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Ionic-Liquid-Supported Synthesis: A Novel Liquid-Phase Strategy for Organic Synthesis

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ABSTRACT

Soluble ionic liquids have recently been used as supports for catalyst/reagent immobilization and synthesis in homogeneous solution phase. The wide range of ionic liquid supports available makes their use as supports compatible with most common chemistries. The solubility properties of these ionic liquid supports can be tuned by the variation of cations and anions to make them phase separate from less polar organic solvents and aqueous media. The ionic-liquid-supported species can therefore be purified from the reaction mixture by simple washings. Ionic-liquid-supported catalysts and reagents have been prepared and used, and they are easily recovered and reused. Parallel and combinatorial libraries of small molecules have been synthesized. Ionic-liquid-supported synthesis (ILSS) has been applied to the preparation of oligopeptides and oligosaccharides. The comparison of ILSS with solid-phase synthesis, soluble-polymer-supported synthesis, and fluorous phase synthesis has been highlighted where applicable.

Introduction

Organic synthesis using insoluble solid polymer resin as support was first proposed by Merrifield more than four decades ago[1] and has since been applied extensively in numerous areas.[2] Although highly successful and readily automated, solid-phase synthesis suffers a series of problems due to the heterogeneous reaction conditions. This has led to alternative "liquid phase" methodologies with the aim to restore homogeneous reaction conditions. Poly(ethylene glycol) (PEG) and other soluble polymers have been used as "soluble polymer supports" for the synthesis of bio-oligomers[3−5] and small molecules[6] and as scaffolds for recoverable catalysts and reagents.[7] Recently, the use of "fluorous phase" synthesis,[8] based on the concept that fluorinated compounds will preferentially dissolve in a fluorous solvent, has been advocated.[9,10] In this Account, the recently introduced concept of using ionic liquids (ILs) as soluble supports for organic synthesis will be discussed. Ionic liquids are organic salts with melting points below ambient or reaction temperature. They have attracted considerable interest as potentially environmentally benign reaction media due to their lack of measurable vapor pressure and high thermal and chemical stability.[11] An attractive feature of ionic liquids is that their solubilities, depending on the choice of cations and anions, can be tuned readily so that they can phase separate from organic as well as aqueous media. Substrate solubility can also be tuned.[12] This suggests the possibility of using these low molecular weight ionic liquids as soluble supports for organic synthesis. This novel liquid-phase strategy can embrace several possibilities: (a) supported catalysts, (b) supported reagents, and (c) supported substrates (Figure 1). In each case, the IL-supported species can be dissolved in a solvent (usually more polar), and the reaction can be conducted in a homogeneous solution. After the reaction, a less polar organic solvent is added in which the IL-supported species is not soluble, and the IL phase separates from the organic phase. The recovered IL-supported species can be regenerated (for reagent) or reused (for catalyst) or further reacted to give the final product, which would then be detached from the ionic

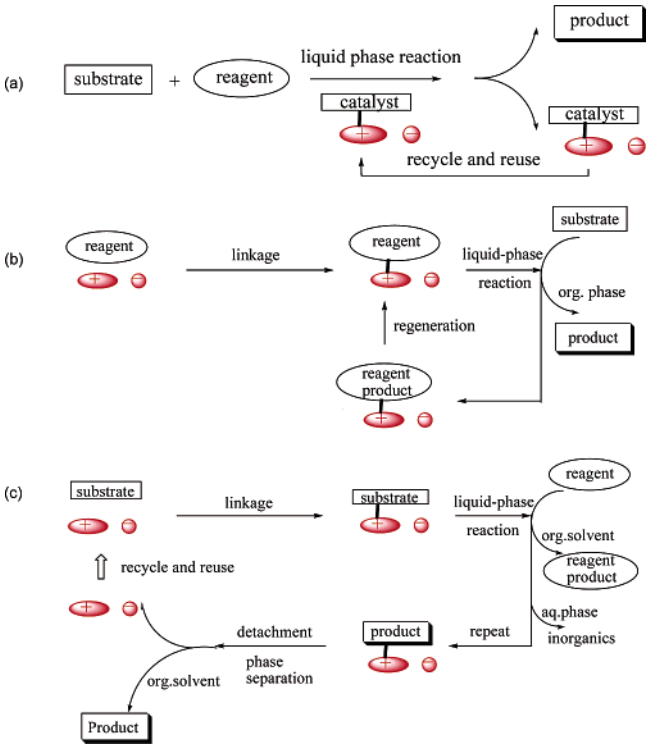

FIGURE 1. Ionic-liquid-supported synthesis: (a) catalyst; (b) reagent; (c) substrate.

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Tak Hang Chan obtained his B.A. (1962) from the University of Toronto (1962) and M.Sc. (1963) and Ph.D. (1966) from Princeton University (supervisor R. K. Hill). From 1965−1966, he was a postdoctoral fellow in R. B. Woodward's group at Harvard University. In 1966, he joined the Department of Chemistry, McGill University, where he is currently Professor Emeritus. He is concurrently the Distinguished Chair Professor of Organic Chemistry at the Hong Kong Polytechnic University. His research interests include organic synthesis, aqueous organometallic chemistry, ionic liquids, and medicinal chemistry. He is the recipient of the Merck Sharp and Dohme Award (1982) and the R. U. Lemieux Award (1993) of the Canadian Society of Chemistry and a Fellow of the Royal Society of Canada.

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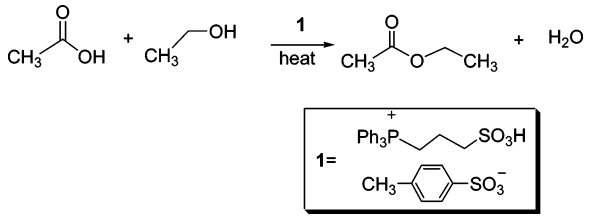
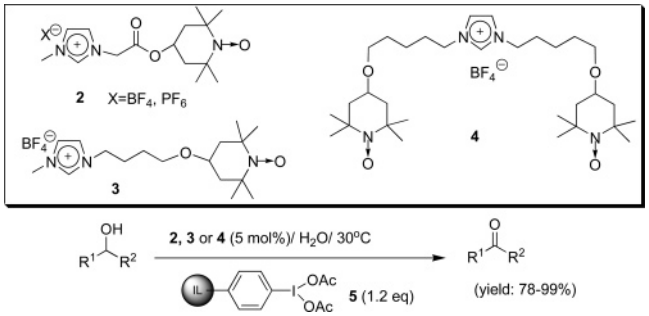
Scheme 1



Scheme 2



liquid support. This Account will summarize the recent advances in this emerging area.

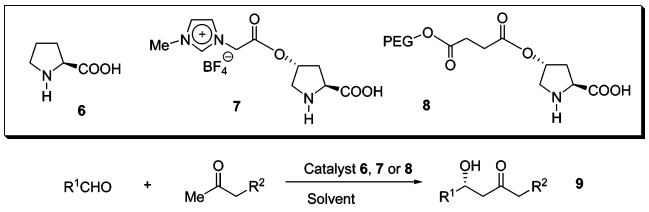
Ionic-Liquid-Supported Catalysis

Davis was the first to recognize that functionalized ionic liquids can serve not just as reaction media but as catalyst as well.[13,14] An example is the phosphonium salt **1**, which catalyzes the formation of esters from alcohols and acids (Scheme 1), dehydration of alcohols to ethers, and pinacol rearrangement of vicinal diols.[15] Compound **1** behaves as a strong Brønsted acid, but unlike small molecule strong acids, it does not fume due to its low vapor pressure. In the use of **1** to catalyze the formation of ethyl acetate, the product can be easily removed from the IL-supported catalyst **1** by simple distillation. The catalyst **1** can be recycled. Other ionic-liquid-supported sulfonic acids have been reported[16,17] for the esterification of aliphatic acids with olefin and hetero-Michael additions.

Gao[18] and Bao[19] independently reported on the IL-supported 2,2,6,6-tetramethyl-piperidinyloxy, free radical TEMPO catalysts **2**−**4** in the oxidation of alcohols (Scheme 2). All the catalysts showed similar activity to that of free TEMPO and could be reused up to five times without loss of catalytic activity. Bao also showed that the IL-supported hypervalent iodine **5** can be used as terminal oxidant together with the IL-supported TEMPO **2**−**4** to carry out the oxidation in aqueous media (Scheme 2).

One advantage of using an IL-supported catalyst is that the catalyst can be recovered simply by solubility difference as illustrated in Figure 1a. This is especially important in a case where the catalyst has to be used in quite substantial amounts, as in the (*S*)-proline (**6**)-catalyzed asymmetric aldol reaction where the catalyst is usually used at 30 mol %.[20] Furthermore, because of the low solubility of proline in less polar solvents, the reaction is usually carried out in dimethyl sulfoxide DMSO or dimethyl formamide DMF, making the purification even more tedious. We have recently prepared the IL-supported

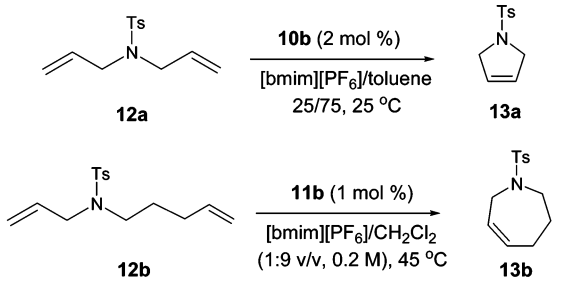
Scheme 3

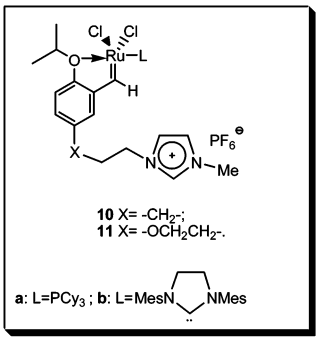


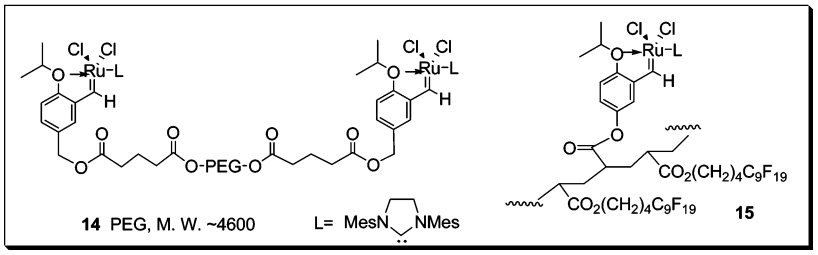
proline derivative **7** and found that it is an efficient catalyst for the asymmetric aldol reaction (Scheme 3).[21] It is instructive to compare the three catalysts **6**, **7**, and **8**, a soluble-polymer (PEG═MeO(CH$_2$CH$_2$O)$_n$CH$_2$CH$_2$, n = ca. 100) supported catalyst,[22] in the same reaction. An important advantage of using IL-supported catalyst **7** is that the use of DMSO as solvent can actually be avoided. The aldol reactions performed in pure ketone with **7** gave comparable or superior results to that obtained in DMSO. In contrast, for the reaction catalyzed by (*S*)-proline **6** (Scheme 3), the products from neat ketone have much lower enantiomeric excess (ee) values than that from DMSO.[21] For benzaldehyde, the difference in ee value was up to 28% ee. Using 4-nitrobenzaldehyde and acetone as the common reaction (Scheme 3, R^1 = 4-NO$_2$Ph−, R^2 = H), the soluble polymer-supported catalyst **8** was reported to give the aldol adduct **9** in DMSO in 36% yield (60% ee) in 20 h and in 73% yield (62% ee) in 48 h.[22] By comparison, the IL-supported catalyst **7** gave the same aldol adduct **9** in DMSO in 60% yield (87% ee) in 25 h. Also, when the same reaction was conducted in acetone, catalyst **8** was reported to give the aldol adduct **9** in 23% yield (21% ee) in 48 h whereas catalyst **7** gave the same adduct in 64% yield (85% ee) in 25 h. In terms of recyclability, the yield of the aldol adduct **9** changed from 68% (77% ee) to 51% (75% ee) in four cycles for catalyst **8**, whereas the yield of **9** changed from 68% (85% ee) to 64% (82% ee) in four cycles for catalyst **7**. Finally, catalyst **8** requires a PEG of M_w 5000 as support per catalytic moiety with a loading capacity of about 0.2 mmol/g, whereas the imidazolium moiety in **7** has a formal molecular weight of about 110 per catalytic moiety, thus a loading capacity of about 9 mmol/g. The lower molecular weight of **7** also allows for easier monitoring of the reaction mixture throughout with conventional spectroscopy such as ^{1}H NMR. The superior catalytic performance of **7** relative to **8** suggests that the ionic moiety in **7** plays more than a silent or simply supporting role in the reaction. It is possible that when the ketone forms an enamine intermediate with the catalyst **7**, as postulated for proline-catalyzed aldol reaction,[20] the enamine intermediate's reaction with the aldehyde may be facilitated by the proximity of the ionic moiety.

The efficient recycling of IL-supported catalysts suggests that the approach can be useful in metal-catalyzed reactions where the reuse of expensive ligands, metal, or both is critical. In 2003, Guillemine[23] and Yao[24] reported independently the synthesis of IL-supported catalysts **10** and **11** for the ring-closing metathesis (RCM) of olefins (Scheme 4). The IL tags in **10** or **11** were crucial to the recyclability of the catalysts since the unsupported cata-

Scheme 4





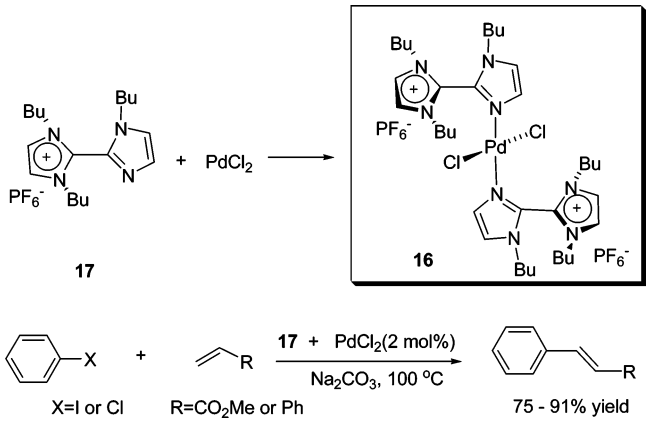


lysts rapidly lose their activity during the recycle experiments. In the RCM reactions of dienetosylamide **12a** or **12b**, the supported catalysts were recycled at least ten times with only a slight decrease in the yield (ranging from 90−98%) of **13** (Scheme 4). Only extremely low residual ruthenium levels, average of 7.3 ppm per run, were detected in the RCM products.[23b] Yao had also prepared the corresponding PEG-supported[25] and poly(fluoroalkyl acrylate)-supported[26] catalysts **14** and **15**. The three supported catalysts, **11b**, **14**, and **15**, show similar reactivities and recyclability with **15** slightly more stable. However, the recovery of **15** had to be carried out by fluorous extraction, and the loading capacity of **15** (0.19 mmol/g) was much lower than that of **11b**.

The IL-supported palladium complex **16** was found to catalyze the Heck reactions (Scheme 5) with good recyclability of up to 10 cycles.[27]

In some cases, the IL-supported catalyst may only perform marginally better than the unsupported catalyst. The catalytic asymmetric hydrogenations of *N*-acetylphenylethenamine (**18**) to **19** were compared, using the IL-grafted rhodium complex **20** or the unsupported catalyst **21** in the ionic liquid [bmim][SbF_6]/*i*-PrOH two-phase system (Scheme 6, bmim = 1-butyl-3-methylimidazolium).[28] While the activity of recovered **21** dropped from 100% conversion to 78% in the third cycle, and the activity of recovered **20** only dropped in the fourth cycle to 82%, the greater synthetic difficulty of obtaining **20** relative to

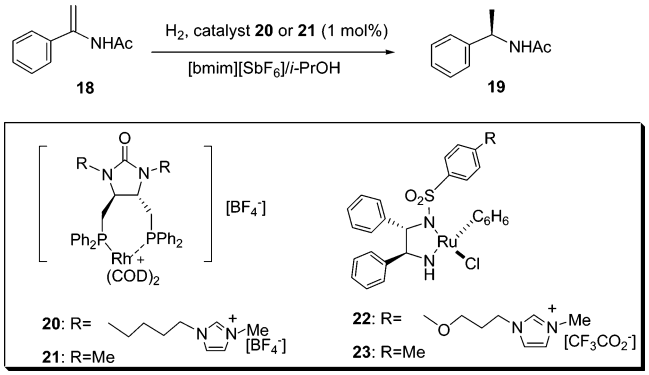
Scheme 5



21 may render the improvement a diminishing return. Similarly marginal improvement in the recyclability of the IL-supported complex **22** over the unsupported complex **23** in the asymmetric hydrogenation of acetophenone in [bmim][PF_6] was observed.[29] The small difference does not seem to offer much advantage in using **22**.

In an interesting study, García compared silica, single-wall carbon nanotube (SWNT), activated carbon (AC), and imidazolium ion as support for chiral vanadyl salen complex **24** in the enantioselective cyanosilylation of benzaldehyde (Scheme 7).[30] The IL-supported complex **25** was compared with the unsupported complex **24**, as well as similar complexes **26**−**28** anchored on solid insoluble

Scheme 6



matrix such as silica, SWNT, and AC. Among the four recoverable catalysts **25**−**28**, **25** showed the highest activity with turnover frequency (TOF) = 18.3 h^{-1}, whereas **26**−**28** had TOF values ranging from 2.6 to 3.75 h^{-1} under similar conditions. This is not unexpected because **25** functioned in homogeneous reaction conditions whereas the solid insoluble catalysts functioned in heterogeneous conditions. Interestingly, the TOF value of **25** was even higher than that of the unsupported catalyst **24** (TOF 3.5 h^{-1}). Unfortunately, the enantioselectivity in the reaction catalyzed by **25** was inferior to those catalyzed by the solid catalysts or the unsupported catalyst.

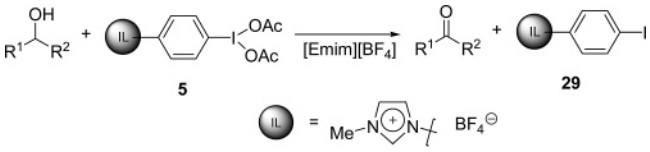
Ionic-Liquid-Supported Reagents

A number of synthetic reagents anchored onto ionic liquids have recently been reported. The anchored reagents can be separated readily from the reaction mixture by simple phase separation after the desired chemical transformation and then be regenerated and reused. Recently, Zhang reported the use of IL-supported hypervalent iodine compound **5**.[31,32] The oxidation of alcohols using **5** as an oxidant in ionic liquid [emim][BF_4] proceeded smoothly to afford the carbonyl compounds in good yields and the reduced reagent **29** (Scheme 8). The supported reagent **5** gave much better yields than the unsupported reagent $PhI(OAc)_2$ under the same reaction conditions suggesting that the imidazolium cation in **5** played a rate-enhancing role in the reaction. Furthermore, the IL-supported product **29** can be recovered and reused after oxidation with peracetic acid.

The IL-supported hypervalent iodine(III) reagents **30** and **31** have been prepared by Handy for the α-tosylation of ketones (Scheme 9).[33] The reaction demonstrated the advantage of the tunable separation properties of the ionic liquid support. Reagent **30** with NTf_2 as the anion was effective for the transformation but its reduction product **32** was soluble in the same range of solvents (ether, ethyl acetate, acetone, methylene chloride) as the α-tosyloxyketone products and can only be recovered by chromatography. However, by using reagent **31** with a harder *p*-toluenesulfonate anion, the reduced supported product **33** was much less soluble in ether and could be readily separated by precipitation from the reaction mixture with ether. The supported iodobenzene **33** could be recovered in >95% yield and converted back into **31** for reuse several times.

Taking advantage of another property of ionic liquids, the lack of vapor pressure, we have prepared a class of odorless and nonvolatile organosulfur compounds grafted to imidazolium ionic liquid scaffold (Scheme 10).[34] The sulfide containing ionic liquids **34** (n = 2, 3, and 6) were prepared from **35** with no need for chromatographic purification and no volatile organosulfur compounds used or generated during the whole synthesis. The oxidation of the sulfides **34** with periodic acid generated the sulfoxides **36**, which were then successfully applied to the oxidation of alcohol substrates to carbonyl compounds under Swern condition. Compared with the normal Swern oxidation where the volatile, malodorous, and toxic dimethyl sulfide was produced, the sulfide **34** was nonvola-

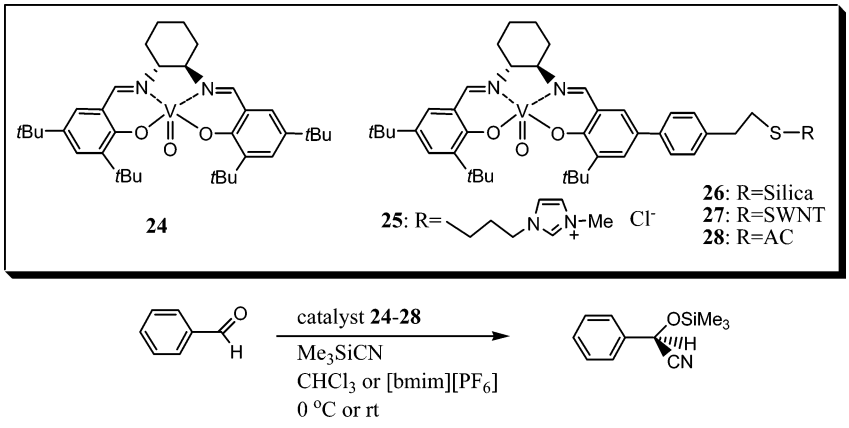
Scheme 8



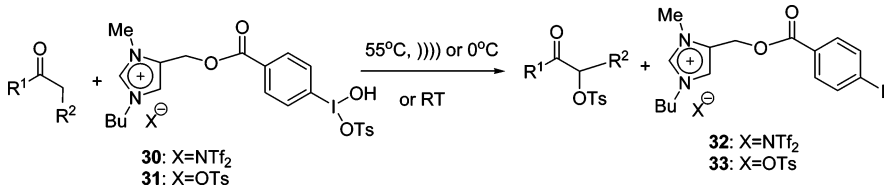
tile, which rendered the whole process odorless and more environmentally friendly. In addition, **34** could be recovered and regenerated easily and used for the Swern oxidation again at least four times with comparable reactivity.

Ionic liquids **37** and **38**, bearing the carboxylic acid functional group, were employed as dual reagents/

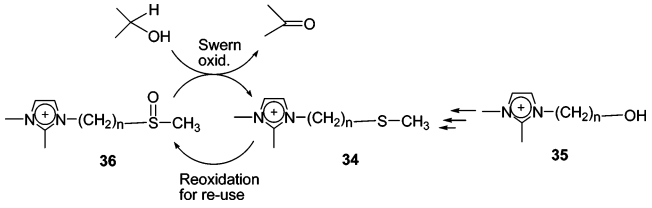
Scheme 7



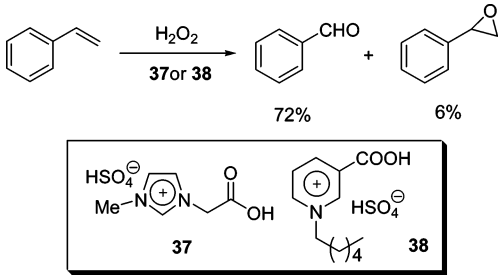
Scheme 9



Scheme 10



Scheme 11



solvents for the oxidation of olefins by Bao.[35] Interestingly, under the conditions of excess reagent (**37** or **38**) and 60% H_2O_2, acyclic alkenes were oxidatively cleaved to give mainly the aldehydes (Scheme 11). On the other hand, for cyclic alkenes, dihydroxylation of the double bond was observed. The IL-supported reagent **37** was found to show very little decline of the reaction rate and product yield in five cycles.

A potentially significant application of IL-supported reagents is their use as recyclable scavengers. Commercially, large scale CO_2 capture in the removal of carbon dioxide from natural gas uses aqueous amines to chemically trap the CO_2 by the formation of ammonium carbamate. However, in these systems, the uptake of water and the volatile amine sequestering agent into the gas stream present problems. Davis showed that when the IL-supported amine **39** was exposed to a stream of carbon dioxide for 3 h at 1 atm at room temperature, nearly 0.5 mol of CO_2 was captured per mole of **39**. The sequestration of carbon dioxide by **39** was *via* the formation of an ammonium carbamate **40** (Scheme 12),[36] similar to what occurred when molecular amines were used commercially to remove CO_2 from natural gas. However, in the case of **39**, the low volatility of the ionic liquid would prevent its loss into the gas stream. Furthermore, the process of CO_2 uptake is reversible, CO_2 being released from the carbamate salt **40** upon heating under vacuum. The free amine **39** can be recovered and reused with no observed loss of efficiency for five cycles.

Recently, the IL-supported amine **41** has been proposed as scavenger for benzoyl chloride, *p*-toluenesulfonyl chloride, phenyl isothiocycanate, and chlorophenyl isocyanate compounds in combinatorial synthesis.[37] An important contribution is the observation that the scavenging time is dependent on the viscosity of the IL-supported reagent. The amine **41** is quite viscous (195.3 $N \cdot m^{-2} \cdot s$) and takes a relatively long time (over 9 h) to scavenge *p*-toluenesulfonyl chloride from a toluene solution. However, the scavenging time can be decreased substantially (to 35 min) by the addition of a conventional ionic liquid, [bmim][PF_6] (1.5 equiv relative to **41**), into the reaction mixture (Figure 2). The application of **41** in

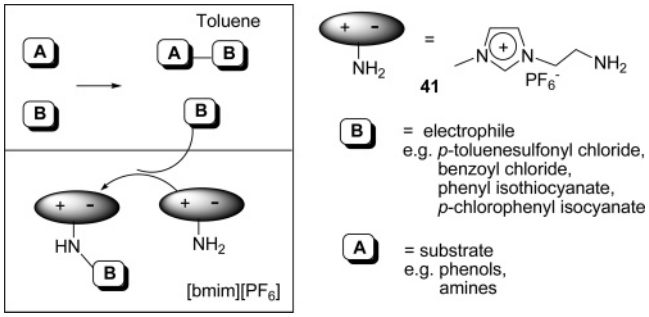


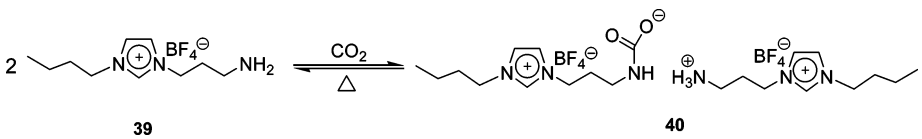
FIGURE 2.

combinatorial synthesis was demonstrated in a 12-member model library of aromatic esters from four substituted benzoyl chlorides with three phenols. All the aromatic esters were obtained in high yields (>97%) and purity (>97%). The recovered **41** can be regenerated and reused for three cycles with comparable activity.

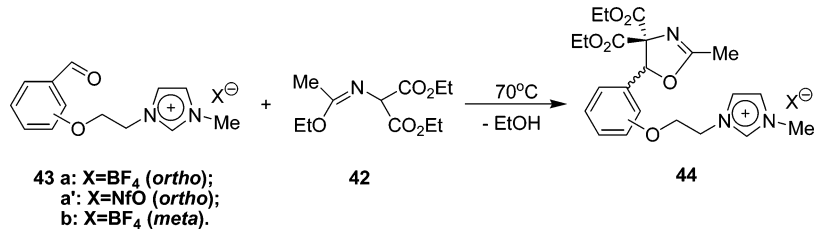
Ionic-Liquid-Supported Synthesis of Small Molecules and Combinatorial Synthesis

Bazureau was the first to propose the use of ionic liquid as soluble support for the synthesis of small organic molecules.[38] They found that the reaction of the IL-anchored dipolarophile **43a** (*ortho*) with the imidate **42** to give the adduct **44** (Scheme 13) was faster than that of the reaction of free 2-ethoxybenzaldehyde with **42** in the ionic liquid [emim][NfO] (emim = 1-ethyl-3-methylimi-

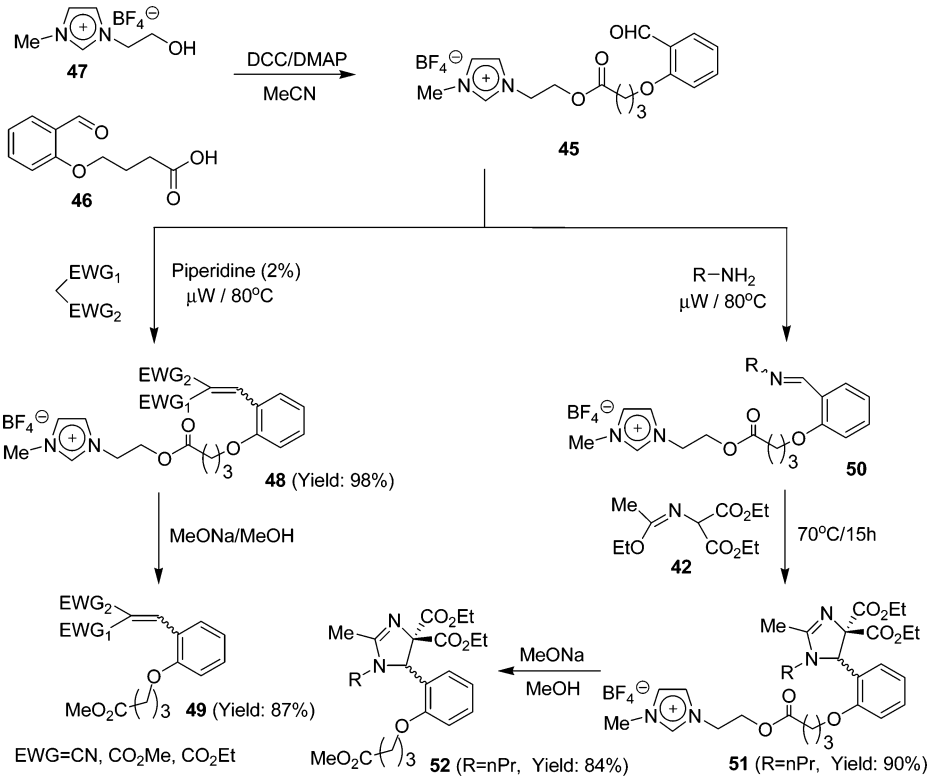
Scheme 12



Scheme 13



Scheme 14

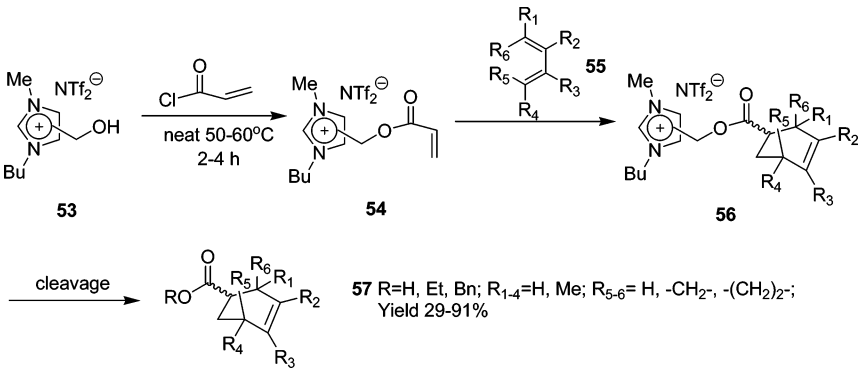


dazolium).[39] This acceleration was attributed to the possible intramolecular interaction between the CHO group of the dipolarophile and the polar 3-methylimidazolium moiety. Based on such observation, they examined the Knoevenagel and 1,3-dipolar cycloadition reactions with the IL-supported benzaldehyde **45** (Scheme 14). Thus, the substituted benzaldehyde **46** was anchored onto the IL-support **47** to give **45**. Knoevenagel reaction of **45** under homogeneous conditions gave the products **48** in high yields. Cleavage of the ionic liquid support from **48** by basic methanolysis gave the small molecule **49** in good isolated yield. Similarly, condensation of **45** with various amines gave the imines **50**, which can undergo 1,3-dipolar cycloaddition reactions with the imidate **42** to give the IL-supported products **51.** Basic methanolysis of **51** gave the product **52** in good yield. Using the IL-supported method, all the side products during the reactions could be removed by simple extraction and washings, and no chromatography was necessary throughout the synthesis. Furthermore, in contrast to the solid-phase synthesis, IL-phase synthesis allows the use of standard analytical methods such as NMR and TLC to monitor the progress of the reaction. The ionic liquid support **47** can also be recycled and reused efficiently in another run of the reaction.

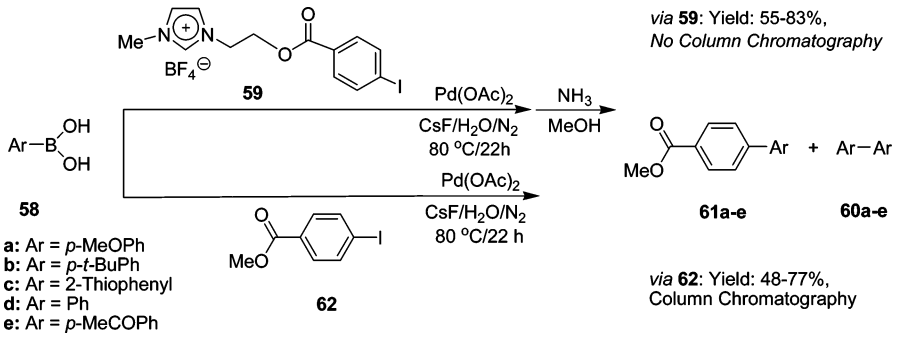
Handy and Okello have reported that the ionic liquid **53** was converted to the acrylate **54**.[40] The Diels−Alder reactions between **54** and various substituted butadienes **55** gave the Diels−Alder adducts **56** (Scheme 15), which could be readily isolated by removal of the volatiles under reduced pressure. Cyanide-mediated transesterification of **56** led to the esters **57** in good overall yields. The ionic liquid support **53** could be recovered in greater than 90% yield and reused.

In order to demonstrate the advantages of IL-supported synthesis over the conventional solution-phase synthesis, we examined a series of Suzuki coupling reactions between boronic acids **58** and the IL-supported iodobenzoates **59** (Scheme 16).[41] During the supported Suzuki reactions, the excess starting material and byproduct **60** were extracted with ether, leaving behind the ether-insoluble IL-supported biaryl products, which were subjected to cleavage with ammonia/methanol to give **61** in pure form, which was easily separated from the ionic

Scheme 15



Scheme 16



liquid phase by ether extraction without the need for chromatographic purification. In contrast, the reaction between the unsupported iodobenzoate **62** and **58** under identical conditions produced a mixture of the coupling products **61**, unreacted **62**, and the byproduct **60**. Column chromatography was essential to obtain the pure coupling product **61** (Scheme 16). Even though the route *via* **59** required two additional steps, the overall yield of **61** by the IL-supported synthesis was in fact higher than the route *via* **62**. Furthermore, the elimination of the chromatography step in obtaining pure **61** in the IL-supported synthesis is a clear advantage.

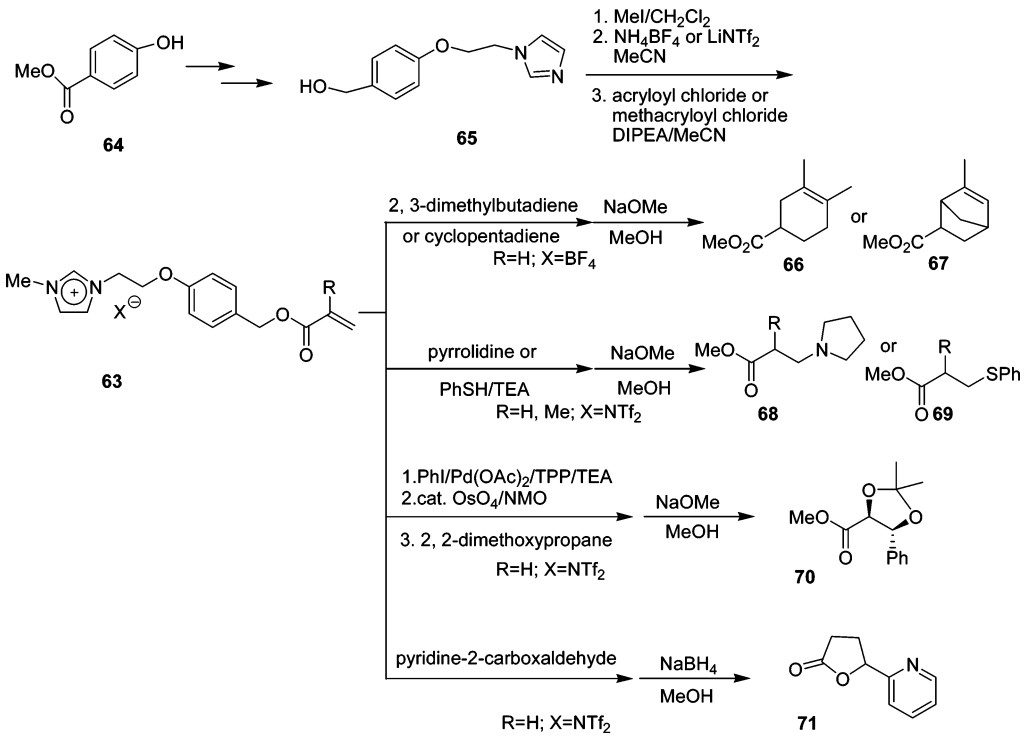
Recently, Grée reported[42] on the synthesis of the IL-supported alkene **63** as shown in Scheme 17. An interesting feature was the introduction of a Wang-type linker, which is known to be very versatile in combinatorial chemistry with flexible lability, into the ionic liquid support. Alkene **63** was compatible with a wide range of reactions such as Diels−Alder cycloaddition, Michael addition, dihydroxylation, and the Stetter reaction to give good yields of the relevant products **66**−**71** after cleavage from the IL support (Scheme 17). It should be noted that in the examples given, methanolysis was used in the cleavage reaction. Presumably, other cleavage reactions for the Wang-type linker can be applied.

The use of ethylene glycol oligomer as linker between the ionic liquid moiety and the substrate was illustrated by the IL-supported isothiocyanato esters **72** (Scheme 18).[43] The ethylene glycol ether group presumably helped in the displacement reaction.

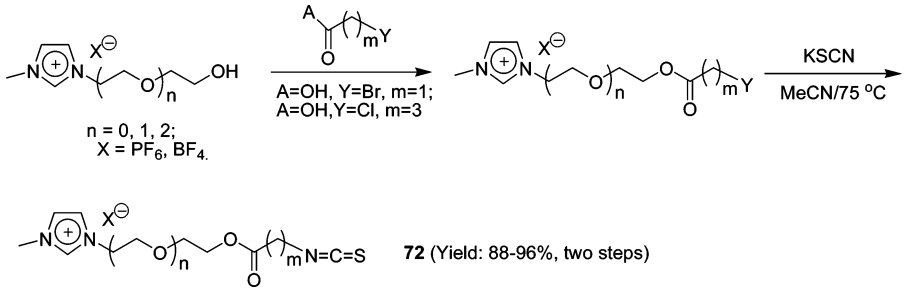
The application of the IL-supported strategy to multistep synthesis was demonstrated by de Kort in the synthesis of compound **73**, a highly potent analog of the antithrombotic drug tirofiban.[44] The ionic liquid support **74**, bearing a formyl functional group, was prepared from 4-hydroxy-2-methoxybenzaldehyde, **1**, 4-dichlorobutane, and 1-methylimidazole (Scheme 19). Reductive amination of the IL-supported **74** with the protected tyrosine **75** gave the IL-supported substrate **76**. The amine **76** was converted to the sulfonamide **77** and the allyl protecting group was removed to give **78**. Alkylation of **78** gave compound **79**, which was cleaved by HPF_6 to give the product **73** in 11% overall yield based on **74**. Several features of this synthesis are worthy of note. First, all five steps of the synthesis were conducted in one pot using [bmim][PF_6] as reaction media. Second, the work up of every reaction step was done simply by consecutive extractions with ether and water to remove excess reagents. Third, in the cleavage of the desired product **73** from the ionic liquid support, HPF_6 was used instead of the more commonly used trifluoracetic acid (TFA). This was because the excess TFA underwent anion exchange with [bmim][PF_6] to give [bmim][TFA] as contaminant in the product. By using HPF_6, the product **73** could be extracted with water without contamination of the water-insoluble [bmim]-[PF_6].

The IL-supported strategy for combinatorial synthesis was demonstrated by the preparation of a small library of 4-thiazolidinones **80** (Scheme 20).[45] The synthesis of the IL-bound 4-thiazolidinones **84** was accomplished by a one-pot condensation among **81**, mercapto acids **82**, and amines **83** under microwave dielectric heating. The cleavage of **80** from the IL support was realized by amide formation also under microwave irradiation. Diversity was introduced at the phenoxy component **81**, the thiol **82**, the amine **83**, and the cleavage step. The advantages of

Scheme 17



Scheme 18

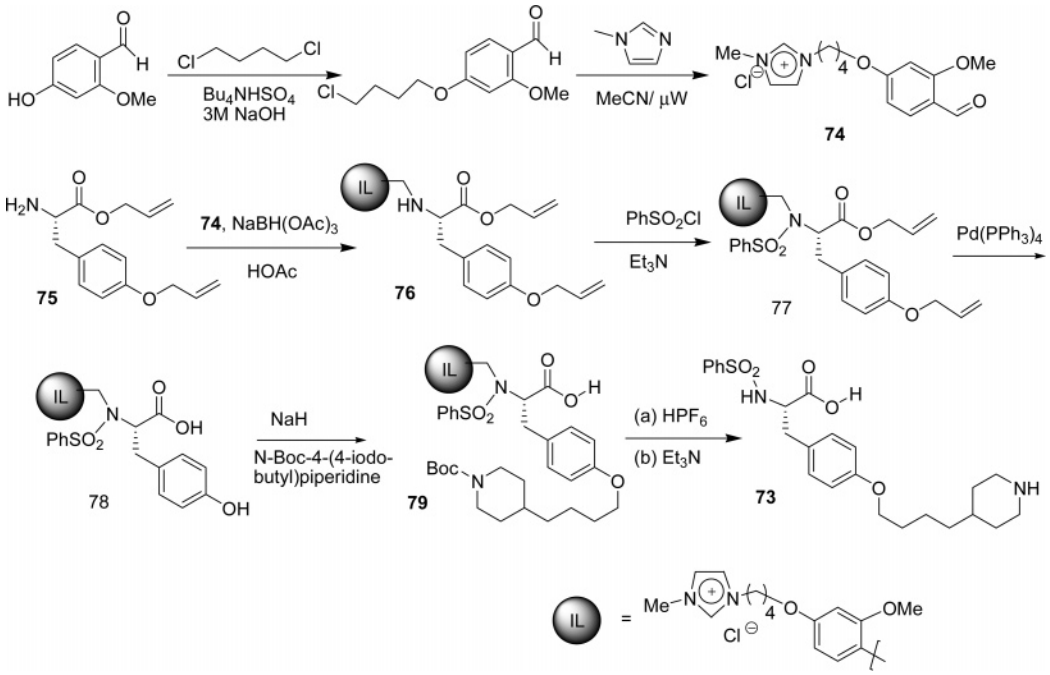


using ionic liquid support are as follows: (1) it provides ease of product isolation because the side products are removed by simple washing with appropriate solvent; (2) in each step, the reaction can be followed by standard analytical technique; (3) due to the high polarity of the ionic liquid support, microwave dielectric heating can be easily applied to enhance the reaction; (4) the final product **80** was usually obtained in high purity after flash chromatography. A small library of 4-aminophenyl ethers was also prepared using an ionic liquid as support.[46]

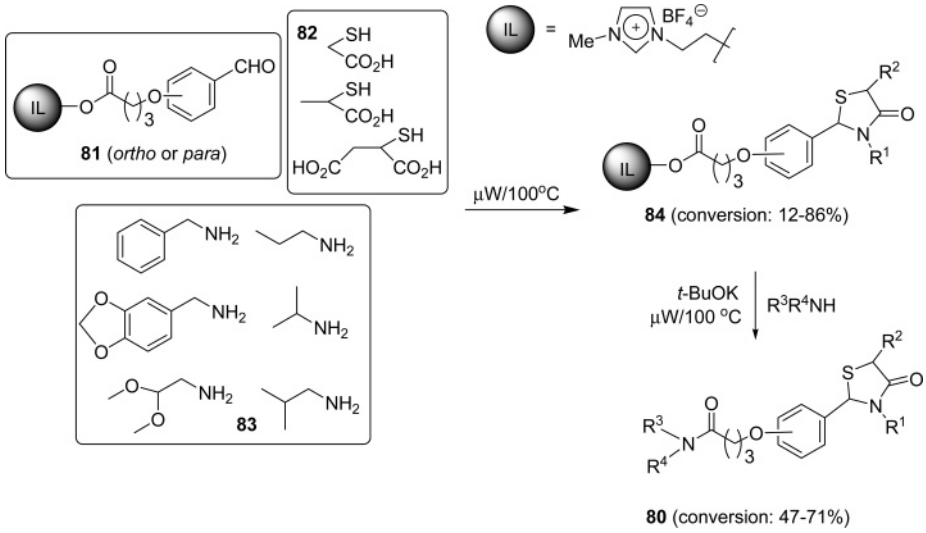
Ionic-Liquid-Supported Synthesis of Bio-Oligomers

With the success of IL-supported synthesis for small molecules, the application of the same strategy to the syntheses of oligomers of biomolecules invites exploration. We recently reported on the use of this new liquid-phase methodology for the synthesis of oligopeptides.[47] The following issues need to be addressed: (1) Are the general synthetic protocols developed for peptide synthesis applicable to ionic liquid support? (2) Is there racemization or epimerization of the peptide units during attachment of the first amino acid to the ionic liquid moiety (loading), the coupling steps, and the detachment step? (3) Is the solubility of the IL-supported oligopeptide molecule modified by the growing peptide chain such that purification by simple washings with organic and aqueous solvents is no longer practical? We used the synthesis of the bioactive pentapeptide Leu^5-enkephalin **85**, to probe these issues (Scheme 21). The approach is similar to the solid-phase and most liquid-phase peptide syntheses in that the IL support **47** is linked to the C-terminus of the growing peptide and serves as a carboxylic acid protecting group. The attachment of the first amino acid, Boc-Leu-OH, onto **47** was accomplished by 1,3-dicyclohexylcarbodiimide (DCC)/4-(*N*,*N*-dimethylamino)pyridine (DMAP) and gave the IL-supported Leu-Boc **86** in greater than 99% conversion (91% isolated yield). No racemization was observed in this coupling step. The removal of the Boc group in **86** was accomplished by TFA/*N*,*N*′-diisopropylethylamine (DIPEA) and followed by the coupling of the second amino acid Boc-PheOH using the (benzotriazol-1-yl-oxy)tripyrrolidinophosphonium hexafluorophosphate (PyBOP)/DIPEA conditions to give the IL-supported dipeptide in

Scheme 19



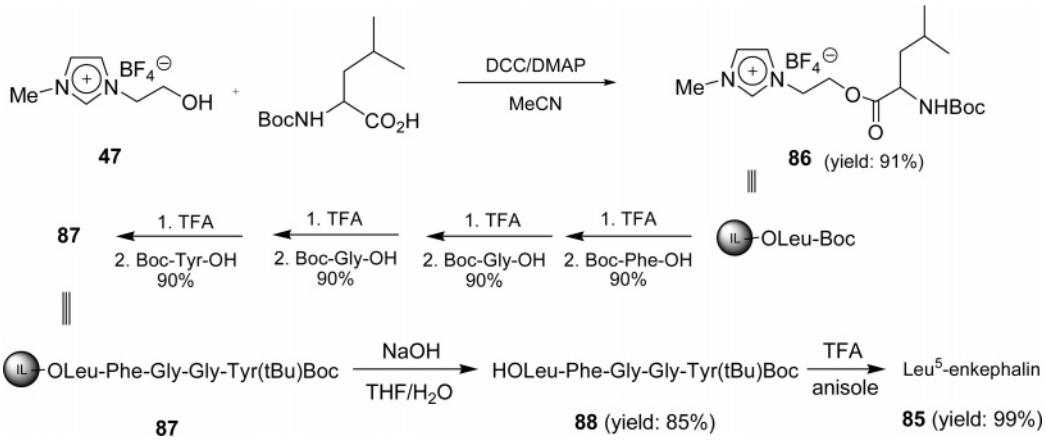
Scheme 20



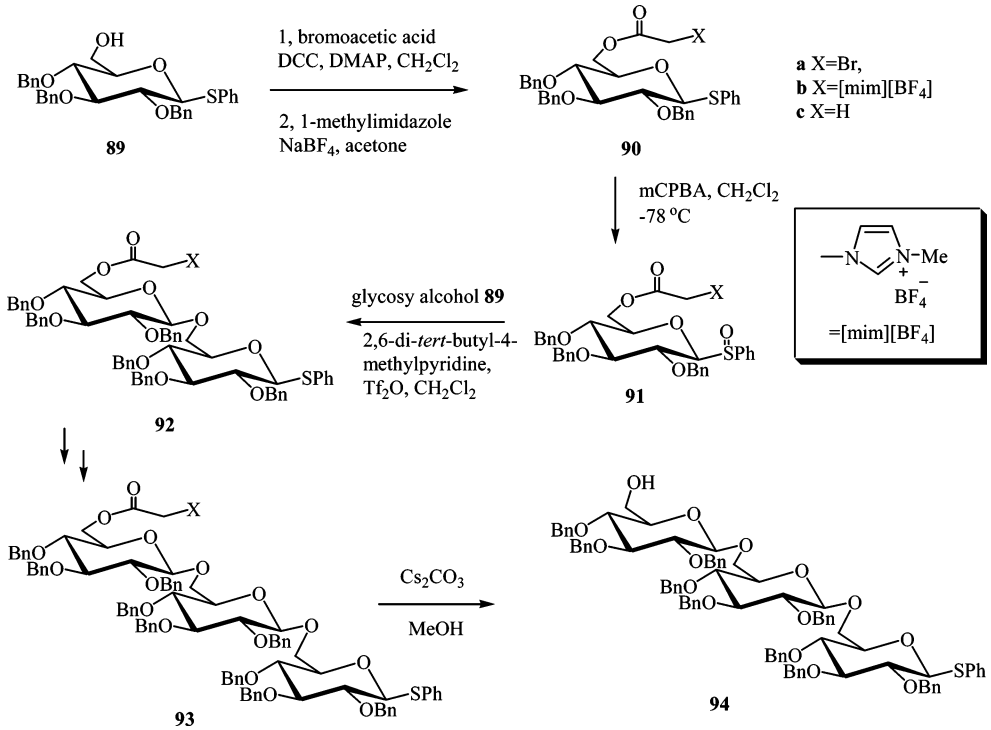
greater than 99% conversion. Again, no racemization or epimerization was observed in the deprotection/coupling sequence. This generic protocol of TFA/DIPEA deprotection plus PyBOP/DIPEA coupling was found to be applicable to other amino acids and the IL-supported pentapeptide **87** was obtained without any difficulties. All the IL-supported peptides thus prepared were soluble in polar organic solvents such as acetone, acetonitrile, and methanol but were essentially not soluble in diethyl ether or hexane. All the intermediates were isolated and purified simply by sequential ether and aqueous washing. Their structures and purities could be confirmed easily by conventional analytical methods such as NMR and MS. Finally, the product Leu^5-enkephalin (**85**) was liberated from the ionic liquid support by basic hydrolysis followed by removal of the protecting groups. The purity of the Leu^5-enkephalin thus obtained without any recrystallization or chromatography procedure in the entire synthetic sequence was found to be >90% pure by HPLC. Such a level of purity was superior to what could usually be obtained by solid-phase peptide synthesis prior to chromatographic purification. The example of Leu^5-enkephalin (**85**) demonstrated that indeed ionic liquid support is compatible with the chemistry developed for peptide synthesis. We have now routinely applied the IL-supported synthesis to oligopeptides of four to six amino acids with similar efficiency. What we have not yet determined is whether the methodology is applicable to longer oligopeptides. This should be the subject of future investigation.

Encouraged by the successful synthesis of oligopeptides, we have recently adopted the approach for the synthesis of oligosaccharides (Scheme 22).[48] The efficient synthesis of oligosaccharides is a challenge of considerable

Scheme 21



Scheme 22



magnitude because the traditional solution-phase synthesis is laborious and requires purification by chromatography after each step. Recent advances in polymer-supported solid-phase oligosaccharide synthesis have led to impressive examples of automated synthesis.[49] However, there are the usual difficulties associated with solid-phase synthesis. The alternative liquid-phase methodologies of using soluble polymer supports[5] or fluorous support[10] have been explored, and each has its limitations. For soluble polymers, the loading capacity is relatively low, whereas for "fluorous" support, the fluorine content declines as the number of saccharide units increases and thus will modify the solubility in fluorous solvent. For the IL-supported synthesis, the β-thioglycoside **89** was covalently anchored onto the IL support as in **90b**. The sugar−sugar assembling method is the sulfoxide glycosylation reaction according to Kahne.[50] The IL-supported sulfoxide **91b** was thus coupled to the glycosyl alcohol **89** to give the disaccharide **92b**. The same sequence of oxidation/coupling can be repeated to give the trisaccharide **93b**. Methanolysis of **93b** liberated the free trisaccharide **94** from the ionic liquid support. As in the case of IL-supported peptide synthesis,[47] all the IL-anchored intermediates in Scheme 22 were simply purified by washing with ether, aqueous media, or both, and their structures were characterized by conventional analytical techniques including NMR and MS. For comparison, the same synthetic sequence was repeated with **90c**, using conventional solution-phase chemistry. Chromatographic purification was however required in each of the reaction steps. At the end, the trisaccharide **94** obtained by the IL-supported synthesis (ILSS) was found to be NMR and TLC pure and identical to the sample of **94** prepared via **90c**. This example suggests that the coupling conditions and stereoselectivity developed for classical solution-phase synthesis in the carbohydrate field can be translated to

ILSS. At this time, the ILSS of oligosaccharides appears to offer the advantages of solution-phase synthesis with homogeneous conditions and likely amenable to large-scale synthesis. However, it remains to be demonstrated whether the approach can be applied to more complex oligosaccharides.

Finally, the possibility of ILSS strategy for the synthesis of oligonucleotides demands to be examined. This is now being pursued in our laboratories.

Conclusions and Outlook

This Account has outlined the development of the recently emerged IL-supported synthesis as a novel liquid-phase strategy in organic synthesis. It is clear that the IL supports are compatible with many chemical reactions in solution chemistry. With the multitude of possible cations and anions in new ionic liquid supports, the stability and the solubility of the IL support can be tuned to meet the different demands expected to be encountered in new synthesis. Compared with insoluble solid supports, ILSS offers the advantages of homogeneous reaction conditions, easier monitoring of reaction processes and easier scalability to large-scale synthesis. Relative to the existing liquid-phase methodologies, IL support offers, in general, a better loading capacity than the soluble polymer supports. Relative to the fluorous phase synthesis, the IL supports are generally easier to synthesize and do not require fluorous solvents for phase separation. On the other hand, the solid-phase synthesis offers the ease of separation and automation, which will be difficult for ILSS to compete with in the near future. Nevertheless, the success of the ILSS strategy thus far should encourage further research into the general scope of ILSS in biopolymer synthesis. It is hoped that this Account will help stimulate the relevant research to move forward.

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