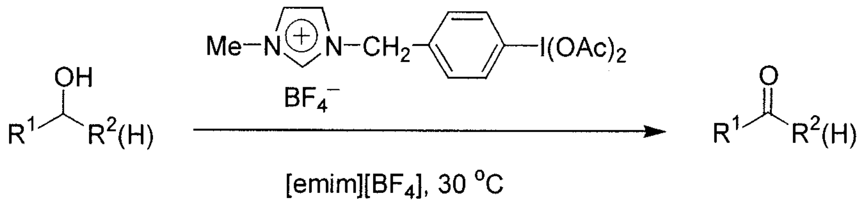
A recent example of ionic liquid-supported organocatalyst for asymmetric Aldol reaction has been done in our group,[10e] in which (2S, 4R)-hydroxyproline is anchored to imidazolium–based ionic liquid. The anchored catalyst gave the products with up to 28% higher enantioselectivity than non-supported (S)-proline.

It is worthy to mention that a task-specific basic ionic liquid [bmim]OH, was successfully used as base catalyst and reaction medium in Michael adition of active methylene compound to conjugated ketones, carboxylic esters and nitriles,[106] and in Markovnikov addition of N-heterocycles to vinyl esters.[107]

1. 4. 3. Ionic liquid-supported reagents

It is well known to organic chemists that functional transformations and carbon-carbon bond formations are the basic motif in organic synthesis. When a multifunctional group has been grafted onto ionic liquid phase tag, this resulting reaction precursor can be used as a functionalized reagent to undergo different kinds of reactions to make interesting molecules. Grée and coworkers simply anchored electrophilic alkenes to imidazolium salt via Wang resin-type linker.[108] This simply functionalized reagent was used for the Diels-Alder cycloaddition, 1,4-addition, Heck Coupling and Stetter reactions. The final products can be easily cleaved from the phase tag through transesterification.

In 2005, Zhang and coworkers reported imidazolium salt-supported hypervalent iodine (III) reagent for the oxidation of primary and secondary alcohols into aldehydes and ketones in the room–temperature ionic liquid [emim][BF_4] as shown in Scheme 40.[109] This reagent can be easily prepared in two steps starting from the reaction of 1-methylimidazole with 4-bromamethyliodobenzene and followed by oxidation with peracetic acid (30% H_2O_2 and acetic anhydride). The importance of this reagent is that this ionic liquid-supported oxidant is stable and environmentally friendly, and more active than non-supported reagent $PhI(OAc)_2$, and highly selective for the oxidation of primary alcohols to aldehydes without overoxidation to carboxylic acids. Also, the supported oxidant can be easily recovered and reused after reoxidation with peracetic acid. Therefore, this reagent may be used to replace the expensive Dess-Martin periodinane (DMP) reagent and *o*-iodoxybenzoic acid (IBX) because the high valence iodine (V) oxidants are potentially explosive.[110]



Scheme 40. Selective oxidation of alcohols to carbonyl compounds by ionic liquid-supported iodine (III) reagent.

Ionic liquid-bound sulfonyl chloride was used as both reagent and solvent in the Beckmann rearrangement of oximes.[111] The products ε-caprolactam could be easily separated from the reaction mixture by water extraction, which was believed to be a serious problem in chemical industry.

In addition, a task-specific ionic liquid [bmim][SCN] was used as thiocyanate reagent and reaction medium for the conversion of alkyl halides to alkyl thiocyanates at room temperature in the yield from 75-95%.[112]

1. 4. 4. Ionic liquid-supported synthesis of biopolymers

The efficient synthesis of biopolymers such as oligosaccharides, oligopeptides and oligonucleotides is still a contemporary challenge even though polymer resin-supported synthesis[113] has permitted the automated assembling of their corresponding monomers.[114, 115]

The central issue is that polymer supported solid-phase synthesis has to use much excess reagents to drive the reaction to completion and its loading level of the monomer is quite low as compared to the mass of support. Also, the coupling process and intermediate products are difficult to be monitored without cleavage by common characterization methods such as NMR, MS spectroscopy. Recently fluorous phase supported synthesis has been advocated in the synthesis of biopolymers. This methodology requires using highly fluorinated compounds as solvents to extract products from reaction mixtures. Our group recently put forward the concept that ionic liquids can be used as soluble supports to synthesize biopolymers. The concept is illustrated in Figure 6. The substrate anchored onto an ionic liquid moiety is soluble in polar organic solvents and can undergo liquid-phase reaction. After completion of the reaction and evaporation of the solvent, the excess reagents can be removed by a less polar organic solvent in which the ionic liquid-anchored product is insoluble. Inorganic reagents or side products can be removed by precipitation or by washing with aqueous solution. Finally, the product can be detached and then separated from the ionic liquid moiety by organic solvent extraction. This idea was firstly demonstrated by using imidazolium salt as phase tag to synthesize oligosaccharides and the total synthetic procedures was exhibited in Canadian Society of Chemistry (CSC) conference in 2004.[10a] The details will be described in the next chapter of this thesis. This approach provides a way to construct oligosaccharides with greatly simplified purification procedures without the need of chromatography during the synthesis and at the end of cleavage of the phase tag. A similar example was reported by Wang and coworkers in 2006.[116] The ionic liquid-supported oligosaccharide synthesis has combined the advantages of homogeneous reaction in the conventional solution-phase synthesis, and heterogeneous phase separation in solid-phase synthesis.

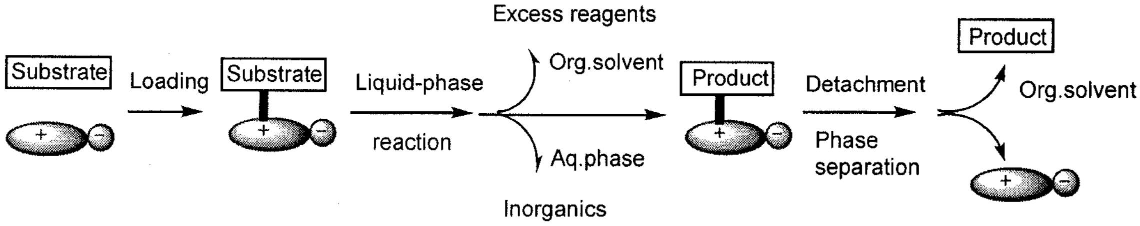
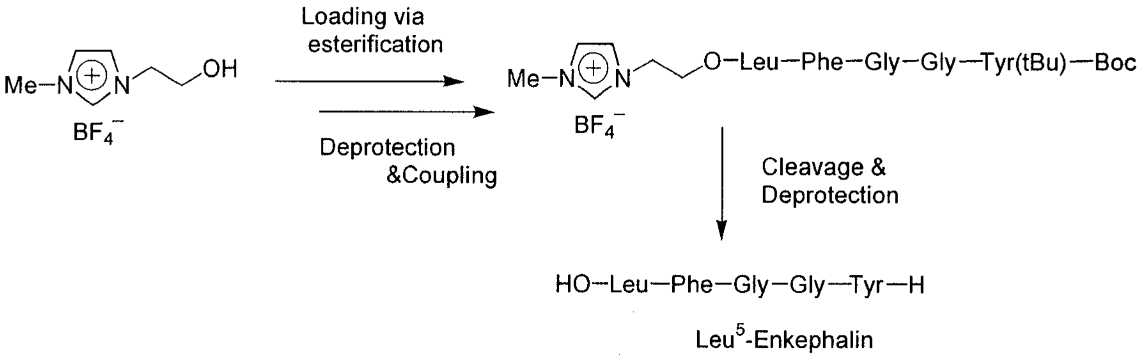


Figure 6. Ionic liquid–supported synthesis of biopolymers.

The first example on ionic liquid-supported oligopeptide synthesis was also reported by our group.[10d] A bioactive pentapeptide, Leu^5-enkephalin, was synthesized in good total yield and reasonable purity as shown in Scheme 41. The reactions were performed in homogenous solution phase and each step was verified by common spectroscopic analysis.



Scheme 41. Ionic liquid-supported oligopeptide synthesis.

In summary, ionic liquid-supported synthesis provides a new strategy in organic synthesis and catalysis. The ionic liquid-supported substrate can undergo chemical assembling in homogeneous phase as conventional solution phase synthesis which results in high reaction efficiency, and the product purification procedures can be much simplified through phase separation as the solid-phase synthesis without requirement of chromatography in most of cases. Those credits are fully demonstrated in the ionic liquid-supported synthesis of biopolymers in which the use of large excess of reagents can be avoided and reaction process and intermediate products can be characterized by routine methods such as NMR, IR and MS spectroscopy in contrast of solid-phase synthesis. In addition, when catalysts are grafted to ionic liquid phase tag, the resulting molecules have better solubility in ionic liquid solvents. This can greatly decrease the catalyst leaching into the organic phase during product extraction procedures in the case of biphasic catalysis, which, therefore, is especially important for ionic liquid-supported noble transition metal catalysts due to environmental and economical concerns. However, the limitation of ionic liquid-supported synthesis is the supports, which are imidazolium salts in most cases, are quite small, so it is difficult to construct large molecules because ionic liquid moiety will lost the role as a phase tag when a large size of substrate has been anchored onto it. And also, ionic liquids are not completely inert in some reactions.[6] The anion exchange of ionic liquid moiety is always a pain on the researcher's neck because it adds to the complexity of the reaction mixture.

1. 5. Ionic liquid-stabilized metal nanoparticles and catalysis

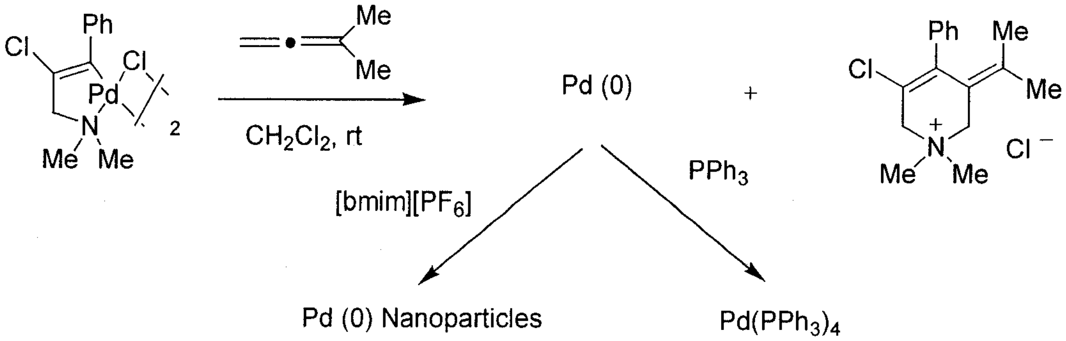
The preparation of metal nanoparticles in ionic liquids has just started in the last 5 years.[117] This research area has attracted increasing attention from scientists due to the fact that ionic liquids can be good solvents and stabilizing reagents to make transition-metal nanoparticles. In many cases, the as-synthesized transition-metal nanoparticle/ionic liquid catalytic systems show good activity and recycling ability in organic catalysis, and can be used over a large range of temperatures. The merits of ionic liquids in preparing metal nanoparticles, besides those properties as "green" solvents, can be based on the following reasons. First of all, ionic liquids can have low interfacial tension, which is a good property to generate small particles because low interfacial tension of solvents results in high nucleation rate and week Ostwald ripening.[117] Secondly, ionic liquids are better considered as "polymeric liquids" than "common solvents". It was reported that pure imidazolium-based ionic liquids are highly organized hydrogen-bonded polymeric liquids.[118] This type of "supramolecular" liquids have possibilities to provide tiny ordered "domains" to confine metal nanoparticles from aggregation into large particles or to be used as a template to fabricate ordered-structured materials.[119] Thirdly, ionic liquids have large melting point ranges (–100 – 400 °C), which makes them good solvents in the preparation of metal nanoparticles at low or high temperatures. Fourthly, the hydrophilic and hydrophobic properties of ionic liquids can be tuned by anion exchange. This makes it possible that ionic liquid-stabilized nanoparticles can phase-transfer from aqueous phase to organic or ionic liquid phase. In this section, ionic liquid-assisted preparations and applications of metal nanoparticles will be reviewed.

1. 5. 1. Ionic liquid-assisted preparation of metal nanoparticle–based catalytic systems

Developing new catalytic systems that possess the advantages of both homogeneous (easy catalyst modulation and high catalytic efficiency) and heterogeneous (easy catalyst recycling and product separation) catalysis has been one of the most challenging issues in modern catalytic chemistry.[120] Ionic liquids as designer solvents have attracted much attention in immobilizing transition metal catalyst precursors in biphasic catalytic systems.[9] This has to be attributed to the advent of air and moisture-stable imidazolium-based room-temperature ionic liquids ten years ago,[121] which tremendously pushed forward scientific investigations on ionic liquid-based catalysis and synthesis. In 2001, Srinivasan and coworkers reported the formation of Pd nanoparticles through *in situ* investigating the reaction mixture after a successful Heck reaction in ionic liquid of [bbim][BF_4] under sonochemical conditions using $Pd(OAc)_2$ or $PdCl_2$ as a catalyst and sodium acetate as a base.[122] TEM images showed that the average size of Pd nanoparticles was 20 nm.

In general, metal nanoparticles are usually prepared by the reduction of metal compounds in the presence of stabilizing reagent such as phosphine, thiols, surfactants, polymers and so on.[123] Accordingly, ionic liquid-stabilized transition-metal nanoparticle systems can also be synthesized through the simple reduction of transition metal compounds with molecular hydrogen or the decomposition of zero-valent transition-metal complexes by other reagents in ionic liquids. In 2002, Dupont and coworkers for the first time reported the intentional use of imidazolium ionic liquid as both solvent and stabilizing reagent for the preparation of iridium nanoparticles.[124] Treatment of the solution of $[IrCl(cod)]_2$ (cod = 1,5-cyclooctadiene) in [bmim]PF_6 with hydrogen at 75 °C for 10 min afforded a black "solution" of nanoparticles with average diameter of 2.0 nm and irregular shape. The resulting catalyst mixture could be used directly as recyclable catalysts for biphasic hydrogenation of olefins, or submitted to centrifugation to isolate the nanoparticles that was then re-dispersed in [bmim][PF_6] to give the catalytic system with the same performance as the freshly prepared. Importantly, the catalytic activity of this system was significantly better than those obtained in conventional biphasic conditions like simply dissolving transition-metal catalyst precursors in room-temperature ionic liquids under similar reaction conditions. High catalytic efficiency was maintained for up to at least seven recycles with total turnover of more than 8400, while the control experiment showed Crabtree's catalyst precursor [Ir(cod)py(Pcy$_3$)][PF$_6$] in water-free [bmim]PF$_6$ under the same reaction conditions lost the activity quickly after the second run. The same strategy was applied to prepare Pt(0),[125] Rh(0),[126] and Pd(0)[127] nanoparticles under similar conditions and the resulting Pt(0), Ir(0) and Rh(0) nanoparticle catalyst systems were used for the hydrogenation of arenes, affording good conversions, especially in the case of Ir (0) nanoparticles. X-ray diffraction (XRD) and TEM analysis confirmed the existence of crystalline Pt and Rh nanoparticles with average diameter of 2.5 nm and 2.3 nm, respectively, evenly dispersed in the ionic liquid solvents. The isolated Pt(0), Ir(0) and Rh(0) nanoparticles could be used as solids (solvent-free) or re-dispersed in ionic liquids (biphasic) or in organic solvent (homogeneous) for the hydrogenation of arenes under mild reaction conditions. The occurrence of C–O bond hydrogenolysis, which is characteristic of a surface metal catalyst,[128] in the experiments indicated that those nanoparticles behaved preferentially as a heterogeneous catalyst rather than a homogenous catalyst in terms of active sites under solvent-free or biphasic condition.[129]

More recently, a modified approach from the abovementioned strategy was developed by the same group to prepare ligand-free Pd(0) nanoparticles dispersed in [bmim][PF$_6$] ionic liquid as shown in Scheme 42. The resulting Pd catalyst was applied to the Heck coupling reaction between n-butylacrylate and aryl halides with good conversion and yield under optimized conditions.[130] When an N-containing palladacycle was treated with allene in dichloromethane at room temperature, Pd(0) would be generated. This soluble Pd(0) species was relatively stable, which could be quickly dispersed in the ionic liquids after removal of organic solvent or treatment with PPh_3 to generate the well-known catalyst $Pd(PPh_3)_4$.[131]



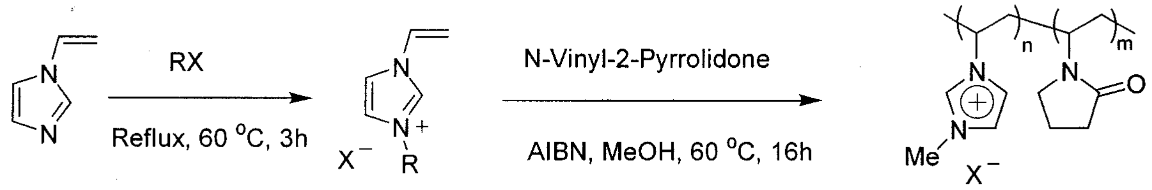
Scheme 42. Preparation of ionic liquid-stabilized Pd(0) nanoparticles.

The Pd(0) nanoparticles obtained display an irregular shape with a monomodal particle size distribution at 1.7 ± 0.3 nm according to TEM images. However, the particle size turned bigger with monomodal size distribution of 6.1± 0.7 nm after the Heck reactions. This indicates the aggregation of nanoparticles during reactions. The TEM and ICP-AS measurements strongly suggested that Pd nanoparticles dispersed in the ionic liquid acted as a reservoir of catalytically active Pd species. The reaction proceeded through the oxidative addition of phenyl iodide on the nanoparticle surface and then the oxidized Pd species were detached from the surface and entered into the catalytic coupling cycles and ended up with either continuing catalytic cycles or falling back to the nanoparticle surface. This is consistent with the fact that the recovered organic phase extracted with diethyl ether after 4h (containing around 25% Pd) was inactive for the coupling of PhI and n-butylacrylate in the presence of $EtN(i\text{-}Pr)_2$ at 80 °C after 20 hours and attempts to identify Pd nanoparticles in the organic phase by TEM was not successful. However, this conclusion on catalytic pathway needs more evidence to prove because the experimental results can also explained by the formation of unknown inactive Pd species in the organic solvent.[132, 133, 134]

A similar approach to make Pd(0) nanoparticles was reported by Caló and coworkers.[135] When a PdI_2 complex with two benzothiazole carbenes or $Pd(OAc)_2$ was dissolved in ionic liquid tetrabutylammonium bromide (TBAB) followed by the addition of tetrabutylammonium acetate (TBAA), a dark suspension of Pd nanoparticles were obtained. The resulting catalytic system could efficiently and specifically catalyze the Heck reactions between cinnamates and aryl halides to give β-arylsubstituted cinnamate esters. Interestingly, the ionic liquid TBAA plays a crucial role in forming Pd nanoparticles and determining the stereospecificity of C-C coupling process in this case, which was explained, respectively, by the ionic liquid stabilization effects on the unstable 12-electron complex ArPdX via forming the more stable 16-electron complex $[ArPdX_3]^{2-}$ $2NR_4^+$ and an intramolecular neutralization of PdH(X) by TBAA as a base.

Han and coworkers reported the synthesis of phenanthroline ligand-stabilized palladium nanoparticles in ionic liquids through *in situ* reduction of $Pd(OAc)_2$ in $[bmim][PF_6]$ by hydrogen in the presence of phenanthroline. The resulting catalytic system showed high activity and selectivity for the hydrogenation of olefins and was reused for 10 times without decrease of activity.[136] Control experiment showed that the phenanthroline ligand was important to stabilize Pd nanoparticles. Otherwise, the nanoparticels would aggregate and precipitate in the first run, which led to the loss of catalytic activity.

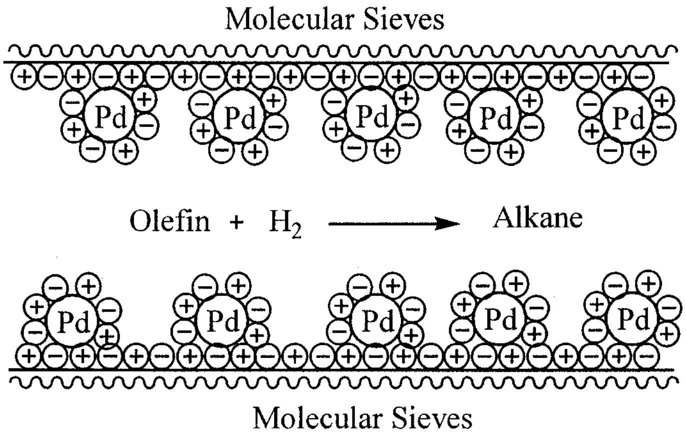
Kou and coworkers synthesized a new family of ionic copolymers via free radical copolymerization of 1-vinyl-3-alkyl imidazolium halide and N-vinyl-2-pyrrolidone as shown in Scheme 43.[137] These copolymers were highly soluble in ionic liquid such as [bmim][BF_4] and used to stabilize Rh(0) nanoparticles to generate a new metal nanoparticle catalyst system, which showed good activity and recyclability in the benzene hydrogenation. It was found that the good stability and activity of this catalytic system was resulted from high synergistic effect among metal nanoparticles, polymer and ionic liquid because any combination of those two components did not afford good catalytic behaviors. It is worthy to mention that not only the ratios of polymer and metal naoparticles, but also the ratio of the two monomers in the copolymers shows considerable effects on the activity and stability of this catalyst system.



Scheme 43. Synthesis of poly[(N-vinyl-2-pyrrolidone)-*co*-(1-vinyl-3-alkylimidazolium halide)] copolymers.

Although ionic liquid biphasic catalyst systems, composed of an organic phase and a catalyst-dispersed ionic liquid phase, have been addressed by many research groups so far, chemical industry still prefers heterogeneous catalytic systems due to the easy product separation and possibility to use fixed-bed reactors. Pd nanoparticles can be immobilized on molecular sieves by ionic liquids to build up a heterogeneous catalyst system for solvent-free hydrogenation. The fist example was addressed by Han and coworkers (Figure 7),[138] who used readily prepared ionic liquid 1,1,3,3-

tetramethylguanidinium lactate to immobilize Pd nanoparticles onto porous molecular sieves because quanidinium ions have a considerable coordinating ability to metal particles.[139]



⊕⊖ = $[H_2N{=}C(NMe_2)_2]^+$ $[CH_3CH(OH)CO_2]^-$

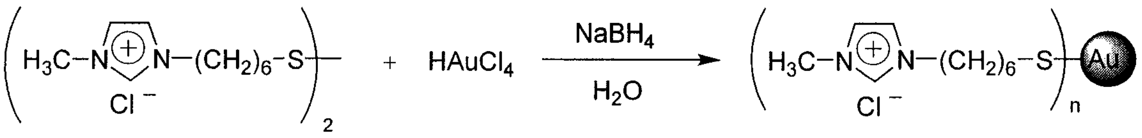
Figure 7. Immobilization of Pd nanoparticles on the surface of molecular sieves with ionic liquid layer

The catalytic system obtained showed excellent synergistic effects on the enhancement of activity and durability of catalysts as compared with biphasic catalytic system and molecular sieves-supported nanoparticle catalyst without ionic liquids. However, the mechanism for this catalytic system with high activity and stability was not fully addressed and the procedures to prepare and immobilize Pd nanopartices were not described in the paper.

The same group reported the immobilization of Ru(0) nanoparticles on mesoporous silicate SBA-15[140] and Montmorillonite[141] by ionic liquid of 1, 1, 3, 3-tetramethylguanidinium lactate and trifluoroacetate, respectively, and their application to the hydrogenation of benzene. The immobilization of Ru(0) nanoparticles onto mesoporous silicate SBA-15 was conducted through mixing the ionic liquid and $RuCl_3$ in methanol and then evaporating off solvent, followed by hydrogen reduction at 150 °C for 2 h to give Ru(0) nanoparticles with further calcination at 220 °C for 3 h to decompose excess free ionic liquid species. The Ru(0) catalyst system obtained had 1 wt% Ru metal. While SBA-15 is a mesoporous silicate with hexagonally ordered empty channels, Montmorillonite (MMT) is naturally occurring clay with laminar structures and each layer is made up from two–dimensional silicate sheet with negative charges, and with the cationic species intercalated between layers by electrostatic interaction with those negative charges. The catalyst system was prepared by treatment of Na-MMT with an aqueous solution of 1, 1, 3, 3-tetramethylguanidinium trifluoroacetate for three times to finish cation exchanges. After filtration and washing with water, the guanidinium-loaded montmorillonite was dispersed into aqueous solution of $RuCl_3$ to absorb Ru^{3+} by coordination, which was followed by evaporation (model system) or filtration to remove water. The nanoparticle catalyst system was obtained by hydrogenation of Ru^{3+}-intercalated Montmorillonite composites at 220 °C for 2 h. The intercalation of ionic liquid and ruthenium nanoparticles was confirmed by surface analysis with nitrogen adsorption and desorption and IR spectroscopy. The resulting Ru/MMT catalyst showed much higher catalytic activity than the traditional Ru/C and Ru/Al_2O_3 systems under the same reaction conditions. Moreover, it is a heterogeneous catalyst system, which can be used in a fixed–bed process. A series of analysis with TEM, EDS (energy-dispersive X-ray spectrometer) and HRTEM showed Ru nanoparticles, less than 3 nm, were present on the outer surface and interface of Montmorillonite composites and the particles in the interfaces could play a main role in the high activity of the catalyst. When the catalyst systems were prepared without being soaked with ionic liquid or Ru^{3+}, the resulting systems showed much lower activity than the model system in the hydrogenation of benzene, which indicates ionic liquid acted as immobilizing reagents for the metal nanoparticles. However, the model system was obtained by evaporation to remove water, which should include immobilized Ru nanoparticles via chemoadsorption and physioadsorption and free Ru nanoparticles. The free nanoparticles and weakly bound nanoparticles might aggregate and leach out during hydrogenation processes. The same problem may also exist in the case of Ru-SBA-15 system.[140]

1. 5. 2. Synthesis of metal nanoparticles using thiol-funtionalized ionic liquids as capping reagents

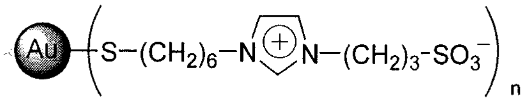
The preparation and processing of gold nanoparticles are one of the most interesting research topics in metal nanotechnology because gold nanoparticles have high optical molar absorbance in the visible light region, which endows them with potential application as nanoprobes and nanosensors.[142] The fist example of preparation of gold nanoparticles by the use of thiol-functionalized ionic liquids as stabilizers was described by Naka and coworkers.[143] The synthetic procedures are very common in the preparation of nanoparticles as shown in Scheme 44, that is, to an aqueous solution of $HAuCl_4$ with 3,3'-[disulfanyl(hexane-1,6-diyl]-bis(1-methyl-1*H*-imidazol-3-ium) dichloride was added an excess amount of reducing reagent $NaBH_4$ dropwise. The resulting nanoparticles were purified by ultrafiltration membrane. The average diameter of as-synthesized gold nanoparticels was 5.0 nm according to TEM images and each particle absorbed 380 sulfur ligands on the surface from calculations. Since the miscibility of ionic liquids in water or organic solvents can be changed by anion exchange, the particle size and surface properties of those gold nanoparticles obtained could be controlled by anion changes due to the induced particle aggregation. This leads to the gold nanoparticles having different optical and hydrophilic behaviors, which make them possible to be optical anion sensors and phase transferring reagents. The nanoparticle phase-transfer phenomenon was also observed by other research groups, who described the phase-transfer of noble transition metel nanoparticles from aqueous phase to ionic liquid phase in detail.[144] Wei and coworkers reported that gold nanoparticles were able to be transferred from aqueous phase to water immiscible ionic liquids phase like [bmim][PF_6] just by vigorous shaking the biphasic mixture and the aggregation of gold nanoparticles in ionic liquid phase could be prevented by adding a small amount of cationic surfactant such as tetradecyltrimethylammonium bromide. While, Roucoux and coworkers reported that the non-conventional room-temperature ionic liquid or cationic surfactant type ionic liquid of N, N-dimethyl-N-dodecyl-N-(hydroxyethyl)ammonium chloride-stabilized rhodium nanoparticles in the aqueous solution were transferred to the *in situ* formed ionic liquid phase N, N-dimethyl-N-dodecyl-N-(hydroxyethyl)ammonium methylsulfonimide after the anion exchange of the surfactant molecules. This phase transfer process provides a new approach to prepare ionic liquid-immobilized metal nanoparticle catalyst systems without using thiol reagents as capping reagents.



Scheme 44. Synthesis of gold nanoparticles using functionalized ionic liquid.

Fujihara and Tatumi reported a new family of gold nanoparticles that were stabilized by zwitterionic imidazolium sulfonate-terminated thiols (Zwitter-Au) (Figure 8). Those

Au nanoparticles were considerably stable in high concentration of aqueous electrolytes such as NaCl, $NaNO_3$, $NaPF_6$, CF_3SO_3Na, and HCl, in sharp contrast to other metal nanoparticles, which, in general, were unstable and aggregated in electrolyte solutions.[142a] The synthetic procedures were similar to the abovementioned case. The gold nanoparticles obtained were found to be stable in solid state, insoluble in many organic solvents such as n-hexane, Benzene, chloroform, THF, ethyl acetate, methanol, acetone, DMF and DMSO and water, but soluble and stable in aqueous electrolyte solution such as 0.2 M NaCl, 6 M NaCl, 2M HCl and various concentrations of $NaNO_3$, $NaPF_6$ and CF_3SO_3Na as well as in ionic liquid like [emim][BF_4]. However, they aggregated in aqueous solution of HPF_6 due to anion exchange. The particle size of Zwitter-Au in several aqueous electrolyte solutions is between 2.4-2.7 nm, indicating their surface properties did not change with the addition of electrolytes. Moreover, these zwitterionic ionic liquid-stabilized gold nanoparticles showed good stability in presence of calix[8]arene *p*-sulfonic acid octasodium salt, poly(sodium 4-styrenesulfonate), carboxylate-terminate PAMAM dentrimer (G1.5-COONa) or bovine serum albumin, suggesting potential application in bioanalytical fields.

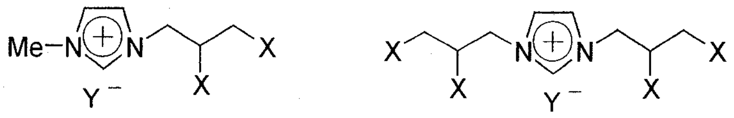


Zwitter-Au

Figure 8. Gold nanoparticles stabilized by zwitterionic imidazolium sulfonate-terminated thiols.

Lee and coworkers reported the one-phase synthesis of gold and platinum nanoparticles via general procedures using multiple thiol-funtionalized ionic liquids as capping reagents.[145] The structures of the ionic liquids used are shown in Figure 9.

Electron diffraction revealed that all of Au and Pt nanoparticles are crystalline with face-centers cubic (fcc) packing arrangement, and average diameters of the nanoparticles are between 2.0 –3.5 nm, lack of plasmon adsorption. The experimental results showed that the nanoparticle size and distribution were dependent on the number and position of thiol groups in the ionic liquids, that is, ionic liquids with symmetrical structures gave smaller particles size and narrower size distribution than the unsymmetrical ones.



X = $HSCH_2CO_2$; Y = Cl, $HS(CH_2)_3SO_3$

Figure 9. The molecular structures of multiple thiol-functionalized ionic liquids.

1. 5. 3. Preparation of metal nanoparticles in ionic liquids

The preparation of transition-metal nanoparticles via reduction of metal complexes in ionic liquids to generate nanoparticle catalyst systems has been described in the above section. In some cases, the transition–metal nanoparticles, dispersed in ionic liquids, tend to aggregate into larger structures after several runs in the catalytic reactions. This leads to the loss of their catalytic activities, especially for Rh(0) and Pd(0) nanoparticles.[146, 126] The reactivation of those nanoparticles may be achieved by break them up into smaller ones again and then evenly dispersed in the ionic liquids. To reach this goal, Dupont and coworkers introduced *in situ* laser radiation of the large nanoparticles dispersed in water immiscible ionic liquid such as [bmim][PF_6] to induce their fragmentation into smaller nanoparticles.[147] This approach is based on the principle that photo-ejection can generate electronic efficiency on metal particle surface, which facilitates fragmentation of the particles and approximation of the ionic liquids, consequently forming a protective layer to make difficult the agglomeration of small nanoparticles into larger clusters.

Recently, Larionova, Guari and coworkers reported the synthesis of cyano-bridged magnetic nanoparticles using ionic liquids as solvents and stabilizers by simply mixing two solutions of $[bmim]_3[Fe(CN)_6]$ and $[M(H_2O)_6]X$ ($M = Cu$, $X = BF_4$; $M = Ni, Co, Fe$, $X = NO_3$) in ionic liquids such as $[bmim][BF_4]$ and $[C_{10}mim][BF_4]$.[148] The as-synthesized nanoparticle colloids of ($M_3[Fe(CN)_6]_2/[RMIM][BF_4]$) were transparent with deep colors and stable for months. The nanoparticle obtained had uniform size, spherical shape with a diameter of about 2-3 nm. Actually, they can be taken as heterometallic cyano-bridged coordination polymers with controlled sizes. In addition, those nanoparticles showed interesting magnetic behaviors at low temperature.

Since ionic liquids possess great thermal stable property, they can be used as solvents to prepare metal nanoparticles at relatively high temperature. Long chain acid or amine-stabilized silver or platinum nanoparticles were prepared by Yang and Zhang[149] via mixing silver trifluoroacetate and oleic acid in ionic liquid of $[bmim][Tf_2N]$ at 200 °C or heating the mixture of platinum acetylacetonate, 1,2-hexandecandiol and oleylamine in $[bmim][Tf_2N]$ at 230 °C, where 1,2-hexandecandiol was used as a reducing reagent. The resulting silver and platinum nanoparticles could settle out from the ionic liquid during the reaction with the particle size of about 4.5 nm. The isolated nanoparticles have an excellent dispersity in conventional organic solvent s such as hexane. Control experiment showed that the long chain acid or amine was necessary to obtain the metal nanoparticles with narrow size distribution and make possible automatic separation of nanoparticles from ionic liquid. Meanwhile, the same group reported the preparation of cobalt-platinum nanorods in ionic liquid of [bmim][Tf_2N] at high temperature of up to 350 °C.[150]

In summary, metallic nanoparticles have large surface area, which are thermodynamically unstable and tend to aggregate into larger particles or bulk metals to decrease their entropy. Thus, they have to be stabilized by other additives such as surfactants, thiols, polymers, tetraalkylammonium salts and so on. In this review, it has been well demonstrated that some ionic liquids, which do not have special functional groups such as thiols, can still be used as stabilizing reagents to synthesize metal nanoparticles with narrow particle-size distribution and good stability. However, even though the mechanism to account for this unique chemistry is still open to researchers, some interesting experimental results have already been described in recent years. First of all, since ionic liquids are highly ordered organic salts, the combination of intrinsic charges and special hindrance of those salts can create an electrostatic and steric stabilization of transition-metal nanoparticles because the surface of metal(0) nanoparticles are not completely neutral, which still possess a small number of positive charges.[151] This is similar to the proposed model in the cases of polyoxoanion or tetraalkyl ammonium salt-stabilized nanoclusters.[152] The second hypothesis is that the surface of transition-metal nanoparticles was coordinated to N-heterocyclic nanoparticles from imidazolium based ionic liquids. This hypothesis was supported by the experimental results described by Finke and coworkers.[153] They detected Ir(0) nanoparticle surface-ligand-coordinated N-heterocyclic carbene formation in [bmim][NTf_2] by using D_2 plus ^2H NMR spectroscopy. The experimental results showed deuterium incorporation was apparent at the 2-H, 4-H, 5-H and 8-H position of the imidazolium cation and it occurred at 2-H and 4-H position only after an induction period. This rules out the possibility that N-heterocyclic carbene formation was due to the H/D exchange from imidazolium moiety and iridium precursor complex before the formation of Ir(0) nanoparticles. Another hypothesis is η^5-coordination of the imidazolium cation to the electronic efficient metal(0) surface. So far, no convincible experimental results have been put forward to support this proposal. It is also quite difficult to imagine that a positively-charged imidazolium ring can coordinate to electron deficient metal surface.

1. 6. Summary and outlook

From the contents of the above review, it is clear that the area of functionalized ionic liquids has expanded significantly in the last several years and their applications in industry will not be too far off in the future since the seminal application equipment of ionic liquids have already been set up in BASF several years ago.[65] The modification of ionic liquid molecules with special functional groups can not only generate new ionic liquids with classical behaviors but also endow them with new properties for special tasks in academic investigations or people's life. The efficient transfer of chirality from solvents to molecules is a frontier research topic. Any breakthrough in this field can cast a new light on the theoretic basis of asymmetric synthesis and catalysis. Ionic liquid-stabilized transition-metal nanoparticle catalyst systems show great enhancement of activity and recyclability. The immobilization of these systems on solid supports has remarkable potential applications in industry because this combination makes the catalyst system have the advantages from both homogeneous and heterogeneous catalysis. Ionic liquids, as soluble supports, can significantly simplify the procedures of organic synthesis. More efforts are supposed to be delivered to new support design and applications, especially for the environmentally benign processes. The following chapters of this thesis will demonstrate how to use ionic liquids as a soluble support for ordorless Swern oxidation, oligosaccharide synthesis and design and synthesis of novel ionic liquid oligomers and their applications to peptide synthesis.

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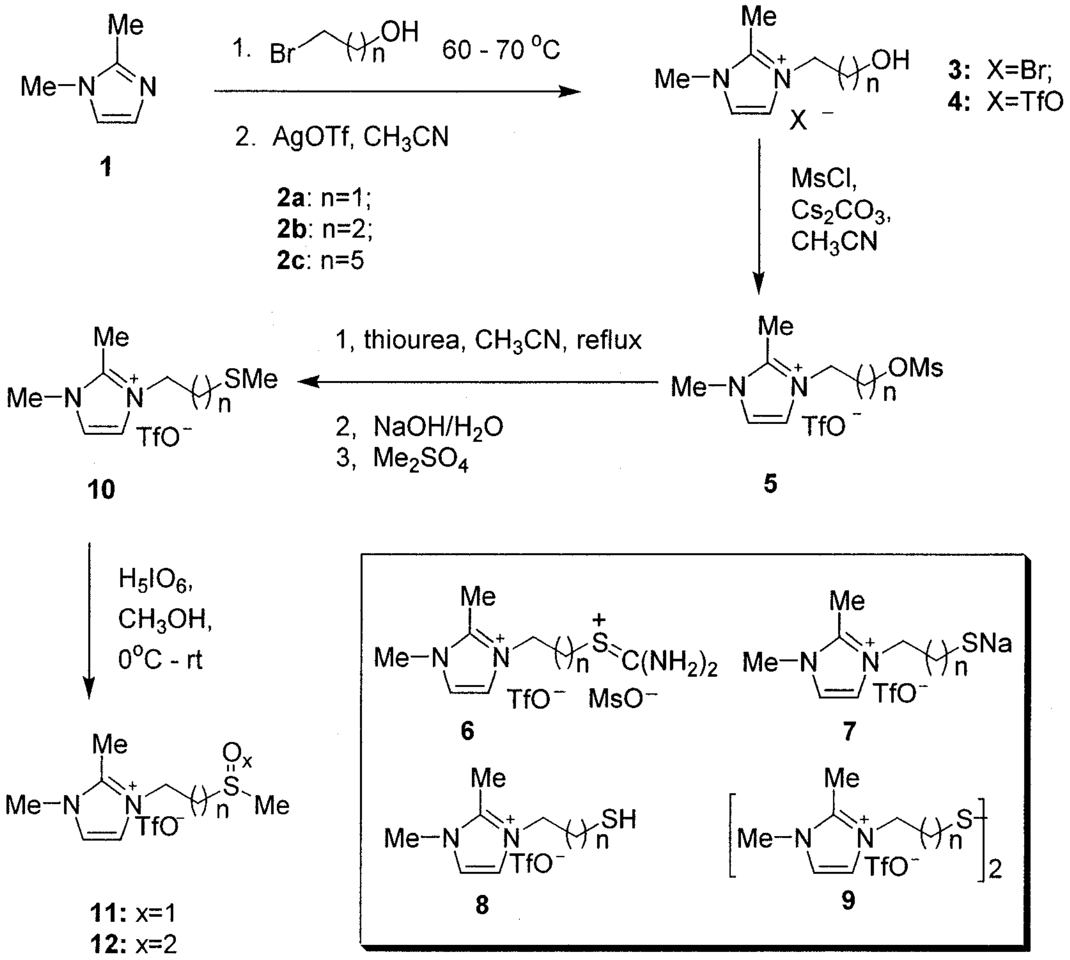
Chapter 2. New Non-Volatile and Odorless Organosulfur Compounds Anchored on Ionic Liquids. Recyclable Reagents for Swern Oxidation

2. 1. Introduction

Organosulfur compounds have played an important role in organic chemistry.[1] An array of organosulfur compounds have been introduced for use in pesticides, medicines,[2] and more recently material sciences.[3] Many organosulfur reagents have important use in synthetic organic chemistry.[4] Volatile organosulfur compounds, especially thiols, often have very unpleasant smells and some are toxic.[2] These properties have reduced their attractiveness for applications. We report here the synthesis of a new class of organosulfur compounds anchored on the imidizolium scaffold commonly used for ionic liquids. Ionic liquids have received much attention in recent years as environmentally benign reaction media for organic reactions.[5] This is due to some intriguing properties of ionic liquids: high thermal and chemical stability, non-flammability, lack of measurable vapour pressure and high loading capacity. By modifying the structure of the cation or the anion, the solubility of the ionic liquids can be tuned readily so that they can phase separate from organic as well as aqueous media. By anchoring the sulfur function to the ionic liquid moiety, we expect to render the organosulfur compounds non-volatile, and easily recoverable and recyclable. We then demonstrate the application of these new organosulfur compounds as reagents for the Swern oxidation.

2. 2. Results and discussion

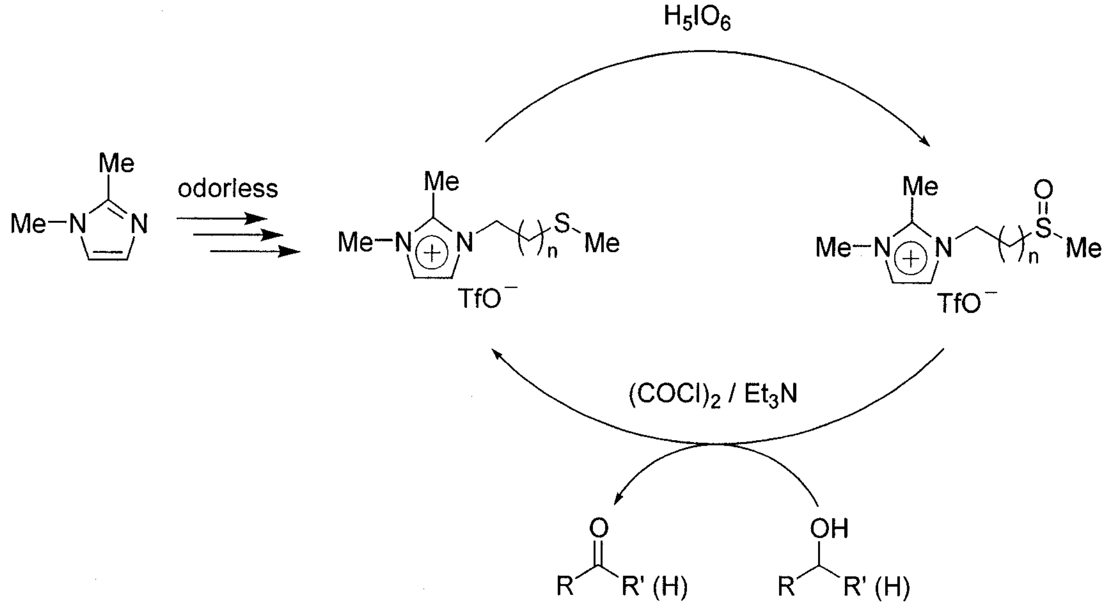


Scheme 1. Preparation of ionic liquid-grafted sulfides and sulfoxides.

The preparation of the ionic liquid-supported sulfur compounds started from 1,2-dimethylimidazole **1** and bromoalkyl alcohols **2** (Scheme 1). The reaction was conducted without solvent at 60–70 °C and the product **3** was obtained in nearly quantitative yield simply by washing the reaction mixture with diethyl ether to remove the trace amount of unreacted starting materials. This was followed by anion exchange to give the triflate salt **4** quantitatively. Mass spectroscopic analysis showed that the anion exchange was complete based on the spectra on anions, which showed the absence of bromide anion. Sodium triflate also worked for the anion exchange reaction, but the reaction went faster with silver triflate. The methanesulfonylation of alcohols **4** was conducted at room temperature under the basic condition provided by Cs_2CO_3 in acetonitrile. This gave excellent yields of product mesylates **5**. The inorganic salt was simply removed by filtration and the organic impurity was easily washed away with diethyl ether. The mesylates **5** were then transformed to the ionic liquid-supported sulfides **10** in one pot with a sequence of reactions but without need of purification of the intermediate products. First, treatment of **5** with thiourea in acetonitrile gave the thiouronium salt **6**.[6] Base hydrolysis of **6** gave the odorless ionic liquid-supported thiol **8** together with the disulfide **9** as a mixture. The sole formation of pure thiol **8** was difficult even though a number of reaction conditions were tested including using different bases such as LiOH, NaOH, KOH and CsOH, or solvents such as THF and acetonitrile, and temperature from room temperature to 60 °C. This is due to ease of thiol oxidative dimerization in air under basic conditions. However, we were able to trap the thiolate intermediate **7** readily as the methyl sulfide **10** by quenching the basic hydrolytic reaction mixture with dimethyl sulfate.[7] The conversion of the ionic liquid **4** to the sulfur compound **10** could be achieved in > 92% overall yield with no need of chromatographic purification of intermediates and there was no foul smell released in any of the operations. This is because in all the reaction steps, the products were separated from the excess organic or inorganic reagents by simply washing with organic or aqueous solvents, an advantage, which we have demonstrated previously in ionic liquid supported synthesis of small molecules,[8] oligopeptides[9] and oligosaccharides.[10] The whole synthetic sequence was odor-free as no volatile organosulfur compounds were used or generated. Previously, sulfur containing imidazolium ionic liquid had been synthesized from N-methylimidazole and 2-(chlorethyl)ethyl sulfide.[11] However, this involved the use of odorous volatile sulfur compound for the synthesis, and ethyl sulfoxides in general are not used for Swern oxidation.

The oxidation of the sulfides **10** with periodic acid generated very cleanly the sulfoxides **11** without over-oxidation to the sulfone **12** under the experimental condition.[12] Potassium periodate did not oxidize **10** under neutral conditions, but under acidic conditions converted **10** to a mixture of sulfoxide **11** as well as sulfone **12** in a ratio of 3 to 1 according to ^{1}H NMR spectra. *m*-chloroperoxybenzoic acid (mCPBA) also oxidized the sulfide **10** to give similar results as acidified potassium periodate. The oxidation of the sulfides with peracetic acid, on the other hand, proceeded slowly at room temperature. It only generated a very small amount of sulfoxide **11** after stirring for 24 h at room temperature.

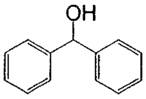
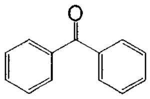
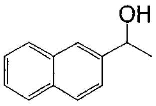
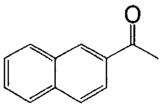
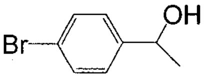
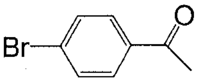
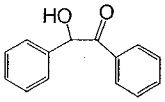
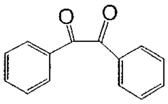
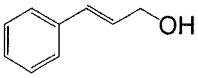
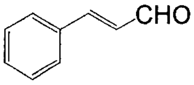
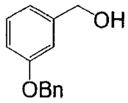
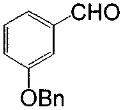
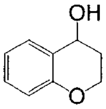
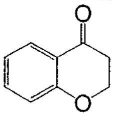
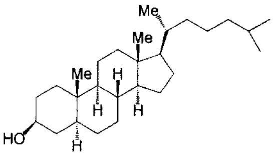
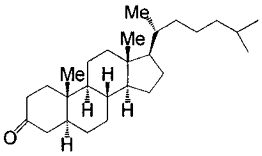
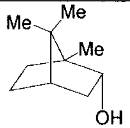
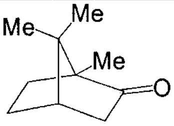
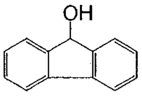
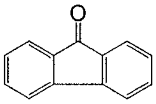
The conversion of alcohols to aldehydes and ketones is one of the key functional transformations in organic chemistry. The Swern oxidation and its numerous variations[13, 14] have been used extensively for that purpose. A major drawback of the Swern oxidation is that dimethyl sulfide, generated in stoichiometric amount, is volatile, malodorous, toxic and difficult to recover. This mitigates its use on a large scale. A number of research groups have attempted to overcome the problem by using polymer-supported sulfoxide reagents,[15] fluorous sulfoxides[16] or dodecyl methyl sulfoxide.[17] Each of these has some inherent deficiencies. In the dodecyl methyl sulfoxide case, recovery of the product sulfide was difficult. The fluorous sulfoxides and sulfides are likely to be expensive and relatively volatile. Polymer-supported sulfoxide reagents,[15] whether using insoluble or soluble polymer support, usually have a low loading level of the effective functional group.

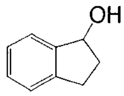
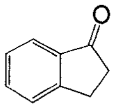
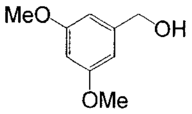
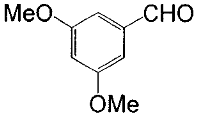


Scheme 2. Recycle of ionic liquid-supported sulfides and sulfoxides in Swern oxidation.

We examined therefore the ionic liquid-supported sulfoxides **11** as recoverable and recyclable reagents for the Swern oxidation reaction (Scheme 2). The Swern oxidations were conducted under standard conditions, using oxalyl chloride as activator and triethylamine as base in acetonitrile/dichloromethane at low temperature. The ionic liquid-attached sulfoxides **11b** or **11c** were quite reactive. A number of alcohols were converted to the corresponding aldehydes or ketones in high yields (Table 1). The carbonyl product was easily separated from the ionic liquid anchored sulfide **10** (**b** or **c**) by simple phase separations with diethyl ether after Swern oxidation. However, it should be pointed out that the sulfoxide **11a**, which has two methylene spacers between the ionic liquid moiety and the sulfoxide part, did not work well as Swern oxidation reagent. It is possible that facile β elimination may have occurred leading to the fragmentation of the imidazolium moiety from the sulfoxide. The oxidation of secondary alcohols to the corresponding ketones worked very efficiently under the reaction conditions (Table 1). On the other hand, oxidation of primary alcohols to aldehydes appears to have worked well only for benzylic or allylic alcohols. Simple aliphatic primary alcohols tended to give low yield, possibly because the sulfoxide **11b** or **11c** reagent was not employed in large excess, in contrast to what was normally used for DMSO.[14] We have conducted one reaction on a larger (10–50 mmol) scale for the oxidation of benzhydrol to benzophenone. The isolated yield of the product was 91%.

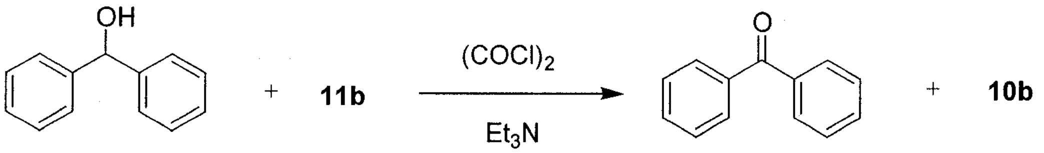
Table 1. Swern oxidation using ionic liquid-supported sulfoxides

Entry	Sulfoxide	Substrate	Product	Yield (%)
1	**11b**			90
2	**11b**			95
3	**11b**			86
4	**11b**			85
5	**11b**			88
6	**11b**			95
7	**11b**			82
8	**11b**			85
9	**11b**			90
10	**11c**			95

11	**11c**			82
12	**11c**			97

The use of ionic liquid-supported reagents allows for the opportunity of recovery and recycle. The sulfide **10b** or **10c**, insoluble in ether, was recovered after aqueous treatment with K_2CO_3 and extraction with acetonitrile/dichloromethane.[18] The recovered sulfide **10b** or **10c** can be re-oxidized with periodic acid and used for the Swern oxidation again. Oxidation of benzhydrol to benzophenone was chosen as an example to test the recovery and recycling efficiency of the **11b** ↔ **10b** system. The results are summarized in Table 2, which show that the product yields and recovered sulfide yields were still quite acceptable after four recycles (Table 2).[18]

Table 2. Recycle of ionic liquid-supported sulfide **10b** in Swern oxidation of benzhydrol to bnzophenone



Recycle times	1	2	3	4
Product yield (%)	90	87	86	81
Recovered Sulfide (%)	88	82	82	80

2. 3. Conclusions

We have prepared a class of novel sulfur containing compounds anchored onto an imidazolium ionic liquid scaffold. Because of the lack of vapor pressure of these ionic liquids, the sulfur compounds do not possess odor. The sulfoxide compounds **11b** and **11c** can be used effectively for the oxidation of alcohols to carbonyl compounds under Swern oxidation conditions. The product sulfide **10b** can be recovered easily from the reaction mixture and regenerated to **11b** and thus reused for at least 4 cycles.

2. 4. Experimental section

General: The procedures to make ionic liquid-attached compounds with two, three, six methylene spacers in the Scheme 1 were the same.

1-(3'-Hydroxypropyl)-2,3-dimethylimidazolium triflate (4b):

To a flask containing 1,2-dimethylimidazole (10.0 mL, 113 mmol) was added 3-bromopropanol (10.0 mL, 114 mmol). The mixture was heated to 70 °C and stirred for 2 h under nitrogen and then cooled to room temperature. The crude product solidified during the cooling process. The solid was washed with diethyl ether for four times and dried in vacuo for 3 h to afford 1-(3'-Hydroxypropyl)-2,3-dimethylimidazolium bromide **(3b)** as white solid (26.2 g, 98% yield).

1-(3'-Hydroxypropyl)-2,3-dimethylimidazolium bromide (3b):

Mp 58–60 °C; ^{1}H NMR (400 MHz, D_2O): δ 7.24 (d, 1H, J = 2 Hz), 7.20 (d, 1H, J = 2 Hz), 4.10 (t, 2H, J = 7.2 Hz), 3.65 (s, 3H), 3.50 (t, 2H, J = 6.4 Hz), 2.48 (s, 3H), 1.93 (m, 2H); ^{13}C NMR (300 MHz, D_2O): δ 144.5, 122.4, 120.9, 58.2, 45.3, 35.0, 31.6, 9.4; HRMS (ESI): calcd for $C_8H_{15}N_2O$ (M^+) 155.1179, found: 155.1178.

To a solution of 1-(3'-hydroxypropyl)-2,3-dimethylimidazolium bromide **(3b)** (4.97 g, 21.1 mmol) in dry acetonitrile (20 mL) was added silver triflate (5.43 g, 21.1 mmol). The mixture was stirred for 2 h in the dark under nitrogen. The mixture was filtered to remove the yellow salt and the filtrate was evaporated by rotary evaporation under reduced pressure and dried *in vacuo* to generate the product **4b** as a clear liquid with a very light brown color (6.42 g, 100% yield).

^{1}H NMR (300 MHz, D_2O): δ 7.27 (d, 1H, J = 1.8 Hz), 7.23 (d, 1H, J = 1.8 Hz), 4.12 (t, 2H, J = 7.2 Hz), 3.68 (s, 3H), 3.53 (t, 2H, J = 6.3 Hz), 2.51 (s, 3H), 1.96 (m, 2H); ^{13}C NMR (300 MHz, D_2O): δ 144.5, 122.4, 120.9, 58.1, 45.2, 34.9, 31.6, 9.1; HRMS (ESI): calcd for $C_8H_{15}N_2O$ (M^+) 155.1179, found: 155.1180.

1-(2'-Hydroxyethyl)-2,3-dimethylimidazolium triflate (4a):

Yield: 100% as clear liquid; ^{1}H NMR (400 MHz, D_2O): δ 7.28 (d, 1H, J = 2.0 Hz), 7.24 (d, 1H, J = 2.0 Hz), 4.15 (t, 2H, J = 5.6 Hz), 3.82 (t, 2H, J = 6 Hz), 3.69 (s, 3H), 2.51 (s, 3H); ^{13}C NMR (300 MHz, D_2O): δ 144.5, 122.5, 121.2, 60.2, 50.4, 35.0, 9.4; HRMS (ESI): calcd for $C_7H_{13}N_2O$ (M^+) 141.1018, found: 141.1022.

1-(6'-Hydroxyhexyl)-2,3-dimethylimidazolium triflate (4c):

Yield: 100% as clear liquid; ^{1}H NMR (300 MHz, D_2O): δ 7.21 (d, 1H, J = 2.4 Hz), 7.17 (d, 1H, J = 2.4 Hz), 3.98 (t, 2H, J = 6.9 Hz), 3.64 (s, 3H), 3.46 (t, 2H, J = 6.6 Hz), 2.46 (s, 3H), 1.70 (m, 2H), 1.42 (m, 2H), 1.23 (m, 4H); ^{13}C NMR (300 MHz, D_2O): δ 144.2, 122.2, 120.8, 61.9, 48.3, 34.8, 31.4, 29.2, 25.5, 24.9, 9.1; HRMS (ESI): calcd for C11H21N2O (MC) 197.1648, found: 197.1646.

Compound 5b:

To a flask containing 4b (6.00 g, 19.7 mmol) and cesium carbonate (8.05 g, 24.7 mmol) was added acetonitrile (30 mL). The mixture was cooled to 0 °C and methanesulfonyl chloride (2.30 mL, 29.6 mmol) was added dropwise. After 2 h of stirring at 0 °C, the mixture was warmed to room temperature and stirring continued for

20 h. The insoluble inorganic salt was filtered off and the filtrate was evaporated by rotary evaporation and dried *in vacuo* overnight. The crude product was washed with diethyl ether for four times to afford white solid product **5b** (7.31 g, 97% yield).

Mp 47–49 °C; ^{1}H NMR (400 MHz, D_2O): δ 7.25 (d, 1H, J = 2.0 Hz), 7.21 (d, 1H, J = 2.0 Hz), 4.23 (t, 2H, J = 5.6 Hz), 4.16 (t, 2H, J = 7.2 Hz), 3.64 (s, 3H), 3.06 (s, 3H), 2.46 (s, 3H), 2.19 (m, 2H); ^{13}C NMR (400 MHz, D_2O): δ 144.7, 122.6, 120.9, 68.2, 44.8, 36.6, 34.9, 28.8, 9.2; HRMS (ESI): calcd for $C_9H_{17}N_2O_3S$ (M^+) 233.0954, found: 233.0953.

Compound 5a:

Yield: 94% as clear liquid; ^{1}H NMR (400 MHz, D_2O): δ 7.30 (d, 1H, J = 1.6 Hz), 7.23 (d, 1H, J = 1.6 Hz), 4.51 (t, 2H, J = 4.8 Hz), 4.42 (t, 2H, J = 5.6 Hz), 3.65 (s, 3H), 3.05 (s, 3H), 2.49 (s, 3H); ^{13}C NMR (400 MHz, D_2O): δ 145.4, 122.8, 121.3, 68.6, 47.3, 36.9, 35.1, 9.5; HRMS (ESI): calcd for $C_8H_{15}N_2O_3S$ (M^+) 219.0795, found: 219.0798.

Compound 5c:

Yield: 95% as clear liquid; ^{1}H NMR (400 MHz, D_2O): δ 7.16 (d, 1H, J = 2.4 Hz), 7.12 (d, 1H, J = 2.4 Hz), 4.15 (t, 2H, J = 6.0 Hz), 3.94 (t, 2H, J = 7.2 Hz), 3.58 (s, 3H), 3.00 (s, 3H), 2.41 (s, 3H), 1.68 (m, 2H), 1.59 (m, 2H), 1.28 (m, 2H), 1.17 (m, 2H); ^{13}C NMR (400 MHz, CD_3CN): δ 144.6, 122.5, 121.0, 71.1, 48.4, 36.8, 35.1, 29.5, 28.9, 25.6, 25.0, 9.6; HRMS (ESI): calcd for $C_{12}H_{23}N_2O_3S$ (M^+) 275.1424, found: 275.1420.

Compound 10b:

To a flask containing 5b (1.00 g, 2.61 mmol) and thiourea (0.32 g, 4.20 mmol) was added dry acetonitrile (20 mL). The mixture was refluxed for 10 h under nitrogen. After removing the solvent, NaOH (0.42 g, 10.5 mmol) and degassed water (20 mL) were added and the mixture was stirred at 45 °C overnight under nitrogen. Dimethyl sulfate

(0.30 mL, 3.15 mmol) was added and the mixture was stirred at room temperature for 20 h. After the pH of the mixture was adjusted to 7 with the addition of aqueous HCl, the mixture was freeze dried to remove water. Acetonitrile was added to the residue to extract the product. The acetonitrile solution was filtered to remove the insoluble inorganic salt, and the filtrate was rotary evaporated under vacuum and then dried in vacuo to give product **10b** as clear oil (0.87 g, 99% yield).

^{1}H NMR (400 MHz, D_2O): δ 7.22 (d, 1H, J = 2.4 Hz), 7.17 (d, 1H, J = 2.4 Hz), 4.08 (t, 2H, J = 6.8 Hz), 3.62 (s, 3H), 2.47 (s, 3H), 2.41 (t, 2H, JZ6.8 Hz), 1.97 (m, 5H); ^{13}C NMR (300 MHz, D_2O): δ 144.5, 122.5, 120.8, 46.9, 34.9, 29.9, 28.3, 14.4, 9.2; HRMS (ESI): calcd for $C_9H_{17}N_2S$ (M^+) 185.1107, found: 185.1103.

Compound 10a:

Yield: 99% as clear oily liquid; ^{1}H NMR (400 MHz, D_2O): δ 7.28 (d, 1H, J = 2.0 Hz), 7.21 (d, 1H, J = 2.0 Hz), 4.22 (t, 2H, J = 6.4 Hz), 3.66 (s, 3H), 2.83 (t, 2H, J = 6.4 Hz), 2.51 (s, 3H), 1.99 (s, 3H); ^{13}C NMR (400 MHz, D_2O): δ 144.7, 122.4, 121.1, 47.2, 35.0, 33.4, 14.7, 9.4; HRMS (ESI): calcd for $C_8H_{15}N_2S$ (M^+) 171.0950, found: 171.0949.

Compound 10c:

Yield: 98% as clear oily liquid; ^{1}H NMR (300 MHz, D_2O): δ 7.16 (d, 1H, J = 1.8 Hz), 7.13 (d, 1H, J = 1.8 Hz), 3.94 (t, 2H, J = 7.2 Hz), 3.60 (s, 3H), 2.42 (s, 3H), 2.36 (t, 2H, J = 7.2 Hz), 1.92 (s, 3H), 1.65 (m, 2H), 1.43 (m, 2H), 1.52 (m, 4H); ^{13}C NMR (300 MHz, D_2O): δ 144.2, 122.2, 120.8, 48.3, 34.7, 33.4, 29.1, 28.3, 27.6, 25.3, 14.4, 9.1; HRMS (ESI): calcd for $C_{12}H_{23}N_2S$ (M^+) 227.1576, found: 227.1575.

Compound 11b:

To a solution of **10b** (5.05 g, 15.1 mmol) in methanol (50 mL), which was cooled with ice bath, was added dropwise a solution of periodic acid (3.45 g, 15.1 mmol) in methanol (15 mL). The mixture was stirred at 0 °C for 2 h. The ice bath was removed and stirring was continued for 20 h. To the orange mixture was added aqueous $Na_2S_2O_3$ solution until the orange color disappeared. The solvent methanol was removed by rotary evaporation *in vacuo* and water was removed by freeze dry. To the residue was then added the mixed solvent (100 mL) of acetonitrile and dichloromethane (v/v = 1:1). After filtering off the inorganic salt, the filtrate was rotary evaporated under vacuum and dried *in vacuo* to afford the product as white sticky foam (5.18 g, 98% yield).

^{1}H NMR (400 MHz, D_2O): δ 7.24 (d, 1H, J = 2 Hz), 7.17 (d, 1H, J = 2 Hz), 4.14 (t, 2H, J = 7.2 Hz), 3.61 (s, 3H), 2.84–2.72 (m, 2H), 2.56 (s, 3H), 2.45 (s, 3H), 2.15 (m, 2H); ^{13}C NMR (400 MHz, D_2O): δ 144.6, 122.7, 120.8, 49.1, 46.9, 37.1, 35.1, 23.0, 9.4; HRMS (ESI): calcd for $C_9H_{17}N_2SO$ (M^+) 201.1056, found: 201.1056.

Compound 11a:

Yield: 99% as thick oil; ^{1}H NMR (400 MHz, D_2O): δ 7.33 (d, 1H, J = 2.4 Hz), 7.26 (d, 1H, J = 2.4 Hz), 4.53 (t, 2H, J = 6.0 Hz), 3.68 (s, 3H), 3.33 (m, 1H), 3.24 (m, 1H), 2.68 (s, 3H), 2.55 (s, 3H); ^{13}C NMR (300 MHz, D_2O): δ 144.9, 123.0, 121.0, 52.1, 42.3, 37.5, 35.2, 9.5; HRMS (ESI): calcd for $C_8H_{15}N_2SO$ (M^+) 187.0900, found: 187.0898.

Compound 11c:

Yield: 96% as thick oil; ^{1}H NMR (300 MHz, D_2O): δ 7.16 (d, 1H, J = 2.1 Hz), 7.13 (d, 1H, J = 2.1 Hz), 3.95 (t, 2H, J = 6.9 Hz), 3.59 (s, 3H), 2.71 (m, 2H), 2.52 (s, 3H), 2.42 (s, 3H), 1.67 (m, 2H), 1.58 (m, 2H), 1.35 (m, 2H), 1.19 (m, 2H); ^{13}C NMR (400 MHz, D_2O):

δ 144.2, 122.2, 120.8, 52.8, 48.3, 36.7, 34.9, 29.0, 27.5, 25.4, 22.0, 9.2; HRMS (ESI): calcd for $C_{12}H_{23}N_2SO$ (M^+) 243.1526, found: 243.1525.

General procedure for the Swern oxidation:

A solution of ionic liquid-attached sulfoxide **11** (0.9 mmol, 3 equiv) in dichloromethane (2.5 mL) and acetonitrile (2.5 mL) was cooled to −78 °C and oxalyl chloride (0.9 mmol, 3 equiv) was added dropwise. The mixture was stirred at −78 °C for 40 min and then the alcohol (0.3 mmol, 1 equiv) solution in dichloromethane (2.5 mL) was added dropwise in 10 min. After stirring at low temperature for 1.5 h, triethylamine (0.25 mL, 6 equiv) was added and the mixture was slowly warmed to room temperature. The solvent was removed by rotary evaporation and the product in the residue was extracted with diethyl ether (6 mL) for five times. The ether extract was evaporated by rotary evaporation *in vacuo*. The product residue was subject to flash column chromatography (silica gel 60 A, 230–400 mesh) using hexane and ethyl acetate as eluant to afford the pure product.

Swern oxidation in larger scale:

A solution of ionic liquid-attached sulfoxide **11b** (16.73 g, 48 mmol) in dichloromethane (50 mL) and acetonitrile (75 mL) was cooled to −78 °C and oxalyl chloride (4.8 mL, 55 mmol) was added dropwise. The mixture was stirred at −78 °C for 40 min and then the alcohol benzhydrol (2.92 g, 16 mmol) solution in dichloromethane (25 mL) was added dropwise in 10 min. After stirring at low temperature for 1.5 h, triethylamine (14 mL, 100 mmol) was added and the mixture was slowly warmed to room temperature in 2 h. The solvent was removed by rotary evaporation and the product in the residue was extracted with diethyl ether (60 mL) for 10 times. The ether extract was evaporated by rotary evaporation *in vacuo*. The product residue was subject to flash column chromatography (silica gel 60 A, 230–400 mesh) using hexane and ethyl acetate as eluant to afford the product benzophenone (2.62 g, 91% yield).

General procedure to recover ionic liquid-attached sulfide after Swern oxidation:

After the extraction of the product with diethyl ether described above, water (10 mL) was added to the residue. The aqueous phase was collected and to which K_2CO_3 (0.16 g, 1.1 mmol) was added. The aqueous phase was stirred for 3 h at room temperature and water was removed by freeze–dry by lypholyser. To the solid residue was then added acetonitrile (10 mL), dichloromethane (5 mL) and anhydrous Na_2SO_4. The mixture was stirred for 20 min to extract the expected sulfide into the organic phase. After filtering off the insoluble inorganic salts, the organic filtrate was evaporated by rotary evaporation under vacuum and dried *in vacuo* to generate the recovered ionic liquid-attached sulfide **10** (Table 2). The NMR spectra of the recovered sulfide showed the same NMR as that of **10** before reaction. The recovered sulfide was used for the next cycle. The recovery yield was about 80%, due to mechanical loss associated with the small scale experimental conditions.

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(7) The sulfide **10** could also be made through the nucleophilic replacement of the mesylate **5** with sodium thiomethoxide. However, this approach was less desirable as the unpleasant smelling methanethiol was inevitably generated in the workup.

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(18) The sulfide **10b** or **10c** were recovered in 75–88% yield of the sulfoxide used. The loss was attributed to mechanical loss because of the small amount of sulfoxide used (0.9 mmol) and the difficulty of complete recovery during transfer between flasks.

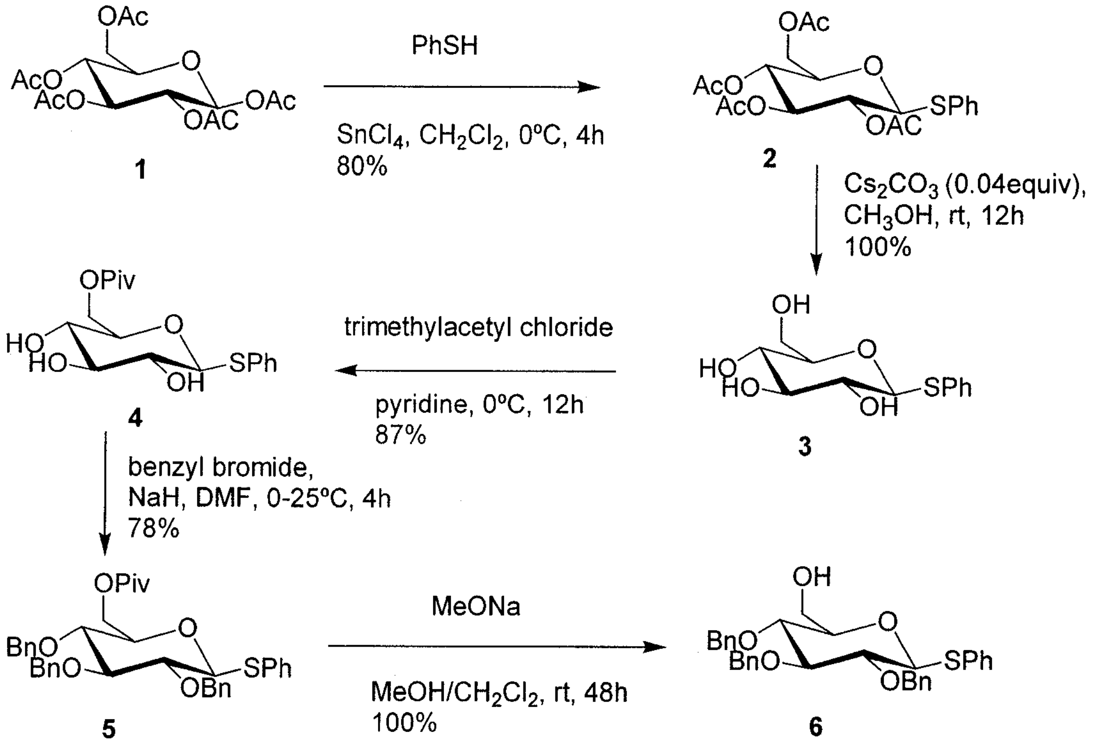
Chapter 3. Ionic Liquid-Supported Oligosaccharide Synthesis

3. 1. Introduction

The efficient synthesis of oligosaccharides is a contemporary challenge which has led to the development of several new strategies for oligosaccharide synthesis. The central issue is that the traditional access to structurally defined oligosaccharides with solution-phase synthesis is laborious and requires purification of the reaction products by chromatography after each step.[1] Recent advances in polymer–supported solid-phase synthesis[2-4] provide an easier way to assemble complex oligosaccharides because it allows for removal of the excess reagents by simply washing the resins and thus minimizes the number of chromatographic steps required.[5,6] This has led to impressive examples of successful automated synthesis.[3,7] However, the disadvantages of solid-phase synthesis are that a large excess of the expensive carbohydrate unit is often required to drive the heterogeneous reaction to completion and it is more difficult to monitor the sugar-sugar coupling process by normal characterization methods such as TLC, NMR and mass spectrometry. The alternative of using soluble polyethyleneglycol (PEG) polymers as supports for oligosaccharide synthesis has been developed to overcome some of the disadvantages of solid-phase synthesis.[8-12] Several problems are still associated with this soluble polymer-supported approach due to the relatively low loading of saccharide onto the soluble polymer and the difficulties in the selective precipitation of the oligosaccharide-attached polymer. More recently, a new solution-phase synthesis based on the use of highly fluorinated (fluorous) soluble supports has been advocated.[13] The approach is based on the preferential solubility of the fluorous support in fluorous solvents and the non-fluorinated reagents can be readily separated from the supported saccharides through fluorous-organic solvent partitioning[14a-d] or fluorous silica gel based solid-phase extraction (SPE).[14e-h] This approach requires the use of highly fluorinated compounds which are not generally readily available. Furthermore, the solubility of the saccharide-anchored support in the fluorous solvent depends on the fluorine content[15] which declines as the number of saccharide unit increases. Therefore, the desirable approach to synthesize oligosaccharides should possess the merits of both solid-phase and solution-phase synthesis, that is, homogenous solution-phase reaction with easy purification of final product. Herein we describe the development of a new approach to oligosaccharide synthesis functionally supported by ionic liquids.

Ionic liquids have received much attention in recent years as environmentally benign reaction media for organic reactions.[16] This is due to some intriguing properties of ionic liquids: high thermal and chemical stability, non-flammability, lack of measurable vapor pressure and high loading capacity. By modifying the structure of the cation or the anion, the solubility of the ionic liquids can be tuned readily so that they can phase separate from organic as well as aqueous media. This offers the potential that ionic liquids can serve as viable soluble functional supports for organic synthesis. The concept is illustrated in Figure 6 of Chapter 1 of this thesis. The substrate anchored onto an ionic liquid moiety is soluble in polar organic solvents and can undergo liquid-phase reaction. After completion of the reaction and evaporation of the solvent, the excess reagents can be removed by a less polar organic solvent, in which the ionic liquid-anchored product is insoluble. Inorganic reagents or side products can be removed by precipitation or by washing with aqueous solution. Finally, the product can be detached and then separated from the ionic liquid moiety by organic solvent extraction. Recently, we and others have demonstrated the concept of ionic liquid supported synthesis (ILSS) for small molecules[17] and small peptides.[18] We demonstrate here that ILSS can be applied to oligosaccharide synthesis using simple phase separations without the need of chromatography for product purification (Scheme 1).

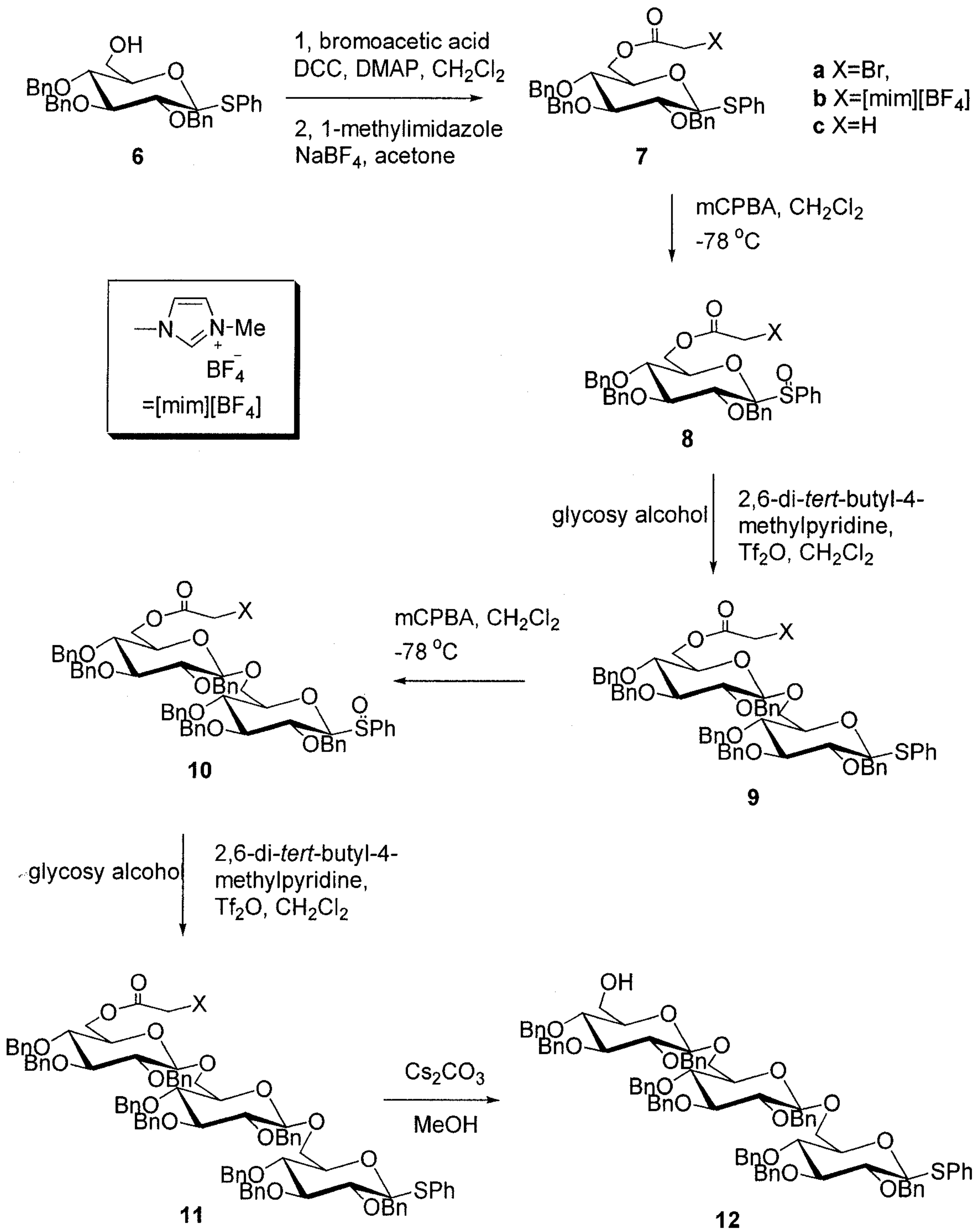
3. 2. Results and Discussion



Scheme 1.

The selectively protected monosaccharide **6** was prepared in five steps from β-D-glucose pentaacetate **1** as shown in Scheme 1. The bulky pivaloyl group was used to selectively protect the primary alcohol[19] of the saccharide **3** after methanolysis deprotection of the four acetyl groups of saccharide **2** under the basic conditions using a catalytic amount of Cs_2CO_3 (less than 5% equivalent to the sugar molecule). The benzylation of compound **4** in DMF under basic conditions generated saccharide **5,** which was then treated with sodium methoxide in methanol to give out the expected β-thioglycoside **6** as building block for the following sugar-sugar couplings.

Saccharide **6** was acylated with bromoacetic acid/DCC/DMAP in CH_2Cl_2 at room temperature to give the bromoacetate **7a** (X=Br) (Scheme 2). Reaction of **7a** (X=Br) with 1-methylimidazole and sodium tetrafluoroborate in acetone at room temperature gave the ionic liquid anchored saccharide **7b** (X=[mim][BF_4]) in 98% yield. Compound **7b** was purified by first washing the crude product with diethyl ether to remove the excess 1-methylimidazole. The product was then dissolved in CH_2Cl_2 and the insoluble inorganic salt NaBr generated in the reaction was removed simply by filtration. The structure of **7b** can be easily confirmed by NMR (^1H, ^{13}C and HMQC), which clearly showed the presence of the imidazolium moiety and the anomeric carbon as the β-anomer. Electrospray ionization mass spectrum (ESI-MS) of **7b** showed the presence of the cation as the only molecular ion. The monosaccharide **7b** was then oxidized by *m*-chloroperbenzoic acid in CH_2Cl_2 at -78 °C for 20 minutes to give the sulfoxide **8b** (X=[mim][BF_4]) as a mixture of diastereomers (due to chirality at the atom sulfur) in 97% yield. The other product of the reaction, *m*-chlorobenzoic acid was removed from the crude product mixture by washing with di-isopropyl ether. The sulfoxide glycosylation reaction was then used as the sugar-sugar assembling method[20-22] with **8b** as the glycosyl donor and **6** as the acceptor (3 equiv). The coupling reaction using 2,6-di-tert-butyl-4-methylpyridine (4 equiv) and Tf_2O (1 equiv) was conducted in dry CH_2Cl_2 at -78 °C because both the glycosyl donor and acceptor were well soluble in dichloromethane at low temperature. The reaction process was monitored by TLC.



Scheme 2.

The product disaccharide **9b** (X=[mim][BF_4]) was obtained by washing away the excess glycosyl alcohol **6**, the acid scavenger base, and other side-products with n-pentane and then di-isopropyl ether. The protonated acid scavenger, 2,6-di-tert-butyl-4-

methylpyridinium triflate, was removed from **9b** by adding n-pentane to a solution of the crude **9b** in CH_2Cl_2 and the solution was then cooled to low temperature to allow **9b** phase-separated from the solution. The ionic liquid-bound disaccharide **9b** was obtained in high purity as indicated by its HMQC NMR showing two anomeric carbons. Furthermore, its ESI-MS not only confirmed its disaccharide structure, but also showed the absence of any unreacted monosaccharide. Repetition of the same sequence of reactions gave the sulfoxide **10b** and then the ionic liquid bound trisaccharide **11b** (X=[mim][BF_4]). The formation of the trisaccharide was confirmed by HMQC NMR showing the presence of three anomeric carbons and by ESI-MS clearly indicating the trisaccharide cation without any contamination of the mono- or disaccharides. Finally, the ionic liquid moiety and the linker were easily cleaved from **11b** by using one equivalent of Cs_2CO_3 in methanol to afford stoichiometric yield of the product **12**. The trisacchairde **12** was easily isolated by evaporation of methanol and dissolving the crude product in CH_2Cl_2 followed by filtration to remove the imidazolium salts. The trisaccharide **12**, thus obtained without any chromatographic or other purification procedures, was found to be NMR and TLC pure. Its HMQC NMR spectrum and ESI-MS ($M+Na^+ = 1429.7$) were found to be identical to an authentic sample of **12** prepared independently by the classical solution phase synthesis starting with **7c** (X=H) following the same sequence of reactions in Scheme 2 but with chromatographic purification in each of the reaction steps. The good purity of **12** obtained by the ionic liquid supported synthesis (ILSS) approach in comparison with the classical solution-phase synthesis through **7c** suggested that the coupling conditions and stereoselectivity developed for classical solution-phase synthesis can be translated to ILSS because the ionic liquid-supported glycals are well soluble in common organic solvents such as dichloromethane and acetonitrile. The homogeneous phase reactions are generally favorable for high reaction efficiency. The present example also presents a contrast to the solid-phase synthesis where chromatography was generally necessary to purify the final product after cleavage from the solid-phase support and monitoring reaction progress also requires the cleavage of the intermediate product from the solid support.[23] Therefore, the ILSS approach possesses the advantages of both conventional solution-phase synthesis and solid-phase synthesis.

3. 3. Conclusions

In conclusion, a new strategy to synthesize oligosaccharides by using ionic liquid as soluble functional support has been demonstrated. This approach appears to provide a way to construct oligosaccharides with greatly simplified purification, requiring no chromatography during the synthesis or at the end of cleavage of the supports. It offers the advantages of solution-phase synthesis, e.g. homogeneous mass transportation and no temperature restriction, and may be suitable for large-scale synthesis. The sugar-sugar coupling processes and product structures can be monitored or characterized by TLC, NMR, MS and other conventional techniques. At this time, the coupling, though highly efficient according to spectroscopy analysis, gave only 50-56% recovery of the products. This may be attributed partly to mechanical loss and partly to the not yet optimal phase separation of **9b** (or **11b**) from the CH_2Cl_2-pentane phase. Furthermore, it remains to be demonstrated whether the approach can be applied to more complex oligosacharides. Nevertheless, the encouraging results suggest that further exploration may prove to be fruitful.

3. 4. Experimental Section

General: All chemicals were obtained from Aldrich, Acros and Fluka and used without further purification except other specially indicated. All solvents were distilled from the appropriate drying reagents. All reactions were performed under anhydrous conditions and monitored by thin-layer chromatography (TLC) on silica gel 60 F-254 polyester-backed plates (250 μm thick), detecting under UV light (254 nm) or charring with aqueous potassium permanganate solution. Column chromatography was performed on silica gel 60A (230-400 mesh). ^{1}H and ^{13}C NMR, HMQC NMR, COSY NMR spectra were recorded on Unity 500, Varian Mercury 400 and Varian Mercury 300 spectrometers equipped with Sun workstations. The chemical shifts were reported in parts per million on the δ scale referenced to residue $CHCl_3$ at δ 7.24 ppm, H_2O at 4.67 ppm for ^{1}H NMR and $CHCl_3$ at 77.0 ppm for ^{13}C NMR. The proton and carbon assignments were made by standard gHMQC and gCOSY experiments. Melting point of sample was taken via melting point apparatus without correcting the thermometer. The electron spray ionization (ESI) mass spectra were recorded on KRATOS MS25RFA Mass Spectrometer.

Phenyl 2, 3, 4, 6-tetra-O-acetyl-1-thio-β-D-glucopyranoside (2):

To a solution of β-D-glucose pentaacetate (49.93 g, 0.128 mol) in dry CH_2Cl_2 (40 mL) was added benzenethiol (14.42 ml, 0.140 mol). The solution mixture was cooled to 0°C by ice bath under the protection of nitrogen and then to which was added 1.0 M solution of $SnCl_4$ in CH_2Cl_2 (127 ml, 0.128 mol) gradually in 10 minutes. After 4 hours of stirring at 0°C, the solution was diluted by CH_2Cl_2 (100ml), transferred into a separatory funnel with of CH_2Cl_2 (200 mL) and washed by water (100 mL) twice. The organic phase was dried over anhydrous Na_2SO_4 and the solvent was removed by rotatory evaporation under reduced pressure and dried overnight *in vacuo.* The product residue was purified by recrystalization in isopropanol to give the product as white needle-like crystal.

Yield: 45.10 g, 80%.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.48 (m, 2H, Ar-H), 7.31 (m, 3H, Ar-H), 5.24 (t, 1H, *J* = 9.6 Hz, H-3), 5.04 (t, 1H, *J* = 10.4 Hz, H-2), 4.97 (dd, 1H, *J* = 9.6 Hz, 9.2 Hz, H-4), 4.70 (d, 1H, *J* = 10 Hz, H-1), 4.24-4.15 (m, 2H, H-6a, b), 3.73 (m, 1H, H-5), 2.09 (s, 3H, acetyl CH_3), 2.08 (s, 3H, acetyl CH_3), 2.02 (s, 3H, acetyl CH_3), 1.99 (s, 3H, acetyl CH_3).

^{13}C NMR (400 MHz, $CDCl_3$): δ 170.66, 170.27, 169.48, 169.35, 133.27, 131.77, 129.12, 128.60, 85.99,77.67, 76.06,74.24, 70.20, 68.48, 62.46, 21.21, 21.05.

ESI-MS: *m/z* [M+Na$^+$] calcd for $C_{20}H_{24}SO_9$: 463, found: 463.

Phenyl 1-thio-β-D-glucopyranoside (3):

To a mixture of phenyl 2, 3, 4, 6-tetra-O-acetyl-1-thio-β-D-glucopyranoside (15.12 g, 34 mmol) in methanol (70 mL) was added Cs_2CO_3 (0.54 g, 1.68 mol). After 12 hours of stirring at room temperature, the solvent was removed by rotatory evaporation under reduced pressure and dried *in vacuo* to give the product as white foam.

Yield: 9.89 g, 100%.

^{1}H NMR (400 MHz, D_2O): δ 7.37 (m, 2H, Ar-H), 7.20 (m, 3H, Ar-H), 4.57 (d, 1H, *J* = 10 Hz, H-1), 3.70 (d, 1H, *J* = 12.4 Hz, H-6a), 3.50 (dd, 1H, *J* = 12.4 Hz, *J* = 5.2 Hz, H-6b), 3.33 (t, 1H, *J* = 9.2 Hz, H-3), 3.27 (m, 1H, H-5), 3.23-3.13 (m, 2H, H-2, H-4).

^{13}C NMR (300 MHz, D_2O): δ 132.09, 131.66, 129.40, 128.17, 87.43, 80.04, 77.38, 71.89, 69.52, 60.97.

ESI-MS: *m/z* [M+Na$^+$] calcd for $C_{12}H_{16}SO_5$: 295, found: 295; *m/z* (M+Cs$^+$) calcd for $C_{12}H_{16}SO_5$: 405, found: 405.

Phenyl 6-O-trimethylacetyl-1-thio-β-D-glucopyranoside (4):

To a flask with phenyl 1-thio-β-D-glucopyranoside (13.05 g, 0.0478 mol) was added dry pyridine (55 mL) under the protection of nitrogen. The stirred solution was cooled to 0°C by ice bath and then to which was gradually added trimethylacetyl chloride (6.50 mL, 0.0528 mol) in 10 hours via syringe, after 6 more hours of stirring at 0°C, the solution was transferred to a saparatory funnel with 750 mL of ethyl acetate, washed with aqueous 0.2 M HCl solution (120 mL) for three times, aqueous saturated $NaHCO_3$ solution (100 mL) and then brine (100 mL). The organic phase was dried over anhydrous $MgSO_4$. The solvent was removed by rotatory evaporation and dried overnight *in vacuo*. The crude product residue was subject to flash column chromatography (silica gel 60 A, 230-400 mesh) using hexane and ethyl acetate (V/V, 2:1, 450 mL; 1:1, 500mL, 1:2, 600 mL; 1:3, 400 mL; 1:4, 500 mL) as an eluant to afford the pure product

Yield: 14.85 g, 87%.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.56 (m, 2H, Ar-H), 7.30(m, 3H, Ar-H), 4.51 (d, 1H, *J* = 11.2 Hz, H-1), 4.48 (m, 1H, H-6a), 4.32 (m, 1H, H-6b), 3.60 (m, 1H, H-3), 3.53 (m, 1H, H-5), 3.25-3.32 (m, 2H, H-2, H-4), 1.22 (s, 9H, pivaloyl CH_3).

^{13}C NMR (400 MHz, $CDCl_3$): δ 179.56, 133.21, 131.45, 129.18, 128.50, 87.92, 78.37, 77.56, 71.77, 69.84, 63.55, 39.32, 27.57.

ESI-MS: *m/z* [M+Na$^+$] calcd for $C_{17}H_{24}SO_6$: 379, found: 379.

Phenyl 2, 3, 4-tri-O-benzyl-6-O-trimethylacetyl-1-thio-β-D-glucopyranoside (5):

To a flask with NaH (60% in mineral oil, 6.35 g, 0.159 mol) in the ice bath under the protection of nitrogen, after washed with dry hexane to remove mineral oil was added a previously ice-bath-cooled solution of phenyl 6-O-trimethylacetyl-1-thio-β-D-glucopyranoside (6.56 g, 0.0178 mol) in dry DMF (100 mL), and then benzyl bromide (9.80 mL, 0.0825 mol) drop by drop. After 5 hours of stirring at 0°C, the solution was poured into ethyl acetate (400 mL) followed by adding methanol (10 mL) to destroy excess NaH, washing it with water (100 mL) for three times and then brine (100 mL). The organic phase was dried over anhydrous $MgSO_4$ and the solvent was removed by rotatory evaporation under reduced pressure and dried overnight *in vacuo* to afford crude product as syrup. To the crude product was added methanol (60 mL) and stirred for 1 hour to give white precipitate. Filtering and fully washing it with methanol to afford white product

Yield: 9.01 g, yield 78%.

^1H NMR (400 MHz, $CDCl_3$): δ 7.58 (m, 2H, Ar-H), 7.41-7.25 (m, 18H, Ar-H), 4.92-4.86 (m, 4H, Ph-CH_2), 4.71 (d, 1H, Ph-CH_2), 4.65 (d, 1H, J = 9.6 Hz, H-1), 4.56 (d, 1H, Ph-CH_2), 4.44 (dd, 1H, J = 11.6 Hz, 1.2 Hz, H-6a), 4.21(dd, 1H, J = 11.6 Hz, 4.4 Hz, H-6b), 3.73(t, 1H, J = 8.4 Hz, H-3), 3.60-3.47 (m, 3H, H-5, H-4, H-2), 1.25 (s, 9H, pivaloyl CH_3).

^{13}C NMR (400 MHz, $CDCl_3$): δ 178.20, 138.31, 138.15, 137.7, 133.4, 132.29, 129.11, 128.76-127.83 (m), 87.67, 86.95, 80.89, 78.05, 77.49, 76.26, 75.71, 75.55, 63.53, 39.23, 27.65.

ESI-MS *m/z:* [M+Na^+] calcd for $C_{38}H_{42}SO_6$ 626; found: 626.

Phenyl 2,3,4-Tri-*O*-benzyl-1-thio-β-D-glucopyranoside (6):

To a flask with phenyl 2,3,4-tri-*O*-benzyl-6-*O*-trimethylacetyl-1-thio-β-D-glucopyranoside (3.02 g, 4.82 mmol) was added NaOMe (0.2 M solution in MeOH, 50 mL) and CH_2Cl_2 (15 mL) (PH 13). The solution was stirred at room temperature for 48 h and then evaporated to remove solvent, dried *in vacuo*. Anhydrous CH_2Cl_2 was added to the crude product residue and the insoluble salt was filtered off via Büchner funnel padded with filtering reagent, Celite 521. The filtrate was collected and the solvent was removed by rotary evaporation and dried *in vacuo* to afford the product as a white solid. Yield: 2.61 g, 100%. mp 127–129 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.51 (m, 2 H), 7.40–7.27 (m, 18H), 4.94–4.85 (m, 4 H), 4.77 (d, J = 10 Hz, 1 H), 4.73 (d, J = 9.6 Hz, 1 H), 4.66 (d, J = 10.8 Hz, 1 H), 3.89 (dd, J = 2.8 Hz, 14.8 Hz, H-6a, 1H), 3.77–3.69 (m, 2 H), 3.59 (t, J = 8.8 Hz, 1 H), 3.50 (t, J = 8.8 Hz, 1 H), 3.40 (m, 1 H).

^{13}C NMR (400 MHz, $CDCl_3$): δ 138.49, 138.09, 138.02, 133.67, 132.06, 129.25, 128.73–127.89 (m), 87.82, 86.84, 81.41, 79.61, 77.90, 76.13, 75.85, 75.43, 62.48.

ESI-MS: *m/z* [M + Na$^+$] calcd for $C_{33}H_{34}SO_5$: 565; found: 565.

Phenyl 2,3,4-Tri-*O*-benzyl-6-*O*-bromoacetyl-1-thio-β-D-glucopyranoside (7a):

To a solution of phenyl 2,3,4-tri-*O*-benzyl-1-thio-β-D-glucopyranoside (0.988 g, 1.82 mmol) and bromoacetic acid (0.308 g, 2.21 mmol) in CH_2Cl_2 (40 mL) was added 1.0 M solution of DCC (2.20 mL, 2.20 mmol) in CH_2Cl_2 and a small amount of DMAP (<5% equivalent to sugar). After being stirred at room temperature for 2 h, the mixture was filtered to remove the side-product 1,3-dicyclohexylurea. The filtrate was evaporated to dryness and the residue was subjected to flash column chromatography (silica gel 60 Å, 230–400 mesh) using hexane–EtOAc (7:1) as an eluant to afford the pure product as white solid.

Yield: 1.08 g, 89%. mp 85–87 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.54 (m, 2 H), 7.41–7.25 (m, 18 H), 4.95–4.84 (m, 4 H), 4.75 (d, J = 10 Hz, 1 H), 4.67 (d, J = 9.6 Hz, 1 H), 4.61 (d, J = 10.8 Hz, 1 H), 4.45 (dd, J = 11.2 Hz, 0.8 Hz, 1 H), 4.28 (m, 1 H), 3.79 s, 2 H), 3.73 (m, 1 H), 3.55 (m, 2 H), 3.51 (t, J = 18.4 Hz, 1 H).

^{13}C NMR (300 MHz, $CDCl_3$): δ 166.91, 138.29, 138.02, 137.70, 133.51, 132.39, 129.14, 128.76–127.94 (m), 87.81, 86.96, 81.06, 77.49, 77.36, 76.19, 75.79, 75.38, 65.07, 25.90.

ESI-MS: *m/z* [M + Na$^+$] calcd for $C_{35}H_{35}SO_6Br$: 685; found: 685.

Phenyl 2,3,4-Tri-*O*-benzyl-6-*O*-[2-(3-methylimidazolium)]acetyl-1-thio-β-D-glucopyranoside Tetrafluoroborate (7b):

To a solution of phenyl 2,3,4-tri-*O*-benzyl-6-*O*-bromoacetyl-1-thio-β-D-glucopyranoside (0.890 g, 1.34 mmol) in acetone (25 mL) was added 1.0 M solution of 1-methylimidazole (1.61 mL, 1.61 mmol) in CH_2Cl_2 and then $NaBF_4$ (0.182 g, 1.66 mmol). After 72 h of stirring at room temperature, the precipitate was filtered off and the filtrate was evaporated to dryness and dried *in vacuo* overnight. The product residue was washed with Et_2O (3 × 15 mL) and the upper layer of solvent was decanted. The solid was dried *in vacuo* and the residue was further purified by adding 15 mL anhydrous CH_2Cl_2 and then filtering off the precipitate. The filtrate was evaporated to dryness and dried *in vacuo* to afford the pure product as white foam.

Yield: 0.989 g, 98%. M. P. 42–44 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.74 (s, 1 H), 7.46 (m, 2 H), 7.36–7.23 (m, 18 H), 7.17 (m, 2 H), 5.01–4.82 (m, 6 H), 4.72 (d, *J* = 10.0 Hz, 1 H), 4.71(d, *J* = 9.6 Hz, 1 H), 4.58 (d, *J* = 11.2 Hz, 1 H), 4.50 (dd, *J* = 11.6 Hz, 2.4 Hz, 1 H), 4.24 (dd, *J* = 6.4 Hz, 12 Hz, 1 H), 3.82 (s, 3 H), 3.73 (m, 1 H), 3.58 (m, 1 H), 3.52–3.43 (m, 2 H).

^{13}C NMR (300 MHz, $CDCl_3$): δ 165.90, 138.33, 138.07, 138.02, 137.83, 133.65, 131.58, 129.37, 128.76–127.92 (m), 123.69, 123.25, 87.41, 86.79, 81.02, 77.53, 76.74, 76.01, 75.70, 75.15, 65.51, 50.03, 36.81.

ESI-MS: *m*/*z* [M^+] calcd for $C_{39}H_{41}SO_6N_2$: 665; found: 665.

Phenyl 2,3,4-Tri-*O*-benzyl-6-*O*-[2-(3-methylimidazolium)]acetyl-1-thio-β-D-glucopyranosylsulfoxide Tetrafluoroborate (8b):

To a solution of **7b** (50.0 mg, 0.066 mmol) in CH_2Cl_2 (2 mL) at –78 °C was added *m*CPBA (15.0 mg, 0.066 mmol) in CH_2Cl_2 (1 mL) dropwise over 5 min. After 20 min of stirring at –78 °C, the mixture was poured into aqueous saturated $NaHCO_3$ solution (10 mL) with 15 mL CH_2Cl_2. The organic phase was separated, washed with aqueous saturated $NaHCO_3$ solution (10 mL) again and was dried over Na_2SO_4. The organic solvent was removed by rotary evaporation under reduced pressure. The product residue was further purified by washing with hexane and isopropyl ether, which was monitored by TLC, to afford the glycosyl sulfoxide as a white solid including two diastereomers.

Yield: 49.5 mg, 97%; ratio of 60:40 by NMR for the two diastereomers.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.08 (s, 1 H), 7.54 (m, 2 H), 7.40–7.16 (m, 20 H), 5.11–4.20 (m, 11 H), 3.97 (m, 2 H), 3.91 (s, 2 H), 3.90 (s, 1 H), 3.85–3.26 (m, 2 H).

ESI-MS: *m*/*z* [M^+] calcd for $C_{39}H_{41}SO_7N_2$: 681; found: 681.

Phenyl 2,3,4-Tri-*O*-benzyl-6-*O*-[2-(3-methylimidazolium)]acetyl-β-D-glucopyranosyl-(1→6)-2,3,4-tri-*O*-benzyl-1-thio-β-D-glucopyranoside Tetrafluoroborate (9b):

To a solution of the monosaccharide sulfoxide bound to ionic liquid **8b** (51.8 mg, 0.067 mmol) as glycosyl donor, phenyl 2,3,4-tri-*O*-benzyl-1-thio-β-D-glucopyranoside (**6**, 114 mg, 0.21 mmol) as glycosyl acceptor and 2,6-di-*tert*-butyl-4-methylpyridine (58.8 mg, 0.286 mmol) as acid scavenger in CH_2Cl_2 (5 mL) at –78 °C was added Tf_2O (12 mL, 0.067 mmol) gradually over 10 min via syringe. After 20 min of stirring at –78 °C, the mixture was slowly warmed to 0 °C over 1 h. The reaction was quenched by adding *n*-pentane (5 mL) and a white precipitate appeared. The mixture was cooled to –78 °C and the white precipitate was immediately removed by centrifugation. The solution phase was added with another portion of *n*-pentane (5 mL) and then cooled to –78 °C. The precipitate was removed by centrifugation again. The solution phase was evaporated and the residue was washed with *n*-pentane several times and then further washed with isopropyl ether until TLC showed the residue was pure. The expected product was obtained as a white solid.

Yield: 39 mg, 50%. mp 45–47 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.10 (s, 1 H), 7.51 (m, 2 H), 7.41–7.13 (m, 35 H), 5.10 (d, *J* = 10.4 Hz, 1 H), 5.00–4.52 (m, 15 H), 4.41 (m, 1 H), 4.19 (dd, *J* = 12.4 Hz, 4.0 Hz, 1 H), 3.99 (t, *J* = 8.8 Hz, 1 H), 3.90–3.75 (m, 6 H), 3.73–3.62 (m, 2 H), 3.55 (m, 2 H), 3.42 (t, *J* = 8.8 Hz, 1 H), 3.29 (t, 1 H).

^{13}C NMR (400 MHz, $CDCl_3$): δ 165.79, 138.78, 138.60, 138.41, 138.38, 138.20, 138.11, 138.03, 134.18, 131.78, 129.32, 128.73–127.69 (m), 123.65, 123.24, 97.30, 88.25, 86.88, 81.82, 81.31, 80.30, 79.06, 77.76, 77.57, 75.99, 75.89, 75.81, 75.25, 75.09, 72.83, 68.68, 66.89, 65.49, 50.51, 37.16.

ESI-MS: *m/z* [M$^+$] calcd for $C_{66}H_{69}SO_{11}N_2$: 1097; found: 1097.

Phenyl 2,3,4-Tri-*O*-benzyl-6-*O*-[2-(3-methylimidazolium)]acetyl-β-D-glucopyranosyl-(1→6)-2,3,4-tri-*O*-benzyl-1-thio-β-D-glucopyranosylsulfoxide Tetrafluoroborate (10b):

To a solution of the disaccharide sulfide **9b** (56.1 mg, 0.047 mmol) in CH_2Cl_2 (2.5 mL) at –78 °C was added *m*CPBA (8.1 mg, 0.047 mmol) in CH_2Cl_2 (1 mL) dropwise over 5 min. After 20 min of stirring at –78 °C under the protection of nitrogen, the mixture was poured into aqueous saturated $NaHCO_3$ solution (10 mL) with CH_2Cl_2 (15 mL). The organic phase was separated, washed with aqueous saturated $NaHCO_3$ solution (10 mL) again and dried over Na_2SO_4. The organic solvent was removed by rotary evaporation *in vacuo*. The product residue was further purified by washing with hexane and isopropyl ether, monitored by TLC, to afford the glycosyl sulfoxide as a white solid including two diastereomers.

Yield: 54.0 mg, 95%; ratio of 60:40 by NMR for the two diastereomers.

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.48 (s, 1 H), 7.58–7.13 (m, 37 H), 5.00–4.40 (m, 18 H), 3.95–3.25 (m, 13 H).

ESI-MS: *m/z* [M$^+$] calcd for $C_{66}H_{69}SO_{12}N_2$: 1113; found: 1113.

Phenyl 2,3,4-Tri-*O*-benzyl-6-*O*-[2-(3-methylimidazolium)]acetyl-β-D-glucopyranosyl-(1→6)-2,3,4-tri-*O*-benzyl-β-D-glucopyranosyl-(1→6)-2,3,4-tri-*O*-benzyl-1-thio-β-D-glucopyranoside Tetrafluoroborate (11b):

To a solution of the disaccharide sulfoxide bound to ionic liquid (**10b**, 45.1 mg, 0.038 mmol) as glycosyl donor, phenyl 2,3,4-tri-*O*-benzyl-1-thio-β-D-glucopyranoside (**6**, 62.1 mg, 0.114 mmol) as glycosyl acceptor and 2,6-di-*tert*-butyl-4-methylpyridine (30.8 mg, 0.150 mmol) as acid scavenger in CH_2Cl_2 (5 mL) at –78 °C was added Tf_2O (6 mL, 0.036 mmol) gradually over 10 min via syringe. After 20 min of stirring at –78 °C, the mixture was slowly warmed to 0 °C over 1 h. The reaction was quenched by adding *n*-pentane (5 mL) and a white precipitate appeared. The mixture was cooled to –78 °C and the precipitate was immediately removed by centrifugation. The solution phase was added with another portion of *n*-pentane (5 mL) and then cooled to –78 °C. The precipitate was immediately removed by centrifugation again. The solution phase was evaporated and the residue was washed with *n*-pentane for several times and then further washed with isopropyl ether until TLC showed the residue to be pure. The expected product was obtained as a white solid.

Yield: 34 mg, 56%.

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.04 (s, 1 H), 7.51 (m, 2 H), 7.42–7.17 (m, 48 H), 7.05 (d, *J* = 10.2 Hz, 2 H), 5.00–4.50 (m, 25 H), 4.39 (d, *J* = 8.0 Hz, 1 H), 4.15 (m, 1 H), 4.00 (m, 2 H), 3.89–3.72 (m, 6 H), 3.70–3.30 (m, 8 H), 3.25 (t, *J* = 8.8 Hz, 1 H).

^{13}C NMR (400 MHz, $CDCl_3$): δ 165.77, 138.95–138.09 (m), 134.22, 131.87, 131.31, 129.29, 128.74–127.36 (m), 123.72, 123.76, 123.01, 103.91,97.47, 97.26, 88.33, 87.74, 86.85, 84.88, 82.66–80.14 (m), 79.21, 79.06, 78.67, 77.54, 75.93–75.85 (m), 75.22–75.00 (m), 72.79, 72.72, 72.51, 70.86, 68.90, 69.58, 68.31, 66.44, 65.81, 65.53, 50.01, 36.90.

ESI-MS: *m/z* [M$^+$] calcd for $C_{93}H_{97}SO_{16}N_2$: 1529; found: 1529.

Cleavage of Ionic Liquid Moiety from 11b: Trisaccharide (12):

To the flask with trisaccharide bound to ionic liquid (**11b**, 30.0 mg, 0.018 mmol) was added Cs_2CO_3 (6.1 mg, 0.018 mmol) and MeOH (5 mL). After 12 h stirring at room temperature, the solvent was removed by rotary evaporation and dried *in vacuo*. To the residue was added anhydrous CH_2Cl_2 (3 mL) and insoluble salts were filtered off. The filtrate was evaporated to dryness and dried *in vacuo* to afford the product.

Yield: 26.1 mg, 100%.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.54 (m, 2 H), 7.43–7.14 (m, 48 H), 5.16 (d, J = 3.2 Hz, 1 H), 5.00 – 4.93 (m, 3 H), 4.91–4.86 (m, 4 H), 4.85 – 4.74 (m, 5 H), 4.71 – 4.53 (m, 9 H), 4.40 (d, J = 8.0 Hz, 1 H), 4.12 (d, J = 10.0 Hz, 1 H), 3.99 (m, 2 H), 3.86–3.38 (m, 12 H), 3.26 (m, 1 H).

^{13}C NMR (400 MHz, $CDCl_3$): δ 138.94–138.22 (m), 134.33, 132.01, 131.55, 129.19, 129.10, 128.59–127.44 (m), 103.91, 97.54, 97.31, 88.31, 87.79, 86.93, 84.81, 82.62, 81.95, 81.85, 81.75, 81.44, 81.33, 80.73, 80.63, 80.49, 79.23, 79.00, 78.12, 77.91, 77.75, 77.51, 75.95–75.80 (m), 75.45–75.25 (m), 72.75, 72.61, 72.57, 71.24, 68.65, 66.02, 65.52, 62.30.

ESI-MS: *m/z* [M + Na$^+$] calcd for $C_{87}H_{90}SO_{15}Na$: 1429; found: 1429.

Phenyl 2,3,4-Tri-*O*-benzyl-6-*O*-acetyl-1-thio-β-D-glucopyranoside (7c):

To a solution mixture of phenyl 2,3,4-tri-*O*-benzyl-1-thio-β-D-glucopyranoside (**6**, 0.801 g, 1.48 mmol), anhydrous pyridine (0.45 mL) and DMAP (less than 5% equivalent to sugar) in CH_2Cl_2 (9 mL) was added acetic anhydride (0.21 mL, 2.22 mmol). After 4 h of stirring at room temperature under the protection of N_2, the reaction mixture was transferred to 150 mL of CH_2Cl_2, washed with aqueous 0.2 M HCl solution (30 mL), H_2O (30 mL), saturated aqueous $NaHCO_3$ solution (30 mL), and then with brine (30 mL). The organic phase was dried over Na_2SO_4 and the solvent was removed by rotary evaporation to generate the crude product residue, which was subjected to flash column chromatography (silica gel 60 Å, 230–400 mesh) using hexane–EtOAc (5:1) as eluant to afford the pure product.

Yield: 0.845 g, 98%.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.55 (m, 2 H), 7.40 (m, 2 H), 7.36–7.25 (m, 16 H), 4.95–4.84 (m, 4 H), 4.75 (d, *J* = 10 Hz, 1 H), 4.67 (d, *J* = 9.6 Hz, 1 H), 4.58 (d, *J* = 10.8, 1 H), 4.37 (d, *J* = 11.6 Hz, 1 H), 4.22 (m, 1 H), 3.73 (t, *J* = 8.4 Hz, 1 H), 3.55 (m, 2 H), 3.50 (t, *J* = 9.6 Hz, 1 H), 2.11 (s, 3 H).

ESI-MS: *m/z* [M + Na$^+$] calcd for $C_{35}H_{36}SO_6Na$: 607; found: 607.

Phenyl 2,3,4-Tri-*O*-benzyl-6-*O*-acetyl-β-D-glucopyranosyl Sulfoxide (8c):

To a solution of **7c** (1.01 g, 1.73 mmol) in CH_2Cl_2 (5 mL) at –78 °C was added *m*CPBA (0.387 g, 1.73 mmol) in CH_2Cl_2 (7 mL) dropwise over 5 min. After 20 min of stirring at –78 °C under the protection of N_2, the mixture was poured into aqueous saturated $NaHCO_3$ solution (100 mL) with CH_2Cl_2 (50 mL). The organic phase was separated, washed with aqueous saturated $NaHCO_3$ solution (50 mL) again and was dried over Na_2SO_4. The organic solvent was removed by rotary evaporation *in vacuo* to generate the crude product residue, which was subjected to flash column chromatography (silica gel 60 Å, 230–400 mesh) using hexane–EtOAc (3:1) as an eluant to afford the pure product as two isomers.

Yield: 0.984 g, 95%; the ratio of two isomers was 3:1 according to NMR spectra.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.62–7.16 (m, 20 H), 5.06–4.78 (m, 6 H), 4.59–4.36 (m, 2 H), 4.19–3.30 (m, 8 H).

ESI-MS: *m/z* [M + Na$^+$] calcd for $C_{35}H_{36}SO_7Na$: 623; found: 623.

Phenyl 2,3,4-Tri-*O*-benzyl-6-*O*-acetyl-β-D-glucopyranosyl-(1→6)-2,3,4-tri-*O*-benzyl-1-thio-β-D-glucopyranoside (9c):

To a solution of the sulfoxide **8c** (0.302 g, 0.503 mmol), phenyl 2,3,4-tri-*O*-benzyl-1-thio-β-D-glucopyranoside (**6**, 0.406 g, 0.754 mmol) and 2,6-di-*tert*-butyl-4-methylpyridine (0.315 g, 1.53 mmol) in CH_2Cl_2 (10 mL) at –78 °C was added Tf_2O solution (0.09 mL, 0.503 mmol) in CH_2Cl_2 (5 mL) gradually over 10 min via syringe. After 20 min of stirring at –78 °C, the mixture was slowly warmed to –5 °C over 1.5 h. The reaction was quenched by adding aqueous saturated $NaHCO_3$ solution (6 mL) and partitioned between CH_2Cl_2 (35 mL) and aqueous saturated $NaHCO_3$ solution (20 mL). The organic phase was separated and further washed with aqueous saturated $NaHCO_3$ solution (40 mL). After it had been dried over Na_2SO_4, the organic phase was evaporated to dryness and the residue was subjected to flash column chromatography (silica gel 60 Å, 230–400 mesh) using hexane–EtOAc (6:1, 5:1, 4:1) as an eluant to afford the pure product as colorless syrup.

Yield: 0.414 g, 81%.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.54 (m, 2 H), 7.42 (m, 2 H), 7.38–7.24 (m, 31 H), 5.05 (m, 2 H), 4.94–4.56 (m, 12 H), 4.25 (m, 2 H), 4.02 (t, *J* = 9.2 Hz, 1 H), 3.92 (m, 1 H), 3.86 (d, *J* = 4.8 Hz, 1 H), 3.80 (m, 1 H), 3.75 (m, 1 H), 3.70 (t, 1 H), 3.62–3.46 (m, 3 H), 3.28 (t, *J* = 8.4 Hz, 1 H), 2.03 (s, 3 H).

ESI-MS: *m/z* [M + Na$^+$] calcd for $C_{62}H_{64}SO_{11}Na$: 1039; found: 1039.

Phenyl 2,3,4-Tri-*O*-benzyl-6-*O*-acetyl-β-D-glucopyranosyl-(1→6)-2,3,4-tri-*O*-benzyl-β-D-glucopyranosyl Sulfoxide (10c):

To a solution of the disaccharide sulfide **9c** (0.202 g, 0.199 mmol) in CH_2Cl_2 (12 mL) at −78 °C was added *m*CPBA (0.045 g, 0.199 mmol) in CH_2Cl_2 (6 mL) dropwise over 5 min. After 20 min of stirring at −78 °C under the protection of N_2, the mixture was poured into aqueous saturated $NaHCO_3$ solution (30 mL) together with CH_2Cl_2 (60 mL). The organic phase was separated, washed with aqueous saturated $NaHCO_3$ solution (30 mL) again and dried over Na_2SO_4. The solvent in organic phase was removed by rotary evaporation *in vacuo* to generate the crude product residue, which was subjected to flash column chromatography (silica gel 60 Å, 230–400 mesh) using hexane–EtOAc (2:1) as an eluant to afford the product as a mixture of two isomers.

Yield: 0.197 g, 96%; the ratio of the two isomers was 4:1 according to NMR spectra.

For one isomer: $R_f = 0.27$ (hexanes–EtOAc, 2:1).

^1H NMR (400 MHz, $CDCl_3$): δ 7.60 (m, 2 H), 7.46 (m, 4 H), 7.42–7.22 (m, 29 H), 5.05 (d, $J = 3.6$ Hz, 1 H), 5.00–4.66 (m, 12 H), 4.60 (d, $J = 10.8$ Hz, 1 H), 4.27 (m, 2 H), 3.87 (m, 3 H), 3.74 (m, 4 H), 3.59–3.47 (m, 3 H), 3.35 (m, 1 H) 2.07 (s, 3 H).

For the other isomer: $R_f = 0.12$ (hexanes–EtOAc, 2:1). ^1H NMR (400 MHz, $CDCl_3$): δ 7.51 (m, 2 H), 7.39–7.19 (m, 31 H), 7.06 (m, 2 H), 4.98–4.88 (m, 3 H), 4.82–4.52 (m, 10 H), 4.43 (d, $J = 8.8$ Hz, 2 H), 4.25 (m, 2 H), 4.39 (t, $J = 9.6$ Hz, 1 H), 3.90–3.69 (m, 6 H), 3.60 (m, 1 H), 3.49 (m, 2 H), 2.05 (s, 3 H).

ESI-MS: *m/z* [M + Na^+] calcd for $C_{62}H_{64}SO_{12}Na$: 1055; found: 1055.

Phenyl 2,3,4-Tri-*O*-benzyl-6-*O*-acetyl-β-D-glucopyranosyl-(1→6)-2, 3, 4-tri-*O*-benzyl-β-D-glucopyranosyl-(1→6)-2,3,4-tri-*O*-benzyl-1-thio-β-D-glucopyranoside (11c):

To a solution of the sulfoxide **10c** (0.110 g, 0.107 mmol), phenyl 2,3,4-tri-*O*-benzyl-1-thio-β-D-glucopyranoside (**6**, 0.088 g, 0.161 mmol) and 2,6-di-*tert*-butyl-4-methylpyridine (0.070 g, 0.34 mmol) in CH_2Cl_2 (6 mL) at −78 °C was added Tf_2O solution (0.018 mL, 0.107 mmol) in CH_2Cl_2 (3 mL) gradually over 10 min via syringe. After 20 min of stirring at −78 °C, the mixture was slowly warmed to −15 °C over 1 h. The reaction was quenched by adding aqueous saturated $NaHCO_3$ solution (6 mL) and then partitioned between CH_2Cl_2 (30 mL) and aqueous saturated $NaHCO_3$ solution (15 mL). The organic phase was separated and further washed by aqueous saturated $NaHCO_3$ solution (20 mL). After it had been dried over Na_2SO_4, the organic phase was evaporated to dryness and the residue was subjected to flash column chromatography (silica gel 60 Å, 230–400 mesh) using hexane–EtOAc (4:1) as an eluant to afford the product as colorless syrup.

Yield: 0.132 g, 85%.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.53 (m, 2 H), 7.44–7.14 (m, 48 H), 5.12 (d, *J* = 3.2Hz, 1 H), 5.04–4.52 (m, 21 H), 4.40 (m, 1 H), 4.24–4.12 (m, 2 H), 4.00 (m, 1 H), 3.90–3.36 (m, 12 H), 3.28 (m, 1 H), 2.00 (s, 3 H).

^{13}C NMR (400 MHz, $CDCl_3$): δ 170.85, 138.99–138.14 (m), 134.27, 134.17, 132.06, 131.66, 129.24, 129.15, 128.64, 128.61–127.48 (m), 103.74, 97.51, 97.23, 88.37, 87.77, 86.91, 86.86, 84.79, 82.59, 81.95, 81.86, 81.41, 81.23, 80.67, 80.36, 80.25, 79.16, 78.99, 78.02, 77.56, 75.88 (m), 75.25 (m), 72.71, 72.49, 72.37, 71.02, 69.04, 68.30, 66.39, 65.94, 65.67, 63.47, 63.36, 21.34.

ESI-MS: *m/z* [M + Na$^+$] calcd for $C_{89}H_{92}SO_{16}Na$: 1471; found: 1471.

Phenyl 2,3,4-Tri-*O*-benzyl-β-D-glucopyranosyl-(1→6)-2,3,4-tri-*O*-benzyl-β-D-glucopyranosyl-(1→6)-2,3,4-tri-*O*-benzyl-1-thio-β-D-glucopyranoside (12):

To a flask with phenyl 2,3,4-tri-*O*-benzyl-6-*O*-acetyl-β-D-glucopyranosyl-(1→6)-2,3,4-tri-*O*-benzyl-β-D-glucopyranosyl-(1→6)-2,3,4-tri-*O*-benzyl-1-thio-β-D-glucopyranoside **11c** (101 mg, 0.069 mmol) was added Cs_2CO_3 (22.4 mg, 0.069 mmol) and MeOH (6 mL). After 14 h stirring at room temperature, the solvent was removed by rotary evaporation and the product was dried *in vacuo*. To the residue was added anhydrous CH_2Cl_2 (3 mL) and insoluble salts were filtered off. The filtrate was evaporated to dryness and dried in vacuo to afford pure product.

Yield: 96.1 mg, 98%. R_f = 0.28 (hexanes–EtOAc, 2:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.54 (m, 2 H), 7.43–7.14 (m, 48 H), 5.16 (d, J = 3.2Hz, 1 H), 5.00–4.93 (m, 3 H), 4.91–4.86 (m, 4 H), 4.85–4.74 (m, 5 H), 4.71–4.53 (m, 9 H), 4.40 (d, J = 8.0 Hz, 1 H), 4.12 (d, J = 10.0 Hz, 1 H), 3.99 (m, 2 H), 3.86–3.38 (m, 12 H), 3.26 (m, 1 H).

^{13}C NMR (400 MHz, $CDCl_3$): δ 138.94–138.22 (m), 134.33, 132.01, 131.55, 129.19, 129.10, 128.59–127.44 (m), 103.91, 97.54, 97.31, 88.31, 87.79, 86.93, 84.81, 82.62, 81.95, 81.85, 81.75, 81.44, 81.33, 80.73, 80.63, 80.49, 79.23, 79.00, 78.12, 77.91, 77.75, 77.51, 75.95–75.80 (m), 75.45–75.25 (m), 72.75, 72.61, 72.57, 71.24, 68.65, 66.02, 65.52, 62.30.

The sample for mass spectroscopy was filtered through silica gel to remove cesium ion.

ESI-MS: *m/z* [M + Na$^+$] calcd for $C_{87}H_{90}SO_{15}Na$: 1429; found: 1429.

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Chapter 4. Synthesis of Structure-Defined Imidazolium Salt Oligomers

4. 1. Introduction

The discovery of air and water-stable imidazolium-based ionic liquids[1] has greatly pushed forward the research and application of ionic liquids in many scientific fields such as organic synthesis,[2] catalysis,[3] electrochemical devices[4] and analytic chemistry.[5] Most of the researches and applications on ionic liquids are based on the utilization of their characteristic properties that they have non-flammability, high thermally and chemical stability and non-measurable vapor pressure. Since ionic liquids are only composed of ions, they show high ionic conductivity and electrochemical stability.[6] Their ionic organic components make them have good miscibility with polymer electrolytes. Because polymer electrolytes, the solid polymeric membranes with dissolved salts, are desirable for people to have all-solid-state batteries which are safer and easier assembling than conventional liquid batteries, ionic liquids are considered to be good candidate materials for electrolytes in the development of lithium batteries,[7] fuel cells,[8] solar cells[9] and supercapacitors.[10] The blending of ionic liquids with polymer electrolytes can considerably improve the performance of polymers as electronic materials.[11] It has been reported that imidazolium based ionic liquids can be used as excellent plasticizers for the processing of poly(methyl methacrylate) to give polymer electrolytes with improved thermal stability and lower glass transition temperatures.[12] Another approach to fabricate ionic liquid-involved electrolytes is to covalently graft ionic liquid units such as imidazolium salts to the polymer chains to generate new ionic liquid polymers, which showed good ionic conductivity grater than 10^{-4} S cm^{-1} at room temperature.[13] Therefore, the design and synthesis of new ionic liquid-type molecules are of considerable importance in the fields of academic research and industrial application.

In recent years, ionic liquids have been successfully used as soluble supports for organic catalysis and synthesis.[2, 14, 15] It was reported that ionic liquid-supported transition metal complex catalysts or organic catalysts showed better catalytic activity than their non-supported counterpart catalysts, and the catalysts were easily recovered and recycled for the next run without loss of catalytic ativity.[14, 15] Also, ionic liquid-supported organic synthesis possesses the advantages of both solution phase synthesis and solid phase synthesis.[2] The chemical reactions between ionic liquid-supported substrates and reagents can be conducted in the homogeneous solution phase, which normally results in high reaction efficiency, while the product purification can proceed through heterogeneous phase separation like solid-phase synthesis because ionic liquid-bound molecules are commonly insoluble in moderately polar and non-polar solvents such as ethyl acetate, ethers and alkanes. The excess reagents can be washed away by less polar organic solvents and the inorganic salts can be filtered off through polar organic mixtures or washed away by water. Therefore, the large excess of reagents that are used to drive the reactions to completion in polymer-supported solid-phase synthesis can be avoided and the reaction progress and intermediate products can be monitored or characterized by common methods used in organic synthesis such as TLC, NMR and MS spectroscopy. The advantages are fully addressed by ionic liquid-supported biopolymer synthesis, which was reported by our group and some other groups.[2] However, in all of those cases, ionic liquids that were used as phase tags have only one ionic unit. This brings about the problem when large molecules are bound to ionic liquids because the role that the ionic liquid moiety plays as a phase tag is reduced obviously. Therefore, it is difficult to synthesize large biopolymeric molecules just by using the ionic liquid with one ionic unit. A possible approach to overcome this issue is to design and synthesize new ionic liquids with multiple ionic units. However, ionic liquid polymers are not very helpful in solving this issue even though the synthesis of those polymers via free radical polymerization have been reported by several research groups[13c,16] (Figure 1) because they can not be used as synthetic supports and also have the same problems as common polymer-supported solid-phase synthesis such as low solubility in common organic solvents and difficulty to characterize intermediate products by NMR and MS spectroscopy.

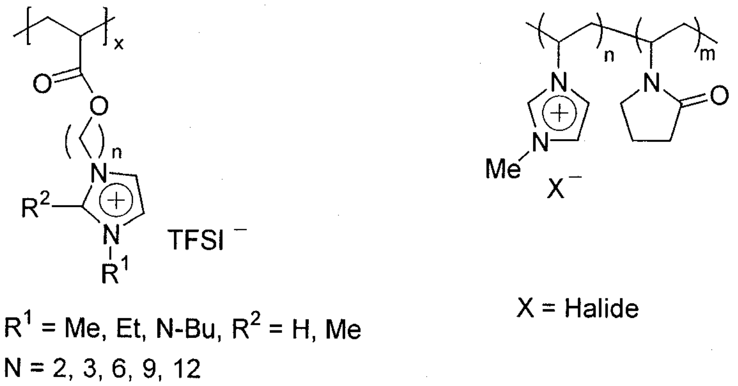
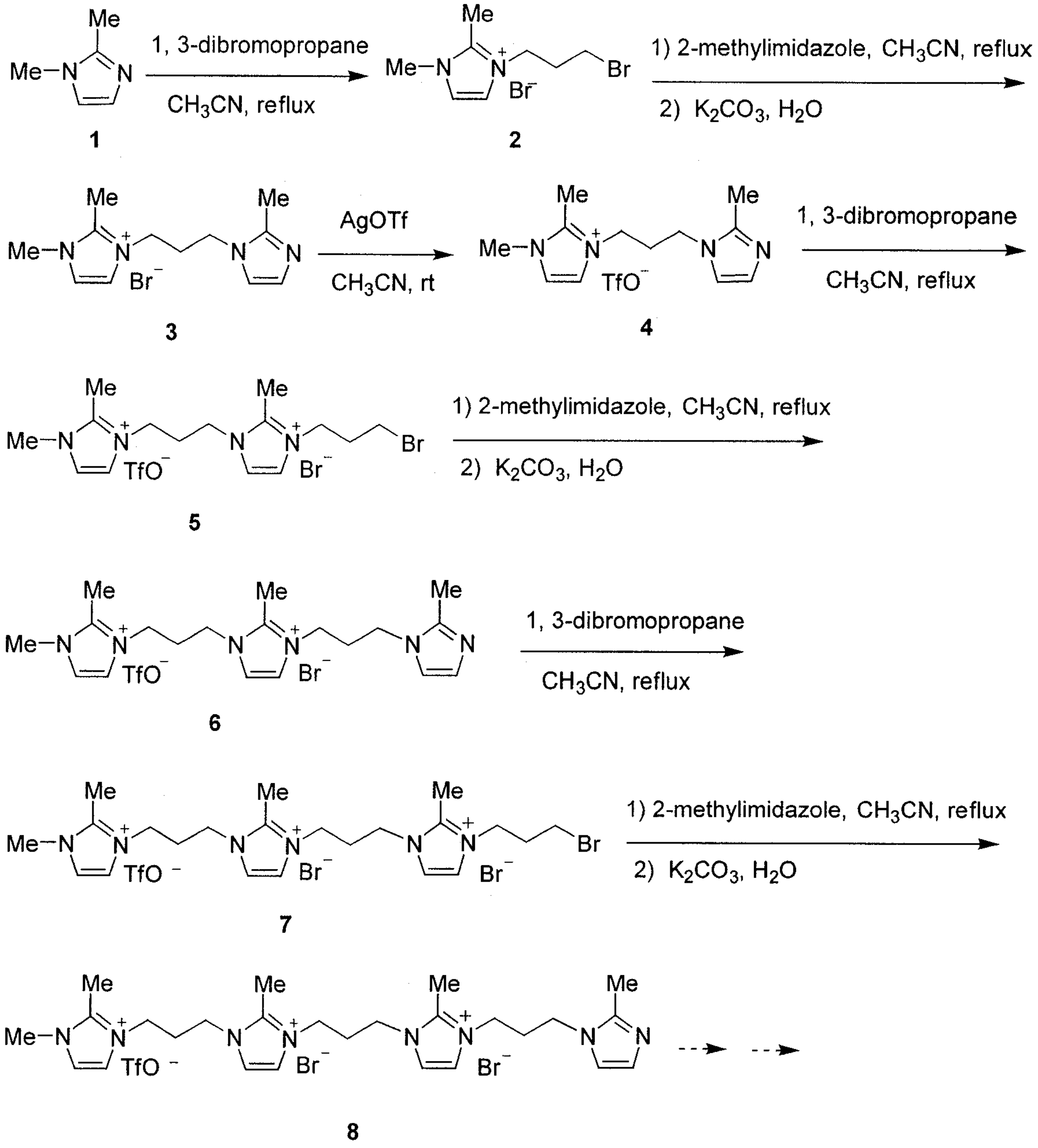


Figure 1. Imidazolium-based polymers. TFSI = bis (trifluoromethanesulfonyl) imide.

Therefore, it is reasonable to anticipate that ionic liquid-type oligomers could be a good choice as soluble supports in the synthesis of large molecules and biopolymers because they are able to provide stronger ionic effects on the support-bound molecules during purification procedures and still have good solubility in common organic solvents. In this chapter, the synthesis of a new family of structure-defined imidazolium oligomers will be described. To my full knowledge, this is the first example of ionic liquid-type oligomers. These molecules are expected to have good thermal and chemical stability and soluble in common polar organic solvents but not soluble in less polar solvents, which indicate that they can be used as soluble supports in organic synthesis.

4. 2. Results and Discussion

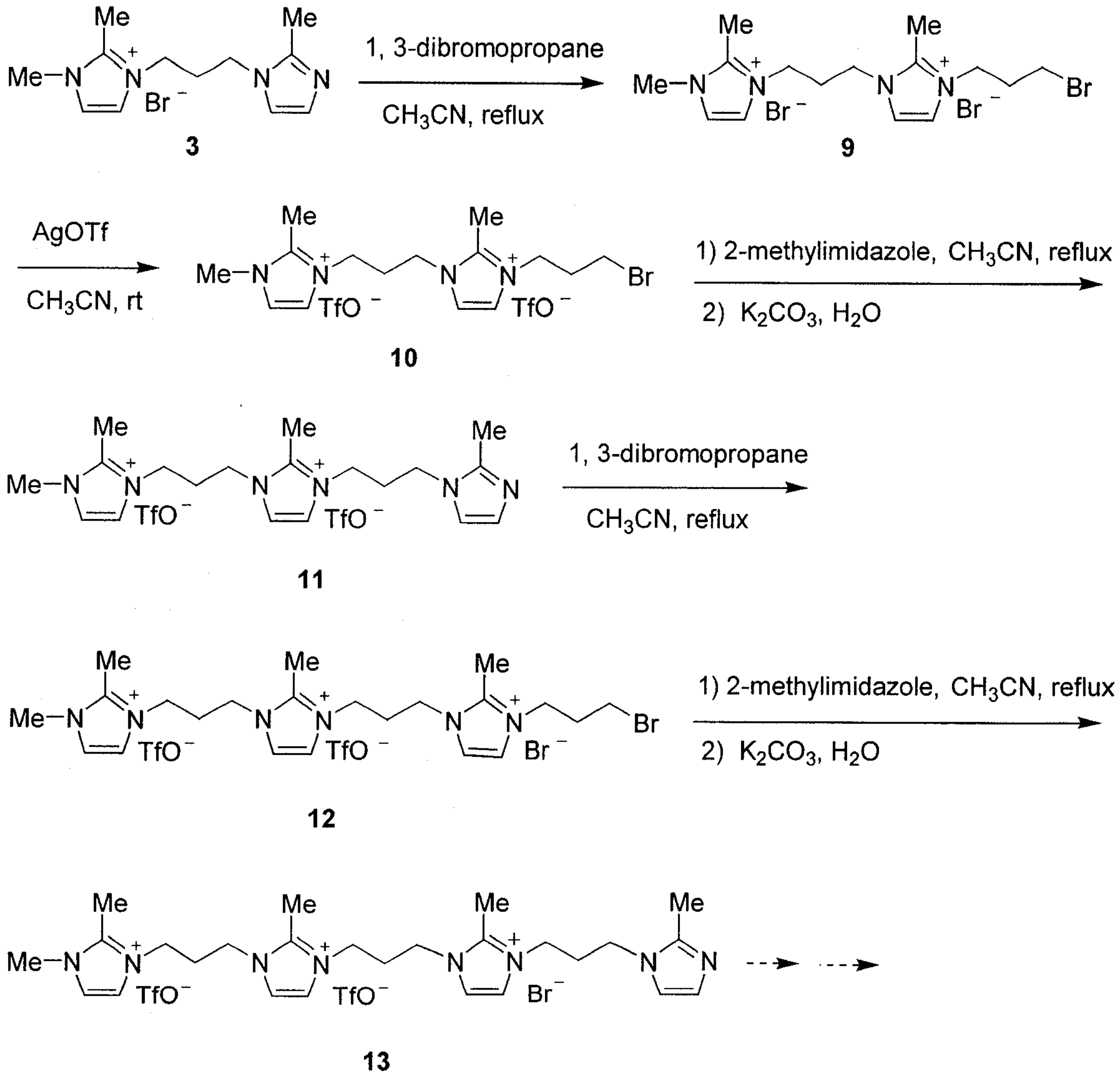
4. 2. 1. Synthesis



Scheme 1. Route 1 to synthesize imidazolium salt oligomers.

The synthesis of ionic liquid-type oligomers, which is shown in Scheme 1, started from the cheap and commercially available compound, 1,2-dimethylimidazole. Treatment of this molecule with excess 1,3-dibromopropane in dry acetonitrile under refluxing condition generated both the expected single-bromine-replaced compound **2** as main product and the unwanted side-product in which two bromines of 1,3-dobromopropane molecule reacted with 1,2-dimethylimidazole. The ratio of the product and side-product can be maximized by adding the acetonitrile solution of 1,2-dimethylimidazole to the solution of 1,3-dobromopropane in acetonitrile slowly under refluxing conditions to keep 1,3-dibromopropane in a large excess during the reaction process. The excess reagent was easily washed away by diethyl ether and the byproduct was removed by decantation after centrifugation because it is insoluble in acetonitrile and the product **2** is well soluble in acetonitrile. The reaction between compound **2** and 2-methylimidazole in acetonitrile under refluxing condition generated the product **3** in its protonated form. After the excess reagent was washed away by diethyl ether and THF, the crude product obtained was further treated with aqueous basic solution of K_2CO_3 for deprotonation and the expected product was extracted by acetonitrile after removing water under freeze-dry conditions. The compound **3** was obtained as white powder and NMR spectra showed it was clean and without contamination by the protonated compound. This step was followed by anion exchange of bromide with triflate to generate compound **4**, which was found to have much better solubility in acetonitrile than compound **3**. The anion exchange could be done by either sodium triflate or silver triflate, but silver triflate worked much faster than the sodium salt. The compound **4** was further treated with 1, 3-dibromopropane in acetonitrle under refluxing condition to generate compound **5**, which has two imidazolium units. The excess reagent was also removed by washing with diethyl ether and the small amount of side-product, which resulted from two bromines of 1, 3-dibromopropane was replaced by compound **4**, was removed by adding dry acetonitrile to the crude product and then centrifugating and decanting to collect the solution phase. The side-product is insoluble in acetonitrile, while the product **5** has good solubility in CH_3CN. The compound **6** was prepared by similar reaction conditions and purification procedures as for compound **3**. This was followed by treating compound **6** with 1, 3-dibromopropane to generate compound **7** with three imidazolium units under similar reaction conditions and purification procedures as for compound **5**. To increase the solubility of compound **7** in acetonitrile, anion exchange was conducted by treating compound **7** with silver triflate. It was found that the C-Br bond on the end of branch chain of compound **7** was partly cleaved by the solver salt, which led to the difficulty to remove this unwanted compound from the expected product. However, when compound **7** was continuously treated with 2-methylimidazole in the same fashion as for compound **6** and **3**, the expected product **8** was obtained. Further treatment of compound **8** with 1,3-dibromopropane and then 2-methylimidazole can extend the imidazolium oligomer chains.

The second route to prepare the imidazolium oligomers is shown in Scheme 2. The molecular assembling sequence is the same as that of Route 1 in Scheme 1. The difference between those two synthetic routes was that the products were obtained with different anions. This makes them having different solubility and different purification procedures. For example, when compound **3** was treated with 1, 3-dibromopropane without anion exchange in acetonitrile under refluxing conditions, the expected product **9** was precipitated out in the reaction mixture because this compound was insoluble in acetonitrile. The product was obtained in 98% yield and has a melting point of up to 201 °C. On the other hand, compound **5**, while, it has the same cationic connecting sequence as **9** but with different anions, is well soluble in acetonitrile and has a melting point of 76 °C. Due to the different anions in the molecules **5** and **9**, their purification procedures were different and they also have different NMR and MS spectra.



Scheme 2. Route 2 to synthesize imidazolium salt oligomers.

4.2.2. Physical properties

Ionic liquid-type oligomers have great potential applications in supported organic synthesis and the preparation of polymer electrolytes because these molecules should have stronger ionic effects and better miscibility with polymers than conventional ionic liquids with one ionic unit. The chemical assembling of the methyl-substituted imidazoles and the dibromoalkane, which is shown in Scheme 1 and 2, provides a straightforward approach to prepare these structure-defined imidazolium oligomers. The 1, 3-dibromoalkane was chosen as the starting reagent instead of 1, 2-dibromoalkane because we believe that oligomers with three-methylene spacer between the two imidazolium cations are likely to be more flexible and chemically and thermally more stable than those with two-methylene spacer. This is partly based on our previous study of organosulfur reagents anchored on ionic liquids (Chapter 2), where the two-methylene-spacer reagent was found to be less stable and base labile. The experimental results showed that imidazolium oligomers with bromine anions have less solubility in acetonitrile and stronger moisture affinity than those with triflate anions and the same cationic structures. This is especially demonstrated in the molecules with two or three bromide anions. For example, compound **9** is insoluble in acetonitrile, while compound **5** is soluble in acetonitrile. The compounds **7** and **8**, which have two bromide anions in the molecule, are less soluble in acetonitrile than their counterpart compounds **12** and **13** with one bromide anion in the molecule. It was also found that compounds with longer molecular chain have less moisture affinity than those with shorter molecular chain. For example, compound **2** absorbs moisture much faster from air than compounds **3** and **4.** Compounds **6** and **8** almost do not absorb moisture from air.

4. 2. 3. Thermal stability

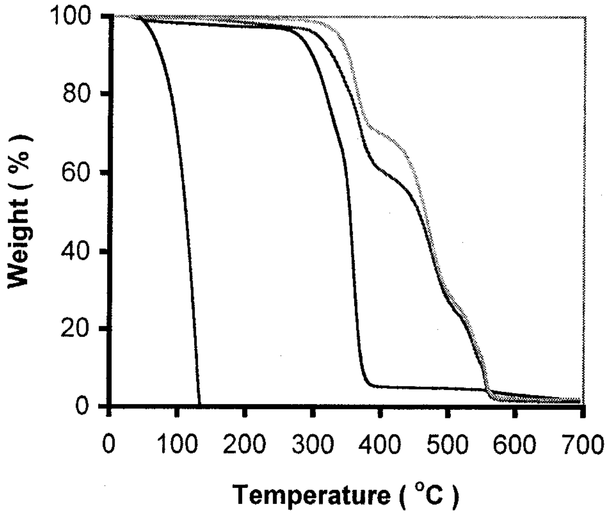


Figure 2. Thermogravimetric analysis (TGA) measurements of imidazolium salt oligomers without bromopropyl chain at the end of molecules. (From left to right) Blue line: 1, 2-dimethylimidazole; Black line: Compound **3**; Pink line: Compound **6**; Green line: Compound **8**.

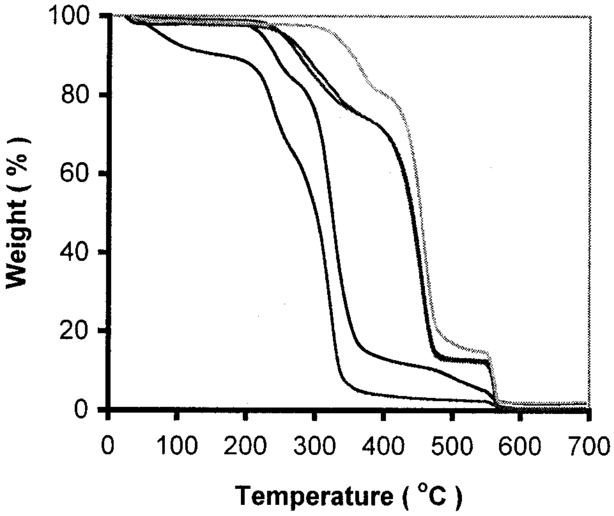


Figure 3. Thermogravimetric analysis (TGA) measurements of imidazolium salt oligomers with bromopropyl chain at the end of molecules. (From left to right) Blue line:

Compound **2**; Black line: Compound **9**; Pink line: Compound **5**; Green line: Compound **7** and yellow line: Compound **12**.

The thermal stability of the imdazolium salt oligomers is measured by thermogravimetric analysis (TGA) as shown in Figure 2 and 3. The plots show that imidazolium salt oligomers are much more thermally stable than non-ionic liquid molecule, 1, 2-dimethylimidazole. Their onset decomposing temperatures, which indicate the starting temperature for the sample to decompose, are more than 200 °C as shown in Table 1. From the data in Table 1, we can draw the general conclusion that the molecules with more imidazolium units have higher onset decomposing temperatures, indicating better thermal stability. This conclusion is supported when we compare the onset decomposing temperatures of compounds **4** (entry 3), **6** (entry 4) and **8** (entry 6). The onset decomposition temperature changes from 293.9 to 329.6 and to 351.6 °C as the number of imidazolium units increases. Similar trend is observed by comparing compounds **2**, **5** and **7**, or the series of compounds **4**, **11** and **13**. Anion exchange from bromide to trifalte also makes the oligomer more thermally stable. For example, compound **9**, **5** and **10** have the same cationic structures, while they have different anions, which are two bromides, one triflate and one bromide, and two triflates, respectively. The data in Table 1 shows that compound **10** has the highest onset decomposing temperature among them and compound **5** has higher onset decomposing temperature than compound **9.** The same result can be obtained when comparing the onset decomposing temperatures of compounds **12** and **7**, or compounds **3** and **4**. A third conclusion is that molecules with the bromopropyl chain at the end of molecule are less stable than those molecules without the bromopropyl chain but with the same number of immidazole units. For example, the onset decomposing temperatures of compounds **3** and **4** are 287.82 °C and 293.91 °C, respectively, and compounds **5, 9** and **10** have the onset decomposing temperatures at 239.48 °C, 212.25 °C and 277.80 °C, respectively, which are lower than those of compounds **3** and **4**. The same results can also be obtained when comparing the onset decomposing temperatures of compounds **6** and **11** with **7** and **12**. Finally, the low residue percentages in Table 1, around 1%, for all samples show that the oligomeric compounds contain a very small amount of inorganic salts, indicating that most inorganic salts have been removed during workup procedures.

Table 1. Decomposing temperatures (onset) and residue percentages of the samples according to TGA measurements.

Entry	Samples	Onset Decomposing Temperature (°C)	Residue (%)
1	Compound **1**	80.60	0.18
2	Compound **3**	287.82	1.53
3	Compound **4**	293.91	1.71
4	Compound **6**	329.64	1.38
5	Compound **11**	326.25	1.76
6	Compound **8**	351.63	0.59
7	Compound **13**	336.41	0.58
8	Compound **2**	215.88	0.10
9	Compound **5**	239.48	0.59
10	Compound **9**	212.25	1.89
11	Compound **10**	277.80	0.50

12	Compound **7**	252.36	0.17
13	Compound **12**	318.96	2.10
14	1-(3'-Hydroxypropyl)-2,3-dimethylimidazolium Bromide	291.85	0.50
15	1-(3'-Hydroxypropyl)-2,3-dimethylimidazolium Triflate	317.03	0.17

4. 3. Conclusion

In conclusion, a new and straightforward approach to synthesize ionic liquid-type oligomers in multi-gram scales has been demonstrated in the synthesis of structure-defined imidazolium salt oligomers. The products were purified by simple washing or centrifugation, which is suitable for large-scale preparation in industry. The compounds obtained with multiple charges are very stable under thermal conditions. Their thermal stability is dependent on the numbers of imidazolium units, anions and the branch chains at the end of molecules. Those molecules with multiple imidazolium units are generally soluble in water and some polar solvents such as DMF, DMSO, CH_3CN and CH_3NO_2, less soluble in CH_2Cl_2 and ethyl acetate, insoluble in alkanes, THF, diethyl ether and chloroform. Their solubility in organic solvents can be tuned by anion exchange and the molecular structures can be characterized by common methods such as IR, NMR and MS spectroscopy. These compounds have significant potential application as soluble supports in organic synthesis, which will be demonstrated in the next chapter for the synthesis of oligopeptides, and as plasticizers for fabricating polymer electrolytes.

4. 4. Experimental Section

General: All chemicals were obtained from Aldrich and used without further purification except otherwise indicated. Acetonitrile and dichloromethane were distilled from CaH_2 as drying reagent. ^{1}H and ^{13}C NMR, COSY NMR spectra were recorded on Varian Mercury 300,Varian Mercury 400 and Unity 500 spectrometers equipped with Sun workstations. The chemical shifts were reported in parts per million on the δ scale referenced to residue $CHCl_3$ at δ 7.24ppm, H_2O at 4.67ppm for ^{1}H NMR and $CHCl_3$ at 77.0ppm for ^{13}C NMR. The proton and carbon assignments were made by standard gCOSY experiments. Melting point of sample was taken via melting point apparatus without correcting the thermometer. High resolution mass spectrometric analysis was performed on a VG Micromass ZAB 2F HS (FAB) or Micromass Quattro II triple quadrupole mass spectrometer (Manchester, UK) equipped with an electrospray ionization source (ESI). Usually, only the ion corresponding to the cation (C) component was analyzed. The thermo-gravimetric analysis (TGA) measurements were performed on a TGA Q500 from TA instruments. The running method used was ramped from 25 °C to 550 °C, 20 °C/min, under nitrogen, switching to air and then ramped at 20 °C/min to 700 °C. The type of pan used was platinum.

Compound 2: To the solution of 1, 3-dibromopropane (12.5 mL, 122.40 mmol) in acetonitrile (25 mL) was added a solution of 1, 2-dimethylimidazole (5.66 g, 58.96 mmol) in acetonitrile (10 mL) dropwise at 90 °C. After refluxing at 90 °C for 14 hours, the solvent was removed by rotary evaporation under reduced pressure and the residue was washed with diethyl ether for 4 times, dried *in vacuo* to give white powder which was added with 40 mL of dry acetonitrile. The insoluble precipitate was removed through phase separation after centrifugation. The solution phase was collected and solvent was removed by rotary evaporation under vacuum. The product was dried *in vacuo* and obtained as white solid (14.23 g, 80% yield).

M. P. 96-98 °C; ^{1}H NMR (400 MHz, D_2O) δ 7.30 (d, 1H, J= 2 Hz), 7.24 (d, 1H, J = 2 Hz), 4.20 (t, 2H, J= 7.2 Hz), 3.67 (s, 3H), 3.37 (t, 2H, J= 5.6 Hz), 2.53 (s, 3H), 2.28 (m, 2H); ^{13}C NMR (400 MHz, D_2O) δ 144.72, 122.67, 121.00, 46.70, 35.29, 31.98, 30.26, 9.81; HRMS (ESI): calcd for $C_8H_{14}N_2Br$ (C^+) 217.0337, found: 217.0334.

Compound 3: To the flask with compound **2** (22.05 g, 74.01 mmol) and 2-methylimidazole (13.53 g, 164.88 mmol) was added dry acetonitrile (200 mL) under the protection of nitrogen. The reaction mixture was refluxed for 24 hours and then cooled to room temperature. The solvent was removed by rotary evaporation under vacuum and the residue was washed with diethyl ether for two times and THF for four times to give white powder. The phase separation during washing process was conducted by centrifugation and decantation. After having been dried *in vacuo* for two hours, the white powder was added with 150 mL of water and K_2CO_3 (pH = 11) and stirred for half an hour. The water was removed under freeze-dry condition and the residue was added with acetonitrile. After filtering off the insoluble inorganic salt, the filtrate was collected and rotary evaporated to dryness and the residue was then washed with THF and ether to afford the final product as white powder (16.41 g, 74% yield).

M. P. 159-161 °C; ^{1}H NMR (400 MHz, D_2O) δ 7.12-7.10 (m, 2H), 6.85 (d, 1H, J = 1.2 Hz), 6.68 (d, 1H, J = 1.2 Hz), 3.95 (t, 2H, J = 7.2Hz), 3.86 (t, 2H, 6.8 Hz), 3.55 (s, 3H), 2.32 (s, 3H), 2.14 (m, 5H); ^{13}C NMR (400 MHz, D_2O) δ 145.99, 144.40, 126.06, 122.60, 120.51, 120.20, 45.62, 43.08, 35.02, 29.70, 12.09, 9.29; HRMS (ESI): calcd for $C_{12}H_{19}N_4$ (C^+) 219.1604, found: 219.1604.

Compound 4: To a solution of compound **3** (4.88 g, 16.32 mmol) in acetonitrile (60 mL) was added a solution of AgOTf (4.18 g, 16.32 mmol) in acetonitrile (10 mL). The mixture was stirred for 1 hour in the dark and filtered to remove the yellow precipitate. The filtrate was rotary evaporated under reduced pressure to give the product as white solid (6.06g, 100% yield).

M. P. 120-122 °C; ^{1}H NMR (400 MHz, D_2O) δ 7.13 (m, 2H), 6.87(d, 1H, J=1.2 Hz), 6.71(d, 1H, J=1.2 Hz), 3.96 (t, 2H, 7.2 Hz), 3.87 (t, 2H, 7.2 Hz), 3.56(s, 3H), 2.33 (s, 3H), 2.14 (m, 5H); ^{13}C NMR (400 MHz, D_2O) δ145.97, 144.42, 125.80, 122.57, 120.45, 120.15, 45.34, 42.84, 34.66, 29.40, 11.63, 8.78; HRMS (ESI): calcd for $C_{12}H_{19}N_4$ (C^+) 219.1604, found: 219.1604.

Compound 5: To the flask with compound **4** (5.51 g, 14.96 mmol) was added 1,3-dobromopropane (30 mL, 293.75 mmol) and dry acetonitrile (100 mL). The reaction mixture was refluxed for 17 hours under the protection of nitrogen, The mixture was cooled to room temperature and then rotary evaporated under reduced pressure to remove solvent. The residue was washed with diethyl ether for four times and then vacuumed to dryness for 30 minutes to give white solid. After adding dry acetonitrile (100 mL) to the solid, the precipitate was removed by phase separation through centrifugation and decantation. The solution phase was collected and rotary evaporated under reduced pressure to give product (6.81 g, 80%) as faun solid.

M. P. 76-78 °C; ^{1}H NMR (400 MHz, D_2O) δ 7.28 (d, 1H, J = 2.4 Hz), 7.24 (d, 1H, J = 2.0 Hz), 7.19 (d, 1H, J = 2.0 Hz), 7.16 (d, 1H, J = 2.4 Hz), 4.13 (t, 2H, J = 6.8 Hz), 4.06(t, 2H, J = 7.6 Hz), 3.58 (s, 3H), 3.29 (t, 2H, J = 5.6 Hz), 2.48 (s, 3H), 2.41(s, 3H), 2.20(m, 4H); ^{13}C NMR (400 MHz, D_2O) δ 144.58, 144.42, 122.67, 121.65, 121.09, 120.43, 46.66, 45.16, 45.10, 34.95, 31.56, 29.70, 29.20, 9.44, 9.21; HRMS (ESI): calcd for $C_{16}H_{25}N_4BrO_3F_3S$ (M-Br$^+$) 489.0780, found: 489.0777.

Compound 6: To the flask with compound **5** (4.89 g, 8.58 mmol) and 2-methylimidazole (2.56 g, 31.21 mmol) was added dry acetonitrile (45 mL). The reaction mixture was refluxed at 90°C for 24 hours and then cooled to room temperature. This was followed by rotary evaporation under reduced pressure to remove solvent. The residue was washed with THF and diethyl ether and then vacuumed to dryness for 30 min to give a white power. To the powder was added 60 mL of water and K_2CO_3 (pH = 11) and stirred for half an hour. The water was removed under freeze-dry condition and the residue was added with acetonitrile. After filtering off the insoluble salt, the filtrate was collected and rotary evaporated to dryness and the residue was further washed with THF and diethyl ether to afford the final product as white foam (3.59 g, 74% yield).

M. P. 121-123 °C; ^{1}H NMR (400 MHz, D_2O) δ 7.27 (m, 4H), 6.92 (s, 1H), 6.74 (s, 1H), 4.14-4.02 (m, 6H), 3.95 (t, 2H, J = 6.4 Hz), 3.65 (s, 3H), 2.48 (s, 3H), 2.43 (s, 3H), 2.21(m, 7H); ^{13}C NMR (400 MHz, D_2O) δ 146.03, 144.68, 144.22, 126.01, 122.77, 121.32, 121.23, 120.52, 120.17, 45.84, 45.23, 45.18, 43.18, 35.04, 29.47, 29.27, 12.02, 9.34; HRMS (ESI): calcd for $C_{20}H_{30}N_6O_3F_3S$ (M-Br$^+$) 491.2049, found: 491.2046.

Compound 7: To the flask with compound **6** (3.22 g, 5.65 mmol) was added 1,3-dibromopropane (11 mL, 107.71 mmol) and dry acetonitrile (35 mL). The reaction mixture was refluxed for 26 hours at 90 °C under the protection of nitrogen, Cooled to room temperature and then rotary evaporated under reduced pressure to remove solvent.

The residue was washed with THF for three times and diethyl ether for two times and then vacuumed to dryness for 30 min to give white solid. After adding dry acetonitrile (100 mL) to the solid, the precipitate was removed by phase separation through centrifugation and decantation. The solution phase was collected and rotary evaporated under reduced pressure to give product as thick oil (3.66 g, 84%).

^{1}H NMR (400 MHz, D_2O) δ 7.31-7.27 (m, 4H), 7.21 (d, 1H, J = 2 Hz), 7.18 (d, 1H, J = 2 Hz), 4.15 (t, 2H, J = 6.8 Hz), 4.11-4.05 (m, 8H), 3.60 (s, 3H), 3.30 (t, 2H, J = 6.4 Hz), 2.50 (s, 3H), 2.46 (s, 3H), 2.42 (s, 3H), 2.21 (m, 6H); ^{13}C NMR (400 MHz, D_2O) δ 144.71, 144.56, 122.78, 121.78, 121.30, 121.24, 120.56, 46.58, 45.13, 45.07, 44.99, 34.84, 31.47, 29.71, 29.06, 29.01, 9.28, 9.20, 9.04; HRMS (ESI) calcd for $C_{24}H_{36}N_6O_6F_6S_2Br$ (M^+) 761.1237, found: 761.1239; calcd for $C_{23}H_{36}N_6O_3F_3SBr$ (M^{2+}-2Br) 306.0847, found: 306.0850.

Compound 8: To the flask with compound **7** (2.42 g, 3.13 mmol) and 2-methylimidazole (0.88 g, 10.74 mmol) was added dry acetonitrile (45 mL). The reaction mixture was refluxed at 90 °C for 24 hours and then cooled to room temperature. This was followed by rotary evaporation under reduced pressure to remove solvent. The residue was washed with THF and diethyl ether and then vacuumed to dryness for 30 min to give white powder. To the powder was added 50 mL of water and K_2CO_3 (pH = 11) and stirred for half an hour. The water was removed under freeze-dry condition and the residue was added with acetonitrile. After filtering off the insoluble inorganic salt, the filtrate was collected and rotary evaporated to dryness and residue was then washed with THF and diethyl ether to afford the final product as sticky white foam (1.81 g, 75% yield).

^{1}H NMR (400 MHz, D_2O) δ 7.30 (m, 2H), 7.25-7.17 (m, 4H), 6.88 (s, 1H), 6.70 (s, 1H), 4.11-4.05 (m, 8H), 4.00 (t, 2H, J = 7.2Hz), 3.91 (t, 2H, J = 6.8 Hz), 3.61 (s, 3H), 2.48 (s, 3H), 2.44 (s, 3H), 2.40 (s, 3H), 2.26-2.14 (m, 9H); ^{13}C NMR (500 MHz, CD_3CN) δ 145.17, 145.13, 144.84, 144.55, 127.12, 122.80, 122.56, 121.54, 120.99, 120.01, 119.37, 45.72, 45.18, 42.66, 35.05, 30.32, 29.42, 29.33, 12.38, 9.70, 9.56, 9.49; HRMS (ESI): calcd for $C_{27}H_{41}N_8O_3F_3S$ (M^{2+}-2Br) 307.1481; found: 307.1483.

Compound 9: To the flask with compound **3** (2.75 g, 9.22 mmol) was added 1,3-dobromopropane (10 mL, 97.92 mmol) and dry acetonitrile (100 mL). The reaction mixture was refluxed for 25 hours under the protection of nitrogen, Cooled to room temperature and then rotarily evaporated under reduced pressure to remove solvent. The residue was washed with diethyl ether for four times and then vacuumed to dryness to give the product as white powder (4.52 g, 98% yield).

M.P. = 201-203 °C; ^{1}H NMR (500 MHz, D_2O) δ7.36 (d, 1H, J = 2 Hz), 7.33 (d, 1H, J = 2 Hz), 7.28 (d, 1H, J = 2 Hz), 7.24 (d, 1H, J = 2 Hz), 4.19 (t, 2H, J = 7 Hz), 4.13 (m, 4H), 3.65 (s, 3H), 3.36 (t, 2H, J = 6 Hz), 2.55 (s, 3H), 2.48 (s, 3H), 2.27(m, 4H); ^{13}C NMR (400 MHz, D_2O) δ 144.71, 144.55, 122.82, 121.80, 121.29, 120.63, 46.87, 45.40, 45.34, 35.23, 31.76, 30.14, 29.38, 9.90, 9.66; HRMS (ESI): calcd for $C_{15}H_{25}N_4Br_2$ (M-Br^+) 419.0446, found: 419.0440.

Compound 10: To a solution of compound **9** (3.19 g, 6.38 mmol) in a mixed solvent of acetonitrile (60 mL) and methanol (18 mL) was added a solution of AgOTf (3.27 g, 12.76 mmol) in acetonitrile (20 mL). The mixture was stirred for 1 hour in the dark and filtered to remove the yellow precipitate. The filtrate was rotary evaporated under reduced pressure to give the product (4.09g, 100% yield) as white solid.

M. P. 84-86 °C; ^{1}H NMR (400 MHz, D_2O) δ 7.32 (d, 1H, J = 2.4 Hz), 7.28 (d, 1H, J = 2.0 Hz), 7.22 (d, 1H, J = 2.0 Hz), 4.16 (t, 2H, J = 6.8 Hz), 4.08 (m, 4H), 3.1(s, 3H), 3.22 (d, 2H, J = 6 Hz), 2.50 (s, 3H), 2.44 (s, 3H), 2.22 (m, 4H); ^{13}C NMR (400 MHz, D_2O) δ 144.69, 144.52, 122.77, 121.74, 121.18, 120.51, 46.54, 45.03, 44.97, 34.78, 31.43, 29.60, 29.02, 9.17, 8.94; HRMS (ESI): calcd for $C_{16}H_{25}N_4BrO_3F_3S$ (M-TfO$^+$) 489.0780, found: 489.0777.

Compound 11: To the flask with compound **10** (3.87 g, 6.07 mmol) and 2-methylimidazole (1.61 g, 19.68 mmol) was added dry acetonitrile (110 mL). The reaction mixture was refluxed at 90°C for 24 hours and then cooled to room temperature. This was followed by rotary evaporation under reduced pressure to remove solvent. The residue was washed with THF and diethyl ether and then vacuumed to dryness for 30 min to give a white power. To the powder was added 50 mL of water and K_2CO_3 (pH = 11) and stirred for half an hour. The water was removed under freeze-dry condition and the residue was added with acetonitrile. After filtering off the insoluble inorganic salt, the filtrate was collected and rotary evaporated to dryness and the residue was further washed with THF and diethyl ether to afford the final product as white solid (3.27 g, 85% yield).

M. P. 107-109 °C; ^{1}H NMR (400 MHz, D_2O) δ 7.22 (s, 2H), 7.21 (d, 1H, J = 2.4 Hz), 7.18 (d, 1H, J = 2.4 Hz), 6.87 (d, 1H, J = 1.6 Hz), 6.70 (d, 1H, J = 1.6 Hz), 4.08-4.01 (m, 4H), 3.99 (t, 2H, J = 7.2 Hz), 3.90 (t, 2H, J = 6.4 Hz), 3.59 (s, 3H), 2.42 (s, 3H), 2.37 (s, 3H), 2.17 (m, 7H); ^{13}C NMR (400 MHz, D_2O) δ 146.00, 144.69, 144.24, 125.82, 122.75, 121.28, 121.18, 120.46, 120.13, 45.57, 44.97, 44.91, 42.94, 34.75, 29.23, 29.00, 11.64, 8.90. HRMS (ESI): calcd for $C_{20}H_{30}N_6O_3F_3S$ (M-TfO$^+$) 491.2049, found: 491.2046.

Compound 12: To the flask with compound **11** (2.07 g, 3.24 mmol) was added 1,3-dibromopropane (7 mL, 68.54 mmol) and dry acetonitrile (45 mL). The reaction mixture was refluxed for 28 hours at 90°C under the protection of nitrogen, Cooled to room temperature, and then rotary evaporated under reduced pressure to remove solvent. The residue was washed with THF for three times and diethyl ether for two times and then vacuumed to dryness for 30 min to give white solid. After adding dry acetonitrile (80 mL) to the solid, the precipitate was removed by phase separation through centrifugation and decantation. The solution phase was collected and rotary evaporated under reduced pressure to give product as white powder (2.19 g, 80% yield).

M. P. 105-107 °C; ^{1}H NMR (400 MHz, D_2O) δ 7.31 (d, 1H, J = 2.4 Hz), 7.28 (m, 2H), 7.27 (d, 1H, J = 2.4 Hz), 7.21 (d, 1H, J = 2.0 Hz), 7.18 (d, 1H, J = 2.0 Hz), 4.15 (t, 2H, J = 6.8 Hz), 4.11-4.06 (m, 8H), 3.60 (s, 3H), 3.31 (t, 2H, J = 6.4 Hz), 2.50 (s, 3H), 2.47 (s, 3H), 2.43 (s, 3H), 2.22 (m, 6H); ^{13}C NMR (400 MHz, D_2O) δ 144.64, 144.48, 122.73, 121.74, 121.33, 121.16, 120.49, 46.73, 45.26, 45.19, 45.12, 34.97, 31.61, 29.78, 29.23, 29.17, 9.46, 9.35, 9.21; HRMS (ESI): calcd for $C_{24}H_{36}N_6O_6F_6S_2Br$ (M-Br$^+$) 761.1231, found: 761.1219.

Compound 13: To the flask with compound **12** (2.05 g, 2.43 mmol) and 2-methylimidazole (0.80 g, 9.85 mmol) was added dry acetonitrile (45 mL). The reaction mixture was refluxed at 90°C for 24 hours and then cooled to room temperature. This was followed by rotary evaporation under reduced pressure to remove solvent. The residue was washed with THF and diethyl ether and then vacuumed to dryness for 30 min to give white powder. To the powder was added 50 mL of water and K_2CO_3 (pH = 11) and stirred for half an hour. The water was removed under freeze-dry condition and the residue was added with acetonitrile. After filtering off the insoluble inorganic salt, the filtrate was collected and rotary evaporated to dryness and the residue was further washed with THF and diethyl ether to give the final product as white solid (1.43 g, 70% yield). M. P. 96-98 °C; ^{1}H NMR (400 MHz, D_2O) δ 7.27 (s, 2H), 7.22 (m, 2H), 7.20 (d, 1H, J = 2.4 Hz), 7.19 (d, 1H, J = 2.4 Hz), 6.86 (d, 1H, J = 1.2 Hz), 6.69 (d, 1H, J = 1.2 Hz), 4.07 (m, 8H), 3.98 (t, 2H, 7.6 Hz), 3.89 (t, 2H, J = 6.8 Hz), 3.59 (s, 3H), 2.46 (s, 3H), 2.42 (s, 3H), 2.37 (s, 3H), 2.19 (m, 9H); ^{13}C NMR (400 MHz, D_2O) δ 145.95, 144.58, 144.42, 144.14, 126.01, 122.67, 121.29, 121.26, 121.12, 120.43, 120.06, 45.72, 45.19, 45.08, 45.06, 43.04, 34.91, 29.43, 29.18, 29.13, 11.92, 9.30, 9.15; HRMS (ESI): calcd for $C_{28}H_{41}N_8O_6F_6S_2$ (M-Br^+) 763.2488, found: 763.2489.

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Chapter 5. Peptide Synthesis Using Imidazolium Oligomers as Soluble Supports

5. 1. Introduction

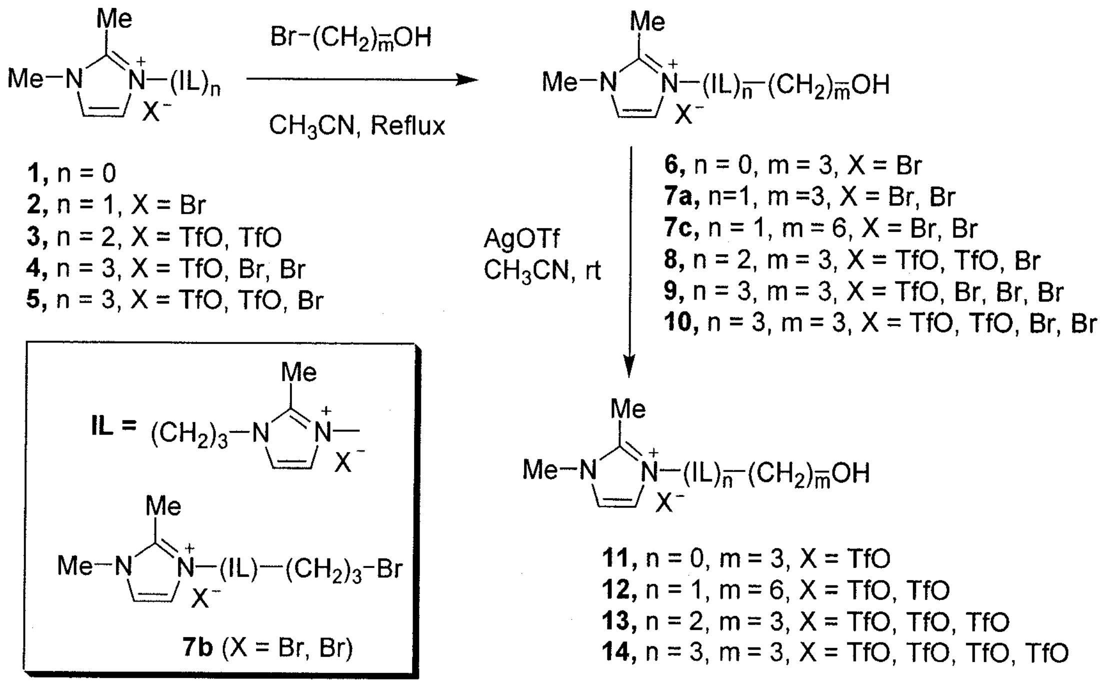
Peptide synthesis is one of central research topics in organic synthesis because a various number of peptides have been used as anticancer agents, protease inhibitors, antibiotics and receptor antagonists, the closest fields to people's health and life.[1] In 1960's, Merrifield introduced the solid-phase peptide synthesis,[2] which was a milestone in the chemical synthesis of peptides. This method led to the advent of automated preparation of biopolymers including peptides,[3] nucleotides[4] and oligosaccharides.[5] However, the drawbacks of solid-phase synthesis are that the chemical reactions are performed in the heterogeneous phase, which generally requires large excess of reagents to drive the reaction to completion, and it is difficult to do large-scale reactions and characterize the polymer resin-bound intermediate products by common methods in organic synthesis such as TLC, NMR and MS spectroscopy.[6] To overcome the solubility problem involved in the solid-phase peptide synthesis, chemists introduced soluble polymers such as polyethylene glycol (PEG)[7] and polyvinyl alcohols (PVA)[8] to the peptide synthesis. The limitations of this approach are low loading capacity, aqueous solubility and inconveniency in the product characterization by NMR and MS. More recently, fluorous phase synthesis was invoked for peptide synthesis.[9] This method is based on the fact that highly fluorinated compounds are preferentially dissolved in fluorous solvents, which are used to extract fluorous phase tag-bound products from the organic solution phase. The high cost of fluorous solvents as compared to the common organic solvents may limit its industrial application.

In the latest a few years, ionic liquid-supported synthesis has been successfully applied to organic synthesis[10] and catalysis.[11, 12] This new approach possesses the advantages of both conventional solution-phase synthesis and solid-phase synthesis. The ionic liquid–supported substrates, generally soluble in polar organic solvents, can perform chemical reactions in homogeneous solution phase, and the product, which is bound to the ionic liquid phase tag, can be purified through simple phase separation from the reaction mixture by washing or precipitation with less polar organic solvents or water. This methodology was applied to synthesize small organic molecules,[10a, d] short oligopetide[10e] and oligosaccharides[10b] by our group and others. However, in all of those cases, ionic liquid supports had only one ionic unit, which were not big enough as phase tags in some cases because their ionic effect disappeared when a large molecular moiety was connected to the ionic liquid phase tag, especially for the synthesis of biopolymers. Moreover, the small ionic liquid supports resulted in liquid-liquid phase separation during product purification process in the case as shown in the 1-methylimidazolium-supported short oligopeptide synthesis reported by our group in 2005.[10e] The liquid-liquid phase separation is difficult to perform in large-scale reactions because the oily product is stuck on the inside surface of flask walls and the researcher has to use spatula to scratch the oil layer in the washing solvent to wash away the excess reagents and byproducts. Ionic liquid-type polymers are not a good choice here because they will have the same problems as polymer resin-supported synthesis such as low solubility and difficulty to characterize the support-bound products. Ionic liquid-type oligomers are chosen as support candidates herein because they are soluble in common polar organic solvents and can provide stronger ionic effect on their supported molecules than one-ionic-unit supports. Moreover, the imidazolium oligomer-bound molecules are likely to be solid, which may be purified by an easier way such as precipitation, centrifugation and decantation. This is a way suitable for large-scale synthesis. The synthesis of the first example of ionic liquid-type oligomers in multi-gram scale is described in Chapter 4 of this thesis. On the other hand, since solid-phase supported peptide block coupling is extremely difficult, we anticipate that these new soluble supports, ionic liquid-type oligomers, can make possible the peptide block coupling in solution phase, which is significantly important for peptide synthesis.

5. 2. Results and Discussion

5. 2. 1. Synthesis and thermal stability of imidazolium salts with hydroxyalkyl linkers

The synthesis of ionic liquid-type oligomer supports for peptide synthesis is shown in Scheme 1. Treatment of 1, 2-dimethylimidazole 1, imidazolium dimer 2 and oligomers 3, 4, and 5 with excess bromoalkyl alcohols in acetonitrile under refluxing conditions generated the imidazolium salts (6, 7, 8, 9 and 10) with hydroxyalkyl linkers. The excess reagents were washed away by diethyl ether. However, when imidazolium dimer 2 was treated with 3-bromopropanol under the same conditions as other cases in Scheme 1, the product obtained was not the expected compound, imidazolium salt alcohol 7a, but the imidazolium salts 7b where OH on the branch chain was replaced by bromine. The reason is that the latter compound 7b has very low solubility in acetonitrile, which precipitates out from the reaction mixture under the refluxing condition to drive the reaction to generate the unwanted product 7b. The molecular structure of the compound 7b obtained was confirmed by NMR and MS spectroscopic analysis.



Scheme 1. Synthesis of imidazolium salts with hydroxyalkyl linkers.

However, this problem may be avoided by use of the starting imidazolium dimer **2** after anion exchange. The anion exchange from bromide to triflate was conducted by silver triflate in the mixed solvents of acetonitile and methanol at room temperature. However, this reaction can also be done by use of sodium triflate in acetonitrile or acetone, which works much slower than the silver salt. The thermal stability of the imidazolium salts obtained were measured by thermogravimetric analysis (TGA), which showed that these compounds have high onset decomposing temperatures up to more than 290 °C, as shown in Figure 1 and Table 1, suggesting good thermal stability. And also, the compound with more imidazolium units has higher onset decomposing temperature. This is consistent with the results obtained from imidazolium oligomers that have been shown in Chapter 4 of this thesis. The low residue percentages in Table 1 show that those compounds contain a small amount of inorganic salt, indicating most of the inorganic compounds have been removed during the product purification procedures.

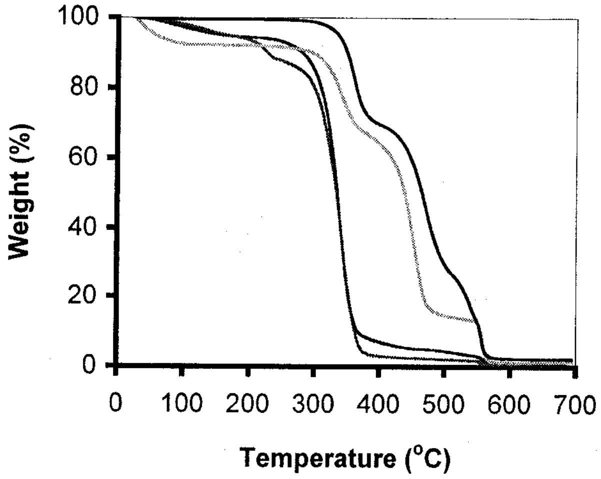
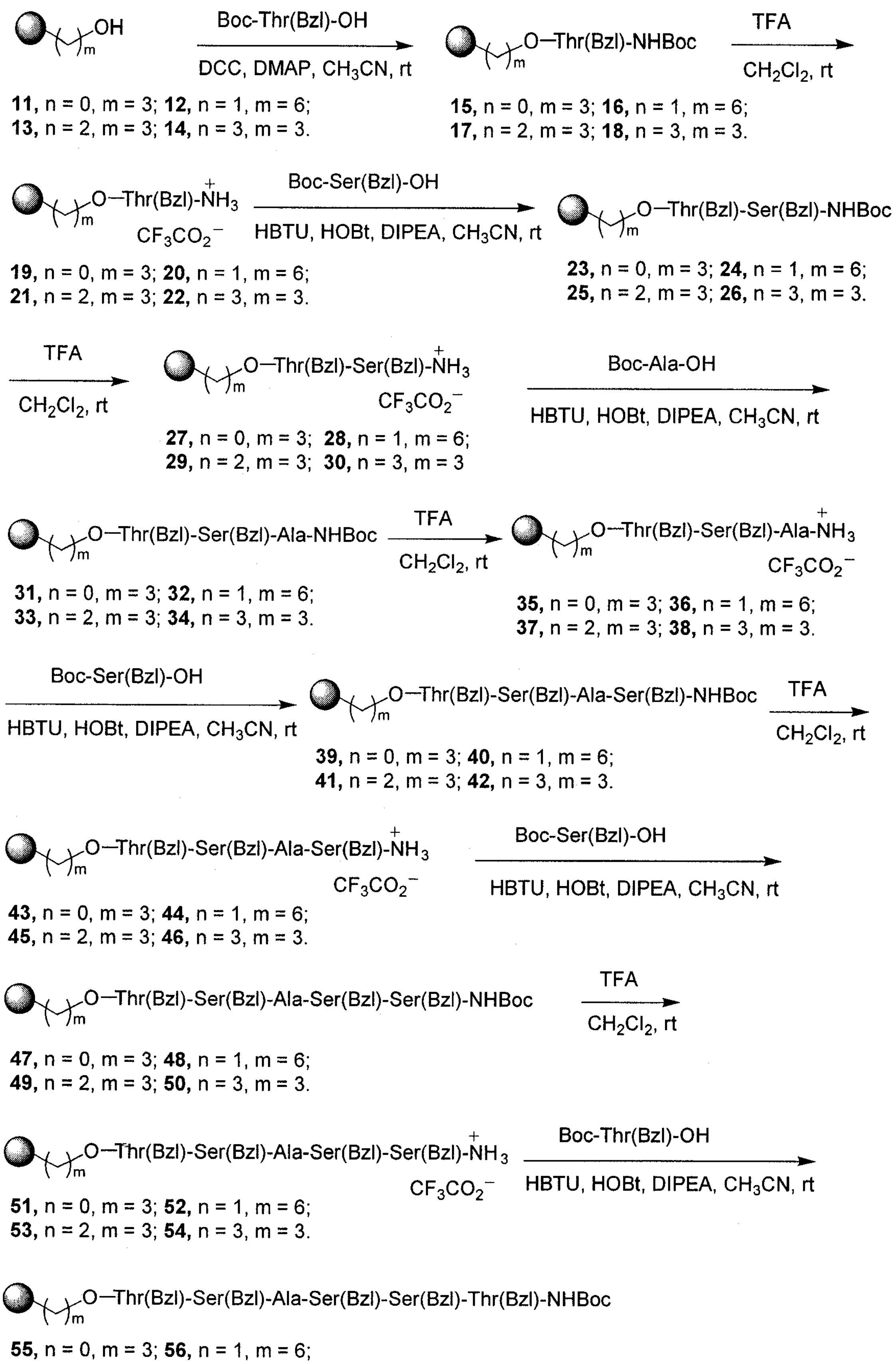


Figure 1. Thermogravimetric analysis (TGA) measurements of imidazolium salts as the synthetic support linker. (From left to right) Pink line: Compound **7**; Blue line: Compound **6**; Green line: Compound **8**; Black line: Compound **10**.

Table 1. Decomposing temperatures (onset) and residue percentages of samples according to TGA measurements.

Entry	Samples	Onset Decomposing Temperature (°C)	Residue (%)
1	Compound **6**	291.85	0.50
2	Compound **7**	296.54	0.19
3	Compound **8**	310.43	1.40
4	Compound **10**	337.96	2.21

5. 2. 2. Peptide synthesis



11, n = 0, m = 3; **12,** n = 1, m = 6;
13, n = 2, m = 3; **14,** n = 3, m = 3.

15, n = 0, m = 3; **16,** n = 1, m = 6;
17, n = 2, m = 3; **18,** n = 3, m = 3.

19, n = 0, m = 3; **20,** n = 1, m = 6;
21, n = 2, m = 3; **22,** n = 3, m = 3.

23, n = 0, m = 3; **24,** n = 1, m = 6;
25, n = 2, m = 3; **26,** n = 3, m = 3.

27, n = 0, m = 3; **28,** n = 1, m = 6;
29, n = 2, m = 3; **30,** n = 3, m = 3

31, n = 0, m = 3; **32,** n = 1, m = 6;
33, n = 2, m = 3; **34,** n = 3, m = 3.

35, n = 0, m = 3; **36,** n = 1, m = 6;
37, n = 2, m = 3; **38,** n = 3, m = 3.

39, n = 0, m = 3; **40,** n = 1, m = 6;
41, n = 2, m = 3; **42,** n = 3, m = 3.

43, n = 0, m = 3; **44,** n = 1, m = 6;
45, n = 2, m = 3; **46,** n = 3, m = 3.

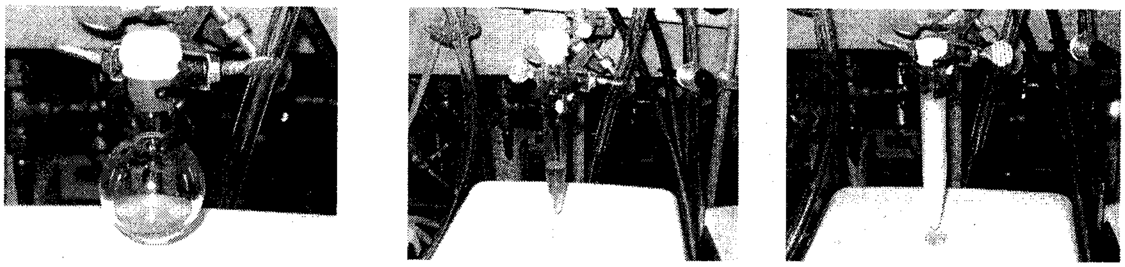
47, n = 0, m = 3; **48,** n = 1, m = 6;
49, n = 2, m = 3; **50,** n = 3, m = 3.

51, n = 0, m = 3; **52,** n = 1, m = 6;
53, n = 2, m = 3; **54,** n = 3, m = 3.

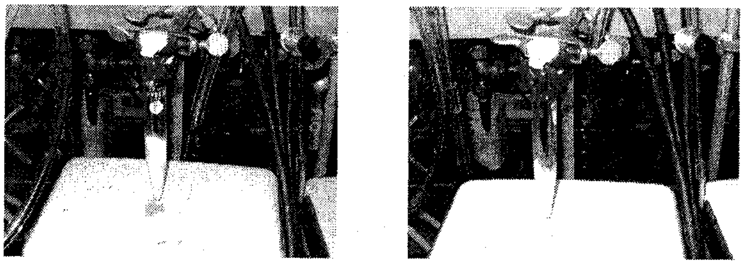
55, n = 0, m = 3; **56,** n = 1, m = 6;
57, n = 2, m = 3; **58,** n = 3, m = 3.

Scheme 2. Ionic liquid-type monomer, dimer and oligomer-supported peptide synthesis. Bzl = benzyl.

The imidazolium oligomer-supported peptide synthesis is shown in Scheme 2. The peptide sequence, which was chosen from a segment of natural peptide Mucin4 (MUC4),[13] is mostly composed of serine and threonine because these two amino acids play an significant role in connecting glycals in glycoproteins.[14] The first amino acid was covalently bound to the imidazolium salt supports through an esterification reaction between them using 1,3-dicyclohexylcarbodimide (DCC) as the coupling reagent and 4-dimethylaminopyridine (DMAP) as the catalyst in acetonitrile at room temperature. The white precipitate, dicyclohexylurea, generated in the reaction process, was filtered off, and the excess reagents and other side-products were washed away by diethyl ether or the mixed solvents of diethyl ether and ethyl acetate (V/V = 1:1). The products **16**, **17**, and **18** were obtained as solid, while compound **15** was obtained as thick oil. The removal of acid-labile Boc protection group on the supported amino acids was realized by treating the compounds with trifluoroacetic acid (TFA) in dichloromethane. The byproduct derived from Boc group was washed away by diethyl ether. The amino acid coupling was conducted by use of the combination of HBTU and HOBt, instead of PyBOP in the former case of our group, as coupling reagent because the piperidine, which was generated from PyBOP,[10e] was very difficult to be washed away during the purification procedures. The Hünig's base, DIPEA, was used to neutralize TFA to release the unprotonated amine and acted as acid scavenger. The purification procedures of the products generated from imidazolium dimer (**24**) and oligomer–supported amino acid couplings (**25** and **26**) are illustrated in Figure 2, showing the greater ease of purification than the one generated from the monomer-supported synthesis (**23**). For example, when the reaction was complete, the reaction mixture was concentrated by rotary evaporation under reduced pressure and then transferred into a conical tube. At this time, diethyl ether was added to precipitate the product and the liquid phase was separated and removed by centrifugation and decantation. The solid phase was transferred to a funnel and washed with water for several times and then diethyl ether. After dried in vacuo, the product was obtained as powder.



Concentrated **Transfer** **Precipitation**



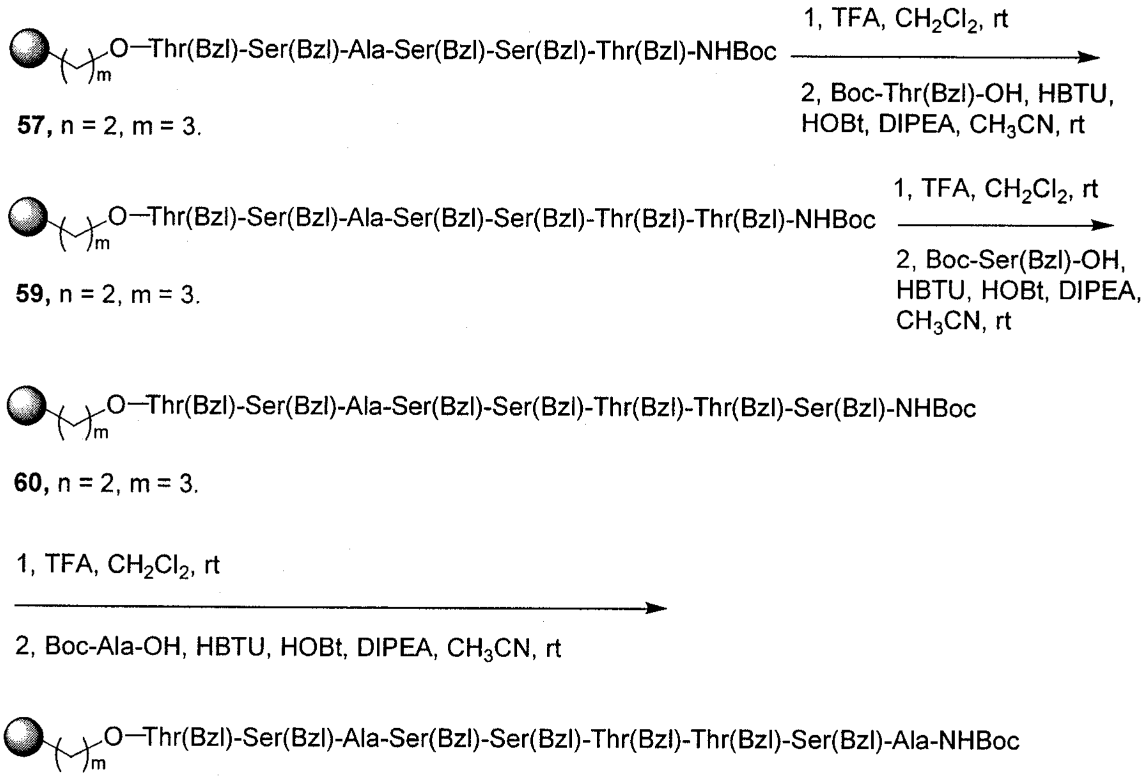
Centrifugation **Decantation**

Figure 2. Product purification procedures of imidazolium oligomer-supported peptide synthesis.

Thus, it is clear that this purification process is much easier than the liquid-liquid phase separation that needs scratching the oily product layer with a spatula to allow the byproducts and excess reagents dispersed into the washing solvents. Here it is worthy to emphasize that the chemical assembling of amino acids in Scheme 2 was carried out in homogeneous solution phase without need of much excess reagents, generally, 2–2.5 equivalents of amino acids as compared to the support-bound substrates were used.

The product for each step can be easily characterized by solution NMR and MS spectroscopy. This is in great contrast to the solid-phase synthesis, which requires much excess reagents (normally more than 10 equivalents) to drive the reaction to completion, and the reaction was conducted in heterogeneous phase and the support-bound products are difficult to be characterized by common instruments for organic synthesis. The ionic liquid-oligomer-supported peptide synthesis is also in contrast to the fluorous phase synthesis, where fluorinated solvents are needed to extract the product from the reaction mixture.

The solubility of peptides is a serious issue in peptide synthesis because the protected oligopeptides have low solubility in organic solvents and water. This means that the non-supported peptide synthesis can be conducted in homogenous solution phase only when the peptide chain is not too long, normally containing less than 10 amino acids. After that, the synthesis must be performed in heterogeneous phase or highly diluted solution and more excess reagents are correspondingly needed to drive the reaction to completion. In order to know how many amino acids can be coupled for our supports in the homogenous solution phase without dilution, the tris-imidazolium oligomer-supported peptide synthesis was chosen as a standard example as shown in Scheme 3. It was found that nine amino acids were satisfactorily coupled in homogeneous solution phase under the same conditions as for the shorter peptide coupling without dilution. This means our support does not negatively influence the solubility of the peptide chain. Since the peptide sequence contains a lot of benzyl protected amino acids, which make the peptide chain having high molecular mass and are more crowded, this could have negatively affected the coupling capacity of the support. Lately, we find that the imidazolium oligomer-supported nona-amino-acid peptide **61** is well soluble in the mixed solvents of acetonotile and THF. Therefore, we presume that, if lower mass amino acids had been chosen and the mixed solvents CH_3CN/THF were used, more amino acids could be coupled using the tris-imidazolium oligomer support in homogeneous phase without dilution.



57, n = 2, m = 3.

59, n = 2, m = 3.

60, n = 2, m = 3.

61, n = 2, m = 3.

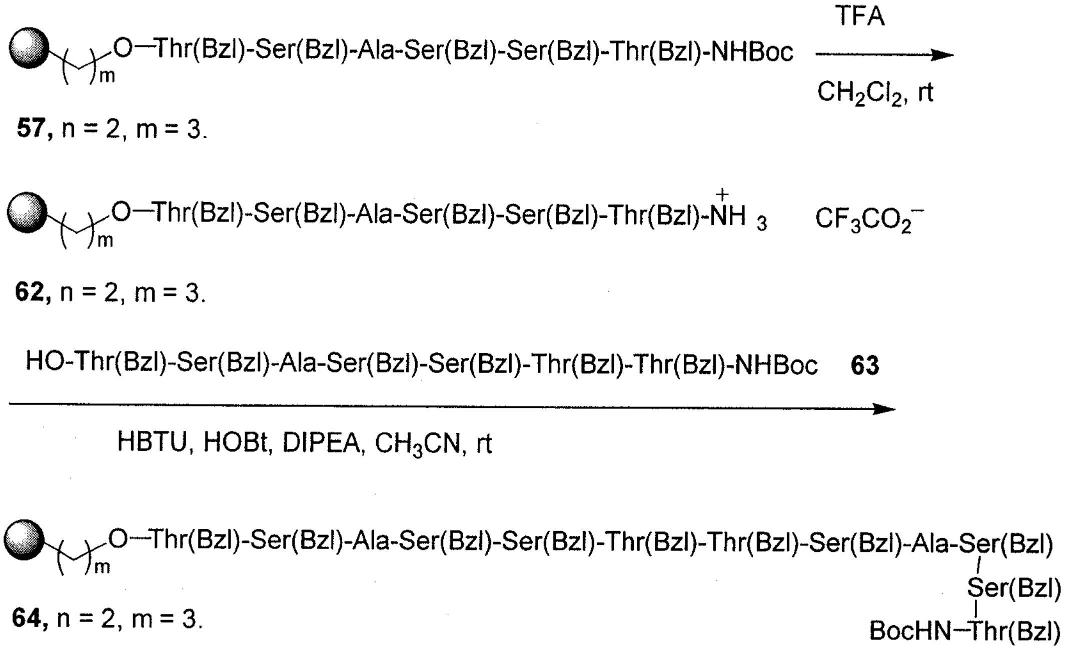
Scheme 3. Tris-imidazolium oligomer-supported peptide synthesis in homogenous solution phase without dilution. Bzl = benzyl.

5. 2. 3. Peptide block coupling

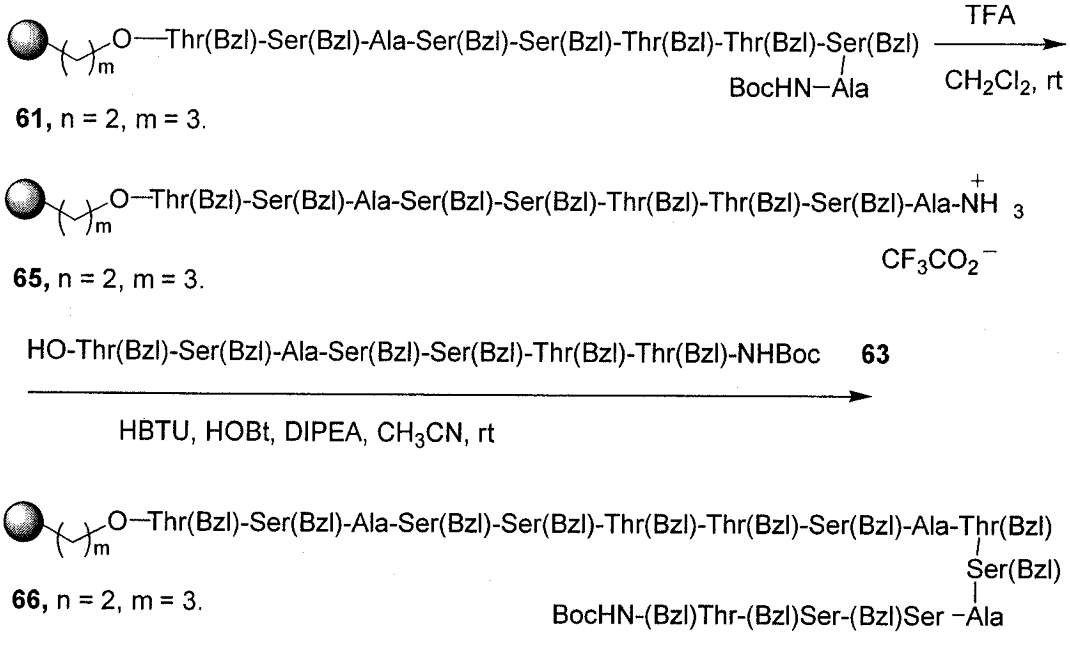
Convergent synthesis is a basic rule in organic total synthesis. The convergent approach makes the synthetic route much shorter than linear synthetic route so that the synthesis can be more efficient and less time-consuming. Since the protected oligopeptides have low solubility in common organic solvents and water, it is extremely difficult for solid-phase synthesis to do peptide block coupling. Therefore, the solid-phase peptide synthesis has to be performed in the linear fashion. However, we found that the peptide block coupling worked well by the use of our imidazolium oligomer support, which is shown in Scheme 4. The block coupling was successfully conducted between two hexa-amino-acid peptides **62** and **63** under the same conditions as the peptide synthesis shown in Scheme 2 and 3 without requiring much excess of reagents and diluting the solution. The product **64** was purified under the standard conditions shown in Figure 2. The molecular structure of the product **64** with 12 amino acids was confirmed by NMR and MS spectroscopy. And also, the peptide coupling between the tris-imidazolium oligomer-supported nona-amino-acid peptide **65** and a hexa-amino-acid peptide **63** was also conducted under similar conditions as the above case. High-resolution mass spectrometry showed that the expected product **66** was obtained. Since this compound is insoluble in common organic solvents, it was difficult to obtain its NMR spectra.

The solubility of supported peptides is an important factor to influence the coupling efficiency of amino acids. In our cases, acetonitrile is an ideal solvent because it is a non-cancergenic solvent as compared to CH_2Cl_2 and $CHCl_3$, and the imidazolium salt-supported peptides are well soluble in it as well as it is much easier to be dried and removed than other polar solvents used in peptide coupling reactions such as DMF and DMSO. It was also found that the liker chain could affect the solubility of the supported peptides.

(a) [6+6] Peptide block coupling



(b) [9+6] Peptide block coupling



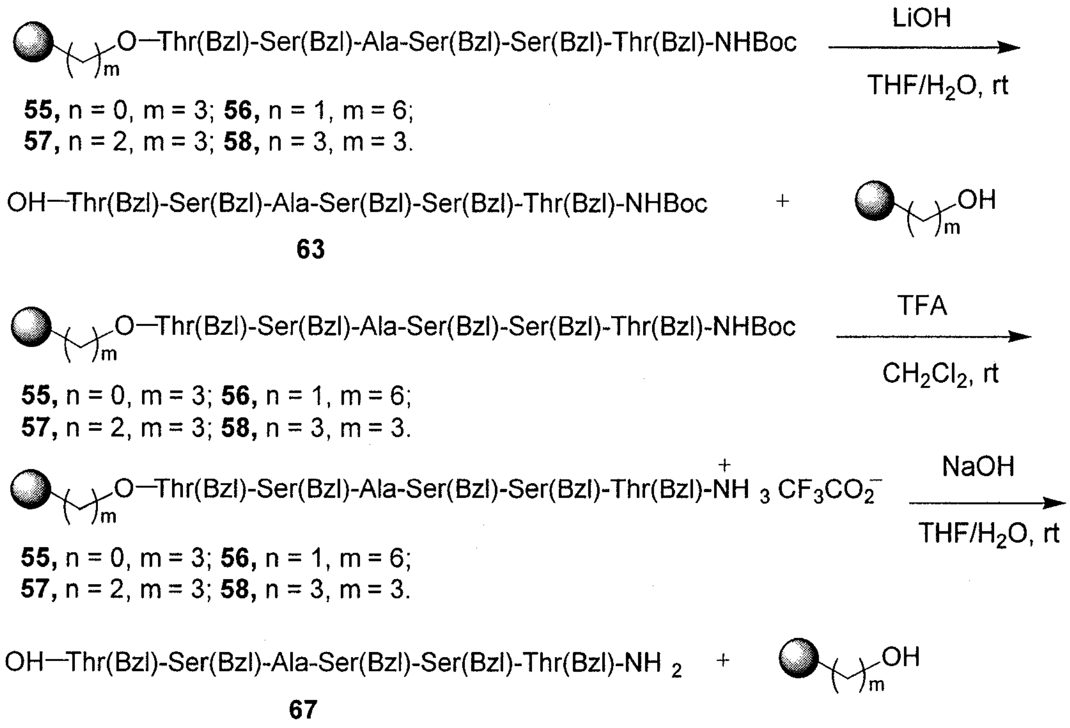
Scheme 4. Imidazolium oligomer-supported peptide block coupling reactions.

For example, the imdazolium dimer-supported hexa-amino-acid peptide **56** has lower solubility than other counterpart peptides **55**, **57** and **58**, indicating that the longer carbon-chain linker decreases the solubility of supported peptides. Obviously, the anions of the imidazolium supports can influence the solubility of supported peptides as shown in the cases of common ionic liquids.

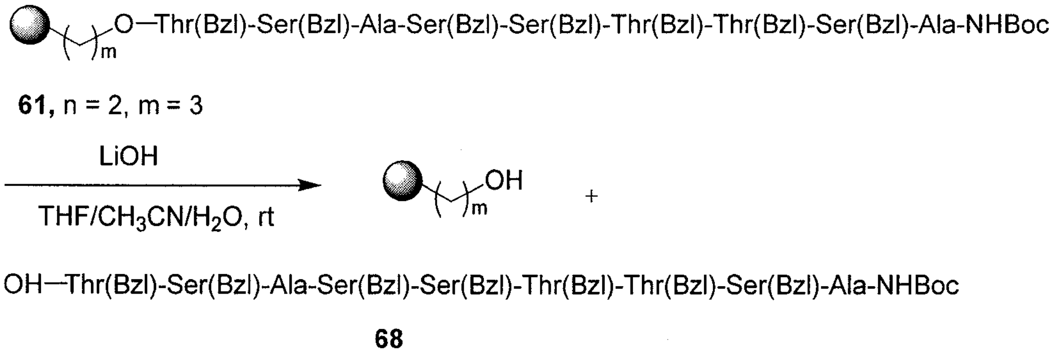
5. 2. 4. Cleavage of peptides from supports

There are two ways to cleave peptides from synthetic supports. One approach is to cleave the peptide first and then remove Boc protection group. The other approach is to remove Boc protection group first and then cleave the peptide from the support. In our case, the cleavage of peptides from the imidazolium support was carried out through hydrolysis of the ester bond under aqueous basic condition as shown in Scheme 5. The imidazolium-supported peptides **55**, **56**, **57**, **61** and **64** were hydrolyzed by aqueous solution of LiOH or NaOH to generate the corresponding products. THF and acetonitrile were added to help the supported peptides dissolve in the solvents. The purification of the peptides **63**, **67**, **68** and **69** after cleavage from the supports was very straightforward without need of chromatography. The general purification procedures are as follows. When the hydrolysis was complete, the volatile solvents were removed by rotary evaporation under reduced pressure. The residue was added with water and the pH value of the mixture was adjusted to 5 with low concentration of aqueous hydrochloric acid. After filtration, the white precipitate was washed with water and then diethyl ether or other polar organic solvents such as acetone and acetonitrile, dried in vacuo to give the product as white powder. NMR and MS spectroscopic measurements showed the product obtained was pure. It is worthy to mention that the imidazolium supports can be easily recovered after the cleavage.

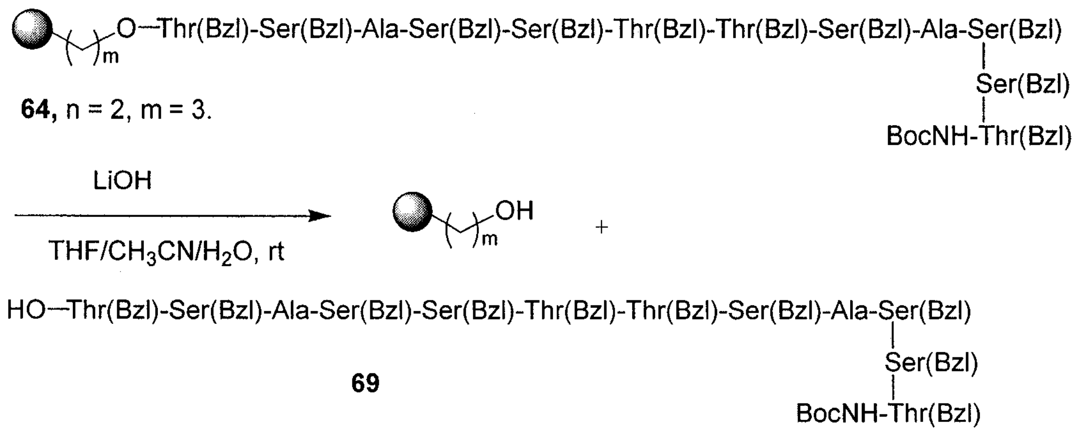
(a) Cleavage of hexa-amino-acid peptide from supports



(b) Cleavage of nona-amino-acid peptide from support

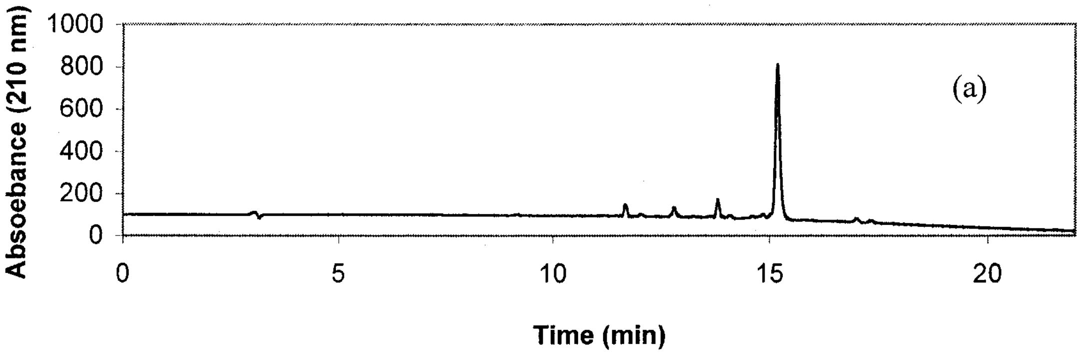


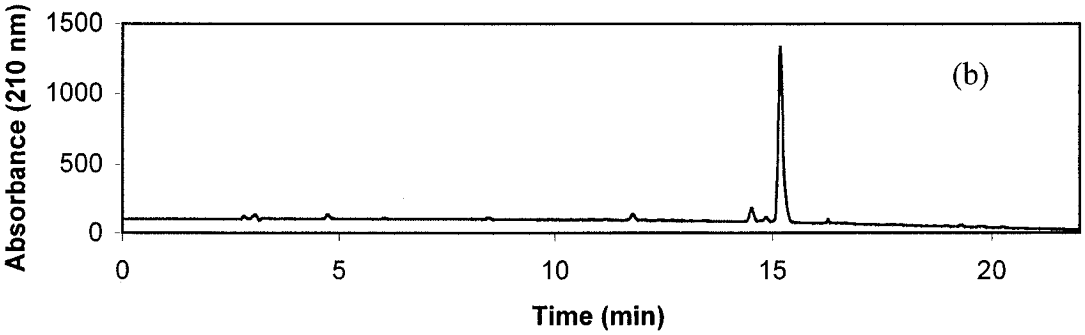
(c) Cleavage of dodeca-amino-acid peptide from support



Scheme 5. Cleavage of peptides from imidazolium supports.

The purity of the peptides **63**, **67**, **68**, and **69** obtained after cleavage from the supports was analyzed by HPLC equipped with reversed phase C_{18} column (Agilent Zorbax Extend-C18, 4.6 × 250 mm). The elution was in a linear gradient fashion from 50% to 100% of B in A over 20 min, followed by a linear gradient elution from 100% to 50% of B in A over 10 min, where A was H_2O/0.05% TFA (v/v) and B was CH_3CN/0.05% TFA (v/v), at a flow rate of 0.8 mL/min. UV absorbance was detected at 210 nm. The results are showed in Figure 3, which give that the purity of peptides **63** (a and b), **67** (c), **68** (d) and **69** (e) are 89%, 90%, 95%, 88% and 86%, respectively. For (a) and (b), the same peptide **63**, but independently prepared from mono-imidazolium salt and tris-imidazolium salt support respectively, were analyzed by HPLC under the same conditions. They showed the same retention times, as shown in Figure 3 (a) and (b).





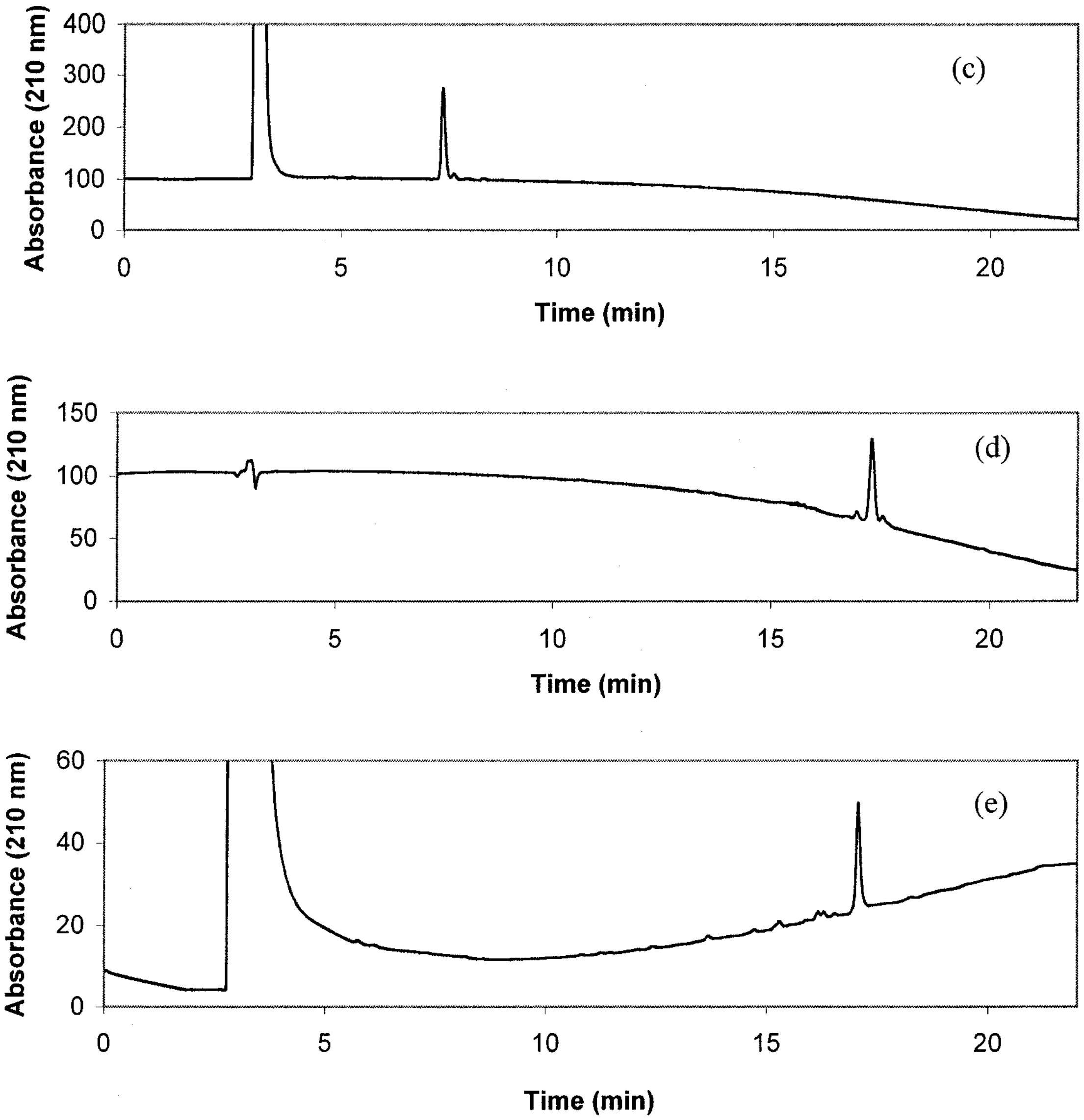


Figure 3. HPLC analysis of compound **63:** (a) derived from compound **55** and (b) derived from compound **57**; compound **67**: (c); compound **68**: (d); compound **69**: (e). The big peaks in Figure 3(c) and 3(e) are due to the solvent DMSO as the injection solvent and the small peaks at 3 min in the Figure 3(a), 3(b) and 3(d) are due to TFA concentration change of the eluent because of TFA-free sample injection.

5. 3. Conclusion

A new approach to efficiently synthesize peptides by use of imidazolium monomer, dimer and oligomers as soluble supports has been demonstrated. This approach provides a new strategy to synthesize peptides in a fast and straightforward fashion. The quantitative chemical assembling of amino acids was conducted in homogeneous solution phase without need of much excess reagents. Importantly, this approach made possible the peptide block coupling which is very difficult for solid phase-supported peptide synthesis. And also, the product of each step was purified by simple washing and precipitation with water and common organic solvents without need of special solvents in contrast to fluorous phase-supported peptide synthesis which requires fluorous solvents to do phase separation. We believe that this new approach is suitable for large-scale synthesis of peptides and likely also for other biopolymer synthesis.

5. 4. Experimental Section

General: All chemicals were obtained from Aldrich and used without further purification except otherwise indicated. Acetonitrile and dichloromethane were distilled from CaH_2 as drying reagent. ^{1}H and ^{13}C NMR, COSY NMR spectra were recorded on Varian Mercury 300, 400, 800 and Unity 500 spectrometers equipped with Sun workstations. The chemical shifts were reported in parts per million on the δ scale referenced to residue $CHCl_3$ at δ 7.24 ppm, H_2O at 4.67 ppm for ^{1}H NMR and $CHCl_3$ at 77.0 ppm for ^{13}C NMR. The proton and carbon assignments were made by standard gCOSY experiments. Melting point of sample was taken via melting point apparatus without correcting the thermometer. High-resolution mass spectrometric analysis was performed on a VG Micromass ZAB 2F HS (FAB) or Micromass Quattro II triple quadrupole mass spectrometer (Manchester, UK) equipped with an electrospray ionization source (ESI). Usually, the ion corresponding to the cation (C^+) component was analyzed. The signs M^+, M^+-Br M^{2+}-2Br and M^{3+}-3TfO in the following HRMS description correspond to molecular cation and the multiple-charged cations derived from molecule after it lost one Br^-, two Br^- and three TfO^- respectively. The thermo-gravimetric analysis (TGA) measurements were performed on a TGA Q500 from TA instruments. The running method used was ramped from 25 °C to 550 °C, 20 °C/min, under nitrogen, switching to air and then ramped at 20 °C/min to 700 °C. The type of pan used was platinum. The high-pressure liquid chromatography (HPLC) analysis was performed using reversed phase C_{18} column (Agilent Zorbax Extend-C18) and eluting in a linear gradient fashion from 50% to 100% of B in A over 20 min, followed by a linear gradient elution from 100% to 50% of B in A over 10 min, where A is H_2O/0.05% TFA (v/v) and B is CH_3CN/0.05% TFA (v/v), at a flow rate of 0.8 mL/min. UV absorbance at 210 nm.

General procedures to anchor linkers onto imidazolium salts: To the flask with the imidazolium salt was added bromoalcohol and dry acetonitrile. The reaction mixture was refluxed at 80-90 °C for 24 hours under the protection of nitrogen, and then cooled to room temperature. The solvent was removed by rotary evaporation under reduced pressure. The residue was washed with diethyl ether for four times and then vacuumed to dryness to give the product.

Compound 7b: white powder. 98% yield. M. P. 201-203 °C. ^{1}H NMR (500 MHz, D_2O) δ δ7.37 (d, 1H, J = 2.0 Hz), 7.34 (d, 1H, J = 2.0 Hz), 7.29 (d, 1H, J = 2.0 Hz), 7.24 (d, 1H, J = 2.0 Hz), 4.20 (t, 2H, J = 7.0 Hz), 4.14 (m, 4H), 3.66 (s, 3H), 3.37 (t, 2H, J = 6.0 Hz), 2.56 (s, 3H), 2.49 (s, 3H), 2.28(m, 4H); ^{13}C NMR (500 MHz, D_2O) δ 144.78, 144.62, 122.81, 121.80, 121.27, 120.60, 46.66, 45.17, 45.11, 34.94, 31.49, 29.78, 29.11, 9.47, 9.23; HRMS (ESI): calcd for $C_{15}H_{25}N_4Br_2$ (M-Br$^+$) 419.0440, found: 419.0442; calcd for $C_{15}H_{25}N_4Br$ (M$^+$-2Br) 170.0625, found: 170.0625.

Compound 7c: white powder. 98% yield. M. P. 116-118 °C. ^{1}H NMR (500 MHz, D_2O) δ 7.29 (d, 1H, J = 2 Hz), 7.28(d, 1H, J = 2 Hz), 7.25(d, 1H, J = 2.5 Hz), 7.22(d, 1H, J = 2.5 Hz), 4.11(m, 4H), 3.98(t, 2H, J = 7.5 Hz), 3.63(s, 3H), 3.44(t, 2H, J = 6.5 Hz), 2.48(s, 3H), 2.46(s, 3H), 2.24(m, 2H), 1.69(m, 2H), 1.39(m, 2H), 1.21(m, 4H); ^{13}C NMR (500 MHz, D_2O) δ 144.74, 144.12, 122.80, 121.70, 120.89, 120.56, 61.75, 48.39, 45.08, 45.03, 34.89, 31.18, 29.08, 28.93, 25.42, 24.71, 9.19, 9.12. HRMS (ESI) calcd for $C_{18}H_{32}N_4OBr$ (C$^+$) 399.1754, found: 399.1754.

Compound 8: white solid. 87% yield. M. P. 90-93 °C. ^{1}H NMR (400 MHz, D_2O) δ 7.30(m, 2H), 7.28(d, 1H, J = 2 Hz), 7.27(d, 1H, J = 2 Hz), 7.22(d, 1H, J = 2.5 Hz), 7.18(d, 1H, J = 2.5 Hz), 4.07(m, 10H), 3.60(s, 3H), 3.46(t, 2H, J = 6 Hz), 2.47(s, 6H), 2.43(s, 3H), 2.22(m, 4H), 1.88(m, 2H); ^{13}C NMR (400 MHz, D_2O) δ 144.74, 144.58, 144.40, 122.80, 121.74, 121.42, 121.08, 120.59, 58.09, 45.37, 45.18, 45.04, 34.90, 31.26, 29.09, 29.05, 9.32, 9.20, 9.14. HRMS (ESI) calcd for $C_{24}H_{37}N_6O_7F_6S_2$ (M$^+$-Br) 699.2063, found: 699.2067.

Compound 9: white solid. 98% yield. ^{1}H NMR (500 MHz, D_2O) δ 7.35(d, 4H), 7.32(s, 2H), 7.27(d, 1H, J = 1.5 Hz), 7.24(d, 1H, J = 1.5 Hz), 4.15(m, 14H), 3.66(s, 3H), 3.51(t, 2H, J = 5.5 Hz), 2.53(s, 9H), 2.49(s, 3H), 2.72(m, 6H), 1.94(m, 2H); ^{13}C NMR (500 MHz, D_2O) δ 144.75, 144.60, 144.41, 122.81, 121.75, 121.43, 121.08, 120.59, 58.12, 45.39, 45.17, 45.03, 34.89, 31.24, 29.02, 9.25, 9.13. HRMS (ESI) calcd for $C_{30}H_{48}N_8O_4F_3S$ (M^{3+}-3Br) 224.4485, found: 224.4488.

Compound 10: white solid, 96% yield. M. P. 115-117 °C. 1H NMR (500 MHz, D_2O) δ 7.32-7.28(m, 6H), 7.23(s, 1H), 7.20(s, 1H), 4.10(m, 14H), 3.62(s, 3H), 3.47(t, 2H, J = 5.5 Hz), 2.49(m, 9H), 2.44(s, 3H), 2.24(m, 6H), 1.91(m, 2H); ^{13}C NMR (400 MHz, D_2O) δ 144.60, 144.46, 144.26, 122.70, 121.65, 121.31, 120.95, 120.47, 58.14, 45.46, 45.24, 45.10, 34.98, 34.91, 31.35, 29.18, 9.38, 9.30. HRMS (ESI) calcd for $C_{31}H_{48}N_8O_7F_6S_2$ (M^{2+}) 411.1490, found: 411.1490.

General procedures to synthesize compounds 11-14: To the solution of starting material in a mixed solvent of acetonitrile and methanol was added a solution of AgOTf in actonitrile. The mixture was stirred for 1 hour in the dark and filtered to remove yellow precipitate. The filtrate was rotary evaporated under reduced pressure and the residue was washed with diethyl ether to give the product.

Compound 12: clear thick oil. 100% yield. ^{1}H NMR (500 MHz, D_2O) δ 7.28 (d, 1H, J = 2 Hz), 7.25 (d, 1H, J = 2 Hz), 7.23 (d, 1H, J = 2.5 Hz), 7.21 (d, 1H, J = 2.5 Hz), 4.09 (m, 4H), 3.97 (t, 2H, J = 7 Hz), 3.62(s, 3H), 3.45 (t, 2H, J = 6.5 Hz), 2.46 (s, 3H), 2.44 (s, 3H), 2.24(m, 2H), 1.71(m, 2H), 1.42(m, 2H), 1.21(m, 4H); ^{13}C NMR (500 MHz, CD_3CN) δ 145.19, 144.57, 122.81, 121.69, 121.43, 121.12, 61.42, 48.43, 45.22, 45.15, 35.20, 32.45, 29.67, 29.36, 25.86, 25.27, 9.78. HRMS (ESI) calcd for $C_{19}H_{34}N_4O_4SF_3$ (C^+) 469.2090, found: 469.2097.

Compound 13: clear thick oil. ^{1}H NMR (400 MHz, D_2O) δ 7.27 (m, 2H), 7.26 (d, 1H, J = 2.4 Hz), 7.24 (d, 1H, 2.4 Hz), 7.20 (d, 1H, J = 2.4 Hz), 7.17 (d, 1H, J = 2.4 Hz), 4.06 (m, 10H), 3.59 (s, 3H), 3.44 (t, 2H, J = 6 Hz), 2.45 (d, 6H), 2.41 (s, 3H), 2.20 (m, 4H), 1.86 (m, 2H). ^{13}C NMR (500 MHz, D_2O) δ 144.74, 144.57, 144.40, 122.79, 121.74, 121.38, 121.06, 121.02, 120.54, 58.08, 45.37, 45.11, 44.97, 34.81, 31.20, 29.03, 28.99, 9.07, 9.02, 8.94. HRMS (ESI) calcd for $C_{24}H_{37}N_6O_7F_6S_2$ (M^+-TfO) 699.2063, found: 699.2065.

Compound 14: white powder. 100% yield. M. P. 141-143 °C. ^{1}H NMR (400 MHz, D_2O) δ 7.29-7.25(m, 6H), 7.21 (d, 1H, J = 2.0 Hz), 7.18 (d, 1H, J = 2.0 Hz), 4.09 (m, 14H), 3.61 (s, 3H), 3.46 (t, 2H, J = 5.6 Hz), 2.47 (s, 9H), 2.43(s, 3H), 2.23 (m, 6H), 1.92 (m, 2H); ^{13}C NMR (500 MHz, D_2O) δ 144.73, 144.57, 122.79, 121.74, 121.39, 121.05, 121.02, 120.53, 58.07, 45.36, 45.08, 44.96, 34.79, 31.20, 28.98, 9.06, 9.01, 8.93. HRMS (ESI) calcd for $C_{31}H_{48}N_8O_7F_6S_2$ (M^{2+}-2TfO) 411.1490, found: 411.1488.

Compound 15: To the flask with compound **11** (1.24 g, 4.07 mmol) and Boc-Thr(Bzl)-OH (2.28 g, 7.38 mmol) and DMAP (0.10 g, 0.82 mmol) was added dry acetonitrile (16 mL) and then 1.0 M solution of DCC (9 mL, 8.99 mmol) in CH_2Cl_2. The reaction mixture was stirred for 24 hours. The white precipitate generated in the reaction was filtered off and the filtrate was collected and subjected to rotary evaporation under reduced pressure. The residue was washed with diethyl ether for four times and dried *in vacuo* to give the product as clear thick oil (2.23 g, 92% yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25 (m, 7H), 5.30 (d, 1H, J = 8.7 Hz), 4.61 (d, 1H, 11.7 Hz), 4.367 (d, 1H, 11.7 Hz), 4.21-4.03 (m, 6H), 3.79 (s, 3H), 2.54 (s, 3H), 2.10 (m, 2H), 1.45 (s, 9H), 1.30 (d, 3H, 6.3 Hz); ^{13}C NMR (400 MHz, $CDCl_3$) δ 171.15, 156.31, 144.32, 137.89, 128.63, 128.09, 127.96, 122.80, 121.30, 80.43, 74.35, 70.97, 61.54, 58.78, 45.51, 35.77, 28.84, 28.73, 16.58, 10.06. HRMS (ESI) calcd for $C_{24}H_{36}N_3O_5$ (C^+) 446.2649, found: 446.2651.

General procedures to couple amino acid and imidazolium dimer and oligomer supports: To the flask charged with imidazolium dimer or oligomer (1 equiv.), amino acid (2 equiv.) and 4-dimethylaminopyridine (DMAP) (0.2 equiv.) was added dry acetonitrile and 1.0 M solution of DCC (2 equiv.) in dichloromethane. The mixture was stirred for 16 hours and the white precipitate, dicyclohexylurea, generated in the reaction was filtered off. The filtrate was collected and then subjected to rotary evaporation under reduced pressure to give syrup to which was added ether. The product precipitated and phase separation was finished by centrifugation and decantation. The precipitate was further washed with mixed solvents of ether and ethyl acetate (V/V = 1:1) for several times and diethyl ether once, dried *in vacuo* to give the product as solid.

Compound 16: white solid. 83% yield. ^{1}H NMR (400 MHz, CD_3CN) δ 7.39-7.28 (m, 9H), 5.50 (d, 1H, J = 9.2 Hz), 4.61 (d, 1H, J = 11.6 Hz), 4.39 (d, 1H, J = 11.6 Hz), 4.23-3.99 (m, 10H), 3.74 (s, 3H), 2.56 (d, 6H), 2.87 (m, 2H), 1.76 (m, 2H), 1.62 (m, 2H), 1.48 (s, 9H), 1.36 (m, 4H), 1.26 (d, 3H, J = 6.4 Hz); ^{13}C NMR (400 MHz, CD_3CN) δ 171.15, 156.15, 145.04, 144.42, 138.72, 128.46, 127.78, 127.73, 122.92, 122.82, 121.63, 121.23, 120.91, 79.37, 74.83, 70.70, 65.19, 58.78, 48.50, 45.32, 45.23, 35.26, 29.64, 29.56, 29.40, 28.48, 27.98, 25.83, 25.40, 15.99, 9.73, 9.67. HRMS (ESI) calcd for $C_{34}H_{53}O_5N_5$ (M^{2+}-2TfO) 305.7017, found: 305.7017.

Compound 17: white powder. 88% yield. M. P. 50-52 °C. ^{1}H NMR (400 MHz, CD_3CN) δ 7.40-7.29 (m, 11H), 5.61 (d, 1H, J = 8.8 Hz), 4.63 (d, 1H, J = 11.6 Hz), 4.41 (d, 1H, J = 11.6 Hz), 4.28 (q, 1H, J = 8.8 Hz, 2.8Hz), 4.19-4.05 (m, 13H), 3.73 (s, 3H), 2.62 (s, 3H), 2.56 (s, 3H), 2.54 (s, 3H), 2.30 (m, 4H), 2.07 (m, 2H), 1.45 (s, 9H), 1.28 (d, 3H, J = 6 Hz); ^{13}C NMR (400 MHz, CD_3CN) δ 171.07, 156.26, 145.10, 145.03, 144.76, 138.67, 128.52, 127.96, 127.84, 122.79, 121.72, 121.56, 121.38, 120.93, 79.52, 74.62, 70.61, 61.57, 58.79, 54.74, 45.27, 35.20, 29.57, 29.49, 28.51, 27.98, 15.88, 9.74, 9.63, 9.59.

HRMS (ESI) calcd for $C_{39}H_{58}O_8N_7F_3S$ (M^{2+}-2TfO) 420.7004, found: 420.6999; calcd for $C_{38}H_{58}O_5N_7$ (M^{3+}-3TfO) 230.8161, found: 230.8161.

Compound 18: white powder. 83% yield. ^{1}H NMR (500 MHz, CD_3CN) δ 7.44-7.29 (m, 13H), 5.62 (d, 1H, J = 9 Hz), 4.61 (d, 1H, J = 11.5 Hz), 4.40 (d, 1H, J = 11.5 Hz), 4.27-4.06 (m, 20H), 3.73 (s, 3H), 2.63 (s, 3H), 2.62 (s, 3H), 2.56 (s, 3H), 2.53 (s, 3H), 2.27 (m, 6H), 2.06 (m, 2H), 1.44 (s, 9H), 1.25 (d, 3H, J = 6 Hz); ^{13}C NMR (400 MHz, CD_3CN) δ 171.18, 156.35, 145.15, 145.09, 144.82, 138.72, 128.54, 127.97, 127.85, 122.82, 122.53, 121.74, 121.59, 121.56, 121.39, 120.94, 119.98, 79.46, 74.55, 70.55, 61.43, 58.68, 45.21, 45.18, 45.15, 35.07, 35.05, 30.16, 29.36, 29.27, 29.24, 28.35, 27.79, 15.66, 9.56, 9.44, 9.39. HRMS (ESI) calcd for $C_{46}H_{69}N_9O_8F_3S$ (M^{3+}-3TfO) 321.4975, found: 321.4975.

General procedures to remove Boc protection group: To the flask with imidazolium salt-supported peptide (1equiv.) was added dichloromethane and then trifluoroacetic acid (TFA) (50 equiv.). The mixture was stirred at room temperature for one hour and then subjected to rotary evaporation under reduced pressure. The residue was washed with diethyl ether and dried *in vacuo* to give the product.

Compound 19: clear thick oil, 100% yield. ^{1}H NMR (400 MHz, DMSO-d6) δ 8.44 (broad, s, 1H), 7.60 (d, 1H, J = 2.4 Hz), 7.54 (d, 1H, J = 2.4 Hz), 7.34-7.27 (m, 5H), 4.62 (d, 1H, J = 12.4 Hz), 4.43 (d, 1H, J = 12.4 Hz), 4.24 (broad, s, 1H), 4.17-4.05 (m, 5H), 3.72 (s, 1H), 2.52 (s, 3H), 1.94 (m, 2H), 1.30 (d, 3H, J = 6.4 Hz). HRMS (ESI) calcd for $C_{19}H_{28}N_3O_3$ (C^+-CF_3CO_2H) 346.2125, found: 346.2130.

Compound 20: white powder, 100% yield. ^{1}H NMR (400 MHz, CD_3CN) δ 7.39-7.30 (m, 9H), 4.68 (d, 1H, J = 11.6 Hz), 4.47 (d, 1H, J = 11.6 Hz), 4.21-4.10 (m, 8H), 4.03 (t, 2H, J = 7.6 Hz), 3.74 (s, 3H), 2.57 (d, 6H), 2.27 (m, 2H), 1.76 (m, 2H), 1.63 (m, 2H), 1.38(m, 7H); ^{13}C NMR (400 MHz, CD_3CN) δ 167.54, 145.03, 144.42, 128.53, 128.05, 128.02, 122.82, 121.64, 121.22, 120.91, 72.28, 70.77, 66.79, 58.36, 48.49, 45.32, 45.23, 35.26, 29.63, 29.36, 28.19, 25.77, 25.24, 15.91, 9.70, 9.64. HRMS (ESI) calcd for $C_{29}H_{45}O_3N_5$ (M^{2+}-2TfO&CF_3CO_2H) 255.6755, found: 255.6755.

Compound 21: white solid. 100% yield. ^{1}H NMR (400 MHz, CD_3CN) δ 7.60(broad), 7.42-7.29 (m, 11H), 4.69 (d, 1H, J = 11.6 Hz), 4.47 (d, 1H, J = 11.6 Hz), 4.25 (m, 1H), 4.20-4.11 (m, 13H), 3.73 (s, 3H), 2.61 (s, 3H), 2.56 (s, 3H), 2.55 (s, 3H), 2.30 (m, 4H), 2.13 (m, 2H), 1.40 (d, 3H, J = 6.4 Hz); ^{13}C NMR (400 MHz, CD_3CN) δ 167.34, 145.13, 145.06, 144.90, 137.87, 128.62, 128.25, 128.13, 122.84, 121.84, 121.59, 121.37, 120.95, 72.04, 70.66, 63.07, 58.35, 45.19, 45.15, 45.11, 35.09, 29.38, 29.28, 28.12, 15.67, 9.58, 9.51, 9.42. HRMS (ESI) calcd for $C_{34}H_{50}O_6N_7F_3S$ (M^{2+}-2TfO) 370.6742, found: 370.6737; calcd for $C_{35}H_{50}O_9N_7F_6S_2$ (C^+-TfO&CF_3CO_2H) 890.3010, found: 890.3003.

Compound 22: white solid. 100% yield. ^{1}H NMR (500 MHz, CD_3CN) δ 7.44-7.29 (m, 13H), 4.68 (d, 1H, J = 12 Hz), 4.47 (d, 1H, J = 12 Hz), 4.28-4.10 (m, 16H), 3.72 (s, 3H), 2.62 (s, 3H), 2.61 (s, 3H), 2.56 (s, 3H), 2.55 (s, 3H), 2.27 (m, 6H), 1.91 (m, 2H), 1.27 (d, 3H, J = 6 Hz); ^{13}C NMR (500 MHz, CD_3CN) δ 167.47, 145.13, 145.07, 137.91, 128.61, 128.23, 128.12, 122.83, 122.52, 121.87, 121.60, 121.57, 121.34, 120.94, 119.96, 72.16, 70.68, 62.97, 58.21, 45.21, 45.15, 35.06, 29.33, 29.22, 28.12, 15.66, 9.55, 9.47, 9.40. HRMS (ESI) calcd for $C_{41}H_{61}N_9O_6F_3S$ (M^{3+}-3TfO&CF_3CO_2H) 288.1467, found: 288.1468.

General procedures to couple amino acids using compound 11 as a support: To the flask charged with imidazolium-bound amino acid (1 equiv.), amino acid (2 equiv.), O-(benzotriazol-1-yl)-N, N, N', N'-tetramethyluroniumhexafluorophosphate (HBTU) (2 equiv.), 1-hydroxybenzotriazole (HOBT) (2 equiv.) was added dry dichloromethane and then N, N-diisopropylethylamine (DIPEA) (4 equiv.). The mixture was stirred at room temperature under nitrogen protection for 24 hours and then subjected to rotary evaporation under reduced pressure. The residue was washed with diethyl ether for four times and added with dichloromethane, The organic solution phase was transferred into separation funnel and washed with water for 3 times. The dichloromethane phase was collected and dried by anhydrous Na_2SO_4. The solvent was removed by rotary evaporation under reduced pressure to give the product.

Compound 23: Faun foam. 98% yield. ^1H NMR (500 MHz, $CDCl_3$) δ 7.30-7.25(m, 8H), 7.21(s, 1H), 7.19(s, 1H), 7.15(s, 1H), 7.09(s, 1H), 5.42(s, 1H), 4.52-4.48(m, 4H), 4,33(d, 1H, J = 11.5 Hz), 4.31(broad, 1H), 4.15-3.91(m, 6H), 3.69(s, 3H), 3.63(m, 1H), 2.45(s, 3H), 1.40(s, 9H), 1.20(d, 3H, J = 6 Hz); ^{13}C NMR (400 MHz, $CDCl_3$) δ 171.50, 170.28, 155.72, 144.33, 137.98, 137.56, 128.68, 128.66, 128.14, 128.04, 128.00, 127.98, 127.94, 122.64, 121.27, 80.68, 74.12, 73.72, 70.94, 69.92, 61.58, 57.35, 54.60, 45.31, 35.27, 28.45, 16.36, 9.32. HRMS (ESI) calcd for $C_{34}H_{47}O_7N_4$ (C^+) 623.3439, found: 623.3437.

General procedures to couple amino acids using imidazolium salt dimer or oligomers (compounds 12, 13 or 14) as a support: To the flask charged with imidazolium-bound amino acid (1 equiv.), amino acid (2.5 equiv.), HBTU (2.5 equiv.), HOBT (2.5 equiv.) was added dry actonitrile and then diisopropylethylamine (DIPEA) (5 equiv.). The reaction mixture was stirred at room temperature under nitrogen protection for 24 hours and then concentrated by rotary evaporation under reduced pressure to give a syrup-type solution, which was transferred into conical vial and added with diethyl ether. White precipitate appeared and the mixture was subjected to centrifugation and the top liquid phase was decanted. The solid phase was then transferred to a funnel and washed with diethyl ether, water and diethyl ether for several times to give the product as powder.

Compound 24: white powder. 100% yield. M. P. 63-65 °C. ^{1}H NMR (400 MHz, CD_3CN) δ 7.37-7.29 (m, 13H), 7.13 (d, 1H, J = 9.6), 5.78 (s, 1H), 4.60-4.50 (m, 4H), 4.40 (d, 1H, J = 12 Hz), 4.30 (m, 1H), 4.16-4.01 (m, 9H), 3.80-3.67 (m, 5H), 2.55 (s, 3H), 2.54 (s, 3H), 2.24 (m, 2H), 1.74 (m, 2H), 1.59 (m, 2H), 1.44 (s, 9H), 1.36 (m, 4H), 1.21 (d, 3H, J = 6.4); ^{13}C NMR (400 MHz, CD_3CN) δ 170.80, 170.43, 155.71, 145.01, 144.71, 144.40, 138.66, 138.32, 128.51, 128.52, 127.95, 127.82, 121.69, 121.14, 120.84, 79.63, 74.74, 73.08, 70.66, 70.54, 70.41, 70.11, 65.29, 57.08, 54.77, 48.46, 45.25, 45.17, 35.23, 29.71, 29.51, 29.35, 28.64, 28.37, 27.92, 26.10, 25.97, 25.74, 25.33, 15.83, 9.60, 9.54. HRMS (ESI) calcd for $C_{44}H_{64}O_7N_6$ (M^{2+}-2TfO) 394.2412, found: 394.2411.

Compound 25: white powder. 100% yield. M. P. 220-222 °C, decompose. ^{1}H NMR (400 MHz, CD_3CN) δ 7.35-7.30 (m, 15H), 7.16 (d, 1H, J = 8.8 Hz), 5.85 (s, 1H), 4.62 (d, 1H, J = 11.6 Hz), 4.53 (m, 3H), 4.41 (d, 1H, J = 11.6 Hz), 4.30 (m, 1H), 4.13-4.06 (m, 16H), 3.79 (m, 1H), 3.73 (s, 3H), 3.68 (m, 1H), 2.58 (s, 3H), 2.54 (s, 3H), 2.51 (s, 3H), 2.25 (m, 4H), 2.06 (m, 2H), 1.42 (s, 9H), 1.22 (d, 3H, J = 6 Hz); ^{13}C NMR (400 MHz, CD_3CN) δ 171.01, 170.28, 156.26, 145.02, 144.92, 144.69, 138.57, 138.28, 128.53, 128.51, 128.06, 127.95, 127.92, 127.85, 122.86, 121.84, 121.54, 121.28, 120.84, 79.77, 74.51, 73.13, 70.70, 70.02, 61.67, 57.28, 55.02, 45.39, 45.34, 45.29, 35.27, 29.50, 29.40, 28.46, 27.98, 15.89, 9.70, 9.63, 9.59. HRMS (ESI) calcd for $C_{48}H_{69}O_8N_7$ (M^{3+}-3TfO) 289.8424, found: 289.8423.

Compound 26: white solid. 96% yield. ^{1}H NMR (500 MHz, CD_3CN) δ 7.38-7.25 (m, 17H), 7.16 (d, 1H, J = 8.5 Hz), 5.86 (s, 1H), 4.61 (d, 1H, J = 12 Hz), 4.54 (m, 2H), 4.40 (d, 1H, J = 12 Hz), 4.30 (s, 1H), 4.15 (m, 16H), 3.78 (m, 1H), 3.73 (m, 4H), 2.60 (s, 6H), 2.54 (s, 3H), 2.51 (s, 3H), 2.27 (m, 6H), 2.05 (m, 2H), 1.41 (s, 9H), 1.22 (d, 3H, J = 6 Hz); ^{13}C NMR (400 MHz, CD_3CN) δ 171.05, 170.31, 155.84, 145.05, 144.96, 144.71, 138.59, 138.30, 128.55, 128.52, 127.96, 127.93, 127.86, 122.86, 121.83, 121.55, 121.29, 120.86, 79.75, 74.48, 73.11, 70.68, 70.00, 61.64, 57.25, 54.99, 45.43, 45.31, 45.25, 35.22, 29.45, 29.33, 28.41, 27.92, 15.83, 9.65, 9.57, 9.54. HRMS (ESI) calcd for $C_{56}H_{80}O_{10}N_{10}F_3S$ (M^{3+}-3TfO) 380.5238, found: 380.5238.

Compound 27: faun sticky foam, 100% yield. ^{1}H NMR (500 MHz, CD_3CN) δ 7.53 (d, 1H, J = 8.5 Hz), 7.38-7.28 (m, 9H), 7.20 (d, 1H, J = 2.0 Hz), 7.18 (d, 1H, J = 2.0 Hz), 4.63 (m, 4H), 4.14 (d, 1H, J = 11.5 Hz), 4.37 (s, 1H), 4.19 (m, 1H), 4.17 (m, 1H), 4.07 (m, 1H), 3.99 (m, 4H), 3.67 (s, 3H), 2.40 (s, 3H), 2.00 (m, 2H), 1.26 (d, 3H, J = 6.5 Hz). HRMS (ESI) calcd for $C_{29}H_{39}O_5N_4$ (C^+-CF_3CO_2H) 523.2915, found: 523.2927.

Compound 28: faun powder, M. P. 64-66 °C. ^{1}H NMR (400 MHz, CD_3CN) δ 8.00 (broad), 7.43 (d, 1H, J = 8.4 Hz), 7.37-7.29 (m, 13H), 4.60 (m, 4H), 4.41 (d, 1H, J = 11.6 Hz), 4.36 (s, 1H), 4.21-4.01 (m, 7H), 3.95 (m, 3H), 3.87 (m, 1H), 3.73 (s, 3H), 2.55 (s, 3H), 2.53 (s, 3H), 2.24 (m, 2H), 1.72 (m, 2H), 1.58 (m, 2H), 1.37 (m, 4H), 1.25 (d, 3H, J = 6.4 Hz); ^{13}C NMR (400 MHz, CD_3CN) δ 169.91, 167.24, 144.99, 144.37, 138.57, 137.66, 128.59, 128.50, 128.04, 128.00, 127.82, 122.85, 121.64, 121.14, 120.84, 74.58, 73.42, 70.76, 68.36, 65.57, 57.61, 53.24, 48.47, 45.28, 45.20, 35.22, 29.59, 29.40, 28.43, 25.84, 25.40, 15.81, 9.60. HRMS (ESI) calcd for $C_{39}H_{56}O_5N_6$ (M^{2+}-2TfO&CF_3CO_2H) 344.2150, found: 344.2149.

Compound 29: white powder. 100% yield. M. P. 185-187 °C. ^{1}H NMR (400 MHz, CD_3CN) δ 7.51 (d, 1H, J = 8.4 Hz), 7.37-7.30 (m, 14H), 7.25 (d, 1H, J = 1.6 Hz), 4.64-4.56 (m, 3H), 4.42 (d, 1H, J = 12.0 Hz), 4.35 (br, 2H), 4.20-3.95 (m, 10H), 3.95 (m, 1H), 3.86 (m, 1H), 3.73 (s, 3H), 2.59 (s, 3H), 2.54 (s, 3H), 2.49 (s, 3H), 2.29 (m, 4H), 2.09 (m, 2H), 1.26 (d, 3H, J = 6.0 Hz); ^{13}C NMR (400 MHz, CD_3CN) δ 169.91, 145.00, 144.71, 128.63, 128.57, 128.11, 128.08, 128.00, 127.91, 122.88, 121.81, 121.58, 121.30, 120.87, 74.19, 73.33, 70.59, 68.11, 61.83, 57.58, 53.17, 45.23, 45.16, 45.11, 35.06, 29.32, 29.22, 28.29, 15.51, 9.42, 9.33. HRMS (ESI) calcd for $C_{43}H_{61}O_5N_8$ (M^{3+}-3TfO&CF_3CO_2H) 256.4916, found: 256.4917.

Compound 30: faun powder, 100% yield. ^{1}H NMR (300 MHz, CD_3CN) δ 7.56 (d, 1H, J = 8.4 Hz), 7.39-7.24 (m, 17H), 4.60 (m, 3H), 4.43 (d, 1H, J = 12.0 Hz), 4.35 (s, br, 1H), 4.16-3.86 (m, 23H), 3.73 (s, 3H), 2.61 (s, 6H), 2.55 (s, 3H), 2.50 (s, 3H), 2.32 (m, 6H), 2.03 (m, 2H), 1.27 (d, 3H, J = 6.3 Hz). HRMS (ESI) calcd for $C_{51}H_{72}N_{10}O_8F_3S$ (M^{3+}-3TfO&CF_3CO_2H) 347.1730, found: 347.1732; Calcd for $C_{50}H_{72}N_{10}O_5$ (M^{4+}-4TfO&CF_3CO_2H) 223.1416, found: 223.1419.

Compound 31: faun foam. 97% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28-7.20 (m, 10H), 7.07 (m, 2H), 5.06 (d, 1H, J = 5 Hz), 4.53 (m, 4H), 4.32 (d, 1H, J = 11.5 Hz), 4.13-3.99 (m, 6H), 3.69 (s, 3H), 3.62 (m, 1H), 2.45 (s, 3H), 2.00 (s, 2H), 1.37 (s, 9H), 1.30 (d, 3H, J = 7 Hz), 1.18 (d, 3H, J = 5 Hz); ^{13}C NMR (500 MHz, $CDCl_3$) δ 173.27, 170.96, 170.28, 155.89, 144.32, 138.06, 137.54, 128.67, 128.63, 128.15, 128.11, 128.08, 128.00, 122.59, 121.42, 80.50, 74.18, 73.75, 70.91, 69.50, 61.47, 57.53, 53.35, 50.75, 45.29, 35.26, 28.43, 18.26, 16.22, 9.32; HRMS (ESI) calcd for $C_{37}H_{52}O_8N_5$ (C^+) 694.3810, found: 694.3819.

Compound 32: white powder. 100% yield. M. P. 74-76 °C. ^{1}H NMR (400 MHz, CD_3CN) δ 7.36-7.29 (m, 12H), 7.15 (s, 1H), 7.10 (d, 1H, J = 9.2 Hz), 5.63 (s, 1H), 4.51 (m, 5H), 4.40 (d, 1H, J = 12 Hz), 4.14-3.99 (m, 10H), 3.84 (m, 1H), 3.73 (s, 3H), 3.67 (m, 1H), 2.54 (d, 6H), 2.24 (m, 2H), 1.76 m, 2H), 1.59 (m, 2H), 1.41 (s, 9H), 1.36 (m, 4H), 1.26 (d, 3H, J = 6 Hz), 1.20 (d, 3H, J = 6.4 Hz). ^{13}C NMR (300 MHz, CD_3CN) δ 173.31, 170.39, 155.71, 145.02, 144.42, 138.67, 138.26, 128.57, 128.51, 127.97, 127.87, 127.82, 127.79, 122.87, 121.69, 121.14, 120.83, 79.47, 74.72, 73.19, 70.64, 69.94, 65.35, 57.17, 53.34, 50.59, 48.45, 45.25, 45.17, 35.19, 29.71, 29.54, 29.35, 28.39, 28.02, 25.77, 25.36, 17.94, 15.88, 9.54, 9.49. HRMS (ESI) calcd for $C_{47}H_{69}O_8N_7$ (M^{2+}-2TfO) 429.7598, found: 429.7594.

Compound 33: white powder. 100% yield. M. P. 213-215 °C, decompose. ^{1}H NMR (400 MHz, CD_3CN) δ 7.36-7.29 (m, 14H), 7.23 (d, 1H, J = 6.4 Hz), 7.14 (d, 1H, J = 8.4 Hz), 5.67 (d, 1H, J = 5.2 Hz), 4.61-4.51 (m, 5H), 4.40 (d, 1H, J = 11.6 Hz), 4.13-4.04 (m, 16H), 3.87 (m, 1H), 3.73 (s, 3H), 3.67 (m, 1H), 2.58 (s, 3H), 2.54 (s, 3H), 2.51 (s, 3H), 2.25 (m, 4H), 2.06 (m, 2H), 1.39 (s, 9H), 1.27 (d, 3H, J = 7.6 Hz), 1.22 (d, 3H, J = 6 Hz); ^{13}C NMR (400 MHz, CD_3CN) δ 173.56, 170.66, 170.35, 155.91, 145.10, 144.99, 144.77, 138.65, 138.29, 128.59, 128.55, 128.01, 127.92, 127.87, 122.90, 121.93, 121.67, 121.56, 121.24, 120.85, 79.48, 74.41, 73.12, 70.56, 69.66, 61.51, 57.20, 53.59, 50.64, 45.22, 45.16, 45.11, 35.07, 29.31, 29.20, 28.22, 27.80, 17.52, 15.58, 9.42, 9.36, 9.32. HRMS (ESI) calcd for $C_{51}H_{74}O_9N_8$ (M^{3+}-3TfO) 313.5214, found: 313.5213.

Compound 34: faun solid. 100% yield. ^{1}H NMR (500 MHz, CD_3CN) δ 7.36-7.30 (m, 16H), 7.24 (s, 1H), 7.15 (d, 1H, J = 7.5 Hz), 5.68 (s, 1H), 4.58 (m, 4H), 4.40 (d, 1H, J = 12 Hz), 4.17-4.06 (m, 16H), 3.88 (m, 1H), 3.72 (s, 3H), 3.68 (m, 1H), 2.59 (d, 6H), 2.54

(s, 3H), 2.51 (s, 3H), 2.27 (m, 6H), 2.06 (m, 2H), 1.39 (s, 9H), 1.26 (d, 3H, J = 7 Hz), 1.20 (d, 3H, J = 6 Hz); ^{13}C NMR (300 MHz, CD_3CN) δ 173.47, 170.55, 170.23, 155.84, 145.05, 144.95, 144.71, 138.60, 138.24, 128.55, 128.51, 128.32, 128.06, 127.97, 127.88, 127.83, 122.87, 121.90, 121.69, 121.54, 121.23, 120.83, 79.57, 74.49, 73.19, 70.66, 69.74, 61.62, 57.31, 53.68, 50.78, 45.30, 45.24, 35.20, 29.44, 29.33, 28.39, 27.96, 17.71, 15.78, 9.58, 9.53, 9.49. HRMS (ESI) calcd for $C_{58}H_{85}N_{11}O_8$ (M^{4+}-4TfO) 265.9140, found: 265.9142.

Compound 35: faun sticky foam. 99% yield. ^{1}H NMR (500 MHz, CD_3CN) δ 7.58 (d, 1H, J = 7.5 Hz), 7.45 (broad, 1H), 7.37-7.27 (m, 10H), 7.11 (d, 1H, J = 7.5 Hz), 4.66 (m, 1H), 4.55 (m, 4H), 4.40 (d, 1H, J = 12 Hz), 4.16-4.01 (m, 6H), 3.83 (m, 1H), 3.70 9m, 1H), 3.68 (s, 3H), 2.43 (s, 3H), 2.02 (m, 2H), 1.46 (d, 3H, J = 6.5 Hz), 1.22 (d, 3H, J = 6.5 Hz); ^{13}C NMR (500 MHz, CD_3CN) δ 170.31, 169.97, 169.89, 144.82, 138.57, 138.19, 128.56, 128.01, 127.98, 127.92, 127.91, 122.62, 121.12, 74.36, 73.22, 70.60, 69.59, 61.62, 57.19, 53.70, 49.55, 45.14, 35.01, 28.39, 16.91, 15.65, 9.25.

Compound 36: faun powder. 100% yield. ^{1}H NMR (400 MHz, CD_3CN) δ 7.68 (broad), 7.61 (d, 1H, J = 7.2 Hz), 7.36-7.26 (m, 12H), 7.11 (d, 1H, J = 7.6 Hz), 4.66 (m, 1H), 4.56 (m, 4H), 4.39 (d, 1H, J = 11.6 Hz), 4.15-3.98 (m, 8H), 3.83 (m, 1H), 3.73 (s, 3H), 3.68 (m, 1H), 2.54 (s, 3H), 2.53 (s, 3H), 2.42 (m, 2H), 1.72 (m, 2H), 1.54 (m, 2H), 1.47 (d, 3H, J = 6.0 Hz), 1.30 (m, 4H), 1.21 (d, 3H, J = 6.0 Hz); ^{13}C NMR (400 MHz, CD_3CN) δ 170.34, 170.02, 169.93, 145.00, 144.38, 138.56, 138.08, 128.55, 128.52, 127.99, 127.89, 127.81, 122.85, 121.65, 121.13, 120.83, 74.73, 73.30, 70.68, 69.80, 65.51, 57.25, 53.72, 49.68, 48.48, 45.28, 45.20, 35.21, 29.59, 29.40, 28.44, 25.85, 25.42, 17.28, 15.94, 9.57. HRMS (ESI) calcd for $C_{42}H_{61}O_6N_7$ (M^{2+}-2TfO&CF_3CO_2H) 379.7336, found: 379.7335.

Compound 37: white powder. 100% yield. M. P. 195-197 °C, decompose. ^{1}H NMR (400 MHz, CD_3CN) δ 7.63 (d, 1H, J = 7.2 Hz), 7.35-7.27 (m, 14H), 7.11 (d, 1H, J = 8.8 Hz), 4.63-4.52 (m, 5H), 4.40 (d, 1H, J = 12.0 Hz), 4.17-4.04 (m, 16H), 3.83 (m, 1H), 3.73 (s, 3H), 3.69 (m, 2H, overlap), 2.58 (s, 3H), 2.55 (s, 3H), 2.50 (s, 3H), 2.25 (m, 4H), 2.05 (m, 2H), 1.45 (s, br, 3H), 1.22 (d, 3H, J = 6.4 Hz). HRMS (ESI) calcd for $C_{46}H_{66}N_9O_6$ (M^{3+}-3TfO&CF_3CO_2H) 280.1706, found: 280.1706.

Compound 38: faun powder. 100% yield. ^{1}H NMR (500 MHz, CD_3CN) δ 7.61 (d, 1H, J = 6.5 Hz), 7.37-7.28 (m, 16H), 7.10 (d, 1H, J = 8.5 Hz), 4.64-4.53 (m, 5H), 4.40 (d, 1H, J = 12.0 Hz), 4.16-4.04 (m, 23H), 3.85 (m, 1H), 3.73 (s, 3H), 3.69 (m, 1H), 2.62 (s, 6H), 2.55 (s, 3H), 2.51 (s, 3H), 2.26 (m, 6H), 2.09 (m, 2H), 1.46 (d, 3H, J = 6.5 Hz), 1.22 (d, 3H, J = 6.5 Hz). HRMS (ESI) calcd for $C_{53}H_{77}N_{11}O_6$ (M^{4+}-4TfO&CF_3CO_2H) 240.9009, found: 240.9011.

Compound 39: faun foam. 98% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33-7.23 (m, 15H), 7.04 (s, 1H), 6.88(s, 1H), 5.39 (s, 1H), 4.61 (m, 2H), 4.55-4.40 (m, 5H), 4.36 (d, 1H, J = 12 Hz), 4.28 (broad, 1H), 4.15-4.02 (m, 6H), 3.87 (m, 1H), 3.66 (s, 4H), 3.45 (m, 1H), 2.44 (s, 3H), 2.01 (s, 2H), 1.40 (s, 9H), 1.33 (d, 3H, J = 6.5 Hz), 1.18 (d, 3H, J = 6 Hz); ^{13}C NMR (500 MHz, $CDCl_3$) δ 172.69, 171.11, 170.80, 170.27, 156.15, 144.25, 138.21, 137.68, 137.62, 128.74, 128.60, 128.54, 128.20, 128.15, 128.04, 127.93, 127.86, 127.80, 122.54, 121.62, 80.84, 74.52, 73.51, 73.42, 71.09, 69.64, 69.42, 61.36, 57.48, 54.97, 53.38, 50.30, 45.26, 35.25, 28.60, 28.45, 28.36, 17.87, 16.21, 9.35. HRMS (ESI) calcd for $C_{47}H_{63}O_{10}N_5$ (C^+) 871.4600, found: 871.4592.

Compound 40: faun solid. 100% yield. M. P. 66-68 °C. ^{1}H NMR (400 MHz, CD_3CN), δ 7.37-7.28 (m, 17H), 7.1 7(s, 1H), 7.14 (d, 1H, J = 9.2 Hz), 5.72 (s, 1H), 4.60-4.46 (m, 7H), 4.41 (d, 1H, J = 12 Hz), 4.34 (m, 1H), 4.21-3.98 (m, 10H), 3.83 (m, 1H), 3.73 (s, 3H), 3.67 (m, 3H), 2.54 (d, 6H), 2.24 (m, 2H), 1.76 (m, 2H), 1.59 (m, 2H), 1.44 (s, 9H), 1.37 (m, 4H), 1.33 (d, 3H, J = 6 Hz), 1.21 (d, 3H, J = 6.4 Hz); ^{13}C NMR (400 MHz, CD_3CN) δ 172.52, 170.48, 170.32, 170.25, 155.94, 144.99, 144.39, 138.70, 138.36, 138.27, 128.56, 128.53, 128.50, 127.91, 127.86, 127.83, 127.80, 122.87, 121.68, 121.14, 120.84, 79.82, 74.81, 73.10, 72.97, 70.71, 70.60, 70.48, 69.98, 65.34, 57.24, 55.13, 53.41, 49.71, 48.50, 45.31, 45.23, 35.24, 29.76, 29.59, 29.39, 28.44, 28.09, 27.89, 26.16, 26.07, 25.90, 25.81, 25.41, 17.98, 16.01, 9.61, 9.53. HRMS (ESI) calcd for $C_{57}H_{80}O_{10}N_8$ (M^{2+}-2TfO) 518.2993, found: 518.2987.

Compound 41: white powder. 100% yield. M. P. 200-202 °C, decompose. ^{1}H NMR (400 MHz, CD_3CN) δ 7.38-7.20 (m, 21H), 5.76 (d, 1H, J = 6.4 Hz), 4.61-4.46 (m, 7H), 4.42 (d, 1H, J = 11.6 Hz), 4.28 (M, 1H), 4.18-4.01 (m, 16H), 3.80 (m, 1H), 3.72 (s, 3H), 3.68 (m, 1H), 3.61 (m, 1H), 3.54 (m, 1H), 2.58 (s, 3H), 2.54 (s, 3H), 2.51 (s, 3H), 2.25 (m, 4H), 2.06 (m, 2H), 1.42 (s, 9H), 1.27 (d, 3H, J = 6.4 Hz), 1.22 (d, 3H, J = 6 Hz); ^{13}C NMR (400 MHz, CD_3CN) δ 172.92, 171.13, 170.50, 170.33, 156.28, 145.09, 144.98, 144.78, 138.73, 138.36, 128.60, 128.56, 128.55, 127.95, 127.93, 127.89, 122.90, 122.00, 121.56, 121.23, 120.85, 79.87, 74.57, 72.90, 72.83, 70.64, 69.71, 69.57, 61.44, 57.26, 55.26, 53.57, 50.14, 45.22, 45.15, 45.11, 35.08, 29.32, 29.21, 28.21, 27.81, 17.21, 15.61, 9.43, 9.38, 9.33. HRMS (ESI) calcd for $C_{61}H_{85}N_{10}O_{10}$ (M^{3+}-3TfO) 372.5477, found: 372.5474.

Compound 42: faun solid. 100% yield. M. P. 227-229 °C, decompose. ^{1}H NMR (500 MHz, CD_3CN) δ 7.36-7.29 (m, 21H), 7.19 (s, 2H), 5.72 (s, 1H), 4.66-4.44 (m, 7H), 4.42 (d, 1H, J = 11.5 Hz), 4.29 (s, 1H), 4.22-4.04 (m, 19H), 3.82 (m, 1H), 3.72 (m, 4H), 3.64

(m, 1H), 3.57 (m, 1H), 2.59 (d, 6H), 2.54 (s, 3H), 2.51 (s, 3H), 2.27 (m, 6H), 2.08 (m, 2H), 1.42 (s, 9H), 1.32 (d, 3H, J = 7 Hz), 1.20 (d, 3H, J = 6 Hz); ^{13}C NMR (500 MHz, CD_3CN) δ 172.89, 171.08, 170.50, 170.33, 156.26, 145.11, 145.01, 144.79, 138.74, 138.47, 138.37, 138.35, 128.59, 128.55, 128.53, 128.05, 127.94, 127.92, 127.89, 127.86, 127.84, 122.90, 121.99, 121.74, 121.56, 121.23, 120.85, 79.87, 74.58, 73.80, 72.93, 72.87, 70.67, 69.72, 69.62, 62.06, 61.46, 57.89, 57.27, 55.25, 53.59, 50.09, 45.25, 45.11, 35.07, 35.06, 29.27, 29.17, 28.30, 28.22, 27.81, 17.22, 15.65, 15.58, 9.39, 9.35, 9.30. HRMS (ESI) calcd for $C_{68}H_{96}O_{10}N_{12}$ (M^{4+}-4TfO) 310.1837, found: 310.1839.

Compound 43: faun foam. 100% yield. ^{1}H NMR (500 MHz, CD_3CN) δ 7.71 (d, 1H, J = 5.5 Hz), 7.37-7.20 (m, 14 H), 7.23 (s, 1H), 7.20 (s, 1H), 7.13 (d, 1H, J = 9 Hz), 4.59-4.48 (m, 7H), 4.37 (m, 2H), 4.24 (s, 1H), 4.14-4.02 (m, 5H), 3.89 (m, 1H), 3.81 (m. 2H), 3.67 (s, 3H), 3.64 (m, 1H, overlap), 2.42 (s, 3H), 2.01 (m, 2H), 1.32 (d, 3H, J = 7 Hz), 1.20 (d, 3H, J = 6.5 Hz); ^{13}C NMR (500 MHz, CD_3CN) δ 172.26, 170.47, 170.34, 166.44, 144.81, 138.56, 138.25, 137.68, 128.63, 128.57, 128.09, 128.06, 128.00, 127.92, 127.90, 122.62, 121.14, 74.45, 73.22, 73.13, 70.61, 69.68, 67.92, 61.58, 57.13, 53.44, 53.38, 49.75, 45.12, 35.00, 28.38, 17.70, 15.67, 9.24.

Compound 44: faun powder. 100% yield. M. P. 88-90 °C. ^{1}H NMR (400 MHz, CD_3CN) δ 7.91 (broad), 7.42 (d, 1H, J = 6.8 Hz), 7.36-7.26 (m, 17H), 7.19 (d, 1H, J = 7.2 Hz), 4.62-4.46 (m, 8H), 4.39 (d, 1H, J = 11.6 Hz), 4.15-3.97 (m, 9H), 3.89-3.78 (m, 2H), 3.76 (m, 1H), 3.73 (s, 3H), 3.61 (m, 1H), 2.54 (s, 3H), 2.53 (s, 3H), 2.24 (m, 2H), 1.72 (m, 2H), 1.58 (m, 2H), 1.33 (m, 7H), 1.18 (d, 3H, J = 6.0 Hz); ^{13}C NMR (400 MHz, CD_3CN) δ 172.27, 170.41, 170.37, 166.82, 144.97, 144.36, 138.56, 138.16, 137.14, 128.57, 128.55, 128.53, 127.95, 127.83, 122.86, 121.65, 121.16, 120.85, 74.74, 73.28, 73.17, 70.65, 69.97, 68.48, 65.48, 57.20, 53.46, 53.31, 49.75, 48.47, 45.29, 45.21, 35.22, 29.62, 29.41, 28.44, 25.86, 25.43, 18.25, 15.97, 9.58. HRMS (ESI) calcd for $C_{52}H_{72}O_8N_8$ (M^{2+}-23TfO & F_3CCO_2H) 468.2731, found: 468.2727.

Compound 45: faun powder. 100% yield. M. P. 196-198 °C, decompose. ^{1}H NMR (400 MHz, CD_3CN) δ 7.80 (broad, 1H), 7.36-7.29 (m, 19H), 7.17 (d, 1H, J = 8.8 Hz), 4.59-4.43 (m, 7H), 4.40 (d, 1H, J = 12.0 Hz), 4.25 (br, 1H), 4.14-4.04 (m, 15H), 3.88-3.78 (m, 3H), 3.73 (s, 3H), 2.59 (s, 3H), 2.54 (s, 3H), 2.49 (s, 3H), 2.24 (m, 4H), 2.04 (m, 2H), 1.32 (d, 3H, J = 6.0 Hz), 1.26 (d, 3H, J = 7.0 Hz); ^{13}C NMR (400 MHz, CD_3CN) δ 172.32, 170.49, 170.39, 145.09, 144.98, 144.73, 138.56, 138.25, 137.74, 128.63, 128.59, 128.58, 128.05, 128.03, 128.02, 127.94, 127.91, 122.88, 121.90, 121.56, 121.50, 121.31, 120.87, 74.41, 73.17, 73.08, 70.59, 69.64, 61.59, 57.15, 53.47, 49.80, 45.15, 45.11, 35.07, 29.33, 29.22, 28.25, 17.66, 15.67, 9.42, 9.33. HRMS (ESI) calcd for $C_{56}H_{77}N_{10}O_8$ (M^{3+}-3TfO & F_3CCO_2H) 339.1969, found: 339.1968.

Compound 46: faun powder. 100% yield. ^{1}H NMR (400 MHz, CD_3CN) δ 7.56 (s, 1H), 7.41-7.28 (m, 21H), 7.13 (d, 1H, J = 6.4 Hz), 4.67-4.38 (m, 10H), 4.15-4.05 (m, 19H), 3.86 (m, br, 1H), 3.81 (m, 1H), 3.73 (s, 3H), 3.66 (m, 1H), 2.59 (s, 6H), 2.54 (s, 3H), 2.50 (s, 3H), 2.25 (m, 6H), 2.12 (m, 2H), 1.33 (d, 3H, J = 7.2 Hz), 1.20 (d, 3H, J = 5.6 Hz). HRMS (ESI) calcd for $C_{63}H_{88}N_{12}O_8$ (M^{4+}-4TfO & F_3CCO_2H) 285.1706, found: 285.1707.

Compound 47: faun solid. 100% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52 (d, 1H, J = 5.5 Hz), 7.41 (d, 1H, J = 9.5 Hz), 7.33-7.20 (m, 18H), 7.04 (s, 1H), 7.01 (d, 1H, J = 5.5 Hz), 4.73 (q, 1H), 4.66 (q, 1H), 4.52-4.34 (m, 8H), 4.27 (m, 1H), 4.18 (m, 1H), 4.12-4.05 (m, 5H), 3.96 (m, 1H), 3.89 (m, 1H), 3.78 (m, 1H), 3.70 (s, 3H), 3.64-3.54 (m, 3H), 3.36

(q, 1H), 2.49 (s, 3H), 2.05 (broad, 2H), 1.40 (d, 3H, J = 7.5 Hz), 1.36 (s, 9H), 1.19 (d, 3H, J = 6.5 Hz); ^{13}C NMR (500 MHz, $CDCl_3$) δ 173.43, 171.55, 170.85, 170.77, 170.36, 156.80, 144.23, 138.42, 138.11, 137.62, 137.17, 128.85, 128.73, 128.55, 128.51, 128.45, 128.21, 128.06, 128.03, 127.91, 127.83, 127.73, 122.47, 121.95, 81.71, 75.07, 73.67, 73.39, 73.27, 71.29, 69.95, 68.67, 67.97, 61.24, 57.35, 56.60, 55.08, 53.73, 50.87, 45.41, 35.33, 28.43, 28.33, 17.12, 16.11, 9.47. HRMS (ESI) calcd for $C_{57}H_{74}O_{12}N_7$ (C^+) 1048.5390, found: 1048.5381.

Compound 48: faun solid. 100% yield. M. P. 120-122 °C. ^{1}H NMR (500 MHz, CD_3CN), δ7.40-7.28 (m, 23H), 7.19 (d, 1H, J = 7.5 Hz), 5.97 (s, 1H), 4.58-4.44 (m, 9H), 4.39 (d, 1H, J = 12.5 Hz), 4.32 (m, 1H), 4.23 (s, 1H), 4.11-3.99 (m, 10H), 3.81 (m, 1H), 3.68 (m, 5H), 3.63 (m, 2H), 3.53 (m, 1H), 2.52 (s, 6H), 2.22 (m, 2H), 1.73 (m, 2H), 1.59 (m, 2H), 1.40 (s, 9H), 1.36 (m, 4H), 1.31 (d, 3H, J = 6.5 Hz), 1.19 (d, 3H, J = 6 Hz); ^{13}C NMR (400 MHz, CD_3CN) δ 172.96, 171.87, 170.53, 170.41, 170.07, 156.63, 145.08, 144.48, 138.80, 138.36, 138.50, 138.34, 128.66, 128.61, 128.54, 128.51, 127.86, 127.77, 122.89, 121.71, 121.17, 120.87, 80.15, 74.79, 72.89, 72.80, 70.53, 70.37, 69.47, 69.04, 65.18, 57.13, 55.80, 54.64, 53.51, 49.68, 48.43, 48.33, 45.14, 45.07, 35.06, 29.40, 29.19, 28.23, 27.89, 25.88, 25.70, 25.58, 17.99, 15.64, 9.39, 9.31. HRMS (ESI) calcd for $C_{67}H_{91}O_{12}N_9$ (C^{2+}) 606.8388, found: 606.8375.

Compound 49: white powder. 100% yield. M. P. 201-203 °C, decompose. ^{1}H NMR (400 MHz, CD_3CN) δ 7.52 (d, 1H, J = 6 Hz), 7.45 (d, 1H, J = 8.4 Hz), 7.41 (d, 1H, J = 5.6 Hz), 7.39-7.24 (m, 23H), 6.05 (d, 1H, J = 4 Hz), 4.61-4.49 (m, 7H), 4.46 (d, 1H, J = 8 Hz), 4.39 (M, 1H), 4.26 (m, 1H), 4.15-4.03 (m, 16H), 3.84 (m, 1H), 3.78 (m, 1H), 3.72 (s, 3H), 3.68-3.59 (m, 3H), 3.46 (m, 1H), 3.54 (m, 1H), 2.58 (s, 3H), 2.54 (s, 3H), 2.51 (s, 3H), 2.24 (m, 4H), 2.08 (m, 2H), 1.39 (s, 9H), 1.32 (d, 3H, J = 7.2 Hz), 1.20 (d, 3H, J = 6.8 Hz); ^{13}C NMR (400 MHz, CD_3CN) δ 173.26, 172.40, 170.54, 170.47, 170.36, 157.00, 145.09, 144.97, 144.81, 138.80, 138.48, 138.23, 138.14, 128.69, 128.64, 128.55, 128.52, 128.00, 127.97, 127.90, 127.84, 127.76, 122.89, 122.03, 121.58, 121.55, 121.21, 120.85, 80.52, 74.74, 72.96, 72.84, 70.66, 69.95, 68.90, 68.22, 61.40, 57.35, 56.51, 55.35, 54.01, 50.34, 45.23, 45.19, 45.15, 45.11, 35.07, 29.32, 29.21, 28.15, 27.77, 16.87, 15.53, 9.43, 9.39, 9.33. HRMS (ESI) calcd for $C_{71}H_{96}N_{11}O_{12}$ (M^{3+}-3TfO) 431.5741, found: 431.5736.

Compound 50: faun solid, 100% yield. M. P. 225-227 °C, decompose. ^{1}H NMR (500 MHz, CD_3CN) δ 7.50 (d, 1H, J = 5.5 Hz), 7.44 (d, 1H, J = 7.5 Hz), 7.38-7.25 (m, 26H), 6.01(s, 1H), 4.64-4.41 (m, 9H), 4.39 (d, 1H, J = 12.5 Hz), 4.28-4.05 (m, 21H), 3.84 (m, 1H), 3.75 (m, 1H), 3.73 (s, 3H), 3.67 (m, 3H), 3.47 (m, 1H), 2.59 (s, 3H), 2.58 (s, 3H), 2.54 (s, 3H), 2.51 (s, 3H), 2.27 (m, 6H), 2.08 (m, 2H), 1.40 (s, 9H), 1.32 (d, 3H, J = 7 Hz), 1.20 (d, 3H, J = 6 Hz); ^{13}C NMR (300 MHz, CD_3CN) δ 173.21, 172.23, 170.37, 170.23, 156.88, 145.03, 144.94, 144.75, 138.75, 138.43, 138.18, 138.09, 128.64, 128.59, 128.55, 128.51, 128.47, 128.02, 127.92, 127.87, 127.80, 127.73, 122.88, 122.01, 121.88, 121.72, 121.54, 121.20, 120.83, 80.56, 74.81, 73.87, 73.06, 72.95, 70.76, 70.03, 69.02, 68.37, 62.14, 61.50, 57.64, 56.57, 55.42, 54.12, 50.41, 45.39, 45.30, 45.24, 35.21, 29.43, 29.32, 28.32, 27.93, 17.05, 15.74, 9.59, 9.53, 9.50. HRMS (ESI) calcd for $C_{78}H_{107}N_{13}O_{12}$ (M^{4+}-4TfO) 354.4535, found: 354.4534.

Compound 51: faun foam, 100% yield. ^{1}H NMR (500 MHz, CD_3CN) δ 7.94 (d, 1H, J = 6.0 Hz), 7.36-7.19 (m, 26H), 4.59-4.45 (m, 11H), 4.39 (d, 1H, J = 12 Hz), 4.36 (m, 1H), 4.27 (s, 1H), 4.14-4.02 9m, 5H), 3.91 (s, broad, 2H), 3.80 (m, 1H), 3.72 (m, 1H), 3.65 (s, 3H), 3.62 (m, 2H, overlap), 2.42 (s, 3H), 2.30 (m, 2H, overlap), 1.25 (d, 3H, J = 7 Hz), 1.20 (d, 3H, 6 Hz); ^{13}C NMR (500 MHz, CD_3CN) δ 172.74, 170.59, 170.32, 169.48, 167.69, 144.80, 138.68, 138.29, 138.27, 137.64, 128.65, 128.59, 128.57, 128.54, 128.09, 128.05, 128.01,127.95, 127.91, 127.84, 122.58, 121.22, 74.49, 73.31, 72.98, 72.96, 70.58, 69.59, 69.26, 68.07, 61.47, 57.22, 54.58, 53.41, 53.20, 49.62, 45.11, 35.00, 28.36, 17.36, 15.64, 9.24.

Compound 52: faun powder. 100% yield. M. P. 130-132 °C. ^{1}H NMR (400 MHz, CD_3CN) δ 7.98 (broad), 7.33-7.29 (m, 23H), 7.17 (d, 1H, J = 8.8 Hz), 4.58-4.46 (m, 9H), 4.39 (d, 1H, J = 11.6 Hz, overlap), 4.37 (broad, 1H), 4.13-3.98 (m, 9H), 3.90 (broad, 2H), 3.77 (m, 2H), 3.73 (s, 3H), 3.61 (m, 2H), 2.52 (s, 3H), 2.51 (s, 3H), 2.22 (m, 2H), 1.72 (m, 2H), 1.58 (m, 2H), 1.32 (m, 4H), 1.26 (d, 3H, J = 7.2 Hz), 1.18 (d, 3H, J = 6.4 Hz); ^{13}C NMR (400 MHz, CD_3CN) δ 172.58, 170.45, 169.25, 167.54, 145.06, 144.43, 138.70, 138.29, 138.24, 137.66, 128.65, 128.60, 128.58, 128.52, 128.07, 128.02, 128.00, 127.90, 127.89, 127.80, 122.88, 121.71, 121.20, 120.90, 74.63, 73.28, 72.96,72.95, 70.54, 69.69, 69.43, 68.14, 65.22, 57.05, 54.34, 53.26, 53.16, 49.34, 48.32, 45.13, 45.07, 35.80, 29.38, 29.19, 28.20, 25.57, 25.16, 17.71, 15.70, 9.41, 9.36. HRMS (ESI) calcd for $C_{62}H_{83}O_{10}N_9$ (M^{2+}-2TfO&CF_3CO_2H) 556.8126, found: 556.8117.

Compound 53: faun powder. 100% yield. M. P. 190-192 °C, decompose. ^{1}H NMR (400 MHz, CD_3CN) δ 7.87 (broad, 1H), 7.36-7.29 (m, 24H), 7.17 (d, 1H, J = 8.8 Hz), 4.60-4.48 (m, 9H), 4.40 (d, 1H, J = 12.0 Hz), 4.32 (m, 1H), 4.24 (br, 1H), 4.14-4.04 (m, 15H), 3.90 (br 2H), 3.78 (m, 1H), 3.73 (s, 1H, overlap), 3.73 (s, 3H, overlap), 3.63 (m, 2H), 2.59 (s, 3H), 2.54 (s, 3H), 2.49 (s, 3H), 2.24 (m, 4H), 2.04 (m, 2H), 1.25 (d, 3H, J = 6.0

Hz), 1.20 (d, 3H, J = 7.0 Hz). HRMS (ESI) calcd for $C_{66}H_{88}O_{10}N_{11}$ (M^{3+}-3TfO&CF_3CO_2H) 398.2233, found: 398.2230.

Compound 54: faun powder, 100% yield. ^{1}H NMR (400 MHz, CD_3CN) δ 8.04 (s, 1H), 7.39 (m, 27H), 4.59-4.44 (m, 10H), 4.36 (d, 1H, J = 11.8 Hz), 4.24 (m, 19H), 3.92 (s, br, 2H), 3.76 (m, 2H, overlap), 3.73 (s, 3H), 3.64 (m, 2H), 2.60 (s, 6H), 2.55 9s, 3H), 2.51 (s, 3H), 2.28 (m, 6H), 2.20 (m, 2H), 1.26 (d, 3H, J = 7.2 Hz), 1.21 (d, 3H, J = 6.4 Hz).

Compound 55: faun solid. 99% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 (s, 2H), 7.30-7.19 (m, 23H), 7.01 (s, 2H), 5.39 (d, 1H, J = 4.5 Hz), 4.70 (s, 1H), 4.63 (d, 1H, J = 6 Hz), 4.50 (m, 4H), 4.40 (m, 6H), 4.24 (m, 2H), 4.07 (m, 7H), 3.93 (m, 2H), 3.77 (m, 1H), 3.72 (m, 5H), 3.48 (m, 2H), 2.48 (s, 3H), 2.05 (broad, 2H), 1.40 (m, 12H), 1.17 (m, 6H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 173.34, 172.23, 171.23, 170.87, 170.63, 170.35, 156.46, 144.24, 138.41, 138.06, 138.01, 137.81, 137.21, 128.82, 128.73, 128.54, 128.52, 128.37, 128.23, 127.97, 127.86, 127.81, 127.57, 122.48, 121.93, 81.20, 74.82, 74.11, 73.56, 73.19, 73.04, 71.71, 71.16, 69.87, 68.44, 68.04, 61.27, 59.79, 57.58, 55.68, 55.38, 53.64, 50.68, 45.40, 35.37, 28.44, 28.40, 17.25, 15.56, 16.14, 9.51. HRMS (ESI) calcd for $C_{68}H_{87}O_{14}N_8$ (C^+) 1239.6336, found: 1239.6283; for $C_{68}H_{88}O_{14}N_8$ (C^++H^+) 620.3204, found: 620.3197.

Compound 56: faun powder, 100% yield, M. P. 173-175 °C. ^{1}H NMR (400 MHz, CD_3CN), δ 7.50-7.28 (m, 23H), 7.17 (d, 1H, J = 8.4 Hz), 5.78 (d, 1H, J = 6.4 Hz), 4.57-4.26 (m, 15H), 4.10-3.98 (m, 11H), 3.81-3.71 (m, 7H), 3.60 (m, 2H), 2.51 (s, 6H), 2.21 (m, 2H), 1.73 (m, 2H), 1.59 (m, 2H), 1.40 (s, 9H), 1.30 (m, 7H), 1.18 (m, 6H); ^{13}C NMR (400 MHz, CD_3CN) δ 172.87, 172.14, 171.25, 170.44, 170.30, 169.91, 156.64, 145.04, 144.47, 138.82, 138.70, 138.43, 138.37, 138.08, 128.67, 128.54, 128.48, 127.99, 127.96, 127.94, 127.84, 127.80, 127.71, 122.80, 121.76, 121.18, 120.88, 80.01, 74.64, 74.45, 72.98, 72.93, 72.74, 70.98, 70.52, 69.88, 68.88, 68.61, 64.99, 59.47, 57.11, 55.01, 53.49, 49.70, 48.33, 45.15, 45.06, 35.11, 29.37, 29.15, 28.15, 27.78, 25.43, 25.08, 17.08, 15.86, 15.65, 9.48, 9.39. HRMS (ESI) calcd for $C_{78}H_{104}O_{14}N_{10}$ (M^{2+}-2TfO) 702.3861, found: 702.3866.

Compound 57: faun powders. 100% yield. M. P. 212-214 °C, decompose. ^{1}H NMR (500 MHz, CD_3CN) δ 7.52 (s, 1H), 7.43 (d, 1H, J = 5 Hz), 7.37-7.24 (m, 29H), 5.75 (s, 1H), 4.60-4.46 (m, 9H), 4.40 (m, 3H), 4.32-4.21 (M, 3H), 4.12-4.02 (m, 16H), 3.99 (m, 1H), 3.83 (m, 1H), 3.76-3.70 (m, 5H), 3.67 (m, 1H), 3.59 (m, 1H), 3.52 (s, 1H), 2.59 (s, 3H), 2.54 (s, 3H), 2.51 (s, 3H), 2.25 (m, 4H), 2.15-2.06 (m, 2H), 1.41 (s, 9H), 1.32 (d, 3H, J = 7 Hz), 1.20 (m, 6H); ^{13}C NMR (500 MHz, CD_3CN) δ 173.16, 172.38, 171.49, 170.50, 170.35, 170.29, 156.58, 145.10, 144.99, 144.80, 138.79, 138.70, 138.44, 138.36, 138.07, 128.68, 128.54, 128.51, 128.01, 127.96, 127.92, 127.89, 127.81, 127.71, 122.90, 122.00, 121.57, 121.23, 120.86, 80.08, 74.62, 74.41, 73.01, 72.93, 72.73, 71.00, 70.63, 69.91, 68.75, 61.44, 59.62, 57.34, 55.34, 53.84, 50.12, 45.25, 45.21, 45.17, 45.13, 35.09, 35.06, 29.30, 29.19, 28.18, 27.82, 17.00, 15.94, 15.60, 9.41, 9.39, 9.32, 9.31. HRMS (ESI) calcd for $C_{82}H_{109}O_{14}N_{12}$ (M^{3+}-3TfO) 495.2723, found: 495.2722.

Compound 58: faun solid. 100% yield. ^{1}H NMR (500 MHz, CD_3CN) δ 7.53 (s, 1H), 7.43 (s, 1H), 7.35-7.29 (m, 31H), 5.77 (s, 1H), 4.64-4.40 (m, 12H), 4.26 (m, 3H), 4.28-3.99 (m, 20H), 3.83 (m, 1H), 3.73 (m, 4H), 3.68 (m, 2H), 3.60 (m, 1H), 3.50 (m, 1H), 2.59 (s, 3H), 2.58 (s, 3H), 2.54 (s, 3H), 2.51 (s, 3H), 2.27 (m, 6H), 2.08 (m, 2H), 1.41 (s, 9H), 1.32 (d, 3H, J = 7 Hz), 1.20 (d, 3H, J = 6 Hz); ^{13}C NMR (400 MHz, CD_3CN) δ 173.00, 172.24, 171.35, 170.35, 170.19, 170.15, 156.48, 145.02, 144.92, 144.71, 138.72, 138.62, 138.37, 138.29, 137.98, 128.63, 128.54, 128.49, 128.47, 128.28, 128.02, 127.96, 127.92, 127.88, 127.83, 127.79, 127.76, 127.67, 122.86, 121.97, 121.72, 121.53, 121.20, 120.82, 80.17, 74.70, 74.46, 73.89, 73.10, 73.02, 72.82, 71.09, 70.76, 70.72, 70.00, 68.83, 68.62, 62.18, 61.54, 59.74, 58.02, 57.47, 55.38, 53.98, 50.29, 45.41, 45.34, 45.28, 35.26, 29.49, 29.37, 28.51, 28.38, 28.02, 17.20, 16.16, 15.84, 9.65, 9.56. HRMS (ESI) calcd for $C_{89}H_{120}O_{14}N_{14}$ (M^{4+}-4TfO) 402.2271, found: 402.2273.

Compound 59: faun powders. 100% yield. M. P. 211-213 °C, decompose. ^{1}H NMR (400 MHz, CD_3CN) δ 7.60 (s, 1H), 7.50 (d, 1H, J = 4.2 Hz), 7.42-7.24 (m, 34H), 5.84 (d, 1H, J = 6.4 Hz), 4.60-4.36 (m, 14H), 4.33-4.19 (M, 4H), 4.12-4.00 (m, 17H), 3.84 (m, 1H), 3.76-3.70 (m, 6H), 3.60 (m, 1H), 3.53 (m, 1H), 2.56 (s, 3H), 2.54 (s, 3H), 2.50 (s, 3H), 2.25 (m, 4H), 2.15-2.06 (m, 2H), 1.38 (s, 9H), 1.33 (d, 3H, J = 7.2 Hz), 1.19 (d, 3H, J = 6.6 Hz), 1.12 (m, 6H).

Compound 60: faun powders. 100% yield. M. P. 213-215 °C, decompose. ^{1}H NMR (400 MHz, CD_3CN) δ 7.63 (s, 1H), 7.52 (s, 1H), 7.43-7.28 (m, 39H), 7.00 (broad, 1H), 5.84 (s, br, 1H), 4.56-4.36 (m, 16H), 4.33 (M, 3H), 4.24-4.04 (m, 17H), 3.84 (m, 1H), 3.76 (m, 1H), 3.72 (m, 5H), 3.63 (m, 2H), 3.53 (m, 2H), 2.56 (s, 3H), 2.53 (s, 3H), 2.51 (s, 3H), 2.25 (m, 4H), 2.06 (m, 2H), 1.36 (s, 9H), 1.34 (d, 3H, J = 7.6 Hz), 1.19 (d, 3H, J = 6.4 Hz), 1.15 (d, 3H, J = 6.0 Hz), 1.11 (m, 3H. J = 6.4 Hz).

Compound 61: faun powders. 100% yield. M. P. 214-216 °C, decompose. ^{1}H NMR (500 MHz, CD_3CN) δ 7.73 (s, 1H), 7.59 (s, 1H), 7.45-7.25 (m, 39H), 7.05 (broad), 5.61 (s, 1H), 4.56-4.36 (m, 16H), 4.30 (M, 5H), 4.24-4.04 (m, 20H), 3.95 (m, 1H), 3.83 (m, 1H), 3.72 (m, 9H), 3.65 (m, 2H), 3.52 (m, 2H), 2.56 (s, 3H), 2.53 (s, 3H), 2.51 (s, 3H), 2.25 (m, 4H), 2.06 (m, 2H), 1.37 (s, 9H), 1.34 (d, 3H, J = 7.0 Hz), 1.19 (d, 3H, J = 6.5 Hz), 1.16 (d, 3H, J = 7.0 Hz), 1.14 (m, 3H. J = 7.5 Hz), 1.11 (d, 3H, J = 6.5 Hz). HRMS (ESI) calcd for $C_{106}H_{138}O_{19}N_{15}$ (M^{3+}-3TfO) 641.6759, found: 641.6759.

Compound 62: faun powder. 100% yield. ^{1}H NMR (500 MHz, CD_3CN) δ 8.35 (broad), 7.43-7.20 (m, 31H), 4.52 (m, 2H), 4.38 (m, 8H), 4.17-4.02 (m, 21H), 3.73 (s, 3H), 3.70 (m, 5H, overlap), 3.46 (m, 2H), 2.61 (s, 3H), 2.55 (s, 3H), 2.48 (s, 3H), 2.26 (m, 4H), 1.98 (m, 2H), 1.15 (br, 9H); ^{13}C NMR (500 MHz, CD_3CN) δ 172.99, 170.90, 170.24, 169.79, 167.82, 145.10, 145.02, 144.66, 138.40, 138.07, 128.50, 127.69, 128.68, 128.54, 128.51, 128.01, 127.96, 127.92, 127.89, 127.81, 127.71, 122.84, 121.86, 121.63, 121.60, 121.33, 120.97, 78.11, 75.61, 74.50, 72.87, 72.50, 71.32, 70.49, 69.91, 68.75, 61.59, 59.62, 57.18, 55.34, 53.80, 50.12, 45.16, 45.14, 45.13, 35.04, 29.36, 29.27, 28.23, 15.83, 15.57, 9.41, 9.39, 9.32, 9.31.

General procedures to cleave hexa-amino-acid peptide from imidazolium salt supports: To the flask charged with imidazolium salt-bound hexa-amino-acid peptide was added THF and H_2O (V/V=3:1). The mixture was stirred at room temperature for a few minutes to completely dissolve the supported peptide into the mixed solvents. Aqueous LiOH (0.1 M, 1 equiv.) or NaOH (1.0 M, 1 equiv.) solution was then added. The reaction mixture was stirred at room temperature for 20 hours. The volatile solvent was removed by rotary evaporation under reduced pressure and the residue was added with water and then aqueous HCl (0.1M) to adjust its pH to 5. The white precipitate was filtered and washed with water for 3 times and ether for 3 times to give the product as faun powder.

Compound 63: white powder. 81% yield. M. P. 167-169 °C. $[\alpha]_D^{20}$ = 33.0 (c = 1, in THF). ^{1}H NMR (500 MHz, CD_3COCD_3) δ 7.75 (s, 1H), 7.70 9s, 1H), 7.62 (d, 1H, J = 7.5

Hz), 7.51 (d, 1H, J = 7.0 Hz), 7.42 (d, 1H, J = 9.0 Hz), 7.35-7.21 (m, 20H), 6.11 (d, 1H, J = 7.5 Hz), 4.73 (m, 1H), 4.63-4.43 (m, 15H), 4.23 (m, 2H), 4.10 (s, 1H), 3.86 (m, 3H), 3.73 (m, 1H), 3.67 (m, 1H), 3.60 (m, 1H), 1.40 (s, 9H), 1.30 (d, 3H, J = 7.0 Hz), 1.21 (m, 6H); ^{13}C NMR (500 MHz, THF-d^4, concentrated) δ 174.18, 173.87, 172.31, 170.93, 171.10, 157.77, 141.15, 140.55, 130.02, 129.96, 129.87, 129.50, 129.08, 128.96, 80.42, 77.61, 74.77, 74.68, 73.25, 72.85, 72.48, 72.17, 60.68, 58.98, 55.53, 55.00, 54.89, 50.75, 29.78, 20.56, 18.12, 17.61. HRMS (ESI) calcd for $C_{60}H_{75}O_{14}N_6$ (M+H$^+$) 1103.5335, found: 1103.5313.

Compound 64: To the flask charged with imidazolium oligomer-bound peptide **62** (65.7 mg, 0.034 mmol), hexa-amino-acid peptide **63** (91.8 mg, 0.083 mmol), HBTU (35.9 mg, 0.085 mmol), HOBT (13.1 mg, 0.085 mmol) was added dry actonitrile (6 mL) and then diisopropylethylamine (DIPEA) (31 μL, 0.17 mmol). The reaction mixture was stirred at room temperature under nitrogen protection for 31 hours and then concentrated by rotary evaporation under reduced pressure. The residue was added with diethyl ether and then transferred into conical vial. The mixture was subjected to centrifugation and the top liquid phase was decanted. The solid phase was washed with diethyl ether (3 mL) twice, CH_2Cl_2 (3 mL) twice, THF (3 mL) twice and then ether (3 mL) once, dried in vacuo to give the product **64** as faun powder (93.5 mg, 95% yield).

^{1}H NMR (800 MHz, CD_3CN) δ 7.92 (s, 1H), 7.78 (s, 1H), 7.71 (s, 1H), 7.60 (m, 3H), 7,51 (m, 4H), 7.42-7.20 (m, 38H), 7.20-6.60 (broad, 20H), 5.81 (d, 1H, J = 6.4 Hz), 4.57 (m, 4H), 4.53-4.37 (m, 17H), 4.32 (m, 3H), 4.22-4.04 (m, 27H), 3.98 (m, 2H), 3.84-3.68 (m, 14H, 3.62 (m, 3H), 3.59 (m, 2H), 3.46 (m, 2H), 2.55 (s, 3H), 2.53 (s, 3H), 2.51 (s, 3H), 2.24 (m, 2H, overlap), 1.40 (s, 9H), 1.38 (d, 3H, J = 8 Hz), 1.32 (d, 3H), 1.20 (m, 6H), 1.56 (m, 6H). HRMS (ESI) calcd for $C_{137}H_{173}O_{25}N_{18}$ (M^{3+}-3TfO) 823.4267, found: 823.4262.

Compound 66: To the flask charged with imidazolium oligomer-bound peptide **65** (51.6 mg, 0.021 mmol), hexa-amino-acid peptide **63** (50.2 mg, 0.045 mmol), HBTU (18.7 mg, 0.049 mmol), HOBT (6.8 mg, 0.049 mmol) was added dry actonitrile (15 mL) and then diisopropylethylamine (DIPEA) (21 μL, 0.12 mmol). The reaction mixture was stirred at room temperature under nitrogen protection for 31 hours and then concentrated by rotary evaporation under reduced pressure. The residue was added with diethyl ether and then transferred into conical vial. The mixture was subjected to centrifugation and the top liquid phase was decanted. The solid phase was washed with diethyl ether (3 mL) twice, CH_2Cl_2 (3 mL) twice, THF (3 mL) twice and then ether (3 mL) once, dried in vacuo to give the product **66** as faun powder (70.8 mg, 99% yield).

HRMS (ESI) calcd for $C_{161}H_{202}O_{30}N_{21}$ (M^{3+}-3TfO) 969.8303, found: 969.8291.

Compound 67: faun powder. 80% yield. ^{1}H NMR (500 MHz, DMSO-d^6) δ 8.44 (s, 1H), 8.38 (d, 1H, J = 6.5 Hz), 8.20 (d, 1H, J = 6.0 Hz), 8.06 (d, 1H, J = 6.0 Hz), 7.79 (d, 1H, J = 7.0 Hz), 7.26 (m, 20H), 4.64 (m, 3H), 4.51-4.35 (m, 12H), 4.05 (s, 1H), 3.90 (s, 1H), 3.59 (m, 7H), 3.28 (broad, H_2O), 3.23 (s, 1H), 1.17 (d, 3H, J = 5.5 Hz), 1.13 (d, 3H, J = 4.5 Hz), 1.06 (d, 3H, J = 4.5 Hz); ^{13}C NMR (500 MHz, DMSO-d^6) δ 173.01, 172.76, 172.62, 172.23, 170.22, 170.08, 169.28, 139.40, 139.24, 138.81, 138.79, 138.73, 128.82, 128.82, 128.73, 128.18, 128.13, 128.10, 128.08, 128.03, 127.94, 127.92, 75.94, 75.52, 72.80, 72.77, 72.70, 70.97, 70.88, 70.78, 70.46, 59.16, 57.20, 53.40, 53.31, 52.95, 48.74, 19.15, 17.35, 16.91. HRMS (ESI) calcd for $C_{55}H_{67}O_{12}N_6$ ($M+H^+$) 1003.4811, found: 1003.4781.

Compound 68: To the flask charged with imidazolium oligomer-bound nine-amino-acid peptide **61** (35.8 mg, 0.015 mmol) was added THF (3 mL) and CH_3CN (2 mL). The mixture was stirred at room temperature for a few minutes to completely dissolve the supported peptide into the mixed solvents. Aqueous 0.1 M LiOH (0.23 mL, 0.0225 mmol) solution was then added. The reaction mixture was stirred at room temperature for 24 hours. The volatile solvent was removed by rotary evaporation under reduced pressure and the residue was added with water (3 mL) and then aqueous HCl (0.05 M) to adjust its pH to 5. The white precipitate was filtered and washed with water for 3 times and diethyl ether for 3 times and acetone for 3 times to give the product (19.0 mg, 83% yield) as faun powder.

M. P. 236-238 °C. ^{1}H NMR (500 MHz, DMSO-d^6) δ 8.28 (s, 1H), 8.20 (d, 1H, J = 7.0 Hz), 8.05 (d, 1H, J = 7.5 Hz), 7.97 (m, 2H), 7.91 (s, 1H), 7.26 (m, 28H), 6.96 (d, 1H, J = 8.0 Hz), 4.69-4.64 (m, 3H), 4.58-4.52 (m, 5H), 4.43 (m, 15H), 4.03 (m, 2H), 3.96 (m, 2H), 3.60-3.52 (m, 8H), 1.34 (s, 9H), 1.15 (d, 6H), 1.02 (m, 9H); ^{13}C NMR (500 MHz, DMSO-d^6) δ 173.45, 172.57, 172.07, 170.51, 170.27, 170.11, 170.00, 169.26, 155.66, 139.31, 139.24, 138.79, 138.76, 138.70, 128.80, 128.77, 128.67, 128.17, 128.14, 128.05, 128.00, 127.83, 78.70, 75.80, 75.72, 72.76, 72.70, 71.17, 70.89, 70.58, 70.47, 58.41, 56.91, 53.40, 53.12, 50.26, 49.27, 45.30, 28.85, 19.14, 18.85, 17.00, 16.78. HRMS (ESI) calcd for $C_{84}H_{103}O_{19}N_9$ (M+Na$^+$) 1564.7262, found: 1564.7265.

Compound 69: To the flask charged with imidazolium oligomer-bound dodeca-amino-acid peptide **64** (34.4 mg, 0.012 mmol) was added THF (3 mL) and CH_3CN (2 mL). The mixture was stirred at room temperature for a few minutes to dissolve the supported peptide into the mixed solvents. Aqueous 0.1 M LiOH (0.17 mL, 0.018 mmol) solution was then added. The reaction mixture was stirred at room temperature for 24 hours. The volatile solvent was removed by rotary evaporation under reduced pressure and the residue was added with water (3 mL) and then aqueous HCl (0.05 M) to adjust its pH to 5. The white precipitate was filtered and washed with water for 3 times and diethyl ether for 3 times and acetone for 2 times to give the product (19.2 mg, 100% yield) as faun powder.

^{1}H NMR (400 MHz, DMSO-d^6) δ 8.32-8.21 (m, 3H), 8.09-8.03 (m, 3H), 7.91 (d, 1H, J = 8.0 Hz), 7.62 (m, 2H), 7.24 (m, 40H), 6.58 (m, 1H, J = 8.8 Hz), 4.68 (m, 2H), 4.55 (m, 5H), 4.40-4.36 (m, 21h), 4.13 (m, 3H), 3.97 (m, 3H), 3.84 (m, 1H), 3.56 (m, 11H), 1.36 (m, 9H), 1.57 (m, 6H), 1.03 (m, 12H).

The high-resolution mass spectra (HRMS) were obtained after debenzylation of compound **69**. HRMS (ESI) calcd for $C_{45}H_{76}O_{12}N_{25}$ (M^{2-}) 592.2527, found: 592.2530; calcd for $C_{45}H_{77}O_{12}N_{25}$ (M^-) 1185.5128, found: 1185.5089.

General procedures to recover imidazolium oligomer supports after the cleavage of peptides: After filtration, the aqueous phase was collected and the water was removed under freeze-dry conditions. The white solid obtained was added with acetonitrile and then filtered to remove insoluble inorganic salt. The organic phase was collected and the solvent was removed by rotary evaporation. The residue was washed with diethyl ether to give the imidazolium oligomer as solid.

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Chapter 6. Summary and Conclusions

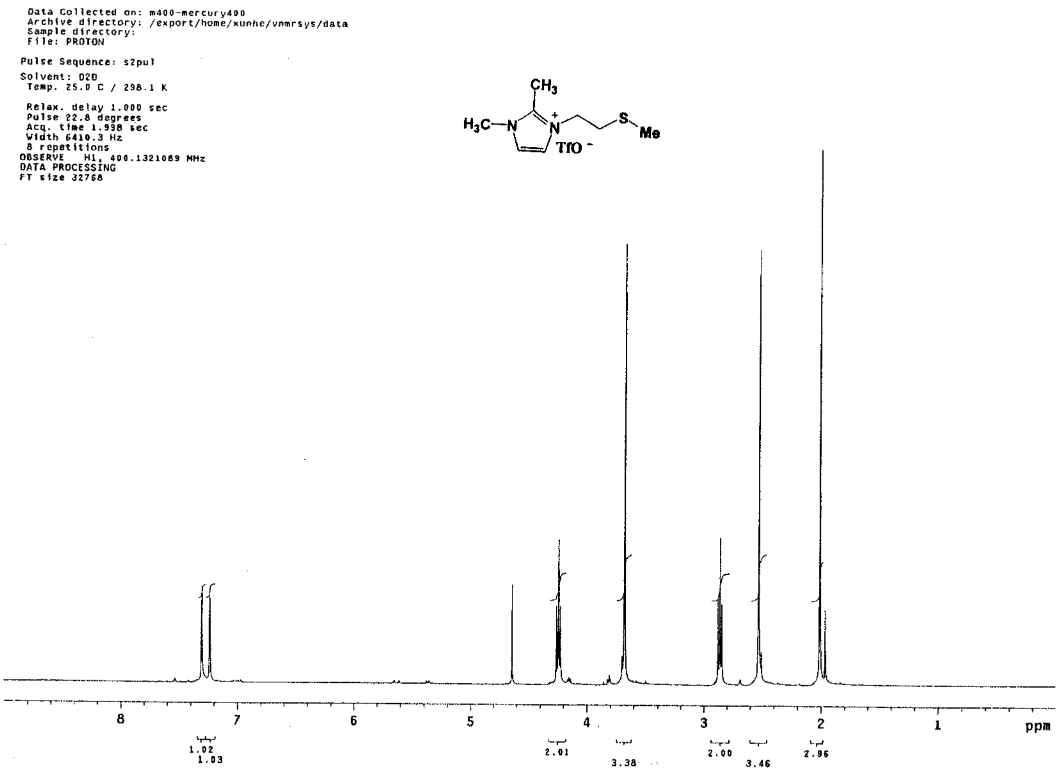
Ionic liquid-supported organic synthesis is a new approach in organic chemistry. This approach has been well demonstrated in this thesis by ionic liquid-supported Swern oxidation, oligosaccharide synthesis and imidazolium oligomer synthesis and peptide synthesis. The advantages of ionic liquid-supported Swern oxidation as compared to the conventional oxidant, DMSO, used in this reaction are that the oxidation reactions are odorless and the supported sulfide reagents can be recovered and recycled without obvious loss of the activity and yield. These new reagents are also suitable for large-scale reactions, which is very useful for the application in industry. Ionic liquid-supported oligosaccharide synthesis is an important example in oligosaccharide synthesis because it provides a new way to chemically assemble glycosides without need of chromatographic purification. A problem inherent in the use of one-ionic-unit ionic liquid support was identified because the ionic effect of support was found to decrease obviously when large molecules were connected to it. To overcome this solubility problem, we designed and synthesized imidazolium oligomers. These novel compounds were prepared in a straightforward way in multi-gram scale and the synthetic approach is suitable for large-scale synthesis. These compounds have good thermal stability and good solubility in common organic solvents, which render them good soluble supports for organic synthesis. The synthetic utility of imidazolium dimer and oligomers has been demonstrated in peptide synthesis especially in the peptide block coupling reactions. Peptide block coupling is a significantly important way to avoid linear synthetic route which is expensive and time-consuming and used in solid phase supported-synthesis. The imidazolium oligomer-supported peptide synthesis was conducted in homogeneous solution phase in quantitative yield without need of much excess reagents to drive reactions to completion as it does in solid-phase synthesis. The product purification was also performed in a simple way without need of special solvents as it does in fluorous phase-supported synthesis, which needs fluorous solvents to extract the product from the reaction mixtures. Importantly, our approach is likely suitable for large-scale peptide synthesis. This can significantly decrease the cost of peptide synthesis in industry. For example, if people use solid phase-supported synthesis to make 1 kg of nonapeptide, they have to use at least more than hundred kilograms of polymer resin. The reaction has to be done in a big and special reactor and a large amount of expensive amino acids have to be wasted during synthetic process because they have to be used to drive the reaction to completion. Otherwise, it is difficult to purify the nona-amino-acid peptide from its close numbered amino-acid-derived peptides such as octa-amino-acid peptide and hepta-amino-acid peptide. Moreover, 18 steps of reactions are necessary to finish the synthesis. However, if our approach is used to prepare the same peptide, the reaction can be done in big glassware that can be found in common chemistry lab. If we use [5+4] block coupling to finish the synthesis, the total number of synthetic steps can be shorten to be 10 steps. And also this approach does not need much excess of reagents to push the reaction to completion so that a large amount of money can be saved. Moreover, the cost on the synthesis of imidazolium oligomers can be offset by the recovery and recycle of the supports after the cleavage of peptides.

However, everything has two aspects. Since it has been reported that peptides with more than 100 amino acids can be prepared by automated solid phase-supported synthesis, the disadvantages of ionic liquid-supported synthesis is that it is a new approach and, so far, it is difficult to say if this approach is suitable for the preparation of very large peptides or other molecules. And also, anion exchange could bring out problems in some cases.

Appendix: Supporting Information

This section will include the important NMR and MS spectra.

Chapter 2. New Non-Volatile and Odorless Organosulfur Compounds Anchored on Ionic Liquids. Recyclable Reagents for Swern Oxidation



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 Archive directory: /export/home/xunhc/vnmrsys/data
 Sample directory:
 File: PROTON

Pulse Sequence: s2pul

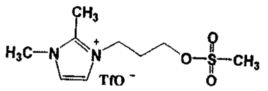
Solvent: D2O
 Temp. 25.0 C / 298.1 K

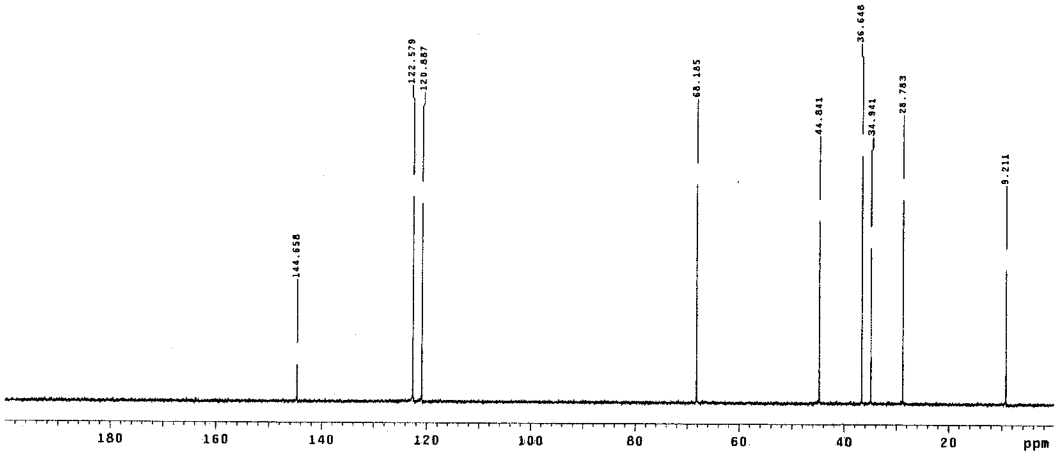
 Relax. delay 1.000 sec
 Pulse 22.8 degrees
 Acq. time 1.998 sec
 Width 6410.3 Hz
 8 repetitions
OBSERVE   H1, 400.1321089 MHz
DATA PROCESSING
FT size 32768
```

```
Data Collected on: m400-mercury400
Archive directory: /export/home/xunhe/vnmrsys/data
Sample directory:
File: CARBON

Pulse Sequence: s2pul
Solvent: D2O
 Temp. 20.0 C / 293.1 K

 Relax. delay 1.000 sec
 Pulse 45.0 degrees
 Acq. time 1.199 sec
 Width 25125.6 Hz
 2560 repetitions
OBSERVE  C13, 100.6116367 MHz
DECOUPLE  H1, 400.1276310 MHz
 Power 34 dB
 continuously on
 WALTZ-16 modulated
DATA PROCESSING
 Line broadening 1.0 Hz
FT size 65536
```





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Sample directory:
File: PROTON

Pulse Sequence: s2pul
Solvent: D2O
 Temp. 20.0 C / 293.1 K

 Relax. delay 1.000 sec
 Pulse 45.0 degrees
 Acq. time 1.998 sec
 Width 6410.3 Hz
 8 repetitions
OBSERVE   H1, 400.1255945 MHz
DATA PROCESSING
FT size 32768
```

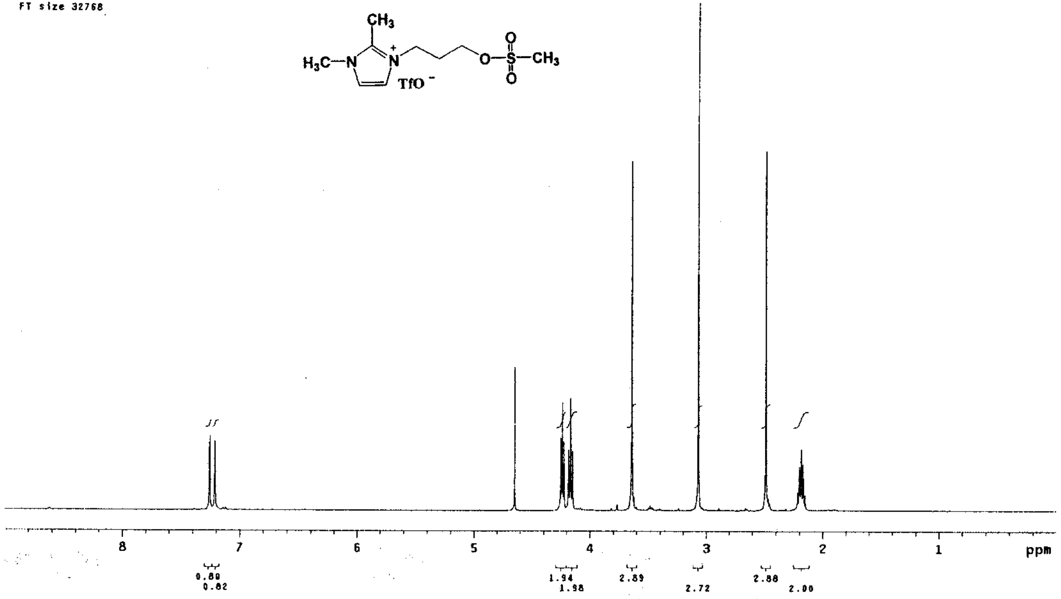

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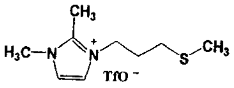
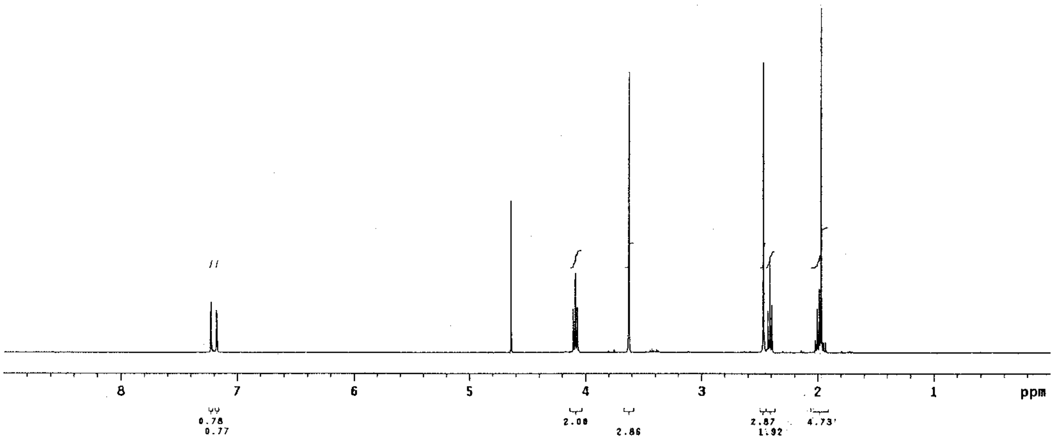
Archive directory: /export/home/xunhe/vnmrsys/data
Sample directory:
File: PROTON

Pulse Sequence: s2pul

Solvent: D2O
Temp. 23.0 C / 296.1 K

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.998 sec
Width 6410.3 Hz
8 repetitions
OBSERVE H1, 400.1255945 MHz
DATA PROCESSING
FT size 32768



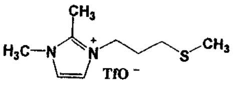


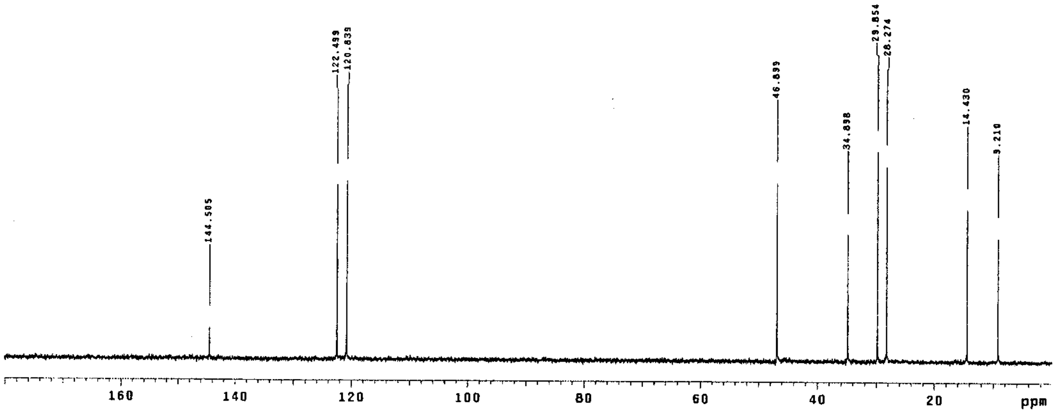
Data Collected on: m300-mercury300
Archive directory: /export/home/xunhe/vnmrsys/data
Sample directory:
File: HX-II-8-4-3-P-1-C13

Pulse Sequence: s2pul

Solvent: D2O
Temp. 25.0 C / 298.1 K

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.815 sec
Width 18867.9 Hz
320 repetitions
OBSERVE C13, 75.4502098 MHz
DECOUPLE H1, 300.0618010 MHz
Power 35 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 131072





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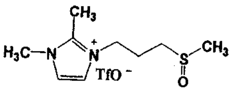
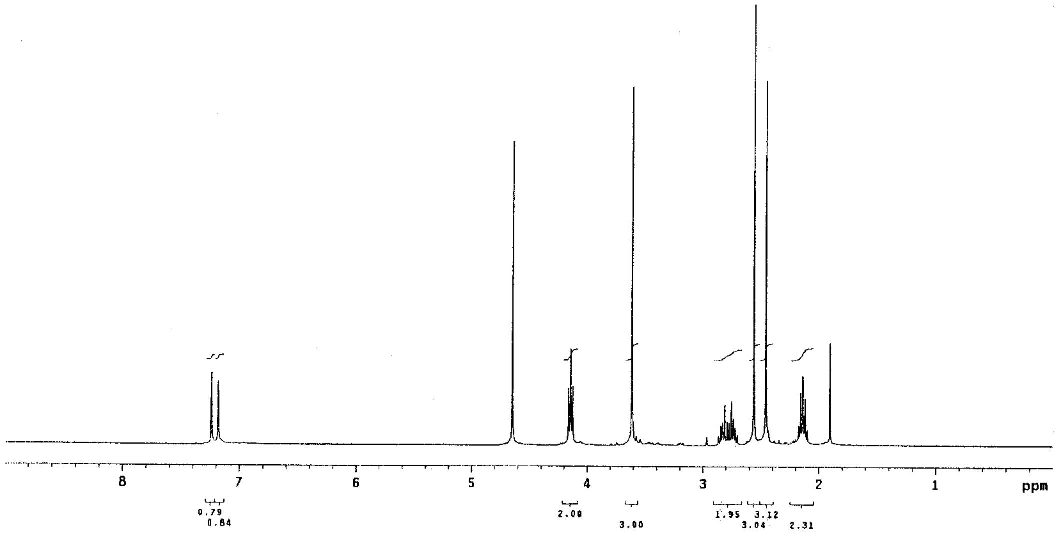
Data Collected on: m400-mercury400
Archive directory: /export/home/xunhe/vnmrsys/data
Sample directory:
File: PROTON

Pulse Sequence: s2pul

Solvent: D2O
 Temp. 20.0 C / 293.1 K

 Relax. delay 1.000 sec
 Pulse 45.0 degrees
 Acq. time 1.998 sec
 Width 6410.3 Hz
 8 repetitions
OBSERVE   H1, 400.1255945 MHz
DATA PROCESSING
```



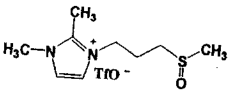


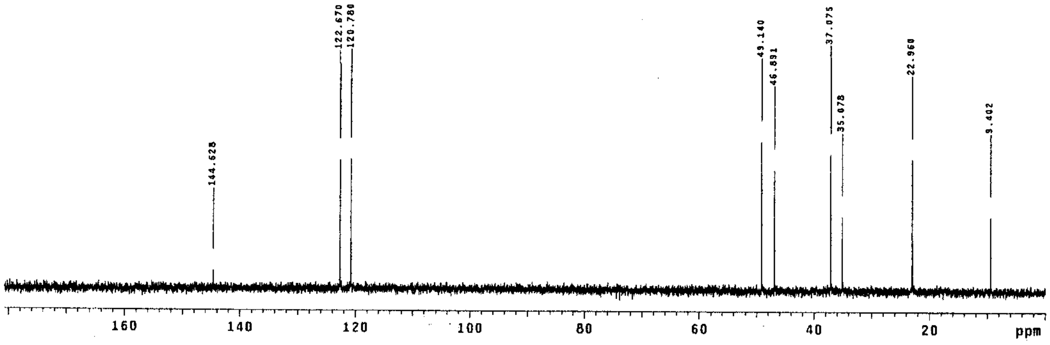
```
Data Collected on: m400-mercury400
Archive directory: /export/home/xunhe/vnmrsys/data
Sample directory:
File: CARBON

Pulse Sequence: s2pul

Solvent: D2O
 Temp. 23.0 C / 296.1 K

 Relax. delay 1.000 sec
 Pulse 45.0 degrees
 Acq. time 1.199 sec
 Width 25125.6 Hz
 768 repetitions
OBSERVE  C13, 100.6116367 MHz
DECOUPLE  H1, 400.1276310 MHz
 Power 34 dB
 continuously on
 WALTZ-16 modulated
DATA PROCESSING
 Line broadening 1.0 Hz
FT size 65536
Total time 63 hr, 35 min
```





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 Data Collected on: m300-mercury300
 Archive directory: /export/home/xunhe/vnmrsys/data
 Sample directory:
 File: PROTON

Pulse Sequence: s2pul

Solvent: D2O

 Relax. delay 1.000 sec
 Pulse 45.0 degrees
 Acq. time 1.998 sec
 Width 4803.1 Hz
 8 repetitions
OBSERVE   H1, 300.0603212 MHz
DATA PROCESSING
FT size 32768
```

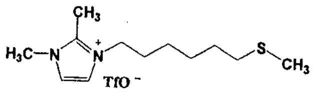

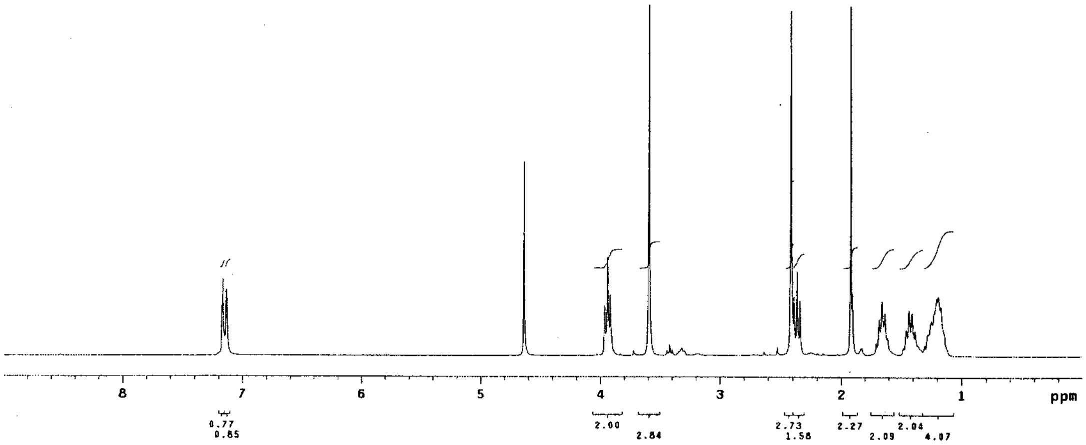

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 Data Collected on: m300-mercury300
 Archive directory: /export/home/xunhe/vnmrsys/data
 Sample directory:
 File: PROTON

Pulse Sequence: s2pul

Solvent: D2O

 Relax. delay 1.000 sec
 Pulse 45.0 degrees
 Acq. time 1.998 sec
 Width 4803.1 Hz
 8 repetitions
OBSERVE   H1, 300.0603212 MHz
DATA PROCESSING
FT size 32768
Total time 0 min
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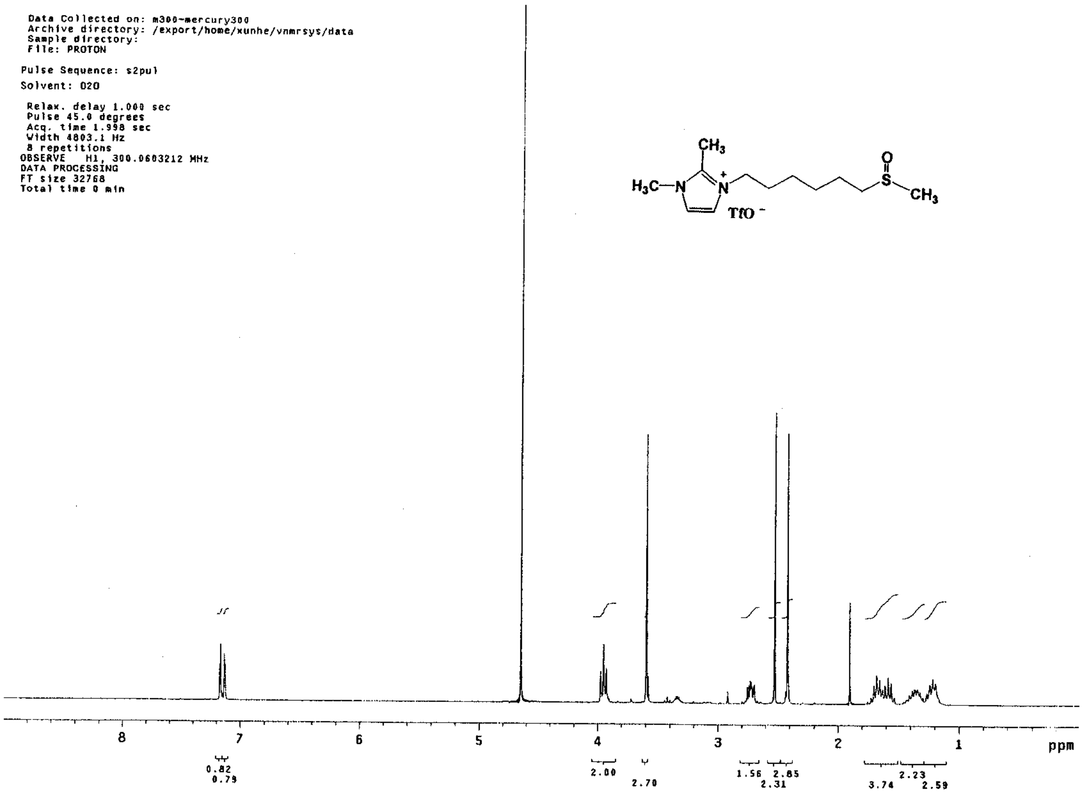

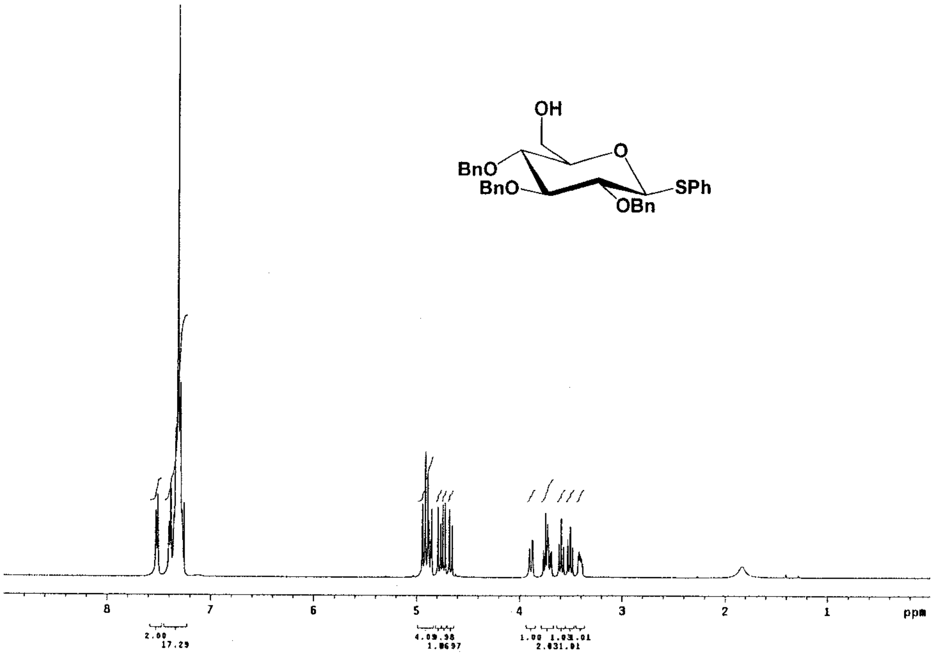
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BnO
O
SPh
OBn
8
7
6
5
4
3
2
1
ppm
2.00
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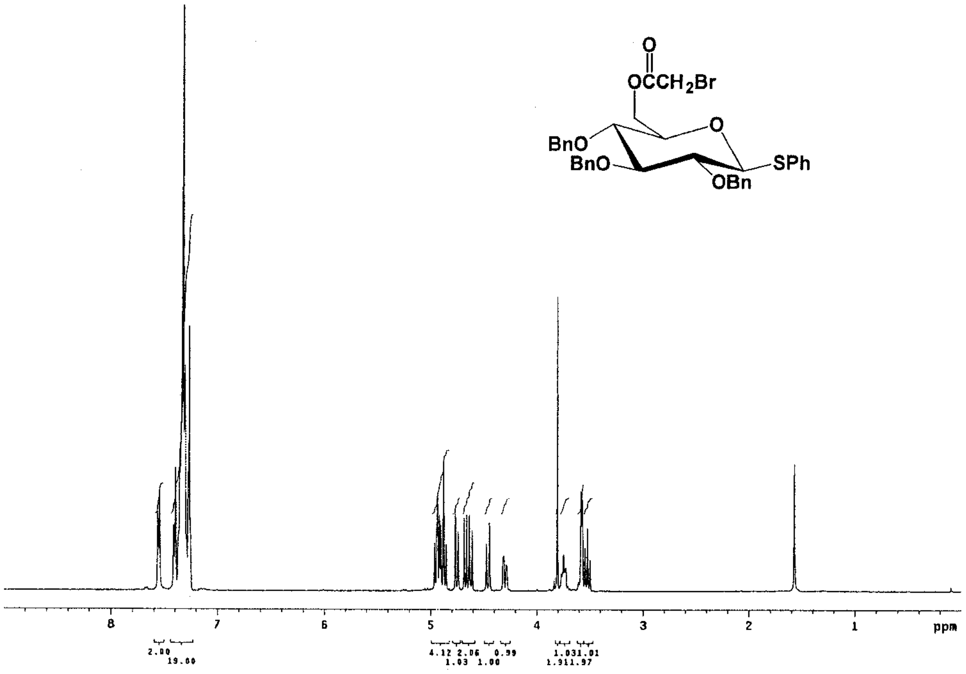
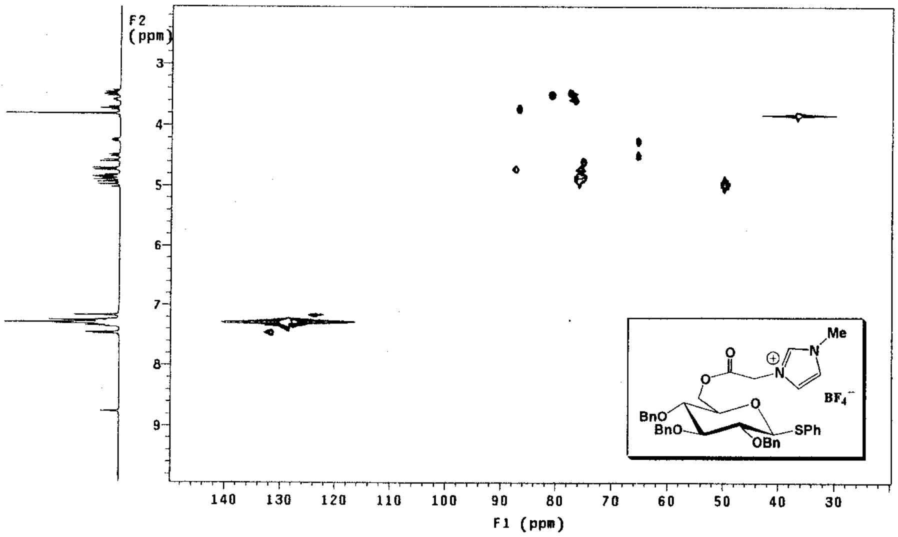
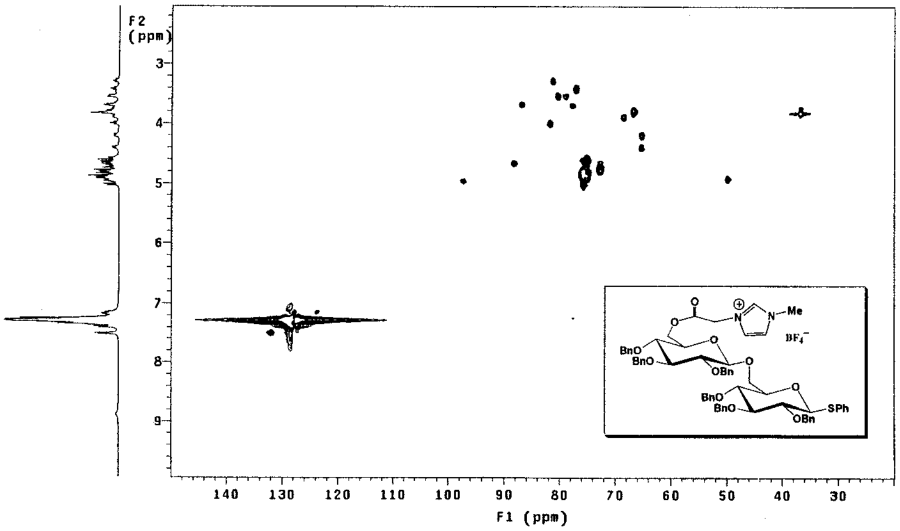
1.0697
1.00 1.03.01
2.031.01


O
OCCH$_2$Br
BnO
BnO
O
SPh
OBn
8
7
6
5
4
3
2
1
ppm
2.00
19.00
4.12 2.06 0.99
1.03 1.00
1.031.01
1.911.97

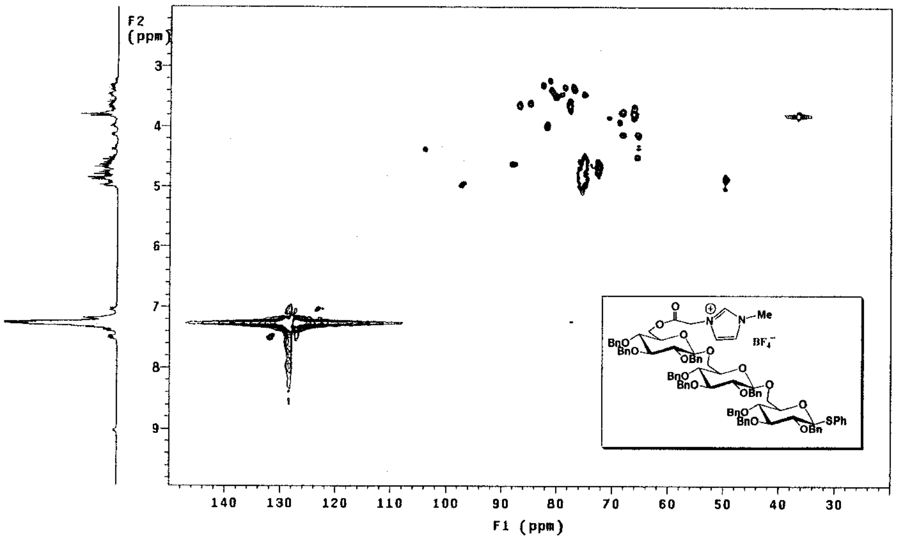
```
               HMQC

 Data Collected on: m400-mercury400
 Archive directory: /export/home/xunhe/vnmrsys/data
 Sample directory:
 File: HX-I-07-8-P-1-2DHMQC

Pulse Sequence: gHMQC

Solvent: CDCl3
 Temp. 20.0 C / 293.1 K

 Relax. delay 1.000 sec
 Acq. time 0.128 sec
 Width    4000.0 Hz
 2D Width 17094.0 Hz
 60 repetitions
 2 x 256 increments
OBSERVE   H1, 400.1310805 MHz
DECOUPLE C13, 100.6205622 MHz
 Power 52 dB
 on during acquisition
 off during delay
 GARP-1 modulated
DATA PROCESSING
 Gauss apodization 0.059 sec
F1 DATA PROCESSING
 Gauss apodization 0.014 sec
FT size 1024 x 2048
Total time 10 hr, 29 min
```

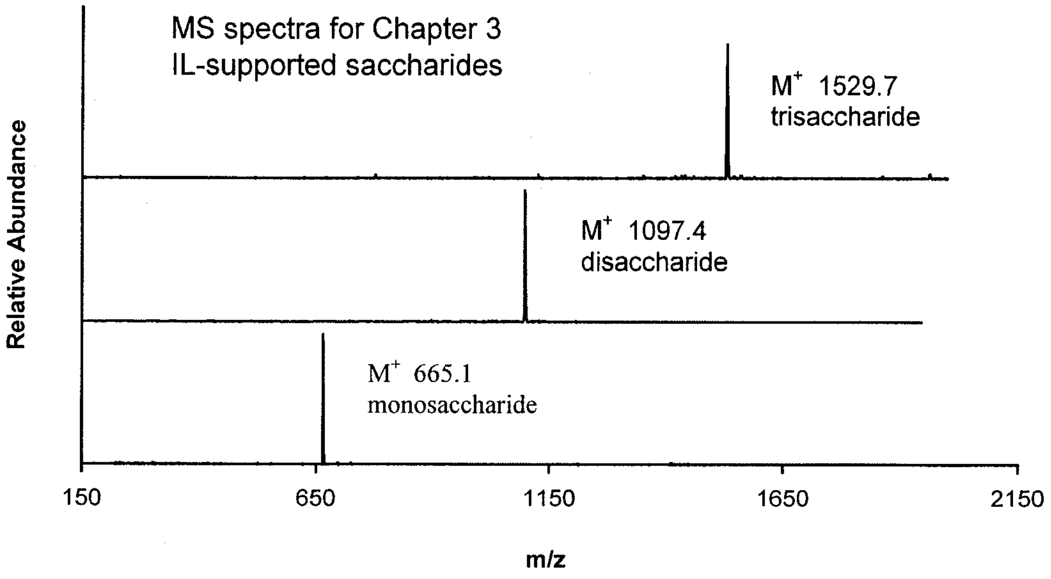


```
               HMQC

 Data Collected on: m400-mercury400
 Archive directory: /export/home/xunhe/vnmrsys/data
 Sample directory:
 File: HX-I-09-1-B-1-P-3-2DHMQC

Pulse Sequence: gHMQC

Solvent: CDCl3

 Relax. delay 1.000 sec
 Acq. time 0.256 sec
 Width    4000.0 Hz
 2D Width 17094.0 Hz
 16 repetitions
 2 x 256 increments
OBSERVE   H1, 400.1310805 MHz
DECOUPLE C13, 100.6205622 MHz
 Power 52 dB
 on during acquisition
 off during delay
 GARP-1 modulated
DATA PROCESSING
 Gauss apodization 0.059 sec
F1 DATA PROCESSING
 Gauss apodization 0.014 sec
FT size 1024 x 2048
Total time 3 hr, 6 min
```

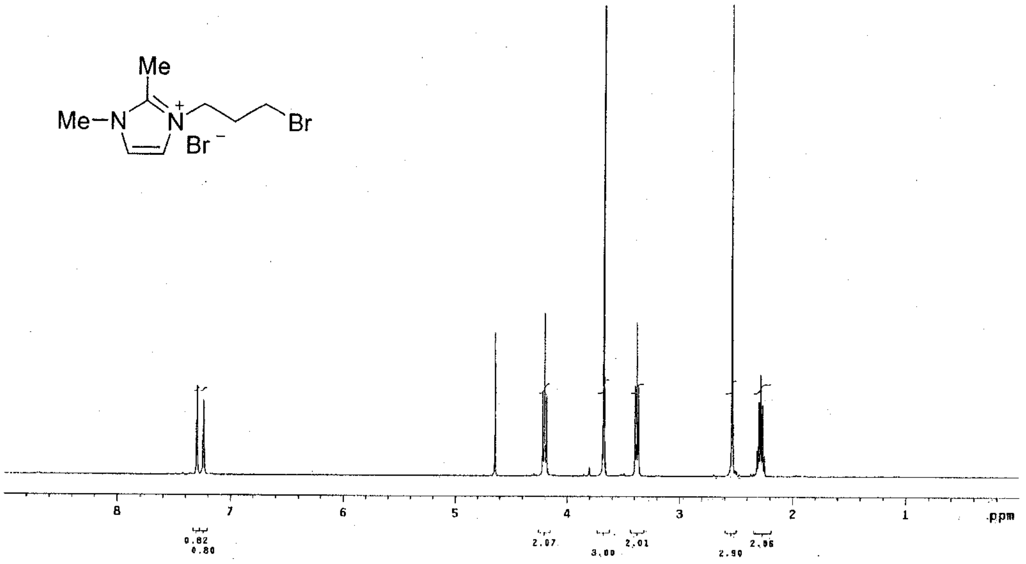


```
                HMQC

 Data Collected on: m400-mercury400
 Archive directory: /export/home/xunhe/vnmrsys/data
 Sample directory:
 File: HX-I-11-1-D-P-1-2DHMQC

Pulse Sequence: gHMQC

Solvent: CDCl3

 Relax. delay 1.000 sec
 Acq. time 0.256 sec
 Width    4000.0 Hz
 2D Width 17094.0 Hz
 60 repetitions
 2 x 256 increments
OBSERVE   H1, 400.1310805 MHz
DECOUPLE C13, 100.6205622 MHz
 Power 52 dB
 on during acquisition
 off during delay
 GARP-1 modulated
DATA PROCESSING
 Gauss apodization 0.059 sec
F1 DATA PROCESSING
 Gauss apodization 0.014 sec
FT size 1024 x 2048
Total time 11 hr, 37 min
```

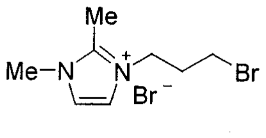


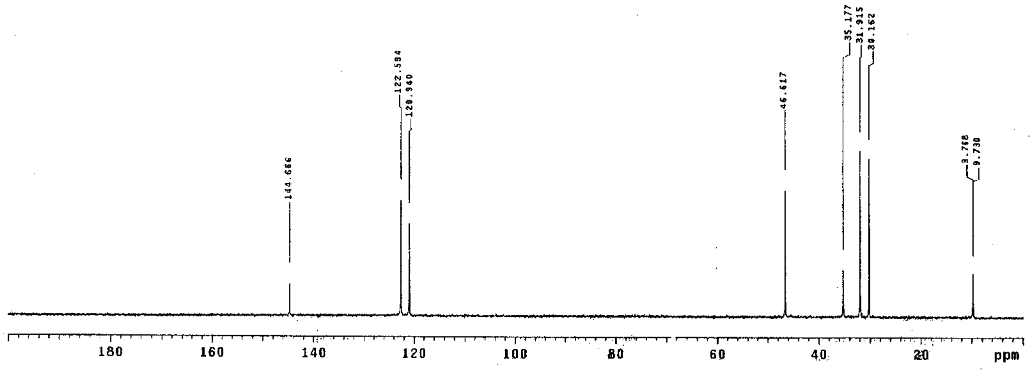

MS spectra for Chapter 3
IL-supported saccharides

```
HX-III-C-1-2-P-I

 Data Collected on: m400-mercury400
 Archive directory: /export/home/xunhe/vnmrsys/data
 Sample directory:
 File: PROTON

Pulse Sequence: s2pul

Solvent: D2O
 Temp. 25.0 C / 298.1 K

 Relax. delay 1.000 sec
 Pulse 45.0 degrees
 Acq. time 1.998 sec
 Width 6410.3 Hz
 8 repetitions
OBSERVE   H1, 400.1255945 MHz
DATA PROCESSING
FT size 32768
Total time 0 min
```

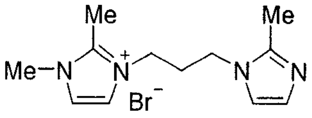


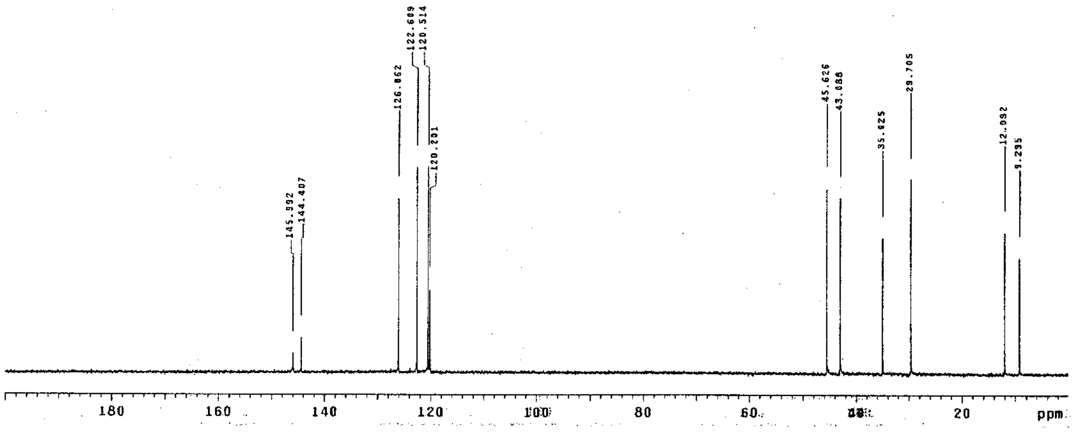
```
HX-III-C-1-1-P-3-C13-b

 Data Collected on: m400-mercury400
 Archive directory: /export/home/xunhe/vnmrsys/data
 Sample directory:
 File: CARBON

Pulse Sequence: s2pul

Solvent: D2O
 Temp. 20.0 C / 293.1 K

 Relax. delay 1.000 sec
 Pulse 45.0 degrees
 Acq. time 1.199 sec
 Width 25125.6 Hz
 3200 repetitions
OBSERVE  C13, 100.6116367 MHz
DECOUPLE  H1, 400.1276310 MHz
 Power 34 dB
 continuously on
 WALTZ-16 modulated
DATA PROCESSING
 Line broadening 1.0 Hz
FT size 65536
Total time 63 hr, 35 min
```



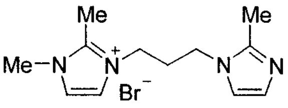


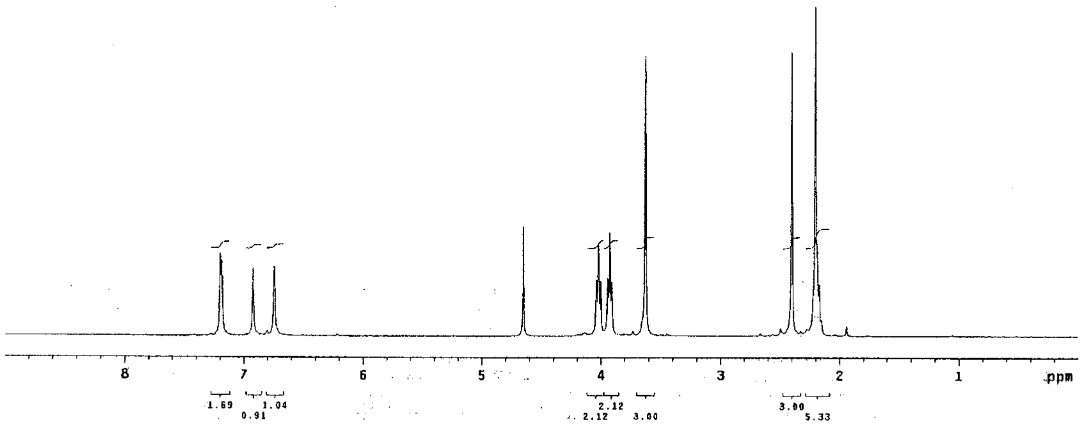
```
HX-III-C-2-1-P-5-C13

 Data Collected on: m400-mercury400
 Archive directory: /export/home/xunhe/vnmrsys/data
 Sample directory:
 File: CARBON

Pulse Sequence: s2pul

Solvent: D2O
 Temp. 25.0 C / 298.1 K

 Relax. delay 1.000 sec
 Pulse 45.0 degrees
 Acq. time 1.199 sec
 Width 25125.6 Hz
 5504 repetitions
OBSERVE  C13, 100.6116367 MHz
DECOUPLE  H1, 400.1276310 MHz
 Power 34 dB
 continuously on
 WALTZ-16 modulated
DATA PROCESSING
 Line broadening 1.0 Hz
FT size 65536
Total time 63 hr, 35 min
```



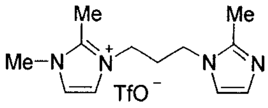


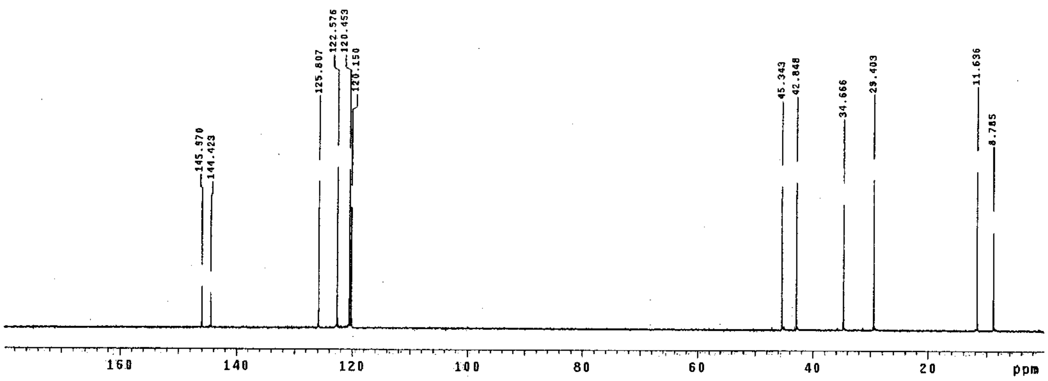
```
HX-III-C-2-1-P-5

 Data Collected on: m400-mercury400
 Archive directory: /export/home/xunhe/vnmrsys/data
 Sample directory:
 File: PROTON

Pulse Sequence: s2pul

Solvent: D2O
 Temp. 25.0 C / 298.1 K

 Relax. delay 1.000 sec
 Pulse 45.0 degrees
 Acq. time 1.998 sec
 Width 6410.3 Hz
 8 repetitions
OBSERVE   H1, 400.1255945 MHz
DATA PROCESSING
FT size 32768
Total time 0 min
```



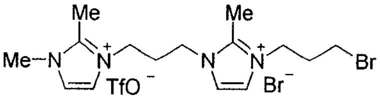


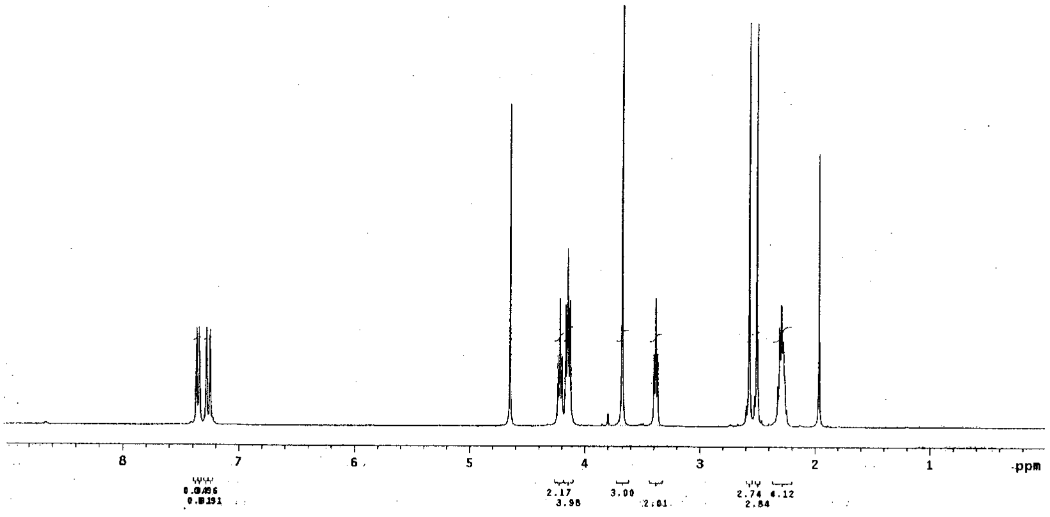
```
HX-III-C-3-5-P-1-C13

Pulse Sequence: s2pul
 Solvent: D2O
 Ambient temperature
Mercury-400BB  "m400"

 Relax. delay 2.500 sec
 Pulse 42.6 degrees
 Acq. time 1.199 sec
 Width 25000.0 Hz
 10320 repetitions
OBSERVE  C13, 100.6108815 MHz
DECOUPLE  H1, 400.1250217 MHz
 Power 35 dB
 continuously on
 WALTZ-16 modulated
DATA PROCESSING
 Line broadening 1.0 Hz
FT size 65536
Total time 110 hr, 10 min, 45 sec
```



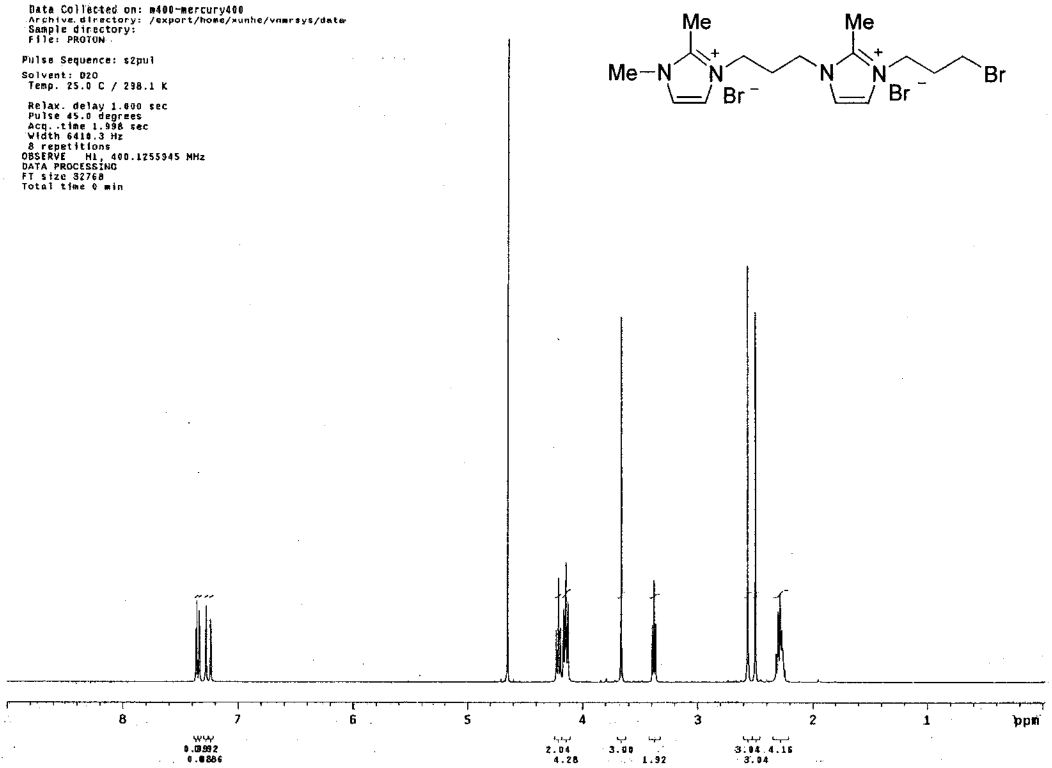


```
HX-III-C-4-9-P-1, the liquid phase

 Data Collected on: m400-mercury400
 Archive directory: /export/home/xunhe/vnmrsys/data
 Sample directory:
 File: PROTON

Pulse Sequence: s2pul

Solvent: D2O
 Temp. 23.0 C / 296.1 K

 Relax. delay 1.000 sec
 Pulse 34.2 degrees
 Acq. time 1.998 sec
 Width 6410.3 Hz
 8 repetitions
OBSERVE  H1, 400.1255945 MHz
DATA PROCESSING
FT size 32768
Total time 0 min
```

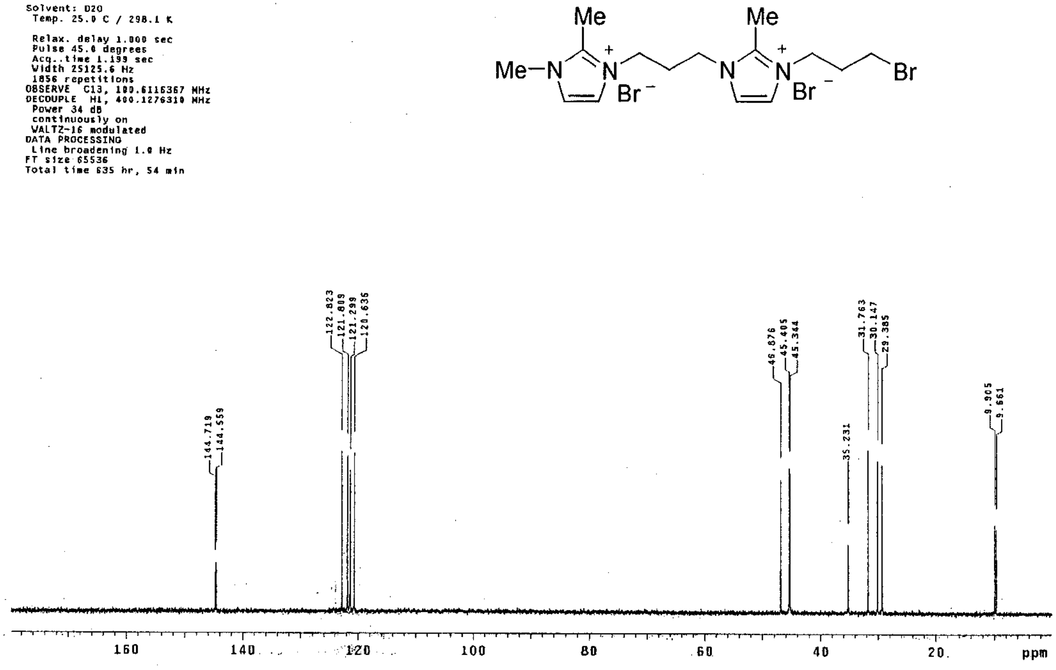




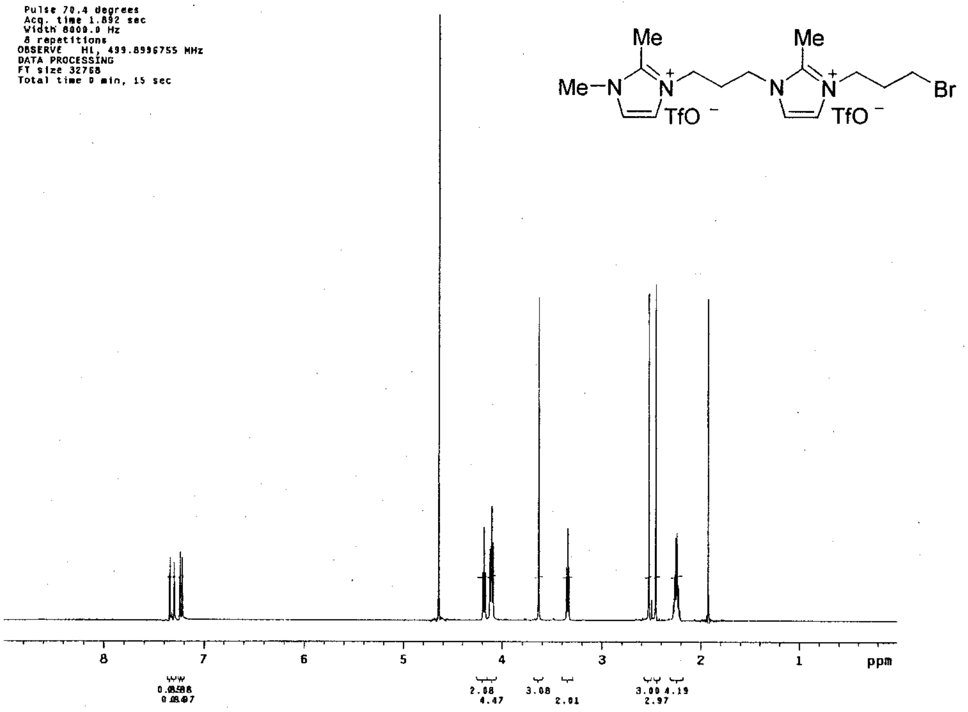
```
HX-III-C-4-13-P-1

 Data Collected on: m400-mercury400
 Archive directory: /export/home/xunhe/vnmrsys/data
 Sample directory:
 File: PROTON

Pulse Sequence: s2pul

Solvent: D2O
 Temp. 25.0 C / 298.1 K

 Relax. delay 1.000 sec
 Pulse 45.0 degrees
 Acq. time 1.998 sec
 Width 6410.3 Hz
 8 repetitions
OBSERVE   H1, 400.1255945 MHz
DATA PROCESSING
FT size 32768
Total time 0 min
```



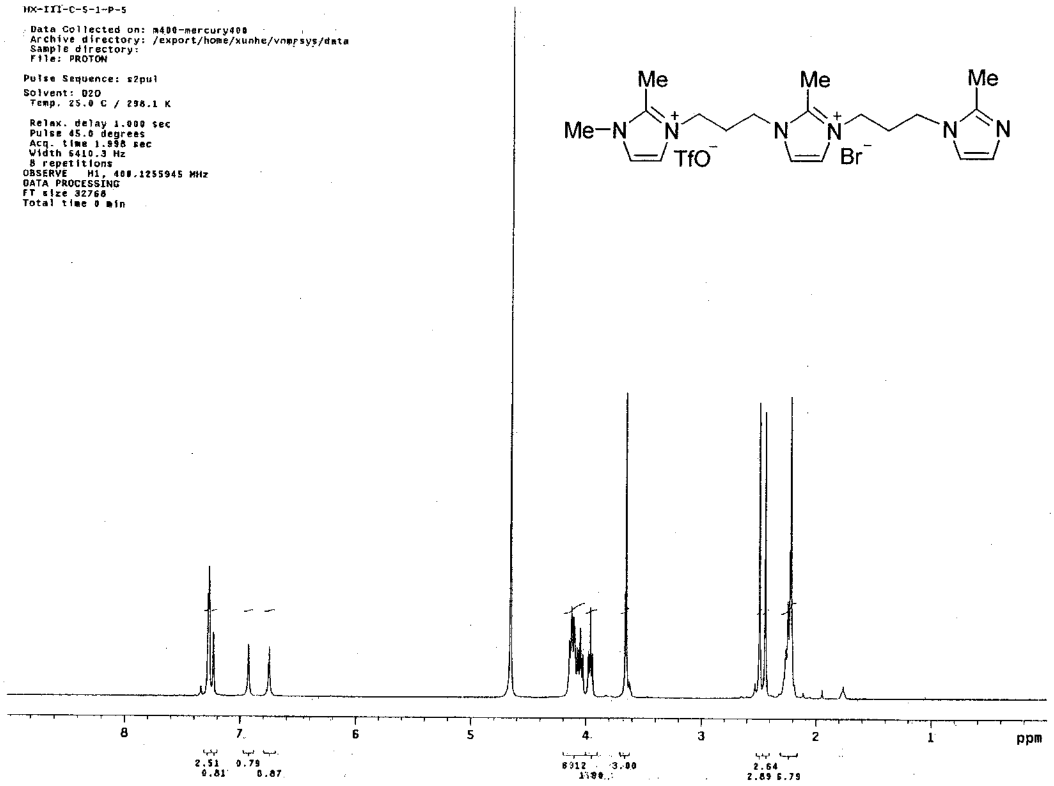
```
HX-III-C-4-13-P-1

 Data Collected on: m400-mercury400
 Archive directory: /export/home/xunhe/vnmrsys/data
 Sample directory:
 File: CARBON

Pulse Sequence: s2pul

Solvent: D2O
 Temp. 25.0 C / 298.1 K

 Relax. delay 1.000 sec
 Pulse 45.0 degrees
 Acq. time 1.199 sec
 Width 25125.6 Hz
 1856 repetitions
OBSERVE  C13, 100.6116367 MHz
DECOUPLE  H1, 400.1276310 MHz
 Power 34 dB
 continuously on
 WALTZ-16 modulated
DATA PROCESSING
 Line broadening 1.0 Hz
FT size 65536
Total time 635 hr, 54 min
```



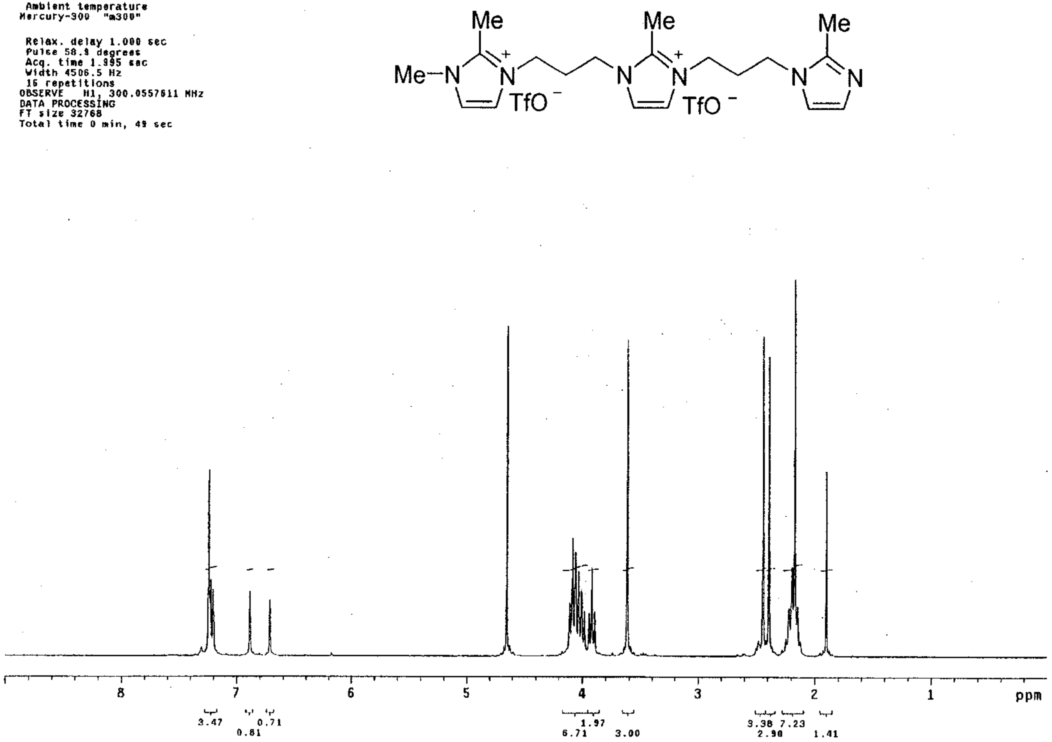
```
Pulse Sequence: s2pul

 Solvent: D2O
 Ambient temperature
UNITY-500  "dante"

 Pulse 70.4 degrees
 Acq. time 1.892 sec
 Width 8000.0 Hz
 8 repetitions
OBSERVE   H1, 499.8996755 MHz
DATA PROCESSING
FT size 32768
Total time 0 min, 15 sec
```



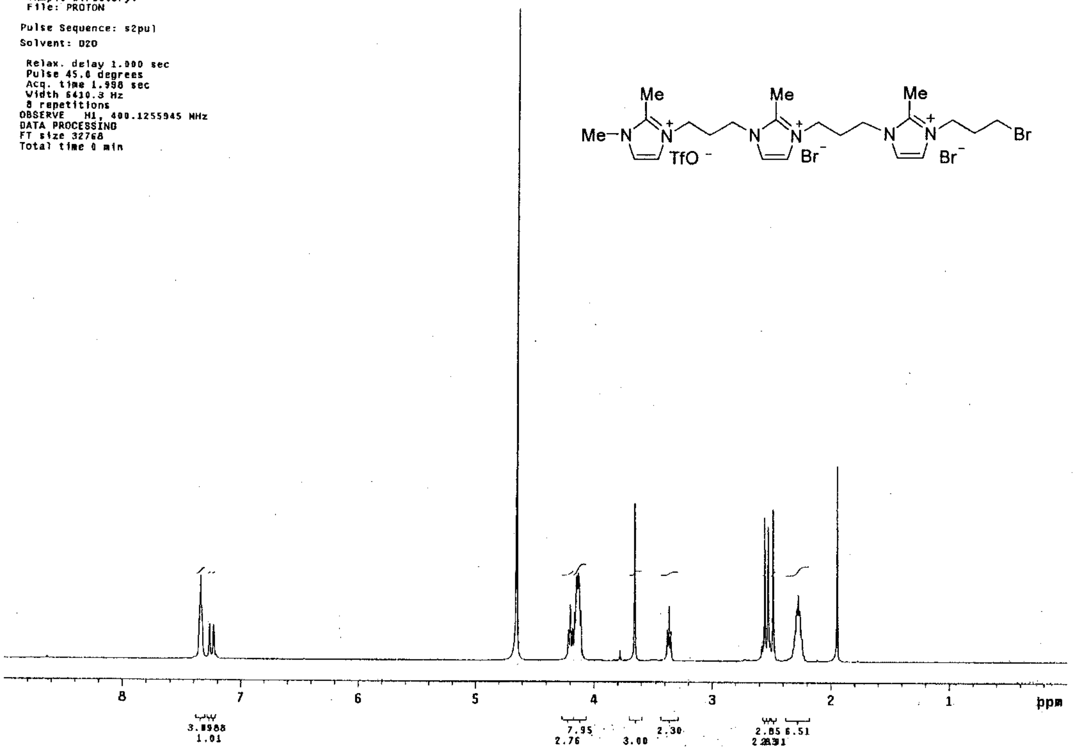
```
HX-III-C-5-1-P-5

 Data Collected on: m400-mercury400
 Archive directory: /export/home/xunhe/vnmrsys/data
 Sample directory:
 File: PROTON

Pulse Sequence: s2pul

Solvent: D2O
 Temp. 25.0 C / 298.1 K

 Relax. delay 1.000 sec
 Pulse 45.0 degrees
 Acq. time 1.998 sec
 Width 6410.3 Hz
 8 repetitions
OBSERVE   H1, 400.1255945 MHz
DATA PROCESSING
FT size 32768
Total time 0 min
```

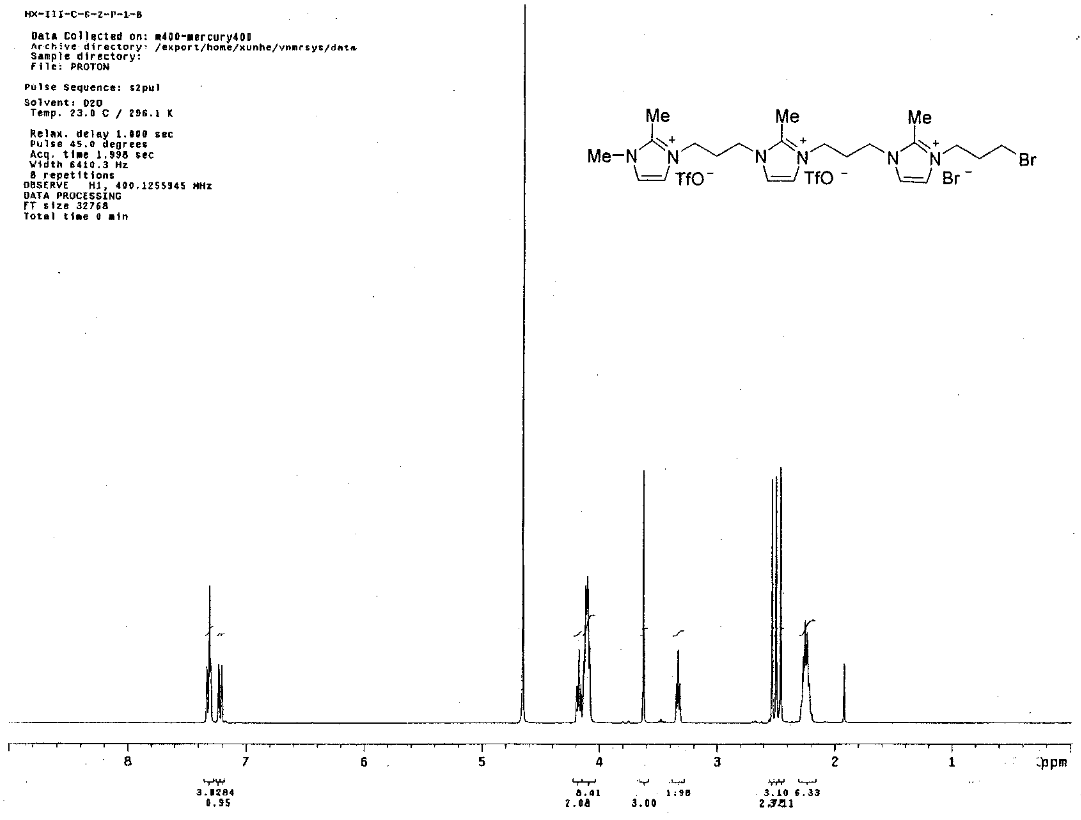


```
HX-III-C-5-8-P-1

Pulse Sequence: s2pul
 Solvent: D2O
 Ambient temperature
Mercury-300  "m300"

 Relax. delay 1.000 sec
 Pulse 58.9 degrees
 Acq. time 1.995 sec
 Width 4506.5 Hz
 16 repetitions
OBSERVE   H1, 300.0557611 MHz
DATA PROCESSING
FT size 32768
Total time 0 min, 49 sec
```

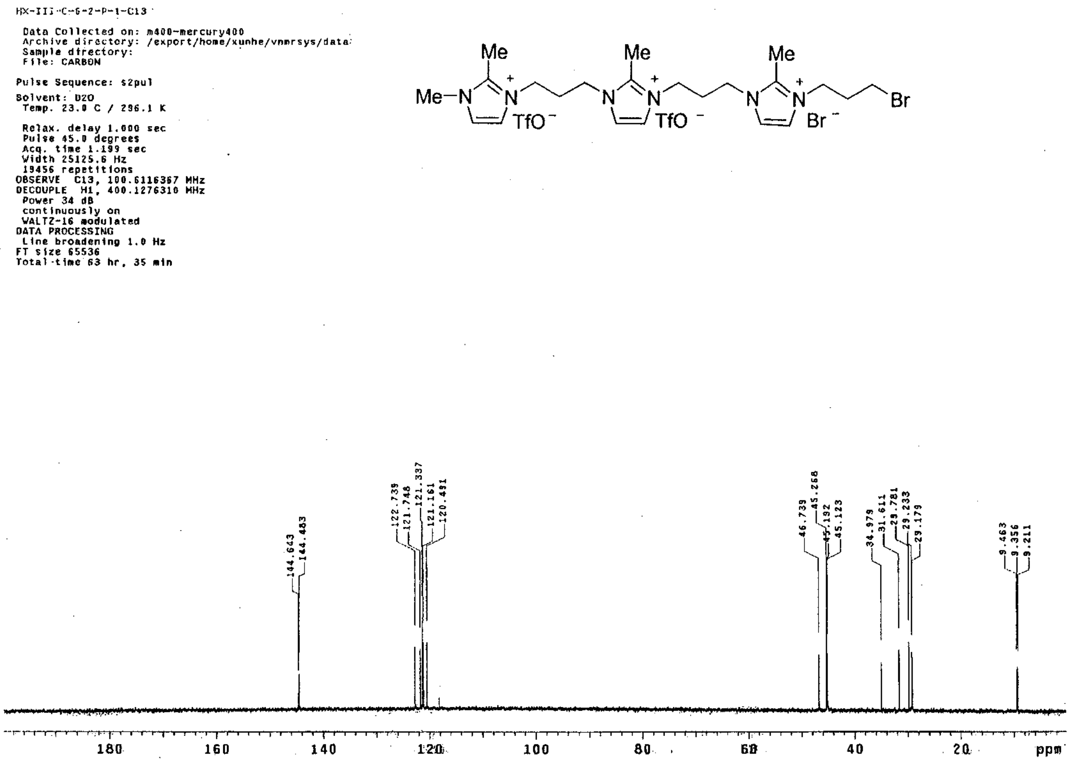


```
HX-III-C-6-4-P-1

 Data Collected on: m400-mercury400
 Archive directory: /export/home/xunhe/vnmrsys/data
 Sample directory:
 File: PROTON

Pulse Sequence: s2pul

Solvent: D2O

 Relax. delay 1.000 sec
 Pulse 45.0 degrees
 Acq. time 1.998 sec
 Width 6410.3 Hz
 8 repetitions
OBSERVE   H1, 400.1255945 MHz
DATA PROCESSING
FT size 32768
Total time 0 min
```

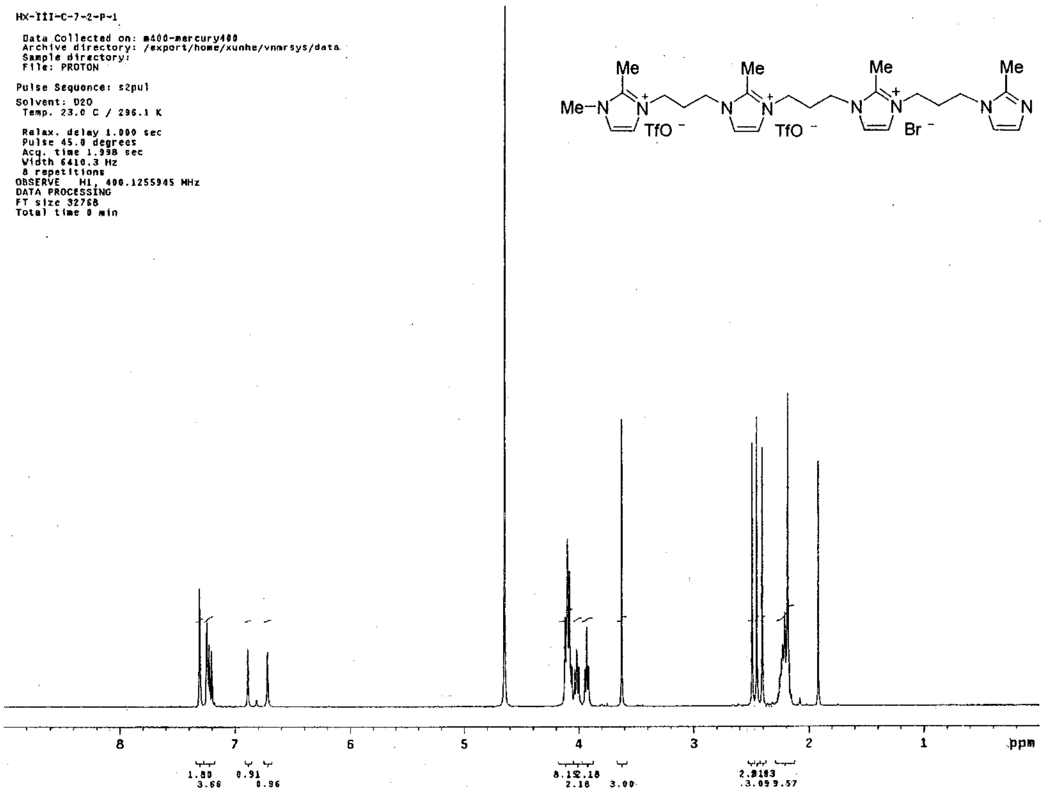




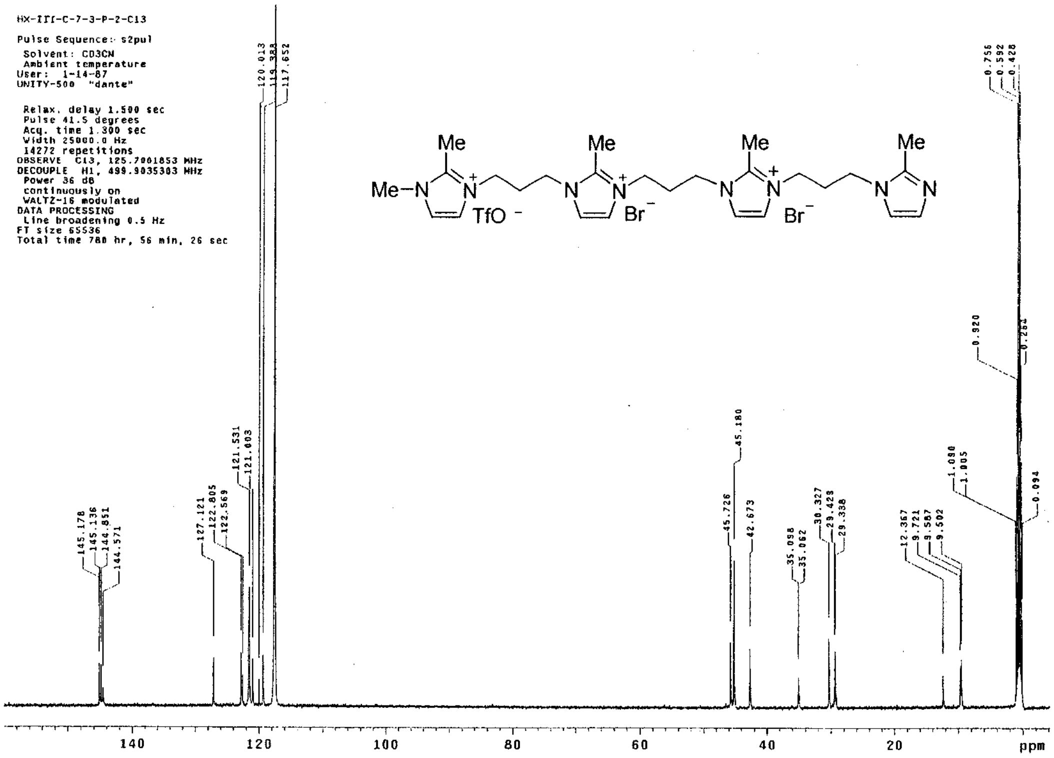
```
HX-III-C-6-2-P-1-B

 Data Collected on: m400-mercury400
 Archive directory: /export/home/xunhe/vnmrsys/data
 Sample directory:
 File: PROTON

Pulse Sequence: s2pul

Solvent: D2O
 Temp. 23.0 C / 296.1 K

 Relax. delay 1.000 sec
 Pulse 45.0 degrees
 Acq. time 1.998 sec
 Width 6410.3 Hz
 8 repetitions
OBSERVE   H1, 400.1255945 MHz
DATA PROCESSING
FT size 32768
Total time 0 min
```



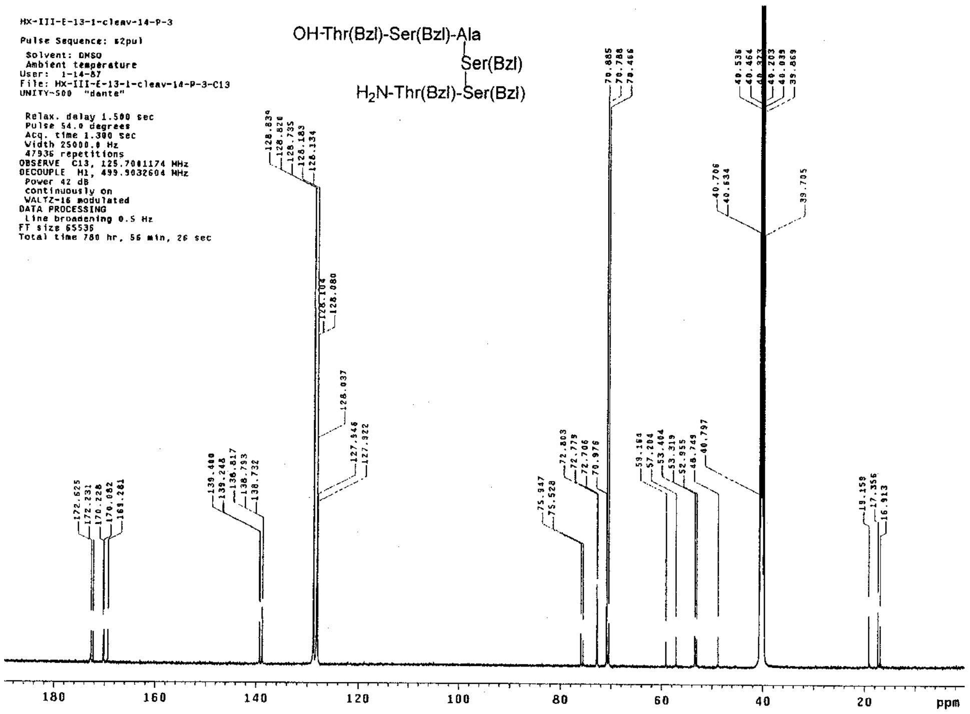
```
HX-III-C-6-2-P-1-C13

 Data Collected on: m400-mercury400
 Archive directory: /export/home/xunhe/vnmrsys/data
 Sample directory:
 File: CARBON

Pulse Sequence: s2pul

Solvent: D2O
 Temp. 23.0 C / 296.1 K

 Relax. delay 1.000 sec
 Pulse 45.0 degrees
 Acq. time 1.199 sec
 Width 25125.6 Hz
 19456 repetitions
OBSERVE  C13, 100.6116367 MHz
DECOUPLE  H1, 400.1276310 MHz
 Power 34 dB
 continuously on
 WALTZ-16 modulated
DATA PROCESSING
 Line broadening 1.0 Hz
FT size 65536
Total time 63 hr, 35 min
```



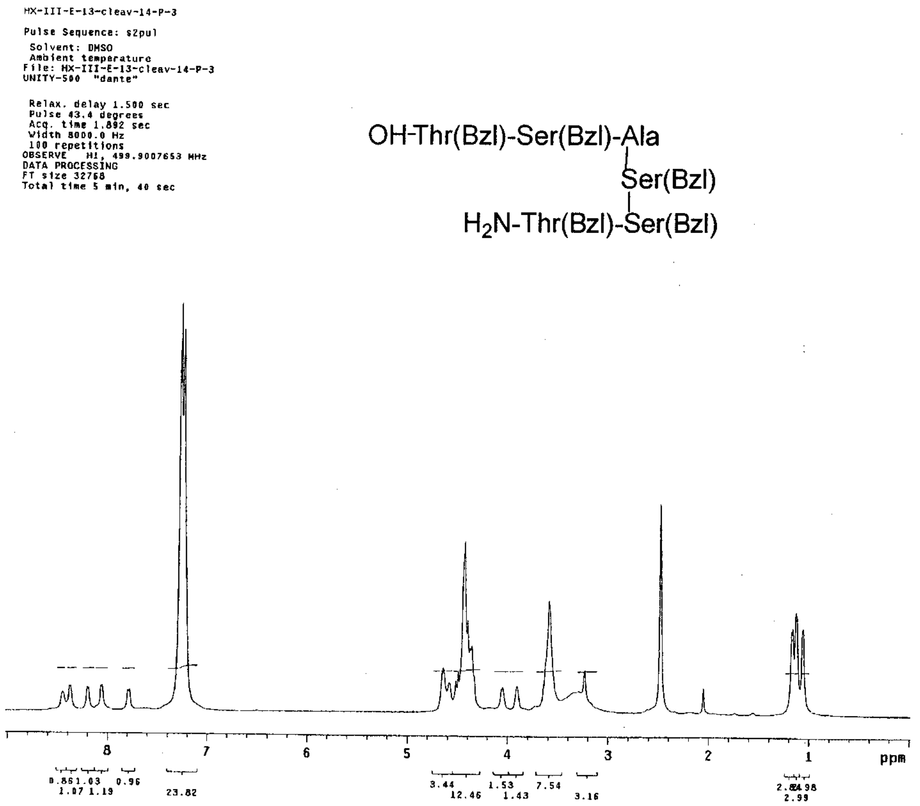
```
HX-III-C-7-2-P-1

 Data Collected on: m400-mercury400
 Archive directory: /export/home/xunhe/vnmrsys/data
 Sample directory:
 File: PROTON

Pulse Sequence: s2pul

Solvent: D2O
 Temp. 23.0 C / 296.1 K

 Relax. delay 1.000 sec
 Pulse 45.0 degrees
 Acq. time 1.998 sec
 Width 6410.3 Hz
 8 repetitions
OBSERVE   H1, 400.1255945 MHz
DATA PROCESSING
FT size 32768
Total time 0 min
```



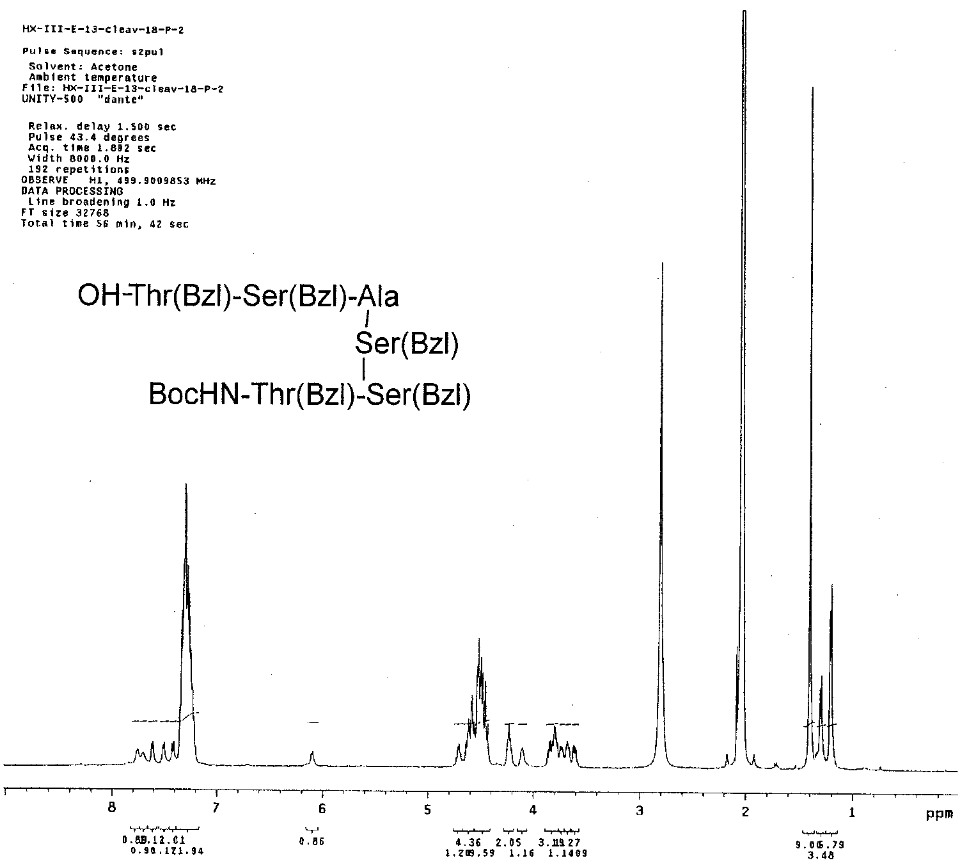
```
HX-III-C-7-3-P-2-C13

Pulse Sequence: s2pul
 Solvent: CD3CN
 Ambient temperature
User:  1-14-87
UNITY-500  "dante"

 Relax. delay 1.500 sec
 Pulse 41.5 degrees
 Acq. time 1.300 sec
 Width 25000.0 Hz
 14272 repetitions
OBSERVE  C13, 125.7001853 MHz
DECOUPLE  H1, 499.9035303 MHz
 Power 36 dB
 continuously on
 WALTZ-16 modulated
DATA PROCESSING
 Line broadening 0.5 Hz
FT size 65536
Total time 780 hr, 56 min, 26 sec
```

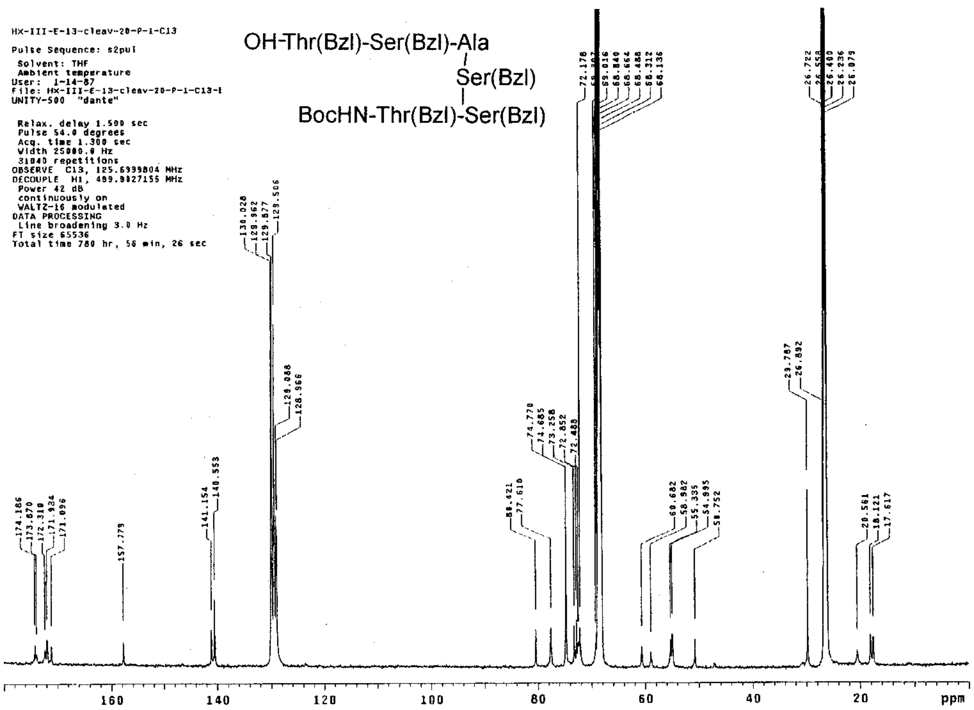


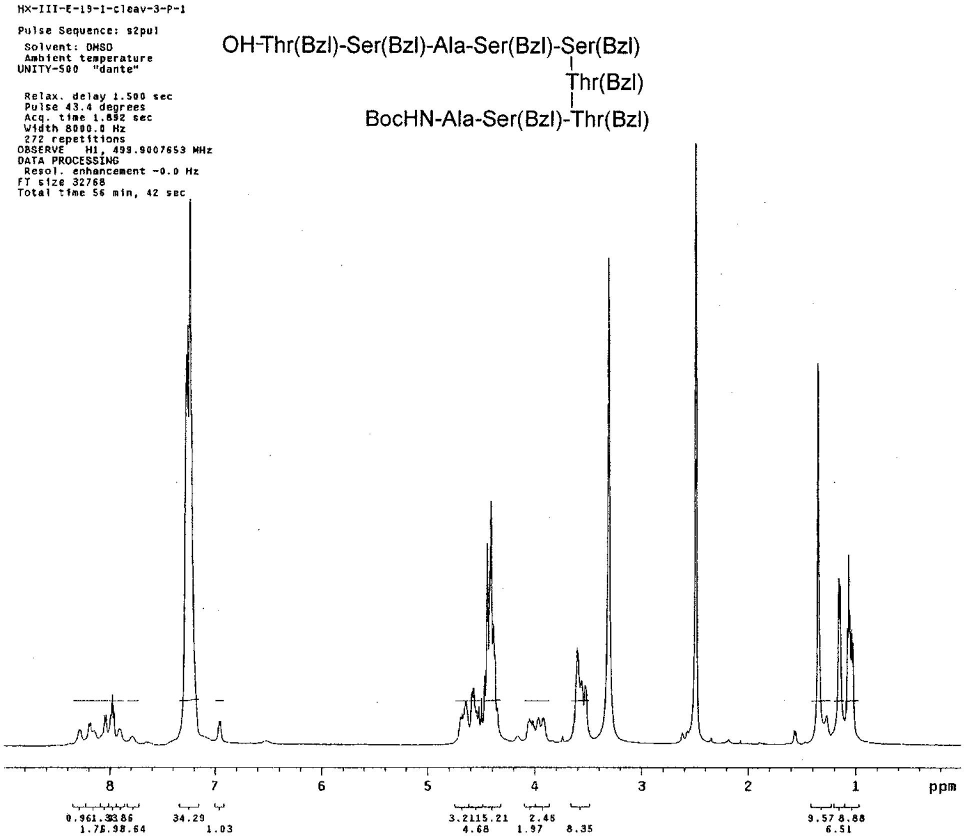
```
HX-III-E-13-1-cleav-14-P-3

Pulse Sequence: s2pul
 Solvent: DMSO
 Ambient temperature
User:  1-14-87
File: HX-III-E-13-1-cleav-14-P-3-C13
UNITY-500  "dante"

 Relax. delay 1.500 sec
 Pulse 54.0 degrees
 Acq. time 1.300 sec
 Width 25000.0 Hz
 47936 repetitions
OBSERVE  C13, 125.7001174 MHz
DECOUPLE  H1, 499.9032604 MHz
 Power 42 dB
 continuously on
 WALTZ-16 modulated
DATA PROCESSING
 Line broadening 0.5 Hz
FT size 65536
Total time 780 hr, 56 min, 26 sec
```



```
HX-III-E-13-cleav-14-P-3

Pulse Sequence: s2pul
 Solvent: DMSO
 Ambient temperature
File: HX-III-E-13-cleav-14-P-3
UNITY-500  "dante"

 Relax. delay 1.500 sec
 Pulse 43.4 degrees
 Acq. time 1.892 sec
 Width 8000.0 Hz
 100 repetitions
OBSERVE   H1, 499.9007653 MHz
DATA PROCESSING
FT size 32768
Total time 5 min, 40 sec
```

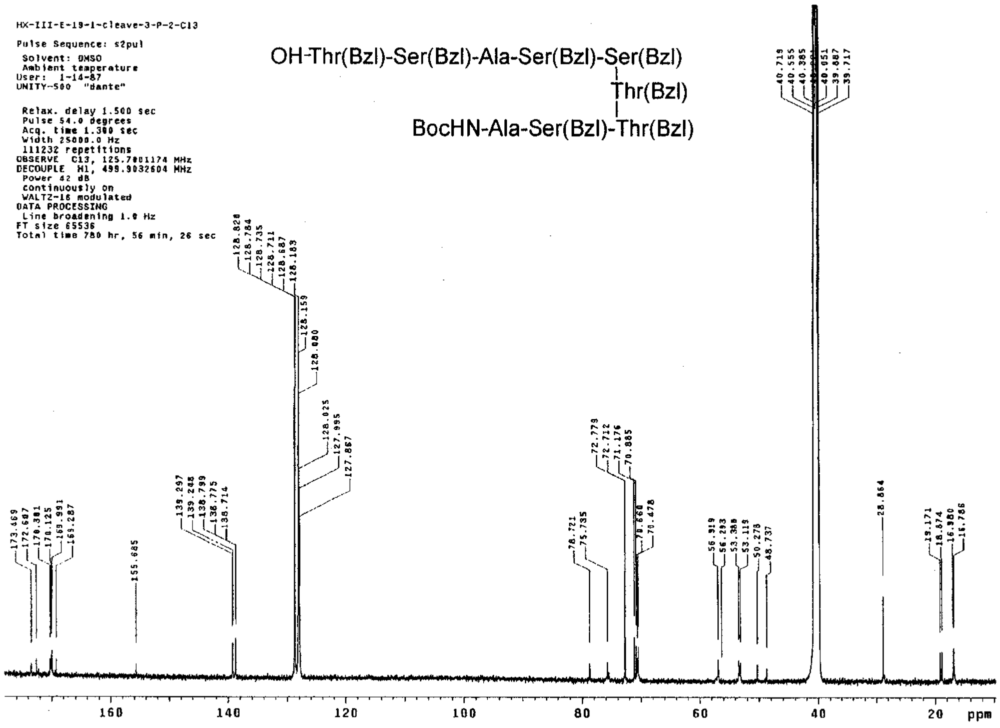

HX-III-E-13-cleav-18-P-2
Pulse Sequence: s2pul
Solvent: Acetone
Ambient temperature
File: HX-III-E-13-cleav-18-P-2
UNITY-500 "dante"
Relax. delay 1.500 sec
Pulse 43.4 degrees
Acq. time 1.892 sec
Width 8000.0 Hz
192 repetitions
OBSERVE H1, 499.9009853 MHz
DATA PROCESSING
Line broadening 1.0 Hz
FT size 32768
Total time 56 min, 42 sec
OH-Thr(Bzl)-Ser(Bzl)-Ala
Ser(Bzl)
BocHN-Thr(Bzl)-Ser(Bzl)
8
7
6
5
4
3
2
1
ppm
0.88.12.01
0.90.121.94
0.86
4.36
1.209.59
2.05
1.16
3.119.27
1.1409
9.06.79
3.48


HX-III-E-13-cleav-20-P-1-C13
Pulse Sequence: s2pul
Solvent: THF
Ambient temperature
User: 1-14-87
File: HX-III-E-13-cleav-20-P-1-C13-1
UNITY-500 "dante"
Relax. delay 1.500 sec
Pulse 54.0 degrees
Acq. time 1.300 sec
Width 25000.0 Hz
31040 repetitions
OBSERVE C13, 125.6999804 MHz
DECOUPLE H1, 499.9027155 MHz
Power 42 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 3.0 Hz
FT size 65536
Total time 780 hr, 56 min, 26 sec
OH-Thr(Bzl)-Ser(Bzl)-Ala
Ser(Bzl)
BocHN-Thr(Bzl)-Ser(Bzl)
174.186
173.670
172.310
171.934
171.096
157.779
141.154
140.553
130.028
129.962
129.877
129.506
129.088
128.966
80.421
77.610
74.770
74.685
73.258
72.852
72.488
72.176
69.016
68.840
68.664
68.488
68.312
68.136
60.682
58.982
55.335
54.995
50.752
29.787
26.892
26.722
26.558
26.400
26.236
26.079
20.561
18.121
17.617
160
140
120
100
80
60
40
20
ppm



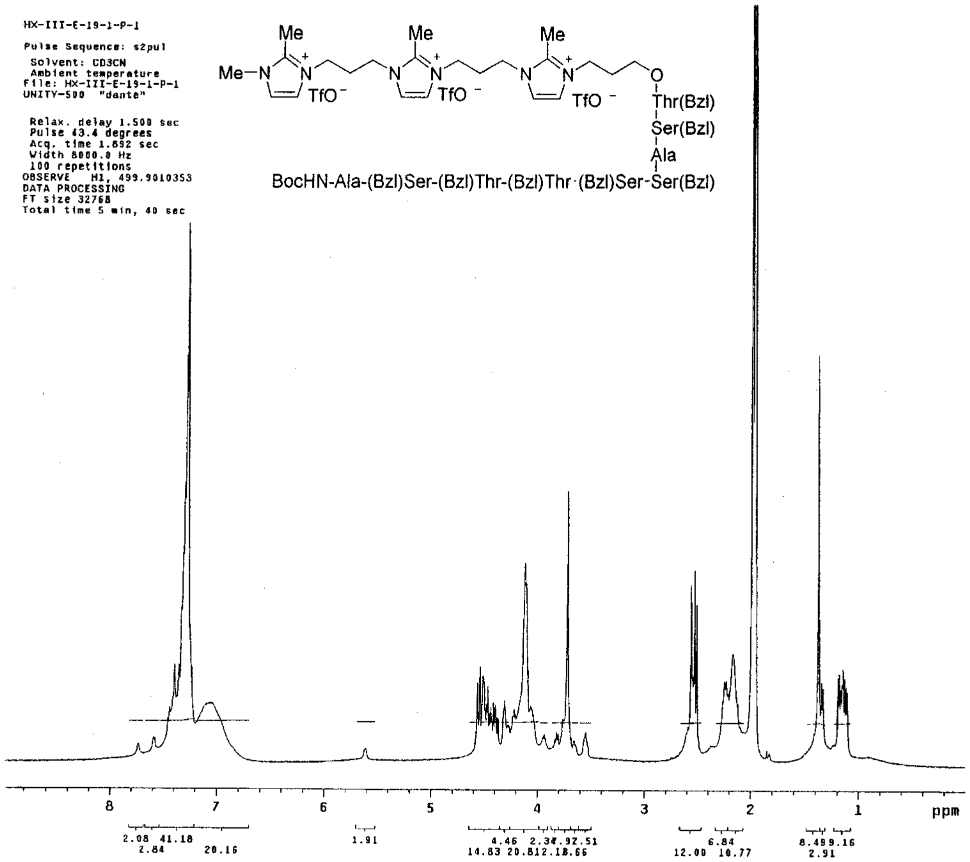
```
HX-III-E-19-1-cleav-3-P-1

Pulse Sequence: s2pul
 Solvent: DMSO
 Ambient temperature
UNITY-500  "dante"

 Relax. delay 1.500 sec
 Pulse 43.4 degrees
 Acq. time 1.892 sec
 Width 8000.0 Hz
 272 repetitions
OBSERVE   H1, 499.9007653 MHz
DATA PROCESSING
 Resol. enhancement -0.0 Hz
FT size 32768
Total time 56 min, 42 sec
```

OH-Thr(Bzl)-Ser(Bzl)-Ala-Ser(Bzl)-Ser(Bzl)
Thr(Bzl)
BocHN-Ala-Ser(Bzl)-Thr(Bzl)

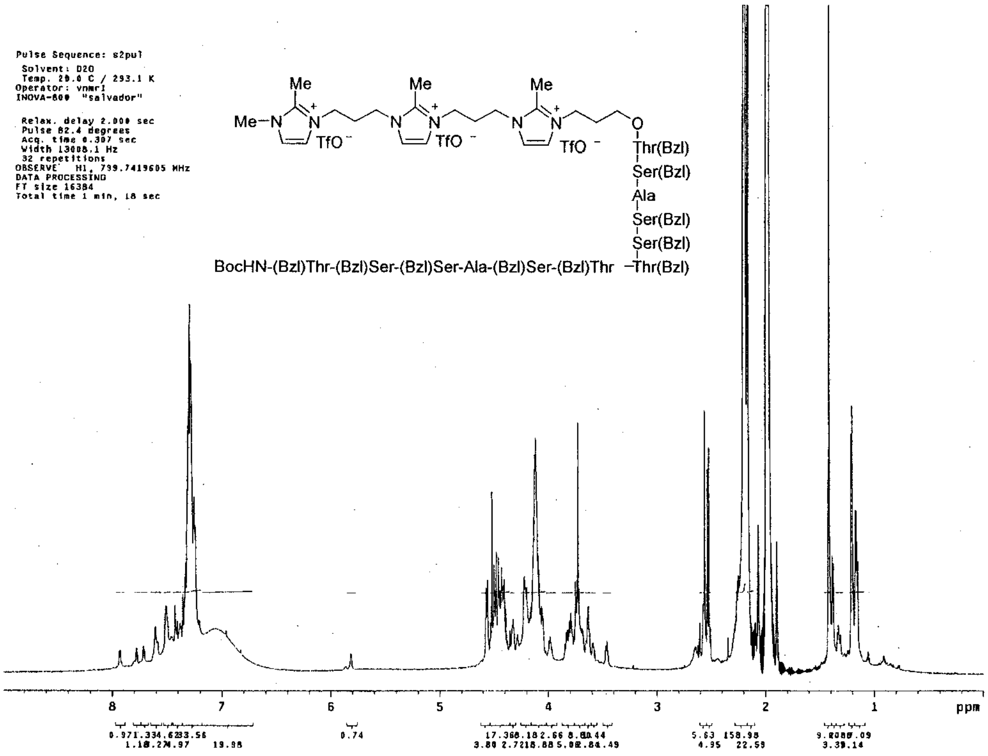


```
HX-III-E-19-1-cleave-3-P-2-C13

Pulse Sequence: s2pul
 Solvent: DMSO
 Ambient temperature
User:  1-14-87
UNITY-500  "dante"

 Relax. delay 1.500 sec
 Pulse 54.0 degrees
 Acq. time 1.300 sec
 Width 25000.0 Hz
 111232 repetitions
OBSERVE  C13, 125.7001174 MHz
DECOUPLE  H1, 499.9032604 MHz
 Power 42 dB
 continuously on
 WALTZ-16 modulated
DATA PROCESSING
 Line broadening 1.0 Hz
FT size 65536
Total time 780 hr, 56 min, 26 sec
```

OH-Thr(Bzl)-Ser(Bzl)-Ala-Ser(Bzl)-Ser(Bzl)
Thr(Bzl)
BocHN-Ala-Ser(Bzl)-Thr(Bzl)

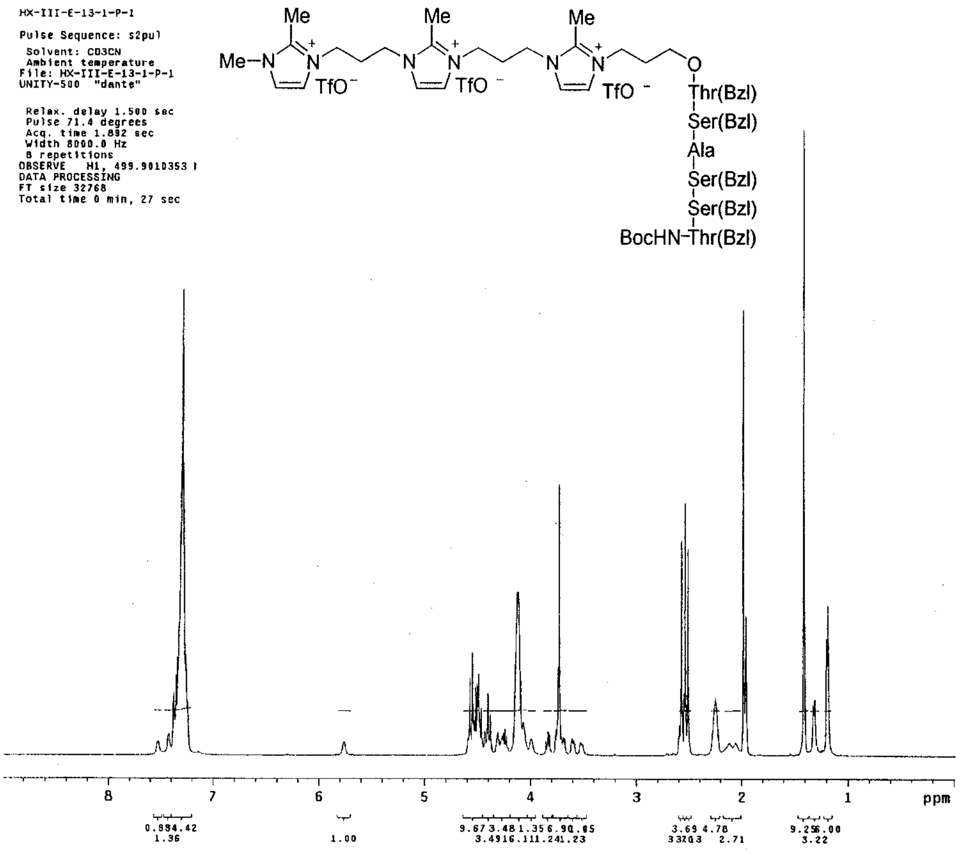


```
HX-III-E-19-1-P-1

Pulse Sequence: s2pul
 Solvent: CD3CN
 Ambient temperature
File: HX-III-E-19-1-P-1
UNITY-500  "dante"

 Relax. delay 1.500 sec
 Pulse 43.4 degrees
 Acq. time 1.892 sec
 Width 8000.0 Hz
 100 repetitions
OBSERVE   H1, 499.9010353
DATA PROCESSING
FT size 32768
Total time 5 min, 40 sec
```

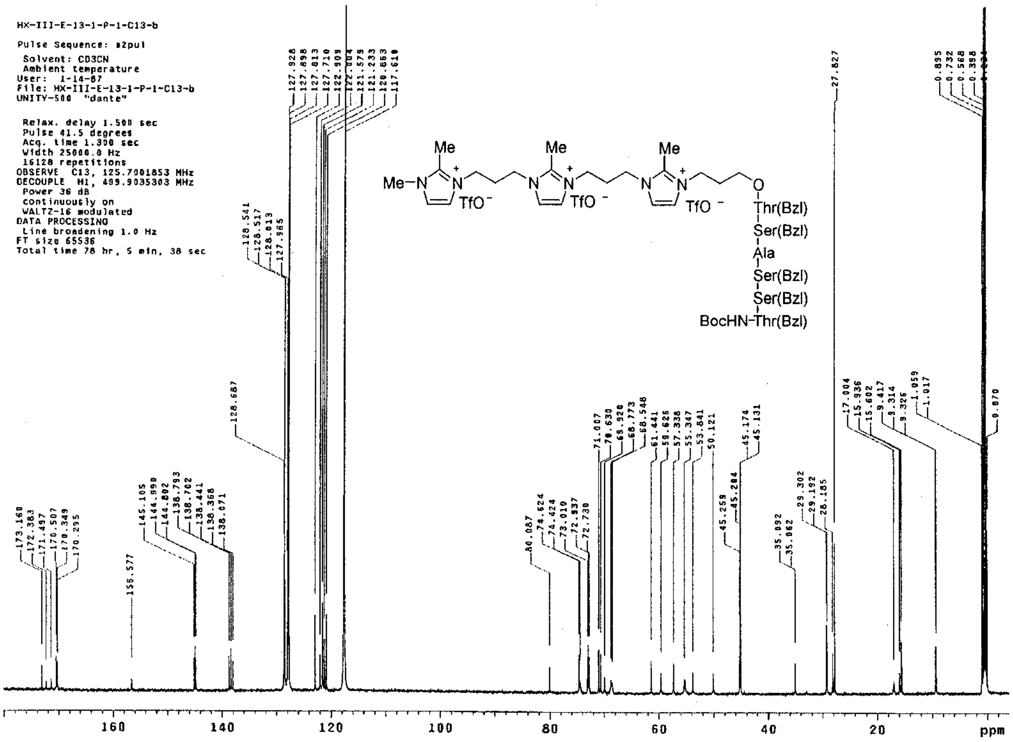


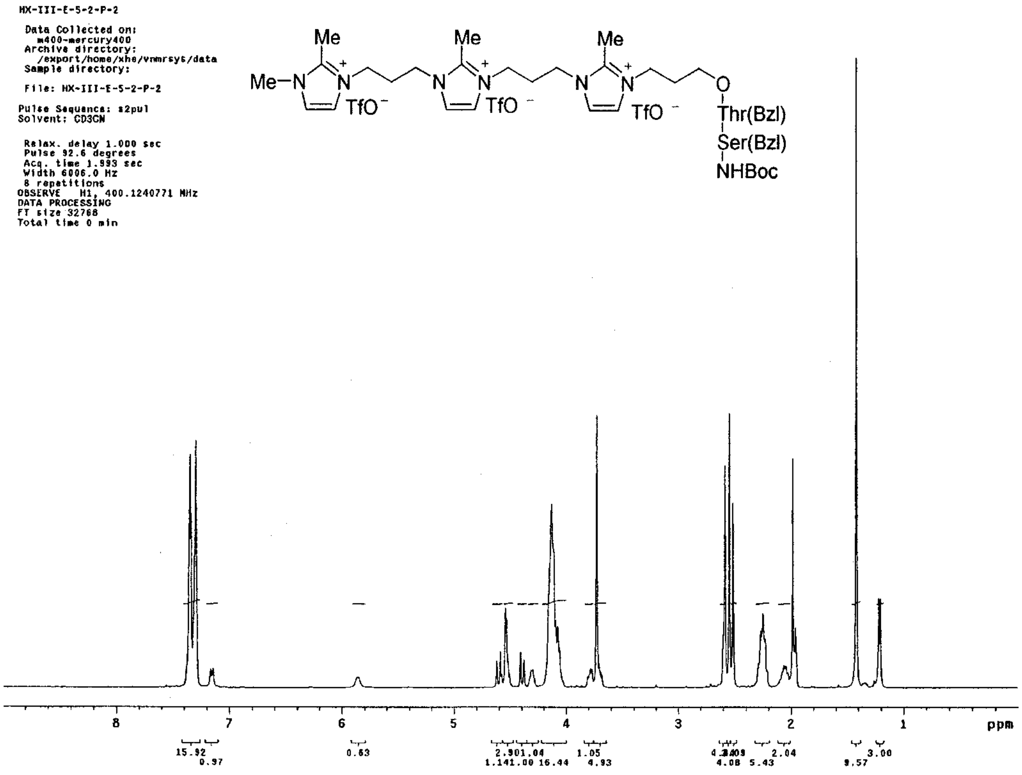
```
Pulse Sequence: s2pul
 Solvent: D2O
 Temp. 20.0 C / 293.1 K
Operator: vnmr1
INOVA-800  "salvador"

 Relax. delay 2.000 sec
 Pulse 82.4 degrees
 Acq. time 0.307 sec
 Width 13008.1 Hz
 32 repetitions
OBSERVE   H1, 799.7419605 MHz
DATA PROCESSING
FT size 16384
Total time 1 min, 18 sec
```

```
HX-III-E-13-1-P-1

Pulse Sequence: s2pul
 Solvent: CD3CN
 Ambient temperature
File: HX-III-E-13-1-P-1
UNITY-500  "dante"

 Relax. delay 1.500 sec
 Pulse 71.4 degrees
 Acq. time 1.892 sec
 Width 8000.0 Hz
 8 repetitions
OBSERVE   H1, 499.9010353 
DATA PROCESSING
FT size 32768
Total time 0 min, 27 sec
```

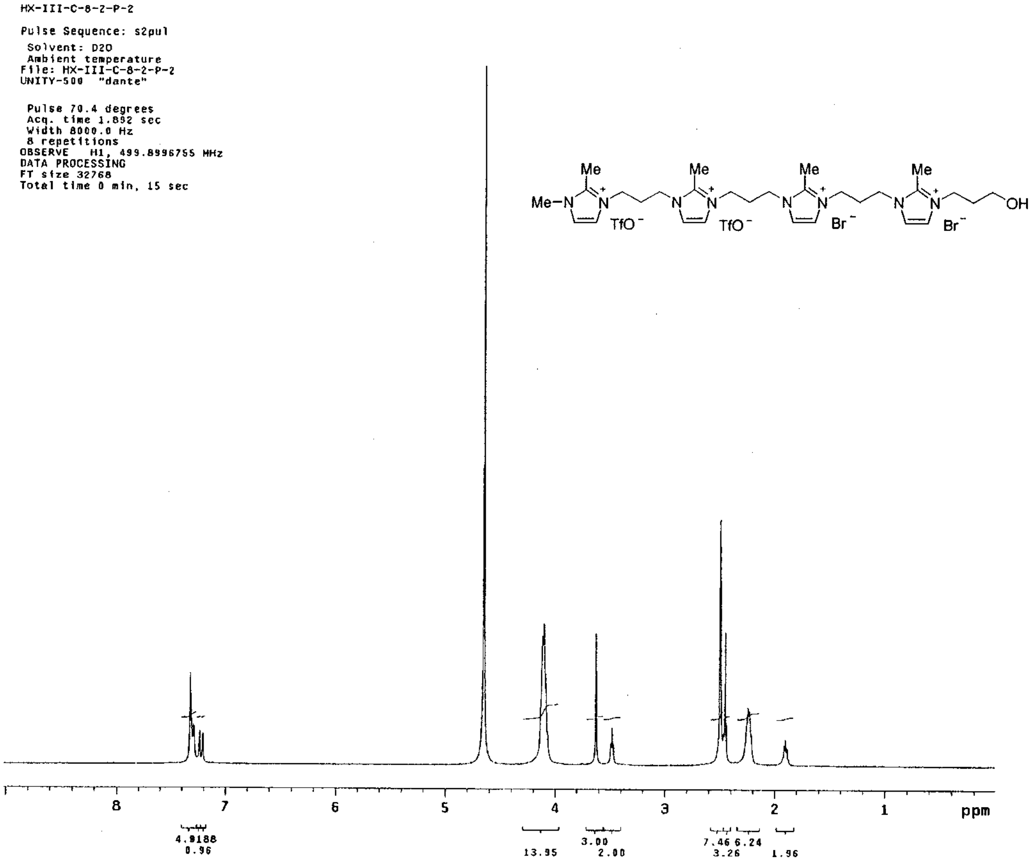


```
HX-III-E-13-1-P-1-C13-b

Pulse Sequence: s2pul
 Solvent: CD3CN
 Ambient temperature
User:  1-14-87
File: HX-III-E-13-1-P-1-C13-b
UNITY-500  "dante"

 Relax. delay 1.500 sec
 Pulse 41.5 degrees
 Acq. time 1.300 sec
 Width 25000.0 Hz
 16128 repetitions
OBSERVE  C13, 125.7001853 MHz
DECOUPLE  H1, 499.9035303 MHz
 Power 36 dB
 continuously on
 WALTZ-16 modulated
DATA PROCESSING
 Line broadening 1.0 Hz
FT size 65536
Total time 78 hr, 5 min, 38 sec
```

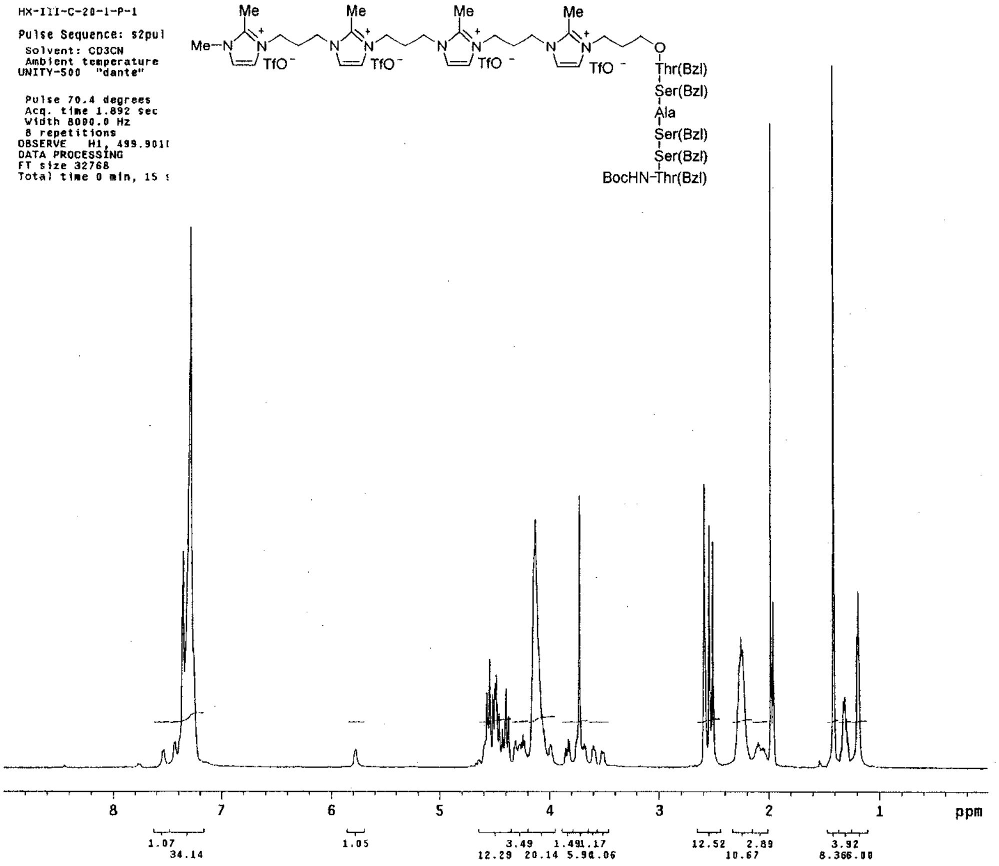




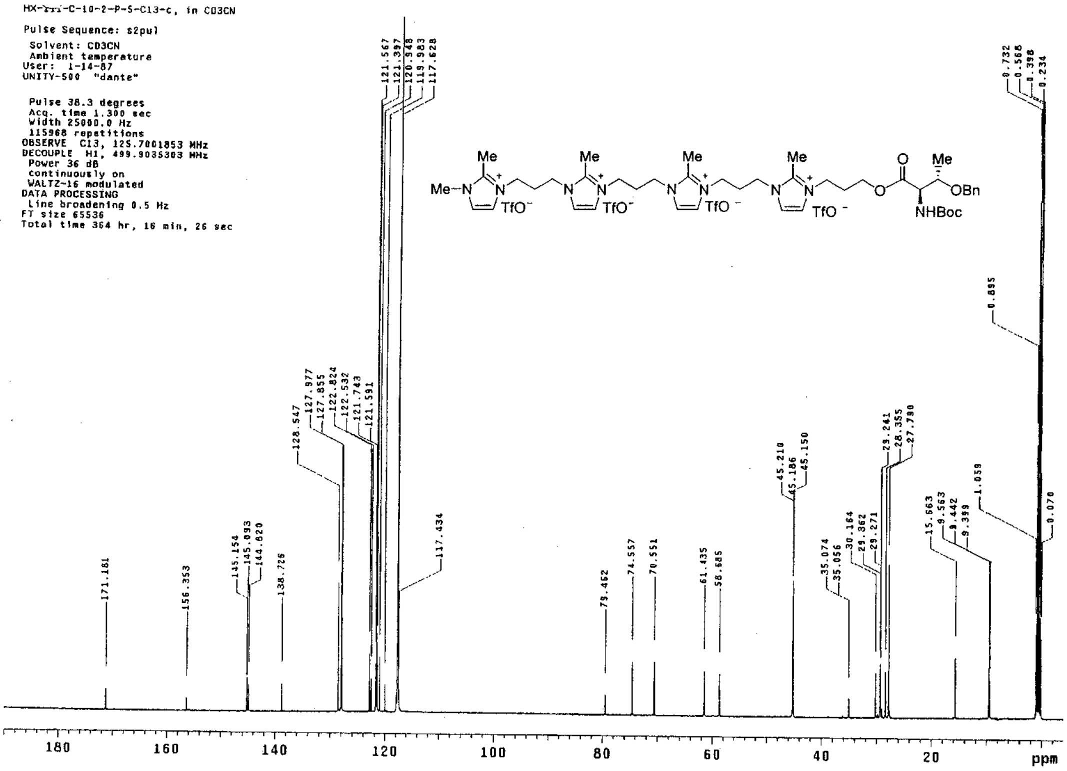
```
HX-III-E-5-2-P-2

 Data Collected on:
   m400-mercury400
 Archive directory:
   /export/home/xhe/vnmrsys/data
 Sample directory:

 File: HX-III-E-5-2-P-2

Pulse Sequence: s2pul
Solvent: CD3CN

 Relax. delay 1.000 sec
 Pulse 92.6 degrees
 Acq. time 1.993 sec
 Width 6006.0 Hz
 8 repetitions
OBSERVE   H1, 400.1240771 MHz
DATA PROCESSING
FT size 32768
Total time 0 min
```



```
HX-III-C-8-2-P-2

Pulse Sequence: s2pul
 Solvent: D2O
 Ambient temperature
File: HX-III-C-8-2-P-2
UNITY-500  "dante"

 Pulse 70.4 degrees
 Acq. time 1.892 sec
 Width 8000.0 Hz
 8 repetitions
OBSERVE   H1, 499.8996755 MHz
DATA PROCESSING
FT size 32768
Total time 0 min, 15 sec
```

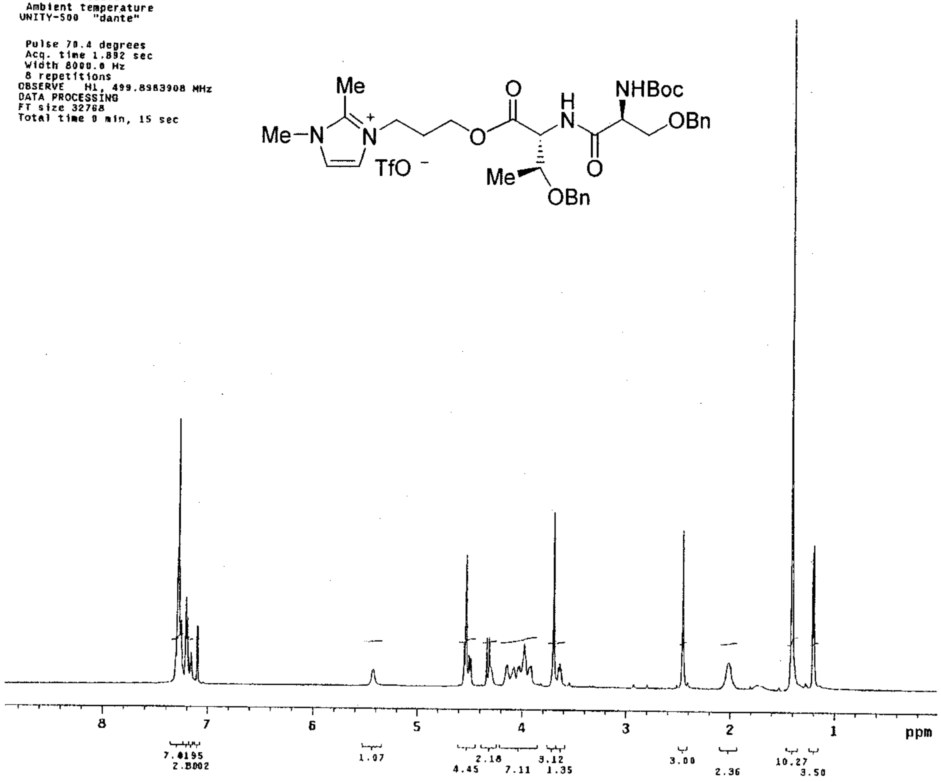


```
HX-III-C-20-1-P-1

Pulse Sequence: s2pul
 Solvent: CD3CN
 Ambient temperature
UNITY-500  "dante"

 Pulse 70.4 degrees
 Acq. time 1.892 sec
 Width 8000.0 Hz
 8 repetitions
OBSERVE   H1, 499.901
DATA PROCESSING
FT size 32768
Total time 0 min, 15
```

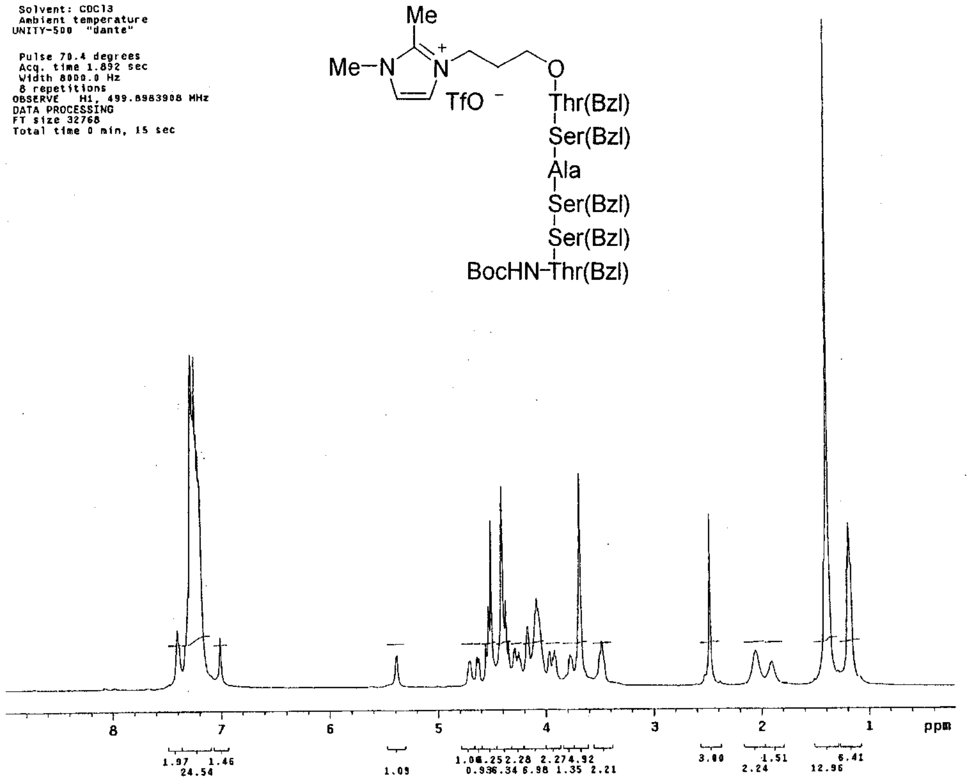


```
HX-III-C-10-2-P-5-C13-c, in CD3CN

Pulse Sequence: s2pul
 Solvent: CD3CN
 Ambient temperature
User:  1-14-87
UNITY-500  "dante"

 Pulse 38.3 degrees
 Acq. time 1.300 sec
 Width 25000.0 Hz
 115968 repetitions
OBSERVE  C13, 125.7001853 MHz
DECOUPLE  H1, 499.9035303 MHz
 Power 36 dB
 continuously on
 WALTZ-16 modulated
DATA PROCESSING
 Line broadening 0.5 Hz
FT size 65536
Total time 364 hr, 18 min, 26 sec
```

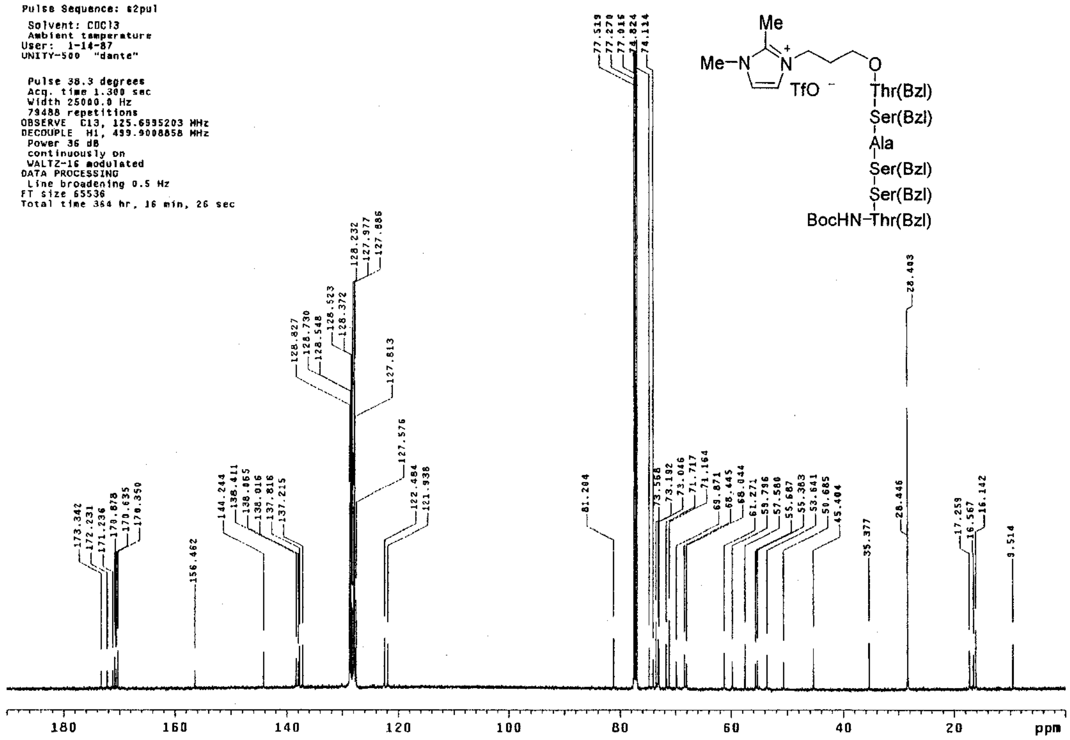
```
HX-III-A-6-4-P-2-b

Pulse Sequence: s2pul
 Solvent: CDCl3
 Ambient temperature
UNITY-500  "dante"

 Pulse 70.4 degrees
 Acq. time 1.892 sec
 Width 8000.0 Hz
 8 repetitions
OBSERVE   H1, 499.8983908 MHz
DATA PROCESSING
FT size 32768
Total time 0 min, 15 sec
```



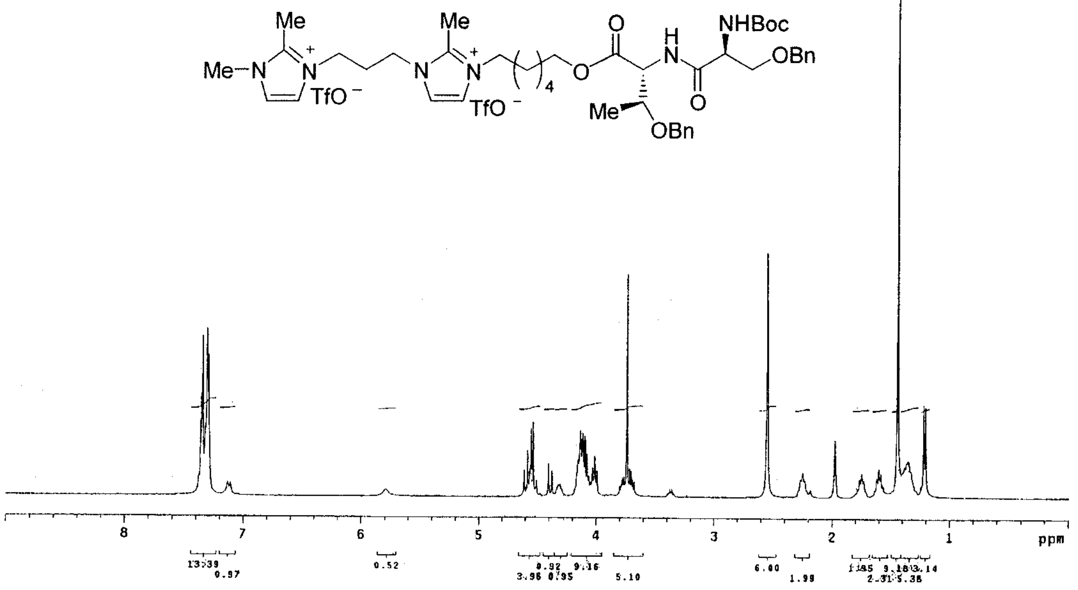
```
HX-III-A-14-1-P-2

Pulse Sequence: s2pul
 Solvent: CDCl3
 Ambient temperature
UNITY-500  "dante"

 Pulse 70.4 degrees
 Acq. time 1.892 sec
 Width 8000.0 Hz
 8 repetitions
OBSERVE   H1, 499.8983908 MHz
DATA PROCESSING
FT size 32768
Total time 0 min, 15 sec
```

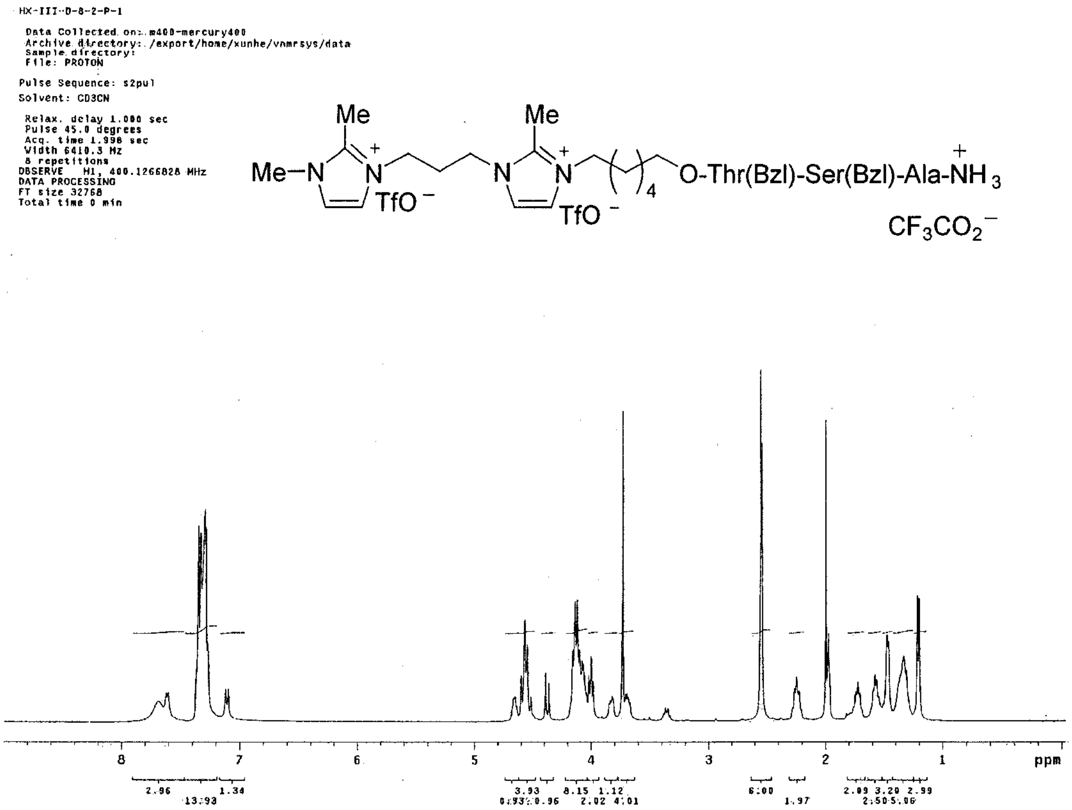


```
HX-III-A-14-1-P-3-C13

Pulse Sequence: s2pul

 Solvent: CDCl3
 Ambient temperature
User:  1-14-87
UNITY-500  "dante"

 Pulse 38.3 degrees
 Acq. time 1.300 sec
 Width 25000.0 Hz
 79488 repetitions
OBSERVE  C13, 125.6995203 MHz
DECOUPLE  H1, 499.9008858 MHz
 Power 36 dB
 continuously on
 WALTZ-16 modulated
DATA PROCESSING
 Line broadening 0.5 Hz
FT size 65536
Total time 364 hr, 16 min, 26 sec
```

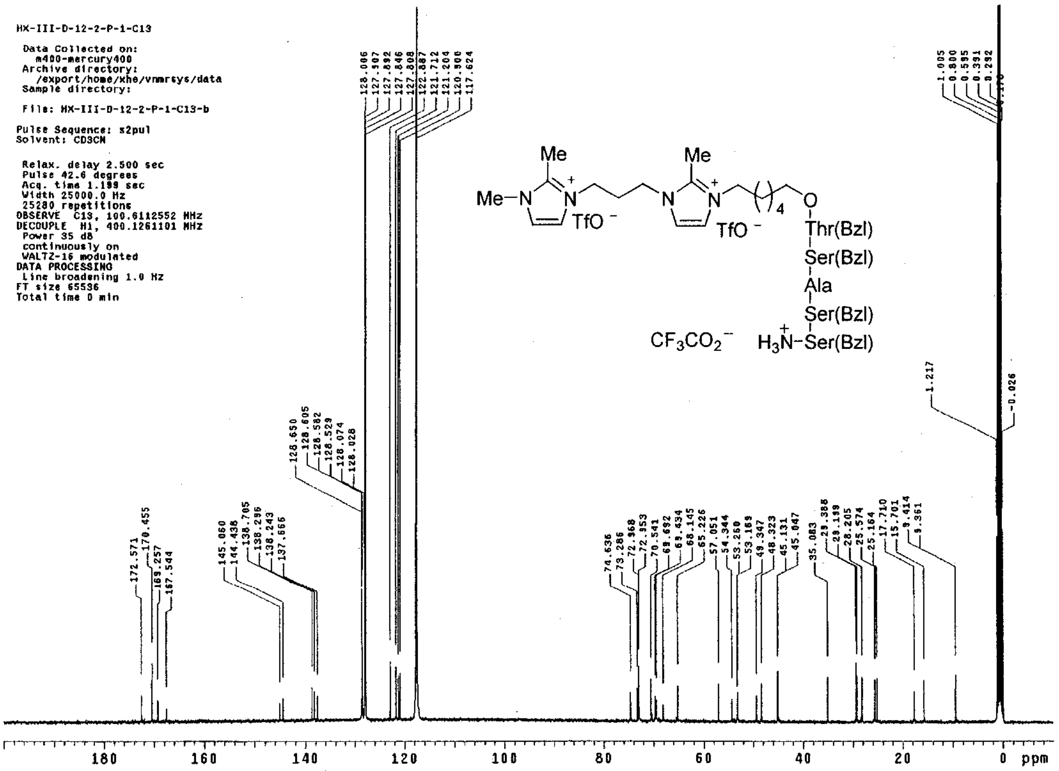


```
HX-III-D-5-1-P-6

 Data Collected on: m400-mercury400
 Archive directory: /export/home/xunhe/vnmrsys/data
 Sample directory:
 File: PROTON

Pulse Sequence: s2pul

Solvent: CD3CN
 Temp. 25.0 C / 298.1 K

 Relax. delay 1.000 sec
 Pulse 45.0 degrees
 Acq. time 1.998 sec
 Width 6410.3 Hz
 8 repetitions
OBSERVE  H1, 400.1266828 MHz
DATA PROCESSING
FT size 32768
Total time 0 min
```

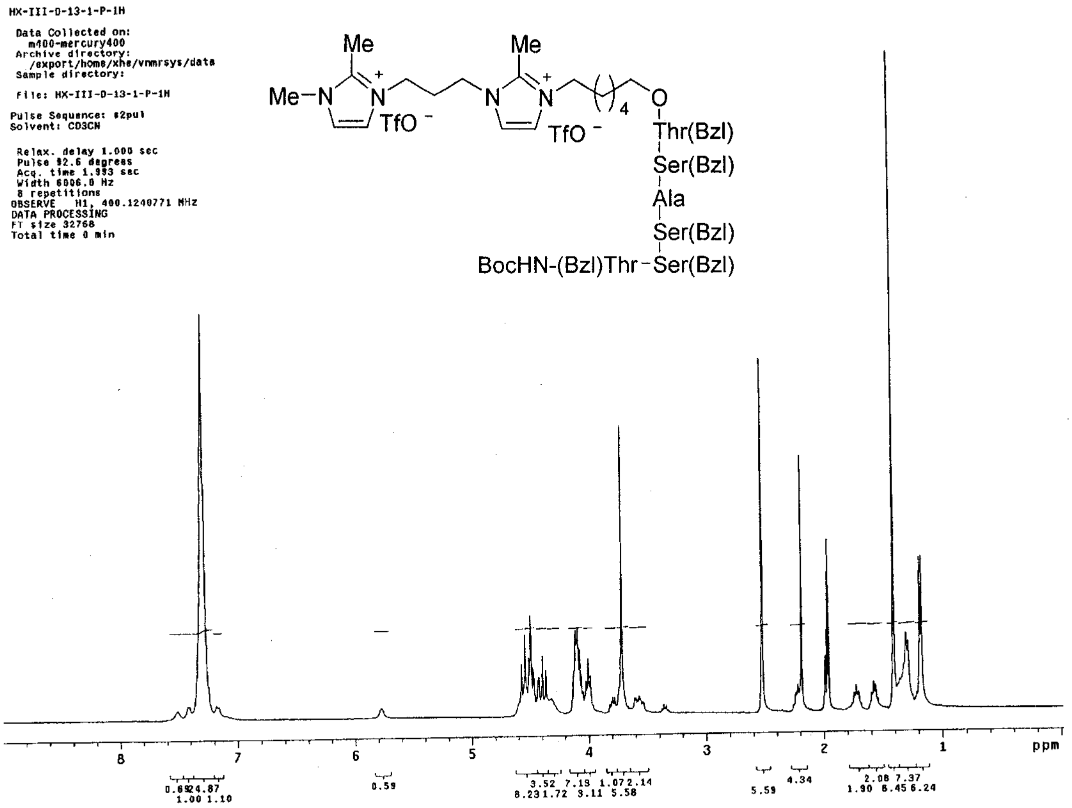




```
HX-III-D-8-2-P-1

 Data Collected on: m400-mercury400
 Archive directory: /export/home/xunhe/vnmrsys/data
 Sample directory:
 File: PROTON

Pulse Sequence: s2pul
Solvent: CD3CN

 Relax. delay 1.000 sec
 Pulse 45.0 degrees
 Acq. time 1.998 sec
 Width 6410.3 Hz
 8 repetitions
OBSERVE   H1, 400.1266828 MHz
DATA PROCESSING
FT size 32768
Total time 0 min
```



```
HX-III-D-12-2-P-1-C13

 Data Collected on:
   m400-mercury400
 Archive directory:
   /export/home/xhe/vnmrsys/data
 Sample directory:

 File: HX-III-D-12-2-P-1-C13-b

Pulse Sequence: s2pul
Solvent: CD3CN

 Relax. delay 2.500 sec
 Pulse 42.6 degrees
 Acq. time 1.199 sec
 Width 25000.0 Hz
 25280 repetitions
OBSERVE  C13, 100.6112552 MHz
DECOUPLE  H1, 400.1261101 MHz
 Power 35 dB
 continuously on
 WALTZ-16 modulated
DATA PROCESSING
 Line broadening 1.0 Hz
FT size 65536
Total time 0 min
```



```
HX-III-D-13-1-P-1H

 Data Collected on:
   m400-mercury400
 Archive directory:
   /export/home/xhe/vnmrsys/data
 Sample directory:

 File: HX-III-D-13-1-P-1H

Pulse Sequence: s2pul
Solvent: CD3CN

 Relax. delay 1.000 sec
 Pulse 92.6 degrees
 Acq. time 1.993 sec
 Width 6006.0 Hz
 8 repetitions
OBSERVE   H1, 400.1240771 MHz
DATA PROCESSING
FT size 32768
Total time 0 min
```