SYNOPSIS

The thesis entitled **"Total synthesis of (+)-Amberketal, its analogues and development of new methodologies in Ionic Liquids"** has been divided into three chapters.

Chapter I: This chapter deals with an introduction to fragrance chemistry and previous approaches to (+)-Amberketal and other amber odorants.

Chapter II: This chapter deals with the total synthesis of (+)-Amberketal and its analogues, which is further divided into two sections:

Section-A: This section describes the total synthesis of (+)-Amberketal and its one analogue from *l*-Abietic acid.

Section-B: This section describes the synthesis of two more Amberketal analogues from *l*-Abietic acid.

Chapter III: This chapter describes the development of new methodologies in ionic liquids, which is further divided into three sections:

Section A: This section deals with an introduction to green chemistry, ionic liquids and their uses in organic synthesis.

Section B: This section describes the conjugate addition of indoles to α,β-unsaturated ketones using $Cu(OTf)_2$ immobilized in ionic liquids.

Section C: This section describes the conjugate addition of thiols to α,β-unsaturated ketones using a $[bmim]PF_6/H_2O$ system.

Chapter I: An introduction to fragrance chemistry and previous approaches to (+)-Amberketal and other amber odorants:

The chemistry of all odor compounds is called the *Fragrance chemistry*. *Fragrance chemistry* is a fascinating blend of natural products, synthetic, analytical, and physical chemistry with a certain amount of creative fantasy for odors, and molecular structures. It is often incorrectly assumed that only compounds with a *pleasant* smell belong to the realm of *fragrance chemistry*. Not only is *pleasant odor* a very subjective notion, but fragrance compositions often include single compounds which in higher concentration or in a pure form have an *animal, faecal, sulfurous* or *sweaty obnoxious* odour. The main

odor notes of perfumery are: “fruity”, “marine”, “green”, “floral”, “spicy”, “woody”, “amber” and “musky”.[13] Among all these odor notes the amber is to be explained as our research work is on the total synthesis of (+)-Amberketal **1** and its analogues. The commercially most important amber chemical is the tricylic ether (-)-Ambrox **3**. Next to ambrox, (+)-amberketal **1** is one of the best-known amber odorants.

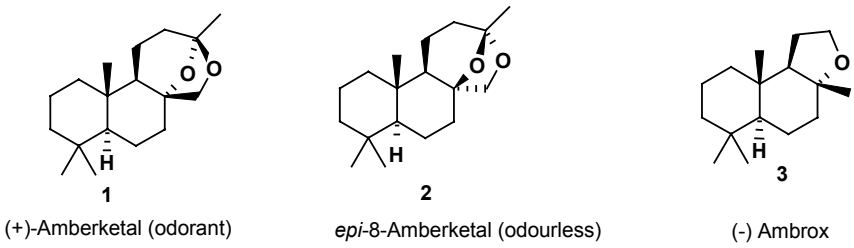


Figure 1

Ambergris, the most important animal perfume other than civet, musk and castreum has been particularly used in perfume industry since ancient times for its unique fragrance and fixative properties. The intense fragrance of unequalled tenacity produced by mixtures of the (+)-amberketal **1** and *epi*-8-amberketal **2** was first described by Jeger *et al*. in 1952. The natural chiral pools of precursors include manool, sclareol the resinic acid anticopalic and communic acid for the synthesis of (+)-amberketal.

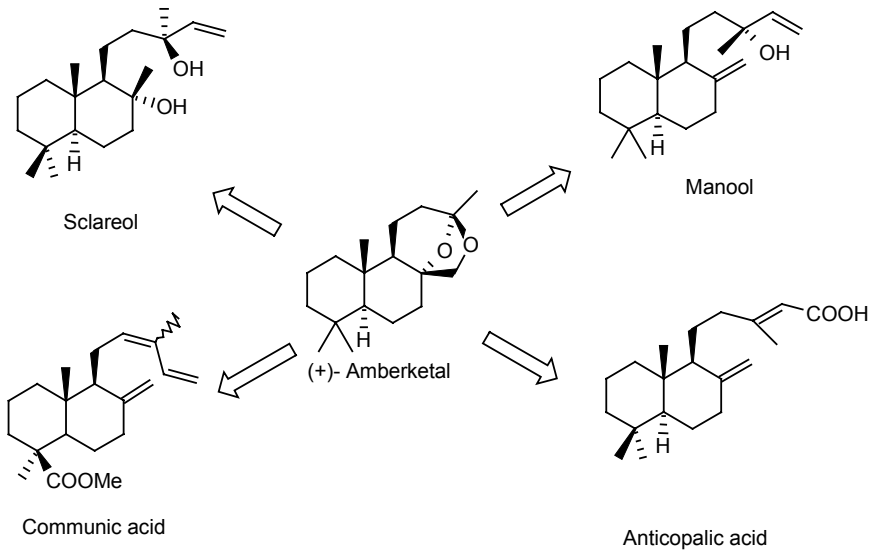


Figure 2

Chapter II:

Section A: Total synthesis of (+)-Amberketal and its one analogue from *l*-Abietic acid.

Ambergris, the metabolic product found in the gut of some blue sperm whales (*Physester macrocephalus*), after one to three years of aging, smell of amber odor which is used in perfumery in the form of an infusion in alcohol. One of the constituents of the ambergris tincture is the cyclic ketal (+)-amberketal, which possess a strong and tenacious amber-type odor. As a consequence of the growing demand for ambergris-type odorants coupled with the almost worldwide ban on whaling, chemists have been looking for new, commercially viable, synthetic substitutes. Among the most synthetic equivalents of the scarce natural ambergris source (+)-amberketal **1** became probably the most important one after the norlabadane oxide (-)-ambrox **3**. The retrosynthetic analysis describes the oxidative degradation of the C-ring of either **8** or **11**, regio-selective construction of a C-7 exocyclic double bond and subsequent conversion of isopropyl ketone to methyl ketone leading the exact chiral synthon of (+)-amberketal **1**. The primary alcohol can also be converted to the intermediate that after intramolecular ketalization, the amberketal analogue **4** can be obtained. The retrosynthetic analysis to afford the (+)-amberketal **1** and its analogue **4** is outlined in the **Figure 3.**

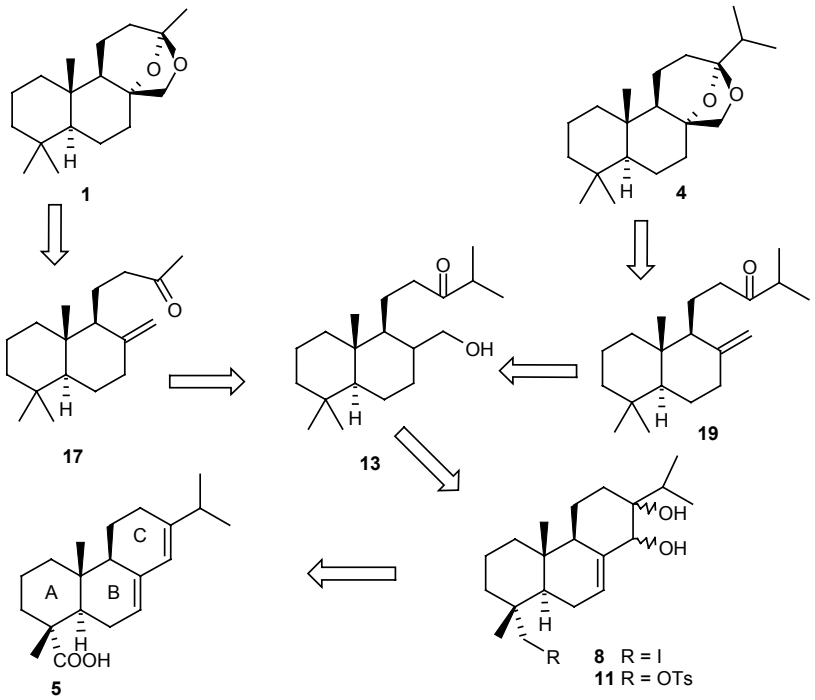
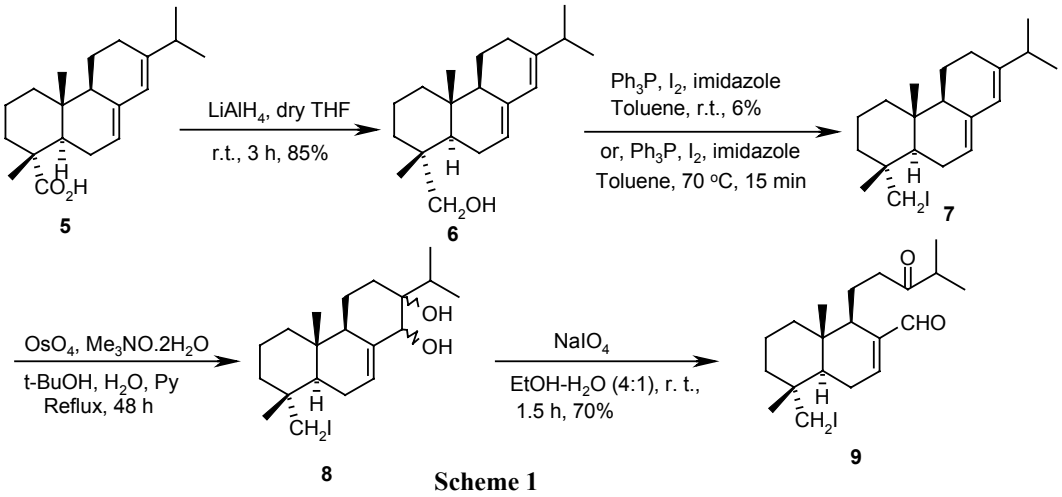


Figure 3. Retrosynthetic analysis of (+)-amberketal **1** and its analogue **4**

l-Abietic acid **5**, the commercially available diterpenoid from pine resin has been used as the main chiral pool of precursor for the synthesis of many ambergris-type odorants as their structural similarity. *l*-Abietic acid was first converted into abietol **6** with 2 equiv. of $LiAlH_4$ in dry THF at room temperature in 85% yield. Treatment of **6** with triphenyl phosphine-iodine-imidazole in toluene at room temperature gave iodo abietane **7** in 6% yield.

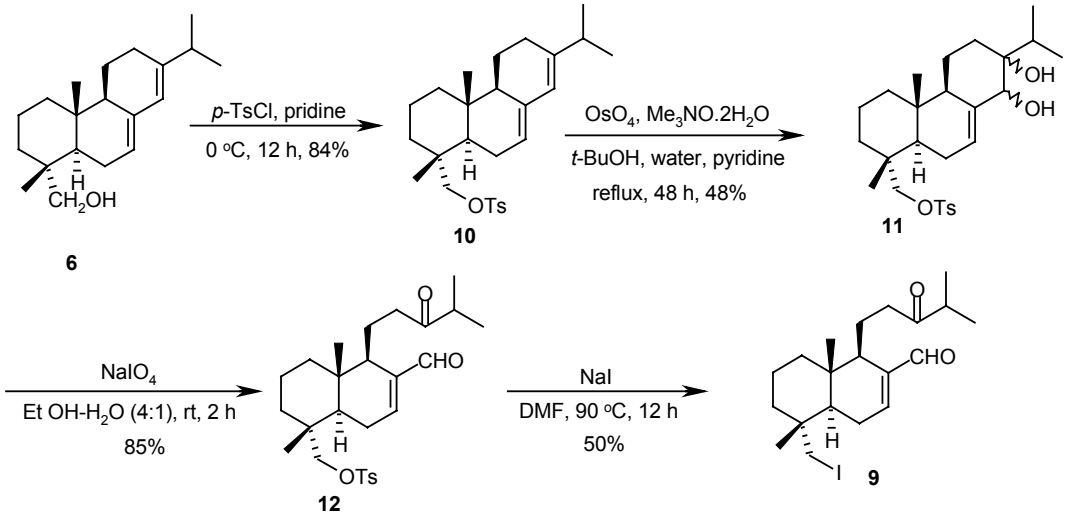


Scheme 1

When the reaction was performed at 70 ^oC, the formation of two inseparable side products along with the iodo abietane were observed in TLC. The crude material obtained after filtration through a small pad of silica gel was directly subjected to regioselective dihydroxylation with a catalytic amount of osmic acid (OsO_4, $Me_3NO.2H_2O$/*t*-BuOH-py-H_2O, reflux 48 h). This reaction furnished an inseparable diastereomeric mixture of the diol **8** in a ratio of 3α: 10β in 25% yield for two steps. The oxidative cleavage of the inseparable mixture of diol **8** was performed in an eco-friendly way using 1.5 equiv. $NaIO_4$ in ethanol-water mixture (4:1) at room temperature which resulted in the formation of the most important intermediate of our strategy, the conjugate aldehyde **9,** in 70% yield (Scheme 1).

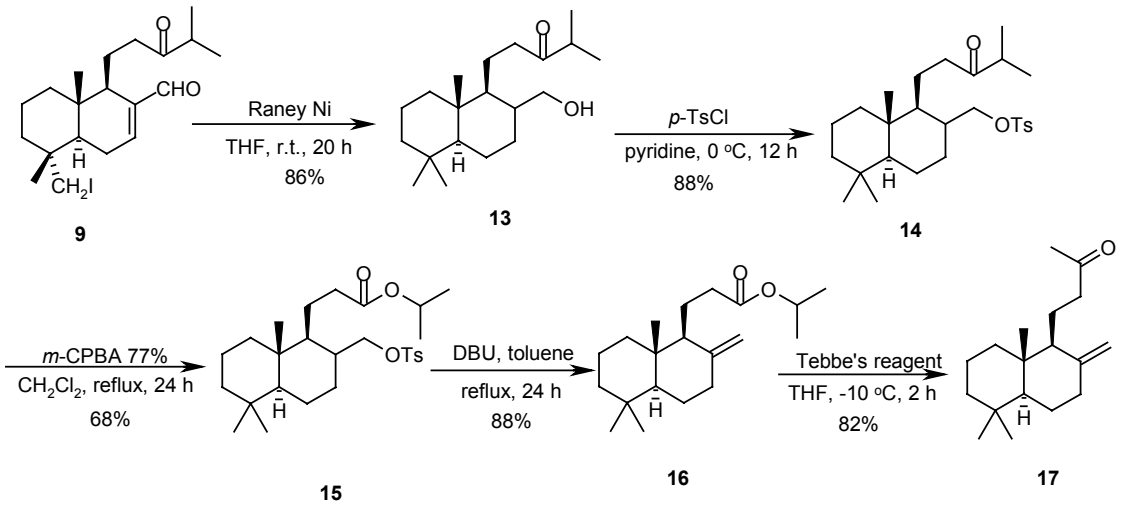
To improve the overall yield of the aldehyde **9** from *l*-abietic acid, abietol **6** was tosylated with *p*-TsCl in pyridine at 0 ^oC to afford the tosylate derivative **10** in 84% yield, which on subjecting to regioselective dihydroxyaltion afforded diol **11** in 48% yield in 1α: 9β mixture. The mixture of the diol **11** was subjected to the oxidative cleavage with $NaIO_4$ in ethanol and water (4:1) mixture to afford the single product aldehyde **12** in 85%

yield. The displacement of tosyl group in **12** by iodide was achieved in 50% yield using 6 equiv. of NaI in DMF at 90 ^{o}C for 12 h along with 20% yield of unidentified product (Scheme 2). The aldehyde **9** was obtained in similar overall yield (14.87% and 14.73%) from *l*-abietic acid in the both **Scheme 1** and **2** respectively.



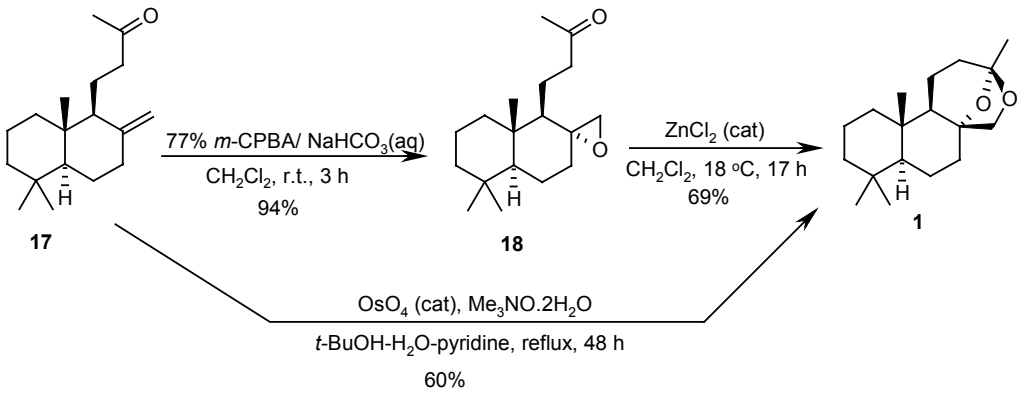
Scheme 2

The selective reduction of both the conjugated double bond and the aldehyde group in the presence of ketone group and simultaneous removal of iodo group was successfully achieved in a single step using aqueous suspension of Raney Ni in THF at room temperature to afford the saturated primary alcohol **13** in 86% yield. Our next aim was to construct the exo-olefin at C-8 position and transform the isopropyl ketone to a methyl ketone. The alcohol **13** was converted to its tosylate derivative **14** in 88% yield with *p*- toluenesulfonyl chloride in pyridine at 0 ^{o}C for 12 h. The tosylate **14** was treated with 70% *m*-CPBA in CH_2Cl_2 at reflux temperature affording the isopropyl ester **15** in 68% yield. The olefin-ester **16** was prepared in 88% yield using a reported procedure by the reaction of primary tosylate with 4 equiv. of DBU in refluxing toluene for 24 h. The olefin-ester **16** was treated with Tebbe's reagent to afford the methyl ketone **17**, the exact synthon for (+)-amberketal synthesis, in 82% yield (Scheme 3).



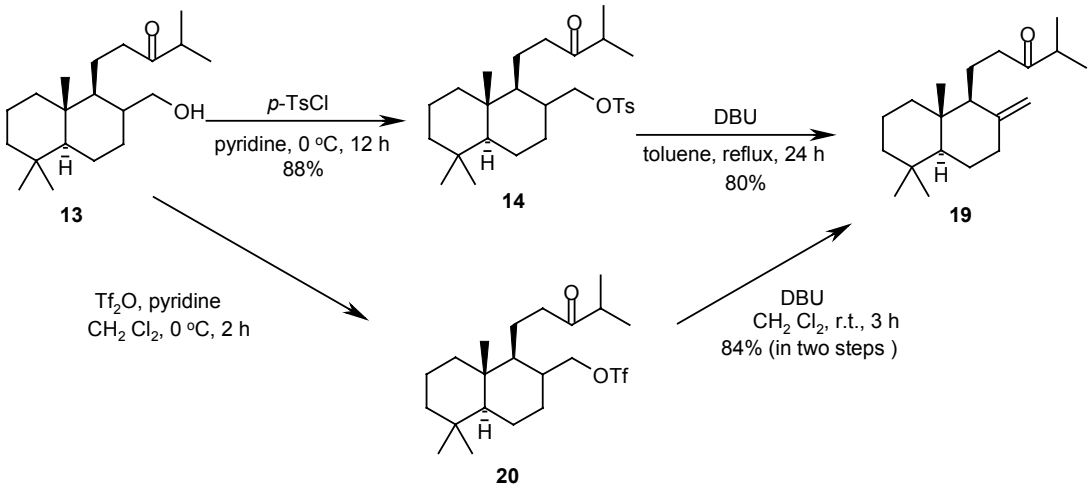
Scheme 3

The synthon **17** was converted to (+)-amberketal **1** by treatment with a catalytic amount of OsO_4 in refluxing *t*-BuOH-H_2O-pyridine mixture with trimethylamine *N*-oxide as co-oxidant in 60% yield (Scheme 4). (+)-Amberketal **1** was also prepared in two steps i.e. epoxidation with *m*-CPBA/aq. $NaHCO_3$ followed by δ,ε-epoxyketone cyclization with $ZnCl_2$ at 18 °C (Scheme 4).



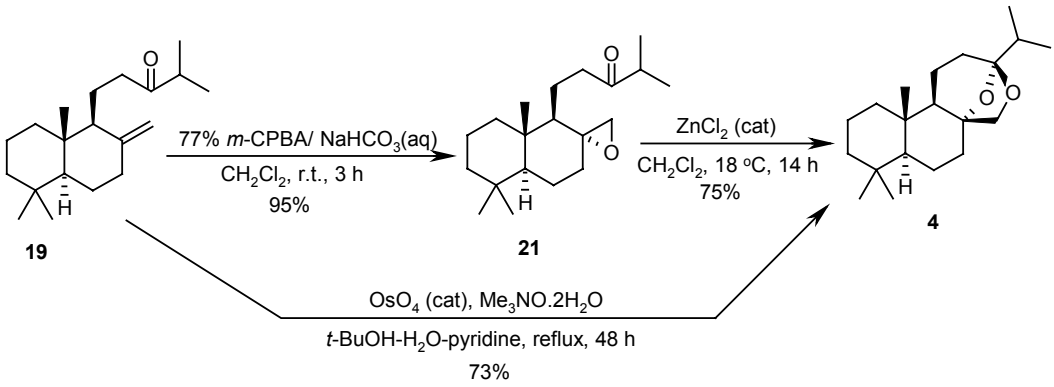
Scheme 4

In order to get the amberketal analogue **4** the alcohol **13** was treated with Tf_2O in CH_2Cl_2 using pyridine as a base to produce the triflate derivative **20**, which on subsequent treatment with 3 equiv. of DBU at room temperature afforded the exo-olefin **19**. The exo-olefin **19** was also obtained from the tosylate **14** by the treatment with 4 equiv. of DBU in refluxing toluene (Scheme 5).



Scheme 5

The epoxidation of **19** with *m*-CPBA/aq. $NaHCO_3$ gave only α-epoxide **21** (95% yield) diastereoselectively which under δ,ε-epoxyketone cyclization with $ZnCl_2$ at 18 ^oC resulted in the amberketal analogue **4** in 75% yield. The exo-olefin **19** was also converted to the analogue **4** in 73% yield by treatment with a catalytic amount of OsO_4 in refluxing *t*-BuOH-H_2O-pyridine mixture with trimethylamine *N*-oxide as co-oxidant (Scheme 6).



Scheme 6

Section B: Synthesis of two more Amberketal analogues from *l*-Abietic acid.

Different research groups used *l*-Abietic acid as the starting material for the synthesis of several analogues of ambergris odorant due to their structural similarity.

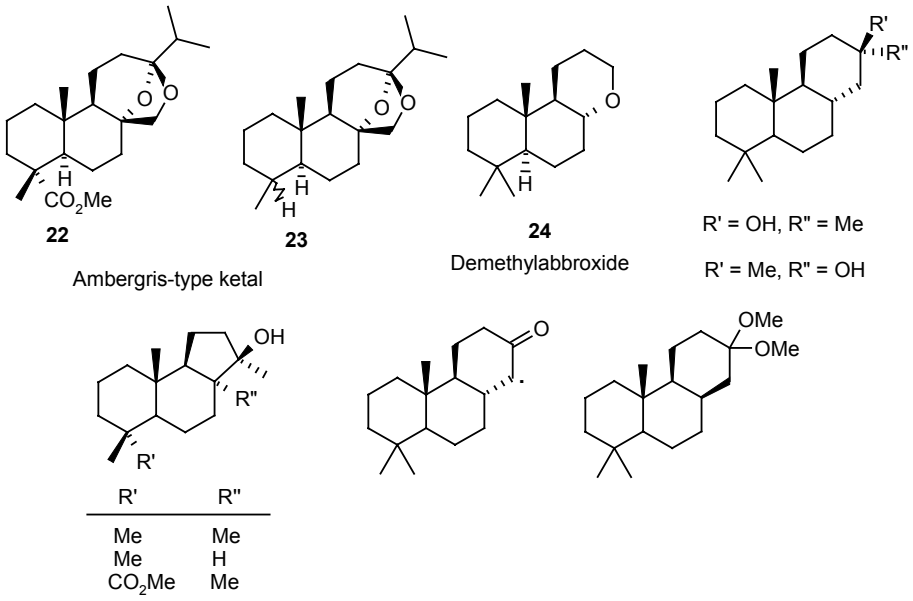


Figure 4. Analogues of ambergris odorants

In our study of synthesis of ambergris-type ketal **22** and its decarboxylated analogue **23,** the *l*-abietic acid **5** has also been chosen as the starting material. The strategy used in our synthesis is based on the oxidative degradation of the C-ring of *l*-abietic acid **5** regioselectively. The retrosynthetic analysis describes the oxidative degradation of the C-ring of abietic acid or methyl abietate, regio-selective construction of a C-8 exocyclic double bond, intramolecular ketalization, deoxygenation and decarboxylation. The retrosynthetic analysis to afford the amberketal analogue **22** and **23** is outlined in the **Figure 5**.

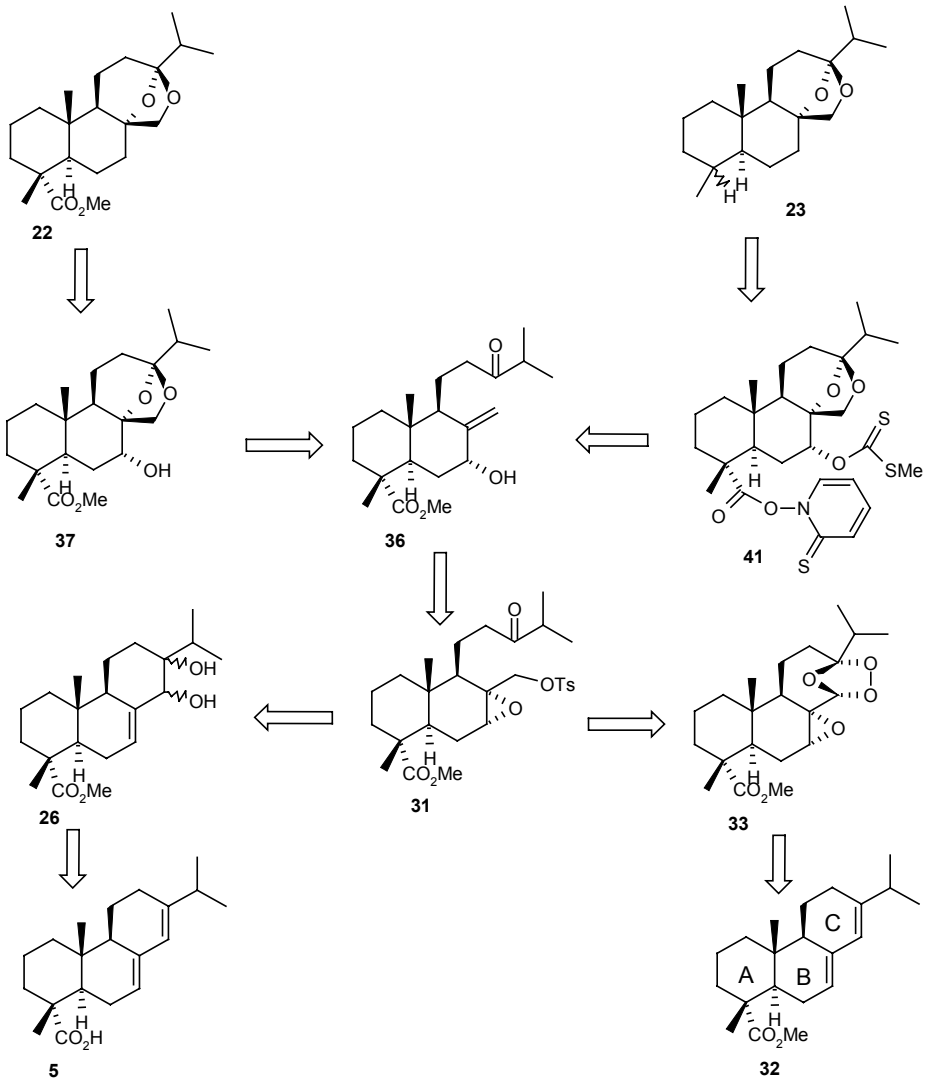
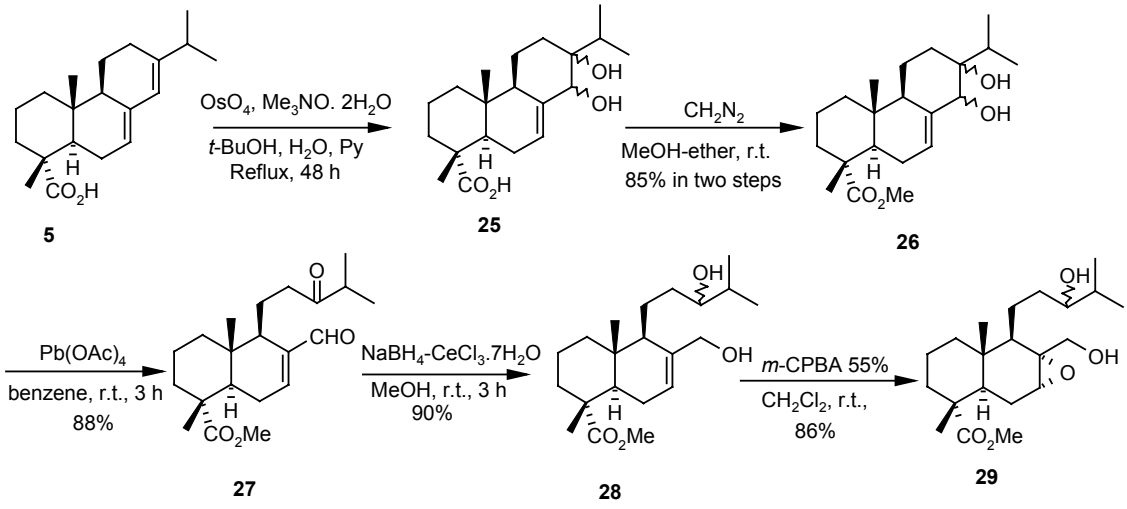


Figure 5. Retrosynthetic analysis

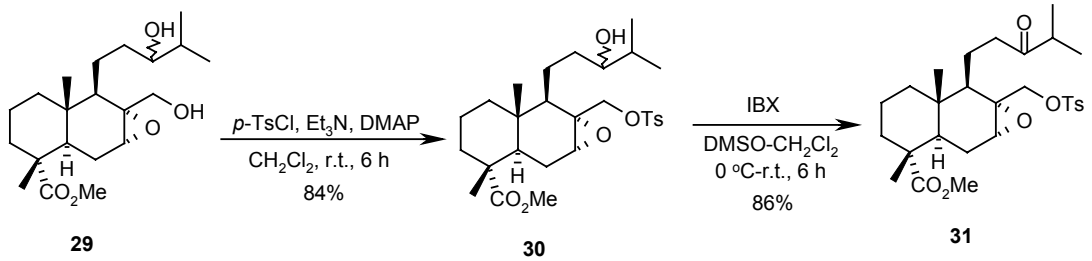
l-Abietic acid **5** was first subjected to the regioselective dihydoxylation with catalytic amount of OsO_4 in refluxing *t*-butanol-pyridine-water solvent mixture in the presence of trimethylamine *N*-oxide as co-oxidant. The mixture of diol **25** obtained after filtration through a small pad of silica gel was directly converted to their methyl esters quantitatively with CH_2N_2 in MeOH. An overall 85% yield (in two steps) of the diol **26** (**β**-diol and **α**-diol) in a ratio of 11β:1α (as measured from their isolated yield) was obtained in two steps. The oxidative cleavage of the mixture of diol **26** was performed using 1.2 equiv. $Pb(OAc)_4$ in benzene at room temperature for 3 h which resulted in the formation of the single product, the conjugate aldehyde **27,** in 88% yield (Scheme 7).



Scheme 7

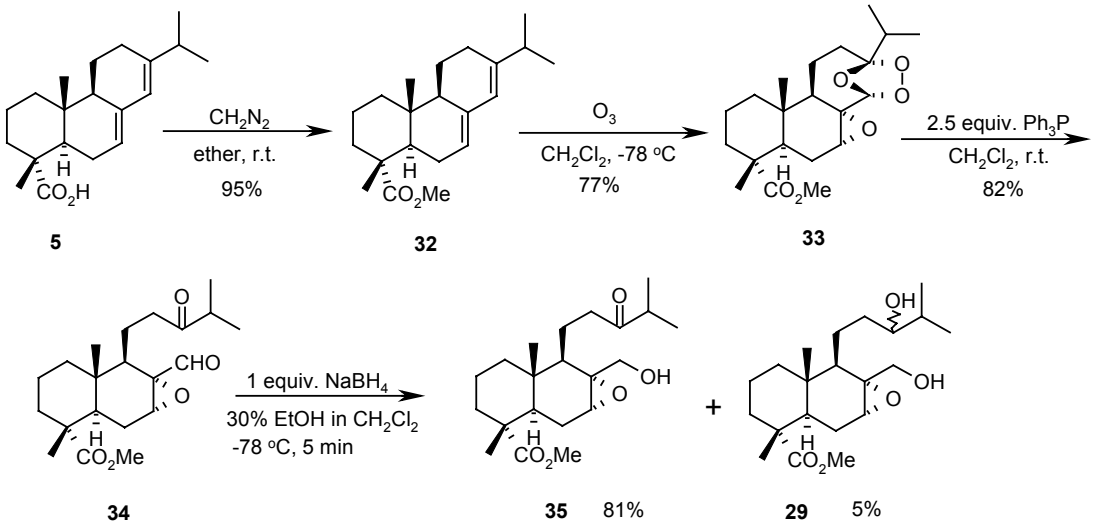
In this strategy, the conjugate aldehyde **27** was subjected to reduction with $NaBH_4/CeCl_3.7H_2O$ in methanol at room temperature affording the mixture of diol **28** in 90% yields. The epoxidation of diol **28** was performed with 55% *m*-CPBA in CH_2Cl_2 at room temperature to get the 7α,8α-epoxide **29** in 86% yield (Scheme 7).

The epoxy-diol **29** was selectively tosylated with 1.2 equiv. of *p*-tolunesulfonyl chloride in dry CH_2Cl_2 using freshly distilled triethylamine as a base with catalytic amount of DMAP for 6 h at room temperature to afford the mono tosylated compound **30** in 84% yield. Then the mono tosylated compound **30** was subjected to oxidation with 1.5 equiv. of iodoxy benzoic acid (IBX) in $DMSO/CH_2Cl_2$ at room temperature affording the tosylated ketone **31** in 86% yield (Scheme 8).



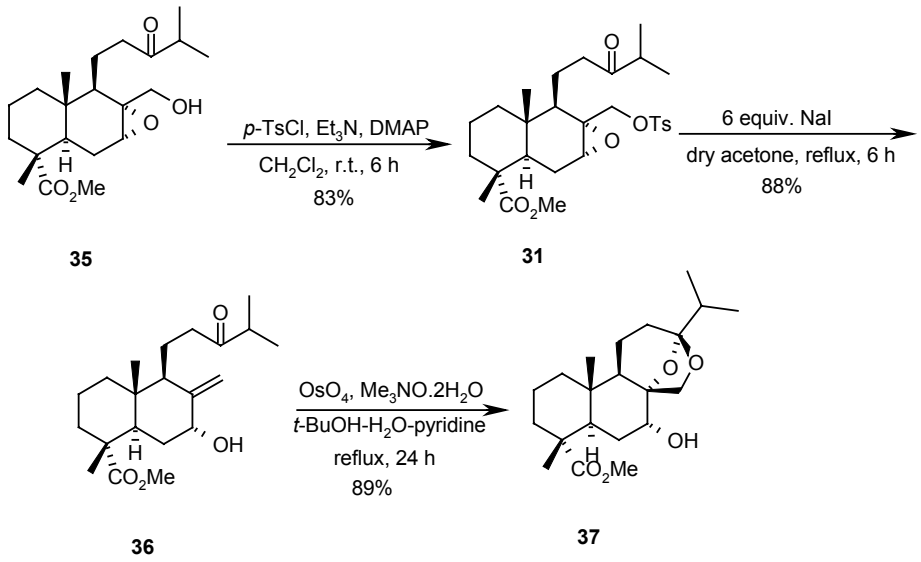
Scheme 8

The compound **31** was also synthesized from abietic acid **5** by another approach. In this approach abietic acid **5** was first converted to its methyl ester **32** with diazomethane in ether in quantitative yield. Then methyl abietate **32** was subjected to ozonolysis in CH_2Cl_2 at -78 ^oC to afford the ozonide **33** in 77% yield. The stable ozonide **33** was treated with 2.5 equiv of triphenylphosphine in CH_2Cl_2 at room temperature for 12 h to afford the epoxy aldehyde **34** in 82% yield as colorless crystal. The epoxy aldehyde **34** underwent selective reduction of aldehyde in presence of ketone using $NaBH_4$ in 30% EtOH in CH_2Cl_2 at -78 ^oC affording the α,β-epoxy alcohol **35** in 81% yield with 5% yield of the epoxy diol **29** (Scheme 9).



Scheme 9

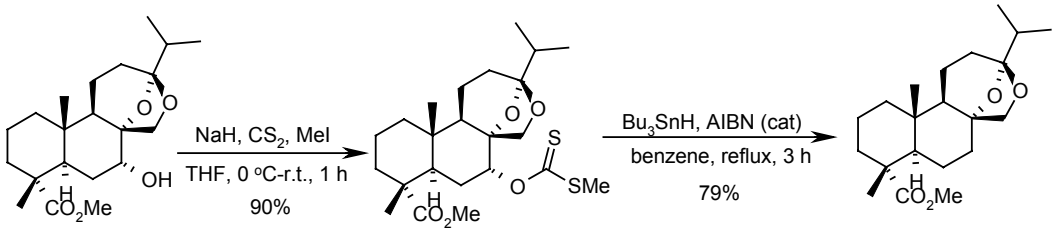
The epoxy alcohol **35** was converted into its tosylate derivative **31** using *p*-TsCl/ Et_3N/DMAP reagent system in CH_2Cl_2 at room temperature in 83% yield. In order to get the exo-cyclic double bond at C-8 position the compound **31** was treated with six equiv. of NaI in dry acetone at reflux temperature for 6 h which produced the allylic alcohol **36** in 88% yield. Treatment of the allylic alcohol **36** with a catalytic amount of OsO_4 in *t*-butanol-water-pyridine solvent mixture using trimethylamine *N*-oxide as co-oxidant at reflux temperature for 24 h resulted in the ketal **37** in 89% yield (Scheme 10).



35 31 36 37

Scheme 10

To knock out the hydroxyl group present in the ketal **37**, it was converted to its corresponding xanthate derivative **38** by treating with 2 equiv. of sodium hydride (60% w/v dispersion of oil), 3 equiv. of carbon disulphide and 2 equiv. of methyl iodide in dry THF at 0 ^{o}C in 90% yield, which was then deoxygenated under Barton-McCombie protocol using 2 equiv. of tri-*n*-butyltinhydride and catalytic amount of azobisisobutyronitrle as a radical initiator in dry benzene at reflux temperature for 3 h to afford the amberketal analogue **22** in 79% yield (Scheme 11).

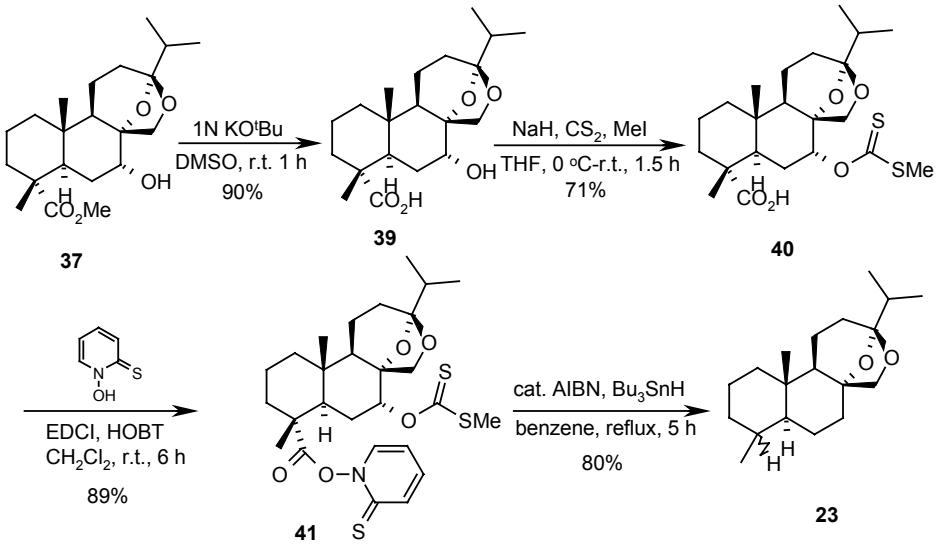


37 38 22

Scheme 11

To synthesize the decarboxylated analogue **23** of amberketal, the strategy of Barton-McCombie and Barton decarboxylation was applied. Thus the ketal **37** was deesterified with 1N solution of KO^{t}Bu in DMSO at room temperature to afford the acid **39** in 90% yield. The compound **39** was converted into its corresponding xanthate ester **40** treating with 4 equiv. of sodium hydride (60% w/v dispersion of oil), 3 equiv. of carbon

disulphide and 3 equiv. of methyl iodide in dry THF at 0 ^{o}C in 71% yield. Then the compound **40** was treated with 1.2 equiv. of 2-mercaptopyridine *N*-oxide in presence of 2 equiv. of each EDCI and HOBT to afford the Barton ester **41** in 89% yield. The Barton ester **41** was then deoxygenated and decarboxylated under Barton-McCombie protocol using 4 equiv. of tri-*n*-butyltinhydride and catalytic amount of azobisisobutyronitrle as a radical initiator in dry benzene at reflux temperature for 5 h to afford the Amberketal analogue **23** in 80% yield (Scheme 12).



Scheme 12

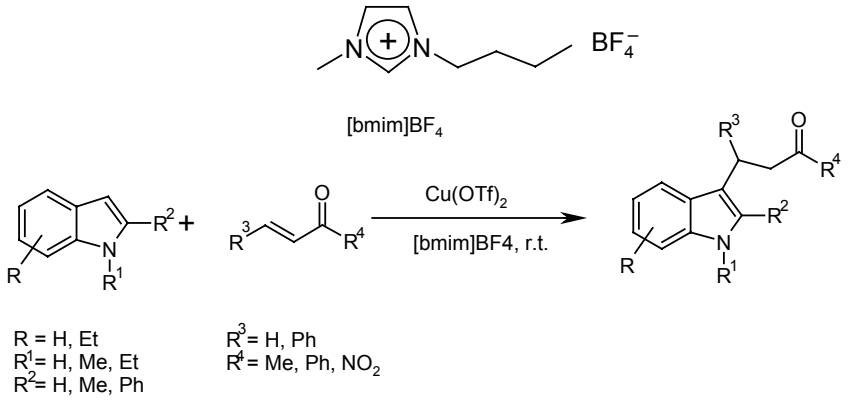
Chapter III:

Section-A: This section deals with an introduction to green chemistry, ionic liquids and their uses in organic synthesis.

Section-B: Conjugate addition of indoles to α,β-unsaturated ketones using $Cu(OTf)_2$ immobilized in ionic liquids.

A simple and direct method for the synthesis of 3-alkylated indoles involves the conjugate addition of indoles to α,β-unsaturated compounds in the presence of acid catalysts such as $Yb(OTf)_3$, $InCl_3$, $InBr_3$, $Bi(NO_3)_3$, $Bi(OTf)_3$, $CeCl_3.7H_2O$-NaI-SiO_2. Since indoles and their derivatives have become increasingly important in the field of pharmaceuticals, the development of simple, efficient, and environmentally benign approaches are desirable. As part of ongoing programme in developing new synthetic methodologies in our research group we developed one environmentally benign method to

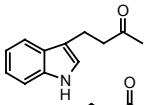
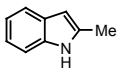
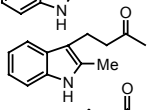
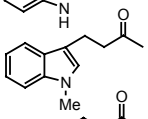
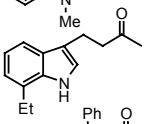
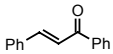
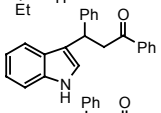
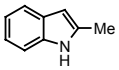
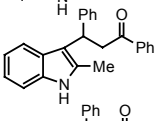
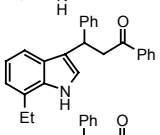
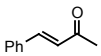
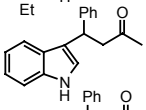
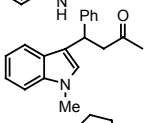
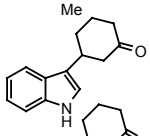
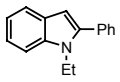
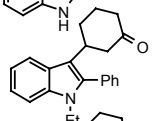
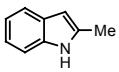
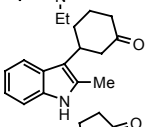
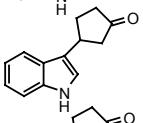
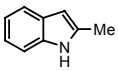
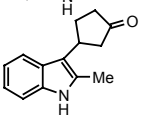
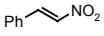
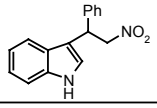
synthesize 3-alkylated indole derivatives using 1,3-dialkyl imidazolium based ionic liquids such as [bmim]BF_4 as a green reaction media. We first examined the reaction of indole with methyl vinyl ketone in the presence of 10 mol% copper(II) triflate immobilized in 1-butyl-3-methylimmidazolium tetrafluoroborate [bmim]BF_4 and the reaction afforded the product 4-(3-indolyl)-2-butanone in 90% yield (Scheme 13). The reaction proceeded efficiently at room temperature with high 1,4-selectivity and complete conversion of the reaction takes place in a short period of time (3.5 h). The product obtained was isolated by simple extraction with diethyl ether. Encouraged by the result obtained with indole and methyl vinyl ketone, we turned our attention to various substituted indoles and electron-deficient alkenes. Interestingly, numerous cyclic enones and chalcones underwent 1,4-addition with a range of indoles under the reaction condition to afford the corresponding 3-alkylated indoles. The recovered ionic liquid containing copper(II) triflate was reused five times without loss of activity, and even after fourth cycle, the product was obtained with similar yield (entry **e**, Table 1). The results are summarized in the **Table 1**.



Scheme 13

In summary, we have demonstrated a mild, clean and efficient protocol for the conjugate addition of indoles to α,β-unsaturated ketones using $Cu(OTf)_2$-[bmim]BF_4 as a novel and recyclable catalytic system. The enones show enhanced reactivity in ionic liquids thereby reducing the reaction times and improving the yield significantly. The simple experimental procedure combined with ease of recovery and reuse of this novel reaction medium is expected to contribute to the development of a green strategy for the conjugate addition reaction of indoles to enones.

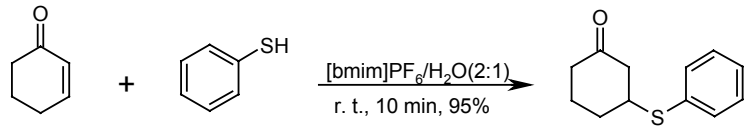
Table 1: $Cu(OTf)_2$- Catalyzed conjugate addition of indoles to enones using $[bmim]BF_4$

Entry	Indole	Enone	Product[a]	Time(h)	Yield(%)[b]
a				3.5	90
b		"		3.0	93
c		"		4.0	91
d		"		3.5	90
e				4.5	85
f		"		2.0	95
g		"		4.0	87
h				4.0	89
i		"		5.0	86
j				6.0	82
k		"		4.0	88
l		"		4.5	87
m				5.0	85
n		"		4.5	89
o				4.0	90

[a]All the products were characterized by ^1H NMR, IR, mass spectra.
[b]Isolated and unoptimized yields.

Section-C: Conjugate addition of thiols to α,β-unsaturated ketones using a [bmim]PF_6/H_2O system.

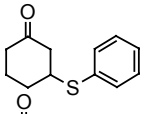
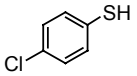
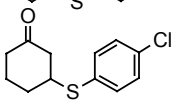
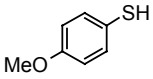
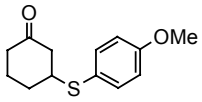
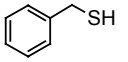
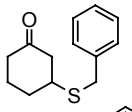
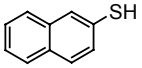
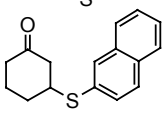
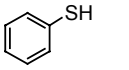
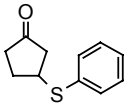
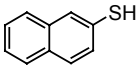
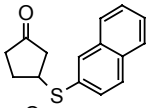
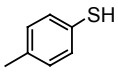
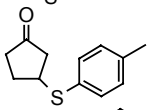
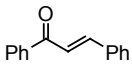
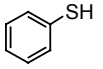
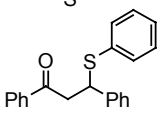
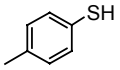
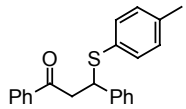
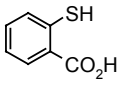
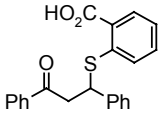
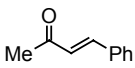
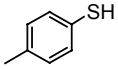
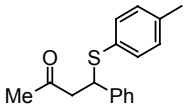
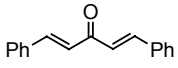
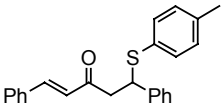
The conjugate addition of thiols to α,β-unsaturated ketones to form carbon-sulfur bond constitutes a key reaction in biosynthetic processes as well as in organic synthesis. The 1,4-addition of thiols to electron-deficient olefins through activation of thiols by bases or activation of acceptors with Lewis acid such as $InBr_3$, $Bi(NO_3)_3$. Increasing importants of organo sulfur compounds emphasize us to develop a simple, convenient, and environmentally benign approach. In this regard we initially examined the reaction of thiophenol with cyclohexen-2-one (entry **a**, Table 2) in 1-butyl-3-methyl imidazolium hexafluorophosphate/water (2:1) i.e. [bmim]PF_6/H_2O solvent system in the absence of catalyst (Scheme 14). The reaction proceeded efficiently at room temperature without the need of any acid or base catalyst affording the corresponding 1,4-adduct in 95% yield in a short time (10 min). After initial reaction of cyclohexen-2-one and thiophenol, the reaction mixture was extracted with diethyl ether and the recovered ionic liquid/water mixture was further washed with diethyl ether and reused five times without loss of activity.



Scheme 14

Various substituted thiophenols and benzylmercaptan also underwent conjugate addition to different enones affording their corresponding organosulfur compounds under this reaction condition and the results were presented in the **Table 2**. In summary, we developed a simple, convenient and efficient protocol for the 1,4-addition of thiols to α,β-unsaturated ketones using ionic liquids as green solvents under mild and neutral condition. The ionic liquids play the dual role of solvent and the promoter. The simple experimental procedure combined with ease of recovery and reuse of this novel reaction medium is expected to contribute to the development of a green strategy for the conjugate addition of thiols to enones.

Table 2: Conjugate addition of thiols to enones in 1-butyl-3-methylimidazolium ionic liquids/water

Entry	Enone	Thiols	Product[a]	[bmim]PF_6/H_2O		[bmim]BF_4/H_2O	
				Time (min)	Yield (%)	Time (min)	Yield (%)
a				10	95	15	93
b	"			15	93	10	92
c	"			10	97	15	95
d	"			25	91	20	90
e	"			20	90	25	89
f				15	95	20	93
g	"			20	90	30	88
h	"			10	94	15	91
i				15	95	20	93
j	"			10	92	15	95
k	"			45	90	60	85
l				20	92	25	90
m				25	89	30	87

[a]All the products were characterized by ^{1}H NMR, IR, mass spectra.
[b]Isolated and unoptimized yields.