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"Synthesis and application of innovative solvents in carbon–carbon bond formation reactions"

"Sintesi di solventi innovativi ed applicazione in reazioni di formazione del legame carbonio–carbonio"

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And finally, I would like to thank my boyfriend Mario, who, against all odds and even after chasing me around labs in the British Isles, has still the patience of dating me. Your love and encouragement are my strength.

Abstract

In this experimental work several different Ionic Liquids (ILs) were synthesised and used in C–C forming reactions. ILs were synthesized according to known literature procedures and under MW irradiation. The MW assisted synthesis of ILs was performed in presence of a solvent (CH_3CN or EtOH) and reaction parameters were optimized with the aid of a prediction software (CROW). The purity of the products was evaluated to derive a set of optimized conditions for the reaction.

Kinetic parameters for the IL formation (rate of quaternisation, k_2, E_a) reactions were measured for the MW assisted process, and compared to the ones obtained under conventional heating in a pressurized container.

Some of the synthesized ILs were employed in selected known catalytic organic reactions. The reactions studied were: Pd–catalysed methylation of aryl halides with DABAL–Me_3 in a biphasic system VOC–IL and metal triflate catalysed electrophilic alkylation and acylation of ferrocene in IL.

For the cross–methylation reaction, a new and air stable aluminum based methylating agent was employed, DABAL–Me_3.

A new protocol for the methylation of aryl halides with DABAL–Me_3 in a two phase system IL/VOC was optimised and tested on various substrates, with good results. Optimization of the reaction parameters, such as choice of the VOC/IL biphasic system, catalytic species and ligand was performed. The best ILs for such reactions were hydrophilic tetrafluoroborates. Reactions were performed in classic alkylmethylimidazolium based IL and in a DABCO based IL in presence of a bulky substituted phosphine (XPhos) and a structurally similar sulfonated phosphine ($XPhosSO_3H$), obtaining in all cases interesting results. Formation of the homocoupling by–products were observed for aryl halides bearing strong electron withdrawing substituents.

A qualitative ^{31}P NMR study of the catalyst retention in the IL phase was performed.

Recycling of the IL catalytic phases was attempted, but in all cases a decrease in the catalyst activity was observed.

Attempts were made to perfom the electrophilic alkylation of ferrocene in alkylmethylimidazolium and *N*–alkylpyridinium based IL. In all cases, modest results were obtained.

Acylation of ferrocene catalyzed by metal triflates was thoroughly investigated. Reaction parameters such as choice of the metal catalyst, reaction time and temperature, ratio between ferrocene and the acylating agent, choice of the IL used as the solvent were optimised for the acetylation of ferrocene. Different aliphatic and aromatic acylating agents were tested. Time and temperature were important parameters for the electrophilic acylation of ferrocene, since prolonged treatment caused substrate decomposition and/or catalyst deactivation. Both hydrophobic and hydrophilic alkylmethylimidazolium based ILs were used as solvents. Hydrophobic ILs gave best results, in particular 1–butyl–3–methylimidazolium bistriflylimide. Anhydrides behave as superior acylating reagents with respect to acyl chlorides. More reactive aliphatic anhydrides gave better results than aromatic anhydrides. MW irradiation allowed to quantitatively acylate ferrocene within minutes. MW irradiation improved the reactivity also of less reactive benzoic anhydride.

In questo lavoro sperimentale sono stati sintetizzati e caratterizzati diversi Liquidi Ionici. I Liquidi Ionici sintetizzati sono stati successivamente impiegati come solventi in reazioni di formazione di legame carbonio–carbonio. I Liquidi Ionici sono stati preparati e caratterizzati ottimizzando procedure riportate in letteratura.

In alcuni casi i Liquidi Ionici sono stati preparati mediante reazioni che prevedevano riscaldamento con le microonde. La sintesi di Liquidi Ionici microonde assistita è stata perfezionata con l'aiuto di un programma di calcolo delle rese (CROW), a partire da dati sperimentali noti. La purezza dei Liquidi Ionici risultanti è stata valutata qualitativamente mediante spettroscopia UV–Visibile: in base ai risultati ottenuti sono stata determinate le migliori condizioni di reazione (tempo e temperatura).

I dati ottenuti per le reazioni in presenza di riscaldamento alle microonde, sono stati utilizzati per determinare i parametri cinetici della reazione di quaternizzazione. Questi parametri sono stati poi confrontati con gli analoghi ricavati per la stessa reazione effettuata con riscaldamento convenzionale in un contenitore pressurizzato. Non sono stati notati effetti specifici dovuti al riscaldamento a microonde.

Alcuni Liquidi Ionici sono stati impiegati come solventi per alcune reazioni già note di formazione di legami C–C: in particolare sono state studiate la reazione di metilazione di alogeno areni Pd catalizzata e due reazioni di sostituzione elettrofila aromatica sul ferrocene, alchilazione ed acilazione di Friedel–Crafts.

Il DABAL–Me_3, un nuovo e più stabile derivato del trimetilalluminio, e stato utilizzato come agente metilante nelle reazioni Pd catalizzate. E' stato messo a punto un nuovo protocollo di reazione in cui la reazione viene effettuata in un sistema bifasico solvente molecolare/Liquido Ionico. Sono stati intrapresi studi preliminari per la scelta del solvente molecolare e del Liquido Ionico da utilizzare nella doppia fase, per la specie di Pd trattenuta in maniera più efficace, e per la scelta del ligando migliore. I migliori risultati sono stati ottenuti con Liquidi Ionici idrofili contenenti l'anione tetrafluoroborato. La reazione è stata effettuata utilizzando i classici Liquidi Ionici derivati dell'imidazolo e utlizzando un nuovo tipo di Liquidi Ionici funzionalizzati derivati del DABCO. Come leganti sono state scelte due diarilfosfine ingombrate stericamente, XPhos ed XPhosSO_3H, che si differenziano per il fatto di essere cariche (XPhosSO_3H) o meno (XPhos). La reazione di metilazione è stata effettuata su alogeno areni variamente sostituiti, ottenendo buoni risultati nella maggior parte dei casi. Nel caso di alogeno areni sostituiti con gruppi fortemente elettron attrattori è stata osservata anche la formazione del prodotto di omoaccoppiamento. La ritenzione della specie catalitica nella fase Liquido Ionico è stata valutata qualitativamente mediante spettroscopia NMR di fosforo. Si è tentato di riciclare la fase Liquido Ionico, contenente la specie catalitica, osservando in tutti i casi tempi di reazione più lunghi.

La reazione di alchilazione del ferrocene catalizzata da $Sc(OTf)_3$ è stata effettuata in diversi Liquidi Ionici idrofobi, con risultati molto modesti.

Risultati migliori ha dato invece la reazione di acilazione del ferrocene, sempre catalizzata da $Sc(OTf)_3$ e triflati di lantanidi. Le varie condizioni di reazione (scelta del catalizzatore, del Liquido Ionico, tempi e temperature di reazione) sono state ottimizzate per la reazione di acetilazione del ferrocene. Il protocollo di reazione è stato quindi esteso ad altri agenti acilanti, sia alifatici che aromatici. I tempi e le temperature di reazione sono risultati parametri fondamentali per questo tipo di reazione, dato che all'aumentare dei tempi di reazione si osservava decomposizione del prodotto, del reagente e/o disattivazione del catalizzatore. I Liquidi Ionici utilizzati per questo tipo di reazione erano sia idrofili che idrofobi; i risultati migliori sono stati

osservati con Liquidi Ionici idrofobi ed in particolare con la bistriflilimmide di 1–butil–3–metilimidazolio, [C_4mim]Tf_2N. Le anidridi si sono dimostrate agenti acilanti più efficienti rispetto ai corrispondenti cloruri acilici.
In presenza di riscaldamento a microonde è stata osservata una drastica diminuzione dei tempi di reazione, con formazione quantitativa del prodotto acilato in pochi minuti e ad un miglioramento delle rese per agenti acilanti meno reattivi, come l'anidride benzoica.

Keywords: alkylmethylimidazolium based ILs, synthesis and purification of ILs, MW heating, Pd–catalysed cross methylation, DABAL–Me_3, DABCO based ILs, Friedel–Crafts alkylation of ferrocene, Friedel–Crafts acylation of ferrocene.

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Table of symbols and abbreviations

$[C_{12}mim]Cl$	1–dodecyl–3–methylimidazolium chloride
$[C_2mim]BF_4$	1–ethyl–3–methylimidazolium tetrafluoroborate
$[C_2mim]EtSO_4$	1–ethyl–3–methylimidazolium ethylsulphate
$[C_2mim]I$	1–ethyl–3–methylimidazolium iodide
$[C_2mim]SbF_6$	1–ethyl–3–methylimidazolium hexafluoroantimoniate
$[C_2mim]TfO$	1–ethyl–3–methylimidazolium triflate
$[C_4mim]BF_4$	1–butyl–3–methylimidazolium tetrafluoroborate
$[C_4mim]Br$	1–butyl–3–methylimidazolium bromide
$[C_4mim]Cl$	1–butyl–3–methylimidazolium chloride
$[C_4mim]N(CN)_2$	1–butyl–3–methylimidazolium dicyanimide
$[C_4mim]PF_6$	1–butyl–3–methylimidazolium hexafluorophosphate
$[C_4mim]Tf_2N$	1–butyl–3–methylimidazolium bistriflylimide
$[C_4mim]TfO$	1–butyl–3–methylimidazolium triflate
$[C_4mmim]BF_4$	1–butyl–2,3–dimethylimidazolium tetrafluoroborate
$[C_4mmim]Cl$	1–butyl–2,3–dimethylimidazolium chloride
$[C_4mmim]N(CN)_2$	1–butyl–2,3–dimethylimidazolium dicyanimide
$[C_4mpyr]Tf_2N$	1–butyl–1–methylpyrrolidinium bistriflylimide
$[C_4py]BF_4$	*N*–butylpyridinium tetrafluoroborate
$[C_4py]Br$	*N*–butylpyridinium bromide
$[C_4py]Tf_2N$	*N*–butylpiridinium bistriflylimide
$[C_5mim]PF_6$	1–methyl–3–pentylimidazolium hexafluorophosphate
$[C_6DABCO]BF_4$	1–hexyl–4–aza–1–azaniabicyclo[2.2.2]octane tetrafluoroborate
$[C_6DABCO]Br$	1–hexyl–4–aza–1–azaniabicyclo[2.2.2]octane bromide
$[C_6mim]Br$	1–hexyl–3–methylimidazolium bromide
$[C_6mim]Cl$	1–hexyl–3–methylimidazolium chloride
$[C_6mim]PF_6$	1–hexyl–3–methylimidazolium hexafluorophosphate
$[C_6mim]Tf_2N$	1–hexyl–3–methylimidazolium bistriflylimide
$[C_8mim]Cl$	1–methyl–3–octylimidazolium chloride

$[C_8mim]Tf_2N$	1–methyl–3–octylimidazolium bistriflylimide
$[C_8py]Cl$	*N*–octylpyridinium chloride
$[C_nmim]X$	1–alkyl–3–methylimidazolium salt/IL
$[C_npy]X$	*N*–alkylpyridinium salt/IL
$1,1'–Cy_2Fc$	1,1'–(dicyclohexyl)ferrocene
AcFc	Acetylferrocene
Cp	Cyclopentadienyl
CROW	Chemical Reactions Optimization Wand
Cy	Cyclohexyl
CyFc	Cyclohexylferrocene
D	Dissipation Factor
$DABAL–Me_3$	1,4–diazabicyclo[2.2.2]octane trimethylaluminum adduct
DABCO	1,4–diazabicyclo[2.2.2]octane
ESI–MS	Electrospray Ionization Mass Spectrometry
Fc–	Ferrocenyl
FcCOEt	Propanoylferrocene
FcH	Ferrocene
FG	Functional Group
HILIC	Hydrophilic Interaction Liquid Chromatography
HRMS	High Resolution Mass Spectrum
ILs	Ionic Liquids
MAOS	Microwave Assisted Organic Synthesis
MeIm	1–methylimidazole
Mepyr	1–methylpyrrolidine
MW	Microwave Energy
OF	Optical Fibre
SILP	Supported Ionic Liquid Phase
T_b	Boiling Temperature (°C)
T_{bulk}	Internal Temperature of the MW Irradiated Sample
Tf_2N	Bis(trifluoromethansulphonyl)imide = bistriflylimide
TfO	(Trifluoromethan)sulphonate = triflate
T_m	Melting Temperature (°C)

VOC	Volatile Organic Compound
x	Penetration Coefficient
δ	Loss/Displacement Angle
ε'	Dielectric Constant (with MW applied field)
ε''	Dielectric Loss Factor
ε_s	Dielectric Constant
τ	Half Life

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Foreword

Sustainability has become a key concept in modern organic synthesis, as well as a needed paradigm to transpose also to industrial processes. [1,2]

In order to set some standard toward sustainability, the Twelve Principles of Green Chemistry were stated back in 2001, and at the same time some parameters of practical use were developed in order to measure the "greenness" of a determined process. [1,3]

The Twelve Principles of Green Chemistry

... in theory...	**... in practice...**
1. **It is better to prevent waste than to treat or clean up waste after it is formed.**	Avoid processes that imply separation, treatment and disposal of hazardous material. The sustainabilityof a process can be measured through the E–Factor. $\text{E–Factor} = \frac{Total\ Waste\ (Kg)}{Product\ (Kg)}$
2. **Synthetic methods should be designed to maximize the incorporation of all materials used in the process into the final product.**	Measure the atom economy of the process rather than the yield. $\text{Atom economy} = \frac{Mass\ of\ desired\ product}{Mass\ of\ all\ reactant} \times 100$
3. **Wherever practicable, synthetic methodologies should be designed to use and generate substances that possess little or no toxicity to human health and the environment.**	Elimination or severe limitation of all hazards when designing an experiment.
4. **Chemical products should be designed to preserve efficacy of function while reducing toxicity.**	Structural modifications of the product to make it innocuous or decrease its bioavailability.
5. **The use of auxiliary substances (e.g. solvents, separation agents, etc.) should be made unnecessary wherever possible and, innocuous when used.**	Avoid the use of separation/ purification techniques involving the use of large amounts of solvents (i.e. crystallization, chromatography). When possible prefer alternative solvents (i.e. supercritical fluids, ionic liquids, acqueous systems), solventless reactions or immobilised solvents.
6. **Energy requirements should be recognized for their environmental and economic impacts and should be minimized. Synthetic methods should be conducted at ambient temperature and pressure.**	Minimisation of the energy requirement: avoiding separation steps and heating/cooling. Design of catalysts to perform the reaction at r.t. and p.a. When needed, use of "smart" energy such as microwave or sonic.

The Twelve Principles of Green Chemistry

… in theory…	**… in practice…**
7. **A raw material of feedstock should be renewable rather than depleting wherever technically and economically practicable.**	Usage of biological feedstock rather than fossil fuels. Feedstocks that can be regenerated in relatively short times (i.e. human lifetime) should be preferred. Avoid the dependence from a particular type of starting material (like petroleum nowadays), in order to minimize the social and economical effects associated.
8. **Unnecessary derivatization (blocking group, protection/deprotection, temporary modification of physical/chemical processes) should be avoided whenever possible.**	
9. **Catalytic reagents (as selective as possible) are superior to stoichiometric reagents.**	Catalytic are superior to stochiometric reactions: the catalyst enhances the reaction selectivity (regio–, chemo–, stereo–) and/or minimizes the energy requirements.
10. **Chemical products should be designed so that at the end of their function they do not persist in the environment and break down into innocuous degradation products.**	Biodegradability should be considered when choosing a particular starting material/process and materials and processes should be designed in order to ensure that the products obtained will be biodegradable.
11. **Analytical methodologies need to be further developed to allow for real–time, in–process monitoring and control prior to the formation of hazardous substances.**	
12. **Substances and to form of a substance used in a chemical process should be chosen so as to minimize the potential for chemical accidents, including releases, explosions, and fires.**	Use solids or liquids with low vapour pressure instead of volatile solvents. Use of reagents able to transfer halogen atoms rather than molecular halogens. Development of "just–in–time" techniques.

While the uptake of sustainability is still slow and scattered in industrial environment, the academic world response was fast and active.

Restricting our view just to lab scale processes we can consider several ways to improve the sustainability of a process:

- *catalytic methodology:* avoid the use of stoichiometric reagents, preferring catalytic process, with particular emphasis on developing new efficient catalytic systems (such as metal/ligand catalysts, organocatalysts); [4,5]
- *alternative reagents:* use of biological feedstock and "smart" synthesis, targeting a particular molecule of interest rather than modeling with a simpler molecule; [6]
- *alternative reaction media and approaches:* with particular emphasis on the use of ionic liquids, supercritical fluids and reactions performed in aqueous media, use of

supported reagents or solvents. Innovative approaches include one–pot rather than multistep synthesis and the development of reaction protocols characterized by the extensive use of cascade reactions; [7,8]

- *alternative energy sources:* use of microwave energy complementarily to conventional heating;

- *implementation in industrial environments:* the possibility of scaling up the process without significant loss on sustainability, selectivity and efficiency.

Many research programs have been developed in this respect, implementing and developing one (or more) of the Green Chemistry principles.

In this respect, the work summarized in this thesis aims to improve the sustainability of known organic reactions by means of synthesizing and using alternative and potentially more sustainable solvents, such as Ionic Liquids (ILs). This was possible thanks to the Italian Ministry of Education, which founded a Ph. D. position on synthesis and application of alternative reaction media, as part of a funding program for young researchers. Various ILs were synthesized by standard literature condition and also by using a possible sustainable technology, such as MW heating. The MW assisted synthesis of ILs was undertaken at the QUILL Research Centre, Queen's University, Belfast, UK by means of a Marie Curie Fellowship funded by the European Union.

Productive interaction between European Union labs was also possible for the application of ILs in synthetically useful reactions. As a matter of fact, the development of new reaction protocols for the formation of C–C, C–H and C–X bond is the main objective of the European Cost Action D40. [9] Ways to achieve such an ambitious target include improving the sustainability of the reactions by using alternative reaction media (such as ILs, supercritical fluids, biphasic catalysis or supported reagents) and by more efficient reaction protocols (cascade and domino reactions are to be preferred to conventional multistep synthesis) that should be used directly on "real" synthetic problems. The latter point of interest should also ensure a fast implementation in industrial contexts. The part of the work on methylation of aryl halides presented in this Ph. D. thesis was performed within the framework of COST D40, by means of a scientific short term mission in Prof. Simon Woodward labs, University of Nottingham, Nottingham, UK.

In a continuous effort to improve the sustainability of know organic chemistry reactions, an efficient protocol for the Friedel–Crafts acylation of ferrocene in ILs was developed. Improvements included the use of catalytic amounts of metal triflates Lewis acids (rather than the stoichiometric amounts needed in conventional synthesis), and the use of MW heating to decrease reaction times.

Chapter 1: Introduction and synthesis of ILs

1.1. What is an ionic liquid?

The term "ionic liquid" defines a salt which is liquid at temperatures below 100 °C. [10,11] Being liquids salts, ILs are very different from molecular solvents, and chemically analogous to molten salts.

ILs are exclusively composed of ions; [10,12] this simple yet crucial feature results in their unique physico–chemical properties, among which can be ascribed: [12,13]

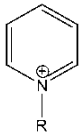
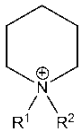
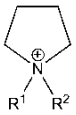
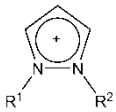
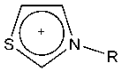
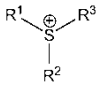
- high thermal stability;
- low vapour pressure;
- wide liquid range (up to 200 °C);
- high thermal conductivity;
- large electrochemical window;
- low nucleophilicity, thus providing a weakly or non coordinating reaction environment;
- limited solubility in most of the commonly used VOCs.

With more than 15 years of extensive research on their synthesis and applications, they are still, potentially, an excellent and, in most cases, sustainable alternative to organic solvents.

ILs are very different from their inorganic molten salts counterpart, although in principle these two classes of compounds should be very similar, at least when considering their composition. Comparing the melting point of a molten salt (*i.e.* 801 °C for NaCl and 614 °C for LiCl), [13] to the melting points of ILs, which are generally liquid at r.t. or at T<100 °C, we can foresee that ILs have a much wider applicability.

In order to understand why this class of solvents has a unique array of properties, we have to look closely at their structure and composition. Being salts, ILs are composed exclusively of ions and the chosen combination anion/cation strongly affects the properties of the resulting IL. Some of the most common cations and anions found in ILs are summarised in Table 1.1 and Table 1.2 respectively.

Table 1.1. Selected common organic cations present in ILs.

Most commonly used cations	
	1–alkyl–3–methylimidazolium $[C_nmim]^+$
	*N*–alkylpyridinium $[C_npy]^+$
	*N*–alkyl–*N*–methylpiperidinium $[C_nmpyp]^+$
	Tetraalkylammonium $[N_{wxyz}]^+$
	Tetralkylphosphonium $[P_{wxyz}]^+$
	*N*–alkyl–*N*–methylpyrrolidinium $[C_nmpyr]^+$
	1,2–dialkylpyrazolium
	*N*–alkylthiazolium
	Trialkylsolfonium $[S_{xyz}]^+$

$R^{1,2,3,4} = CH_3(CH_2)_{n-1}$ (n = 0, 2, 4, 6, 8); aryl, etc.
The abbreviation $[C_nmim]^+$ stands for the 1–alkyl–3–methylimidazolium cation, were n is the number of carbon atoms in the linear alkyl chain, while *w, x, y, z* represent the length of the corresponding alkyl chains in tetralkylammonium, tetralkylphosphonium and trialkylsolfonium cations.

Table 1.2. Selected anions commonly found in ILs.

Some possible anions	
$[PF_6]^-$	hexafluorophosphate
$[Tf_2N]^-$	bis(trifylimide)
$[BR_1R_2R_3R_4]^-$	tetralkylborate
$[BF_4]^-$	tetrafluoroborate
$[TfO]^-$	triflate
$[N(CN)_2]^-$	dicyanamide
$[CH_3CO_2]^-$	acetate
$[CF_3CO_2]^-$	trifluoroacetate
$[NO_3]^-$	nitrate
Cl^-	chloride
Br^-	bromide
I^-	iodide
$[Al_2Cl_7]^-$, $[AlCl_4]^-$	epta– and tetrachloroaluminate mixtures

COORDINATION POWER

MISCIBILITY WITH WATER

The cations present in the IL scaffold, are generally large organic derivatives, characterised by unsymmetrical substituents. To date the most widely used are 1–alkyl–3–methylimidazolium, $[C_nmim]^+$ cation, and among these, the most common and investigated are the $[C_2mim]^+$ and $[C_4mim]^+$. [14] From the structure (Entry 1, Table 1.1) it can be seen why this type of cations is so interesting, a double unsymmetrical substitution is possible (on both *N*–1 and *N*–3); such substitution is crucial since, along with the chain length, it strongly affects the mp and the miscibility with VOCs of the resulting IL. [14,15]

The variety of ILs so far synthesised IL arises mainly from the anions used. The nature and the type of anion is critical for some physico–chemical properties of the resulting IL such as viscosity, thermal stability, and, to some extent, mp and miscibility with VOCs. [14]

The first anions used in an IL system were chloroaluminate anions: those ILs are usually referred as "first generation ILs". [16,17] They were characterised by tunable Lewis acidity/basicity, that was easily achieved by changing the molar ratio between the organic cation and $AlCl_3$ used. The resulting ILs generally displayed strong coordinating power and high viscosity; moreover chloroaluminate ILs were highly hygroscopic and reactive with water, so their use was limited to dry atmosphere or dry box conditions.

A turning point for the circulation of ILs in research laboratories, was the development of "second generation ILs" containing anions such as BF_4^-, PF_6^-, TfO^-, AcO^-, NO_3^- and Tf_2N^-. [17-19] All of these ILs are air stable and water stable (with the exception of BF_4^- and PF_6^-, which are somewhat sensitive towards hydrolysis) and can be handled in standard lab conditions. These ILs are also less hygroscopic and viscous when compared to the first generation counterpart, and much more "inert" when used in chemical transformations.

The possible cation/anion combinations are continuously increasing; in recent years ILs bearing non fluorinated anions were synthesised, the main representatives being dicyanamide and alkylsulphate containing ILs. This type of ILs displays several benefits in terms of viscosity, thermal stability and robustness towards hydrolysis, when compared to the fluorinated anion containing counterpart.

1.2. Synthesis of ILs

ILs are generally synthesised by a sequence of two reactions: [15,20]

- *quaternisation* of an appropriate Lewis base (amine, phosphine, sulphide) with the alkyl halide of interest;
- *metathesis* of the halide salt obtained, to be displaced by a salt or an acid containing the anion of interest.

This reaction protocol is the most widespread for the lab scale synthesis of IL, since it is an easy way to obtain IL with good purity; it has, however, some limitations, which will be highlighted step–by–step.

1.2.1. Quaternisation reaction

The cationic part of the IL is generally formed by a quaternisation reaction between an appropriate Lewis base (the "scaffold" of the cation) and an alkyl halide (or an alkyl sulphate). [16,19,21,22] These reactions are known to be exothermic and need temperature control, in particular when using alkyl halides with short alkyl chain (C_2–C_3) and moving to more reactive bromides and iodides instead of chlorides.

Quaternisations are usually solventless reactions: this has the advantage of making this reaction more sustainable, since in these conditions the atom economy of the process is 1; in practice the product formed is either a solid or an highly viscous liquid, so the formation of "hot spots" during the course of the reaction is not avoidable and results in colouring of the reaction mixtures (which turn from colourless to yellow). This means that, to obtain a pure and colourless product, washings or crystallizations are required. [15,20].

Another drawback of the quaternisation reaction, is that the product is obtained in high but not quantitative yields (generally, the product can be obtained with a 93–94 % yield); again this means that the product still contains some reagents (in particularly the less volatile Lewis base), that have to be removed (generally by drying *in vacuo*).

Some possible solutions to the limitations highlighted for the quaternisation reaction include:

- performing these reactions under vigorous stirring, temperature control, and inert atmosphere (oxygen can accelerate the formation of by products);
- performing these reactions in presence of a solvent: this prevents the formation of "heat sacs", but involves an extra step (removal of an high boiling point solvent, since there reactions are usually carried out in toluene or 1,1,1–trichloroethane) in the reaction work up;
- use of a small excess of alkyl halide (generally just 1.1 equiv. is necessary) with respect to the Lewis base, to ensure that all the Lewis base has reacted.

The standard protocol for the lab scale quaternisation reaction includes: [20]

- purification of the reagents used (with particular care on the Lewis base chosen);
- reaction performed under inert atmosphere, heating is sometimes needed as the reaction temperature depends on the reagents used (alkyl bromides react at r.t., while chlorides need heating at ca. 70 °C, operating T depends strongly also on the Lewis base chosen);
- solventless reaction;
- the product obtained dried *in vacuo* to eliminate the residual reagents;
- consecutive crystallizations from CH_3CN/ethyl acetate (or diethyl ether), until a colourless crystalline solid is obtained (also this is a critical step, being quite laborious and costly); [16,21]
- purity check of the starting material: generally by ^{1}H NMR and ^{13}C NMR spectra (usually the halide salts are not the final product so purity can be easily checked by routine spectra).

This protocol has the advantage of obtaining a clean product in relatively good yields (90 %, even with a crystallization step), starting from cheap and readily available reagents and without the need of a solvent. Apart for the disadvantages highlighted above, there are some practical limitations to this reaction, in particular on the work–up step: the resulting halide salts are highly hygroscopic so it is advisable to carry out the purification in a dry box, or do the purification operations quickly in order to maintain the product free of moisture.

It is important to stress the fact that much of the purification efforts are concentrated on this first step, since the salt obtained is usually a solid and its

purification by crystallization is easier and more efficient than working with the IL itself, which cannot be purified by distillation.

1.2.2. Metathesis reactions

Once obtained the halide salt it is necessary to introduce the "right" anion in the ionic couple. For the ILs mostly used in the laboratory, this is efficiently done by anion metathesis of the halide salt with a salt containing the anion of interest. Examples of anions used for metathesis are reported in Table 1.3.

Table 1.3. Examples of ILs prepared by anion metathesis. [20]

IL	Anion source	Reference
[cation][PF_6]	HPF_6	[23-25]
[cation][BF_4]	HBF_4, NH_4BF_4, $NaBF_4$	[18,19,25-28]
[cation][Tf_2N]	$LiTf_2N$	[19,25]
[cation][TfO]	$CF_3SO_3CH_3$, $NH_4[(CF_3SO_3)]$	[19]
[cation][AcO]	$Ag[CH_3CO_2]$	[18]
[cation][CF_3CO_2]	$Ag[CF_3CO_2]$	[18]
[cation][$CF_3(CF_2)_3CO_2$]	$K[CF_3(CF_2)_3CO_2]$	[19]
[cation][NO_3]	$AgNO_3$, $NaNO_3$	[19,25,29]
[cation][$N(CN)_2$]	$Ag[N(CN)_2]$	[30]
[cation][$CB_{11}H_{12}$]	$Ag[CB_{11}H_{12}]$	[31]
[cation][$AuCl_4$]	$HAuCl_4$	[32]

The metathesis is usually performed in water (mostly when hydrophobic ILs are synthesized) or in an appropriate organic solvent (for hydrophilic ILs). When possible, cheaper Group 1 metal salts are used. In cases where the resulting IL is poorly soluble in organic solvents or the purification from the salt by-product is not efficient, anion exchange from Ag(I) salts is required.

Metathesis is particularly demanding in the case of water–miscible IL, due to the complex separation of the desired IL from the undesired salt. The use of silver salts can overcome this limitation, but is a rather expensive choice. Some alternative have been raised in the case of water miscible ILs:

- to perform the metathesis reaction in water, extract the IL with CH_2Cl_2 and wash the organic layer with deionised water until a negative $AgNO_3$ test is obtained; [28,33]
- to perform the metathesis reaction in an organic solvent, such as acetone or CH_2Cl_2, where the salt by–product has a limited solubility. [25,34]

Both these methods have some limitations: when using the "water approach" there is a loss of product in the washing step, while, when the reaction is carried out in an organic solvent, the solubility of the by–product in the mixture VOC–IL cannot be ignored and washing steps with water are still required, affecting the yield of the isolated IL.

The resulting IL is generally characterized by ^{1}H and ^{13}C NMR spectra.

1.3. Issues on the purity specifications of IL

ILs have been synthesized and used extensively, particularly in the past 15 years, and while they are still massively present in the literature, little has been published on rationalization of the analytical techniques for the determination of impurities in ILs. To date it is still not possible to purchase commercial ionic liquids of well defined purity, and the situation does not improve when we consider lab scale synthesized ILs: purity is generally improved when compared to the commercial products, but the analytical techniques employed for purity determinations are various and not standardized.

As we have seen previously, impurities can form both in the quaternisation and in the metathesis step. Coloured impurities are usually formed during the quaternisation reaction: this step is probably the least clean since the reaction itself is quite exothermic but in some cases requires heating. Unluckily, the nature of coloured impurities is still unclear and can be ascribed to several reasons:

- coloured impurities in the starting materials;
- oxidation products;
- thermal degradation of the starting material.

What is known, is that coloured impurities are normally detected only by UV–Vis spectroscopy and not by the techniques normally used for the characterization of ILs and their precursors (mainly NMR, but also IR spectroscopy). These impurities affect prominently the colour of the resulting IL, but have little effect on its properties, unless, of course, it is used in spectroscopy.

A larger effect on the properties of ILs is observed when the impurities left from the quaternisation step are unreacted starting material. While the alkylating agent can be easily separated from the reaction mixture simply by drying *in vacuo*, the left over

Lewis base is more problematic. The problems arise from the fact that the base has a high boiling point (in particular in the case of MeIm) or that it can be a solid, or it generally has more affinity with the IL phase than the alkylating agent; its persistence can dramatically affect the properties of the resulting IL, in particular when used in catalysis. Thus, in order to overcome this limitation, quaternisation reactions are usually performed in a slight excess of alkylating agent.

On the basis of the discussion reported above, the importance of analytical methodologies to determine quantitatively the "total ionic liquid content" of the product obtained after the quaternisation step is self–evident. [35] Several methods have been developed among which UV–Vis measurements, [36] ESI–MS spectrometry, capillary electrophoresis, [37,38] HILIC, [39] GC analysis [35] and HPLC paired up with UV detection. [35,40,41] These methods are both direct and indirect, which means that in most cases it is easier to measure the quantity of the impurity present, rather than the quantity of IL. It is worth to mention that the UV–Vis method developed by Holbrey *et al.* [36] and the HPLC methods developed by Stepnowski [41] and Stark [35] are easy and applicable to both lab and industrial scale synthesis of ILs.

While for the quaternisation step it is possible, to some extent, to minimize the formation of undesired impurities and avoid reagent residues, this is not so straightforward for the impurities obtained from the metathesis step. In fact, regardless if the metathesis is performed in water or in VOC, a salt or an acid residue is always formed. The former have a limited solubility in most of the crude IL, but have their own solubility in the IL/solvent system, which is not known and is the cause of the halide impurities found in the resulting IL. [20] The determination of halide impurities in ILs is the field in which most of the "analytical efforts" are concentrated: [35] a large number of methods for their determination have been tested and developed (mostly for chloride containing precursors) from chloride selective electrodes, [29] to gravimetric precipitations ($AgNO_3$ test, Volhard titration and/or Nessler cylinder method), [42,43] voltammetry [44,45] and ion chromatography. [46,47]

Total removal of the halide salt or minimization and quantitative determination of it, is desirable, since its presence in the IL affects tremendously the IL physical properties, as well as its performance in the application of choice.

Another contaminant which needs to be taken care of is water. As we have seen, some key steps during the preparation of an IL are performed in water and/or need extractions with water. [20,28,33] The IL can be initially dried, when in solution with an organic solvent, with the most commonly used drying agents (neutral alumina or anhydrous Na_2SO_4), and, after removal of the organic solvent, dried *in vacuo* under gentle heating for 24 h. The water content of the IL can then be determined quantitatively by Karl–Fischer titration. [48] This treatment is also effective to remove residuals of VOCs that might be present in the IL synthesized.

1.4. Issues on the large scale synthesis of ILs

Most of the literature concerning ILs synthesis deals with lab scale processes, however there is a need for one or more reliable industrial scale processes for the synthesis of ILs. This development would have, some important practical effects:

- decrease in the cost of the IL product;
- a product of defined and quantified purity;
- a more widespread use of ILs in industrial processes.

As we have seen previously, there are still some issues concerning the scaling up of the synthesis of ILs, *e.g.* tight temperature control during the quaternisation step, the need of several crystallizations of the quaternisation product, the extensive use of VOCs in the quaternisation and metathesis step; all of them are drawbacks in terms of costs and sustainability.

In recent years, some alternatives have arisen: from the use of water and activated charcoal (instead of recrystallizations) to eliminate the coloured impurities formed during the quaternisation step, [49] to the use of microreactors [50] and MW energy for the quaternisation step. [51-54] The latter two also have the advantage of being techniques that permit a tight control over reaction conditions (mainly T and p), giving drastic reduction of reaction times.

1.5. Experimental section

1.5.1. Instruments, materials and methods

All solvents used were of reagent grade and used without further purification. CH_3CN was purchased from Riedel–de–Haën and Carlo Erba, Et_2O from Riedel–de–Haën and Carlo Erba, ethyl acetate from Riedel–de–Haën, dichloromethane from Fluka and Carlo Erba, acetone from Fluka. All deuterated solvents ($CDCl_3$, acetone–d_6) were purchased from Sigma Aldrich and used as received.

1–Methylimidazole was purchased from Fluka and used as received, in some cases it was distilled from KOH *prior* to use. [20] 1,2–Dimethylimidazole was purchased from Sigma Aldrich and used as received. Pyridine was purchased from Sigma Aldrich and distilled *prior* to use. [55] DABCO was purchased from Sigma Aldrich and sublimed under reduced pressure *prior* to use. [55]

Alkyl halides were purchased from several sources (1–bromobutane from Acros, 1–bromohexane and 1–chlorobutane from Sigma Aldrich) and used without further purification.

Metathesis salts were purchased from several sources: $LiTf_2N$ and $Na[N(CN)_2]$ from Fluka, $NaBF_4$ from Sigma Aldrich and KPF_6 from Alfa Aesar. They were all used as received.

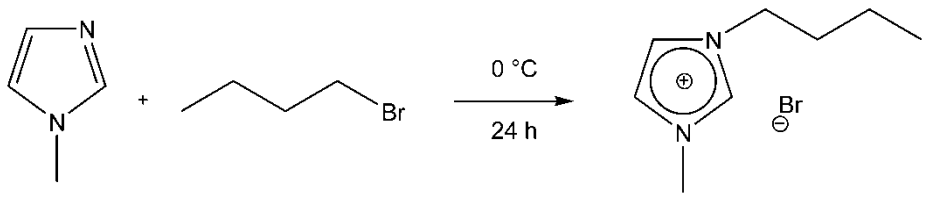
Activated charcoal was purchased from Carlo Erba, neutral alumina from Fluka and anhydrous Na_2SO_4 from Riedel–de–Haën and Carlo Erba.

NMR analysis were performed with Bruker Avance 300 and 400 spectrometers operating at a 300.1 MHz and 400.1 MHz frequency, respectively, for the proton and 75.4 MHz (Avance 300) for the ^{13}C, using the residual signal of the solvent as the internal reference.

1.5.2. Synthesis of IL precursors

All quaternisation reactions were performed solventless except for the DABCOnium IL precursor. Purification methods varied.

1.5.2.1. Synthesis of 1–butyl–3–methylimidazolium bromide [C4mim]Br



Scheme 1.1. Synthesis of [C4mim]Br.

This ionic liquid precursor was synthesised according to reported literature procedures, [21,33] with slight modifications.

In a typical experiment, 120 ml (1.51 mol) of 1–methylimidazole, were poured into a single–necked, 500 ml round bottom flask, equipped with a magnetic bar. The flask was charged with a 250 ml dropping funnel, which contained 162 ml (1.51 mol, 1.00 equiv.) of 1–bromobutane. The flask was then immersed in an ice bath and 1–bromobutane was added dropwise to the stirred MeIm neat in ca. 3 h. After all the alkyl halide was added, the solution was left under vigorous stirring for 24 h. At first the solution turned cloudy white (as the quaternisation reaction takes off, a non homogenous solution is observed, since the resulting salt is not miscible with the alkyl halide), while, at the end of the reaction a viscous and yellowish liquid was obtained.

The resulting salt is generally purified from unreacted starting material and coloured side products, through recrystallization. Recrystallization has the advantage of giving a purified product, but, with this class of compounds also shows several drawbacks. Imidazolium, pyridinium and DABCOnium halides are all fairly hygroscopic salts, therefore a "long" procedure such as several crystallization/washing steps carried out in normal lab conditions, could result in loss of product due to water incorporation. Secondly, all the salt synthesised are solid at r.t., but their mp is fairly close to the bp of CH_3CN (*i.e.* [C4mim]Br mp is 79.5 °C, [19] which is almost equal to 81–82 °C, the bp of CH_3CN), so it is ambiguous whether we can talk about crystallisation in CH_3CN or to what extent it is just a melting process. A third problem is that all salt precursors are soluble also in cold CH_3CN, therefore it is necessary to recycle the mother liquors in order to retrieve the maximum product possible.

In general, the purification procedure involves several recrystallizations from CH_3CN and washings with EtOAc/Et_2O. [20,21] With this procedure, however, major loss of the resulting product was observed, and this can probably be ascribed to the number of crystallizations required (>10!), which results in water incorporation from the product.

Different purification methods were tested: the widely used crystallization, [20,21] and a protocol which involves decolourisation with activated charcoal. [49]

Method 1: the viscous liquid obtained from the quaternisation reaction was transferred in an Erlenmeyer flask of the appropriate size, then put in a freezer overnight to allow solidification.

The resulting solid was crushed to tiny pieces (*CARE!:* this operation must be performed quickly, because [C_4mim]Br is very hygroscopic!) and dissolved in the minimum amount of boiling CH_3CN. The resulting solution was allowed to cool down; once cool, a crystal of [C_4mim]Br obtained from previous synthesis was added, in order to trigger the crystallization. The solid obtained was washed over a Buchner funnel with AcOEt and Et_2O. The crystallization procedure was repeated until a white salt and white mother liquors were obtained. Mother liquors from the various steps were also concentrated on the hot plate and reused according to the method just reported: this was necessary since [C_4mim]Br is soluble also in cold CH_3CN.

Method 2: the viscous liquid obtained from the quaternisation reaction was transferred in an Erlenmeyer flask of appropriate size. A crystal of [C_4mim]Br obtained from previous synthesis was added, and instantaneous exothermic solidification of the reaction mixture was observed. The solid was washed with Et_2O and recrystallised as reported in Method 1.

For both Method 1 and 2, once the white solid was obtained, it was washed on a Buchner funnel with portions of Et_2O, and dried *in vacuo* at r.t. for 8 h, then at T=50 °C for 5 h.

Method 3: [49] the viscous liquid obtained was dissolved in distilled water (a yellowish solution was obtained), and activated charcoal was added. The mixture was heated at 70 °C for 12 h, allowed to cool down and filtered. The procedure was repeated until the solution became clear. The water solution was then quantified, by

drying *in vacuo* exactly 1 ml of solution, and weighting the resulting solid, and used in such form for the metathesis step.

Results obtained with the various purification methods are summarised in Table 1.4.

Table 1.4. Synthesis of [C_4mim]Br: comparison between the different purification methods tested.

Entry	MeIm		1–bromobutane		Purification method	Yield of crude quaternisation product(%)	Yield after purification(%)
	ml	mol	ml	mol			
1	100	1.26	138	1.28	1	n.d.	11
2	120	1.51	162	1.51	1	94	15
3	120	1.51	166	1.55	2	n.d.	34
4	80	0.94	102	0.95	2	n.d.	54
6	244	3.06	340	3.17	3	n.d.	30

In all cases the final product was characterized by ^{1}H NMR analysis (solvent: acetone–d_6); for the product obtained from Method 3 the resulting dried solid was used for the analysis. NMR spectrum is in excellent agreement with literature data, as it can be seen in Figure 1.1. [21]

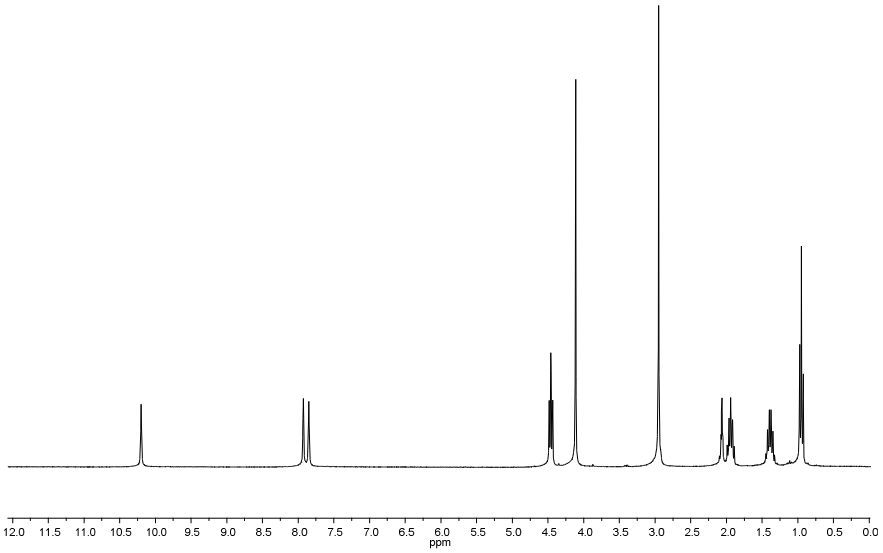
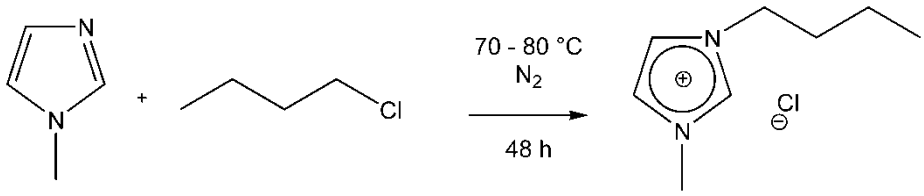


Figure 1.1. ^{1}H NMR spectrum of [C_4mim]Br (solvent: acetone–d_6).

δ_H (300 MHz, acetone–d_6): 10.09 (s, 1H, *H*–2); 7.81 (s, 1H, *H*–5); 7.74 (s, 1H, *H*–4); 4.35 (t, 2H, *J*=7.4 Hz, –C*H*$_2$– 1a); 4.00 (s, 3H, –C*H*$_3$ on C–3); 2.84 (s, H_2O); 1.95 (s, acetone); 1.82 (m, 2H, –C*H*$_2$– 2a); 1.28 (m, 2H, –C*H*$_2$– 3a); 0.84 (t, 3H, *J*=7.4 Hz, –C*H*$_3$ 4a).

1.5.2.2. Synthesis of 1–butyl–3–methylimidazolium chloride, [C4mim]Cl



Scheme 1.2. Synthesis of [C4mim]Cl.

The synthesis was performed according to literature procedures. [33] 50 ml (0.63 mol) of 1–methylimidazole purified by distillation over KOH *prior* to use, were poured in a double neck, 250 ml round bottom flask, equipped with a magnetic bar. Under an inert atmosphere and vigorous stirring, 73 ml (0.69 mol, 1.09 equiv.) of 1–chlorobutane were added. The flask was heated to 70–80 °C by an heating mantle for 48 h (consumption of MeIm was monitored by TLC, eluent: ethyl acetate). The mixture obtained (a cloudy solution when the quaternisation reaction triggers, that turns clear, viscous and yellowish at the end of the reaction) was allowed to cool down a transferred in a 500 ml Erlenmayer flask and washed with ca. 200 ml of Et_2O: upon washing, instant exothermic solidification of the product was observed. The resulting [C4mim]Cl, was further purified by crystallizations with CH_3CN, using the same methodology described in the previous section. Two crystallizations were necessary to obtain a white solid with transparent mother liquors. The product obtained was washed using a Buchner funnel with portions of Et_2O and dried *in vacuo* at r.t. for 48 h.

52.20 g (0.30 mol) of [C4mim]Cl were obtained, with a 48 % yield.

The product was characterised by ^1H NMR analysis (solvent: $CDCl_3$), the spectrum is in good agreement with literature data, as can be seen in Figure 1.2. [25]

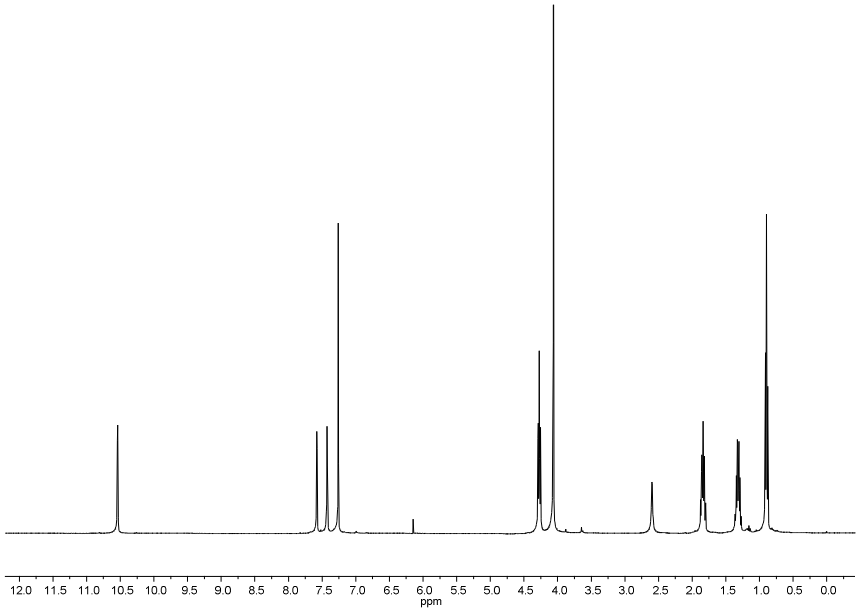
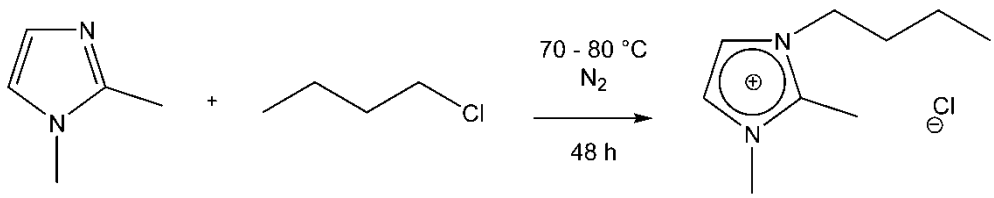


Figure 1.2. ^{1}H NMR spectrum of [C_4mim]Cl (solvent: $CDCl_3$).

δ_H (400 MHz, $CDCl_3$): 10.54 (s, 1H, *H*–2); 7.58 (s, 1H, *H*–5); 7.43 (s, 1H, *H*–4); 7.26 (s, C*H*Cl_3); 4.27 (t, 2H, *J*=8.0 Hz, –C*H*$_2$– 1a); 4.06 (s, 3H, –C*H*$_3$ on C–3); 1.88 (m, 2H, –C*H*$_2$– 2a); 1.37 (m, 2H, –C*H*$_2$– 3a); 0.90 (t, 3H, *J*=6.0 Hz, –C*H*$_3$ 4a).

1.5.2.3. Synthesis of 1–butyl–2,3–dimethylimidazolium chloride, [C_4mmim]Cl



Scheme 1.3. Synthesis of [C_4mmim]Cl.

The synthesis was performed according to literature procedures. [56,57] 46.06 g (0.50 mol) of 1,2–dimethylimidazole and 58 ml (0.55 mol, 1.10 equiv.) of 1–chlorobutane were introduced under inert atmosphere in a 2–neck 250 ml round bottom flask, equipped with a magnetic bar. The mixture was put under vigorous stirring and heated, using an heating mantle, to 70–80 °C. The reaction was followed by TLC (eluent: ethyl acetate) until complete consumption of 1,2–dimethylimidazole. A yellowish solid was obtained along with some unreacted liquid starting material.

The liquid was decanted and the solid washed with several portions of Et_2O. Three crystallizations from CH_3CN were performed in order to obtain colourless crystals and mother liquors. The solid obtained was washed over a Buchner funnel with portions of Et_2O and dried *in vacuo* for 8 h.

46.01 g (0.26 mol) of [C_4mmim]Cl were obtained, with a 49 % overall yield.

The product obtained was characterised by ^{1}H NMR analysis (solvent: $CDCl_3$), which is in good agreement with literature values, as can be seen in Figure 1.3. [25,57]

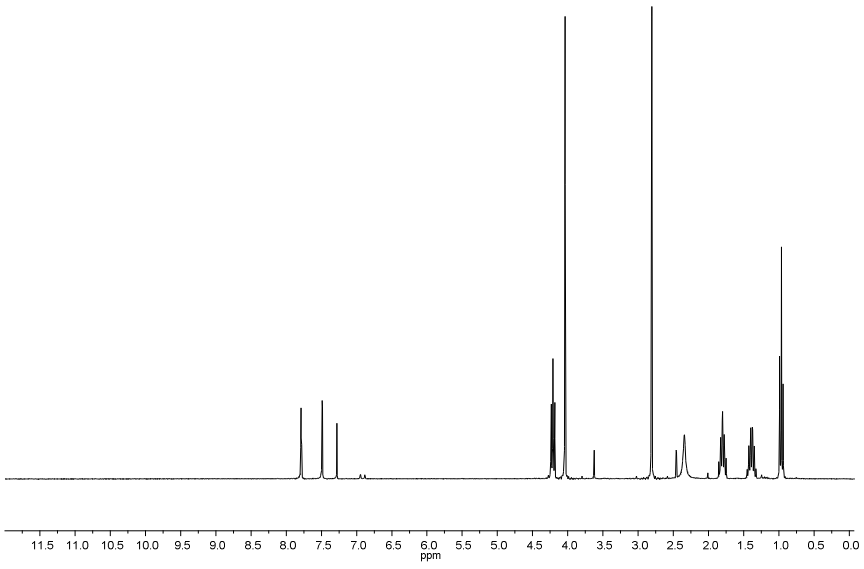
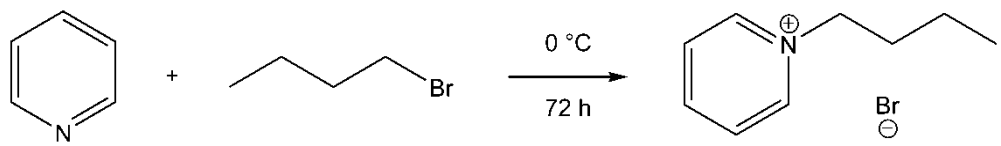


Figure 1.3. ^{1}H NMR spectrum of [C_4mmim]Cl (solvent: $CDCl_3$).

δ_H (300 MHz, $CDCl_3$): 7.78 (s, 1H, *H*–5); 7.48 (s, 1H, *H*–4); 7.27 ($CDCl_3$); 4.20 (t, 2H, *J*=6.0 Hz, –C*H*$_2$– 1a); 4.03 (s, 3H, –C*H*$_3$ on C–3); 2.80 (s, 3H, –C*H*$_3$ on C–2); 1.82 (m, 2H, –C*H*$_2$– 2a); 1.28 (m, 2H –C*H*$_2$– 3a); 0.96 (t, 3H, *J*=7.5 Hz, –C*H*$_3$ 4a). Traces of unreacted starting material are still present.

1.5.2.4. Synthesis of N*–butylpyridinium bromide, [C_4py]Br*



Scheme 1.4. Synthesis of [C_4py]Br.

The synthesis was performed according to literature procedures. [19] 108 ml (1.33 mol) of freshly distilled pyridine were introduced in a 500 ml round bottom flask, equipped with a magnetic bar. The flask was charged with a 500 ml dropping funnel, which contained 143 ml (1.33 mol, 1.00 equiv.) of 1–bromobutane. The flask was immersed in an ice bath and 1–bromobutane was added dropwise to the MeIm solution in ca. 2h 30'. After all the alkyl halide was added, the solution was left under vigorous stirring for 72 h. At first the solution turned cloudy white (as the quaternisation reaction takes off, a non homogenous solution is obtained, since the resulting salt is not miscible with the alkyl halide), while, at the end of the reaction a yellowish solid was obtained.

Since some reagents were still present in the reaction mixture, the solid was isolated and dried *in vacuo* for 5 h.

85.15 g (0.40 mol) of [C_4py]Br were obtained. The isolated product, was further purified by 5 recrystallizations from CH_3CN, with the method described previously. A white crystalline solid was obtained, which was washed over a Buchner funnel with portions of EtOAc and dried *in vacuo* for 24 h, heating the flask with a water bath up to 100 °C.

27.90 g (0.13 mol) of [C_4py]Br were collected, with a 10 % overall yield.

The product obtained was characterised by ^{1}H NMR analysis (solvent: acetone–d_6); as it can be seen in Figure 1.4 the spectrum is in good agreement with literature data. [21]

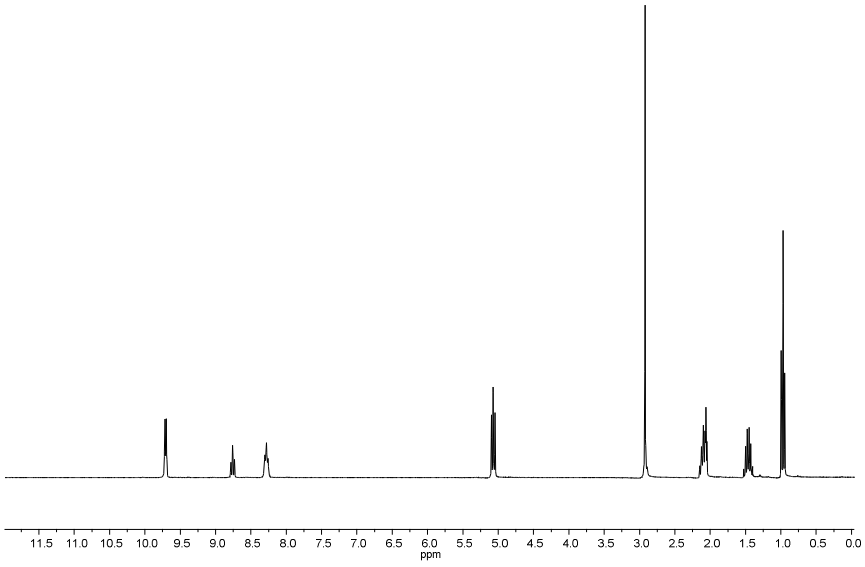
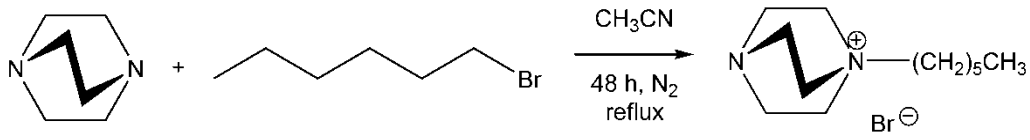


Figure 1.4. ^{1}H NMR spectrum of [C_4py]Br (solvent: acetone–d_6).

δ_H (300 MHz, acetone–d_6): 9.62 (d, 2H, *J*=2.74 Hz, *H*–2 and *H*–6); 8.67 (t, 1H, *J*=7.73 Hz, *H*–4); 8.20 (t, 2H, *J*=6.98 Hz, *H*–3 and *H*–5); 4.99 (t, 2H, *J*=7.48 Hz, –C*H*$_2$– 1a); 2.84 (s, H_2O); 1.98 (m, 2H, –C*H*$_2$– 2a); 1.39 (m, 2H, –C*H*$_2$– 3a); 0.88 (t, 3H, *J*=7.23 Hz, –C*H*$_3$ 4a).

1.5.2.5. Synthesis of 1–hexyl–4–aza–1–azaniabicyclo[2.2.2]octane bromide, [C$_6$DABCO]Br



Scheme 1.5. Synthesis of [C_6DABCO]Br.

The reaction was performed according to literature procedures. [58] Since the desired product is the monoalkylated one, the reaction was performed in excess of DABCO.

In a typical experiment, 10 g (89.1 mmol, 2.00 equiv.) of freshly sublimed DABCO were transferred in a 100 ml two–necked round bottom flask , equipped with a magnetic stir bar, under inert atmosphere. DABCO was then dissolved in the minimum amount necessary of CH_3CN (70 ml). The flask was equipped with a

dropping funnel, charged with 6.3 ml (44.6 mmol, 1.00 equiv.) of 1–bromohexane, which was added to the solution over approximately 30'. The mixture was then heated to reflux (81 °C) for 48 h. The reaction was followed by TLC (eluent: ethyl acetate), until the alkyl halide spot disappeared.

Once the reaction was complete, the reaction mixture was allowed to cool down, and, once cold, carefully transferred into an Erlenmeyer flask containing ca. 300 ml of Et_2O. The product instantaneously precipitated as a white solid. [C_6DABCO]Br was washed using a Buchner funnel with portions of Et_2O, then dried *in vacuo* for 8 h.

If the solid appeared yellowish, purification with activated charcoal in water [49] was performed.

Results for the various synthesis attempts are summarised in Table 1.5.

Table 1.5. Synthesis of [C_6DABCO]Br in refluxing CH_3CN.

Entry	DABCO		$C_6H_{13}Cl$		V CH_3CN (ml)	t (h)	Purification method	Yield before purification (%)	Yield after purification (%)
	g	mmol	ml	mmol					
1	10.00	89.1	6.3	44.6	70	48	–	78	–
2	15.00	133.7	9.4	66.9	75	48	Activated charcoal	87	62

The product obtained was characterised by ^1H and ^{13}C NMR spectroscopy (Figure 1.5 and Figure 1.6 respectively).

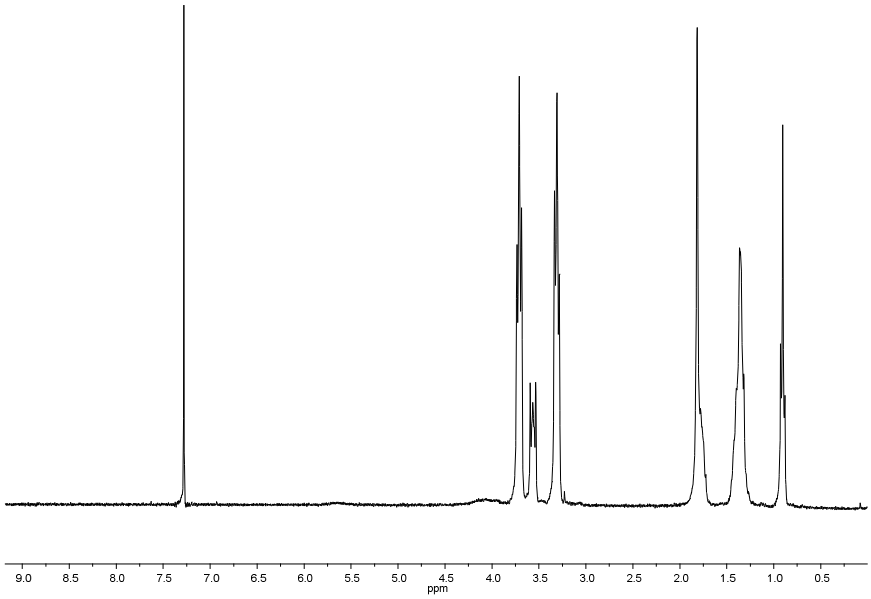


Figure 1.5. ^{1}H NMR spectrum of [C_6DABCO]Br (solvent:$CDCl_3$).

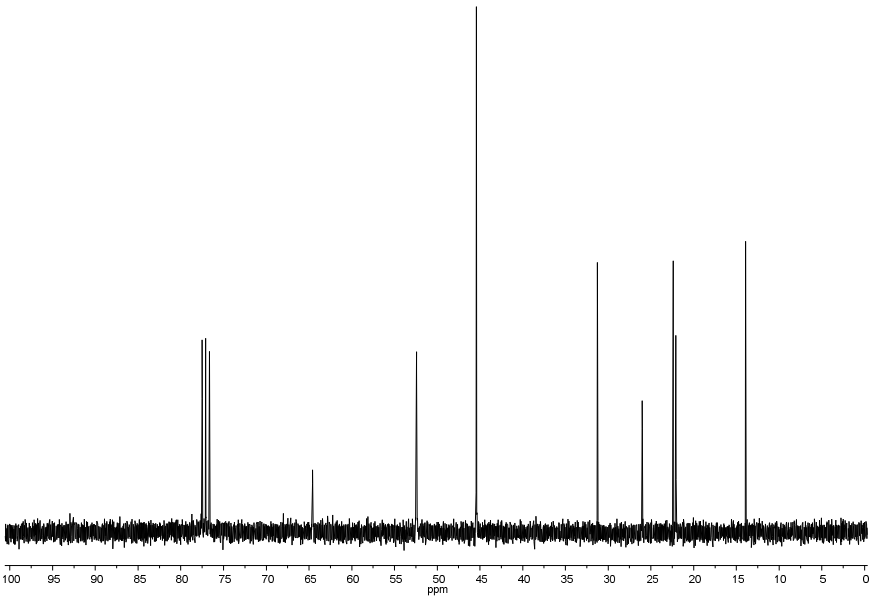


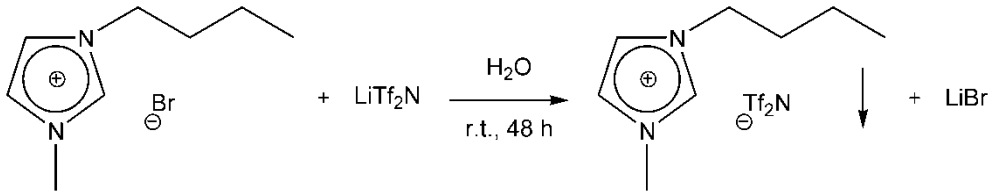
Figure 1.6. ^{13}C spectrum of [C_6DABCO]Br (solvent: $CDCl_3$).

δ_H (300 MHz, $CDCl_3$): 7.27 (C*H*Cl_3); 3.69 (d, 6H, *J*=6.0 Hz, –C*H*$_2$– on 2, 6 and 7); 3.54 (t, 2H, *J*=9.0 Hz, –C*H*$_2$– 1a); 3.29 (t, 6H, *J*=6.0 Hz, –C*H*$_2$– on 3, 5 and 8); 1.79 (m, 2H, –C*H*$_2$– 2a); 1.32 (m, 6H, –C*H*$_2$– 3a, 4a and 5a); 0.88 (t, 3H, *J*=9.0 Hz, –C*H*$_3$ 6a).

δ_C (75 MHz, $CDCl_3$): 77.1 (*C*DCl_3); 64.6 (*C*–1a), 52.5 (*C*–2, *C*–6 and *C*–7); 45.5 (*C*–3, *C*–5 and *C*–8); 31.3 (*C*–2a); 26.1 (*C*–3a); 22.4 (*C*–4a);22.1 (*C*–5a); 14.0 (*C*–6a).

1.5.3. Synthesis of ILs

1.5.3.1. Synthesis of 1–butyl–3–methylimidazolium bis(triflyl)imide, [C4mim]Tf2N



Scheme 1.6. Synthesis of [C4mim]Tf2N.

This hydrophobic IL metathesis reaction was carried out according to known literature procedures. [19] In a typical experiment, 30.13 g (0.14 mol) of [C4mim]Br were weighted in a 250 ml one neck round bottom flask, then dissolved, under vigorous stirring, in the minimum amount necessary of deionised water (15 ml). 39.48 g (0.14 mol) of $LiTf_2N$ were weighted in a beaker and added batchwise to the reaction mixture, waiting for the solution to become homogeneous before adding more salt. 10 ml extra of deionised water were used to clean the beaker and the spatula from any residual $LiTf_2N$. The mixture was kept under vigorous stirring at room temperature for 48 h.

A double phase formed in the course of the reaction: the upper phase being water and the bottom phase the IL of interest. At the end of the 48 h, water was carefully decanted away from the flask. The water phase was then extracted with 5 portions (15 ml each) of CH_2Cl_2. The organic phases were collected and used to dissolve the resulting IL. The organic solution was then dried by adding ca. 1 g of neutral Al_2O_3 and left uder vigorous stirring overnight. The mixture was filtered (by gravity): a yellowish solution was obtained. To ensure complete discolouration ca. 1 g of activated charcoal was added, and the solution left under vigorous stirring for 24 h. The solution was filtered, concentrated at the rotary evaporator, and dried *in vacuo* (8 h, heating up to 100 °C), to afford 48.93 g (0.12 mol) of [C4mim]Tf2N, with an overall yield of 86 %.

This procedure was repeated for the synthesis of several batches of IL, quantities and results are summarised in Table 1.6.

Table 1.6. Synthesis of $[C_4mim]Tf_2N$.

Entry	[C4mim]Br		Li(Tf2N)		Yield (%)
	g	mol	g	mol	
1	26.98	0.14	39.27	0.14	76
2	12.58	0.06	16.48	0.06	71
3	30.13	0.14	39.48	0.14	86

The resulting IL was characterised by ^1H NMR spectrometry (solvent: acetone–d_6), as can be seen in Figure 1.7 the spectrum obtained is in good agreement with literature data. [19]

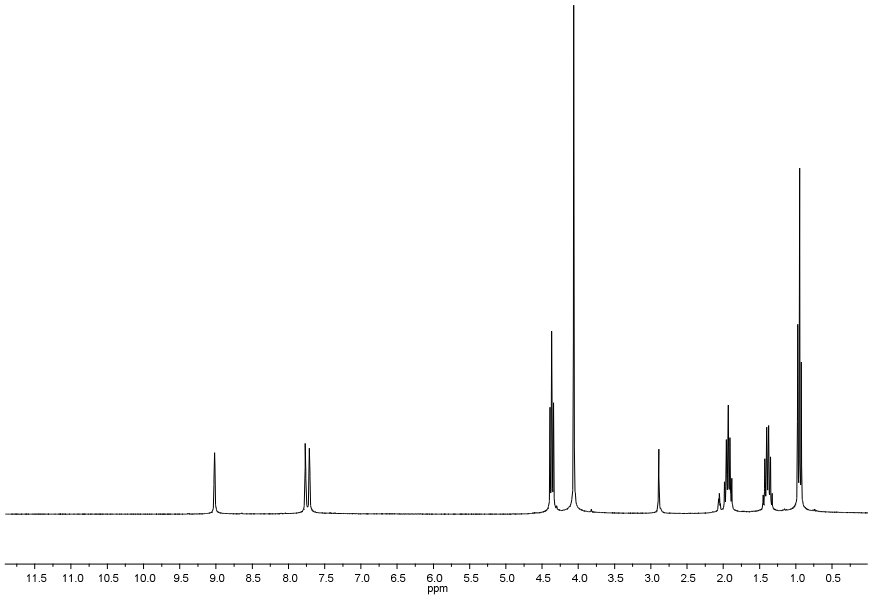
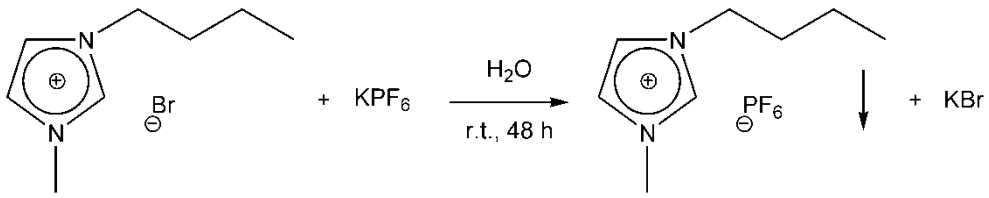


Figure 1.7. ^1H NMR spectrum of $[C_4mim]Tf_2N$ (solvent: acetone–d_6).

δ_H (300 MHz, acetone–d_6): 9.01 (s, 1H, *H*–2); 7.76 (s, 1H, *H*–5); 7.70 (s, 1H, *H*–4); 4.36 (t, 2H, *J*=6.0 Hz, –C*H*$_2$– 1a); 4.06 (s, 3H, –C*H*$_3$ on C–3); 2.88 (s, H_2O); 2.05 (s, acetone); 1.92 (m, 2H, –C*H*$_2$– 2a); 1.38 (m, 2H, –C*H*$_2$– 3a); 0.94 (t, 3H, *J*=6.0 Hz, –C*H*$_3$ 4a).

1.5.3.2. Synthesis of 1–butyl–3–methylimidazolium hexafluorophosphate, [C4mim]PF6



Scheme 1.7. Synthesis of [C4mim]PF6.

This hydrophobic IL was synthesised according to literature procedures. [19] The synthesis was analogous to the one reported for [C4mim]Tf2N, except that this IL was dried *in vacuo* at r.t. for 24 h: this was done because PF_6^- containing ILs can potentially be decomposed by high temperatures, due to formation of HF. [14,20] Several batches of [C4mim]PF6 were synthesised, quantities and results are summarised in Table 1.7.

Table 1.7. Synthesis of [C4mim]PF6.

Entry	[C4mim]Br		KPF6		Activated charcoal elimination	Yield (%)
	g	mol	g	mol		
1	32.87	0.15	27.61	0.15	consecutive filtrations	54
2	30.00	0.14	25.20	0.14	double filter	82

The resulting IL was characterised by ^{1}H NMR spectrometry (solvent: acetone–d_6), the spectrum, reported in Figure 1.8, is in good agreement with literature data. [21,34]

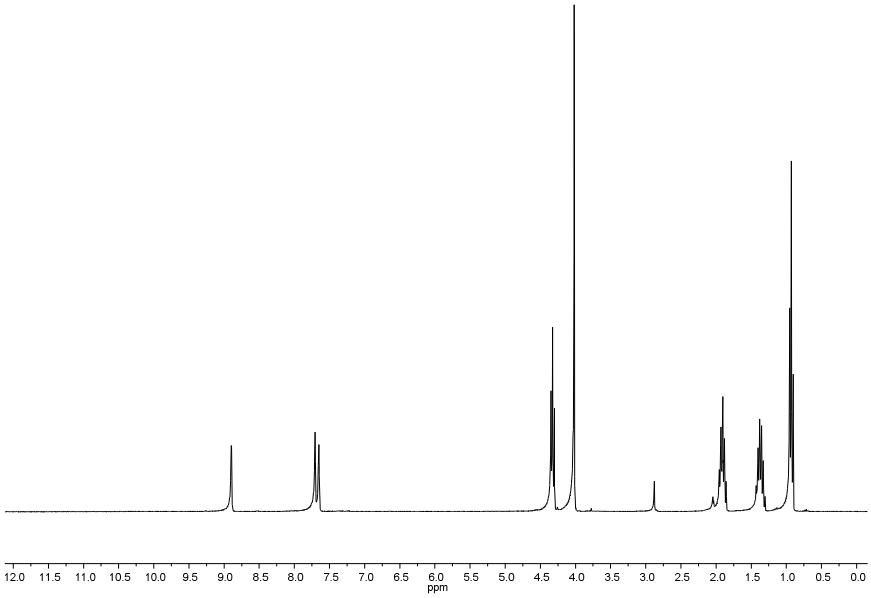
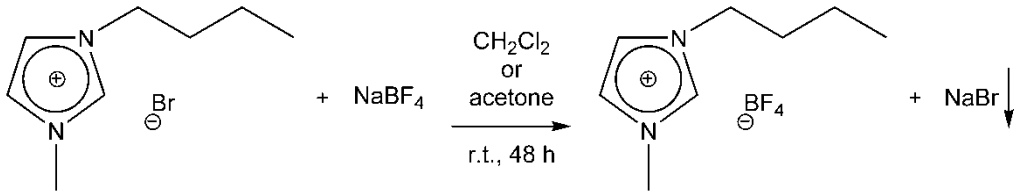


Figure 1.8. ^{1}H NMR spectrum of [C_4mim]PF_6 (solvent: acetone–d_6).

δ_H (300 MHz, acetone–d_6): 8.90 (s, 1H, *H*–2); 7.71 (s, 1H, *H*–5); 7.65 (s, 1H, *H*–4); 4.33 (t, 2H, *J*=7.5 Hz, –C*H*$_2$– 1a); 4.02 (s, 3H, –C*H*$_3$ on C–3); 2.88 (s, H_2O); 2.05 (s, acetone); 1.89 (m, 2H, –C*H*$_2$– 2a); 1.37 (m, 2H, –C*H*$_2$– 3a); 0.93 (t, 3H, *J*=7.5 Hz, –C*H*$_3$ 4a).

1.5.3.3. Synthesis of 1–butyl–3–methylimidazolium tetrafluoroborate, [C$_4$mim]BF$_4$

This hydrophilic IL was synthesised by two different literature procedures: employing both VOCs [29,34,56] and deionised water [28,33] as solvents for the metathesis reaction.



Scheme 1.8. Synthesis of [C_4mim]BF_4 in VOCs.

Method 1: in a typical experiment 30.89 g (0.14 mol) of [C_4mim]Br were weighted in a 250 ml round bottom flask and suspended in 50 ml of acetone. 15.47 g (0.14 mol) of $NaBF_4$ were added to the mixture, which was then left under vigorous stirring at

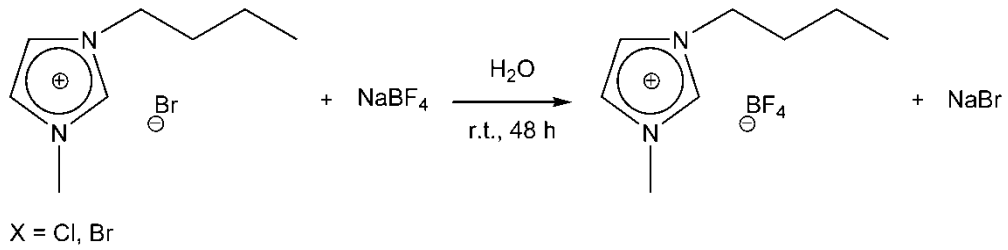
r.t. for 48 h. At the end of the reaction time, the mixture was filtered to remove the NaBr formed. A small sample of the resulting solution was collected and tested with $AgNO_3$, to check the presence of any NaBr left; formation of AgBr precipitate gave a positive response. The solution was concentrated at the rotary evaporator, the IL dissolved in CH_2Cl_2, and extracted with small portions of deionised water (<5ml) until a negative $AgNO_3$ test on the aqueous phase was obtained. The resulting solution was dried by adding ca. 1 g of neutral Al_2O_3 and left stirring at r.t. overnight. The alumina was filtered away, giving a colourless solution, which was concentrated and dried *in vacuo* at r.t. for 24 h.

14.73 g (0.06 mol) of $[C_4mim]BF_4$ were obtained, with a 46 % overall yield.

Several batches of $[C_4mim]BF_4$ were synthesised, quantities and results are summarised in Table 1.8.

Table 1.8. Synthesis of $[C_4mim]BF_4$ in VOCs.

Entry	[C4mim]Br		$NaBF_4$		Solvent	Yield (%)
	g	mol	g	Mol		
1	29.22	0.13	14.72	0.13	CH_2Cl_2	38
2	30.89	0.14	15.47	0.14	acetone	46



Scheme 1.9. Synthesis of $[C_4mim]BF_4$ in H_2O.

Method 2: 91.7 ml of a 2.18 M solution of $[C_4mim]Br$ in deionised water (0.20 mol) were transferred in a 250 ml round bottom flask. 22.13 g (0.20 mol) of $NaBF_4$ were added to the solution; the resulting homogeneous solution was left under vigorous stirring at r.t. for 48 h. At the end of the reaction time, the solution was transferred to a separation funnel and extracted with 3 portions (50 ml each) of CH_2Cl_2. The organic phases were collected and the $AgNO_3$ test performed, giving a positive response (NaBr present). The organic phase was then extracted with small portions of deionised water (<5 ml) until a negative $AgNO_3$ test on the aqueous phase was obtained. The resulting yellowish organic solution was dried over anhydrous

Na_2SO_4, filtered, discoloured by adding ca. 1 g of activated charcoal and left under vigorous stirring overnight. The solution was then concentrated and dried *in vacuo* at r.t. for 24 h.

22.71 g (0.10 mol) of $[C_4mim]BF_4$ were obtained, with a 50 % overall yield.

The resulting IL was characterised by ^1H NMR spectrometry (solvent: $CDCl_3$), the obtained spectrum is in good agreement with literature data, as can be seen in Figure 1.9. [21,27]

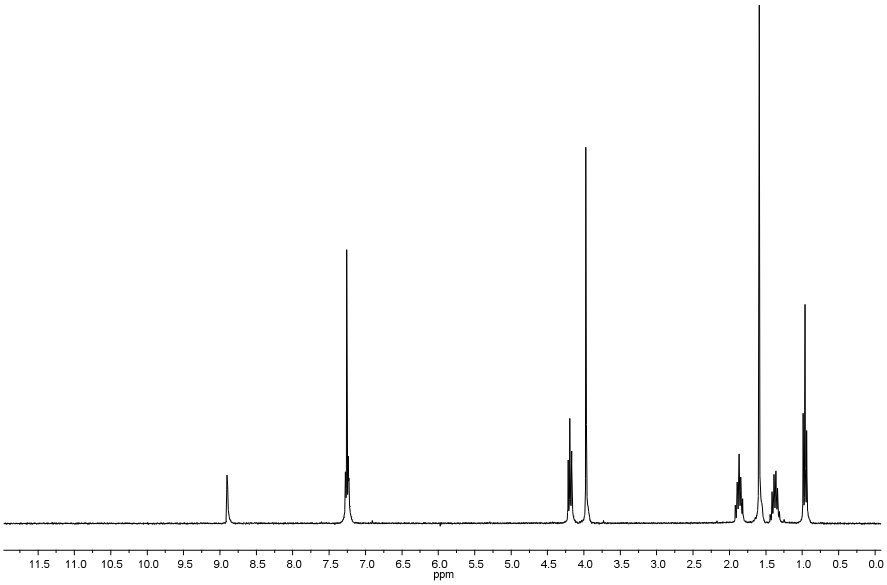
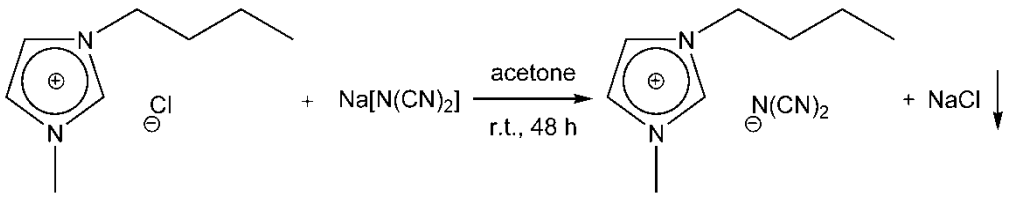


Figure 1.9. ^1H NMR spectrum of $[C_4mim]BF_4$ (solvent: $CDCl_3$).

δ_H (300 MHz, $CDCl_3$): 8.91 (s, 1H, *H*–2); 7.28 (s, 1H, *H*–5); 7.26 (s, C*H*Cl_3); 7.24 (s, 1H, *H*–4); 4.19 (t, 2H, *J*=7.5 Hz, –C*H*$_2$– 1a); 3.98 (s, 3H, –C*H*$_3$ on C–3); 1.88 (m, 2H, –C*H*$_2$– 2a); 1.60 (s, H_2O); 1.38 (m, 2H, –C*H*$_2$– 3a); 0.97 (t, 3H, *J*=7.5 Hz, –C*H*$_3$ 4a).

These two different methodologies were employed since results in VOC were quite disappointing (low yield of isolated IL). In order to evaluate if the poor outcome was due to the spare solubility of $NaBF_4$ in both acetone and CH_2Cl_2, the metathesis reaction was performed in water as well, where the $NaBF_4$ readily dissolves.

1.5.3.4. Synthesis of 1–butyl–3–methylimidazolium dicyanamide, [C4mim]N(CN)2



Scheme 1.10. Synthesis of $[C_4mim]N(CN)_2$ in acetone.

This hydrophilic IL was synthesised according to known literature procedures. [59] For dicyanamide containing ILs it is advisable to avoid using water as the metathesis solvent, especially when synthesising short alkyl chain imidazolium based IL: the affinity of such ILs with water is far greater than the one observed with the solvents commonly used for the extraction of ILs (typically CH_2Cl_2).

10.00 g (0.06 mol) of $[C_4mim]Cl$ were weighed in a 100 ml round bottom flask, and then suspended in 20 ml of acetone. 5.10 g (0.06 mol) of $Na[N(CN)_2]$ were added and the resulting suspension left under vigorous stirring at r.t. for 48 h. At the end of the reaction time, the mixture was filtered to remove the precipitated NaCl. Then the solution was filtered through Celite 505 (eluent: acetone/CH_2Cl_2 7:3). The resulting yellowish solution was concentrated and redissolved in acetone (20 ml). To ensure discolouration, it was treated twice with activated charcoal. The obtained colourless solution was concentrated and dried *in vacuo* at r.t. for 24 h.

The resulting IL was characterised by ^1H NMR spectrometry (solvent: $CDCl_3$), the obtained spectrum is in good agreement with literature data, as can be seen in Figure 1.10. [59]

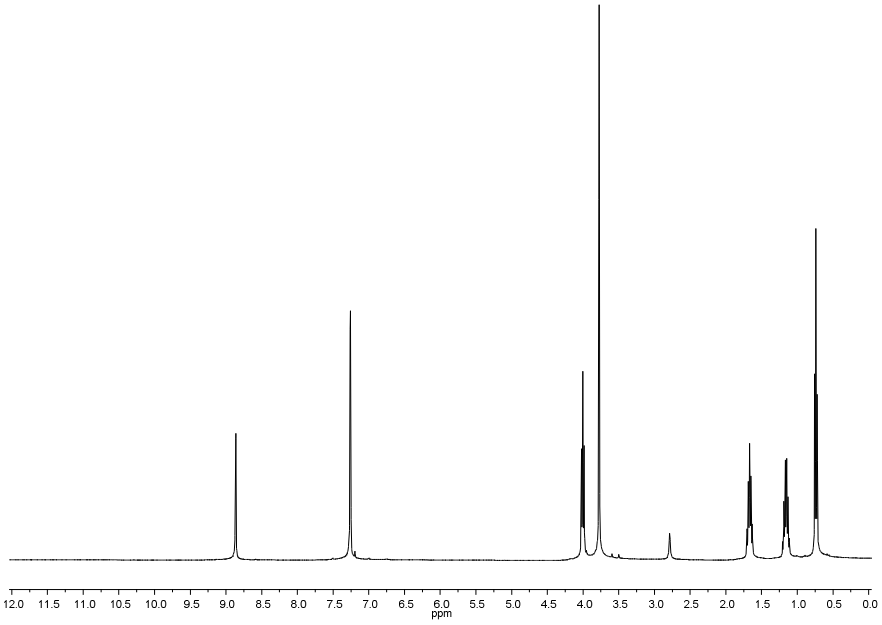
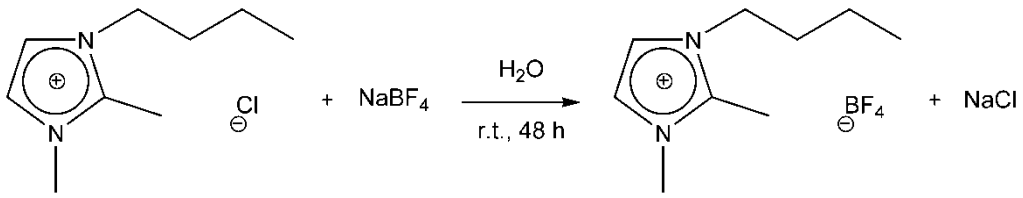


Figure 1.10. ^{1}H NMR spectrum of $[C_4mim]N(CN)_2$ (solvent:$CDCl_3$).

δ_H (400 MHz, $CDCl_3$): 8.86 (s, 1H, *H*–2); 7.26 (s, C*H*Cl_3); 4.00 (t, 2H, *J*=6.00 Hz, –C*H*$_2$– 1a); 3.77 (s, 3H, –C*H*$_3$ on C–3); 1.67 (m, 2H, –C*H*$_2$– 2a); 1.16 (m, 2H, –C*H*$_2$– 3a); 0.74 (t, 3H, *J*=8.00 Hz, –C*H*$_3$ 4a).

1.5.3.5. Synthesis of 1–butyl–2,3–dimethylimidazolium tetrafluoroborate, [C$_4$mmim]BF$_4$



Scheme 1.11. Synthesis of $[C_4mmim]BF_4$.

This hydrophobic IL was synthesised according to known literature procedures. [33] For the synthesis of $[C_4mim]BF_4$ (see Section 1.5.3.3) the yield of the isolated IL improved when the metathesis reaction was performed in water, therefore was chosen as the metathesis solvent for the synthesis of $[C_4mmim]BF_4$. 20.94 g (0.11 mol) of $[C_4mmim]Cl$ were weighed in a 100 ml round bottom flask and dissolved in 25 ml of deionised water. 12.20 g (0.11 mol) of $NaBF_4$ were added and

the resulting solution was left under vigorous stirring at r.t. for 48 h. A double phase was formed, the upper phase being water, and the bottom phase the resulting [C_4mmim]BF_4. The aqueous layer was decanted into a separating funnel and extracted with four portions (15 ml each) of CH_2Cl_2 (extractions were carried out until the organic phase was no longer fluorescent at the UV lamp). The organic phases were collected and added to the isolated IL, dried over anhydrous Na_2SO_4 and concentrated. The resulting IL was then dried *in vacuo* at r.t. for 48 h. After drying, 18.94 g (0.08 mol) of white solid were obtained, with an overall yield of 72 %.

The resulting [C_4mmim]BF_4 is a white solid with mp ~37 °C, which is in agreement with literature data. [60]

[C_4mmim]BF_4 was characterised by ^{1}H NMR spectrometry (solvent: $CDCl_3$); the spectrum obtained is in good agreement with literature data, as can be seen in Figure 1.11. [25]

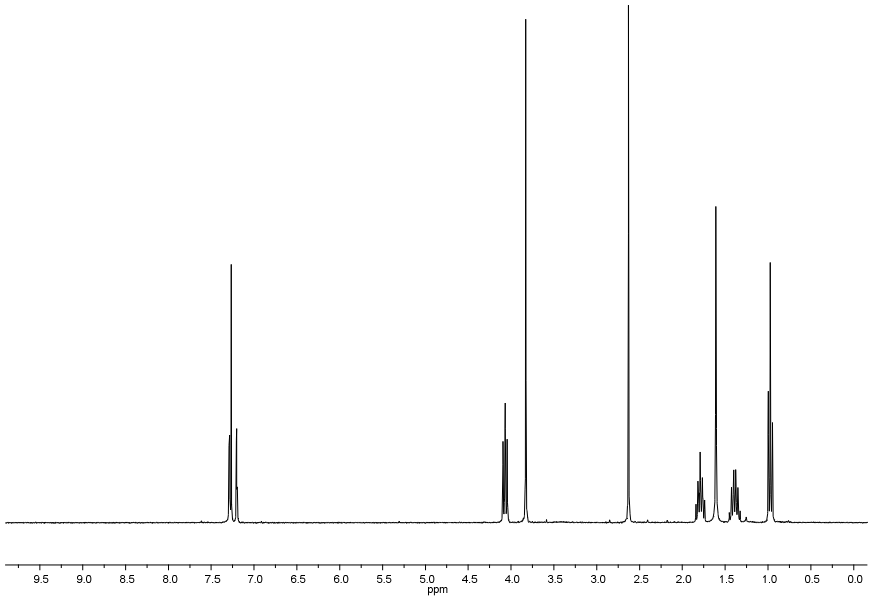
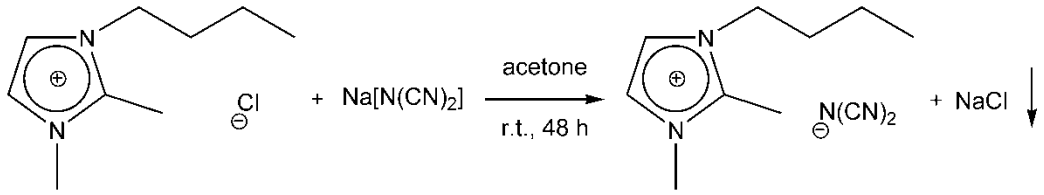


Figure 1.11. ^{1}H NMR spectrum of [C_4mmim]BF_4 (solvent: $CDCl_3$).

δ_H (300 MHz, $CDCl_3$): 7.28 (d, 1H, *J*=2.1 Hz, *H*–5); 7.19 (d, 1H, *J*=2.1 Hz, *H*–4); 7.26 ($CDCl_3$); 4.05 (t, 2H, *J*=7.5 Hz, –C*H*$_2$– 1a); 3.83 (s, 3H, –C*H*$_3$ on C–3); 2.62 (s, 3H, –C*H*$_3$ on C–2); 1.78 (m, 2H, –C*H*$_2$– 2a); 1.60 (s, H_2O); 1.38 (m, 2H –C*H*$_2$– 3a); 0.97 (t, 3H, *J*=7.4 Hz, –C*H*$_3$ 4a).

1.5.3.6. Synthesis of 1–butyl–2,3–dimethylimidazolium dicyanamide, [C4mmim]N(CN)2



Scheme 1.12. Synthesis of $[C_4mmim]N(CN)_2$ in acetone.

This hydrophilic IL was synthesised according to known literature procedures. [59,61] 20.24 g (0.11 mol) of $[C_4mmim]Cl$ were weighed in a 250 ml round bottom flask and suspended in 50 ml of acetone. 9.58 g (0.11 mol) of $Na[N(CN)_2]$ was then added to the suspension, which was left under vigorous stirring at r.t. for 48 h. At the end of the reaction, the mixture was concentrated and filtered through a silica plug (eluent: acetone/CH_2Cl_2 7:3), the resulting solution was concentrated and the obtained IL dissolved in CH_2Cl_2 (30 ml); immediately after the dissolution, the mixture becomes turbid (precipitation of NaCl). The mixture was transferred in freezer overnight to ensure quantitative precipitation of the salt present, then filtered and concentrated. This procedure was repeated until precipitation of NaCl was no longer observed. Then the solution was concentrated and dried *in vacuo* at r.t. to afford 6.77 g (0.03 mol) of $[C_4mmim][N(CN)_2]$, with a 28 % overall yield.

The resulting IL was characterised by ^1H NMR spectrometry (solvent: $CDCl_3$),the spectrum obtained is in good agreement with literature data, as can be seen from Figure 1.12. [61]

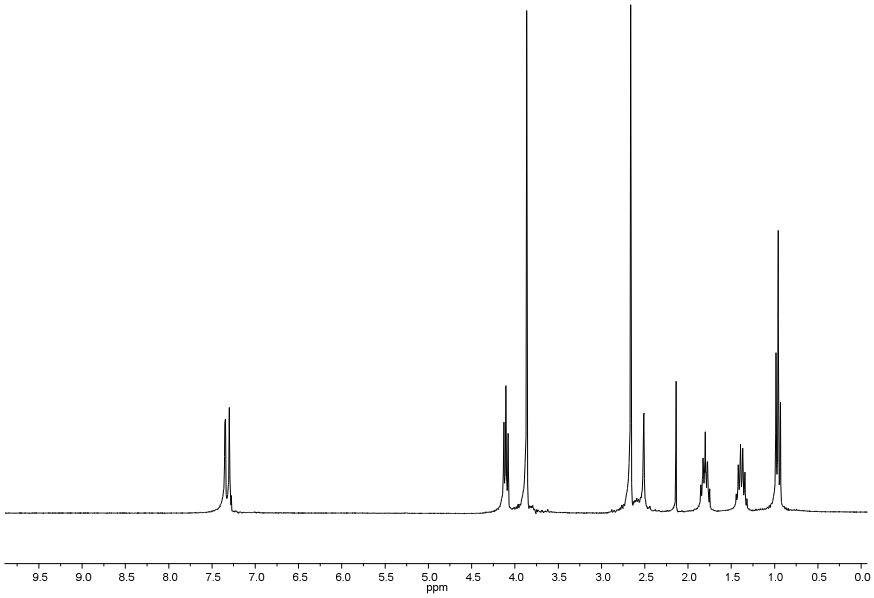
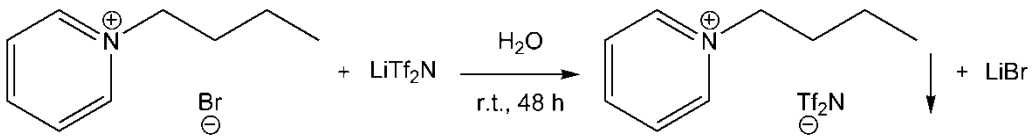


Figure 1.12. ^{1}H NMR spectrum of $[C_4mmim]N(CN)_2$ (solvent:$CDCl_3$).

δ_H (300 MHz, $CDCl_3$): 7.50 (d, 1H, *J*=1.8 Hz, *H*–5); 7.30 (d, 1H, *J*=1.8 Hz, *H*–4); 7.26 ($CDCl_3$); 4.10 (t, 2H, *J*=7.5 Hz, –C*H*$_2$– 1a); 3.85 (s, 3H, –C*H*$_3$ on C–3); 2.66 (s, 3H, –C*H*$_3$ on C–2); 2.14 (s, acetone); 1.80 (m, 2H, –C*H*$_2$– 2a); 1.38 (m, 2H –C*H*$_2$– 3a); 0.96 (t, 3H, *J*=7.4 Hz, –C*H*$_3$ 4a).

1.5.3.7. Synthesis of N*–butylpyridinium bis(triflylimide), [C$_4$py]Tf$_2$N.*



Scheme 1.13. Synthesis of $[C_4py]Tf_2N$.

This hydrophobic IL was synthesised according to literature procedures. [21,62] 8.07 g (0.04 mol) of $[C_4py]Br$ was weighed in a 100 ml round bottom flask and dissolved in 10 ml of deionised water. 10.77 g (0.04 mol) of $LiTf_2N$ was added batchwise to the solution, with particular care that all the added salt dissolved before adding some more. The resulting homogenous mixture was left under vigorous stirring at r.t. for 12 h. Formation of a double phase was observed. The aqueous layer was carefully decanted away from the flask and extracted with portions of CH_2Cl_2. The organic phases were collected and used to dissolve the

resulting IL. The organic solution was then dried by adding ca. 1 g of neutral Al_2O_3 and left under stirring overnight. The mixture was then filtered (by gravity) giving a yellowish solution. To ensure complete discolouration ca. 1 g of activated charcoal was added and the solution left under vigorous stirring overnight. The solution was filtered, concentrated, and dried *in vacuo* (8 h, heating up to 100 °C), to afford 7.51 g (0.02 mol) of $[C_4py]Tf_2N$, with an overall yield of 48 %.

The resulting IL was characterised by ^1H NMR spectrometry (solvent: acetone–d_6), the spectrum obtained is in good agreement with literature data, as can be seen from Figure 1.13. [62]

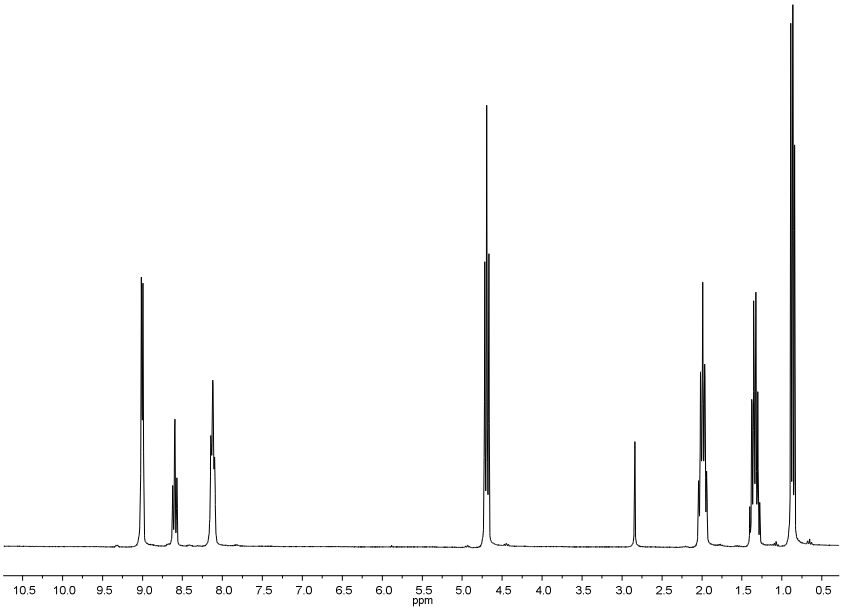
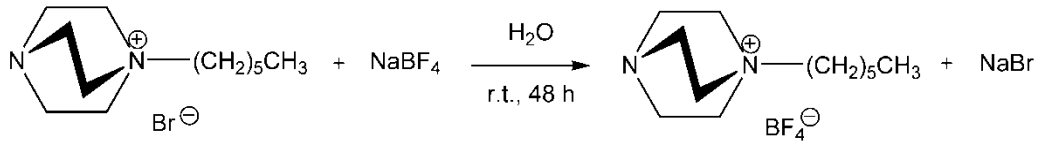


Figure 1.13. ^1H NMR spectrum of $[C_4py]Tf_2N$ (solvent: acetone–d_6).

δ_H (300 MHz, acetone–d_6): 9.00 (d, 2H, *J*=6.00 Hz, *H*–2 and *H*–6); 8.60 (t, 1H, *J*=7.80 Hz, *H*–4); 8.12 (t, 2H, *J*=6.75 Hz, *H*–3 and *H*–5); 4.69 (t, 2H, *J*=7.65 Hz, –C*H*$_2$– 1a); 2.84 (s, H_2O); 1.99 (m, 2H, –C*H*$_2$– 2a); 1.34 (m, 2H, –C*H*$_2$– 3a); 0.86 (t, 3H, *J*=7.35 Hz, –C*H*$_3$ 4a).

1.5.3.8. Synthesis of 1–hexyl–4–aza–1–azaniabicyclo[2.2.2]octane tetrafluoroborate, [C_6DABCO]BF_4



Scheme 1.14. Synthesis of [C_6DABCO]BF_4.

This hydrophilic IL was synthesised according to know literature procedures. [33] 5.06 g (0.02 mol) of [C_6DABCO]Br were weighed in a 10 ml round bottom flask and dissolved in 5 ml of deionised water. 2.00 g (0.02 mol) of $NaBF_4$ were added and the resulting homogeneous solution was kept under vigorous stirring at r.t. for 48 h.

The solution was then transferred to a separation funnel, and extracted with five portions (25 ml each) of CH_2Cl_2. The organic phases were collected together and, on a small portion, the $AgNO_3$ test was performed, with positive result (precipitation of AgBr): to remove the NaBr present, the organic phase was extracted with small volumes (<5 ml) of deionised water, until the $AgNO_3$ test (performed on the aqueous phase) gave a negative result. The resulting yellowish organic phase was dried over anhydrous Na_2SO_4, and discoloured by adding ca. 1 g of activated charcoal and stirring at r.t. overnight. The solution was then filtered, concentrated and dried *in vacuo* at T=50 °C for 16 h, to afford 2.99 g (0.01 mol) of a white solid, [C_6DABCO]BF_4, with an overall yield of 71 %. [C_6DABCO]BF_4 is a white solid which melts at T below 100 °C (approximately mp ~84 °C).

Several batches of [C_6DABCO]BF_4 were synthesised, quantities and results are summarised in Table 1.9.

Table 1.9. Synthesis of [C_6DABCO]BF_4 in H_2O.

Entry	[C_6DABCO]Br		$NaBF_4$		Yield (%)
	g	mol	g	mol	
1	9.44	0.03	3.85	0.03	30
2	5.06	0.01	2.00	0.01	71

The resulting IL was characterised by ^{1}H NMR spectrometry (solvent: $CDCl_3$).

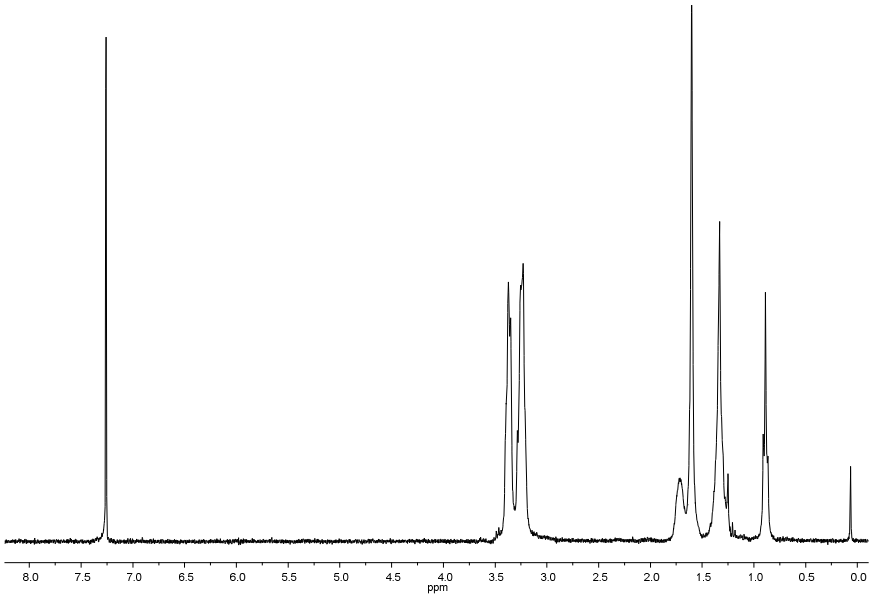


Figure 1.14. ^{1}H NMR spectrum of $[C_6DABCO]BF_4$ (solvent:$CDCl_3$).

δ_H (300 MHz, $CDCl_3$): 7.26 (C*H*Cl_3); 3.36 (d, 6H, *J*=6.3 Hz, –C*H*$_2$– on 2, 6 and 7); 3.27 (m, 8H, –C*H*$_2$– on 3, 5, 8 and 1–a); 1.71 (m, 2H, –C*H*$_2$– 2a); 1.33 (m, 6H, –C*H*$_2$– 3a, 4a and 5a); 0.89 (t, 3H, *J*=6.6 Hz, –C*H*$_3$ 6a).

1.6. Discussion and conclusions

1.6.1. Quaternisation reactions

As discussed previously, quaternisation is the key step in the overall synthesis of ILs:

1) it is a step which need a strict control on the reaction conditions;
2) the resulting halide salt is a key compound whose purity affects derived ILs resulting from subsequent metathesis step.

As it can be seen from the data collected in the experimental data, the purification of the halide salt is often a time and product consuming step, involving several crystallization steps of a "sensitive" hygroscopic material or iterative treatments with a discolouring agent, such as activated charcoal.

As it was pointed out also in the previous sections of this chapter, control over the reagents used (both the Lewis base and the alkyl halide) is crucial for a "cleaner" formation of the product, especially for the base used. Temperature control during

the course of the reaction and the use of inert atmosphere are also important parameters to avoid (or minimise) the formation of coloured impurities.

The colourless nature of the resulting salt is an important qualitative parameter for the purity, however it needs to be paired up with a quantitative determination of the impurities present in the quaternisation product. [35] Among the methods studied, there are some routine laboratory techniques such as UV–Vis quantitative analysis (for the colorimetric determination of unreacted MeIm), [36] HPLC separation [40] and GC analysis. [35]

Another parameter which could be used to improve the purity of the resulting quaternisation product is the use of a solvent in the quaternisation reactions, rather than performing the reaction solventless. Typically, 1,1,1–trichloroethane [19] or toluene [63] were used: in both these solvents the resulting salt precipitates out.

More recently, colourless [$C_n$mim]Br (with n=4 and 6) were obtained by using water as the quaternisation solvent: [64] in this case the biphasic system obtained is composed by water, in which MeIm and the resulting [$C_n$mim]X are dissolved, and the hydrophobic alkyl halide. These methods are all valid alternatives to the work–up purification extensively reported in the chapter.

1.6.2. Issues on the synthesis of hydrophilic ILs

The experimental data so far collected clearly show that the synthesis of hydrophilic ILs is more laborious when compared with that of hydrophobic ones. This can be mainly ascribed to the solubility of the resulting IL in both the phases involved in the extraction of the by–product. In the experimental section, we used two different methods to synthesize hydrophilic ILs using a VOC (such as acetone or CH_2Cl_2) [29,34,56] or water [28,33] as the metathesis solvent and results obtained with both protocols are comparable.

The efficiency of the process and the overall yield can be likely improved by employing a continuous extractor, [49] or by performing the metathesis reactions with anion exchange resins. [65]

1.6.3. Issues on the synthesis of ILs containing pseudohalogen anion

Attempts were made to synthesise ILs containing the dicyanamide anion, however with modest results. Among the problems encountered with the purification of this kind of ILs are:

- the scarce solubility of the resulting IL in most of the organic solvents;
- the pseudohalide nature of the dicyanamide anion, which makes all commonly used halide determination tests useless.

Dicyanamide containing ILs are generally synthesised by a metathesis reaction with the corresponding Ag(I) salt, [30] to overcome the purification issues highlighted previously. The use of silver salts, however, affects the overall properties of the resulting IL, in particular its stability, [66], therefore alternative reaction protocols are advisable.

Since the results obtained with Group 1 metal salts are modest, anion exchange chromatography [65] is potentially the best method to synthesise this class of ILs.

1.6.4. Conclusions

Several ILs and ILs precursors were synthesised in the course of this work, bearing different cation (from the commonly used $[C_nmim]^+$ and $[C_npy]^+$ to DABCOnium based ILs) and anion moieties. Different synthetic methods were tested and compared. The choice of synthetic/purification method strongly depends on the anion/cation combination of the resulting IL: huge differences in terms of procedures and yields are observed simply by switching from hydrophobic to hydrophilic ILs.

From the data collected and the literature survey performed it becomes clear that a standardisation of the synthetic techniques employed is advisable and a reliable quantitative determination of impurities in both the quaternisation and metathesis step is necessary in order to make IL a common lab reagent and extend their potential in most of their current and future applications.

Chapter 2: Microwave assisted synthesis of 1–alkyl–3–methylimidazolium chloride ILs

2.1. Introduction

2.1.1. Principles of MW heating

"Microwaves" are the portion of the electromagnetic spectrum between the frequencies of 0.3 and 300 GHz: this region corresponds to wavelengths that stretch approximately between 1 mm and 1 m. [67,68]

Commercial MW ovens (both for domestic and laboratory use) operate at a frequency of 2.45 GHz, which corresponds to a wavelength of 12.24 cm; [68] among the many possible frequencies operating in the MW region, this frequency was chosen to minimize the possible interferences.

MW ovens became common household objects from the 1970s, although MW energy was discovered a while before (1950s) and used mainly for communications; only in the 1970s did the technology to build the ovens became affordable, thus leading to their mass production. About the same time, MW ovens started to appear in the labs, mainly to be used by inorganic chemists. The application of this technology in organic synthesis was much slower: the first report of MAOS (Microwave Assisted Organic Synthesis) was published in the mid 1980s. The reason for this slow uptake of MW technology from the organic chemistry community was mainly ascribed to the lack of knowledge over the principles of microwave heating, and poor reproducibility associated with the use of domestic MW ovens for lab purposes. A turning point for MAOS was the development and diffusion of solvent less reaction protocols and reactions involving a minimized amount of VOCs: this happened mainly in the 1980s, with many examples of reactions performed in aqueous media, solvent less and with immobilized reagents.

Unfortunately, some organic solvents are poor candidates for MW heating. To understand why, we have to look at "how" MW irradiation can generate heat.

Being an electromagnetic radiation, microwaves can be divided in two components: the electrical field component and the magnetic field component. Heating is generated only by the electrical field component by two distinct mechanisms:

- dipolar polarization;
- ionic conduction.

The dipolar polarization mechanism arises when the reaction mixture is irradiated with energy on the MW frequency. When irradiated, the dipoles present in the mixture (which are mainly solvent molecules) will align to the applied external field. Being in a liquid solution, their alignment will be somehow "delayed" by both the dielectric loss (which will be discussed shortly) and, to some extent, by molecular friction: the combination of these factors generates heat. The amount of heat generated mainly depends on the ability of the matrix to realign itself with the external field: if the dipole realigns itself too slowly or too quickly no heating occurs. One of the reasons why the 2.45 GHz frequency was chosen for both domestic and laboratory MW ovens, is that it is at "mid–point" in the MW region of the electromagnetic spectrum, and at this frequency the molecular dipole has time to align itself with the external field, but cannot follow precisely the oscillation. Moreover the energy of MW at this frequency is approximately 1 $J \cdot mol^{-1}$, which should guarantee no interference with the chosen reaction. [67,68].

It is clear that the dipole moment of the solvent chosen is crucial for efficient heating. Solvents with high dipole moments, such as water, are the best candidates for MW assisted reactions.

The ionic conduction mechanism, instead, is due to the presence of charged ions in the solution. In presence of an applied electrical field, the ions will move through the solution, colliding with the other molecules present; this collision will generate heat in a much more efficient way (the interactions involved are stronger) that the dipole polarization. If MW irradiation of an organic solvents is needed, a common practice in organic synthesis is to add a small amount of an ionic substance (such as an ionic liquid) to the solution. [68,69]

Looking at the possible heating mechanisms, it is clear that the performance of a particular solvent under MW depends on its dielectric properties, in particular on its dielectric constant. The dielectric constant, however, is not sufficient to fully describe the behaviour of a solvent under MW irradiation: for example, the ability of solvents to absorb MW energy and to convert it in heat must be taken in account. This is done by introducing the parameter δ, [67,70] which represents the displacement angle between the applied electrical field and the electrical current

generated from the dipole in the electrical field. From Maxwell's laws we know that the dipole immersed in an electrical field will generate an electrical current and this current will be perpendicular to the applied field, if the dipole follows precisely the oscillations of the external applied field. In the case of MW irradiation, there is a displacement between the two components, with value δ: this means that there will be only one component of the current generated in phase with the applied electrical field with value $I \sin \delta$.

In practice the value used to measure the efficiency of dielectric heating is the loss factor *D*, [71] rather than δ itself, which is correlated to the dielectric constant and defined as (Equation 2.1):

$$D = \tan \delta = \frac{\varepsilon''}{\varepsilon'}$$

Equation 2.1. Mathematical definition of the loss factor, *D.* [71]

where ε' is the dielectric constant or relative permittivity, and represents the ability of the molecules to be polarized by the electrical field applied (it should be noted that at room temperature with a static electrical field applied $\varepsilon' = \varepsilon_s$, where ε_s is the dielectric constant) and ε'' is the loss factor, a measure of the efficiency of the conversion of the absorbed energy into heat. For solvents with comparable ε', ε'' is a convenient discrimination factor.

D values for solvents commonly used in organic synthesis are reported in Table 2.1.

Table 2.1. Dielectric constant and *D* values measured for some common solvents in organic synthesis. [70]

Solvent	Dielectric constant (ε_S)	D^a
Hexane	1.9	
Benzene	2.3	
Carbon tetrachloride	2.2	
Chloroform	4.8	
Acetic acid	6.1	0.091
Ethyl acetate	6.2	0.174
THF	7.6	0.059
Dichloromethane	9.1	0.047
Acetone	20.6	0.042
Ethanol	24.6	0.054
Methanol	32.7	0.941
Acetonitrile	36	0.659
Dimethylformamide	36.7	0.062
DMSO	47	0.161
Formic acid	58	0.722
Water	80.4	0.123

[a]Measured at 2.45 GHz and r.t.

D can also be correlated to the penetration depth of the MW radiation into the material, x, through Equation 2.2:

$$D \sim \frac{1}{x}$$

Equation 2.2. Correlation between the loss factor *D* and the penetration depth of the MW radiation, x. [71]

where the penetration depth is defined as the point were 37 % of the initially irradiated power is still present. [67,70,71]

D and x are crucial parameters for the scaling up of MW assisted processes, since they are both strongly dependent on the temperature.

2.1.2. Technological improvements of MW equipment

One of the major contribution to the development of MAOS was the production of dedicated instruments especially designed for chemical synthesis. Before that, domestic microwave ovens were used as the MW heating source with all the disadvantages associated, which include the lack of reliable temperature control and poor safety. Above all, when using a domestic equipment, the field generated was not homogeneous, thus leading to low reproducibility of the obtained results. T was not efficiently controlled as well, leading to "hot spots" and strange behaviours of

the solutions under MW irradiation (the much famous MW effects). Also the vessels used for these experiments were mainly open vessels, with all the safety issues associated to the possibility of spillage, and with objective problem of solvent/reagents loss at MW working temperatures.

In recent years, several different companies have developed MW instruments dedicated to organic synthesis (CEM, [72] Milestone [73] and Personal Chemistry [74]), both for batchwise and continuous flow synthesis, mainly in closed vessels. Continuous flow reactors are usually more widespread in industrial contexts, [67] while batch reactors are more lab oriented. The main reason is that, when working on industrial quantities (l of solvent and kg of reagents) continuous flow MW systems allow a better control over temperature and pressure, and a sustainable applied MW power.

On the other hand, batch systems, are generally the solution of choice for MW instruments to be used in a chemistry lab. These dedicated instruments have an excellent power control, carefully designed reaction vessels and microwave cavities to ensure the maximum homogeneity possible of the electrical field, efficient control of pressure and temperature, and a cooling system which helps stabilizing the T of the vessel, thus they can be used on the ml and g scale.

2.2. IL and MW heating

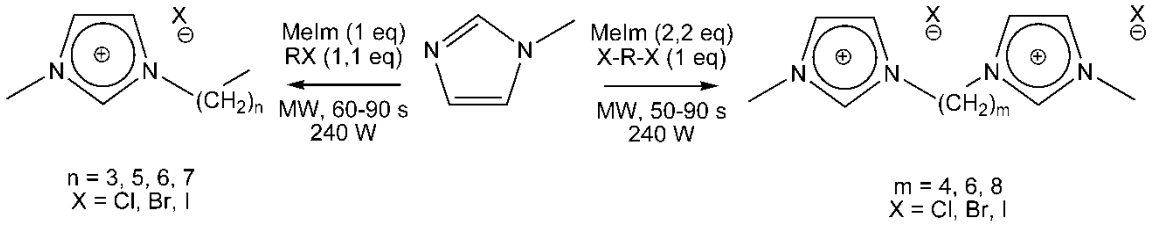
ILs are a widely used “additive” for MAOS: they are able to absorb the MW radiation efficiently and, since one of their major characteristic is they low vapour pressure, they tolerate well the temperatures used in MAOS. [68]

Due to their nature of liquids salts, ILs are soluble in a variety of organic solvents, which makes them an excellent additive to use with MW, both with solvents commonly used for MAOS (water, alcohols) and microwave transparent solvents (being ionic substances, they can contribute to the sample heating through the mechanism of ionic conduction). [68,69]

At the same time, MW energy could be used directly in the synthesis of ILs and ILs precursors. As we have seen previously, one of the important parameters in the synthesis of ILs, particularly for the quaternisation step, is the tight control of the reaction temperature to avoid local overheating. With the actual technology

development in lab MW equipment, the sample can be heated efficiently and homogeneously, leading to an increased purity of the product obtained and a drastic reduction of reaction times. Several examples of microwave assisted synthesis of ILs are present in the literature, from the synthesis of IL precursors [51-53,75,76] and imidazolium based ILs, [51-53,75,77-79] to the synthesis of SILP precursors, [80] chiral ILs, [81] and functionalized ILs. [54]

Varma and Namboodiri [51] synthesized imidazolium based ILs, 1–alkyl–3–methylimidazolium halides, [$C_n$mim]X (n=4,6,7,8) and the corresponding dicationic species with the aid of a domestic MW oven (Scheme 2.1). The reaction proceeded smoothly in all cases, with some limitations due to the instrument used: being a slightly modified domestic MW oven, control of the applied power and of the mixture temperature was not efficient, so pulsed heating was needed. Moreover, the quaternisation reaction was performed solventless, and, as the resulting IL was formed, a double phase was observed (the IL is not miscible with the starting alkyl halide); this required pulsed power cycle and manual shaking of the mixture between the pulses. It was also observed that this method gives good results for alkyl halides bearing long alkyl chains (n>6) and higher boiling points, while for the shorter ones, there was an extensive loss of reagents due to evaporation.

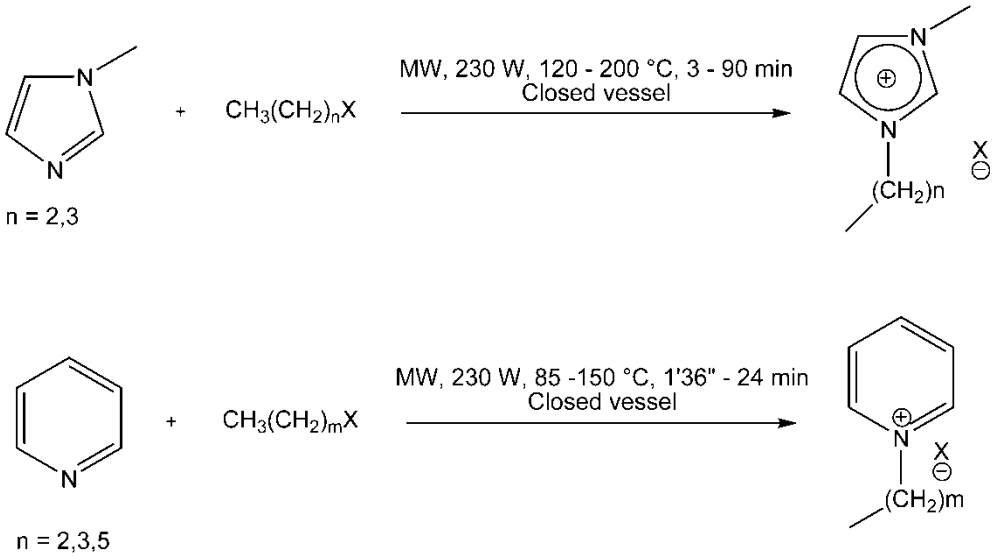


Scheme 2.1. MW assisted solventless synthesis of 1–alkyl–3–methylimidazolium halide and the corresponding dicationic species. [51]

With the same reaction protocol Namboodiri *et al.* performed the direct synthesis of tetrafluoroborate imidazolium based ILs and synthesized chloroaluminate ILs; [77,79] however these results will not be discussed in detail, since it has been observed by several groups that they were not reproducible: this can be ascribed mainly to the use of household instrumentations, where parameters such as irradiation power and bulk temperature cannot be controlled efficiently. [53,76]

Law *et al.* [76] performed the MW assisted quaternisation reactions for the synthesis of a series of 1–alkyl–3–methylimidazolium and *N*–alkylpyridinium ILs precursors, in a domestic microwave oven, and, for the first time, addressed the cooling problem, using an external water bath to ensure some extent of temperature control. All reactions were performed in a excess of the alkylating agent (from a 10 % molar excess, to 300 % molar excess), giving good yields in most cases.

Khadilkar *et al.* [52] studied the quaternisation of 1–alkyl–3–methylimidazolium and *N*–alkylpyridinium ILs precursors. This time the reactions were performed in a closed vessel, using a microwave digester (Scheme 2.2).



Scheme 2.2. Synthesis of 1–alkyl–3–methylimidazolium and *N*–alkylpyridinium ILs precursor under MW irradiation in a closed vessel. [52]

When compared to the previous examples, this method is safer, since all reactions were carried out in a closed vessel, and were performed with stoichiometric amounts of the alkyl halide. T control is still not optimal, but at least it is attempted.

Major improvement were made by Deetlefs *et al.* [53] who performed the quaternisation reactions in a "lab designed" MW oven, a MARS–5 instrument from CEM, with efficient power, T and pressure control. [53,72]

The use of a lab designed MW oven improves the control over the various reaction conditions, leading to reproducible results. The instrument used in this work was a multimode reactor, which means that energy is channelled in the MW chamber in such a way that multiple sample could be heated simultaneously. [67,68,71]

Reactions were all performed without solvent, scaling up of the process was attempted with negligible effects on the isolated yield. Results for the ”medium size” scale synthesis of 1–alkyl–3–methylimidazolium and *N*–alkylpyridinium salts are summarized in Table 2.2.

Table 2.2. MW assisted preparation of 1–alkyl–3–methylimidazolium and *N*–alkylpiridinium salts on a medium scale (150–300 mmol). [53]

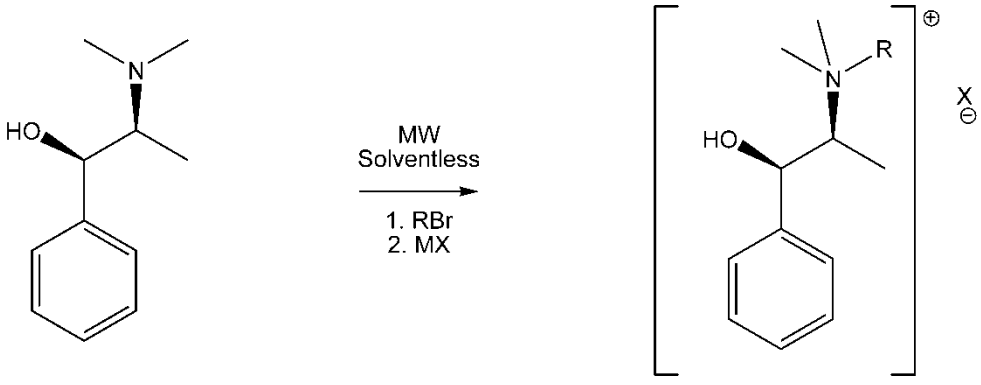
Heterocycle	***n=4***	***n=6***	***n=8***	***n=10***	***n=4***	***n=6***	***n=8***	***n=10***	***n=4***	***n=6***	***n=8***	***n=10***
[$C_n$mim]X	**Cl**	**Cl**	**Cl**	**Cl**	**Br**	**Br**	**Br**	**Br**	**I**	**I**	**I**	**I**
Power (W)	300	300	300	300	240	240	240	240	200	200	200	200
T (°C)	150	150	180	120	80	80	110	120	165	190	210	165
MW irradiation t (min)	20	20	20	10	6	8	8	10	4	7	9	11
Conventional heating t (min)	1440	1440	1440	1080	840	960	960	1080	640	720	720	720
Conversion (%)[a]	99.95											
Work–up yield (%)[a]	95	95	90	95	87	91	95	95	93	90	95	94
Conversion (%)[b]	99.95											
Work–up yield (%)[b]	96	93	91	92	93	90	97	95	92	94	97	94
[$C_n$py]X	**Cl**	**Cl**	**Cl**	**Cl**	**Br**	**Br**	**Br**	**Br**	**I**	**I**	**I**	**I**
Power (W)	300	300	300	300	240	240	240	240	200	200	200	200
T (°C)	120	120	150	180	130	130	130	130	165	190	210	165
MW irradiation t (min)	40	60	60	60	30	30	30	20	10	12	15	15
Conventional heating t (min)	3360	3360	3360	2880	2880	2880	2880	2880	960	960	1080	1140
Conversion (%)[a]	99.9											
Work–up yield (%)[a]	87	94	94	93	98	100	98	93	95	97	97	93
Conversion (%)[b]	99.9											
Work–up yield (%)[b]	90	93	94	94	95	98	99	95	95	91	97	95

[a]Employing a 10 % molar excess of alkyl halide. [b]Employing a 1–2 % molar excess of alkyl halide.

The reactivity order of the alkyl halides used (and reported in Table 2.2) is the same observed for quaternisation reactions under conventional heating: R–I>R–Br>R–Cl. Experimentally this is highlighted by a decrease on the applied MW power as the nucleophilicity of the alkyl halide rises.

In the same work, the large scale synthesis of [C_4mim]Cl was also attempted. The main problem encountered was the non availability of large scale closed vessels for MW. To overcome it, the reaction was performed on a 1.5 mol scale in open vessels: this meant that an excess of alkyl halide was necessary (about 10 % mol) and efficient cooling was required; this was easily obtained by placing a normal reflux condenser over the reaction vessel. Conversions were quantitative and the yield of the isolated product was above 85 % in most cases. This method is more sustainable when compared to the work of Law *et al.* discussed previously, which was the first one with efficient T control by water moderation, but needed a 300fold excess of alkylating agent (!) to obtain quantitative yields. [76]

MW assisted synthesis was also employed successfully for the synthesis of chiral ILs. The first example present in the literature is the MW assisted synthesis of chiral ILs based on (1*R*–2*S*)–(−)–ephedrinium salts (Scheme 2.3). [81]



Scheme 2.3. One pot solvent–free MW assisted preparation of (1*R*,2*S*)–*N*–methylephedrinium salts. [81]

These synthesis were performed with a CEM Discovery unit, working in monomode channel (only one sample at the time can be irradiated) in both open or closed vessels. The reaction was performed as a "one pot" synthesis, with all the three reaction components mixed together, or in a modified "one pot" synthesis: the crude product of the quaternisation reaction between (1*R*,2*S*)–*N*–methylephedrine and the alkylating agent, was charged with the metathesis salt and irradiated with MW

energy; in both cases all the reaction steps were performed without addition of a solvent. Results obtained are summarized in Table 2.3.

Table 2.3. One pot solvent–free MW assisted preparation of (1*R*,2*S*)–*N*–methylephedrinium salts. [81]

Entry	RBr	Method	MX	MW system	t (s)/T (°C)[a]	Yield (%)
1	C_4H_9Br	one pot	$NaPF_6$	Closed vessel	10/93	85
2	C_4H_9Br	one pot	NH_4PF_6	Closed vessel	10/93	72 (2)[b]
3	C_4H_9Br	one pot	NH_4BF_4	Closed vessel	10/93	77
4	C_4H_9Br	one pot	KOTf	Closed vessel	20/93	79
5	$C_8H_{17}Br$	one pot	NH_4PF_6	Closed vessel	45/95	10
6	$C_8H_{17}Br$	one pot	NH_4PF_6	Open vessel	45/95	51
7	$C_8H_{17}Br$	two step	NH_4PF_6	Open vessel	30/110 + 35 /95	80
8	$C_8H_{17}Br$	two step	$NaPF_6$	Open vessel	30/110 + 35 /95	77
9	$C_8H_{17}Br$	two step	KOTf	Open vessel	30/110 + 35 /95	91
10	$C_{10}H_{21}Br$	two step	$NaPF_6$	Open vessel	40 (110) + 35 (110)	85
11	$C_{10}H_{21}Br$	two step	KOTf	Open vessel	40 (110) + 35 (95)	84
12	$C_{16}H_{33}Br$	two step	$NaPF_6$	Open vessel	120 (95) + 60 (95)	77
13	$C_{16}H_{33}Br$	two step	KOTf	Open vessel	120 (95) + 60 (95)	88

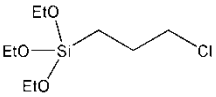
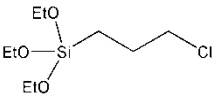
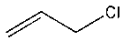
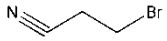
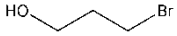
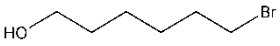
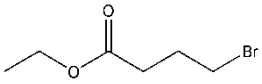
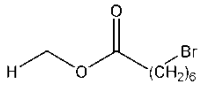
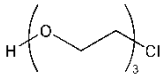
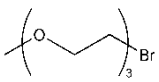
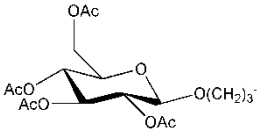
[a]Conditions for alkylation + anion exchange. [b]Yield obtained by conventional heating is given in brackets.

It can be noticed (Entry 2, Table 2.3) that in this case specific MW effects, when comparing to the same reaction performed under conventional heating, are observed. This has been ascribed to the formation of a dipolar TS (typical for these type of S_N2 reactions), with resulting enhancement of the effects of MW irradiation. This is particularly evident in this specific case, since all the reaction are performed solvent less.

Fu and co–workers, [54] synthesised functionalised ILs by direct alkylation of 1–methylimidazole under MW irradiation, under solventless conditions. Again, a common CEM Discovery lab MW oven was used. [72]

All reactions were performed in closed vessels, on a mmol scale, using equimolar amounts of Lewis base and alkylating agent. Results are summarized in Table 2.4.

Table 2.4. MW assisted solvent less synthesis of functionalized 1–alkyl–3–methylimidazolium based ILs. [54]

Entry	Lewis base	RX	Power (W)	t (s)	T (°C)	Atm.	Yield (%)
1	MeIm		245	40	245	N_2	95
2	MeIm		245	40	185	N_2	93
3	MeIm		185	25	180	air	90
4	MeIm		180	30	180	air	95
5	MeIm		100	25	175	air	92
6	MeIm		100	35	180	air	90
7	MeIm		100	35	168	air	90
8	MeIm		180	30	180	air	81
9	MeIm		250	90	185	air	90
10	MeIm		250	90	185	air	85
11	MeIm		30	20	110	air	45

The data collected in Table 2.4 show that MW assisted quaternisation could be a valuable tool also for the synthesis of more complicated IL scaffolds, and for screening or combinatorial synthesis of new ILs.

The last example of MW assisted synthesis of ILs, is from Cravotto *et al.* [78]: in this work, commonly used 1–butyl–3–methylimidazolium, *N*–octylpyridinium ($[C_8py]^+$) and 1–methyl–1–octylpyrrolidinium ($[C_8mpyr]^+$) ILs and ILs precursors were synthesized under a combined MW/US irradiation system (where US stands for "ultrasound"). Both the quaternisation reaction and the "one pot" straight forward (quaternisation + metathesis) synthesis of ILs were performed. The use of US ensures and efficient mixing of the solution, which is crucial for all of these solvent less reactions, and, when teamed up with MW irradiation, strongly discourages the formation of "hot spots" in the reaction mixture. Applying this combined technique

reaction times are drastically reduced. A multimode lab MW oven, from Milestone (Microsynth) was used.

Results obtained for both procedures are reported in Table 2.5.

Table 2.5. One pot synthesis of $[C_n mim]^+$, $[C_8 py]^+$ and $[C_8 mpyr]^+$ based ILs and ILs precursors under a combined MW/US irradiation. [78]

Entry	Lewis base	RX	MY	Irradiation time (min)	MW power (W)	US power (W)	T (°C)[a]	Yield (%)
1	MeIm	C_4H_9Cl	–	150	120[c]	30	75	<5
2	MeIm	C_4H_9Cl	–	10 30[b]	85	–	120 180	98
3	MeIm	$C_8H_{17}Cl$	KPF_6	10 20[b]	90	40	120 140	98
4	MeIm	$C_8H_{17}Cl$	KPF_6	60	60	–	140	88
5	MeIm	$C_8H_{17}Cl$	KBF_4	10 20[b]	75	40	120 140	95
6	MeIm	$C_8H_{17}Cl$	KOTf	10 45[b]	85	45	120 140	72
7	MeIm	$C_8H_{17}Cl$	$LiTf_2N$	10 90[b]	110	45	120 140	62
8	Py	$C_8H_{17}Cl$	–	180	60[c]	25	100	<5
9	Py	$C_8H_{17}Cl$	–	10 30[b]	85	–	120 180	85
10	Py	$C_8H_{17}Cl$	KPF_6	15 50[b]	65	–	120 180	83
11	Py	$C_8H_{17}Cl$	KBF_4	10 40[b]	60	–	120 180	68
12	Py	$C_8H_{17}Cl$	KOTf	10 50[b]	55	–	120 180	60
13	Py	$C_8H_{17}Cl$	$LiTf_2N$	15 50[b]	65	–	120 180	traces
14	Mepyr	$C_8H_{17}Cl$	–	10 60[b]	40	–	80 120	0
15	Mepyr	$C_8H_{17}Cl$	–	15 50[b]	80	–	120 160	20
16	Mepyr	$C_8H_{17}Cl$	–	15 50[b]	90	–	120 180	99
17	Mepyr	$C_8H_{17}Cl$	KPF_6	15 35[b]	95	–	120 180	85
18	Mepyr	$C_8H_{17}Cl$	KBF_4	10 45[b]	113	–	120 180	81
19	Mepyr	$C_8H_{17}Cl$	KOTf	10 45[b]	104	–	120 180	79

[a]Measured by an optical fibre thermometer. [b]Two temperature step. [c]Cooled reactor.

This combined technique works fine with 1–methylimidazole based ILs, particularly in the "one pot" synthesis, the only limitation being the polarity of the anion included in the resulting IL. Looking at the results reported in Table 2.5, it can be noticed that the worst result, in terms of yield, was obtained for the synthesis of

[C_8mim]Tf_2N, and this was ascribed to the lower polarization degree of the Tf_2N anion. For the quaternisation step only, this technique has proved to be not particularly useful, as the yields obtained are disappointing (compare Entry 1 and 2, Table 2.5).

Switching to the synthesis of pyridinium and pyrrolidinium ILs and ILs precursor, the limitations associated to the applicability of this technique become more evident. To pair up US with MW heating it is necessary to work with open vessels, this means either working in an excess of alkylating agent, or working at relatively low T (<150 °C). This is highlighted by the 1–methylpyrrolidine and pyridine based IL: both Lewis bases have lower bp (80° C for 1–methylpyrrolidine and 115 °C for pyridine) when compared with 1–methylimidazole, and this resulted in an almost exclusive use of closed vessels, and no possible application of US (it should also be noted that, when MW/US heating was applied to the the synthesis of [C_8py]Cl, Entry 8, Table 2.5, less than 5 % of the product was formed).

In conclusion, the use of combined MW/US is not beneficial to the synthesis of ILs. This technique shows various limitations, including the applicability range. For the quaternisation step, the use of US should be avoided since in most cases the reaction itself is inhibited (*i.e.* Entries 1, 2, 8 and 9, Table 2.5). For the one pot reaction protocol, results obtained for the combined MW/US technique are comparable with the ones observed for MW heating only (*i.e.* Entries 3 and 4, Table 2.5). From the data collected it seems like no specific US effect was observed: the differences in reactivity observed with different Lewis bases, and for metathesis reactions involving anions with a low degree of polarization, can be ascribed mainly to specific interactions with MW radiation.

It is clear for the examples just shown, that MW heating leads to big improvements when applied to the synthesis of ILs, however the main problem is that the "scattered" data obtained so far, lack of homogeneity giving poor reproducibility as the main outcome. This is particular evident for the first articles published on the subject, [51,75,77,79] in which reactions were performed in open vessels and with household MW ovens, but diminished along with the development of specifically designed MW reactors for laboratory chemistry. [72,73]

The results obtained with dedicated instruments, [53,54,78] show that MW assisted synthesis of ILs could be an innovative and useful technique, both for lab scale and

large scale synthesis. Since these results are so promising, it is a shame that, to date, in the literature there are no examples of optimizations of large scale MW assisted synthesis of ILs and/or continuous flow MW assisted large scale synthesis of ILs.

2.3. Towards predetermination of conditions, yields and/or conversions for MW assisted reactions: the development of prediction programs.

The vast majority of organic reactions are performed under heating. This means that in the literature is present a huge amount of data on reactions conducted under conventional heating, but little is known (or done) to switch from the "conventional heating information" to "microwave conditions". One way to obtain the desired new conditions it to undertake a kinetic study, but this requires a time consuming and often laborious study, which is not applicable, for example, to an industrial context. Another way to solve the problem could be the development of a dedicated software able to predict new reaction conditions under MW irradiation (such as T, t, and yields), starting from known conditions which could also be the conventional heating conditions.

The potential of using this approach in MAOS has already been addressed, mainly for specific problems. Chemat *et al.* [82] developed a software program designed to predict the yield of organic reactions in presence of a "superheating effect" on the solvent used. A MW "superheating effect" on a liquid is defined as the general rise of the boiling T that has been noted when organic solvents are heated with MW (clearly this is valid only for non MW transparent organic solvents). [83]

To develop this program, the dependence of the overheating bulk T of the solvent was parameterized in term of the applied power. The rate of temperature rise $\left(\frac{\partial T}{\partial t}\right)$ was expressed in terms of the applied power and heating rate, and then implemented in the classical reaction rate through the Arrhenius equation; once chosen the solvent, reaction conditions were optimized simply by consecutive iterations to convergence. This program was successfully used to predict reaction parameters, however it needs to be implemented with a database of solvent properties and a database of kinetic parameters of known reactions.

Strauss *et al.* [84,85] undertook a more ambitious task: to develop a predictive tool capable of translating reaction conditions from conventional heating (ambient

pressure) to high temperature conditions (usually the conditions obtained under MW irradiation, high T and elevated pressure).

The objectives of this work can be summarized as follows:

1) development of a predictive tool that would allow a facile and quick translation of conventional heated reaction condition to higher temperature condition, maintaining the yield observed;
2) extent of the protocol developed in 1) to a more general class of reaction;
3) optimization and application of the prediction tool developed also to reactions with poor outcome under conventional heating.

The program developed was named CROW, and works as described below. [84]

Since this prediction software needs to be applicable to potentially all reactions, it was developed as an iterative process. Reaction surfaces for two unrelated reactions (transesterification and intramolecular ring closure) were mapped using experimental data from a wide range of times, temperature, yields and catalyst loadings. The algorithms derived from this mapping process were implemented in the program. The distinctiveness of this program is that time, temperature and yield are considered as equally weighted parameters and can be traded against one another. [85]

Once the parameterization was set, the program was fed with the ”reference conditions” (conditions obtained for the reaction of interest under conventional heating) and theoretical data for two of the three parameters it is of interest to change (*i.e.* starting from experimentally obtained parameters – 78 °C, 5 h, 33 % yield – we want to know the time required to obtain a 90 % yield at 170 °C): for each specific reaction, one set of experimentally determined reference data for temperature, time, yield or conversion is required, along with the desired reaction temperature or time and yield or conversion, summing to a total of three experimentally established and two requested parameters. The program calculates the parameter of interest in an iterative manner, and, once the new reaction conditions are all set, an experimental check is undertaken. If the yield obtained is higher or smaller than the expected, a second iteration, using the experimental results derived from the first iteration as the new reference data set, is performed. [84,85].

An exemplification of how the program works is shown in Figure 2.1.

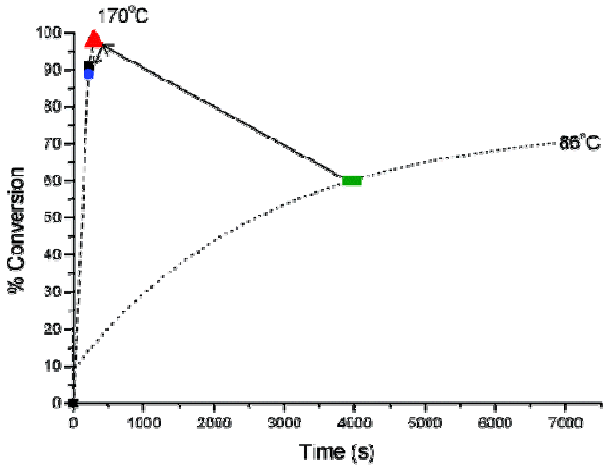
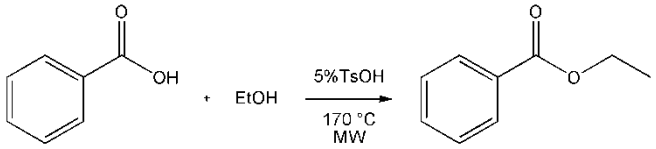
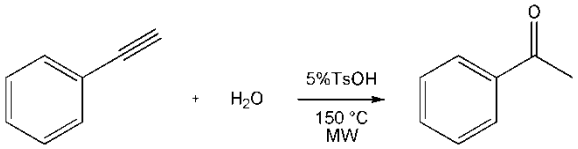
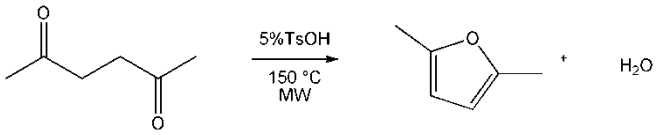
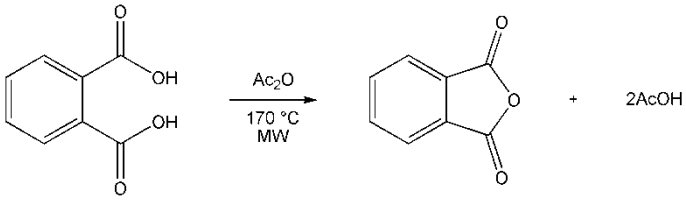
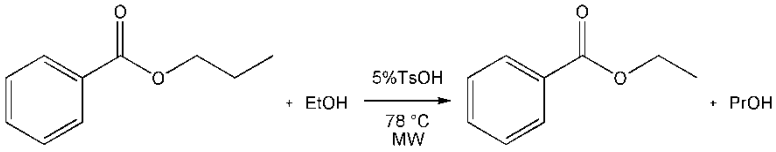
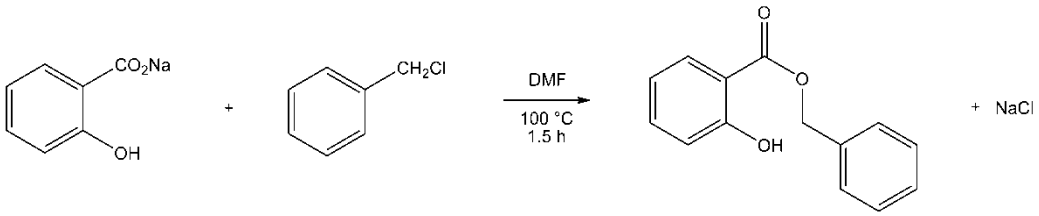
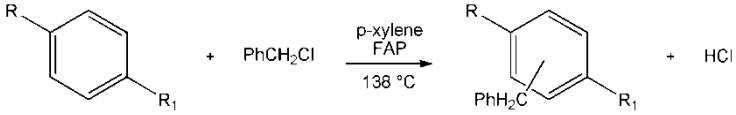
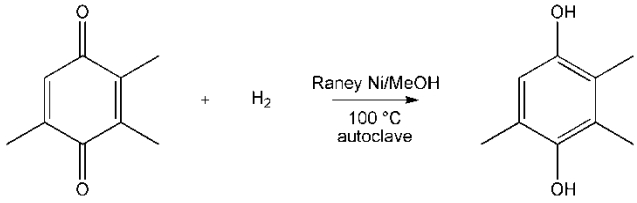
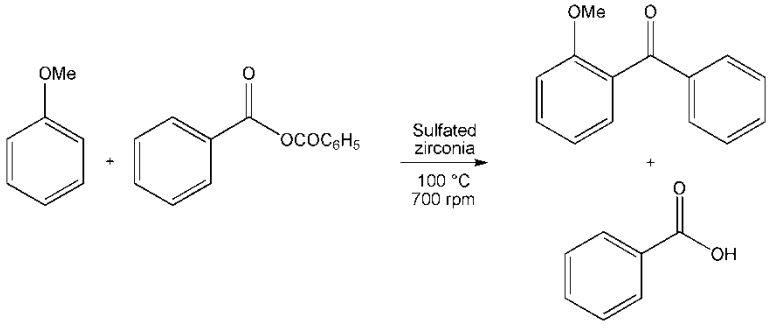
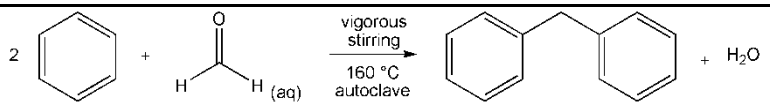
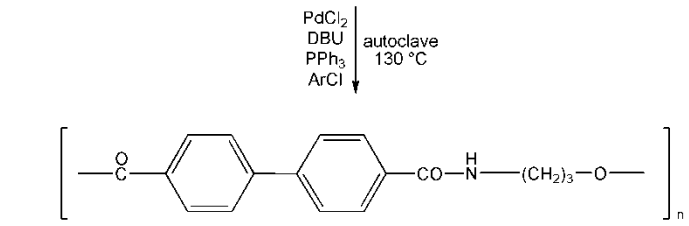
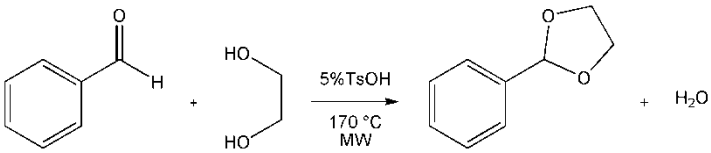


Figure 2.1. Graphical representation of the iterative process implemented in CROW. *Green rectangle:* reference data (starting experimental conditions); *blue square:* desired condition (obtained after one iteration of the program); *black square:* experimental conversion obtained with the conditions calculated from the 1st iteration; *red triangle:* experimental conditions obtained from the second iteration. [85]

CROW has been used for the parameter optimization of a broad range of reaction types. Systems tested include: reactions containing at least four total components between reactants and products, reactions performed in organic and inorganic solvents as well as solventless reactions, homogeneous and heterogeneous systems, acid–catalysed reactions, metal catalysed reaction (both heterogeneous and homogeneous), autocatalytic reactions, uncatalysed reactions. Some examples are shown in Table 2.6.

Table 2.6. Selected reactions optimized by CROW. [85]

Entry	Reaction
1	
2	
3	
4	
5	
6	
7	
8	
9	

Entry	Reaction
10	
11	
12	

A summary of the results obtained for the reactions reported in Table 2.6 is given in Table 2.7.

Table 2.7. Examples of estimated reaction conditions with iterations with CROW. [85]

Entry	Reference data (T, t, conv.)	Translated conditions (T,t)	Desired conversion (%)	1st iteration experimental conversion (%)	2nd iteration experimental conversion (%)	Reaction type
1	86 °C 73 min 60 %	170 °C 4.9 min	90	98		esterification
	170 °C 4.9 min 98 %	170 °C 3.6 min	90		91	
2	130 °C 21 min 20 %	150 °C 98 min	90	91		addition
3	78 °C 18 min 20 %	150°C 4.0 min	80	82		cyclization
4	140 °C 10.0 min 57 %	170 °C 8.0 min	90	70		anhydride formation
	170 °C 8.0 min 70 %	170 °C 15 min	90		84	
5	150 °C 71 min 91 %	78 °C 1740 min	90	90		transesterification
6	90 °C 14.5 min 35 %	110 °C 16 min	90	83		esterification
	110 °C 16 min 83 %	110 °C 21 min	90		90	
7	138 °C 132 min 20 %	138 °C 936 min	80	80		Friedel–Crafts alkylation
8	100 °C 6.0 min 20 %	100 °C 68 min	90	91		hydrogenation
9	100 °C 1.3 min 20 %	100 °C 14.0 min	90	91		Friedel–Crafts acylation
10	160 °C 12 min 40 %	160 °C 62 min	95	84		condensation
	160 °C 62 min 84 %	160 °C 99 min	95		95	
11	90 °C 2.0 min 20 %	130 °C 4.0 min	90	67		carbonylation-polycondensation
	130 °C 4.0 min 67 %	130 °C 8.0 min	90		89	
12	120 °C 30 min 32 %	170 °C 24 min	90	90		dioxolane synthesis

When compared to the previous example of prediction software, [82] CROW is definitely more powerful and of more general application. It has the advantage of

being a program not specifically designed for MW assisted synthesis, but works well also with MW assisted synthesis.

Looking at the data shown in Table 2.7 it can be noticed that in most cases, experimentally obtained conversion is equal (within the experimental error) to the calculated desired conversion just after one iteration of the program.

In some cases (Entries 1, 4, 6, 10 and 11, Table 2.7) this condition is not satisfied, however just one more iteration of the program is needed to obtain the desired conversion. The program was tested on more than 300 reaction, and the correlation coefficient (R^2) between predicted and experimental conversion was 0.75 when only the first iteration was considered, but rose to 0.97 when also the second iteration was taken into account. Data distribution for the experimental values obtained considering also the second iteration are shown in Figure 2.2.

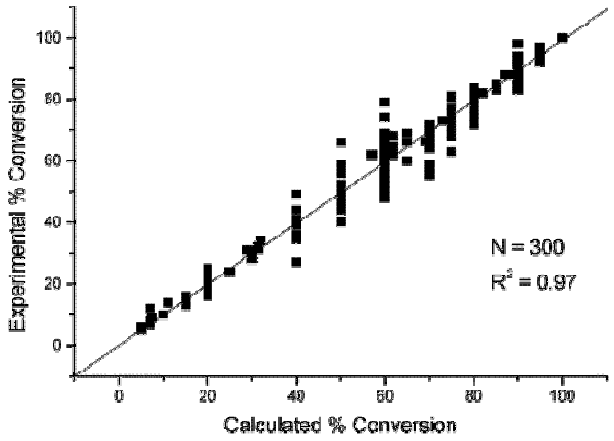


Figure 2.2. Plot of calculated *vs.* experimentally determined conversions, based on CROW calculations (>300 entries, 2nd iteration was also considered). [85]

2.4. Scope of the work

The work presented in this chapter was made during a Marie Curie Fellowship (April 2008–August 2008) at QUILL Research Centre, Queen's University, Belfast, UK.

During this placement, the possibility of using MW technology for the synthesis of ILs was investigated. In particular, the study has focused on:

- the optimization of reaction conditions and yields for selected quaternisation reactions, using a small scale MW reactor;

- the aid of a prediction tool for the optimization of reaction condition; [84,85]
- qualitative purity check of the obtained product in function of temperature and time;
- comparison of the reaction kinetics under MW irradiation and in pressurised container in order to evaluate the presence or absence of a MW effect and calculate kinetic data.

We have already introduced and explained the principles by which the CROW prediction method works in Section 2.3. In this experimental we have applied CROW to the quaternisation reaction of MeIm, in particular to form 1–alkyl–3–methylimidazolium chloride, [$C_n$mim]Cl ILs. The reactions were performed with MW irradiation: this has already been done in the synthesis of ILs and ILs precursors, but it is the first time that the prediction program CROW is applied in this type of S_N2 reactions (Menshutkin reactions).

In order to evaluate the "microwave effects" on the reactions studied, [86] kinetic measurement for the quaternisation reaction performed in a pressurized container (autoclave) were also carried out. Although the Menshutkin reaction is quite old and well known in organic chemistry, [87] little has been published on the kinetics of MeIm quaternisation, regardless the fact that this reaction is crucial for the synthesis of ILs. [88,89]

For the MW assisted reactions, all the experimental conditions (at different T and for different alkyl halides) were optimized, and an evaluation of the best reaction condition was performed for the different alkyl halides, by simple UV–Vis measurements to check the colour formation at a given conversion (70 %).

2.5. Experimental section

2.5.1. Instruments, materials and methods

Several instruments have been used in this experimental work:

- batch MW reactions were performed using a Milestone Microsynth® [90] reactor, equipped with pressure sensor and optical fiber thermometer. The reactions were carried out in quartz vessels;

- NMR spectra were recorded on Bruker AV300 and DPX300 instruments, with an operational frequency of 300.1 MHz and DRX500, with an operational frequency of 500.1 MHz for ^1H NMR. Acetonitrile–d_3 (Apollo Scientifics) and deuterated chloroform (Apollo Scientifics) were used as solvents.
- HPLC analysis was performed with an Agilent 1200 instrument, with a refractive index detector. A BioRad HPX–87H anion exchange column was used. All analyses were performed using deionised water as the eluent, at a flow rate of 0.6 ml min^{-1}. The column was kept at T = 40 °C;
- UV–Vis spectra were recorded using a dual beam Perkin Elmer Lambda 25 spectrometer. All analyses were performed in quartz cuvettes of 1 cm path lenght. All analyses were performed in absolute EtOH.
- Electrospray mass spectra (ESI) were recorded using a Micromass® Tecnologies LCT Premier; all samples were analysed using a 90 % CH_3CN–H_2O mobile phase, at a flow rate of 0.3 ml min^{-1}.

1–methylimidazole was purchased from Acros Organics and Sigma Aldrich and distilled from KOH *prior* to use. Chloroalkanes were purchased from several sources (1–chlorobutane and 1–chlorododecane from Acros Organics, 1–chlorohexane from Fluka, 1–chlorooctane from Sigma Aldrich) and used without further purification. HPLC grade acetonitrile from VWR International was used as received, as was absolute ethanol (Riedel–de–Haën, VWR International).

Autoclave: for the kinetic measurements a stainless steel autoclave (chamber V = 50 ml) and a glass autoclave (chamber V = 1000 ml) were used. Both the autoclaves were equipped with a temperature sensor (embedded in the case of the 50 ml stainless steel autoclave, a simple IKA ETS–D54 fuzzy logic T controller was used in the case of the glass autoclave), and an heating unit. Both autoclaves were equipped with a mechanical stirrer (stainless steel mechanical stirrer for the stainless steel autoclave, and a Teflon–coated mechanical stirrer in the case of the glass autoclave). Reactants (MeIm and hexyl chloride) were measured separately in distinct cylinders, the solvent of choice (CH_3CN or EtOH) was measured in a separated cylinder as well. All the reaction components were then mixed together in the autoclave chamber, that was then closed and heated to the desired T. Once reached the reaction T, the

reaction mixture was sampled every 5 or 10 minutes (depending on the T and on the reaction extent) sampling through the appropriate valve connected to the liquid phase, a small amount of reaction mixture (ca. 1 ml).
Samples were collected in lip vials, and allowed to cool down at r. t. A sample (Pasteur pipette tip of the solution sampled) was then collected for ^{1}H NMR analysis and diluted in 0.4 ml of $CH_3CN–d_3$ (for the reactions performed in CH_3CN) or $CDCl_3$ (for reactions performed in EtOH).

*MW assisted: f*or MW assisted reactions, a Microwave Microsynth instrument was used. This MW oven operates in multimode channel and with the closed vessel technique. It is equipped with an internal pressure sensor and a double T control: an internal OF (Optical Fibre) thermometer and an external IR (Infrared) sensor. All microwave reaction were performed in quartz vessels, with a minimum volume of reaction mixture >10 ml (to ensure homogeneous heating of the sample).
All the reaction components, previously measured with distinct cylinder, were mixed together into the MW vessel, which was then charged with the pressure (p) and temperature (T) sensors, closed and irradiated with MW energy, according to a specific program. Details on the different MW programs used are given in Appendix A. At the end of the irradiation and the cooling time, the reaction mixture was removed from the MW chamber, opened and transferred in a lip vial. A sample (Pasteur pipette tip of the solution sampled) was then collected for ^{1}H NMR analysis and diluted in 0.4 ml of $CH_3CN–d_3$ (for the reactions performed in CH_3CN) or $CDCl_3$ (for reactions performed in EtOH).

Yield calculation:

- for the HPLC quantitative analysis, a sample (100 µl) of the reaction mixture was diluted with 1 ml of deionised water and analysed by HPLC. Quantitative analysis was possible by constructing a calibration curve for $[C_6mim]Cl$.
- titrimetic titrations were made using the Mohr method: [43] an aqueous solution of K_2CrO_4 0.1 % w/w and an aqueous solution of $AgNO_3$ $1.00 \cdot 10^{-2}$ M were prepared. 2 ml of the K_2CrO_4 were mixed with 100 µl of the collected sample and titrated with the $AgNO_3$ solution until color changed from yellow to red. The calibration curve was constructed in the same way.

- NMR yields were calculated as the ratio the integrals of the H–2 signal of the MeIm, and the corresponding H–2 signal of the [C_6mim]Cl formed, to check if this measurement was consistent the ratio between the integrals of the –CH_3 group bond to the C–3 on the imidazole ring for both MeIm and [C_6mim]Cl was also measured. The integral for the –CH_2– in position 1 and the –CH_2– in position 1a were also measured, however, since 1–chlorohexane is more volatile than MeIm, particularly in the range of operating temperatures, only the ratio MeIm signals/[C_6mim]Cl was used in the calculations.

The numbering for the positions on MeIm, 1–chlorohexane and [C_6mim]Cl is shown in Figure 2.3.

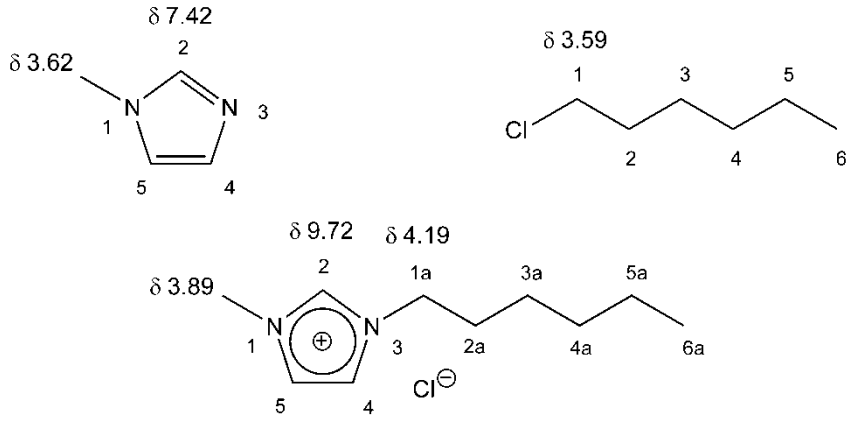


Figure 2.3. Numbering of positions for MeIm (upper left), hexyl chloride (upper right) and [C_6mim]Cl (bottom centre).

For a quick graphical understanding of the signals involved, a scheme with a comparison of the ^{1}H NMR spectra of MeIm, hexyl chloride and [C_6mim] Cl is shown in Figure 2.4.

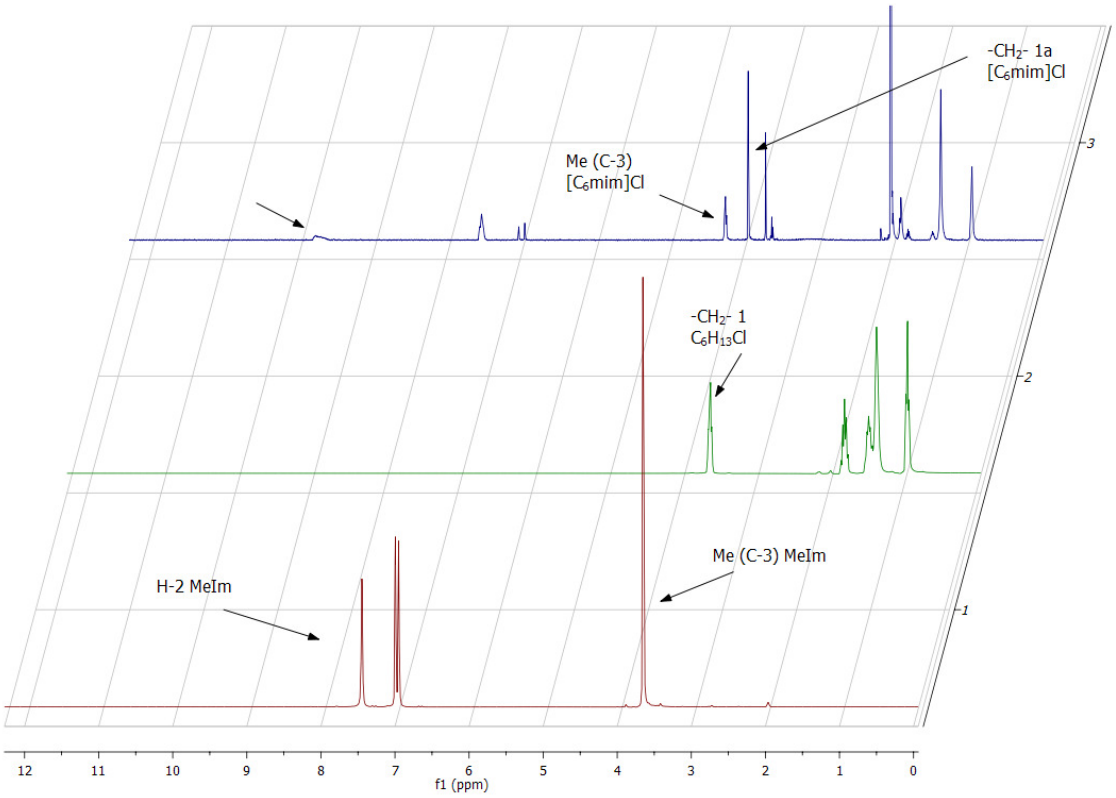


Figure 2.4. Comparison of ^{1}H NMR spectra for MeIm (red),1–chlorohexane (green) and a reaction mixture containing MeIm, 1–chlorohexane and [C_6mim]Cl (blue) in CH_3CN–d_3. Signals used in the yield calculation are highlighted.

Yield (in %) were calculated according to Equation 2.3:

$$\%_{[C_6mim]Cl} = \frac{Int_{[C_6mmim]Cl} \times 100}{(Int_{MeIm} + Int_{[C_6mim]Cl})}$$

Equation 2.3. Formula applied to calculate the yield of [C_6mim]Cl formed during the quaternisation reaction.

Kinetics: to check the reaction order, the integrated rate law for a 2nd order reaction (with different reagent concentrations) was used. Its mathematical expression is reported in Equation 2.4 [91]:

$$\frac{1}{[C_6H_{13}Cl]_0 - [MeIm]_0} \times \ln\frac{[C_6H_{13}Cl]}{[MeIm]} = kt + \frac{1}{[C_6H_{13}Cl]_0 - [MeIm]_0} \times \ln\frac{[C_6H_{13}Cl]_0}{[MeIm]_0}$$

Equation 2.4. Integrated rate law for a 2nd order reaction with different concentrations of reagents; $[C_6H_{13}Cl]_0$=initial concentration of 1–chlorohexane, $[MeIm]_0$=initial concentration of 1–methylimidazole; $[C_6H_{13}Cl]$=concentration of 1–chlorohexane at a given time; [MeIm]=concentration of MeIm at a given time; k=kinetic constant (expressed in $M^{-1}\cdot s^{-1}$); t=time expressed in seconds.

The above equation was applied to obtain a linear regression of the experimental data, using the software SigmaPlot 2000.

2.5.2. MW assisted synthesis of 1–alkyl–3–methylimidazolium ILs

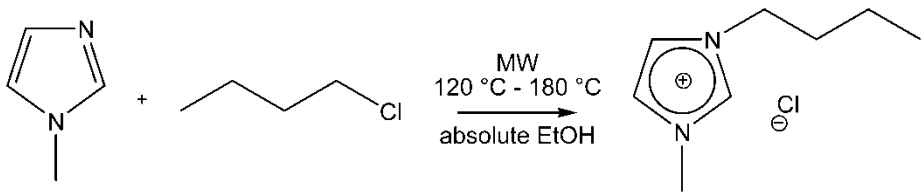
Reactions were all performed in presence of a solvent (CH_3CN and/or EtOH) in order to minimise the viscosity of the resulting product (Cl^- containing ILs are highly viscous liquids), thus guaranteeing an homogeneous heating of the solution. This is not crucial for batchwise synthesis, but becomes important when switching to continuous flow apparatus. [67]

The first choice of solvent was CH_3CN (used mainly for the optimisation of reaction conditions for the synthesis of [C_6mim]Cl and [C_8mim]Cl). This solvent was chosen since it is a polar aprotic solvent, able to dissolve efficiently both MeIm and the alkyl chloride of interest; at the same time it is a good candidate solvent for MW assisted reactions, due to its relatively high dielectric constant and moderate loss factor. [70]

If we bear in mind the possibility of scaling up the process, the solvent choice becomes crucial and acetonitrile is not the best candidate for large scale both for its properties, and, in recent times, because its limited availability on the market. Since the solvents requirements for the quaternisation reactions are quite general (the reaction proceeds smoothly in most solvents, and is strongly accelerated in non polar solvents, were the resulting quaternary salt precipitates out), we have decided to switch to a more sustainable solvent, EtOH in which the reaction mixture is still homogeneous. [92]

2.5.2.1. MW assisted synthesis of [C_4mim]Cl

This reaction was performed only in EtOH.



Scheme 2.4. MW assisted synthesis of [C_4mim]Cl in EtOH.

In a typical experiment, 2.5 ml (31.5 mmol) of 1–methylimidazole, 3.4 ml (32.3 mmol, 1.02 equiv.) of 1–chlorobutane and 6.0 ml of absolute EtOH were introduced in a MW tube containing a magnetic stirrer bar. The tube was then sealed and equipped with the pressure sensor and the optical fibre thermometer, and finally heated under MW irradiation. The reaction was performed at 5 different temperatures (120, 135, 150, 165, and 180 °C). Reaction conditions were optimised to achieve a 70 % conversion of the starting material, with the aid of the prediction tool CROW we have discussed previously. [84,85]

Results are summarised in Table 2.8.

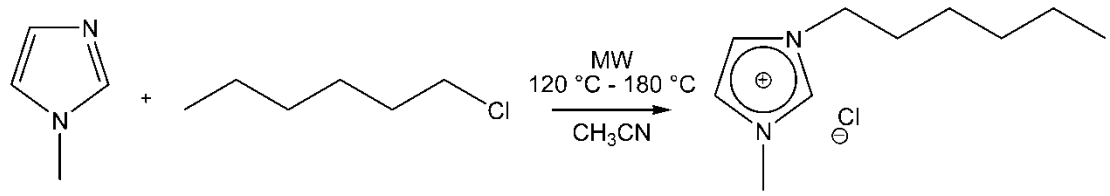
Table 2.8. MW assisted synthesis of [C_4mim]Cl in EtOH: optimisation of reaction conditions to achieve a 70 % conversion.

Entry	Reference data (T, t, conv.)	Translated conditions (T,t)	Desired conversion (%)	1st iteration experimental conversion (%)	2nd iteration experimental conversion (%)
1	120 °C 45’00” 40 %	120 °C 1h 45’00”	70	54	
	120 °C 1h 45’00” 54 %	120 °C 2h 39’00”	70		74
2	135 °C 30’00” 47 %	135 °C 55’12”	70	71	
3	150 °C 20’00” 68 %	150°C 20’ 54”	70	66	
4	165 °C 10’00” 57 %	165°C 11’30”	70	73	
5	180 °C 4’00” 66 %	180 °C 4’24”	70	69	

2.5.2.2. MW assisted synthesis of [C_6mim]Cl

This reaction was performed in CH_3CN and in EtOH.

- in CH_3CN



Scheme 2.5. MW assisted synthesis of [C_6mim]Cl in CH_3CN.

In a typical experiment, 2.0 ml (25.2 mmol) of 1–methylimidazole, 3.5 ml (25.4 mmol, 1.01 equiv.) of 1–chlorohexane and 5.5 ml of CH_3CN were introduced in a MW tube containing a magnetic stirrer bar. The tube was then sealed and equipped with the pressure sensor and the optical fibre thermometer, and finally heated under MW irradiation. The reaction was performed at 5 different temperatures (120, 135, 150, 165, and 180 °C).

Reaction conditions were optimised to achieve a 70 % conversion of the starting material, with the aid of the prediction tool CROW we have discussed previously. [84,85]

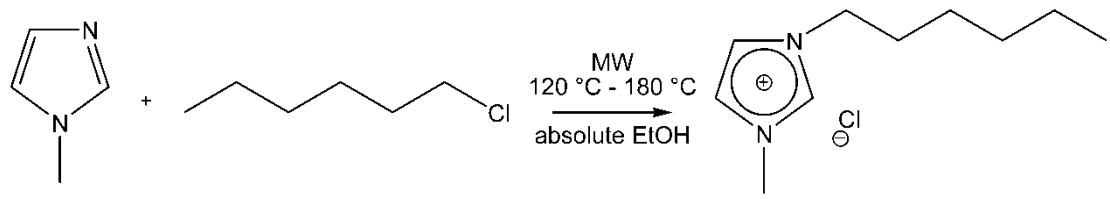
For one T (150 °C), optimisation of the reaction conditions to obtain quantitative yields was also attempted.

Results obtained are shown in Table 2.9.

Table 2.9. MW assisted synthesis of [C_6mim]Cl in CH_3CN: optimisation of reaction condition to achieve a 70 and 99 % conversion.

Entry	Reference data (T, t, conv.)	Translated conditions (T,t)	Desired conversion (%)	1st iteration experimental conversion (%)	2nd iteration experimental conversion (%)
1	120 °C 34'00" 28 %	120 °C 2h 4'00"	70	76	
2	135 °C 25'00" 44 %	135 °C 50'12"	70	69	
3	150 °C 15'30" 55 %	150°C 22' 30"	70	73	
	150 °C 22'30" 73%	150 °C 70'00"	100		91
4	165 °C 12'00" 73 %	–	70	–	
5	180 °C 5'00" 66 %	–	70	–	

- in EtOH



Scheme 2.6. MW assisted synthesis of [C_6mim]Cl in EtOH.

In a typical experiment, 2.0 ml (25.2 mmol) of 1–methylimidazole, 3.5 ml (25.4 mmol, 1.01 equiv.) of 1–chlorohexane and 5.5 ml of absolute EtOH were introduced in a MW tube containing a magnetic stirrer bar. The tube was then sealed and equipped with the pressure sensor and the optical fibre thermometer, and finally heated under MW irradiation. The reaction was performed at 7 different temperatures (120, 135, 145, 150, 155, 165, and 180 °C).

Reaction conditions were optimised to achieve a 70 % conversion of the starting material, with the aid of the prediction tool CROW we have discussed previously. [84,85]

For one T (150 °C), optimisation of the reaction conditions to obtain quantitative yields was also attempted.

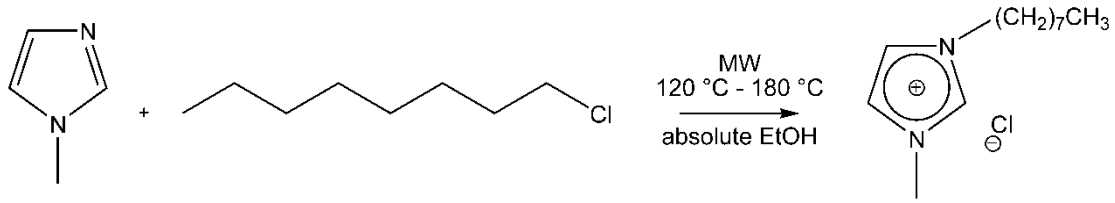
Results obtained are summarized in Table 2.10.

Table 2.10. MW assisted synthesis of [C_6mim]Cl in EtOH: optimisation of reaction conditions to achieve a 70 and 99 % conversion.

Entry	Reference data (T, t, conv.)	Translated conditions (T,t)	Desired conversion (%)	1st iteration experimental conversion (%)	2nd iteration experimental conversion (%)
1	120 °C 34'00" 27 %	120 °C 2h 4'00"	70	61	
	120 °C 2h 4'00" 61 %	120 °C 2h 37'00"	70		63
2	135 °C 25'00" 41 %	135 °C 50'12"	70	59	
	135 °C 50'12" 59 %	135 °C 1h 07'00"	70		68
3	145 °C 30'00" 65 %	145 °C 34'24"	70	69	
4a	150 °C 22'30" 68 %	150 °C 23'42"	70	63	
4b	150 °C 2h 00'00" 94% (in CH_3CN)	150 °C 3h16'00"	100	92	–
	150 °C 3h 16'00" 92 %	150 °C 5h 57'00"	100		>99
5	155 °C 30'00" 79 %	155 °C 23'08"	70	71	
6	165 °C 12'00" 74 %	165 °C 10'18"	70	69	
7	180 °C 5'00" 70 %	–	70	–	–

2.5.2.3. MW assisted synthesis of [C_8mim]Cl

The reaction conditions were optimised only in EtOH.



Scheme 2.7. MW assisted synthesis of [C_8mim]Cl in EtOH**.**

In a typical experiment, 2.0 ml (25.2 mmol) of 1–methylimidazole, 4.3 ml (25.4 mmol, 1.01 equiv.) of 1–chlorooctane and 6.3 ml of absolute EtOH were introduced in a MW tube, equipped with a magnetic stirrer bar. The tube was then sealed and equipped with the pressure sensor and the optical fibre thermometer, and finally heated under MW irradiation. The reaction was performed at 5 different temperatures (120, 135, 150, 165, and 180 °C).

Reaction conditions were optimised to achieve a 70 % conversion of the starting material, with the aid of the prediction tool CROW we have discussed previously. [84,85] For one T (150 °C), optimisation of the reaction conditions to obtain quantitative yields was also attempted.

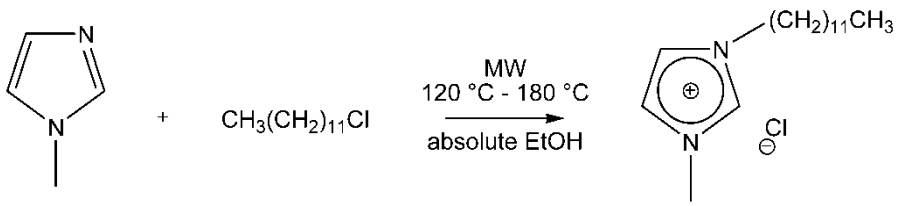
Results obtained are summarized in Table 2.11.

Table 2.11. MW assisted synthesis of [C_8mim]Cl in EtOH: optimisation of reaction condition to achieve a 70 and 99 % conversion.

Entry	Reference data (T, t, conv.)	Translated conditions (T,t)	Desired conversion (%)	1st iteration experimental conversion (%)	2nd iteration experimental conversion (%)
1	120 °C 34'00" 12 %	120 °C 2h 10'00"	70	56	
	120 °C 2h 10'00" 56 %	120 °C 3h 16'00"	70		68
2	135 °C 25'00" 37 %	135 °C 55'00"	70	57	
	135 °C 55'00" 57 %	135 °C 1h 07'00"	70		60
3a	150 °C 22'00" 59 %	150°C 29' 00"	70	66	
3b	150 °C 29'00" 69%	150 °C 89'00"	100	86	
	150 °C 89'00" 86 %	150 °C 2h 40'00"	100		91
4	165 °C 12'00" 64 %	165 °C 13'48"	70	67	
5	180 °C 5'00" 59 %	180 °C 6'30"	70	72	

2.5.2.4. MW assisted synthesis of [C_{12}mim]Cl in EtOH

The reaction was performed only in EtOH, preliminary proving experiments in CH_3CN were attempted, but then abandoned since 1–chlorododecane is not miscible with CH_3CN.



Scheme 2.8. MW assisted synthesis of [C_{12}mim]Cl in EtOH.

In a typical experiment, 2.0 ml (25.2 mmol) of 1–methylimidazole, 6.0 ml (25.5 mmol, 1.01 equiv.) of 1–chlorododecane and 8.0 ml of EtOH absolute were introduced in a MW tube containing a magnetic stirrer bar. The tube was then sealed and equipped with the pressure sensor and the optical fibre thermometer, and finally heated under MW irradiation. The reaction was performed at 5 different temperatures (120, 135, 150, 165, and 180 °C).

Reaction conditions were optimised to achieve a 70 % conversion of the starting material, with the aid of the prediction tool CROW we have discussed previously. [84,85]

Results obtained are summarised in Table 2.12.

Table 2.12. MW assisted synthesis of [C_{12}mim]Cl in EtOH: optimisation of reaction conditions to achieve a 70 % conversion.

Entry	Reference data (T, t, conv.)	Translated conditions (T,t)	Desired conversion (%)	1st iteration experimental conversion (%)
1	120 °C 80'00" 29 %	120 °C 4h 40'00"	70	54
2	135 °C 50'00" 49 %	135 °C 87'00"	70	59
3a	150 °C 40'00" 63 %	150°C 47' 30"	70	68
4	165 °C 25'00" 73 %	165 °C 23'06"	70	70
5	180 °C 12'00" 78 %	180 °C 9'48"	70	73

2.5.3. Verification of the reaction order

Although quaternisation is the key step in the synthesis of ILs, and has a certain appeal also in terms of industrial application, its kinetics have not been studied in detail. If we restrict our survey only to the quaternisation of MeIm, there are only three articles published on the subject [88,89,93].

Große Böwing *et al.* [88] studied the kinetics of the quaternisation reaction between MeIm and butyl chloride to form [C_4mim]Cl. The reaction was studied in both

solvent and solvent free conditions, the latter case being more complicated in terms of mechanism study, since butyl chloride is not miscible with both MeIm and the resulting IL, [C_4mim]Cl. For reactions with solvent, EtOH was the choice. The authors applied the conclusions of their kinetical study to a practical case, the synthesis of [C_2mim]$EtSO_4$ with particular emphasis on the reaction engineering and reaction vessel design. [93]

Schleicher *et al.* performed a systematic study on the kinetic and solvent effects involved on the quaternisation of MeIm, performing the synthesis of a model IL, [C_6mim]Br in a wide range of organic solvents. [89]

In our own experimental work we have measured kinetic parameters for the synthesis of [C_6mim]Cl in CH_3CN in an autoclave reactor and verified that the mechanism was the same also when we used EtOH. Since the Menshutkin reaction proceeds with an S_N2 mechanism, 2nd order kinetics were postulated for this reaction.

2.5.3.1. Synthesis of [C_6mim]Cl in CH_3CN in a pressurised container (autoclave)

All reactions were performed in a stainless steel autoclave, except for T=60 °C which was performed in a Stem block. Reaction conditions and reagents ratios are summarised in Table 2.13.

Table 2.13. Reaction conditions for the synthesis of [C_6mim]Cl in CH_3CN in a pressurised container.

T (°C)	t (h)	MeIm		$C_6H_{13}Cl$		V CH_3CN (ml)
		mmol	M	mmol	M	
60	72	75.6	5.0	76.3	5.1	15
110	7	81.9	4.6	82.2	4.6	18
120	9	81.9	4.6	82.2	4.6	18
140	3	81.9	4.6	82.2	4.6	18
150	1	41.6	1.5	42.2	1.6	27
150	1	81.9	4.6	90.2	5.0	18
150	1	81.9	4.6	98.2	5.5	18

The kinetic data derived from the above mentioned reactions, fitted to a 2nd order model, are summarised in Table 2.14.

Table 2.14. 2nd order kinetic constant for the synthesis of [C_6mim]Cl in CH_3CN in a pressurized container at different temperature. Linear correlation coefficient (R^2) is reported.

Entry	T (°C)	t (h)	MeIm (M)	$C_6H_{13}Cl$ (M)	Ratio MeIm:$C_6H_{13}Cl$	k ($M^{-1}\cdot s^{-1}$)	$\frac{1}{[C_6H_{13}Cl]_0 - [MeIm]_0}$ (M^{-1})	R^2
1[a]	60	72	75.6	76.3	1.00:1.01	$(4.24\pm0.21)\cdot10^{-7}$	0.189±0.003	0.97
2	110	8	81.9	82.2	1.00:1.00	$(2.38\pm0.57)\cdot10^{-5}$	0.12±0.08	0.71
3	120	9	81.9	82.2	1.00:1.00	$(1.13\pm0.12)\cdot10^{-4}$	0.01±0.15	0.94
4	140	3	81.9	82.2	1.00:1.00	$(1.27\pm0.05)\cdot10^{-4}$	0.12±0.02	0.99
5	150	1	41.6	42.2	1.00:1.00	$(5.40\pm8.10)\cdot10^{-4}$	$(1.16\cdot10^{-9})\pm0.23$	0.91
6	150	1	81.9	98.2	1.00:1.01	$(3.75\pm0.87)\cdot10^{-4}$	$(5.47\cdot10^{-9})\pm0.25$	0.84
7	150	1	81.9	90.2	1.00:1.10	$(2.84\pm0.18)\cdot10^{-4}$	$(2.72\cdot10^{-10})\pm0,04$	0.98

[a]Reaction performed in lip vials heated by a stem block.

2.5.3.2. Synthesis of [C_6mim]Cl in EtOH in a pressurised container (autoclave)

The reaction was performed both in the steel and the glass autoclave. In both cases the T was 150 °C. Results are shown in Table 2.15.

Table 2.15. 2nd order kinetic constants for the synthesis of [C_6mim]Cl in EtOH at T= 150 °C, performed in a pressurised container.

Entry	t (h)	MeIm (M)	$C_6H_{13}Cl$ (M)	V EtOH (ml)	Ratio MeIm:$C_6H_{13}Cl$	k ($M^{-1}\cdot s^{-1}$)	$\frac{1}{[C_6H_{13}Cl]_0 - [MeIm]_0}$ (M^{-1})	R^2
1[a]	1	0.73	0.74	34.5	1.00:1.01	$(3.96\pm0.03)\cdot10^{-4}$	0.91±0.11	0.94
2	5	4.21	4.22	418	1.00:1.00	$(3.56\pm0.03)\cdot10^{-4}$	$(4.44\cdot10^{-10})\pm0.11$	0.93

[a]Regression performed with HPLC yields.

For the reaction in the steel autoclave the same procedure as the in the above section was followed. For the reaction performed in the glass autoclave, the volumes involved were higher and a comparison between NMR, HPLC and Mohr titration for the determination of the yield was undertaken.

A graphical comparison between those data is reported below.

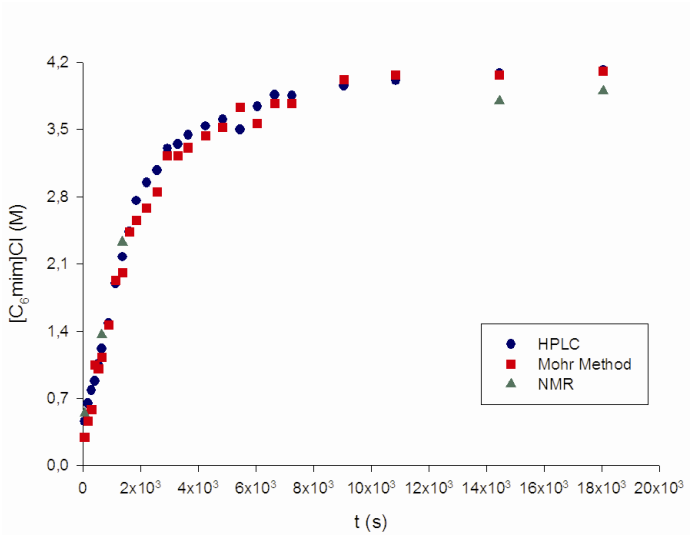


Figure 2.5. Product formation for the synthesis of [C_6mim]Cl in EtOH at 150 °C, comparison between different yield determination methods: blue circles=HPLC determined yield, red squares=yield determined by Mohr method gravimetric titration, green triangles=yield determined by ^{1}H NMR measurements.

It can be seen from the graph on Figure 2.5, all methods are consistent with each other and have the same level of precision. In all cases, the uncertainty rises as quantitative conversion is achieved (conversion >85 %).

For this kinetic experiment, the 2nd order product formation was also plotted, with respect to the HPLC and Mohr method measurements. A comparison of the obtained results is depicted in Figure 2.6; as it can be seen the fitting between calculated and experimental data is good in both cases.

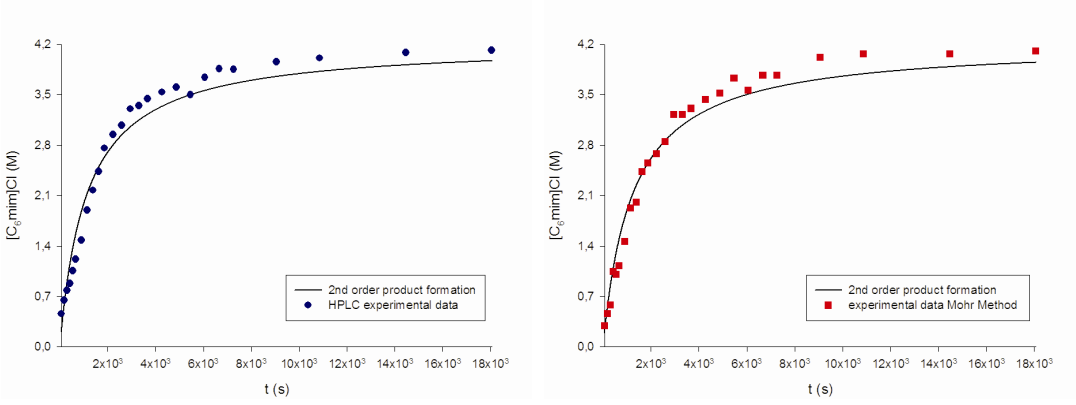


Figure 2.6. Comparison between the experimentally measured (HPLC *vs.* Mohr method) and calculated yield, for the synthesis of [C_6mim]Cl in EtOH at T=150 °C, performed under conventional heating in a glass autoclave.

The good agreement between experimentally measured and calculated values is also shown, in Figure 2.7, were a 2nd order linear fit was performed on the data obtained

from the synthesis of [C_6mim]Cl in the glass autoclave. Conversions above 85 % were discarded since the yield measurements used were not accurate.

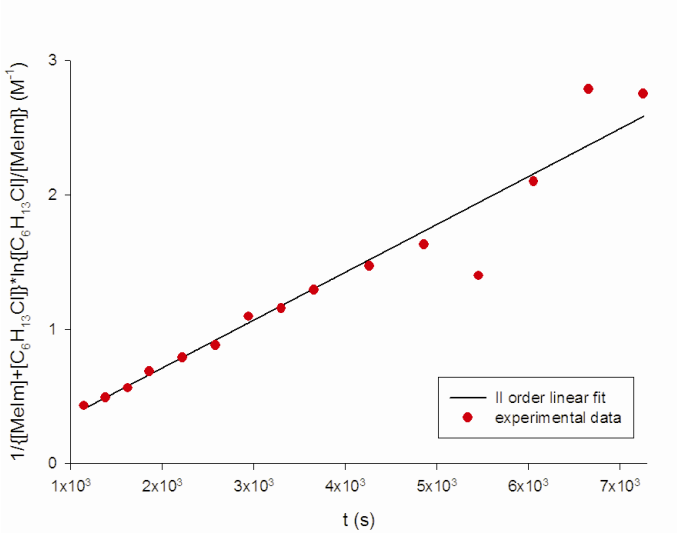


Figure 2.7. 2nd order linear fit for the synthesis of [C_6mim]Cl in EtOH at T=150 °C, performed in a glass autoclave.

2.5.3.3. MW assisted synthesis of [C_6mim]Cl in CH_3CN

The data obtained during the optimisation of MW conditions were also used (when possible, which means that at least 3 different points were available) to derive kinetic data for the MW assisted reactions. Results are summarised in Table 2.16.

Table 2.16. 2nd order kinetic constant for the MW assisted synthesis of [C_6mim]Cl in CH_3CN.

Entry	T (°C)	t (min)	MeIm(M)	$C_6H_{13}Cl$ (M)	V CH_3CN (ml)	Ratio MeIm:$C_6H_{13}Cl$	k ($M^{-1}\cdot s^{-1}$)	R^2
1	120	34–124	4.58	4.61	5.5	1.00:1.01	$(8.14\pm4.09)\cdot10^{-5}$	0.87
2	135	25–67	4.58	4.61	5.5	1.00:1.01	$(1.13\pm0.22)\cdot10^{-4}$	0.97
3	150	15'30"–70	4.58	4.61	5.5	1.00:1.01	$(4.67\pm0.89)\cdot10^{-4}$	0.95

Calculation of the kinetic constant was possible in three cases (T=120, 135 and 150 °C) in which more than one iteration (apart from the ones to optimise the MW program) was necessary to fulfil the conversion requirement. An Arrhenius plot was derived (Figure 2.15).

2.5.3.4. MW assisted synthesis of [C_6mim]Cl in EtOH

The data obtained during the optimisation of MW conditions were also used (when possible, which means that at least 3 different points were available) to derive kinetic data for the MW assisted reactions. Results are summarised in Table 2.17.

Table 2.17. 2nd order kinetic constants for the MW assisted synthesis of [C_6mim]Cl in EtOH.

Entry	T (°C)	t (min)	MeIm (M)	$C_6H_{13}Cl$ (M)	V EtOH (ml)	Ratio MeIm:$C_6H_{13}Cl$	k ($M^{-1}\cdot s^{-1}$)	R^2
1	120	34–157	4.58	4.61	55	1.00:1.01	$(4.09\pm0.88)\cdot10^{-5}$	0.96
2	135	25–67	4.58	4.61	5.5	1.00:1.01	$(1.13\pm0.22)\cdot10^{-4}$	0.97
3	150	22'30"–357	4.58	4.61	5.5	100:1.01	$(6.00\pm3.83)\cdot10^{-4}$	0.78

2.6. Results and discussion

2.6.1. Application of a prediction tool

In general, the prediction tool worked well in most of the quaternisation reactions, giving the expected conversion (within a margin of ± 5 % in most cases) with only one iteration (one calculation from the starting data set). The predictions were less accurate when the reaction was pushed to 99 % conversion and when reactions were performed at lower temperature (120°C and 135 °C).

In the first case, at least 3 subsequent iterations were necessary to get to 99 % conversion, while in the latter case, the yield observed with the data sets calculated in the first iteratio was generally lower than the calculated value (the difference between the expected and the experimental values (Δ) for all of the reactions performed at 135 and 120 °C is Δ = 18 %, while for the same reactions performed at higher T – 150, 165 and 180 °C – average Δ is only 3 %).

The applicability of the prediction tool to MW assisted quaternisation reactions has been evaluated according to several guidelines:

- overall efficacy for a selected substrate, at various T for a selected conversion;
- efficacy for a selected T;
- efficacy for a class of substrates (for example a series of alkyl halides in a given solvent).

For the discussion of first point, results obtained for the MW assisted synthesis of [C_6mim]Cl both in CH_3CN and EtOH will be analysed. Then, results obtained in the synthesis of [C_6mim]Cl in EtOH at 150 °C will be used and finally the series of alkyl halides C_4–C_{12} used for the quaternisation reaction in EtOH will be taken into account.

The results obtained for the synthesis of [C_6mim]Cl in CH_3CN and in EtOH for a 70 % conversion at various T, are reported in Figure 2.8 and Figure 2.9 respectively.

Figure 2.8. MW assisted synthesis of [C_6mim]Cl in CH_3CN, results obtained after the first iteration of the prediction program for a 70 % conversion.

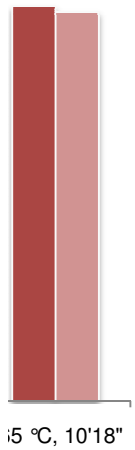


Figure 2.9. MW assisted synthesis of [C_6mim]Cl in EtOH, results obtained after the first iteration of the prediction program for a 70 % conversion.

Limiting the analysis to the first iteration of the program, it can be seen that the prediction program gives accurate results (within ±5 %) in all the cases where the prediction is calculated from reference data collected in the same conditions (*i.e.* same solvent and same T). If we change one parameter, for example the solvent (which is the case of T=120, 135 and 150 °C for the MW assisted synthesis of [C_6mim]Cl in EtOH, Figure 2.9) using the prediction results obtained for the same reaction in CH_3CN, the difference between the calculated and the experimental conversion value rises up to 20 %.

In general, for the lower T conditions analysed (T=120 and 135 °C) the prediction program was less effective (*i.e.* more than one iteration was needed) than when applied to reaction conditions with T≥150 °C.

If we analyse all the iterations needed to obtain a quantitative conversion of [C_6mim]Cl (as it can be seen in Figure 2.10) starting from a known data set, we have used the prediction program to predict the new reaction conditions for a 70 % conversion (Entry 1, Figure 2.10). From this results, we have predicted the reaction conditions to achieve a 100 % conversion, however from the calculated conditions the experimental conversion was not quantitative and the iteration process was repeated three times before obtaining the desired quantitative conversion.

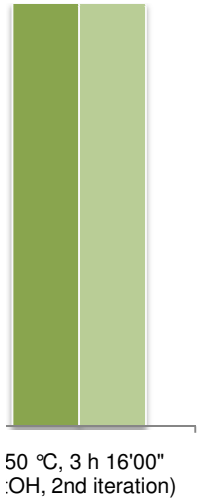


Figure 2.10. MW assisted synthesis of [C_6mim]Cl at T=150 °C, steps and iterations needed to achieve quantitative conversion.

This behaviour can also be ascribed to the change of solvent (from CH_3CN to EtOH) or the loss of sensitivity for the NMR method used for the determination of the yield for conversions above 95 %.

If we compare the experimental results obtained for all the analysed substrates at T=150 °C, in the conditions calculated to expect a 70 % conversion, as done in Figure 2.11, we can see that in all cases after one iteration the yield is satisfied (with a ±5 % uncertainty). The accuracy increases as the chain length of the alkyl halides increases.

Figure 2.11. MW assisted synthesis of [$C_n$mim]Cl (n=4–12) in EtOH at T=150 °C. Results obtained after one iteration of the program to achieve a 70 % conversion.

2.6.2. Qualitative optimisation of MW conditions: colour formation studies

A purity check of the solutions of the MW reactions at 70 % conversion was performed. The solutions obtained were analysed by UV–Vis spectroscopy and the reaction conditions under which colour formation was minimised were taken as the conditions to "push" the reaction to >99 % conversion. This analysis has been performed for both the synthesis of [C_6mim]Cl and [C_8mim]Cl in EtOH. For the synthesis of [C_6mim]Cl in EtOH, formation of colour in function of the reaction time (or the conversion) has also been studied when the reaction was performed at T=150 °C. Results are shown in Figure 2.12, Figure 2.13 and Figure 2.14.

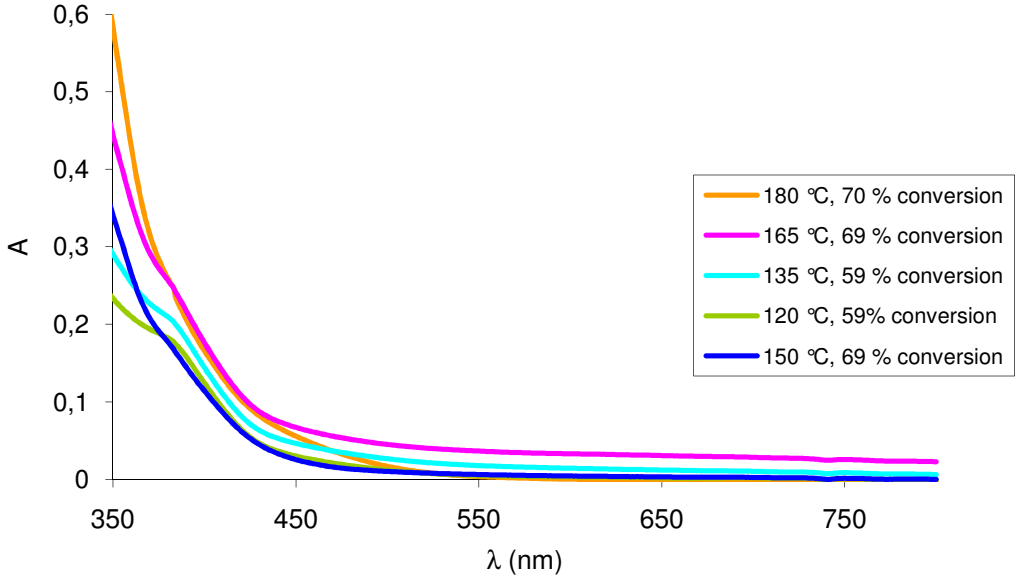


Figure 2.12. MW assisted synthesis of [C_6mim]Cl in EtOH: colour formation for a 70 % conversion (predicted) at various T.

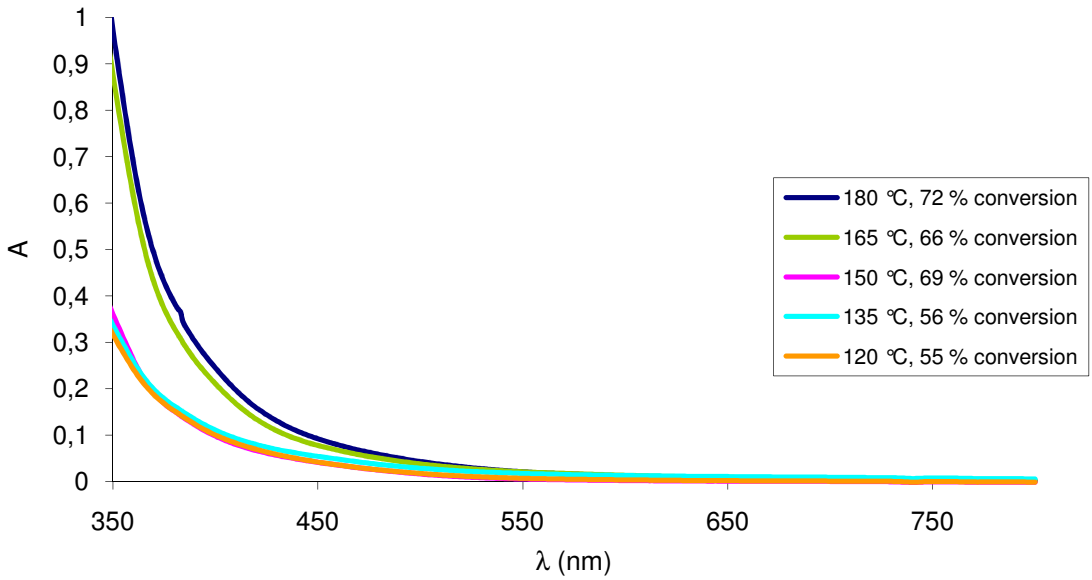


Figure 2.13. MW assisted synthesis of [C_8mim]Cl in EtOH: colour formation for a 70 % conversion (predicted) at various T.

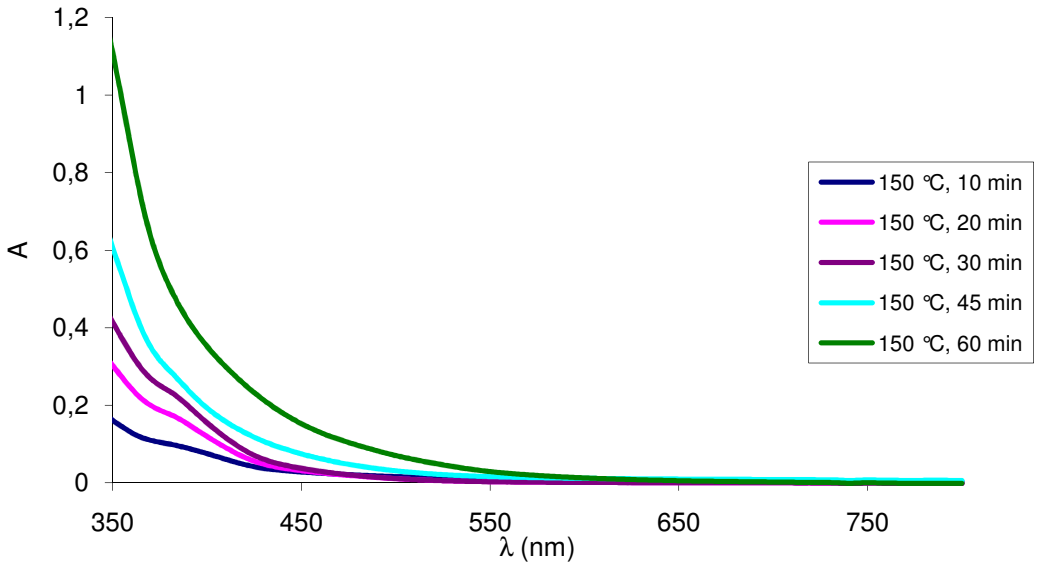


Figure 2.14. MW assisted synthesis of [C_6mim]Cl in EtOH: colour at T=150 °C in function of the irradiation t.

For both [C_6mim]Cl and [C_8mim]Cl (Figure 2.12 and Figure 2.13 respectively) the conditions in which the colour formation is minimised are at mid–point T in the interval studied: this means that the optimal conditions are a compromise between the length of reaction time and the operating T.

Fixing one operating T (as was done in Figure 2.14 for the synthesis of [C_6mim]Cl in EtOH at 150 °C) it can be seen that colour formation is proportional to the irradiation time.

2.6.3. Kinetics

2.6.3.1. Problems associated with the determination of kinetic parameters: autoclave vs. *MW.*

There were several limitations related to both the techniques employed for the determination of the primary kinetic data.

A general lack of precision of all the analytical methods used for the yield determination (^{1}H NMR, HPLC, Mohr method) was observed for conversions above 90 %: this however is a more general problem associated with the quantitative determination of trace amounts of substrates in presence of massive amounts of

product, and applies to all the techniques used for determination of the yield (see drawbacks of conductivity measurements in Ref. [88]).

It can also be noticed that there is a gap in the reaction temperature switching from MW heating to conventional heating in an autoclave; in fact, with MW heating higher temperatures are easily obtained (up to T_{bulk}=180 °C), while for the autoclave experiments 150 °C was the upper temperature limit. When using conventional heating systems, operating temperatures were somehow lowered in order to minimise the heat loss and prolonged heating time associated to the use of metal reaction vessels.

In general, the use of the autoclave for kinetics measurements provided poor results. This is evident in the graphs in Appendix B where low R^2 values were obtained when applying the 2nd order fit linearization and on the error associated to the derived k. This can be ascribed to several problems and limitations encountered in the attempts of optimisation and control of the reaction parameters:

- reagents and solvents were mixed together in the autoclave chamber at r.t., the system was subsequently heated; this implies a "dead time" (of at least 10 minutes!) in which there was a variation of T which could not be controlled while the reaction was proceeding;
- pressure was also a weak point of both the pressurised containers used: both of them were not equipped with a pressure controller unit; moreover samples were collected through a valve that depressurised the container, therefore constant pressure during the experiments was not achieved;
- attempts were made to measure the initial velocities, however the results obtained were not reliable, since the system lacks of the needed T and p control;
- reactions were performed at T>100 °C, which means that the composition of the gas phase cannot be ignored and that the concentrations of the reagents could have been altered.

It becomes therefore clear that in order to obtain reliable measurement, and to expand the possible applications of the kinetics data obtained, reliable measurements are needed. This might be achieved by performing the reactions at lower T (<70 °C), in closed vials, starting from a "mother" homogeneous solution, so that T and p equilibrium is satisfied. If the measurement are to be conducted at

higher T and higher p, specific equipment needs to be designed accordingly; in this respect a very good example of kinetic measurement set up is described in Shleicher's work, [94] where a stainless steel autoclave analogue to the one used for our experiment was employed, this time equipped with a pressure control unit. The autoclave was preheated and the reagents were added through a preheated syringe pump. Samples were collected after efficient cooling of the reactor, and in a batchwise manner (one experiment, one sample).

If we consider the results obtained with the MW experiments, we can see that the potential of this technique as a suitable candidate for kinetic measurements is highly underestimated. The reactions were all performed in closed vessels, with efficient instantaneous control over the various physical parameters (such as applied power, T and p). Heating was generally fast (from 40 s to reach 120 °C, to approximately 2 min to reach 180 °C) and efficient cooling (the reaction mixture was cooled to r.t. at the end of the MW program in ca. 30 s for all cases) was achieved. It becomes then clear that MW assisted synthesis is a great tool for the determination of kinetic data; however, there is a major drawback on the applicability of the data obtained, which can be affected by MW effects (mainly MW heating effects).

2.6.3.2. Comparison between MW assisted and conventional heating reactions

We have seen the differences between the two techniques and the limitations associated to both measurements. A useful tool is the comparison of the Arrhenius plots derived for the synthesis of $[C_6mim]Cl$ in CH_3CN under conventional heating in a pressurised container and under MW irradiation, as depicted in Figure 2.15.

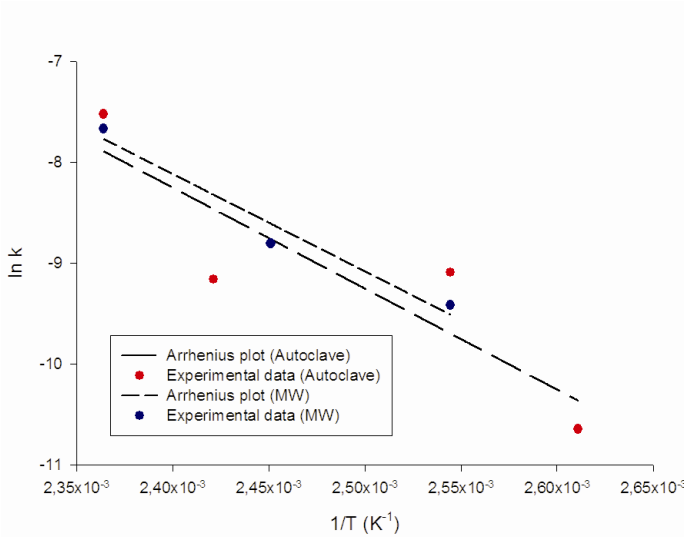


Figure 2.15. Comparison between the Arrhenius plot for the synthesis of $[C_6mim]Cl$ in CH_3CN under conventional heating in autoclave (red dots, dashed line) and MW heating (blue dots, dotted line).

We have to bear in mind that the determination of kinetic constants had several limitations on accuracy (especially for the conventional heating data), which we have discussed previously, so we will comment the graph just in a qualitative manner. The activation energies, E_a, were calculated according to the Arrhenius Equation (Equation 2.5) [95].

$$\ln k = \ln A - \frac{E_a}{RT}$$

Equation 2.5. Arrhenius equation.

From the Ea, $\Delta H^{\neq}$ was then derived according to the formula (Equation 2.6): [95]

$$E_a = \Delta H^{\neq} + RT$$

Equation 2.6. Determination of the enthalpy of activation, $\Delta H^{\neq}$.

$\Delta S^{\neq}$ was also calculated, applying Equation 2.7 below: [95]

$$\ln\left(\frac{k}{T}\right) = \ln\left(\frac{R}{Nh}\right) + \frac{\Delta S^{\neq}}{R} - \frac{\Delta H^{\neq}}{RT}$$

Equation 2.7. Determination of the entropy of activation, $\Delta S^{\neq}$.

The results obtained are summarised in Table 2.18.

Table 2.18. Activation energies, enthalpies and entropies for the synthesis of $[C_6mim]Cl$ in CH_3CN under conventional and MW assisted heating.

Entry	Method	E_a (kcal·mol^{-1})	$\Delta H^{\neq}$ (kcal·mol^{-1})	$\Delta S^{\neq}$ (cal·mol^{-1}·K^{-1})
1	Conventional heating/autoclave	19,9	19,3	-120,8
2	MW	19,1	18,5	-92,4

Quite surprisingly, the values obtained for the enthalpy and entropy of activation are in good agreement with the tabulated values measured for S_N2 reactions.
Another practical and qualitative value we can derive from the data collected with both method is an estimation of the half–life, this can be of practical use since kinetics should be followed for 10 half–lives. A comparison between the time needed for conventional *vs.* MW assisted process can also be helpful. Half–lives were calculated from the data obtained for the synthesis of $[C_6mim]Cl$ in CH_3CN and EtOH at 150 °C, with both methods are reported in Table 2.19.

Table 2.19. Half –lives (τ) of MeIm estimated for the synthesis of $[C_6mim]Cl$ in CH_3CN and EtOH at T=150°C.

Entry	Solvent	$MeIm_{Autoclave}$ (M)	$C_6H_{13}Cl_{Autoclave}$ (M)	$\tau_{Autoclave}$ (min)	$MeIm_{MW}$ (M)	$C_6H_{13}Cl_{MW}$ (M)	τ_{MW} (min)
1	CH_3CN	4.55	5.01	27	4.58	4.62	16
2	EtOH	4.21	4.22	23	4.58	4.62	11

As it can be seen from the data reported, there is a difference between the times obtained with conventional heating and in the MW assisted processed; this can be ascribed to efficient heating obtained under MW irradiation, and to specific MW effects, in particular due to the ionic conduction mechanism.

2.7. Conclusion

In this Chapter we have successfully applied MW energy to the quaternisation of MeIm.

MW assisted conditions where optimised with the aid of a prediction program, whose efficacy was also tested for this class of reaction. Once the optimised reaction conditions, a simple qualitative test was performed to choose the optimal conditions for the synthesis.

Due to the quick output of MW assisted processes and the thigh control over the physical parameters of the reactions, it was decided also to attempt a kinetic analysis of the MW assisted quaternisation reaction, comparing the results with the ones obtained by conventional heating in a pressurised container, but in this step several problems were encountered. MW has the advantage of being a high–throughput and reliable (efficient control of reaction parameters, efficient cooling) technique, however for reliable kinetic data a systematic study is needed. It would also be interesting and useful toward specific applications, such as optimisation of reaction conditions in a continuous flow reactor for the large scale synthesis of IL, to evaluate the effect of ionic conduction on this MW assisted processes. It is well known that IL are additives extensively used for MAOS, due to their ionic nature (they are able to efficiently "heat" MW transparent organic solvents, through the ionic conduction heating mechanism), [68] but what happens when the MW assisted reaction is the formation of an ionic product starting from uncharged reagents? This would be an interesting kinetic study, along with the determination of the initial velocities (for which MW is an optimal technique, due to the rapid reaching of operating T).

For the kinetic data obtained under conventional heating, the main drawbacks of the experiment set up were the use of the autoclave as a continuous reactor rather than a batch one and the scarce control over T and pressure. The autoclave was equipped with a T controller, but the use of metal autoclave (in our case a stainless steel container) means taking into account long heating and cooling times (due to the high thermal inertia of the metal), high heat loss and possible pyrolitic effects. [85] When the kinetics are to be performed under conventional heating, the experiments needs to be carefully designed in order to exploit the full potential of this technique. For

example in our case, a better control over the reaction parameters, could have meant the possibility of an accurate measure of the initial velocities and an effective evaluation of the acceleration of ionic reactions postulated by Brønsted [88].

It is worth to note that applying both heating system (conventional and MW) to the quaternisation reactions, the ionic nature of product formed could affect, in both cases, the speed of the reactions. It would be elucidating and practical to evaluate and compare the extent of both the distinct effects.

The prediction tool has proved to be a useful add–on for the optimisation of reaction parameters also for the quaternisation reactions. Its range of application could be further extended by testing its efficiency on different classes of ILs (*N*–alkylpyridinium, 1–alkyl–1–methylpyrrolidinium etc.) and to the large scale continuous flow MW assisted synthesis of ILs, having the chance to test the program efficiency also on large scale processes.

IL synthesis and application is still a growing topic in Chemistry; it has been estimated that ca. 10^{18} IL combinations could potentially be possible [14]. MW could be used for the "IL discovery" phase, and teamed up with CROW for a quick optimisation of reaction parameters.

Chapter 3: Methylation of aryl halides with DABAL–Me_3 in a two–phase system VOC/IL

3.1. Organoalane reagents in Pd–catalysed reactions

Organoalanes are well known compounds in organic chemistry. These compounds are of widespread use in the petrochemical industry as effective additives in polymerization processes, but their use in organic synthesis is still limited and scattered.

To understand why, a closer look to the characteristics of these compounds is needed. The behaviour of common organometallic aluminum (III) compounds, in particular their pyrophoric nature, arises from their high Lewis acidity, which is marked by the tendency of the aluminum atom to complete the electron octet. Bonds between aluminum and electronegative atoms (such as oxygen and halogens) are extremely strong, therefore most organoaluminum compounds react violently with oxygen and/or ignite spontaneously in air. Replacement of one or more alkyl groups, with halogen atoms generally reduces pyrophoricity. [96,97] Replacement of the alkyl groups bonded to the aluminum core can be exploited to modulate the reactivity and mobility of such substituents, for example by replacing one or more substituents with alkoxy or other heteroatoms containing alkyl chains. [97]

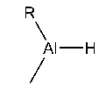
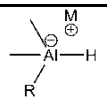
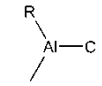
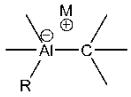
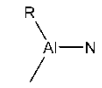
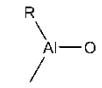
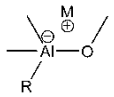
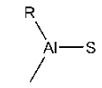
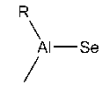
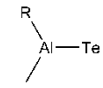
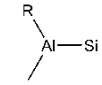
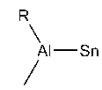
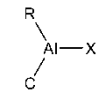
Neutral aluminum (III) compounds tend to form 1:1 complexes by covalent or coordination bonds, especially with neutral bases, such as ethers. Covalent bonds are formed with anionic (and more reactive) species, such as R–M, RO–M or RNH–M, while coordination bonds are usually formed by interaction with neutral Lewis bases, such as carbonyl compounds, ethers, and nitrogen containing molecules. This is of practical use, since most organoaluminum compounds are stored in ethereal solutions and can be exploited to tune the reactivity of the organometallic reagent according to needs. [96,97]

Regardless of the type of bond formed, aluminum (III) species can undergo easily tetracoordination (sometimes up to penta– or hexa– coordination), forming anionic ("ate") aluminum compounds.

Much of the effort of the scientific community in the field of organoaluminum compounds is focused on quantification of the order of reactivity of such anionic species. Relevant anionic aluminum species are summarised in Table 3.1.

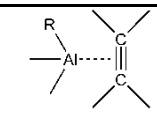
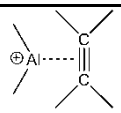
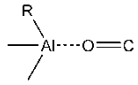
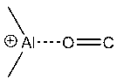
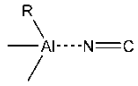
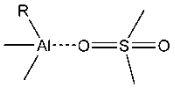
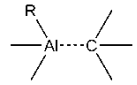
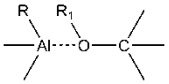
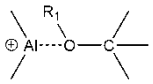
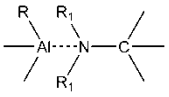
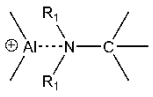
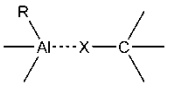
Examples of covalent bonds Al–X (where X = H, C, O, N, S, Se, Te, Si, Sn and halide) are also reported in Table 3.1. These bonds show a discrete mobility, with a reactivity order H^->alkynyl>vinyl>alkyl. Groups covalently bonded to the aluminum centre, such as RO^-, RS^-, RSe, RTe, R_3Si^- and R_3Sn^- can easily form carbon–heteroatom bonds.

Table 3.1. Examples of important covalent bonds in aluminum–Lewis base complexes. [97]

Neutral aluminum species	Reaction type employed	Anionic aluminum intermediate
	Hydride transfer (reduction, hydroalumination)	
	C–C bond formation (addition of C=O, carboallumination)	
 C = sp^3, sp^2, sp	Hydride transfer (β–hydride elimination)	
	Radical reaction (homolytic cleavage)	
	C–N bond formation	
	Deprotonation	
	Oxidation (Oppenauer reaction)	
	Hydride transfer (β–hydride elimination, Meerwein–Ponndorf–Verley reduction)	
	C–O bond formation (Tischenko reaction)	
	C–S bond formation (Michael addition, Tischenko reaction)	
	C–Se bond formation	
	C–Te bond formation	
	C–Si bond formation (Silylalumination)	
	Alkylhalide reduction	
	C–Sn bond formation	
	Strong Lewis Acids	
	Movement of Al–C group	
	Source of Aluminum cations	

Cationic aluminum species are of synthetic interest as well; due to their positively charged nature they are excellent Lewis acids and are used mainly in catalytic polymerization/oligomerisation processes. Relevant structure of aluminum based cations are collated in Table 3.2.

Table 3.2. Example of important coordination bonds in aluminum–Lewis base complexes. [97]

Neutral aluminum species	Reaction type employed	Cationic aluminum intermediate
		
		
		
	Activation of the corresponding FG by coordination bond.	
	Movement of covalently–attached R group.	
		
		
		

R = H, C, O, N, X, etc.; X = F, Cl, Br, I.

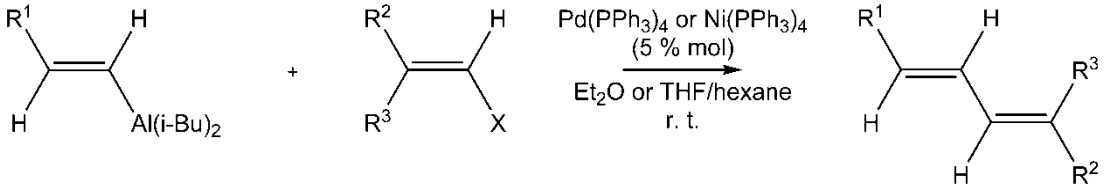
Although organoalanes are distinct by a quite versatile chemistry, their use as transmetallation reagents in Pd–catalysed reactions is very limited, which is in contrast to other organometallic reagents based on metal of the same period, such as boron.

3.1.1. Examples of Pd(0) catalysed alkylations with organoalane reagents

A successful example of the use of organoalane in Pd–catalysed reactions is the alkenylation of allyl halides. Alkenylaluminum reagents are the organoaluminum compounds most exploited in Pd–catalysed cross–coupling reactions. Their prompt reactivity is due to lack of stabilization of the Al–C bond (which is observed for example in organocopper reagents). [96]

Several examples of Pd(0) catalysed alkenylation are present in the literature. [98-101]

Negishi *et al.* [98] successfully synthesised substituted conjugated dienes by Pd or Ni catalysed cross–coupling reaction between (*E*)–alkenylalanes with variously substituted alkenyl halides.

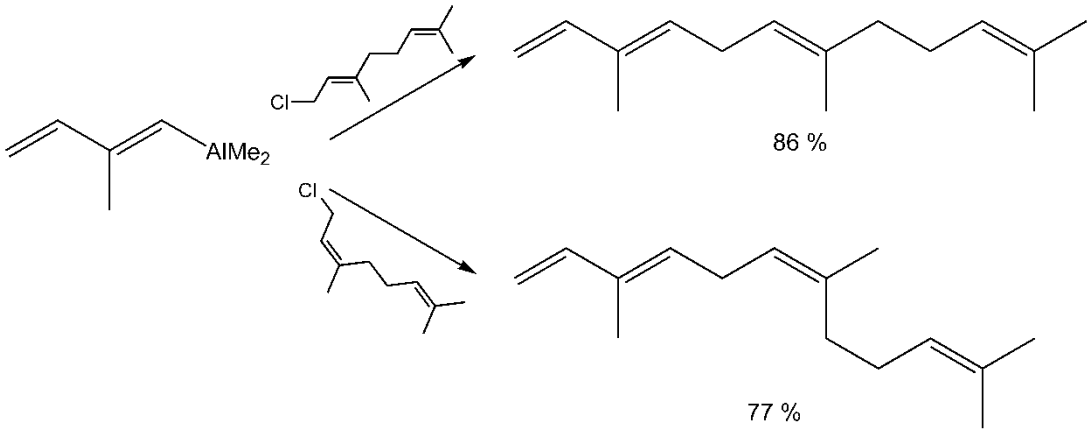


R^1 = butyl, *t*-butyl, pentyl; R^2 = H, butyl, *t*-butyl, acetate; R^3 = H, methyl, butyl; X = I, Br

Scheme 3.1. Synthesis of conjugated dienes by transition metal catalyzed cross–coupling reaction between alkenylalanes and alkenyl halides. [98]

Cross–coupling is efficient in most cases, and highly stereospecific, particularly for Pd–catalysed reactions (selectivity towards the *E,E* diene >97 %). Yields are quantitative as long as the R^2 groups on the alkenyl halides are not particularly bulky. In all cases some homocoupling of the alkenyl halide is observed, yields of the homocoupled product increase when Ni (0) is used as the catalyst (up to 15 % of the overall yield).

Negishi and co–workers, again, used the same reaction protocol for the synthesis of more complicated scaffolds, such as the terpenes depicted in Scheme 3.2. [99,100]



Reaction conditions: $Pd(PPh_3)_4$ (5 % mol), THF, r.t.

Scheme 3.2. Synthesis of α–farnesene and the corresponding *Z*–isomer by Pd–catalysed cross–coupling of geranyl (*E*) and neryl (*Z*) chloride with 2–methyl–1,3–butendimethylaluminum. [99,100]

The alkenylalane was generated *in situ* from $AlMe_3$ and the corresponding alkyne using Cp_2ZrCl_2 as the catalyst. The reaction mixture was directly charged with the appropriate allyl chloride and the Pd(0) catalyst. The products were obtained in quantitative yield with excellent regio– and stereoselectivity (>98 %). No homocoupling of the allylchloride was observed.

The postulated mechanism for this type of reactions starts with the oxidative addition of the alkenyl halide on the Pd(0) species, to form an organopalladium (II) complex; subsequent rate–determining transmetallation of the alkenylalane gives the dialkylpalladium (II) species, which then undergoes reductive elimination to afford the cross–coupling product and the regenerated Pd(0) catalyst. [101,102]

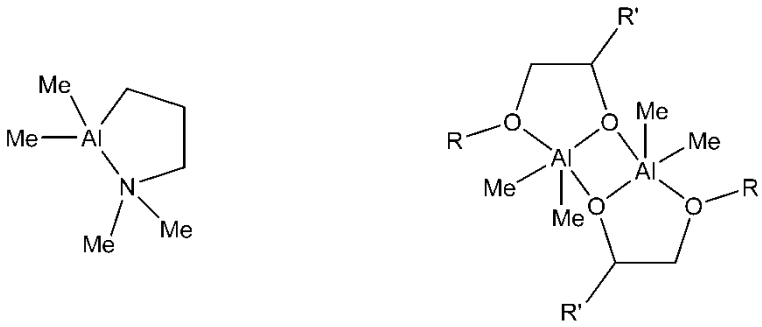
3.1.2. Aluminum based methylating agents

Alkylaluminum reagents are present much less in the literature and seldom employed in Pd–catalysed reactions. This is due mainly to the difficulties in handling this type of compounds, which are extremely pyrophoric and need to be treated accordingly. Apart from their widespread use as cocatalyst in olefin polimerisation catalytic processes, organoaluminum compounds, in particular bearing a methyl group, have a significant synthetic value. [103]

In order to improve the stability of methylaluminum reagents, several coordination complexes bearing this moiety have been synthesised.

The major contribution in this field is due to the work of Blum, Schumann and co–workers, who, throughout the years, synthesized and tested several $Al–(CH_3)_n$ coordination complexes in Pd–catalysed cross–methylation reactions. [104-108]

The most effective species in term of stability and reactivity are depicted in Figure 3.1.

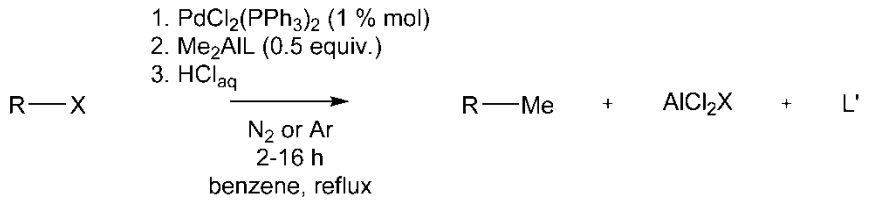


1

2a: R = Me R' = H
2b: R = Me R' = Me

Figure 3.1. Schumann–Blum reagents.

Reagent **1** in Figure 3.1 was successfully employed in the Pd(0) cross–methylation of substituted aryl, benzyl, and vinyl bromides. [104]
Reaction conditions are reported in Scheme 3.3.



R = aryl, benzyl or vinyl; X = Br, I; L = chelating ligand; L' = ligand residue after hydrolysis

Scheme 3.3. General procedure for the Pd–catalysed cross–methylation of aryl, benzyl or vinyl halides. [104]

Results for several different aryl, benzyl and vinyl halides are summarised in Table 3.3. Aryl halides bearing vulnerable functional groups were also used, the results obtained are collated in Table 3.4.

Table 3.3. Palladium catalysed methylation of representative aryl, benzyl and vinyl bromides and iodides by Schumann–Blum reagent **1**. [104]

Entry	Substrate	t (h)	Product(s)	Yield (%)
1	Bromobenzene	8	toluene	97
2	Iodobenzene	1	toluene	91
3	1–bromonaphthalene	12	1–methylnaphthalene	98
4	2–bromonaphthalene	8	2–methylnaphthalene	98
5	9–bromoanthracene	2	9–methylantracene	92
6	2–iodobromobenzene		*o*–xylene	80
			2–bromotoluene	13
7	1,8–diiodonaphthalene	3	1,8–dimethylnaphthalene	84
			1–iodo–8–methylnaphthalene	7
			1–iodonaphthalene	0.5
			1–methylnaphthalene	0.5
8	2,2'–diiodo–1,1'–biphenyl	6,5	2,2'–dimethyl–1,1'–biphenyl	99
9	bis(2–iodophenyl)methane	6	bis(2–methylphenyl)methane	87
10	3,4–dibromothiophene	3	3–bromo–4–methylthiophene	76
			3,4–dimethylthiophene	14
11	benzyl bromide	3	ethylbenzene	99
12	9–bromo–9–phenylfluorene	12	9–methyl–9–phenylfluorene	100
13	(1–naphtyl)phenylbromomethane	6	α–(1–naphtyl)ethylbenzene	60
14	(*E*)–β–bromostyrene	5	(*E*)–1–phenyl–1–propene	97
15	(*Z*)–α–bromostilbene	8	(*Z*)–α–methylstilbene	96
16	2–bromoindene	2	2–methylindene	88
			indene	traces
			2,3–dimethylindene	traces

Reaction conditions: 1 mmol of alkyl halide, $PdCl_2(PPh_3)_2$ (2 % mol), in 4 ml of benzene at T =50 °C for 30 min; addition of 0.505 mmol of **1** in 3 ml of benzene. The mixture was then kept under inert atmosphere (N_2 or Ar) at T=80 °C for 1–12 h.

Table 3.4. Pd–catalysed methylation of some functionalized aryl bromides by **1**.

Entry	Substrate	t (h)	Product	Yield (%)
1	4–BrC_6H_4CHO	8	4–MeC_6H_4CHO	62
			4–$MeC_6H_4CH_2OH$	18
			4–$MeC_6H_4CO_2H$	18
2	4–BrC_6H_4COPh	19	4–$MeC_6H_4C(Me)(Ph)OH$	17
			4–MeC_6H_4COPh	3
3	2–$BrC_6H_4CO_2Et$	12	2–$MeC_6H_4CO_2Et$	13
			$C_6H_5CO_2Et$	18
4	3–$BrC_6H_4CO_2Et$	12	3–$MeC_6H_4CO_2Et$	40
			$C_6H_5CO_2Et$	6
5	4–$BrC_6H_4CO_2Et$	12	4–$MeC_6H_4CO_2Et$	75
			$C_6H_5CO_2Et$	10
6	4–BrC_6H_4CN	8	4–MeC_6H_4CN	81
7	4–$BrC_6H_4CH_2Br$	3	4–MeC_6H_4Et	
			bi– and poly– phenyl and benzyl byproducts	16
8	4–$BrC_6H_4CH{=}CHCOPh$	8	4–$MeC_6H_4CH{=}CHCOPh$	85
9	2–$BrC_6H_4C{\equiv}CC_6H_4$–2–Br	3	2–$MeC_6H_4C{\equiv}CC_6H_4$–2–Me	96

Reaction conditions: 1 mmol of alkyl halide, $PdCl_2(PPh_3)_2$ (2 % mol), in 4 ml of benzene at r.t.; heating for 30 min at T=80 °C; addition of 0.505 mmol of **1** in 3 ml of benzene. The mixture was then kept under inert atmosphere (N_2 or Ar) at T=85 °C for 3–12 h.

As can be seen from the data reported in Table 3.3, the system works well in most cases, including primary benzyl bromides (Entries 11–13, Table 3.3). Worse results were observed when aryl dihalides were used (Entries 3 and 10, Table 3.3), but only for non hindered systems (Entry 8, Table 3.3 is a sterically hindered dihalide which undergoes a clean and quantitative double methylation). The reaction protocol is particularly sensitive to steric effects (Entries 3 and 4, Table 3.3, and Entries 3–5, Table 3.4).

Vinyl bromides underwent a clean methylation (Entries 14 and 15, Table 3.3), with efficient retention of the configuration.

Reagent **1** methylates efficiently carbonyl compounds, however with a mechanism different than the one proposed for the Pd–catalysed cross–methylation. [109] Thus, the cross–methylation reaction was performed also on aryl halides bearing "vulnerable" carbonyl containing substituents. As it can be seen from the data collected in Table 3.4, for most of these compounds methylation was a clean process, although in some cases by–products due to double methylation (Entry 2, Table 3.4), hydrogenolysis (Entries 3–5, Table 3.4), Cannizzaro–type side reactions (Entry 1, Table 3.4), and oligomerization (Entry 7, Table 3.4) were observed.

Schumann, Blum and co–workers used similar methylating agents for the Pd(0) catalysed methylation of activated aryl chlorides. [106]

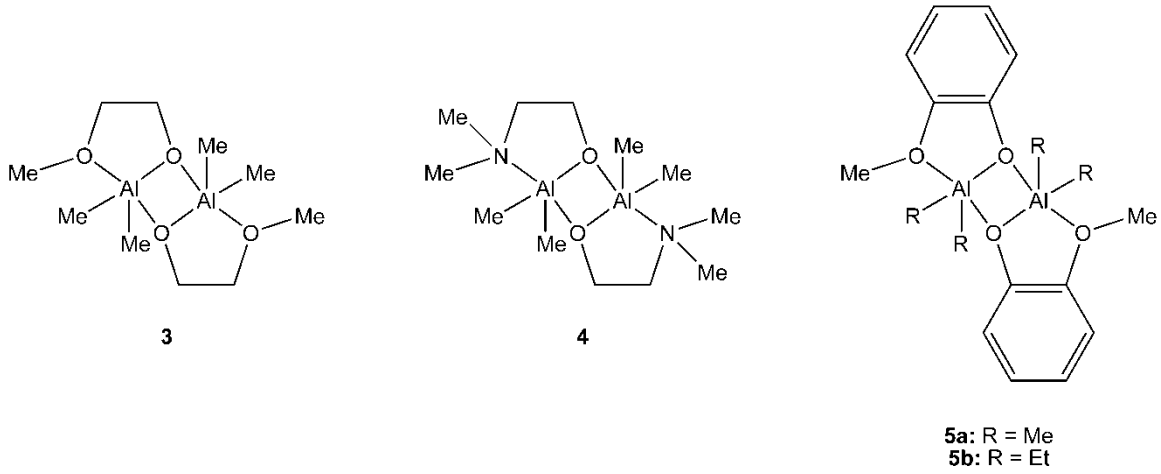


Figure 3.2. Methylaluminum reagents used in Ref. [106].

Results using commercially available Pd catalysts are summarised in Table 3.5.

Table 3.5. Cross–alkylation of nitrated aryl chlorides by dialkylaluminum complexes catalysed with commercially available Pd complexes. [106]

Entry	Substrate	Methylating agent	Catalyst	Molar ratio S:M	Product	Yield (%)
1	2–$(NO_2)C_6H_4Cl$	**3**	$Pd(PPh_3)_4$	2:1	2–$(NO_2)C_6H_4Me$	12
2	2–$(NO_2)C_6H_4Cl$	**3**	$Pd(PPh_3)_4$	1:1	2–$(NO_2)C_6H_4Me$	32
3	4–$(NO_2)C_6H_4Cl$	**3**	$Pd(PPh_3)_4$	2:1	4–$(NO_2)C_6H_4Me$	14
4	4–$(NO_2)C_6H_4Cl$	**3**	$Pd(PPh_3)_4$	1:1	4–$(NO_2)C_6H_4Me$	37
5	4–$(NO_2)C_6H_4Cl$	**3**	$PdCl_2(PPh_3)_2$	2:1	4–$(NO_2)C_6H_4Me$	8
6	2,4–$(NO_2)C_6H_3Cl$	**1**	$Pd(PPh_3)_4$	2:1	2,4–$(NO_2)C_6H_3Me$	36
7	2,4–$(NO_2)C_6H_3Cl$	**3**	$Pd(PPh_3)_4$	2:1	2,4–$(NO_2)C_6H_3Me$	49
8	2,4–$(NO_2)C_6H_3Cl$	**3**	$PdCl_2(PPh_3)_2$	2:1	2,4–$(NO_2)C_6H_3Me$	34
9	2,4–$(NO_2)C_6H_3Cl$	**3**	$Pd(PPh_3)_4$	1:1	2,4–$(NO_2)C_6H_3Me$	58
10	2,4–$(NO_2)C_6H_3Cl$	**3**	$Pd(PPh_3)_4$	1:10	2,4–$(NO_2)C_6H_3Me$	93
11	2,4–$(NO_2)C_6H_3Cl$	**4**	$Pd(PPh_3)_4$	1:1	2,4–$(NO_2)C_6H_3Me$	23
12	2,4–$(NO_2)C_6H_3Cl$	**5a**	$Pd(PPh_3)_4$	1:1	2,4–$(NO_2)C_6H_3Me$	39
13	4–$(NO_2)C_6H_3$–1,2–Cl_2	**1**	$Pd(PPh_3)_4$	1:1	2–Cl–4–$(NO_2)C_6H_4Me$	21
14	4–$(NO_2)C_6H_3$–1,2–Cl_2	**3**	$Pd(PPh_3)_4$	1:1	2–Cl–4–$(NO_2)C_6H_4Me$	58

Reaction conditions: 1 mmol of the nitrated chloroaryl, Pd catalyst (2 % mol), in 2 ml of benzene at r.t.; heating for 15 min at T=90 °C; addition of the alkylating agent of choice in 1 ml of the same solvent. The mixture was then kept under inert atmosphere (N_2 or Ar) at T=90 °C for 22 h; quenching with 2 % HCl_{aq}.

It can be noticed that the reaction works particularly well with dinitro substituted arenes (Entries 6–12, Table 3.5). The use of an excess of methylating agent (Entry 10, Table 3.5) results in a remarkable improvement of the yields. In general, Pd(0) catalyst gives better performances than the Pd(II) counterpart (Entries 4, 5, 7 and 8, Table 3.5). This lead to the use of Pd(0) catalysts containing electron rich phosphines.

Results obtained with the different Pd(0) catalysts are summarised in Table 3.6.

Table 3.6. Cross–methylation of aryl halides by dialkylaluminum complexes in presence of electron rich Pd catalysts. [106]

Entry	Substrate	Methylating agent	Catalyst	Molar ratio S:M	Product	Yield (%)
1	4–$(NO_2)C_6H_4Cl$	**3**	$Pd(dippp)_2$	2:1	4–$(NO_2)C_6H_4Me$	66
2	2,4–$(NO_2)_2C_6H_3F$	**3**	$Pd(dippp)_2$	1:1	2,4–$(NO_2)_2C_6H_3Me$	>99 (4.5 h)
3	2,4–$(NO_2)_2C_6H_3Cl$	**3**	$Pd(dippe)_2$	1:1	2,4–$(NO_2)_2C_6H_3Me$	94
4	2,4–$(NO_2)_2C_6H_3Cl$	**3**	$Pd(dippp)_2$	1:1	2,4–$(NO_2)_2C_6H_3Me$	>99
5	2,4–$(NO_2)_2C_6H_3Cl$	**3**	$Pd(dippb)_2$	1:1	2,4–$(NO_2)_2C_6H_3Me$	>99
6	2,4–$(NO_2)_2C_6H_3Cl$	**5a**	$Pd(dippp)_2$	1:1	2,4–$(NO_2)_2C_6H_3Me$	21
7	2,4–$(NO_2)_2C_6H_3Br$	**3**	$Pd(dippp)_2$	1:1	2,4–$(NO_2)_2C_6H_3Me$	80
8	2,4–$(NO_2)_2C_6H_3I$	**3**	$Pd(dippp)_2$	1:1	2,4–$(NO_2)_2C_6H_3Me$	43
9	4–$(CF_3)C_6H_4Cl$	**3**	$Pd(dippp)_2$	1:1	4–$(CF_3)C_6H_4Me$	65
10	4–$ClC_6H_4CO_2Et$	**3**	$Pd(dippp)_2$	1:1	4–$MeC_6H_4CO_2Et$	28
11	4–ClC_6H_4CN	**3**	$Pd(dippp)_2$	1:1	4–MeC_6H_4CN	19
12	4–$(NO_2)C_6H_3$–1,2–Cl_2	**3**	$Pd(dippp)_2$	1:1	2–Cl–4–$(NO_2)C_6H_3Me$	61
13	1,4–$C_6H_4Cl_2$	**3**	$Pd(dippe)_2$	1:1	1,4–$C_6H_4Me_2$	10
14	1,4–$C_6H_4Cl_2$	**3**	$Pd(dippb)_2$	1:1	1,4–$C_6H_4Me_2$	14
15	4–ClC_6H_4Br	**3**	$Pd(dippp)_2$	1:1	4–ClC_6H_4Me	10
16	4–ClC_6H_4Br	**3**	$Pd(dippb)_2$	1:1	4–ClC_6H_4Me	16
17	4–ClC_6H_4Me	**3**	$Pd(dippp)_2$	1:1	1,4–$C_6H_4Me_2$	17
18	4–ClC_6H_4Me	**3**	$Pd(dippp)_2$	1:10	1,4–$C_6H_4Me_2$	45
19	C_6H_5Cl	**3**	$Pd(dippp)_2$	1:1	C_6H_5Me	37
20	1–$C_{10}H_7Cl$	**1**	$Pd(dippp)_2$	2:1	1–$C_{10}H_7Me$	35
21	1–$C_{10}H_7Cl$	**3**	$Pd(dippp)_2$	2:1	1–$C_{10}H_7Me$	38
22	1–$C_{10}H_7Cl$	**3**	$Pd(dippp)_2$	1:1	1–$C_{10}H_7Me$	56
23	1–$C_{10}H_7Cl$	**3**	$Pd(dippp)_2$	1:5	1–$C_{10}H_7Me$	76
24	1–$C_{10}H_7Cl$	**3**	$Pd(dippp)_2$	1:10	1–$C_{10}H_7Me$	83
25	1–$C_{10}H_7Cl$	**4**	$Pd(dippp)_2$	1:1	1–$C_{10}H_7Me$	7
26	1–$C_{10}H_7Cl$	**5a**	$Pd(dippp)_2$	1:1	1–$C_{10}H_7Me$	20
27	1–$C_{10}H_7Cl$	**5b**	$Pd(dippp)_2$	1:1	1–$C_{10}H_7Et$ $C_{10}H_8$	13 5
28	1–$C_{10}H_7Cl$	**3**	$Pd(dippp)_2$	1:1	1–$C_{10}H_7Me$	15
29	BrC_6H_4–$CH_2C_6H_4$–4–Cl	**3**	$Pd(dippp)_2$	1:1	BrC_6H_4–$CH_2C_6H_4$–4–Me ClC_6H_4–4–$CH_2C_6H_4$–4'–Me	36 ~1

Reaction conditions: 1 mmol of the nitrated chloroaryl, Pd catalyst (2 % mol), in 2 ml of benzene at r.t.; heating for 15 min at T=90 °C; addition of the alkylating agent of choice in 1 ml of benzene. The mixture was then kept under inert atmosphere (N_2 or Ar) at T=90 °C for 22 h; quenching with 2% HCl_{aq}.
$Pd(dippe)_2$= [1,2–bis(diisopropylphosphino)ethane]palladium; $Pd(dippp)_2$= [1,3–bis(diisopropylphosphino)propane]palladium ;$Pd(dippb)_2$= [1,4–bis(diisopropylphosphino)butane]palladium.

The use of electron rich Pd complexes affects positively the yields of the corresponding methylated products. Ethylation was also attempted (Entry 27, Table 3.6), but increased reaction times were observed, leading to the isolation of some dehalogenated material as well. Results improved in presence of electron withdrawing substituents on the aryl halide.

Methylation with **3** was also attempted on 4–chlorobenzaldehyde, but results were analogous to those obtained employing methylating agent **1** (Entry 1, Table 3.6), with a low yield of the corresponding methylated aldehyde and formation of Cannizzaro–like side products.

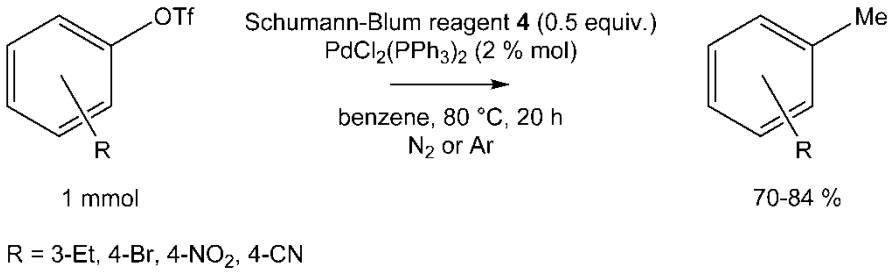
Aryl triflates underwent methylation successfully, in presence of Schumann–Blum reagents **1** and **4**. [107] 1– and 2–naphtyltrifluoromethansulfonate were efficiently methylated by reagent **1**, in presence of a Pd(II) catalyst, as reported in Table 3.7.

Table 3.7. Pd–catalysed cross–methylation of naphtyltrifluoromethanesulfonates with **1**. [107]

Entry	Triflate	Catalyst	t (h)	Product	Yield (%)
1	1–naphtyl	$PdCl_2(PPh_3)_2$	1	1–methylnaphthalene	98
2	2–naphtyl	$PdCl_2(PPh_3)_2$	1	2–methylnaphthalene	86

Reaction conditions: 1 mmol of the naphthalene derivative, the alkylating agent containing 1 equiv. of the metal, Pd catalyst (2 % mol), in 7 ml of benzene at r.t. under inert atmosphere; heating for the required time at T=80 °C; addition of in 1 ml of benzene.; quenching with 5 % HCl_{aq}.

Substituted aryl triflates were efficiently methylated with the same system, using methylating agent **4**. Results are summarised in Scheme 3.4.



Scheme 3.4. Pd–catalysed cross–methylation of substituted aryl triflates with **4**. [107]

Gallium and indium based methylating agents were also tested for such reactions. While gallium based reagents gave worst performances, [106] indium based reagents underwent successfully selective methylation of the halogen moiety also in presence of reactive H bonds (–OH, $–OSO_2CF_3$,$–CO_2H$). [108]

This type of methylaluminum complexes were also employed in the kinetic resolution of racemic 2,2'–bis(trifluoromethanesulfonyloxy)–1,1'–binaphthalene. [105]

The kinetic resolution was performed with an achiral methylating agent (such as reagents **1** and **3**) in presence of a chiral Pd catalyst, (±)–Pd(binap)$(OAc)_2$, or with chiral methylaluminum derivatives **6** and **7** (Figure 3.3) with an achiral Pd catalyst.

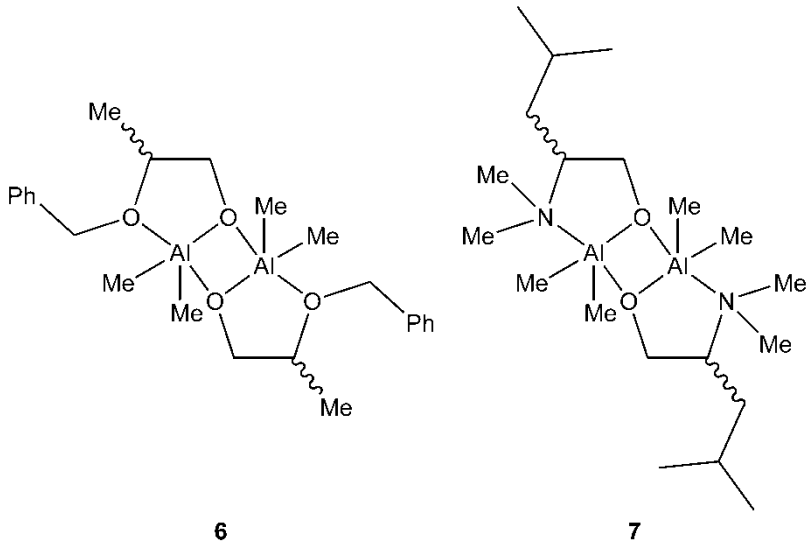


Figure 3.3. Chiral methylaluminum reagents. [105]

The e.e. values of the resolved binaphtyl derivatives by the two methods were 69 and 12 % respectively. Even if the results were not encouraging, this is the first application of a stabilised dimethylaluminum complex with a chiral chelating ligand used for asymmetric induction.

More recently Woodward *et al.* employed a different air stable methylaluminum (DABAL–Me_3) complex in several methylation reactions including Pd(0) catalysed cross–methylation. [103,110-113]

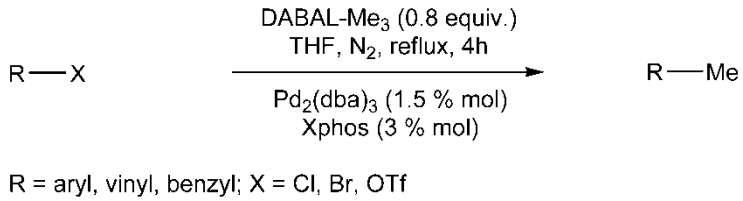
DABAL–Me_3 is the adduct between 1,4–diazabicyclo[2.2.2]octane (DABCO) and two molecules of $AlMe_3$. This complex is air stable (for some hours) under standard lab conditions, can be stored indefinitely under inert atmosphere and, differently from its non–stabilised counterpart, is non pyrophoric.

Figure 3.4. Bis(trimethylaluminum)–1,4–diazabicyclo[2.2.2]octane, DABAL–Me_3.

This complex was previously synthesised, [114] and characterised by X–ray crystallography, [115] but, until recently, has never been used as a methylating agent.

DABAL–Me_3 was successfully employed in the Pd–catalysed cross–methylation of aryl and vinyl halides. [110]

Optimised reaction conditions are summarised in Scheme 3.5.



Scheme 3.5. Optimised conditions for the Pd(0) catalysed cross methylation of aryl and vinyl halides with DABAL–Me_3. [110]

In this case, instead of the previously used $Pd(PPh_3)_4$, a catalytic system composed of a Pd(0) source in the presence of a phosphine ligand was employed. This was necessary in order to ensure quantitative conversion of the halide containing substrates in the corresponding methylated product, and avoid a delicate separation step (see Ref. [104]). Several 1,1'–biarylphosphines were screened, the best results given by the Buchwald type ligand XPhos (2–dicyclohexylphosphino–2',4',5'–triisopropylbiphenyl). [116,117]

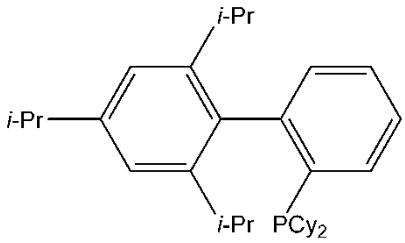
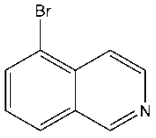
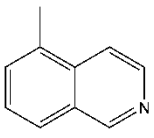
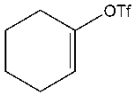
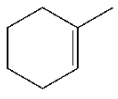
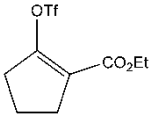
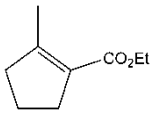


Figure 3.5. 2–dicyclohexylphosphino–2',4',5'–triisopropylbiphenyl, XPhos. [116,117]

The reaction was performed with several different aryl and vinyl halides and pseudohalides. Results obtained are summarised in Table 3.8.

Table 3.8. Methylation of aryl and vinyl halides with DABAL–Me_3. [110]

Entry	Sustrate	Product	Yield (%)
1	C_6H_5Br	C_6H_5Me	>99
2	C_6H_5OTf	C_6H_5Me	>99
3	4–MeC_6H_4Br	1,4–$Me_2C_6H_4$	>99
4	4–MeC_6H_4Cl	1,4–$Me_2C_6H_4$	>99
5	4–FC_6H_4Br	4–FC_6H_4Me	>99
6	4–ClC_6H_4Br	4–ClC_6H_4Me 1,4–$Me_2C_6H_4$	65 34
7	4–$(CF_3)C_6H_4Br$	4–$(CF_3)C_6H_4Me$	>99
8	4–*t*–BuC_6H_4Br	4–*t*–BuC_6H_4Me	96
9	4–$(CN)C_6H_4Br$	4–$(CN)C_6H_4Me$	95
10	4–$(CN)C_6H_4Cl$	4–$(CN)C_6H_4Me$	95
11	3–$(CN)C_6H_4Br$	3–$(CN)C_6H_4Me$	95
12	2–$(CN)C_6H_4Br$	2–$(CN)C_6H_4Me$	96
13	4–$(CH_2{=}CH)C_6H_4Br$	4–$(CH_2{=}CH)C_6H_4Me$	>99
14	4–$(CH_2{=}CH)C_6H_4Cl$	4–$(CH_2{=}CH)C_6H_4Me$	98
15	4–$(MeO)C_6H_4Br$	4–$(MeO)C_6H_4Me$	>99
16	4–$(MeO)C_6H_4Cl$	4–$(MeO)C_6H_4Me$	>99
17	4–$(MeO)C_6H_4OTf$	4–$(MeO)C_6H_4Me$	>99
18	2–$(MeO)C_6H_4Br$	2–$(MeO)C_6H_4Me$	>99
19	4–$(CO_2Et)C_6H_4Br$	4–$(CO_2Et)C_6H_4Me$	99
20	4–$(CO_2Et)C_6H_4Cl$	4–$(CO_2Et)C_6H_4Me$	98
21	4–$(CHO)C_6H_4Br$	4–$(CHO)C_6H_4Me$	94 (1.6 equiv. DABAL–Me_3)
22	4–$(CHO)C_6H_4Br$	4–$(CHO)C_6H_4Me$	88 (0.5 equiv. DABAL–Me_3)
23	4–$(NO_2)C_6H_4Br$	4–$(NO_2)C_6H_4Me$	76
24	4–$(NO_2)C_6H_4Cl$	4–$(NO_2)C_6H_4Me$	81
25	4–$(NO_2)C_6H_4OTf$	4–$(NO_2)C_6H_4Me$	59
26	4–$(CH_2OH)C_6H_4Br$	4–$(CH_2OH)C_6H_4Me$	79
27	$C_6H_5CH_2Br$	$C_6H_5CH_2Me$	72
28	1–$X_{10}H_7OTf$	1–$C_{10}H_7Me$	>99
29	2–$C_{10}H_7OTf$	2–$C_{10}H_7Me$	98
30	1–$C_{10}H_7Cl$	1–$C_{10}H_7Me$	90
31	2–$C_{10}H_7Cl$	2–$C_{10}H_7Me$	98
32	3–C_4H_3SBr	3–C_4H_3SMe	90
33	3–C_5H_3NBr	3–C_5H_3NMe	16
34			59
35			>99
36			98

Reaction conditions: 0.25 mmol of the aryl/vinyl halide, $Pd_2(dba)_3$ (1.5 % mol), Xphos (3 % mol), 0.8 equiv. of DABAL–Me_3, in 3 ml of anhydrous THF. The mixture was then kept under inert atmosphere (N_2 or Ar) at reflux T for 4 h. Yields are determined by GC analysis *vs.* an internal standard.

As can be seen from the data collected in Table 3.8, the system works well in most cases, even for substrates bearing "sensitive" functional group, and for a variety of vinyl halides. Interestingly, also with triflate containing substrates, which showed poor reactivity with previously reported systems, quantitative yields of the corresponding methylated product were obtained. [108]

Moreover, DABAL–Me_3 is an effective methylating agent also in non strictly anhydrous conditions, as reported in Table 3.9.

Table 3.9. Pd–catalysed cross–methylation using DABAL–Me_3 under aerobic conditions. [110]

Entry	Sustrate	Ligand	Product	Yield (%)
1	C_6H_5Br	XPhos	C_6H_5Me	79
2	4–$(CF_3)C_6H_4Br$	XPhos	4–$(CF_3)C_6H_4Me$	91
3	4–$(CN)C_6H_4Br$	XPhos	4–$(CN)C_6H_4Me$	>99
4	4–$(MeO)C_6H_4Br$	XPhos	4–$(MeO)C_6H_4Me$	98
5	4–$(CO_2Et)C_6H_4Br$	XPhos	4–$(CO_2Et)C_6H_4Me$	92
6	4–$(NO_2)C_6H_4Br$	XPhos	4–$(NO_2)C_6H_4Me$	71
7	1–$C_{10}H_7OTf$	Cy–JohnPhos	1–$C_{10}H_7Me$	>99
8	2–$C_{10}H_7OTf$	Cy–JohnPhos	2–$C_{10}H_7Me$	96

Cy–JohnPhos = 2–(dicyclohexylphosphino)–1,1'–byphenyl.
Reaction conditions: 0.25 mmol of the aryl/vinyl halide, $Pd_2(dba)_3$ (1.5 % mol), XPhos (3 % mol), 0.8 equiv. of DABAL–Me_3 in 3 ml THF at reflux T for 4 h. Yields are determined by GC analysis *vs.* an internal standard.

Looking at the overall performance and its wide range of application, DABAL–Me_3 stands out as a versatile methylating agent in various reaction types and conditions.

3.2. Scope of the work

The work presented in this section was performed in collaboration with Prof. S. Woodward from University of Nottingham. Part of the work was carried out during a 3 month Short Term Scientific Mission (STSM) at University of Nottingham within the COST D40 framework.

Aim of the work was to develop a reaction protocol for the Pd–catalysed methylation of aryl halides with DABAL–Me_3 using a two–phase system VOC/IL. This was done to retain the catalytic species in the IL phase, in order to allow recycling of the catalytic system. Reaction parameters (such as the IL chosen, Pd source, choice of the ligand) were optimised accordingly. Recycling of the IL phase was attempted.

The use of a functionalised IL (DABCOnium IL) was also evaluated.

3.3. Experimental section

3.3.1. Instruments, materials and methods

Substrates and ligands were purchased from Sigma Aldrich, Alfa Aesar, Lancaster, Merck and used without further purification. DABAL–Me_3 was purchased from Sigma Aldrich and stored under inert atmosphere (Ar). $Pd_2(dba)_3$ was purchased from Sigma Aldrich and used as received. $PdCl_2(CH_3CN)_2$ was synthesised according to literature procedures. [118]

Sulfuric acid 96 % was purchased from Pharmacos and oleum from Sigma Aldrich.

Solvents were purchased from Fluka, Lancaster and Carlo Erba either of anhydrous grade or, starting from reagent grade solvents, were dried according to literature procedures. [55]

GC analysis were performed using an Hewlett Packard HP 4890A instrument and a Varian 3900 instrument. The former was equipped with a Hewlett Packard HP–5 capillary column (15 m length, 0.53 mm internal diameter, 0.15 μm film thickness), while the latter mounted a Supelco SPB–5 capillary column (30 m length, 0.25 mm internal diameter, 0.25 μm film thickness). Analyses were performed using undecane as internal standard with HP 4890A and dodecane as external standard with Varian 3900.

HP4890A: injector temperature 250 °C; detector temperature 250 °C; initial temperature 50 °C, hold for 5 min, 10 °C/min, 225 °C for 17.5 min.

Varian 3900: injector temperature 250 °C; detector temperature 240 °C; initial temperature 120 °C, hold for 5 min, 10 °C/min, 250 °C for 13 min.

ESI–MS analyses were performed using a Bruker MicroTOF instrument.

NMR spectra were recorded using Bruker Avance 300 and 400, operating respectively at 300.1 MHz (Avance 300) and 400.1 MHz (Avance 400) for protons. The residual signal of the solvent ($CDCl_3$, CD_3OD or DMSO–d_6) was used as internal reference.

^{13}C NMR analyses were performed with a Bruker Avance 400 spectrometer, operating at 100.6 MHz. The residual signal of the solvent ($CDCl_3$) was used as internal reference.

^{31}P NMR analyses were performed with a Bruker Avance 400 and Bruker Avance 300 spectrometers, operating at 162.0 and 121.4 MHz respectively. When stated, PPh_3 was used as a reference compound.
All deuterated solvents were purchased form Sigma Aldrich.

3.3.2. Results

3.3.2.1. Optimisation of the reaction conditions

Initially, two alkylmethylimidazolium based ILs were tested: the hydrophobic $[C_4mim]Tf_2N$ and the hydrophilic $[C_4mim]BF_4$. The synthesis and characterization of these ILs is described in Chapter 1.
Retention of the catalytic Pd catalysts in the IL phase was studied for both ILs when operated in a biphasic system with THF. For the Pd source, $Pd_2(dba)_3$ was chosen initially but extensive leakage of Pd from the ILs phases to THF was observed. In order to overcome this limitation $PdCl_2(CH_3CN)_2$, a Pd(II) source largely used in IL media, [119-121] was subsequently synthesised and used for the cross–methylation reactions. [118]
Due to the extensive leakage of the catalyst into the THF solvent (both for Pd(0) and Pd(II) precursors) $[C_4mim]Tf_2N$ was not a suitable candidate. With $[C_4mim]BF_4$, retention of the metal species was improved, especially when $PdCl_2(CH_3CN)_2$ was used as the Pd source. Therefore, $[C_4mim]BF_4$ was the IL used for subsequent studies.
Another hydrophilic IL was subsequently prepared and used: $[C_6DABCO]BF_4$, a functionalised IL which bears a basic moiety. The synthesis and characterization of $[C_6DABCO]BF_4$ are described in Chapter 1.
As reported beforehand, in previous works on cross–methylation it was shown that the best ligand for this type of reaction was XPhos. [110]
To enhance the retention of the catalytic species in the IL phase, a charged ligand (derived from XPhos) was synthesised, $XPhosSO_3H$ (dicyclohexyl–(2',6'–diisopropyl–4'–sulfonylbiphenyl)phosphonium hydrogensulfonate). The synthesis was carried out accordingly to literature procedures, with slight modifications during the work up. [122]

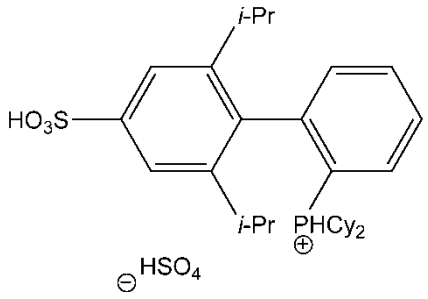


Figure 3.6. Dicyclohexyl–(2',6'–diisopropyl–4'–sulfonylbiphenyl)phosphonium hydrogensulfonate, $XPhosSO_3H$.

Solid XPhos (433.0 mg, 0.90 mmol) was stirred in CH_2Cl_2 (3.0 ml) under an inert atmosphere in an appropriate flask. The flask was immersed in a dry ice–acetone bath maintained at -40 °C and concentrated H_2SO_4 (84 %) (1.0 ml) was added dropwise, the solution turned yellow. Then highly concentrated H_2SO_4 oleum (20 % SO_3) (*CARE!* Corrosive) (3.0 ml) was carefully added dropwise causing the solution to darken. The mixture was stirred vigorously for 24 h, allowing the bath to reach r.t. After 24 h, crushed ice was added: two layers formed, a white cloudy upper aqueous phase and a lower brown oily layer. The aqueous phase was decanted, and the oil was diluted by adding portions of Et_2O. At an approximate 2:1 ratio of Et_2O:CH_2Cl_2 a beige powder slowly precipitated. The powder was filtered off and dried under high vacuum (0.1 mmHg) at room temperature for 6 h. The resultant $XPhosSO_3H$ (540.3 mg, 98 % yield) was used as obtained.

The product was characterized by ^{1}H, ^{13}C, ^{31}P NMR and ESI–MS (Figures 3.7 – 3.11).

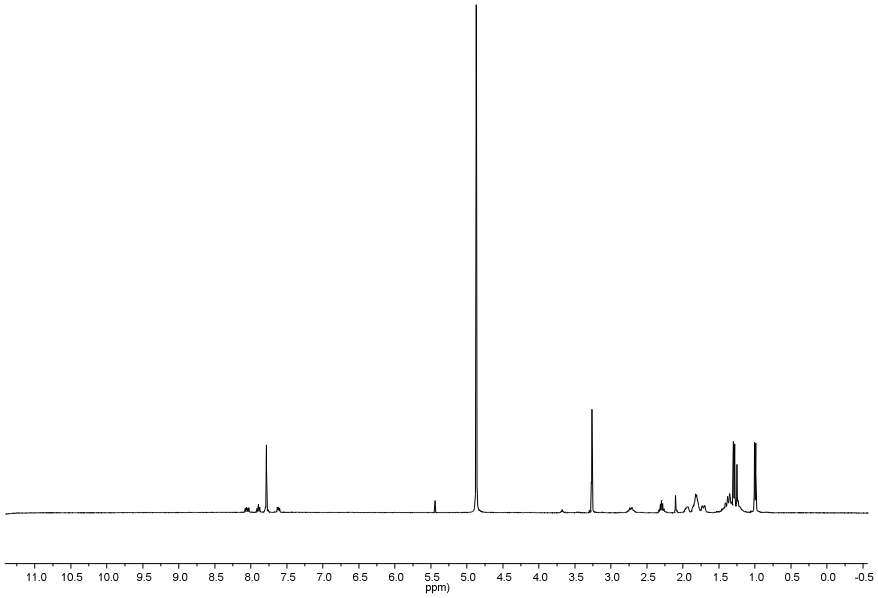


Figure 3.7. ^{1}H NMR spectrum of $XPhosSO_3H$ (solvent: CD_3OD).

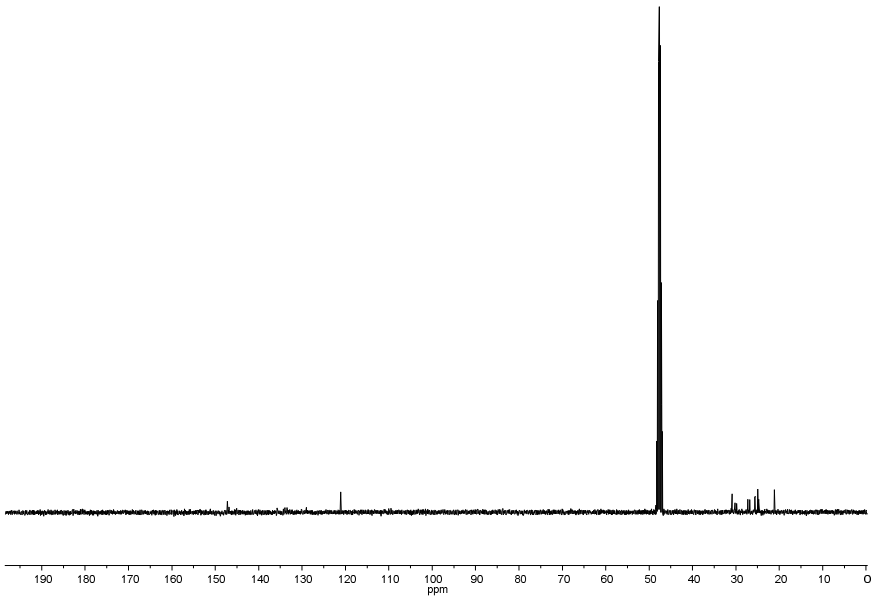


Figure 3.8. ^{13}C NMR spectrum of $XPhosSO_3H$ (solvent: CD_3OD).

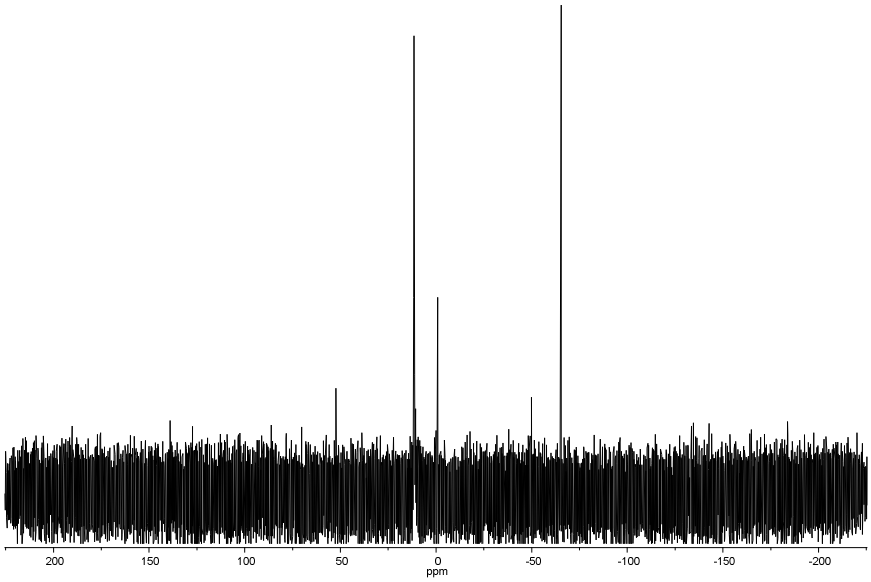


Figure 3.9. ^{31}P NMR spectrum of $XPhosSO_3H$ (solvent: CD_3OD).

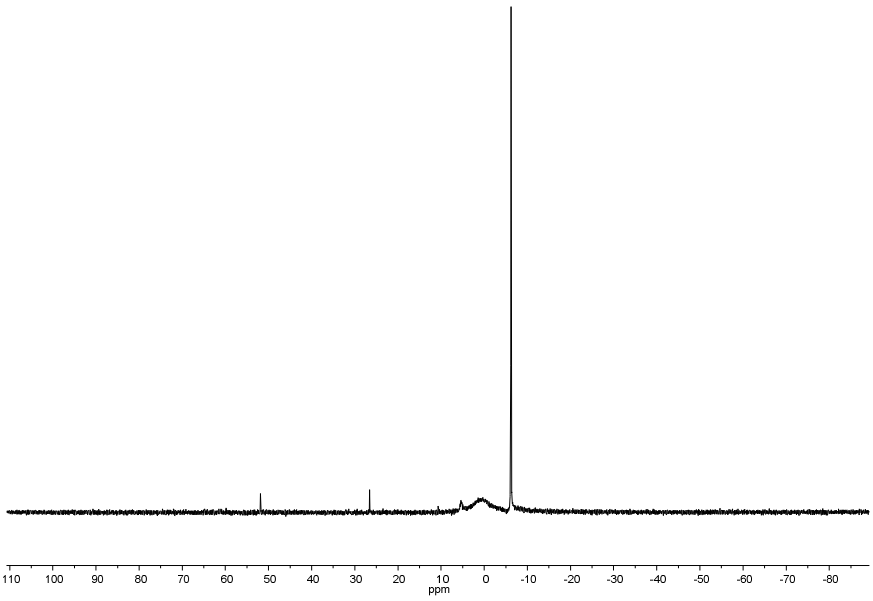


Figure 3.10. ^{31}P NMR spectrum of $XPhosSO_3H$ (solvent: DMSO–d_6).

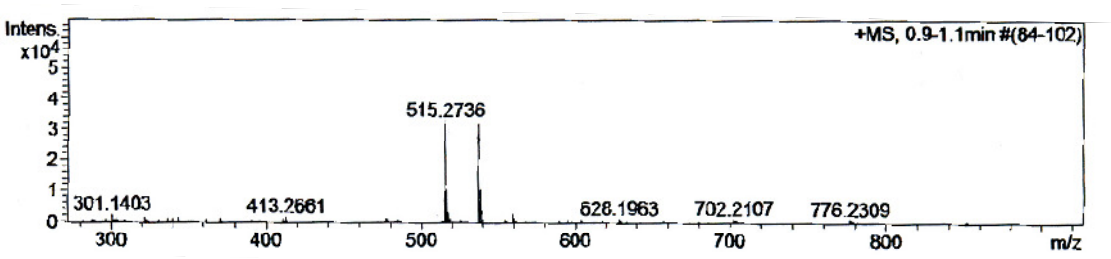


Figure 3.11. HRMS ESI–MS spectrum of $XPhosSO_3H$ (solvent: CH_3CN, positive mode).

^{1}H NMR: δ_H (400 MHz, CD_3OD): 8.03 (dd, 1H), 8.00 (dd, 1H), 7.86 (s, 3H), 7.58 (m, 1H), 2.68 (m, 2H), 2.26 (m, 2H); 1.62 (OH); 1.66–0.80 (m, 32H).

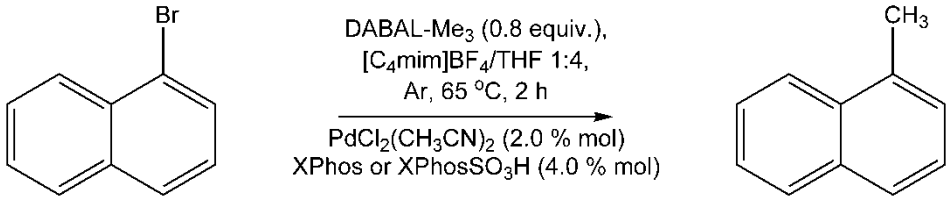
^{13}C NMR δ_C (100 MHz, CD_3OD): 148.2; 147.9; 147.8; 139.4; 136.8; 135.4; 135.3; 134.8; 134.5; 134.4; 130.0; 124.0; 122.1; 115.1; 31.9; 31.2; 30.8; 28.33; 28.30; 27.9; 26.8; 26.7; 26.5; 26.0; 25.8; 22.1.

^{31}P NMR δ_P (162 MHz, CD_3OD): -65.4; 10.4 (–SO_3Na ligand), traces of unreacted XPhos.

^{31}P NMR δ_P (121 MHz, DMSO–d_6): 1.51 (broad signal). Some deprotonated ligand on the P is present (53.1) and oxidised ligand (27.8).

HRMS (ESI; pos, CH_3CN): calcd. for $C_{30}H_{44}O_3PS$ ([M + H] $^+$): *m/z* = 515.2743. Found: 515.2736 $[M]^+$, 537.2561 $[M+Na]^+$.

XPhosSO_3H and its uncharged counterpart (XPhos) were both used on a test reaction, methylation of 1–bromonaphthalene.



Scheme 3.6. Pd–catalysed cross–methylation of 1–bromonaphthalene in a two–phase system THF/$[C_4mim]BF_4$.

In a typical experiment $[C_4mim]BF_4$ (0.25 ml), $PdCl_2(CH_3CN)_2$ (1.2 mg, 5.0 μmol) and XPhos (4.8 mg, 1.0 μmol) were added to a 5 ml flame–dried Shlenk tube kept under inert atmosphere (Ar or N_2). The mixture was vigorously stirred at r. t. for 20 minutes, to ensure complete formation of the active catalyst. To the resultant orange solution, anhydrous THF (1.0 ml), 1–bromonaphthalene (35 μl, 0.25 mmol) and DABAL–Me_3 (51.3 mg, 0.20 mmol) were added and the mixture heated at reflux for 2 h. The organic layer was collected and the IL extracted with 8 x 1 ml aliquots of Et_2O. A sample of 30 μl of internal standard (undecane) was added to the organic phase obtained. The mixture was filtered through a pad of silica with CH_2Cl_2 and dried. A sample was taken for GC analysis.

When XPhosSO_3H was used, the procedure was carried out in an identical manner to above, except for the ligand used: XPhosSO_3H (6.1 mg, 1.0 μmol).

Results for the methylation of 1–bromonaphthalene using both the uncharged and charged ligand, are reported in Table 3.10.

Table 3.10. Pd–catalysed cross–methylation of 1–bromonaphthalene in a two–phase system THF/[C_4mim]BF_4.

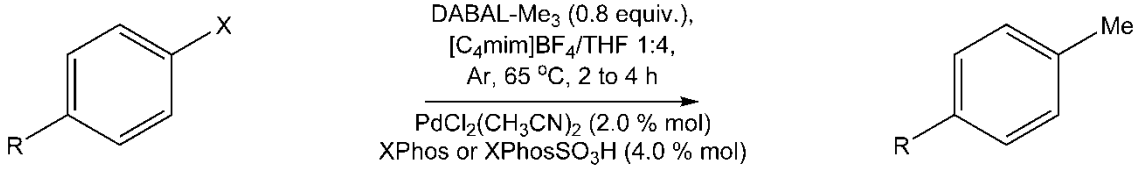
Entry	Substrate	Ligand	t (h)	Product	Conversion (%)	GC Yield (%)	Isolated yield (%)
1	1–$C_{10}H_7Br$	XPhos	2	1–$C_{10}H_7CH_3$	>99	99	60
2	1–$C_{10}H_7Br$	XPhosSO_3H	2	1–$C_{10}H_7CH_3$	>99	99	79

Conversion and GC yields are determined by GC analysis *vs.* an internal standard.

Results with both ligands are comparable when considering reaction times and yields, however retention of the catalytic species is improved when using a charged ligand (*vide infra*).

3.3.2.2. Results with the optimised system THF/[C_4mim]BF_4

Reaction conditions are reported in Scheme 3.6.



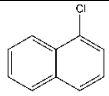
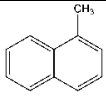
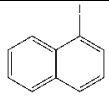
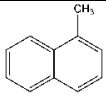
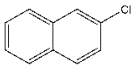
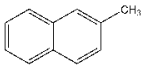
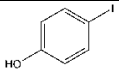
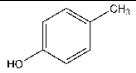
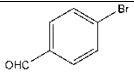
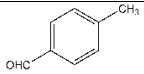
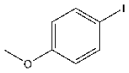
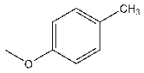
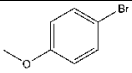
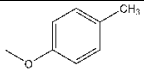
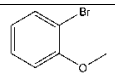
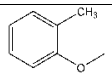
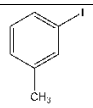
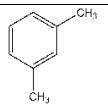
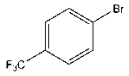
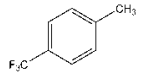
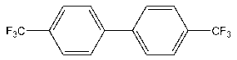
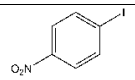
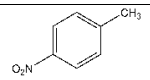
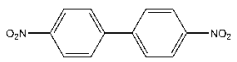
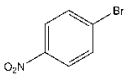
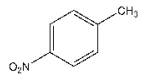
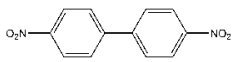
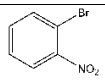
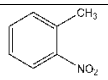
Scheme 3.7. Pd–catalysed cross–methylation of aryl halides with DABAL–Me_3 in a two phase system THF/[C_4mim]BF_4.

The reaction was tested with several different substrates. In a typical experiment, [C_4mim]BF_4 (0.25 ml), $PdCl_2(CH_3CN)_2$ (1.2 mg, 5.0 μmol) and XPhos (4.8 mg, 1.0 μmol), or XPhosSO_3H (6.1 mg, 1.0 μmol) were added to a 5 ml flame–dried Schlenk tube, kept under inert atmosphere (Ar or N_2). The mixture was vigorously stirred at r.t. for 20 minutes, to ensure complete formation of the active catalyst. To the resultant orange solution, anhydrous THF (1.0 ml), 0.25 mmol of the substituted haloarene of interest, and 51.3 mg (0.20 mmol) of DABAL–Me_3 were then added and the mixture was heated at reflux for 2 h. The organic layer was collected and the IL extracted with portions of Et_2O, filtered through a pad of silica with CH_2Cl_2 and dried

at the rotary evaporator. The product obtained was weighted and a sample analysed by ^{1}H NMR spectroscopy (solvent: $CDCl_3$).

The obtained results are collated in Table 3.11. ^{1}H NMR chemical shifts of the synthesised compounds are summarised in Appendix C.

Table 3.11. Pd–catalysed cross–methylation of aryl halides with DABAL–Me_3 in a two phase system THF/[C_4mim]BF_4.

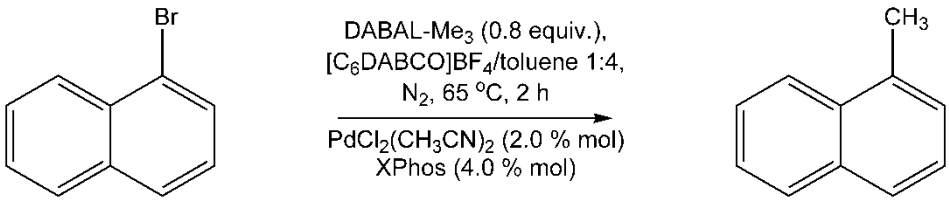
Entry	Substrate	Ligand	t (h)	Conversion (%)	Cross–methylation	Yield (%)	Homocoupling	Yield (%)
1		XPhosSO$_3$H	2	63[a]		63[a]		
2		XPhosSO$_3$H	2	>99[a]		90[b]		
3		XPhosSO$_3$H	2	>99[a]		87[b]		
4		XPhosSO$_3$H	2	>99[a]		57[b]		
5		XPhosSO$_3$H	2	>99[a]		95[b]		
6		XPhosSO$_3$H	4	>99[a]		63[b]		
7		XPhosSO$_3$H	4	>99[a]		94[b]		
8		XPhosSO$_3$H	4	>99[a]		56[b]		
9		XPhosSO$_3$H	4	>99[a]		73[b]		
10		XPhos	2	>99[a]		71[b]		11[a]
11		XPhosSO$_3$H	2	>99[a]		44[a]		10[a]
12		XPhos	2	90[a]		36[a]		54[a]
13		XPhos	2	>99[a]		56[a]		6[a]
14		XPhosSO$_3$H	2	>99[a]		86[a]		4[a]
15		XPhosSO$_3$H	2	63[a]		63[a]		

[a] ^{1}H NMR. [b]Isolated yield.

As it can be seen from Table 3.11, with the exception of the more sterically hindered 1–bromo–2–nitrobenzene and of the less reactive 1–chloronaphthalene, the conversion of the substrate is always very high. In addition, in several instances the selectivity toward the formation of the methylated product is synthetically useful. Quite surprisingly, with 4–substituted arenes containing electron withdrawing groups, formation of homocoupling product (hc), occasionally in quite high yield (Entry 15, Table 3.11), was observed.

3.3.2.3. Methylation reactions in [C$_6$DABCO]BF$_4$

The catalytic reaction was also performed using a basic IL, [C$_6$DABCO]BF$_4$; in this occasion the other phase was toluene. In preliminary experiments using THF, it was observed that upon addition of DABAL–Me$_3$ a sluggish mixture was obtained. This did not happen when toluene was used, so it was decided to switch to toluene, since [C$_6$DABCO]BF$_4$ is not soluble in this solvent, but DABAL–Me$_3$ is.
Furthermore, with this specific IL it was not possible to use the charged ligand XPhosSO$_3$H, since, when added to the reaction mixture, it reacted with the IL used.
The reaction was performed ad higher temperature when compared to the previously described system (110 °C) and quantitative conversion of 1–bromonaphthalene was observed within 45 minutes with good isolated yield of 1–methylnaphthalene.



Scheme 3.8. Pd–catalysed cross–methylation of aryl halides with DABAL–Me$_3$ in a two phase system toluene/[C$_6$DABCO]BF$_4$.

In a typical experiment, [C$_6$DABCO]BF$_4$, (437.9 mg, 1.54 mmol), PdCl$_2$(CH$_3$CN)$_2$ (2.8 mg, 11.0 μmol) and XPhos (4.8 mg, 26.3 μmol) were added to a 5 ml flame dried Shlenk tube, kept under inert atmosphere (Ar or N$_2$). The mixture was heated up to 80 °C (in order to let the IL melt) and kept under vigorous stirring at 80 °C (20 min),

to ensure complete solubilisation of Pd precatalyst and ligand. To the orange solution obtained anhydrous toluene (2.0 ml), 1–bromonaphthalene (70 µl, 0.50 mmol), and DABAL–Me_3 (102.5 mg, 0.40 mmol) were then added. The mixture was heated to reflux for 2 h. During this time GC analysis were performed at t = 0 and 2 h (using 50 µl organic phase samples). After 2 h, the organic layer was collected and the IL extracted with portions of Et_2O as before. The organic phases were collected and washed with water, dried over Na_2SO_4, filtered and concentrated by rotary evaporation.

When 1–iodo–4–nitrobenzene was used the procedure was carried out similarly, except for the substrate: 102.4 mg (0.50 mmol) of 1–iodo–4–nitrobenzene were added.

Results obtained with this two phase system are summarised in Table 3.12.

Table 3.12. Pd–catalysed cross–methylation of aryl halides with DABAL–Me_3 in a double phase system toluene/[C_6DABCO]BF_4.

Entry	Substrate	Ligand	t (h)	Product	Conversion (%)	Yield
1	1–$C_{10}H_7Br$	XPhos	30 45 120	1–$C_{10}H_7Me$	97[a] >99[a] >99[a]	71
2	4–$(NO_2)C_6H_4I$	XPhos	2	4–$(NO_2)C_6H_4Me$	>99[b]	78

[a]GC analysis *vs.* an external standard. [b]Yield calculated by ^1H NMR.

Analogous experimental conditions, see Table 3.12, were used to compare the results obtained with [C_6DABCO] BF_4/toluene two–phase with those related for the methylation of 4–$(NO_2)C_6H_4I$, *i.e.* one of the substrates that produced homocoupling side products (Table 3.11, Entry 15). Interestingly, under these conditions homocoupling product was not observed.

3.3.2.4. Attempts of recycling the IL phase

The possibility of recycling the catalytic phase was studied in the methylation of 1–bromonaphthalene in the different two–phase systems used. In a typical recycling experiment, the IL phase was recharged with anhydrous THF or toluene, 1–bromonaphthalene (1.0 equiv.) and DABAL–Me_3 (0.8 equiv.) were added. The

mixture was heated at reflux T for 8 h. GC analysis were performed at given times. Yields were calculated by GC analysis *vs.* an internal standard (dodecane).
Results are summarised in Table 3.13.

Table 3.13. Results obtained in the recycling experiments.

Entry	Double phase system	Ligand	t (h)	Yield[a] (%)
1	$[C_4mim]BF_4$/THF	XPhos	2	12
2	$[C_4mim]BF_4$/THF	XPhos	2	0[b]
3	$[C_4mim]BF_4$/THF	$XPhosSO_3H$	2	12
4	$[C_4mmim]BF_4$/THF	$XPhosSO_3H$	2	86
			8	97
5	$[C_6DABCO]BF_4$/toluene	XPhos	2	56

[a]In all cases after 8 h, quantitative formation of 1–bromonaphthalene was not achieved. [b]Ligand was recharged.

Another alkylmethylimidazolium based IL, $[C_4mmim]BF_4$ was used in the recycling studies: this ionic liquid bears a methyl group attached to the C–2 position (the same position in $[C_4mim]BF_4$ has an acidic proton) discouraging the formation of Pd–carbene complexes, which is known to affect Pd–catalysed reactions. [123]
The results obtained for the recycle run with $[C_4mmim]BF_4$/THF (Entry 4, Table 3.13) are very different from the ones obtained with the same system in $[C_4mim]BF_4$/THF (Entry 3, Table 3.13). This leads us to think that one of the possible catalyst decomposition patterns involved the formation of catalytically inactive imidazolium–derived Pd–complexes. However further studies are needed to elucidate the nature of the species formed in the IL phase (alkylmethylimidazolium *vs.* DABCO based IL).

3.4. Discussion

Methylation with DABAL–Me_3 proceeds smoothly in all the biphasic IL/VOC systems tested; however, when compared to the reaction performed in VOC alone this system has the advantage of having a catalytic phase which can, in principle, retain the complex (metal + ligand) formed.
In order to confirm such a possibility ^{31}P NMR experiments were carried out with the aim to quantify the leakage of the complex in the organic (VOC) layer and the nature of the phosphorus containing species present in the organic phase at the end of the reaction time. Results are shown in the Table 3.14.

All ^{31}P NMR analysis were performed in a solution of triphenylphosphine ca. 0,1 M in $CDCl_3$ (to allow accurate referencing of the phosphorus signals and qualitative assessment of their intensity).

Table 3.14. Results of the ^{31}P NMR experiments on the organic phase; peaks were assigned by comparison with the ^{31}P NMR spectrum of the ligand, PPh_3 was added as an internal standard.

Entry	Catalytic system	IL	NMR solvent	Species present δ (ppm)
1	$PdCl_2(CH_3CN)_2$/XPhos	$[C_4mim]BF_4$	$CDCl_3$	45.0 (XPhos) 29.6 (XPhos ox) -5.00 (PPh_3)
2	$PdCl_2(CH_3CN)_2$/XPhosSO_3H	$[C_4mim]BF_4$	DMSO–d_6	45.1 (unreacted XPhos) 27.5 (XPhos ox) -5.00 (PPh_3)
3	$PdCl_2(CH_3CN)_2$/XPhos	$[C_6DABCO]BF_4$	$CDCl_3$	45.0 (XPhos) 29.6 (XPhos ox) -5.00 (PPh_3)

Peaks were assigned by comparison with the spectra of the free ligands, and give just a qualitative analysis of the species present in the organic phase.

The ^{31}P NMR data suggest that, when XPhosSO_3H is used as the ligand, improved retention of the catalytic species in the IL is observed. Some leaking is observed also in the case of XPhosSO_3H (Table 3.14, Entry 2), but can be ascribed to traces of unreacted XPhos, residual of the ligand synthesis.

For the methylation of substituted aryl halides in the two phase system $[C_4mim]BF_4$/THF, different functional groups on the aryl moiety were tolerated, with no appreciable formation of side product (in particular, see 4–bromobenzaldehyde, Entry 12, Table 3.11). The catalytic system is sensitive to steric hindrance (Entry 1 and 3 *vs.* Entry 2, Table 3.11) and different relative reactivity of the halide present on the substrate (Entry 4, Table 3.11)

With this reaction protocol, homocoupling products were formed for substrates bearing strong electron–withdrawing groups (–NO_2 and –CF_3). The reason for such behaviour is still unclear, but this side reaction could have some synthetic interest since aryl bromides usually are not reactive enough to undergo homocoupling reactions. DABAL–Me_3 probably plays a non–innocent role in this side reaction, because when the reaction was repeated in the same experimental conditions reported in Table 3.11, without adding the methylating agent, no homocoupling product formation was observed and the substrate was quantitatively recovered.

Switching to a functionalised IL, $[C_6DABCO]BF_4$, results in increased efficiency of the system (T can be raised, with subsequent diminishing of reaction times). The use of $[C_6DABCO]BF_4$ resulted also in no homocoupling side products. However, with such systems it was not possible to use the charged ligand $XPhosSO_3H$, and some leaking of the catalytic species in the organic phase was observed.

3.5. Conclusions

The applicability of the Pd–catalysed cross–methylation of aryl halides with DABAL–Me_3 was broadened by performing these reactions a two phase system VOC/IL.

Several parameters were optimised including the choice of IL, catalyst (Pd(0) *vs.* Pd(II)) catalytic precursor, and ligand (charged *vs.* non–charged biarylphosphine ligands), reaction times and reagent ratios.

Retention of the catalytic system in the IL phase was evaluated by performing simple ^{31}P NMR measurement. It was observed that when the charged phosphine was used, the catalytic system was retained more efficiently by the IL phase.

The methylation reaction was tested with different substituted aryl halides observing overall good tolerance of the functional groups present. When using a $[C_4mim]BF_4$/THF two phase system, homocoupling products were isolated when the methylation reaction was performed on substrates bearing strong electron withdrawing substituents. Although it was not attempted to increase the selectivity towards the homocoupling reaction, the formation of such by–products might be synthetically useful, since biaryl compounds have a wide applicability; moreover homocoupling products were observed with aryl bromides, which usually are not sufficiently reactive to undergo this type of transformation.

The use of a functionalised IL ($[C_6DABCO]BF_4$) resulted in slight modifications of the reaction protocol (THF was replaced with toluene), but also improved the selectivity of the reaction towards the methylating product.

The catalytic phase (IL + M catalyst + ligand) was also recycled. In all cases, reaction times were longer, but, by carefully choosing the IL used (in order to minimise

Pd–carbene bond forming deactivation patterns) quantitative conversions were observed.

Further studies are needed to elucidate possible mechanistic pathways that lead to formation of homocoupling product, and elucidation (for example by ESI–MS) of the different species present in the catalytic phase, to refine the recycle step.

Chapter 4: Friedel–Crafts acylation and alkylation of ferrocene in ILs

4.1. Introduction

Among the possible applications of ILs, homogeneous and heterogeneous catalysis is surely an interesting target, due to some peculiar properties of ILs, which include confinement of the homogeneous/heterogeneous catalyst in the IL phase and enhanced selectivity. [14,124,120,125,126,121]

We will focus on a specific class of reactions performed in IL media: metal–catalyzed reactions with electrophilic reagents, particularly those with electrophilic carbon, such as Friedel–Crafts alkylation and acylation of arenes, which lead to the formation of new carbon–carbon bonds. [127]

4.1.1. Friedel–Crafts alkylation in ILs

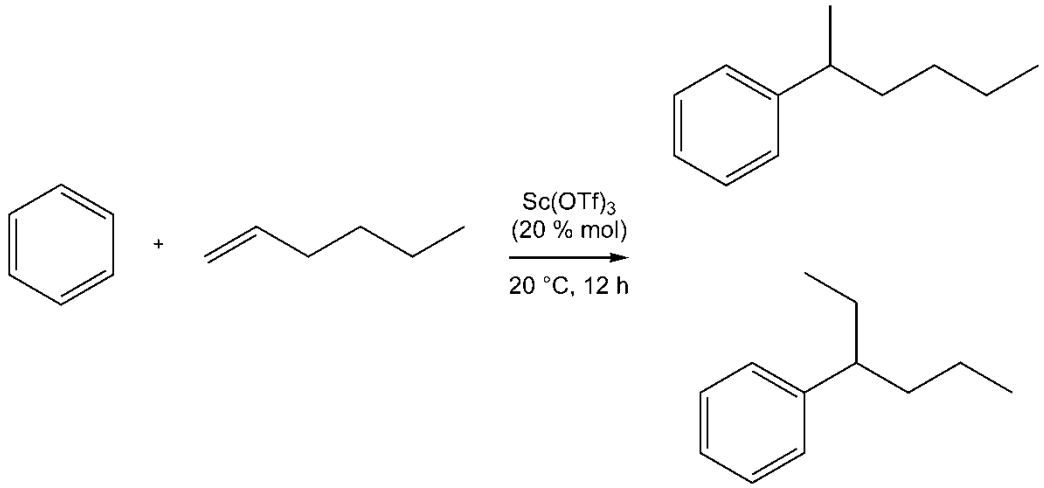
Friedel–Crafts alkylation has not been extensively studied in IL media. This can be ascribed to the scarce control over polyalkylation for this type of reaction, due to the increased reactivity of the alkylarene synthesised with respect to the starting arene.

Most of the literature dealing with Friedel–Crafts alkylation of aromatic compounds in ILs, refers to first generation (chloroaluminate based) ILs. [126] The use of such solvents has the advantage of performing the reaction in a "catalytic solvent", since the counteranion of this type of ILs acts as a catalyst for Friedel–Crafts reactions. At the same time, reaction conditions need to be controlled tightly, since these IL are extremely sensitive towards water traces and moisture, and need to be handled accordingly.

The sustainability of such reactions improved when second generation ILs were used: these are, in fact, significantly more stable toward air and moisture. [14] Reaction conditions were also improved by employing a scandium and/or lanthanide based Lewis acid. [128,129] Still, there are relatively few examples of successful Friedel–Crafts alkylation of aromatic compounds in ILs.

Sc(III) catalysed Friedel–Crafts alkylation of benzene was performed by Song and co–workers both in molecular solvents and ILs. [130]

Reaction conditions were optimised for the alkylation of benzene with 1–hexene (Scheme 4.1), as can be seen from Table 4.1.



Scheme 4.1. $Sc(OTf)_3$ catalysed Friedel–Crafts alkylation of benzene with 1–hexene. [130]

Table 4.1. $Sc(OTf)_3$ catalysed Friedel–Crafts alkylation of benzene with 1–hexene. [130]

Entry	Solvent	Conversion (%)	Product(s)	Yield (%)[a]	Isomers ratio[a]
1	None	0	–	0	–
2	CH_2Cl_2	0	–	0	–
3	CH_3CN	0	–	0	–
4	CH_3NO_2	0	–	0	–
5	$PhNO_2$	0	–	0	–
6	H_2O	0	–	0	–
7	$[C_2mim]SbF_6$	>99	(2–hexyl)benzene (3–hexyl)benzene	96	1.5 1
8	$[C_2mim]BF_4$	0	–	0	–
9	$[C_2mim]OTf$	0	–	0	–
10	$[C_4mim]PF_6$	>99	(2–hexyl)benzene (3–hexyl)benzene	96	2 1
11	$[C_4mim]SbF_6$	~99	(2–hexyl)benzene (3–hexyl)benzene	93	1.5 1
12	$[C_4mim]BF_4$	0	–	0	–
13	$[C_4mim]TfO$	0	–	0	–
14	$[C_5mim]PF_6$	>99	(2–hexyl)benzene (3–hexyl)benzene	95	1.6 1
15	$[C_6mim]PF_6$	>99	(2–hexyl)benzene (3–hexyl)benzene	95	2 1

Reaction conditions: 1–hexene (1mmol) in benzene (2 ml), $Sc(OTf)_3$ (0.2 mmol), solvent (1 ml), 20 °C, 12 h. [a]Conversions and yields, based on 1–hexene, were determined by GC analysis *vs.* an internal standard.

Given the good results obtained in some ILs (Entries 7, 10, 11, 14, 15, Table 4.1) and in particular when using 1–butyl–3–methylimidazolium hexafluoroantimoniate, $[C_4mim]SbF_6$, this IL was subsequently used to extend the scope of the reaction to other substrates and alkylating agents. Results are summarised in Table 4.2.

Table 4.2. $Sc(OTf)_3$ Friedel Crafts alkylation with alkenes in $[C_4mim]SbF_6$. [130]

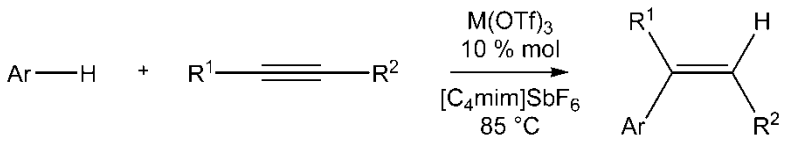
Entry	Aromatic compound	Alkene	Product(s)	Conversion (%)[a]	Yield (%)[a]	Isomers ratio[a]
1	benzene	1–hexene	(2–hexyl)benzene (3–hexyl)benzene	>99	93	1.5 1
2	benzene	cyclopentene	cyclopentylbenzene	>99	84	
3	benzene	cyclohexene	cyclohexylbenzene	>99	90	
4[b]	benzene	cyclohexene	cyclohexylbenzene	>99	92	
5[c]	benzene	cyclohexene	cyclohexylbenzene	>99	92	
6	benzene	bicyclo[2.2.2]–2–octene	1–phenylbicyclo[2.2.2]–3–octene	>99	65	
7	phenol	cyclohexene	1–cyclohexyl–2–methoxybenzene 1–cyclohexyl–4–methoxybenzene	>99	93	2.5 1
8	anisole	cyclohexene	1–cyclohexyl–2–methoxybenzene 1–cyclohexyl–4–methoxybenzene	>99	85	1.8 1

Reaction conditions: 1–hexene (1 mmol) in benzene (2 ml), $Sc(OTf)_3$ (0.2 mmol for entries 1–6 and 0.1 mmol for entries 7–8), solvent (1 ml), 20 °C, 12 h. [a]Conversions and yields, based on 1–hexene, were determined by GC analysis *vs.* an internal standard. [b]Reaction was performed in the recovered IL phase from entry 3. [c]Reaction was performed in the recovered IL phase from entry 4.

In almost all cases the reaction proceeds smoothly with quantitative formation of the alkylated products. Moreover it was possible to recycle the IL containing the metal catalyst for at least two recycle runs, with no appreciable loss in alkene conversion and alkylbenzene yield.

More recently Song *et al.* studied the metal triflate catalysed alkenylation of arenes in ILs, with particular interest on the regio– and stereoselective control. [131,132] The reaction was performed with terminal and internal alkynes with excellent results; moreover, it was performed on aryl phenylpropiolates giving intramolecular Friedel–Crafts alkylation with good results. Optimised reaction conditions are summarised in Scheme 4.2.

Results for the Friedel–Crafts alkenylation of arenes with internal alkynes are summarised in Table 4.3.



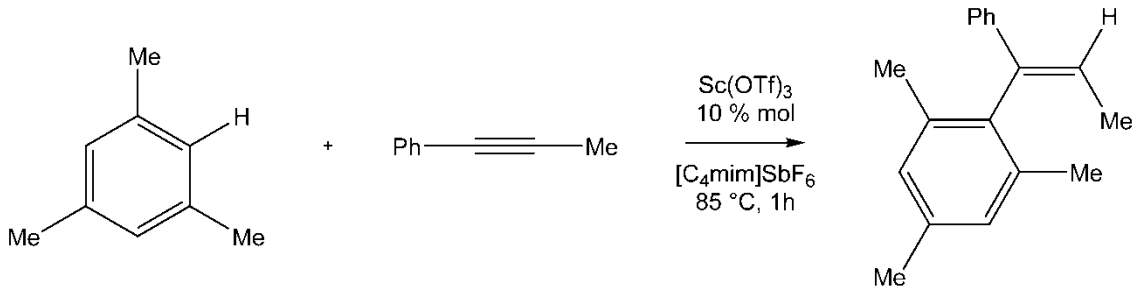
Scheme 4.2. Metal triflates catalysed Friedel–Crafts alkenylation of arenes in $[C_4mim]SbF_6$. [132]

Table 4.3. Metal triflate catalysed Friedel–Crafts alkenylation of arenes with internal alkynes in $[C_4mim]SbF_6$. [132]

Entry	ArH	R^1	R^2	Catalyst	t (h)	Yield	*E/Z*
1	benzene	Ph	Me	$Sc(OTf)_3$	4	91	–
2	benzene	Ph	Ph	$Sc(OTf)_3$	2	79	–
3	benzene	Ph	Ph	$In(OTf)_3$	2	82	–
4	benzene	Ph	Ph	$Hf(OTf)_3$	1	92	–
5	benzene	Ph	CO_2Et	$Hf(OTf)_3$	22	89	–
6	*p*–xylene	Ph	Me	$Sc(OTf)_3$	4	96	4/96
7	*p*–xylene	Ph	Ph	$Sc(OTf)_3$	4	80	12/88
8	*p*–xylene	Ph	CO_2Et	$Hf(OTf)_3$	10	70	13/87
9	mesitylene	Ph	Me	$Hf(OTf)_3$	1	92	1/99
10	mesitylene	Ph	Ph	$Hf(OTf)_3$	1.5	90	1/99
11	mesitylene	Ph	CO_2Et	$Hf(OTf)_3$	0.5	72	1/99
12	mesitylene	Ph	CO_2Et	$Hf(OTf)_3$	13	72	1/99
13	pentamethylbenzene	Ph	Me	$Hf(OTf)_3$	0.25	81	1/99
14	pentamethylbenzene	Ph	Ph	$Hf(OTf)_3$	1	77	1/99
15	pentamethylbenzene	Ph	CO_2Et	$Hf(OTf)_3$	12	67	1/99
16	pentamethylbenzene	Ph	CO_2Et	$Hf(OTf)_3$	29	70	10/90
17	naphthalene	Ph	Me	$Hf(OTf)_3$	0.17	92	n.d.
18	chlorobenzene	Ph	Me	$In(OTf)_3$	1	38	n.d.
19	chlorobenzene	Ph	Ph	$Sc(OTf)_3$	6	44	n.d.

Unless otherwise stated, all reactions were carried out using alkyne (1mmol), arene (6 ml) and $[C_4mim]SbF_6$ (1 ml), in presence of 10 % mol of metal catalyst at 85 °C. [b]Isolated yield based on the alkyne. [c]*E/Z* ratios were determined by ^1H NMR spectrometry. [d]1 equiv. of solid arene based on alkyne (1 mmol) and 4 ml of 1,2–dichloroethane as co–solvent were used. [e]The reaction gave an inseparable mixture of 1–naphthyl (major isomer) and 2–naphthyl (minor) regioisomers, including the corresponding *E/Z* isomers. The isomer ratio determined by GC–MS analysis was 75:19:4:1 (entry 17). [f]The reaction gave an inseparable mixture of *ortho* and *para* isomers, including the corresponding *E/Z* isomers. The isomer ratio determined by GC–MS analysis were 11:15:31:39 (entry 18) ansd 8:18:34:40 (entry 19).

$[C_4mim]SbF_6$ proved to be an excellent media for this type of reaction, with efficient retention of the catalyst in the IL phase. Reaction conditions and results of the recycling experiments are summarised in Scheme 4.3 and Table 4.4 respectively.



Scheme 4.3. Catalytic phase recycling experiments, by Friedel–Crafts alkenylation of mesitylene with 1–phenyl–1–propyne in $[C_4mim]SbF_6$. [132]

Table 4.4. Catalytic phase recycling experiments, by Friedel–Crafts alkenylation of mesitylene with 1–phenyl–1–propyne in $[C_4mim]SbF_6$. [132]

Run	1	2	3	4	5	6	7	8
Yield (%)	91	90	92	90	90	94	93	90

Reaction conditions: 1–phenyl–1–propyne (1 mmol) in mesitylene (6 ml), $Sc(OTf)_3$(0.10 mmol) and $[C_4mim]SbF_6$ (1 ml) under inert atmosphere (Ar) at 85 °C, 1 h.

The recovery of the IL phase was straightforward: at the end of the reaction time the mixture was cooled at -40 °C, to allow solidification of the IL. The mesitylene/product mixture was isolated by decantation and the IL phase used without further purification. This recycle protocol can be performed several times without any appreciable loss of activity and isolated yield of the alkenylated product.

4.1.2. Friedel–Crafts alkylation of ferrocene

When it comes to ferrocene, Friedel–Crafts alkylation would surely be a useful synthetic tool for the synthesis of alkylferrocenes. In practice, this reaction is not used, but rather ferrocene is alkylated by multistep processes. Friedel–Crafts alkylation of ferrocene is not performed because oxidation of the FcH is an unavoidable problem in the required reaction conditions, moreover the alkylferrocene formed has a lower reduction potential with respect to ferrocene and undergoes easily oxidation/protonation. [133,134] Migration of the alkyl group bound to the FcH moiety is also frequently observed, leading to the formation of several alkylferrocene isomers. [135]

4.1.3. Friedel–Crafts acylation in ILs

Friedel–Crafts acylation is much more exploited than its alkylating counterpart for the functionalisation of aromatic compounds. Moreover, it is a convenient way to obtain diaryl or alkyl–aryl ketones, which cannot be easily synthesised by other methods. [136]

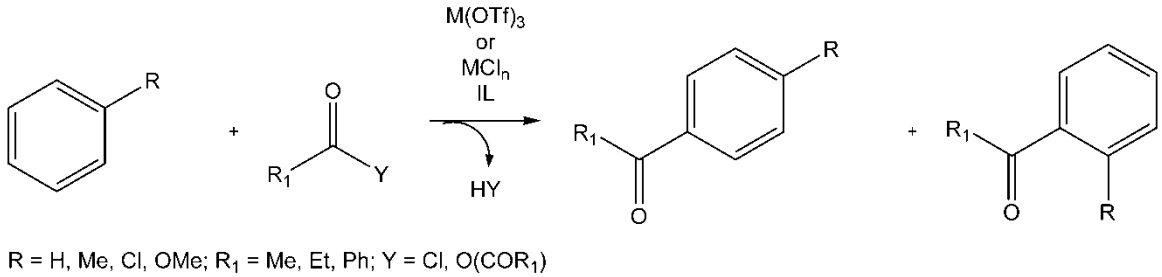
The main advantage of acylation *vs.* alkylation is the much lower reactivity, toward acylation, of the resulting ketone in comparison with that of the starting material, therefore a cleaner reaction outcome is expected. As in the previous case, reactions are generally performed between an arene and an acylating agent (aryl halide or the corresponding anhydride) in presence of stoichiometric amounts of a Lewis acid catalyst, such as $AlCl_3$, $FeCl_3$, $ZnCl_2$, HF or H_3PO_4. The stoichiometric quantity is necessary because the Lewis acid remains complexed to the ketone formed, requiring an hydrolysis step to isolate the product. [136,137]

These reactions were also performed in ILs, mainly in chloroaluminates, which have the advantage of being simultaneously the reaction catalyst and the solvent. [126] Issues on the sustainability and handling of such ILs, as well as their extreme sensitivity toward water and moisture have already been raised in Chapter 1. Pyridinium based second generation ILs were also successfully employed, this time with the advantage of handling an air and moisture stable solvent. [126,138]

In search of a more sustainable reaction protocol, scandium and lanthanides triflates were also effectively used in these reactions, making it possible to utilize catalytic amounts of the Lewis acid. [128,129,139]

Metal triflate (and other metal Lewis acids) catalysed Friedel–Crafts acylation reactions were also performed in second generation ILs. [140]

Results for the Friedel–Crafts acylation of anisole (Scheme 4.4) are summarised in Table 4.5.



Scheme 4.4. Metal catalysed Friedel–Crafts acylation in ILs.

Table 4.5. Metal catalysed Friedel–Crafts acylation of anisole in ILs.

Entry	Acylating agent	Solvent	Catalyst	Catalyst load (% mol)	T (°C)	t (h)	Conversion (%)	Yield (%)	*o*:*p*
1[a]	PhCOCl	$[C_4mim]BF_4$	$Cu(OTf)_2$	10	80	1	100	82	4:96
2[a]	PhCOCl	MeCN	$Cu(OTf)_2$	10	80	1	64	–	7:93
3[a]	PhCOCl	$ClCH_2CH_2Cl$	$Cu(OTf)_2$	10	80	1	73	–	7:93
4[a]	PhCOCl	$[C_4mim]BF_4$	$Sc(OTf)_3$	10	80	1	10	–	16:84
5[a]	PhCOCl	MeCN	$Sc(OTf)_3$	10	80	1	53	–	9:91
6[a]	PhCOCl	$ClCH_2CH_2Cl$	$Sc(OTf)_3$	10	80	1	57	–	5:95
7[a]	$(PhCO)_2O$	$[C_4mim]BF_4$	$Cu(OTf)_2$	10	80	12	–	46	6:94
8[b]	PhCOCl	$[C_2mim]Tf_2N$	$Bi(OTf)_3$	10	80	3	100	–	6:94
9[c]	PhCOCl	$[C_2mim]Tf_2N$	$ZnCl_2$	10	110	18	–	80	–
10[c]	$(PhCO)_2O$	$[C_4mim]Tf_2N$	$In(OTf)_3$	5	60	18	–	88	–
11[c]	$(PhCO)_2O$	$[C_4mim]Tf_2N$	$Hf(OTf)_3$	5	60	18	–	91	–
12[d]	PhCOCl	$InCl_3$–[C4mim]Cl	$InCl_3$	12.5	100	18	–	94	6:94
13[d]	$(PhCO)_2O$	$InCl_3$–[C4mim]Cl	$InCl_3$	5	80	48	–	97	2:98
14[d]	$(PhCO)_2O$	$[C_4mim]Tf_2N$	$InCl_3$	10	80	2	–	70	–
15[d]	$(PhCO)_2O$	$ClCH_2CH_2Cl$	$InCl_3$	10	80	2	50	–	–
16[e]	$(PhCO)_2O$	$[C_4mim]Tf_2N$	$In(OTf)_3$	20	80	2.3	85	–	–
17[e]	$(PhCO)_2O$	$[C_4mim]Tf_2N$	$Al(OTf)_3$	20	80	2.3	83	–	–
18[e]	$(PhCO)_2O$	$[C_4mim]Tf_2N$	$Sc(OTf)_3$	20	80	2.3	75	–	–
19[e]	$(PhCO)_2O$	$[C_4mim]Tf_2N$	$Y(OTf)_3$	20	80	2.3	45	–	–
20[e]	$(PhCO)_2O$	$[C_4mim]Tf_2N$	$Yb(OTf)_3$	20	80	2.3	25	–	–
21[e]	$(PhCO)_2O$	$[C_4mim]Tf_2N$	$Sm(OTf)_3$	20	80	2.3	18	–	–
22[a]	Ac_2O	$[C_4mim]BF_4$	$Cu(OTf)_2$	10	80	12	–	48	0:100
23[d]	Ac_2O	$InCl_3$–[C4mim]Cl	$InCl_3$	5	80	48	–	89	–
24[f]	Ac_2O	$[C_4mpyr]Tf_2N$[g]	$In(OTf)_3$	5	60	5	–	45	–
25[f]	Ac_2O	$[C_4mpyr]Tf_2N$[h]	$In(OTf)_3$	5	60	5	–	49	–
26[a]	$(EtCO)_2O$	$[C_4mim]BF_4$	$Cu(OTf)_2$	10	80	12	–	55	0:100

[a]Ref. [141]. [b]Ref. [142]. [c]Ref. [143]. [d]Ref. [144]. [e]Ref. [137]. [f]Ref. [145]. [g]$[C_4mpyr]Tf_2N$ = *N*–butyl–*N*–methylpyrrolidinium bistriflylimide. [h]Biphasic: 30 MPa $scCO_2$ for 5 h, followed by extraction for 16 h at flow rate of 100 $g{\cdot}h^{-1}$.

Different metal catalyst were tested in several ILs. When available, data obtained in molecular solvents were included for comparison. In all cases, reaction performed in

ILs lead to yields of acylated product from moderate to good, with a good control of the regiochemistry (*p*– substituted product is favoured in most cases, if not the only product). Chloroindate melts, [144] which resemble more a first generation IL, were also used with good results in terms of yield and selectivity. (Entries 12, 13 and 23, Table 4.5) This type of IL has the advantage of being more stable towards water and moisture when compared to the analogous chloroaluminates, moreover the Lewis acid catalyst trapped in the IL phase can be used in catalytic quantities. Occasionally, the use of IL media was paired up with $scCO_2$ (Entry 25, Table 4.5) for efficient extraction of the products. [145]

In most cases, recycle of the IL phase containing the Lewis acid catalyst was possible, product recovery and IL isolation methods varied.

The different methods were extended also to selected aromatic substrates, as reported in Table 4.6.

Table 4.6. Friedel–Crafts acylation in ILs.

Entry	Acylating agent	Solvent	Catalyst	Catalyst load (% mol)	T (°C)	t (h)	Conversion (%)	Yield (%)	*o:m:p*
				Benzene					
1[a]	PhCOCl	$[C_2mim]Tf_2N$	Bi_2O_3	5	150	24	15	–	–
2[a]	PhCOCl	$[C_2mim]Tf_2N$	$Bi(OTf)_3$	5	150	24	70	–	–
3[b]	PhCOCl	$InCl_3$–[C_4mim]Cl	$InCl_3$	5	80	48	–	81	–
4[b]	$(PhCO)_2O$	$InCl_3$–[C_4mim]Cl	$InCl_3$	5	80	48	–	22	–
5[c]	EtCOCl	$[C_2mim]Cl$	$AlCl_3$	–	25	0.5	–	98	–
				Toluene					
6[a]	PhCOCl	$[C_2mim]Tf_2N$	Bi_2O_3	5	150	4	75	–	12:9:79
7[a]	PhCOCl	$[C_2mim]PF_6$	Bi_2O_3	5	150	4	68	–	12:9:79
8[a]	PhCOCl	$[C_4mim]Tf_2N$	Bi_2O_3	5	150	4	98	–	12:9:79
9[a]	PhCOCl	$[C_4mim]PF_6$	Bi_2O_3	5	150	4	60	–	12:9:79
10[a]	PhCOCl	$[C_4mim]BF_4$	Bi_2O_3	5	150	4	<5	–	12:9:79
11[d]	PhCOCl	$[C_4mim]Tf_2N$	$SnCl_4$	1	110	2	–	97	–
12[b]	PhCOCl	$InCl_3$–[C_4mim]Cl	$InCl_3$	12.5	110	18	–	93	15:3:82
13[b]	$(PhCO)_2O$	$InCl_3$–[C_4mim]Cl	$InCl_3$	5	110	48	–	86	16:3:81
14[b]	Ac_2O	$InCl_3$–[C_4mim]Cl	$InCl_3$	5	110	48	–	2	14:5:81
15[c]	AcCl	$[C_2mim]Cl$	$AlCl_3$	–	25	1.5	–	92	–
				Chlorobenzene					
16[a]	PhCOCl	$[C_2mim]Tf_2N$	Bi_2O_3	5	150	24	<5	–	–
17[a]	PhCOCl	$[C_2mim]Tf_2N$	$Bi(OTf)_3$	5	150	24	100	91	–
18[a]	PhCOCl	$[C_4mim]Tf_2N$	$InCl_3$	5	130	96	–	87	
19[b]	PhCOCl	$InCl_3$–[C_4mim]Cl	$InCl_3$	5	120	96	–	75	11:2:87

[a]Ref. [142]. [b]Ref. [144]. [c]Ref. [146]. [d]Ref [143].

In all cases, the nature of the metal Lewis acid catalyst, along with the IL used as the solvent, affects greatly the reaction outcome.

Reaction times, temperatures, conversions and selectivities were improved when using ILs instead of molecular solvents. Recycling of the IL phase is possible in most cases.

4.1.4. Friedel–Crafts acylation of ferrocene

Friedel–Crafts acylation is surely a more versatile reaction to be used for the functionalisation of FcH. In general, the reaction proceeds under relatively mild

conditions with both acyl halides and anhydrides and affords excellent yields of mono– and diacylferrocenes. These, in turn, are useful intermediates for the preparation of less accessible derivatives, see example of synthesised derivatives starting for acetylferrocene in Figure 4.1.

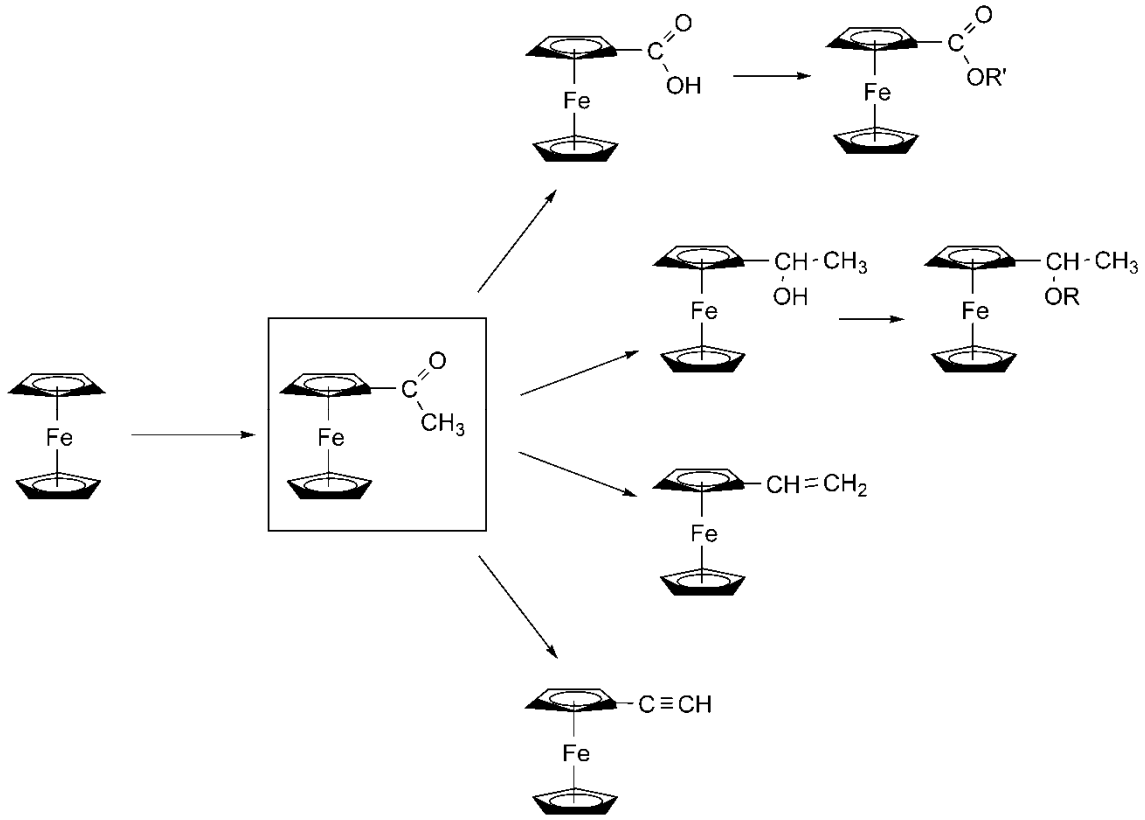


Figure 4.1. Synthetically useful ferrocene derivatives synthesized from acetylferrocene.

In molecular solvents, the reaction is usually carried out at r.t. or 0 °C in solvents like dichloromethane, chloroform of carbon disulfide in presence of a stoichiometric amount of Lewis acid ($AlCl_3$, $SnCl_4$, BF_3, H_3PO_4, HF). Reaction progress is evidenced by the formation of a dark red or purple solution, characteristic of the acylferrocene–Lewis acid complex. [147]

Ferrocene is an excellent aromatic substrate for Friedel–Crafts acylation, being ca. 10^6 more reactive than benzene in such reactions (Table 4.7). [147,148]

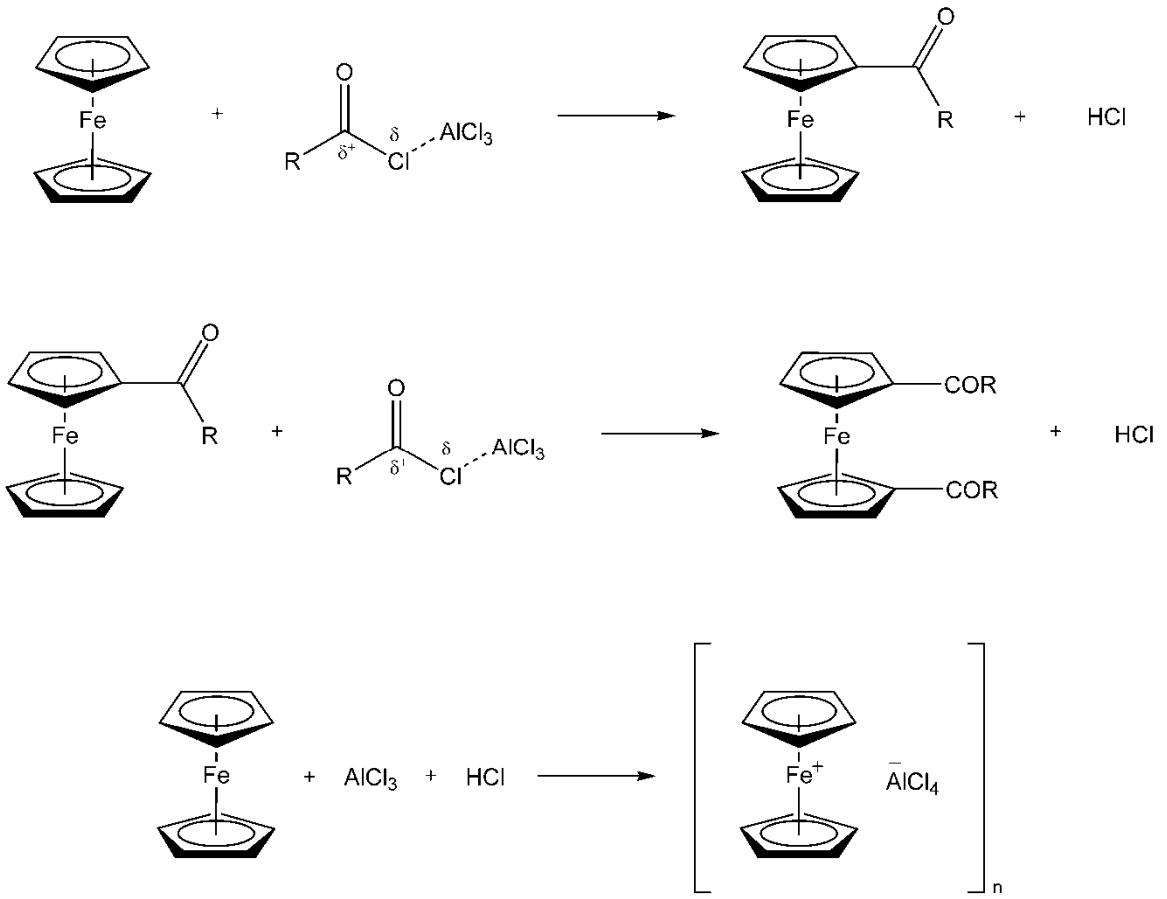
Table 4.7. Relative rates Friedel–Crafts acetylation of aromatic compounds. [147,148]

Aromatic compound	Relative rate
benzene	1.0
acetylferrocene	$1.9 \cdot 10^2$
mesitylene	$2.9 \cdot 10^3$
pentamethylbenzene	$1.3 \cdot 10^4$
ferrocene	$3.3 \cdot 10^6$

In CH_2Cl_2 at 0 °C.

It is worth to note that also the unsubstituted ring of acetylferrocene retains a reactivity considerably greater than that of benzene, even if deactivated by the acyl/acyl–Lewis acid complex.

Friedel–Crafts acylation is to be preferred also in terms of reaction outcome: generally the main (if not the only) product of such reactions is the monoacyl derivative. This is ascribed to the deactivating effect of the conjugated ketone moiety. With ferrocene, however, formation of the corresponding 1,1'–diacylderivate is also observed when the reaction is performed in presence of an excess of Lewis acid. The explanation for this anomalous change in the relative reactivities of FcH and its monoacyl derivatives lies in the fact that FcH is protonated by HCl in presence of an excess of $AlCl_3$ (Scheme 4.5). A similar behaviour was observed in $BF_3 \cdot H_2O$ and H_2SO_4 solutions. [147]



Scheme 4.5. Mono– *vs.* diacylation of FcH in Friedel–Crafts acylations with excess $AlCl_3$. [147]

As it can be seen in Scheme 4.5, the cation resulting from HCl protonation is inert toward acylation, and, by this reactivity pattern, removed from competition with the monoacyl derivative.

Friedel–Crafts acylation of FcH has also been studied in ILs, with both first and second generation ILs, using stochiometric or catalytic amounts of Lewis acids. Related results are summarised in Table 4.8.

Table 4.8. Friedel–Crafts acylation of FcH in ILs. [127]

Entry	Acylating agent	Solvent	Catalyst	Catalyst load (% mol)	T (°C)	t (h)	Conversion (%)	Yield (%)	1:1,1'
1[a]	PhCOCl	$AlCl_3$–[C_2mim]I	$AlCl_3$	200	0	2	95	83	86:14
2[b]	PhCOCl	[C_4py]BF_4	Yb(OTf)$_3$	10	50	8	–	72	100:0
3[a]	AcCl	$AlCl_3$–[C_2mim]I	$AlCl_3$	200	0	2	52	18	35:65
5[b]	AcCl	[C_4py]BF_4	Yb(OTf)$_3$	10	r.t.	6	–	94	100:0
6[a]	Ac_2O	$AlCl_3$–[C_2mim]I	$AlCl_3$	200	0	2	56	16	29:71
7[b]	Ac_2O	[C_4py]BF_4	Yb(OTf)$_3$	10	r.t.	6	–	97	100:0

[a]Ref. [149]. [b]Ref. [150].

As it can be seen from the data collected in Table 4.8, the reaction works well in most cases with good yields of acylated product and, in some cases, excellent selectivities towards monoacylation. Recycling of the IL phase containing the catalyst was also possible for *N*–alkypyridinium based ILs. [138]

Table 4.9. $Yb(OTf)_3$ catalysed Friedel–Crafts acylation of FcH in $[C_4py]BF_4$, recycling of the IL phase attempts. [138]

Entry	Acylating agent	Catalyst load (% mol)	T (°C)	t (h)	Yield (%)[a]
1[b]	Ac_2O	10	r.t.	6	91
2[b]	Ac_2O	10	r.t.	6	89
3[b]	Ac_2O	10	r.t.	6	89
4[b]	Ac_2O	10	r.t.	6	88
5[b]	Ac_2O	10	r.t.	6	88
6	EtCOCl	10	r.t.	6	84
7	PhCH=CHCOCl	10	50	12	85

[a]Isolated yield based on ferrocene. [b]Consecutive recycles of the same IL phase.

Up to 5 consecutive recycle runs with the same IL phase were possible using this system (Entries 1–5, Table 4.9). Also recycling of the IL phase charging a different acylating agent in the 2nd run was possible, with good isolated yields of the monoacylated product (Entries 6 and 7, Table 4.9).

4.2. Scope of the work

In this section, metal triflates catalysed FcH alkylations and acylation were performed in alkylmethylimidazolium based ILs. The reaction parameters were optimised (when possible) in order to maximise the formation of monosubstituted species.

For the acylation reactions, recycle of the IL phase was attempted and a comparison between conventional and MW heating was performed.

4.3. Experimental section

4.3.1. Instruments, materials and methods

Solvents and reagents were purchased from commercial sources. Acetonitrile was purchased from Riedel–de–Haën and Fluka, dichloromethane from Fluka, diethyl ether from Riedel–de–Haën, THF from Carlo Erba, petroleum ether 40–70 °C from Riedel–de–Haën, $NaHCO_3$ from Carlo Erba and Na_2CO_3 from Riedel–de–Haën. Ferrocene was purchased from Fluka and used as received. Anisole was purchased from Sigma Aldrich and used as received. Cyclohexene and *tert*–butyl acetate were purchased from Sigma Aldrich and used as received. Acetic anhydride was purchased from Carlo Erba, propanoic and trifluoroacetic anhydride from Sigma Aldrich, benzoic anhydride from Fluka, and they were all used as received.

Scandium, yttrium and ytterbium triflate were purchased from Fluka (scandium triflate), Fluka and Sigma Aldrich (yttrium and ytterbium triflate), and used without further purification.

ILs were synthesized according to general methods, preparing bromides first and then exchanging the anion with the appropriate salt ($LiTf_2N$, KCF_3SO_3, and KPF_6). Details on the synthesis and characterisations of the synthesised ILs are reported in Chapter 1. [C_4mim]TfO and [C_6mim]Tf_2N were available from previous synthesis, thus used without further purification.

Mass spectra were recorded with a GC–MS Shimadzu CP 6000 instrument. GC analyses were performed with a Varian CP 3900, equipped with a Supelco SPB–1701 capillary column (30 m length, 0.25 mm internal diameter, 0.25 mm film thickness). GC quantitative analysis were performed using an external standard (tetradecane).

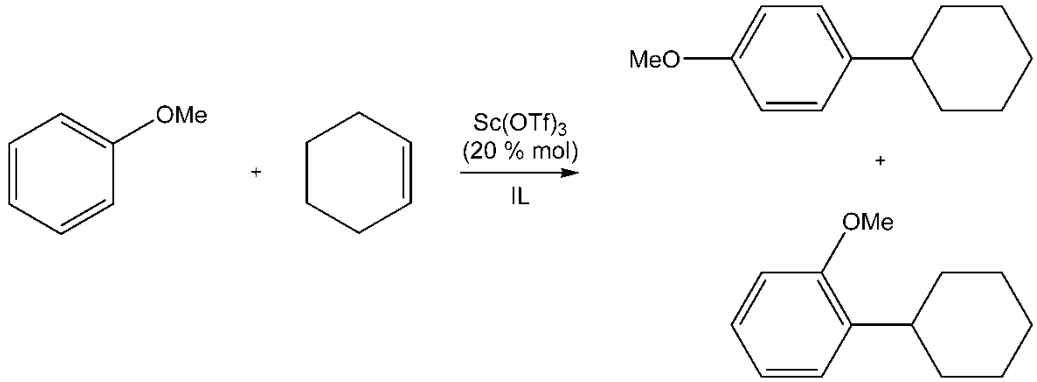
Microwave experiments were performed with a CEM Discovery instrument, which operated in monomode at a 2.45 GHz frequency, with continuous irradiation power.

Purity and identity of products was checked by GC–MS and ^1H NMR analyses and by comparison with authentic samples.

4.3.2. Friedel–Crafts alkylation

4.3.2.1. Friedel–Crafts alkylation of anisole with cyclohexene

The reaction (Scheme 4.6) was performed according to literature procedures. [130]



Scheme 4.6. Sc(III) catalysed Friedel–Crafts alkylation of anisole with cyclohexene. [130]

The reaction was performed in the very same literature conditions, or by varying the ratio anisole:cyclohexene and/or the IL used as the solvent.

In a typical experiment, 0.5 ml of $[C_4mim]PF_6$ were transferred in a 5 ml flask provided with a magnetic bar. 24.5 mg (50 μmol) of $Sc(OTf)_3$ were then added. 50 μl (0.49 mmol) of cyclohexene and the appropriate amount of anisole were then added to the solution, which was then kept under vigorous stirring at r.t.

Samples were collected at given times, extracted with diethyl ether and the organic phase analysed by GC.

Results are summarized in Table 4.10.

Table 4.10. Sc(III) catalysed Friedel–Crafts acylation of anisole in ILs.

Entry	Ratio A:C:cat	IL	T (°C)	t (h)	Products	Yield (%)
1[a]	18:1:0,1	$[C_4mim]SbF_6$	20	12	1–cyclohexyl–2–methoxybenzene 1–cycloheyl–4–methoxybenzene	85 *o*:*p* = 1.8:1
2	18:1:0,1	$[C_4mim]PF_6$	r.t.	48	1–cyclohexyl–2–methoxybenzene 1–cycloheyl–4–methoxybenzene	n. d.
3	1:1:0,2	$[C_4mim]PF_6$	r.t. 40	48 24	1–cyclohexyl–2–methoxybenzene 1–cycloheyl–4–methoxybenzene	95 *o*:*p* = 1:3.7
3	1:1:0,2	$[C_4mim]Tf_2N$	50	216	1–cyclohexyl–2–methoxybenzene 1–cycloheyl–4–methoxybenzene	n. d.
4[b]	1:1:0,2	$[C_4mim]PF_6$	r.t.	48	–	–

Yields were calculated by GC analysis *vs.* an internal standard. [a]Ref. [130]. [b]Recycle of IL from entry 2.

1–Cyclohexyl–2–methoxybenzene and 1–cyclohexyl–4–methoxybenzene were characterized by GC–MS analysis (Figures 4.2–4.4).

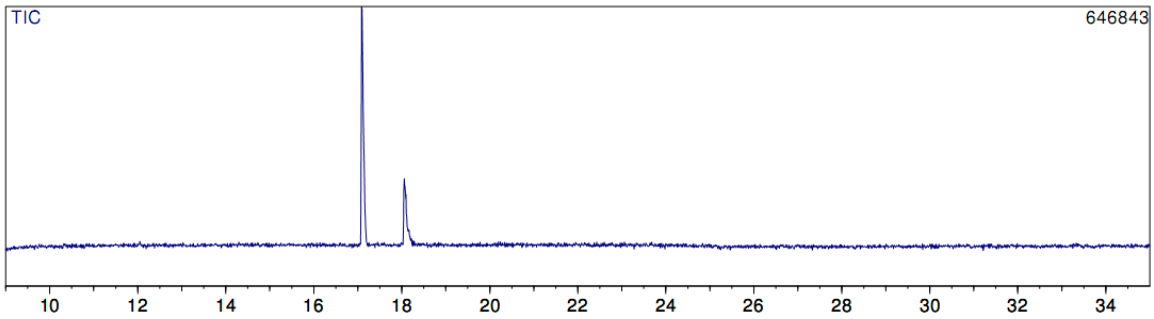


Figure 4.2. GC–MS analysis of the reaction mixture containing 1–cyclohexyl–4–methoxybenzene (t_r=17.0 min) and 1–cyclohexyl–2–methoxybenzene (t_r=18.0 min).

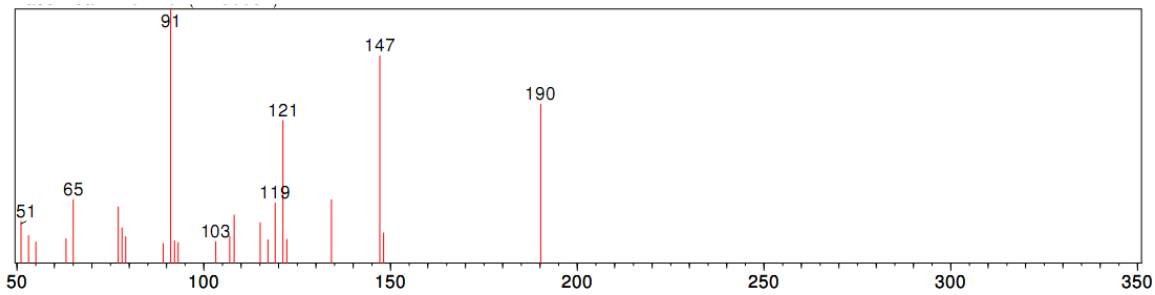


Figure 4.3. Mass spectrum of 1–cyclohexyl–4–methoxybenzene (t_r=17.0 min; molecular peak *m/z*=190).

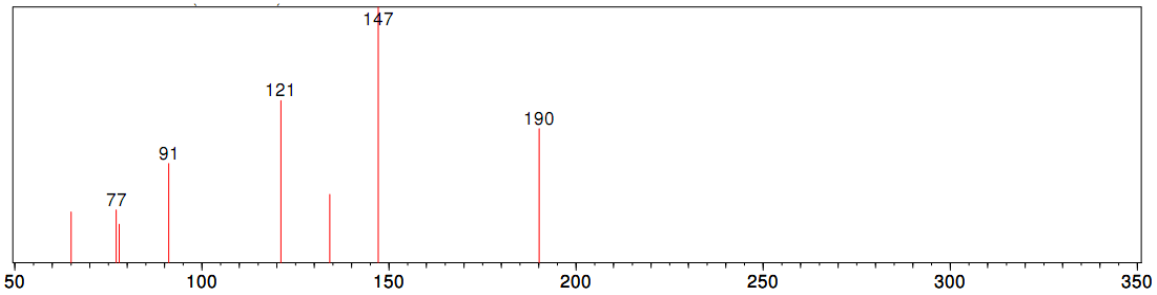
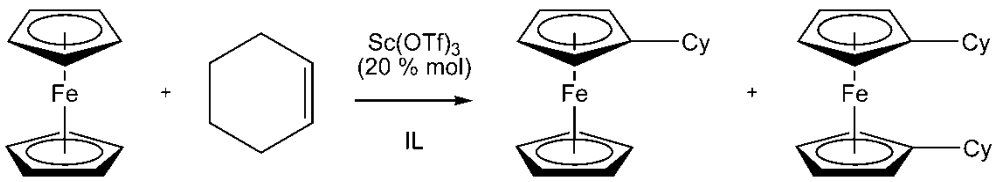


Figure 4.4. Mass spectrum of 1–cyclohexyl–2–methoxybenzene (t_r=18.0 min; molecular peak *m/z*=190).

4.3.2.2. Friedel–Crafts alkylation of ferrocene with cyclohexene



Scheme 4.7. Sc(III) catalysed Friedel–Crafts alkylation of FcH with cyclohexene.

In a typical experiment, 0.5 ml of the selected IL were transferred in a 5 ml flask, provided with a magnetic bar. 93.0 mg (0.50 mmol) of FcH were added and the mixture heated up to T=90°C (to ensure solubilisation of the FcH in the IL). The mixture was then allowed to cool down. Once cool, 24.6 mg (50 μmol) of $Sc(OTf)_3$ and 51 μl (0.50 mmol) of cyclohexene were added. The mixture was then kept under vigorous stirring at r.t.

Samples were collected at given times, extracted with diethyl ether and the organic phase analysed by GC–MS.

The reaction was repeated in several different conditions; results are summarised in Table 4.11.

Table 4.11. Sc(III) catalysed Friedel–Crafts alkylation of FcH with cyclohexene.

Entry	Ratio Fc:C:cat	IL or molecular solvent	T (°C)	t (h)	Products	Yield (%)
1	1:1:0.1	$[C_4mim]PF_6$	r.t.	168	CyFc 1,1'–Cy_2Fc	traces
2	1:1:0.1	$[C_4mim]Tf_2N$	r.t.	168	–	–
3	1:20:0.1	$[C_4mim]PF_6$	r.t.	168	–	–
4	1:1:0.1	$[C_4mim]Tf_2N$	r.t.	168	–	–
5	1:1:0.1	$[C_6mim]Tf_2N$	r.t. 50	48 48	–	–
6	1:1:0.1	$[C_4mim]PF_6$ + cosolvent	r.t.	72	–	–
7	1:1:0.1	CH_2Cl_2 (dried over $CaCl_2$)	r.t.	48	–	–
8	1:1:0.1	$[C_4mim]PF_6$	r.t. 50	48 48	–	–
9	1:1:0.1	$[C_4mim]PF_6$	r.t.	96	–	–
10	1:1:0.1	$[C_4mim]PF_6$	r.t.	96	–	–
11	1:1:0.1	$[C_4py]Tf_2N$	r.t.	48	–	–
12	1:1:0.1	$[C_4py]Tf_2N$	30	48	–	–

CyFc=cyclohexylferrocene; 1,1'–Cy_2Fc= 1,1'–(dicyclohexyl)ferrocene. Apart from Entry 1, no reaction occurred in all cases.

1–Cyclohexylferrocene and 1,1'–dicyclohexylferrocene were characterised by GC–MS (Figures 4.5–4.7).

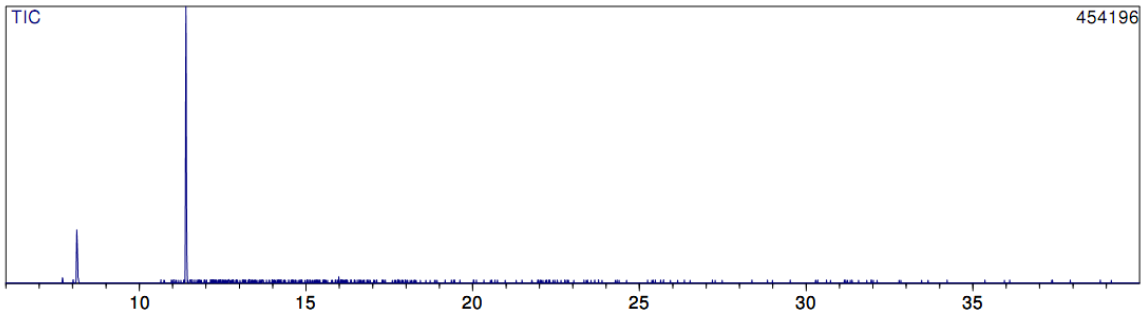


Figure 4.5. GC–MS analysis of the reaction mixture containing 1–cyclohexylferrocene (t_r=8.1 min) and 1,1'–dicyclohexylferrocene(t_r=11.4 min).

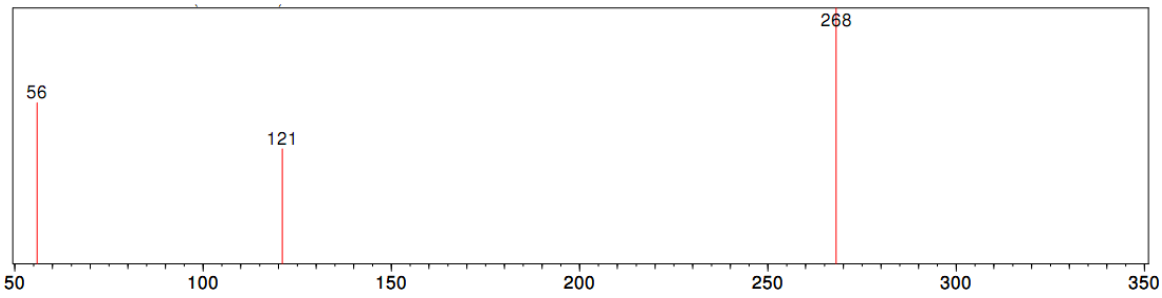


Figure 4.6. Mass spectrum of 1–cyclohexylferrocene (t_r=8.1 min; molecular peak *m/z*=268).

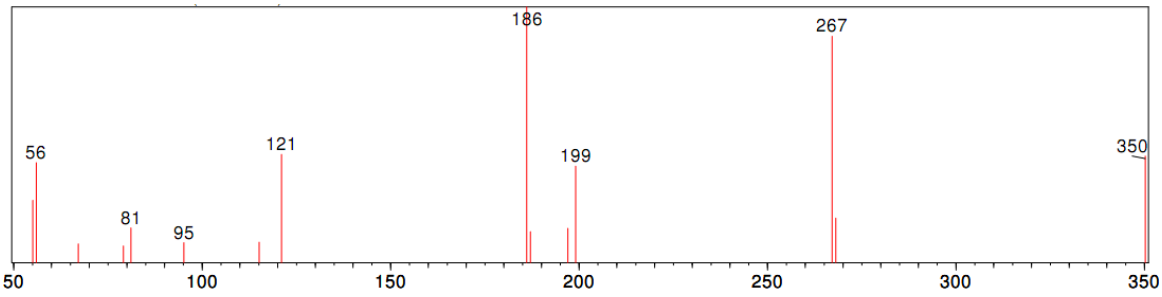
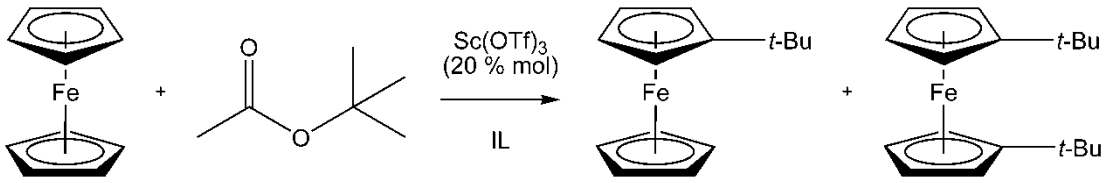


Figure 4.7. Mass spectrum of 1,1'–dicyclohexylferrocene (t_r=11.4 min; molecular peak *m/z*=350).

4.3.2.3. Friedel–Crafts alkylation of ferrocene with tert*–butyl acetate*



Scheme 4.8. Sc(III) catalysed Friedel–Crafts alkylation of FcH with *t*–butyl acetate.

In a typical experiment, 0.5 ml of the selected IL were transferred in a 5 ml flask, provided with a magnetic bar. 24.6 mg (50 μmol) of $Sc(OTf)_3$ were added to the solution. 93.0 mg (0.50 mmol) of FcH and an excess of *t*–butyl acetate (340 μl,

2.52 mmol) were added to the suspension. The mixture was then kept under vigorous stirring at r.t.

Samples were collected at given times, extracted with diethyl ether and the organic phase analysed by GC–MS.

The reaction was repeated in several different conditions; results are summarised in Table 4.12.

Table 4.12. Sc(III) catalysed Friedel–Crafts alkylation of FcH with cyclohexene.

Entry	Ratio FcH:C:cat	IL	T (°C)	t (h)	Product(s)	Yield (%)
1	1:5:0.1	$[C_4mim]PF_6$	50 60	2 24	1–*tert*–butylferrocene 1,1'–di(*tert*–butyl)ferrocene	–
2	1:5:0.1	$[C_4mim]Tf_2N$	60	240	mono–, di–, tri–, tetrasubstituted ferrocenes	–
3	1:1:0.1	$[C_4mim]Tf_2N$	50	168	mono–, di–, tri–, tetrasubstituted ferrocenes	–
4	1:1:0.1	$[C_4py]Tf_2N$	30 40	24 96	mono–, di–, tri–, tetrasubstituted ferrocenes	–

1–*tert*–butylferrocene and 1,1'–di(*tert*–butyl)ferrocene were characterised by GC–MS analysis (Figures 4.8–4.10).

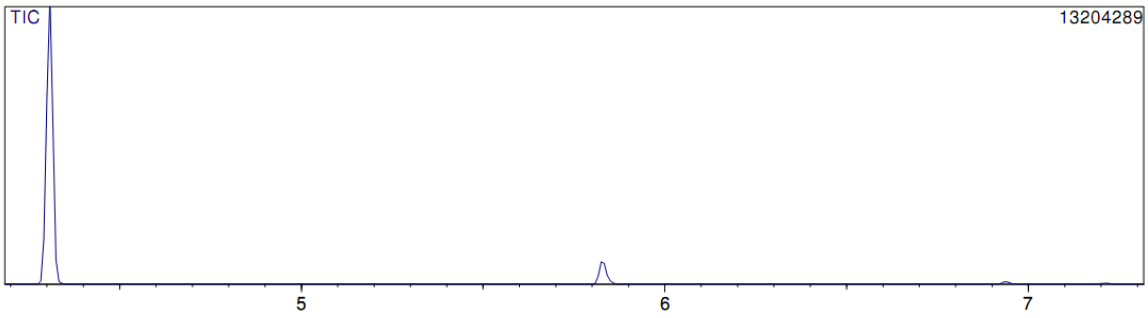


Figure 4.8. GC–MS analysis of the reaction mixture containing 1–*tert*–butylferrocene (t_r=5.8 min) and 1,1'–di(*tert*–butyl)ferrocene (t_r=6.9 min) (FcH is also present at t_r=4.2 min).

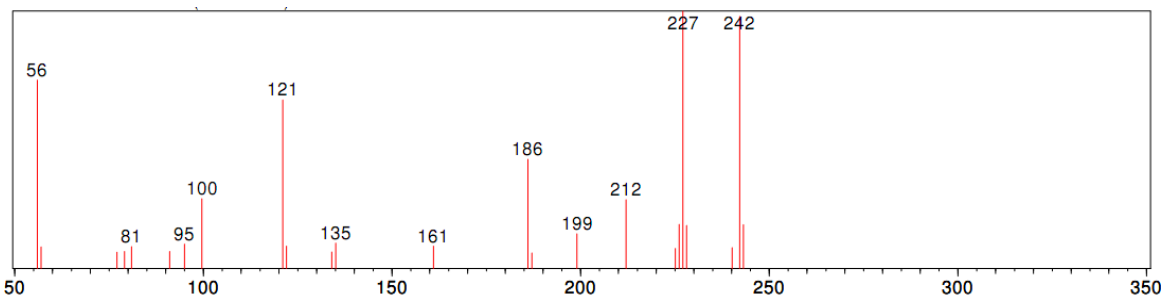


Figure 4.9. Mass spectrum of 1–*tert*–butylferrocene (t_r=5.8 min; molecular peak *m/z*=242).

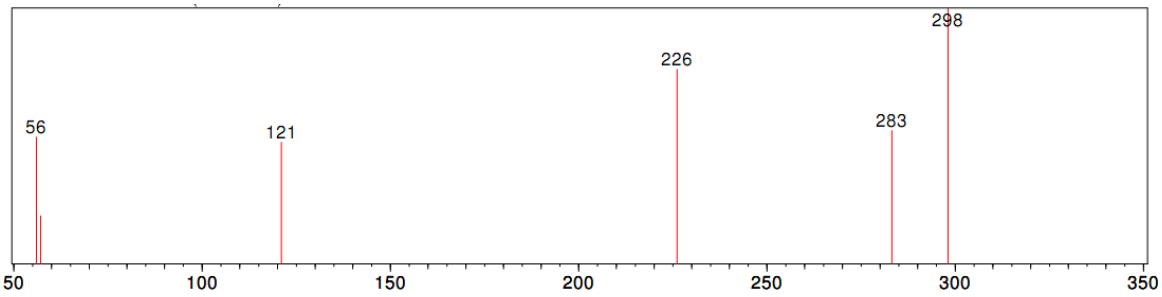
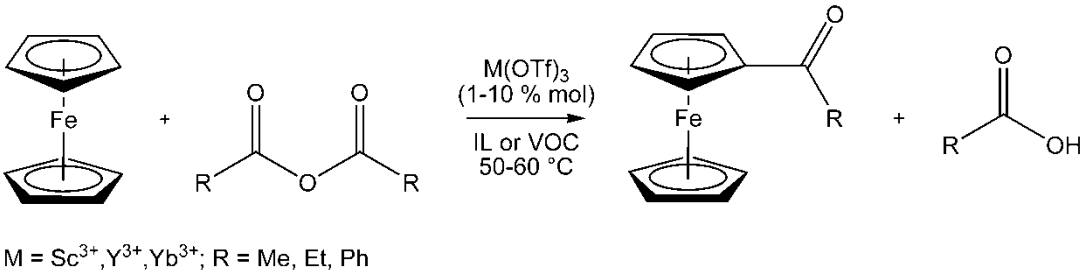


Figure 4.10. Mass spectrum of 1,1'–di(*tert*–butyl)ferrocene (t_r=6.9 min; molecular peak *m/z*=298).

4.3.3. Friedel–Crafts acylation of ferrocene

This reaction was performed with modifications of reported literature procedures. [141]



Scheme 4.9. General procedure for the scandium and lanthanide catalysed Friedel–Crafts acylation of FcH.

In a typical experiment, 1 mmol FcH was weighed in a round–bottomed 10 ml flask, added with known amounts of solvent (either molecular or ionic) and acylating reagent. The resulting mixture was heated in a thermostated oil bath and, finally, the weighed amount of catalyst was introduced. The reaction course was followed by TLC. In the workup, different procedures were followed. For reactions performed in molecular solvents, the solvent was removed under vacuum and the residue separated and purified by column chromatography. For reactions performed in ILs, solvent extraction or distillation was used. Alternatively, the reaction mixture was directly chromatographed on a silica gel column.

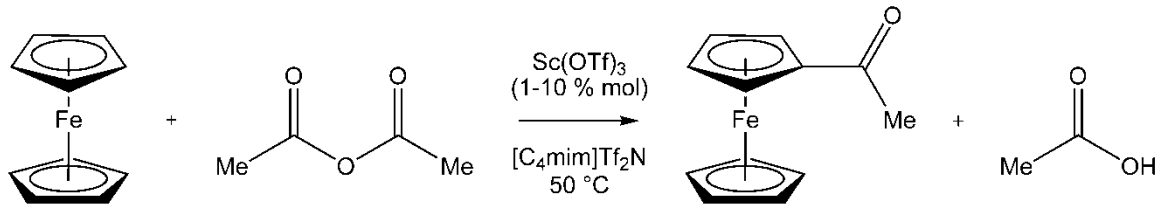
Extraction: the reaction mixture was repetitively extracted with Et_2O until colourless organic phase and acylferrocenes were purified by column chromatography (eluent: hexane or petroleum ether 40–70 °C/Et_2O 99:1 v/v).

Distillation: the reaction flask was introduced into a Kugelrohr distillation apparatus and distilled under reduced pressure. When volatile acids formed as by–products,

pure acylferrocenes were obtained. With less volatile acids, an extraction with aqueous $NaHCO_3$ or a column chromatography yielded pure acylferrocenes.

Purity and identity of products was checked by GC–MS and ^1H NMR analyses and by comparison with authentic samples.

4.3.3.1. Friedel–Crafts acylation of ferrocene with acetic anhydride



Scheme 4.10. Sc(III) catalysed Friedel–Crafts acylation of ferrocene with acetic anhydride.

Results for the acetylation of ferrocene under various different conditions are summarised in Table 4.13.

Table 4.13. Sc(III) catalysed Friedel–Crafts acylation of ferrocene with acetic anhydride at 50 °C.

Entry	Catalyst (% mol)	FcH (M)	t (h)	Ratio FcH:Ac_2O:$Sc(OTf)_3$	Conversion (%)[a]	Relative ratio FcH:FcAc[b]	Yield, (%)[c]
1	10	1.0	2.5	1:5:0.1	94	7:93	76
2	5	1.0	2.5	1:5:0.05	89	32:69	43
3	5	1.0	9.0	1:5:0.05	94	14:86	55
4	5	1.0	2.5 (60 °C)	1:5:0.05	100	0:100	60
5	1	1.0	2.5	1:5:0.01	32	90:10	20
6	1	1.0	29.5	1:2.5:0.01	95	83:17	37

[a]Calculated from recovered FcH. [b]GC analysis *vs.* an internal standard (tetradecane). [c]Isolated FcAc, yield relative to conversion.

Acetylferrocene was characterised by GC–MS analysis (Figures 4.11 and 4.12).

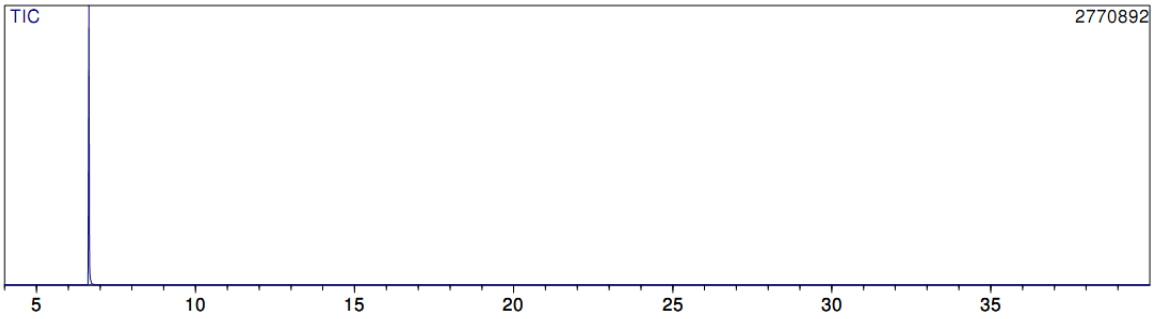


Figure 4.11. GC–MS analysis of a reaction mixture containing acetylferrocene (t_r=6.6 min).

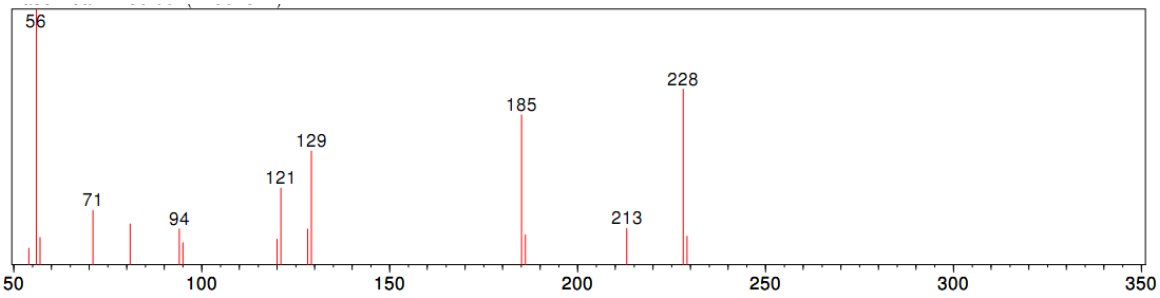
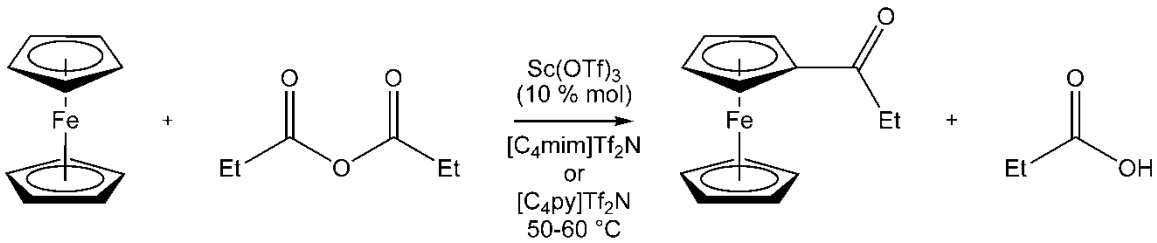


Figure 4.12. Mass spectrum of acetylferrocene (t_r=6.6 min; molecular peak *m/z*=228).

4.3.3.2.Friedel–Crafts acylation of ferrocene with propanoic anhydride



Scheme 4.11. Sc(III) catalysed Friedel–Crafts acylation of ferrocene with propanoic anhydride.

The reaction was performed with different reagent ratios and work up methods. Recycle of the IL phase containing the catalyst was also attempted. Results are summarized in Table 4.14.

Table 4.14. Sc(III) catalysed Friedel–Crafts acylation of ferrocene with propanoic anhydride.

Entry	IL	Ratio Fc:$(EtCO)_2O$:cat	t (h)	T (°C)	Workup method	Conversion (%)[a]	Yield (%)[b]
1	$[C_4mim]Tf_2N$	1:3:0.1	2.5	50	extraction	78	63
2	$[C_4mim]Tf_2N$	1:3:0.1	2	60	extraction	71	71
3	$[C_4mim]Tf_2N$	1:1:0.1	48	50	extraction	57	52
4	$[C_4mim]Tf_2N$	1:1:0.1	48	50	distillation	57	52
5[c]	$[C_4mim]Tf_2N$	1:1:0.1	96	50	distillation	38	6
6	$[C_4mim]Tf_2N$	1:2:0.1	17	60	extraction	98	72
7[d]	$[C_4mim]Tf_2N$	1:2:0.1	17	60	distillation	97	2.4
8	$[C_4py]Tf_2N$	1:2:0.1	56	50	extraction	78	31
9[e]	$[C_4py]Tf_2N$	1:2:0.1	56	50	distillation	83	36

[a]Calculated from recovered FcH. [b]Isolated FcCOEt, yield relative to conversion. [c]Recycle of entry 4. [d]Recycle of entry 6. [e]Recycle of entry 8.

Propanoylferrocene was characterised by GC–MS analysis (Figures 4.13 and 4.14).

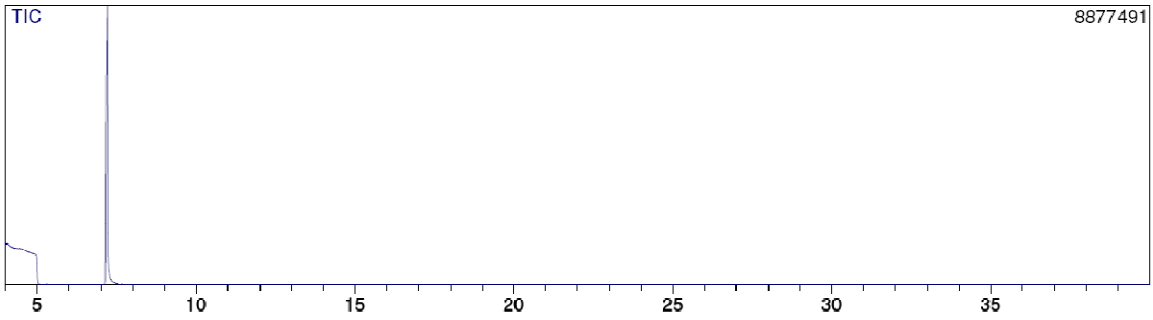


Figure 4.13. GC–MS analysis of a reaction mixture containing propanoylferrocene (t_r=7.2 min).

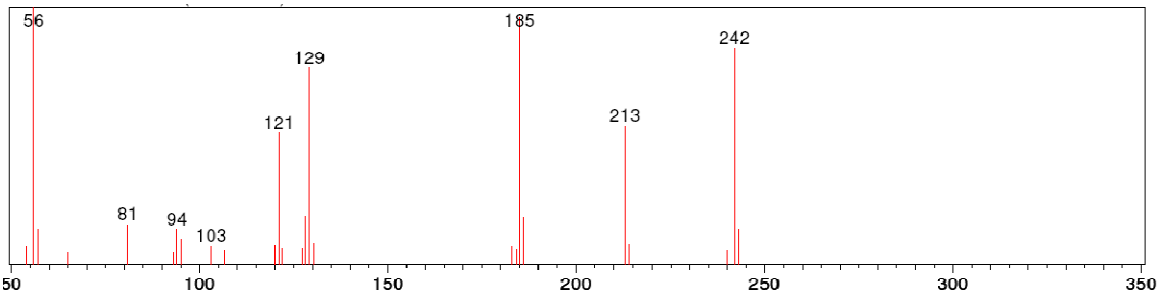


Figure 4.14. Mass spectrum of propanoylferrocene (t_r=7.2 min; molecular peak *m/z*=242).

4.3.3.3. Friedel–Crafts acylation of ferrocene with benzoic anhydride

Scheme 4.12. Sc(III) catalysed Friedel–Crafts acylation of ferrocene with benzoic anhydride.

Different reagent ratios and workup methods were undertaken. The obtained results are summarized in Table 4.15.

Table 4.15. Sc(III) catalysed Friedel–Crafts acylation of ferrocene with benzoic anhydride.

Entry	IL	Ratio FcH:AB:cat	t (h)	T (°C)	Workup method	Recovered FcH (%)	Isolated yield (%)
1	$[C_4mim]Tf_2N$	2:1:0.2	24	60	distillation	50	–
2	$[C_4mim]Tf_2N$	2:1:0.2	16	50	extraction	53	10
3	$[C_4mim]Tf_2N$	3:2:0.2	16	50	extraction	69	2

Benzoylferrocene was characterised by GC–MS analysis (Figures 4.15 and 4.16).

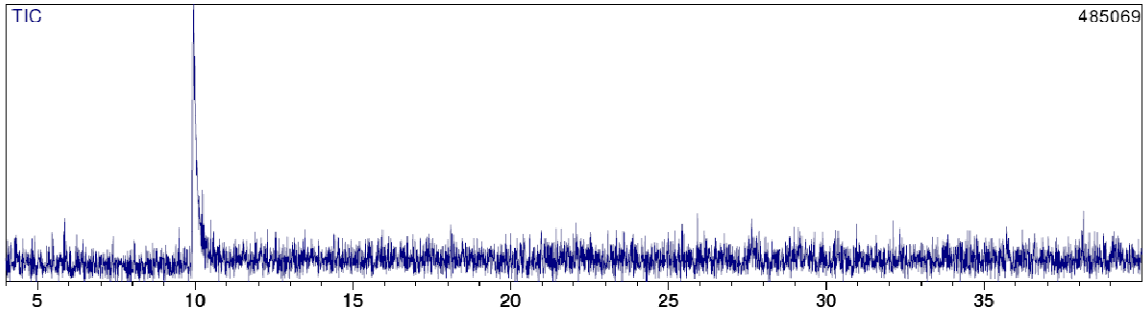


Figure 4.15. GC–MS analysis of the reaction mixture containing benzoylferrocene (t_r=9.9 min).

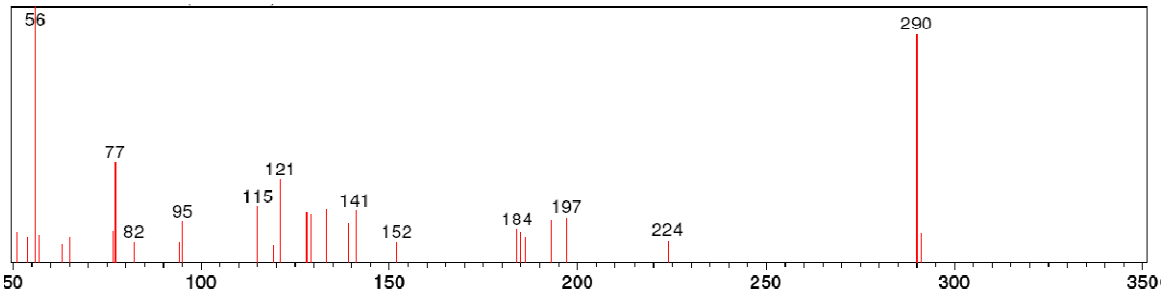
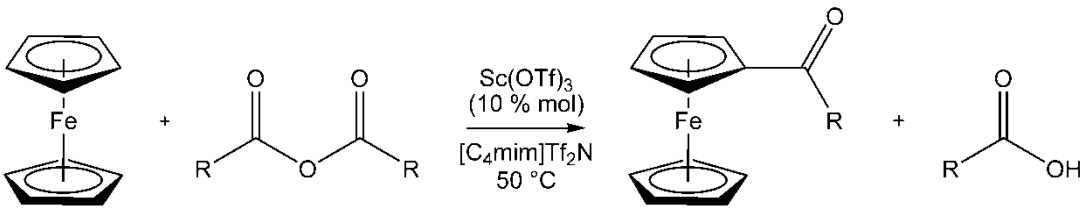


Figure 4.16. Mass spectrum of benzoylferrocene (t_r=9.9 min; molecular peak *m/z*=290).

4.3.3.4. Attempts of Friedel–Crafts acylation of ferrocene with functionalized anhydrides

The reaction was performed with different aliphatic and aromatic substituted anhydrides.



R = CF_3-, CH_2Cl-, 4-$(NO_2)C_6H_4$-, 3-$(NO_2)C_6H_4$-

Scheme 4.13. Sc(III) catalysed Friedel–Crafts acylation of ferrocene with substituted aliphatic and aromatic anhydrides.

Results are summarized in Table 4.16.

Table 4.16. Sc(III) catalysed Friedel–Crafts acylation of ferrocene with substituted aliphatic and aromatic anhydrides.

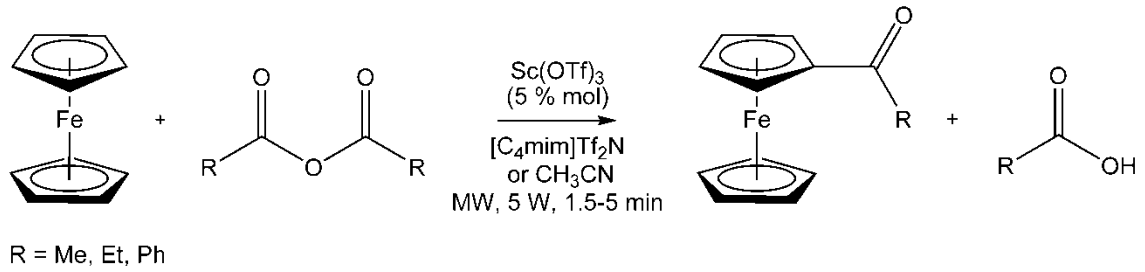
Entry	Anhydride	IL	Ratio FcH:A:cat	t (h)	T (°C)	Recovered FcH (%)	Acylferrocene yield (%)
1	trifluoroacetic anhydride	$[C_4mim]Tf_2N$	1.0:3.0:0.1	62	50	43	trifluoroacetylferrocene <1
2	trifluoroacetic anhydride	$[C_4mim]Tf_2N$ (added Na_2CO_3)	1.0:3.0:0.1	62	50	n. d.	–
3	chloroacetic anhydride	$[C_4mim]Tf_2N$	1.0:5.0:0.1	32	50	n.d.	–
4	*p*–nitrobenzoic anhydride	$[C_4mim]Tf_2N$	1.0:0.5:0.1	96	60	n.d.	–
5	*m*–nitrobenzoic anhydride	$[C_4mim]Tf_2N$	1.0:0.5:0.1	120	60	n.d.	–

No product was obtained, traces were observed only once.

4.3.3.5. MW assisted Friedel–Crafts acylation of ferrocene[*]

The same reaction was performed, with different aliphatic and aromatic anhydrides, under MW irradiation.

[*] In collaboration with Università degli Studi di Padova, Dipartimento di Scienze Chimiche.



Scheme 4.14. Sc(III) catalysed Friedel–Crafts acylation of ferrocene under MW irradiation.

In a typical experiment, FcH (1 mmol) was weighed in a vessel, added with known amounts of solvent, the acylating reagent (5 mmol) and, finally, the weighed amount of catalyst (0.05 mmol). The reaction vessel was placed in the single–mode cavity of the instrument and irradiated for the required time with power at 5 W (with IL) or 40 W (with acetonitrile) under simultaneous stirring and cooling by a stream of compressed air. The reaction was sampled by quantitative GC analysis after dilution in CH_2Cl_2 containing dodecane as internal standard. Blank experiments with ferrocene and Ac_2O in IL without $Sc(OTf)_3$ gave no product with both conventional and MW heating.

Different runs were performed, varying the initial concentration of ferrocene, the acetic anhydride excess, and the number of irradiation cycles.

The results obtained are summarised in Table 4.17.

Table 4.17. Sc(III) catalysed Friedel–Crafts acylation of FcH under MW irradiation,

Entry	Anhydride[b]	Ratio FcH:A:cat	T_{bulk} (°C)	t (min)	Conversion (%)[c]	Yield (%)[c]
1	Ac_2O	1:5:0.05	80	3.5	80	77
2[d]	Ac_2O	1:10:0.05	105–110	3.5	94	93
3[d,e]	Ac_2O	1:5:0.05	105–110	7.0	88	79
4[f]	Ac_2O	1:5:0.05	95	4.5	100	100
5	Ac_2O	1:5:0.05	115	1.5	100	100
6[g]	Ac_2O	1:5:0.05	72–74	2.0		30
7[g]	Ac_2O	1:5:0.05	65	5.0		38
8	$(EtCO)_2O$	1:5:0.05	116–120	4.5[h]	92	84[i]
9	$(EtCO)_2O$	1:5:0.05	92–96	2.0[j]	>99	86[k]
10	$(PhCO)_2O$	1:5:0.05	127–155	4.5	98	42

[a]1 mmol FcH in 1 mL IL, previously dried; MW irradiation at W = 5 W (10 W in entry 1, 40 W in entry 7), under stirring and simultaneous cooling with compressed air at 30–40 (or 40–50) psi. [b]Acylating reagent. [c]Conversion determined by GC analysis *vs.* an internal standard (dodecane). [d]0.5 mmol FcH. [e]Catalyst added in two portions. [f]0.25 mmol FcH. [g]In MeCN. [h]Three irradiation cycles, 1.5 min each. [i]After column chromatography, 72 % propanoylferrocene was isolated, together with 18 % disubstituted ketones. [j]Single irradiation cycle. [k]After column chromatography, 84 % propanoylferrocene was recovered, together with 13 % disubstituted ketones.

4.4. Discussion

4.4.1. Friedel–Crafts alkylation of ferrocene

The results obtained for the Friedel–Crafts alkylation of FcH were quite disappointing. Although the use of ILs as solvents for electrophilic processes generally enhances the selectivity of the reaction, [127] this was not the case in our reactions.

A mono–, di– and polylakylated ferrocenes mixture was present in most cases, regardless of the different carbocation generation pattern (cyclohexene *vs. t*–butyl acetate). The choice of IL seems to give a slight improvement to the reaction outcome: in the more viscous $[C_4mim]PF_6$ only mono– and dialkylated ferrocenes are formed, while in $[C_4mim]Tf_2N$ several different polyalkylated ferrocenes are observed. This can be regarded as a speculation, since in all cases these products are formed in trace amounts; probably the oxidation of the resulting alkylferrocenes needs to be taken into account and cannot be avoided also in IL media.

4.4.2. Friedel–Crafts acylation of ferrocene

Results improved significantly switching from Friedel–Cratfs alkylation to Friedel–Crafts acylation. Reaction conditions, such as the Lewis acid used, the IL choice, catalyst load and reaction temperature were optimised for the Friedel–Crafts acylation of ferrocene with acetic anhydride. Optimised conditions were then transferred to the reaction with different aliphatic and aromatic anhydrides.

4.4.2.1. Effect of the solvent

At first, FcH acetylation were performed in molecular solvents, both with acetyl chloride (AcCl) and acetic anhydride (Ac_2O). 0.1 mmol $Sc(OTf)_3$ were used with 1 mmol FcH and 1 mmol acetylating reagent.

In nitromethane, FcH conversion was quite low with AcCl, (10 % at 25°C, 37 % at 50°C) and isolated yields of acetylferrocene (FcAc) were even lower, most likely because FcH disappearance is partly due to decomposition. With Ac_2O, some better results were obtained (at 25°C, 10 % conversion in dichloromethane, 42 % in $MeNO_2$ and 21 % in MeCN). Increasing the temperature led to an improvement of conversion (38 % in MeCN at 50°C) and also of isolated FcAc, up to 30 % on the basis of initial FcH.

The acetylation reaction improved slightly when performed using Ac_2O as the solvent, with 1 mmol of FcH and 0.1 mmol of $Sc(OTf)_3$, heating at 50 °C for 2.5 h. A 66 % conversion of FcH, with a FcH:FcAc ratio 48:52 was observed after 2.5 h, with 20 % decomposition.

These disappointing results notwithstanding, investigation was extended to ILs as solvents, where improved reactivity is often observed.

Hydrophilic 1–butyl–3–methylimidazolium triflate, $[C_4mim]TfO$, dissolves well $Sc(OTf)_3$, but almost no reaction occurred after days (1 % acetylferrocene). Most likely, TfO^- exerts a common ion effect and interferes with scandium triflate dissociation, thus inhibiting the catalyst.

In hydrophobic $[C_4mim]PF_6$, 1–butyl–3–methylimidazolium hexafluorophosphate, interesting conversions were obtained (around 80 %, Entries 2–4, Table 4.18). Isolated yields of acetylferrocene were up to 64 % on the basis of reacted ferrocene (47 % *vs*. initial FcH). Excess Ac_2O (Entry 3, Table 4.18) did not give any disubstituted product, thus allowing to reduce reaction time and, consequently, the ferrocene decomposition due to prolonged exposure to acid. [151-153] Reduced decomposition was observed also raising the temperature from 25 °C to 50 °C, with resulting shorter reaction time (Entries 2 and 3, Table 4.18).

Table 4.18. Sc(III) catalysed acetylation of ferrocene in $[C_4mim]$ cation based ILs.[a]

Entry	Anion	(T) °C	t (h)	Ratio FcH:Ac_2O:$Sc(OTf)_3$	Conversion (%)[b]	Relative ratio FcH:FcAc[c]	Yield (%)[d]
1	TfO	25	96	1:1:0.1	1	99:1	<1
2	PF_6	25	4	1:1:0.1	79	75:25	21
3	PF_6	50	3	1:1:0.1	67	20:80	57
4	PF_6	50	2.5	1:5:0.1	73	32:68	64
5	Tf_2N	50	2.5	1:5:0.1	94	7:93	78

[a]FcH 1 M. [b]Calculated from recovered FcH. [c]GC analysis *vs.* an internal standard (tetradecane). [d]Isolated FcAc, yield relative to conversion.

Even better results were obtained in $[C_4mim]Tf_2N$, the other hydrophobic IL (Entry 5, Table 4.18), with 93 % FcH conversion and 78 % FcAc isolated yield (73 % *vs*. initial FcH). However, ferrocene is not much soluble in $[C_4mim]Tf_2N$ and therefore other bistriflylimides were tested, with different cationic moieties, in an attempt to improve the solubility. Cations tested include *N*–butylpyridinium ($[C_4py]Tf_2N$, Entry 1, Table 4.19) and 1–hexyl–3–methylimidazolium ($[C_6mim]Tf_2N$, Entry 2, Table 4.19) moieties. Still, $[C_4mim]Tf_2N$ stands out as the solvent where FcH conversion is higher and decomposition is minimised.

Table 4.19. Sc(III) catalysed acetylation of ferrocene in bistriflylimides at 50 °C.[a]

Entry	Cation	t (h)	Ratio FcH:Ac_2O:$Sc(OTf)_3$	Conversion (%)[b]	Relative ratio FcH:FcAc.[c]	Yield (%)[d]
1	$[C_4py]$	2.5	1.0:1.3:0.10	89	15:85	75
2	$[C_6mim]$	2.5	1.0:1.3:0.10	17	93:3	2
3	$[C_4mim]$	2.5	1.0:5.0:0.10	94	7:93	78

[a] FcH 1 M. [b]Calculated from recovered FcH. [c]GC Analysis *vs.* an internal standard (tetradecane). [d]Isolated FcAc, yield relative to conversion.

Since the best IL for the scandium catalysed acetylation of FcH was found to be $[C_4mim]Tf_2N$, these conditions were chosen for subsequent throughout investigation: 1 mmol FcH in 1 mL $[C_4mim]Tf_2N$ in presence of an excess of Ac_2O was heated at 50 °C, added with catalyst, and let to react for 2.5 h, unless otherwise stated.

4.4.2.2. Effect of the reagents' concentration

Increase of FcH concentration (compare Entries 1 and 2, Table 4.20) accelerated the reaction and improved the conversion, but not the isolated yield. When the amount of Ac_2O was reduced (Entries 3 and 4, Table 4.20), conversion was quantitative, but some decomposition of FcH occurred, because isolated FcAc reached 76 % yield only.

Table 4.20. Sc(III) catalysed acetylation of ferrocene in $[C_4mim]Tf_2N$, at 50 °C, with different Ac_2O excess.

Entry	t (h)	FcH (M)	Ratio FcH:Ac_2O:$Sc(OTf)_3$	Conversion (%)[a]	Relative ratio FcH:FcAc[b]	Yield (%)[c]
1	2.5	1.0	1.0:5.0:0.10	94	7:93	78
2	2.0	2.0	1.0:5.0:0.10	>99	1:99	76
3	3.5	1.0	1.0:2.5:0.10	100	0:100	66
4	3.5	2.0	1.0:2.5:0.10	79	22:78	76

[a]Calculated from recovered FcH. [b]GC analysis *vs.* an internal standard (tetradecane). [c]Isolated FcAc, yield relative to conversion.

4.4.2.3. Effect of the reaction conditions

Under all examined conditions, there is a loss of product, because isolated FcAc and recovered FcH did not sum up the initial amount of ferrocene, although no other product is formed. To understand the reason of such behaviour, the reaction was performed also under inert atmosphere (N_2), and the ILs degassed and dehydrated *in vacuo* at 60°C for 2–3 h *prior* to use. Results however, were the same, within experimental error, as those obtained in the presence of air.

On this basis, decomposition is likely due to the acid formed as by–product from the acetylating agent. For example, with acetyl chloride, that produces HCl as by–product of the Friedel–Crafts acylation, the reaction yielded mainly to decomposition of FcH. To verify this hypothesis, experiments in different conditions were accomplished. First, the reaction was performed at higher temperature (with half catalyst load) and repeated on the same batch of IL/catalyst, removing by sublimation FcH and FcAc (Entry 1, Table 4.21) and recharging with FcH and Ac_2O (Entry 2, Table 4.21). After the same reaction time, FcH conversion was higher in the second run, but FcAc was obtained in much lower yield, thus indicating an higher extent of decomposition, no other product being present. Then, the reaction was performed in the presence of a base, such as sodium carbonate, not completely dissolved, in order to neutralized the acid formed. However, in this basic conditions a very low conversion was achieved (Entry 3, Table 4.21), thus indicating that deactivation of the catalyst occurs. Finally, the reaction was carried on with added AcOH (Entry 4, Table 4.21), with no effect on either conversion or FcAc yield. These experiments suggest that the prolonged contact with acids (that in ILs are expected to have an increased acidity) decomposes ferrocene and, likely, the catalyst. To

verify such hypothesis, the reaction was made in the presence of an equimolar amount of triflic acid. However, extensive decomposition resulted, with very low amount of acetylferrocene recovered (Entry 5, Table 4.21). This results seems to indicate that catalysis by free acid, that is at work in metal triflate catalyzed benzoylation of anisole in ILs, [137] is not effective with ferrocene. Therefore with FcH it is advisable to perform the reaction under conditions that ensure a fast transformation, keeping decomposition at the minimum.

Table 4.21. Sc(III) catalysed acetylation of ferrocene in $[C_4mim]Tf_2N$, under different conditions.[a]

Entry	IL	T(°C)	t (h)	Ratio FcH:Ac_2O:$Sc(OTf)_3$	Conversion (%)[b]	Ratio FcH:FcAc[c]	Yield (%)[d]
1[e]	$[C_4mim]Tf_2N$	60[f]	2.5	1:2.5:0.05	85	7:93	61
2[e]	$[C_4mim]Tf_2N$[g]	60	2.5	1:2.5:0.05	96	10:90	34
3	$[C_4mim]Tf_2N + Na_2CO_3$	50	2.5	1:3.0:0.10	17	94:6	57
4	$[C_4mim]Tf_2N$ + AcOH[h]	50	2.5	1:2.5:0.05	95	6:94	78
5	$[C_4mim]Tf_2N$ + TfOH[h]	50	2.5	1:2.5:0.05	100	0:100	10

[a]FcH 1 M. [b]calculated from recovered FcH. [c]GC analysis *vs.* an internal standard (tetradecane). [d]Isolated FcAc, yield relative to conversion. [e]Workup: sublimation. [f]Temperature was increased with the aim to completely transform ferrocene. [g]Recycle of entry 1. [h]Equimolar with FcH.

4.4.2.4. Effect of the different triflate salts catalysts

Different catalysts were also tested, under the chosen best reaction conditions (FcH 1 M, 50°C, 2.5 h, 10 % molar catalyst load, fivefold excess Ac_2O). After comparable reaction times (2.5 h), scandium triflate resulted more efficient than the corresponding yttrium and ytterbium salts (Entries 5, 1 and 3, Table 4.22), giving the highest isolated yield of FcAc, whereas FcH conversion was slightly lower.

Table 4.22. Acetylation of ferrocene in $[C_4mim]Tf_2N$, at 50 °C, with different metal triflates.[a]

Entry	Catalyst	t (h)	Ratio FcH:Ac_2O:$Sc(OTf)_3$	Conversion (%)[b]	Ratio FcH:FcAc[c]	Yield (%)[d]
1	$Y(OTf)_3$	2.5	1:5:0.10	94	12:88	66
2	$Y(OTf)_3$	8.0	1:5:0.10	100	0:100	67
3	$Yb(OTf)_3$	2.5	1:5:0.10	95	17:83	59
4	$Yb(OTf)_3$	5.5	1:5:0.10	95	5:95	64
5	$Sc(OTf)_3$	2.5	1:5:0.10	94	7:93	78

[a]FcH 1 M. [b]Calculated from recovered FcH. [c]GC analysis *vs.* an internal standard (tetradecane). [d]Isolated FcAc, yield relative to conversion.

With longer reaction times, the yttrium catalyst caused quantitative disappearance of FcH, without any increase of FcAc yield (Entry 2, Table 4.22).

As to the ytterbium catalyst, FcH conversion is the same as that with scandium, but yields are definitely lower (Entry 4, Table 4.22). Thus, the less expensive $Sc(OTf)_3$ was a better Friedel–Crafts catalyst for ferrocene acetylation than the corresponding lanthanides triflates.

4.4.2.5. Effect of the catalyst load (with $Sc(OTf)_3$)

Although 10 % molar for the Lewis acid is an improvement with respect of the stoichiometric $AlCl_3$, it is still a considerable amount of a precious catalyst. Therefore, experiments were performed reducing the catalyst. 5 % molar $Sc(OTf)_3$ is still efficient in terms of catalysis, but requires a temperature increase (from 50 to 60 °C), to avoid prolonged reaction times (Entries 2–4, Table 4.23). When the catalyst load was lowered to 1 % molar of $Sc(OTf)_3$, efficiency decreased sharply and increasing reaction times did not improve significantly FcH conversion, nor isolated quantity of ketone (Entries 5 and 6, Table 4.23).

Table 4.23. Acetylation of ferrocene in $[C_4mim]Tf_2N$, at 50 °C, with different amounts of $Sc(OTf)_3$.

Entry	$Sc(OTf)_3$ (% mol)	FcH (M)	t (h)	Ratio FcH:Ac_2O:$Sc(OTf)_3$	Conversion (%)[a]	Ratio FcH:FcAc[b]	Yield (%)[c]
1	10	1.0	2.5	1:5:0.1	94	7:93	76
2	5	1.0	2.5	1:5:0.05	89	32:69	43
3	5	1.0	9.0	1:5:0.05	94	14:86	55
4	5	1.0	2.5 (60 °C)	1:5:0.05	100	0:100	60
5	1	1.0	2.5	1:5:0.01	32	90:10	20
6	1	1.0	29.5	1:2.5:0.01	95	83:17	37

[a]Calculated from recovered FcH. [b]GC analysis *vs.* an internal standard (tetradecane). [c]Isolated FcAc, yield relative to conversion.

To summarize results, acetylferrocene can be obtained in good yields using scandium triflate as Lewis acid and $[C_4mim]Tf_2N$ as solvent. Excess Ac_2O is advisable, because it helps in solubilizing FcH and speeding up the reaction; moreover, it doesn't interfere with the reaction outcome, since 1,1'–diacetylferrocene was never found. No oxidation of ferrocene occurred in $[C_4mim]Tf_2N$, differently from what reported for the reaction in $[C_4py]BF_4$. [150]

4.4.2.6. Effect of different acylating agents

In order to establish the scope of the reaction, different acylating reagents were used. Experiments with acyl chlorides were abandoned after some initial attempts with disappointing results, clearly due to the formation of HCl, that causes extensive decomposition of ferrocene, especially in ILs. When using propanoic anhydride as acylating agent good yields of propanoylferrocene were obtained (*vide infra*). Propanoylferrocene was isolated either by extraction with diethyl ether, or by direct distillation under vacuum from the reaction mixture. After the latter workup, recycling of the IL was attempted, that was reloaded with FcH and propanoic anhydride. Unfortunately, even after prolonged reaction times, only small amounts of propanoylferrocene were obtained (Entry 5, Table 4.14). In an attempt to improve the recycle step, the reaction was performed also a pyridinium based IL, $[C_4py]Tf_2N$. However, worst results in comparison to the reaction performed in $[C_4mim]Tf_2N$ were attained (Entries 8 and 9, Table 4.14).

These recycle confirmed that prolonged exposure to acidic medium is detrimental for FcH and/or the catalyst. No product at all was obtained with butanedioic or chloroethanoic anhydride and only traces of trifluoroacetylferrocene were detected. As for aromatic anhydrides, benzoic anhydride was scarcely reactive, since 24 h heating produced, at best, only 25 % isolated benzoylferrocene.

4.4.2.7. Effect of MW activation

To complete the exploration of reaction parameters, we decided to investigate the effect of microwaves, that should be readily absorbed by the ionic solvent. When microwave irradiation was used to heat the reaction mixture, it was possible to drastically reduce reaction times, from hours to minutes. Addition of the catalyst in two portions did not improve the yield (Entry 3, Table 4.17).

The best conditions for the MW assisted acetylation of FcH in $[C_4mim]Tf_2N$, were found to be with a 5 % molar catalyst load, acetylferrocene was obtained quantitatively in 1.5 min (Entry 5, Table 4.17).

On the other hand, no appreciable improvement was observed when performing the reaction in molecular solvent under MW irradiation (Entries 6 and 7, Table 4.17).

Despite the fact that the irradiation power was increased when switching to molecular solvents, T_{bulk} in MeCN remained lower than in IL. This can be ascribed to the more efficient MW absorption by ionic species, which was presented in detail in Chapter 2.

MW heating improved the reaction outcome also with propanoic anhydride (Entries 9 and 10, Table 4.17). In all cases, fast quantitative conversion of ferrocene was accompanied by a high yield of propanoylferrocene. The reaction mixture was also purified by column chromatography and isolated yields were similar to GC ones (*i.e.* Entry 10, Table 4.17 propanoylferrocene was isolated in 84 % yield, together with 13 % 1,1'–dipropanoylferrocene; total isolated products account for 97 % of initial ferrocene, thus confirming that decomposition is due to prolonged heating)

MW irradiation was beneficial also for Friedel–Crafts acylation with less reactive anhydrides, such as benzoic anhydride; the isolated yield of benzoylferrocene yield improved from 25 % when the reaction was performed under conventional heating to 42 % under MW irradiation.

The experimental work on improvement of scandium and lanthanide triflates catalysed Friedel–Crafts acylation of FcH in alkylmethylimidazolium based IL has been published. [154]

4.5. Conclusions

Preliminary studies on Friedel–Crafts alkylation of ferrocene and an extensive investigation of Friedel–Crafts acylation of ferrocene were performed.

Alkylmethylimidazolium–based ILs were superior to pyridinium based ones as solvents for ferrocene acylation, and scandium triflate as catalyst was better than yttrium or ytterbium triflates. A major improvement was realized using microwaves as heating source, where, in the best performance, quantitative GC and isolated yields of ferrocenylketones were reached within minutes. Thus, the results presented above clearly show that the protocol IL–MW–$Sc(OTf)_3$ is, at present, the most efficient in ferrocene acylation.

Appendix A

Optimized MW programs for 1–alkyl–1–methylimidazolium chlorides

All programs are optimized for a 70 % conversion.

Key to the graphs:

Calc Power (yellow) = expected calculated power (in W) from the machine based on the program specifics;

Power (mustard) = effective erogated power (in W) of the MW source;

Temp1 (red) = T (in degrees Celsius) measured by the OF thermometer inside the sample;

Temp2 (green) = T (in degrees Celsius) measured by the IR sensor in the MW chamber;

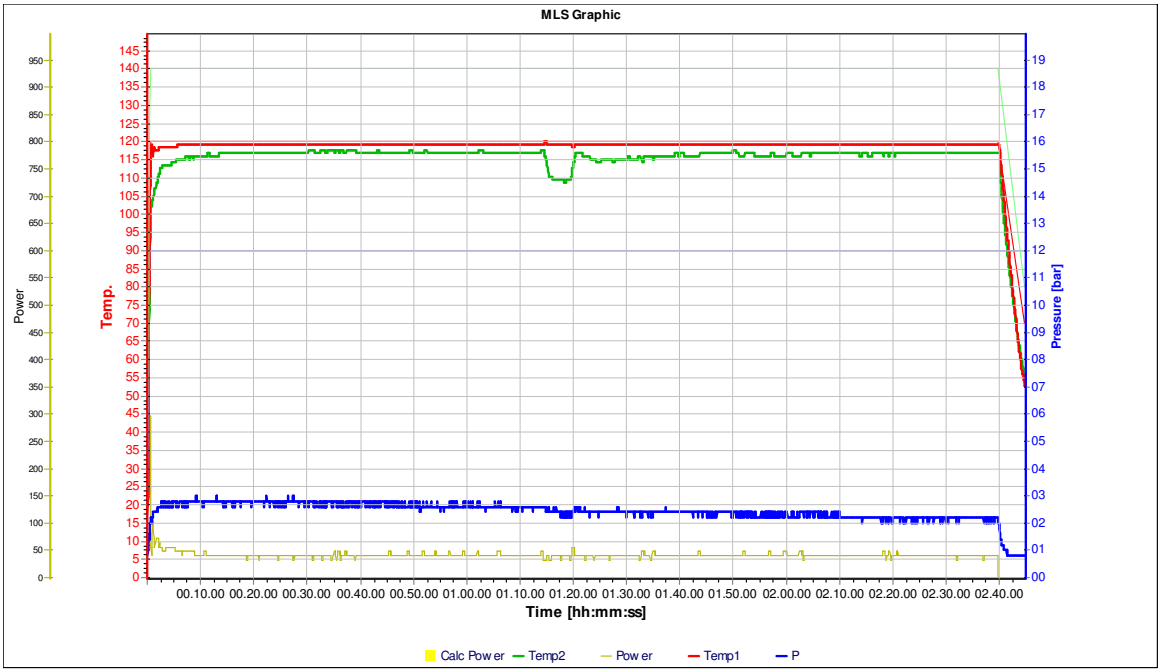
P (blue) = pressure (in bar) measured by the pressure controller inside the sample.

1. [C_4mim]Cl in EtOH

- 120 °C (conversion: 74 %)

t (s)	Max W (W)	T_{OF} (°C)	T_{IR} (°C)	Max p (bar)
30	500	125	145	12
10	500	125	145	12
2h 39'05"	300	135	155	12

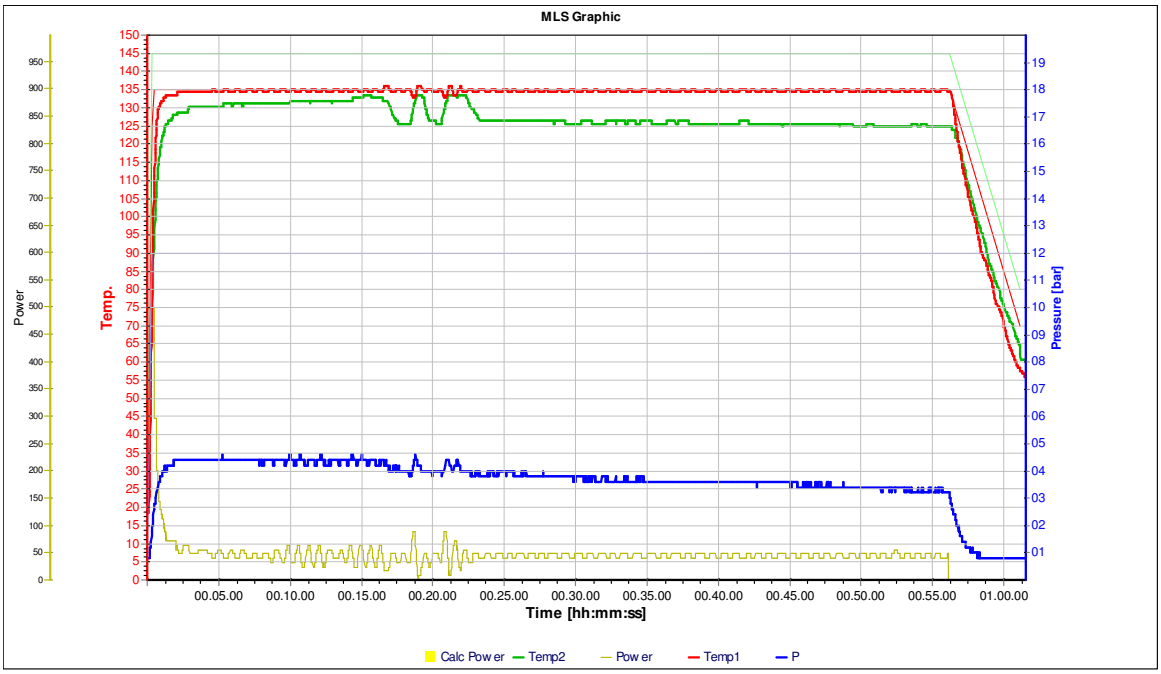
It takes 45 s to reach T=120 °C.



- 135 °C (conversion: 71 %)

t (sec)	Max W (W)	T_{OF} (°C)	T_{IR} (°C)	Max p (bar)
30	500	125	145	12
10	500	125	145	12
20	300	135	155	12
54'08"	200	135	155	12

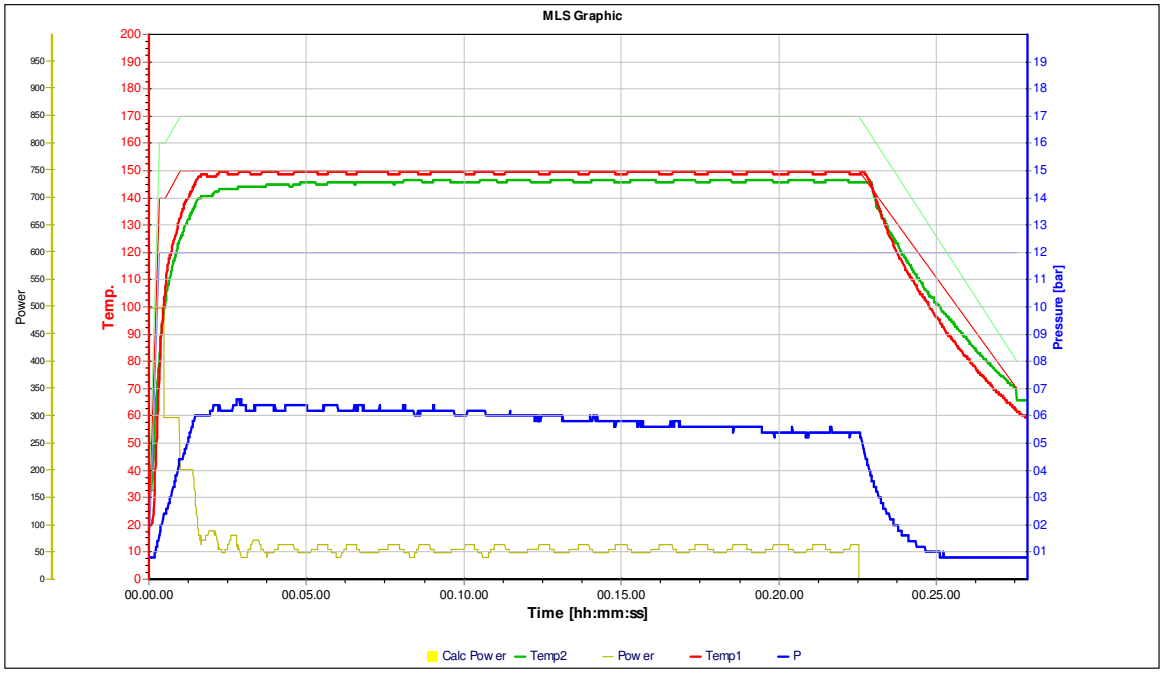
It takes 1'04" (64 s) to reach T=135 °C.



- 150 °C (conversion: 68 %)

t (s)	Max W (W)	T_{OF} (°C)	T_{IR} (°C)	Max p (bar)
20	500	140	160	12
10	500	140	160	12
30	300	150	170	12
20'30"	200	150	170	12

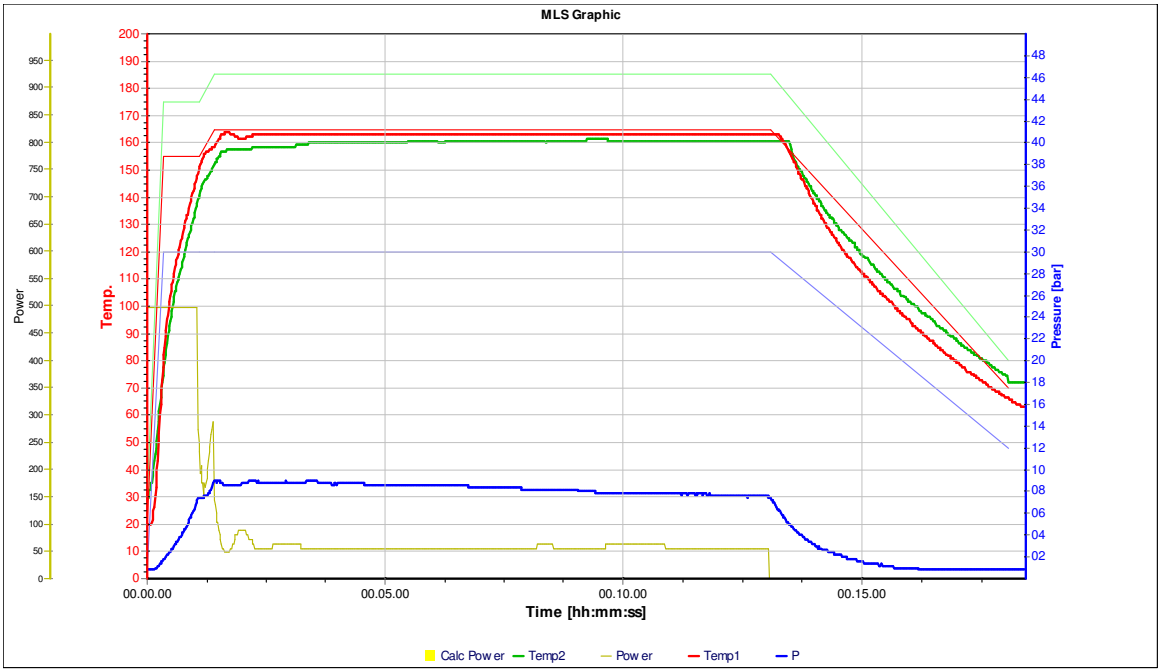
It takes 1'24" (84 s) to reach T=150 °C.



- 165 °C (conversion: 73 %)

t (s)	Max W (W)	T_{OF} (°C)	T_{IR} (°C)	Max p (bar)
20	500	155	175	12
45	500	155	175	12
20	300	165	185	12
11'21"	200	165	185	12

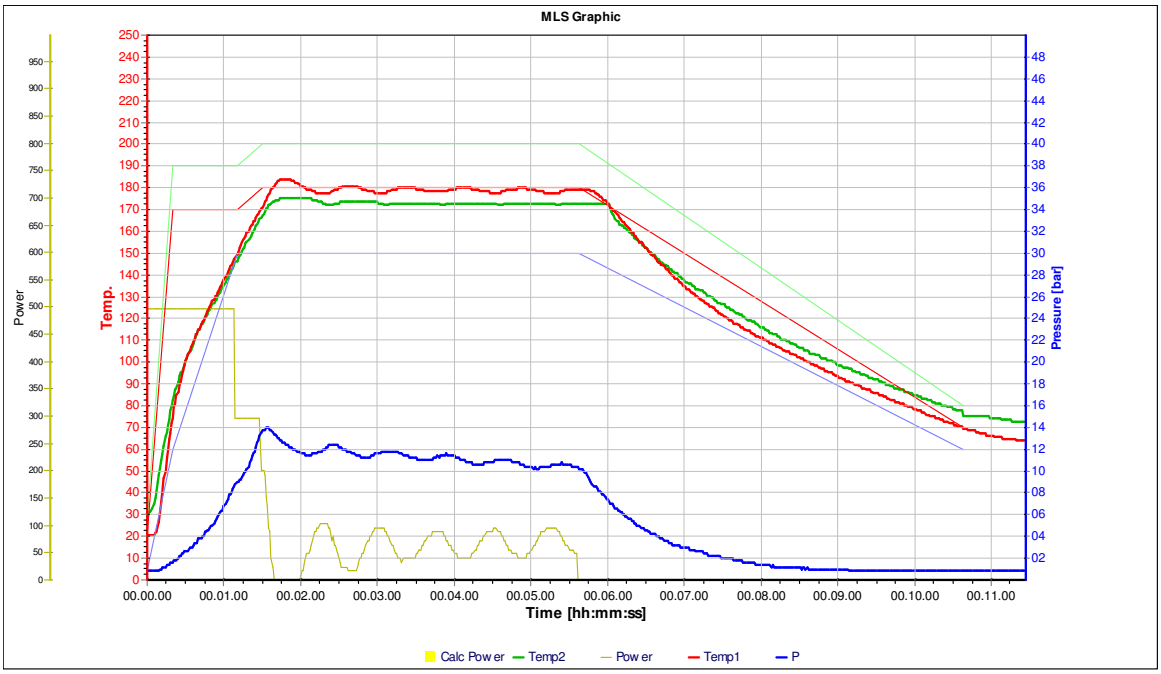
It takes 1'16" (76 s) to reach T= 164 °C.



- 180 °C (conversion: 66 %)

t (s)	Max W (W)	T_{OF} (°C)	T_{IR} (°C)	Max p (bar)
20	500	170	190	12
50	500	170	190	12
20	300	180	200	12
4'32"	200	180	200	12

It takes 1'38" (98 s) to reach T = 180 °C.

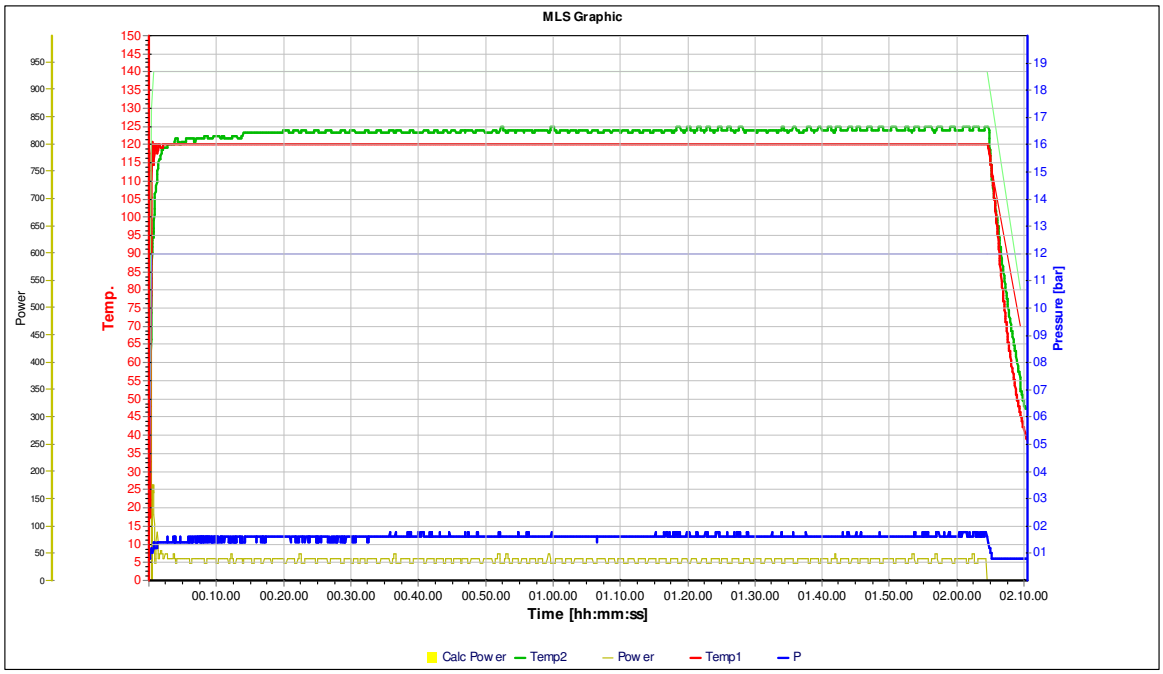


2. [C_6mim]Cl in CH_3CN

- 120 °C (conversion: 76 %)

t (sec)	Max W (W)	T_{OF} (°C)	T_{IR} (°C)	Max p (bar)
20	500	110	130	12
20	300	120	140	12
2h 03'43"	200	120	140	12

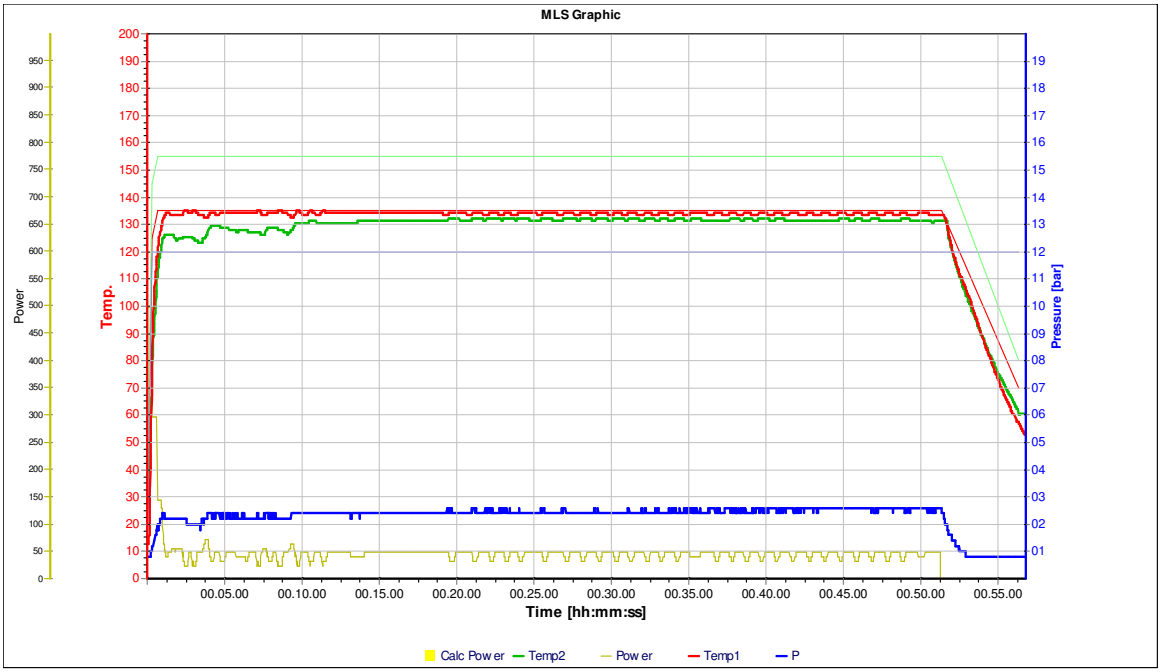
It takes 27 s to reach T=120 °C:



- 135 °C (conversion: 69 %)

t (sec)	Max W (W)	T_{OF} (°C)	T_{IR} (°C)	Max p (bar)
20	500	125	145	12
20	300	135	155	12
50'39"	150	135	155	12

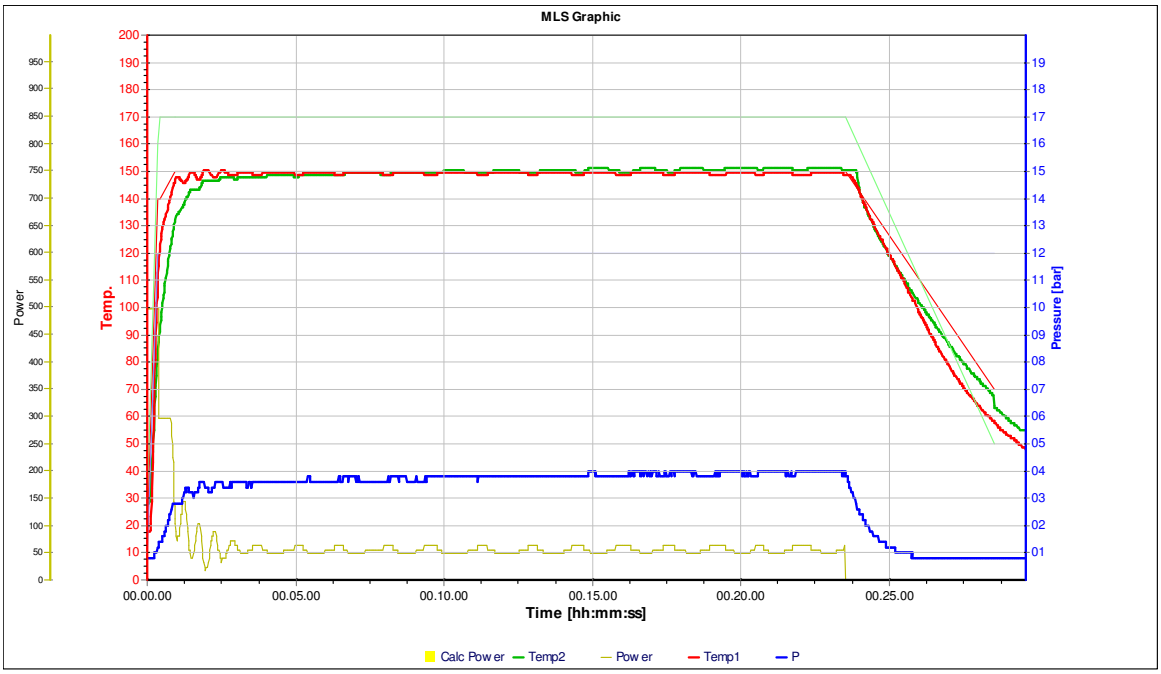
It takes 1'07"(67 s) to reach T=135 °C.



- 150 °C (conversion: 73 %)

t (sec)	Max W (W)	T_{OF} (°C)	T_{IR} (°C)	Max p (bar)
20	500	140	160	12
5	500	140	160	12
30	300	150	170	12
22'36"	200	150	170	12

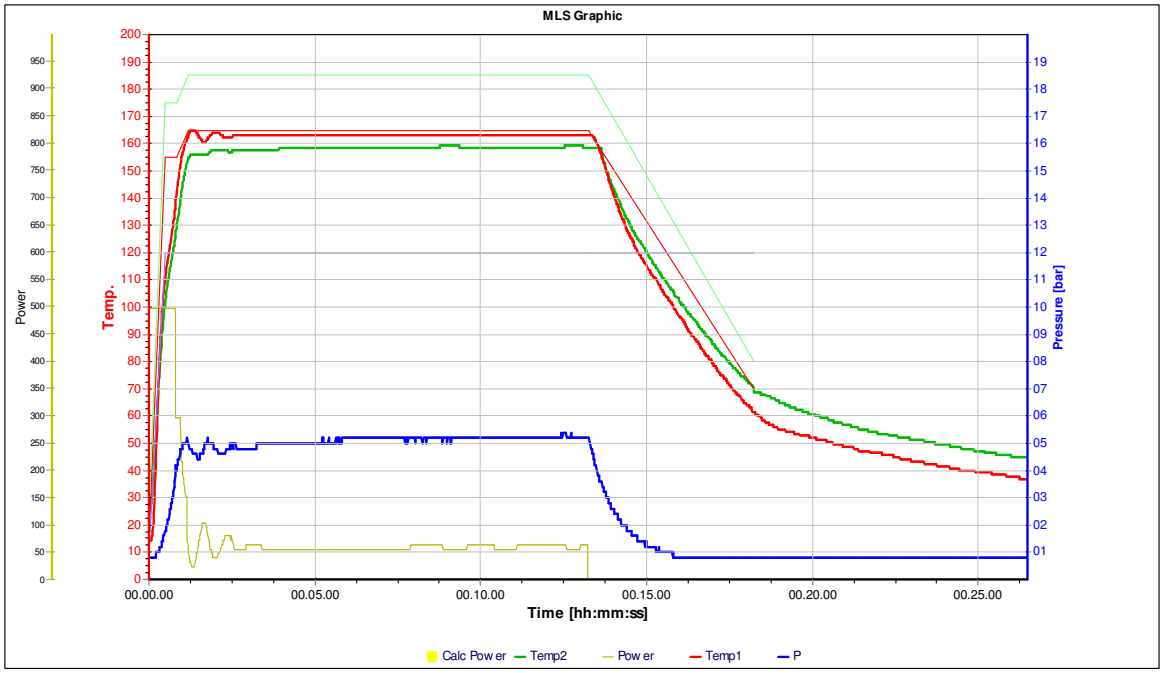
It takes 1'01" (61 s) to reach T = 149 °C.



- 165 °C (conversion: 76 %)

t (sec)	Max W (W)	T_{OF} (°C)	T_{IR} (°C)	Max p (bar)
30	500	155	175	12
20	500	155	175	12
40	300	165	185	12
12'10"	200	165	185	12

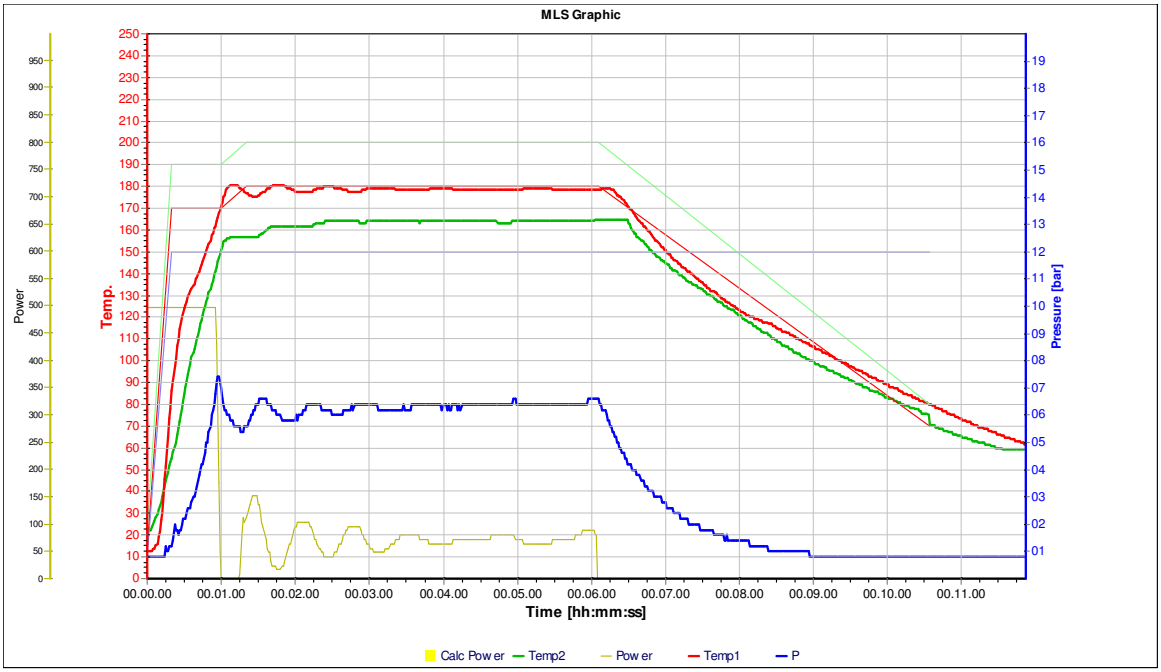
It takes 1'20" (80 s) to reach T = 163 °C.



- 180 °C (conversion: 71 %)

t (sec)	Max W (W)	T_{OF} (°C)	T_{IR} (°C)	Max p (bar)
20	500	170	190	12
30	500	170	190	12
20	300	180	200	12
4'07"	200	180	200	12

It takes 1'17" (77 s) to reach T=180 °C.

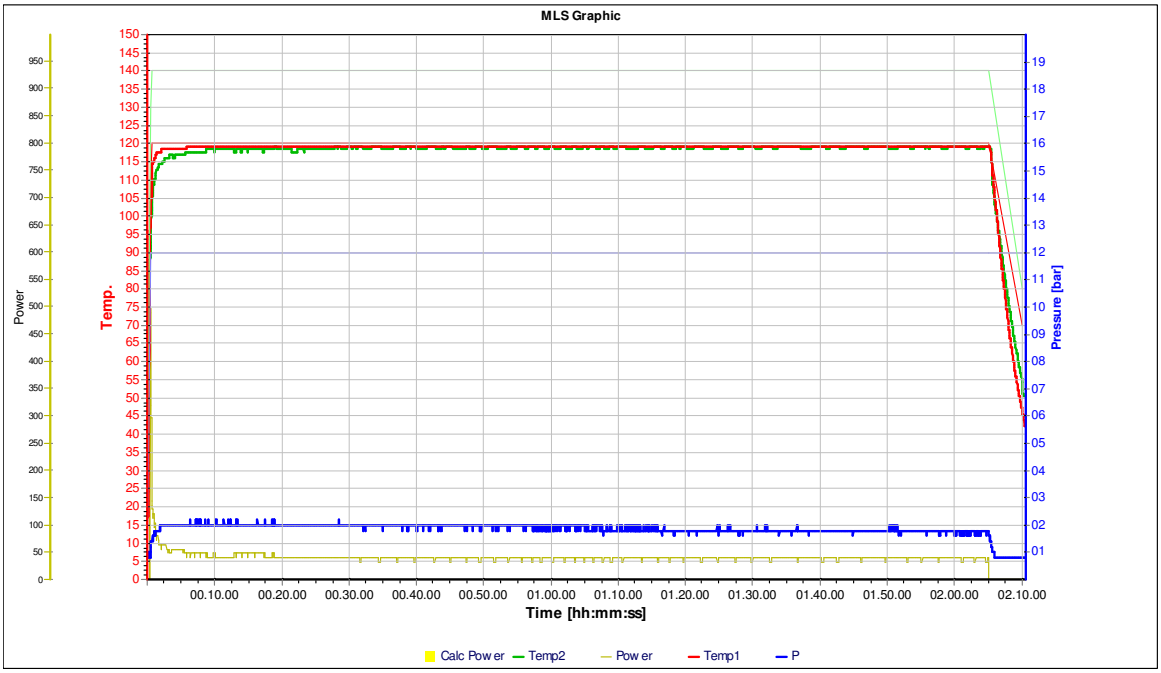


3. [C_6mim]Cl in EtOH

- 120 °C (conversion: 63%)

t (s)	Max W (W)	T_{OF} (°C)	T_{IR} (°C)	Max p (bar)
30	500	110	130	12
10	300	120	140	12
2 h 37'40"	200	120	140	12

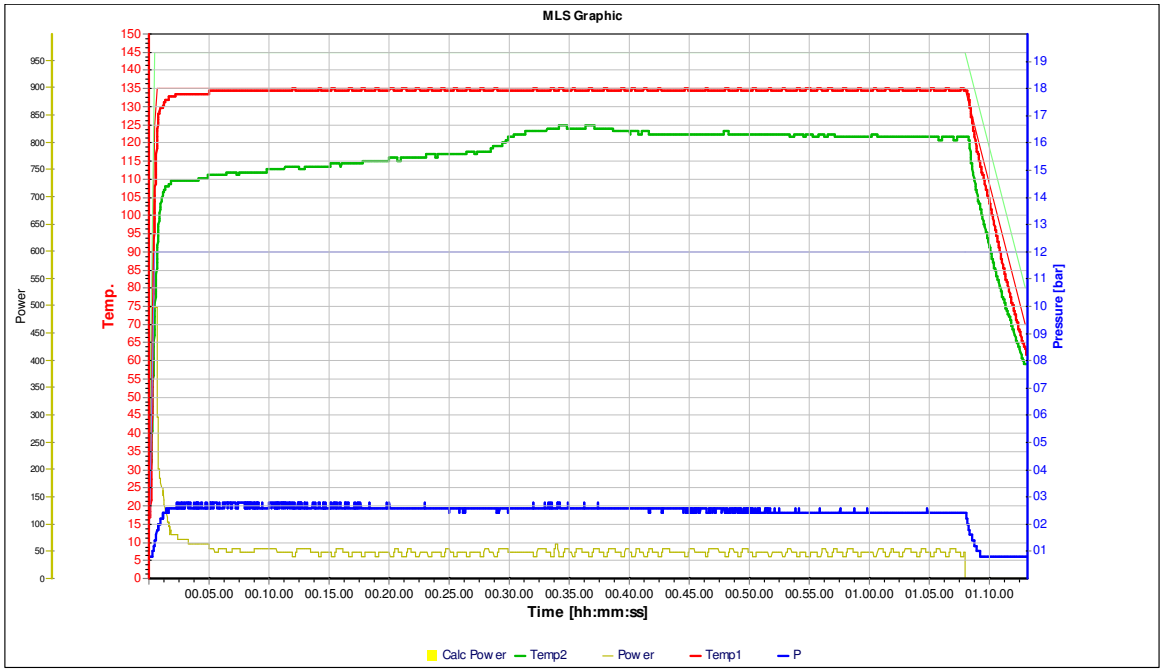
It takes 50 s to reach T = 117 °C.



- 135 °C (conversion: 68 %)

t (s)	Max W (W)	T_{OF} (°C)	T_{IR} (°C)	Max p (bar)
30	500	125	145	12
10	500	125	145	12
20	300	135	155	12
1h 07'07"	200	135	155	12

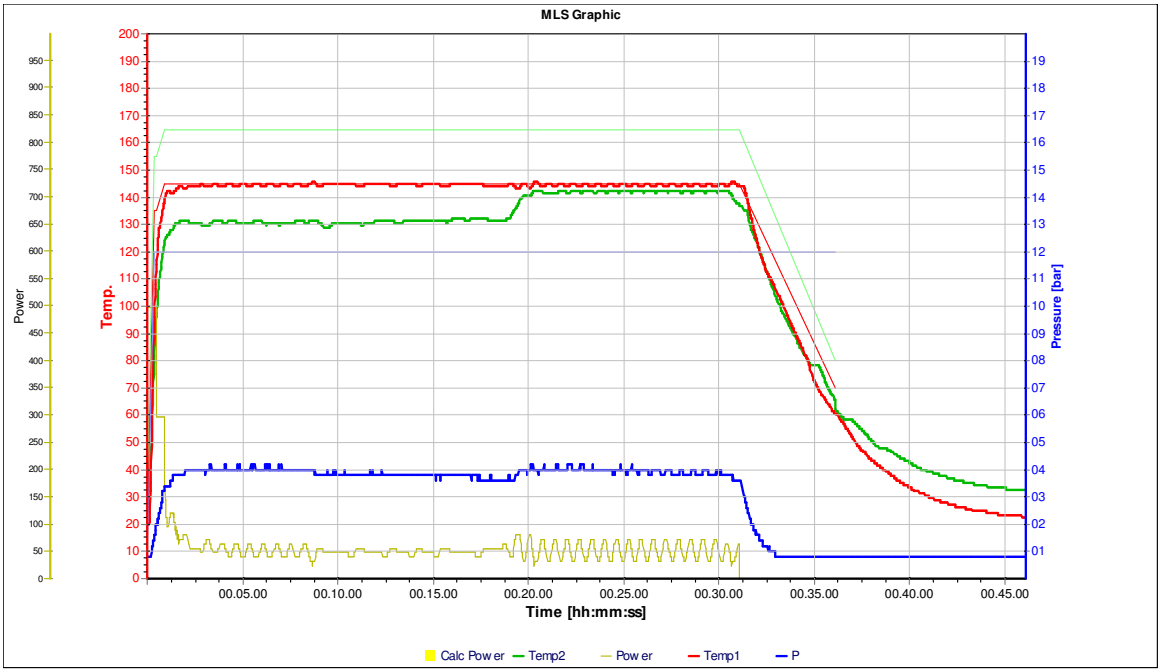
It takes 1'07" (67 s) to reach T = 130 °C.



- 145 °C (conversion: 69 %)

t (s)	Max W (W)	T_{OF} (°C)	T_{IR} (°C)	Max p (bar)
20	500	135	155	12
10	500	135	155	12
25	300	145	165	12
35'22"	200	145	165	12

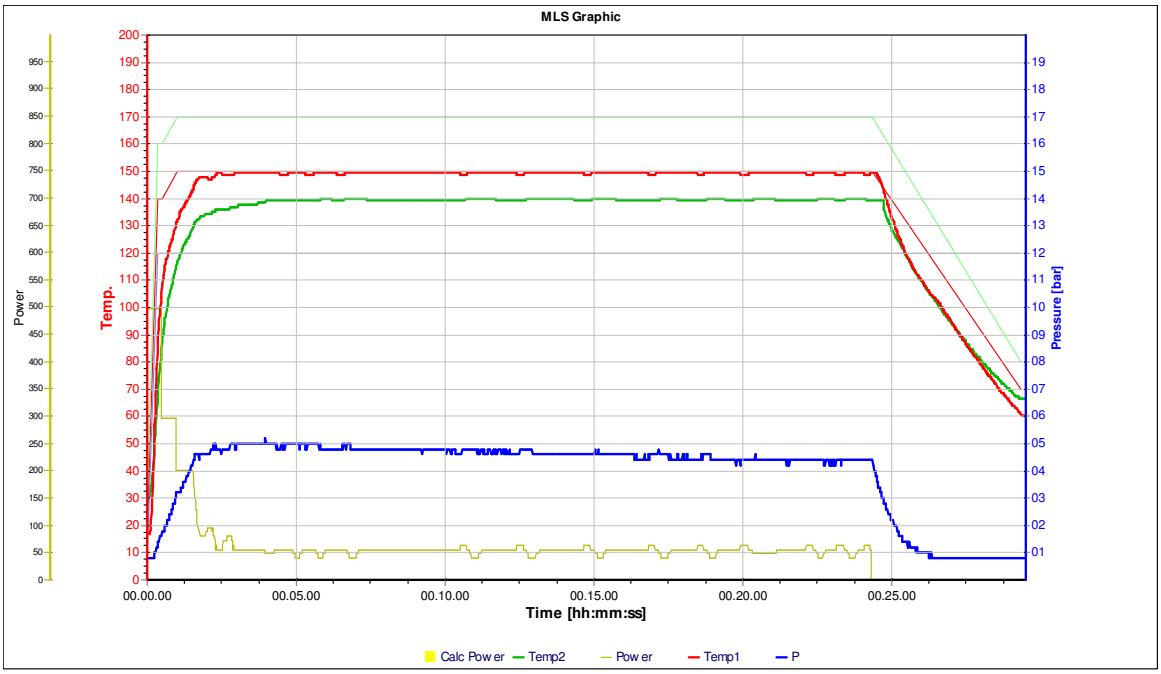
It takes 1'53" (113 s) to reach T=143 °C.



- 150 °C (conversion 69 %)

t (s)	Max W (W)	T_{OF} (°C)	T_{IR} (°C)	Max p (bar)
20	500	140	160	12
10	500	140	160	12
30	300	150	170	12
23'02"	200	150	170	12

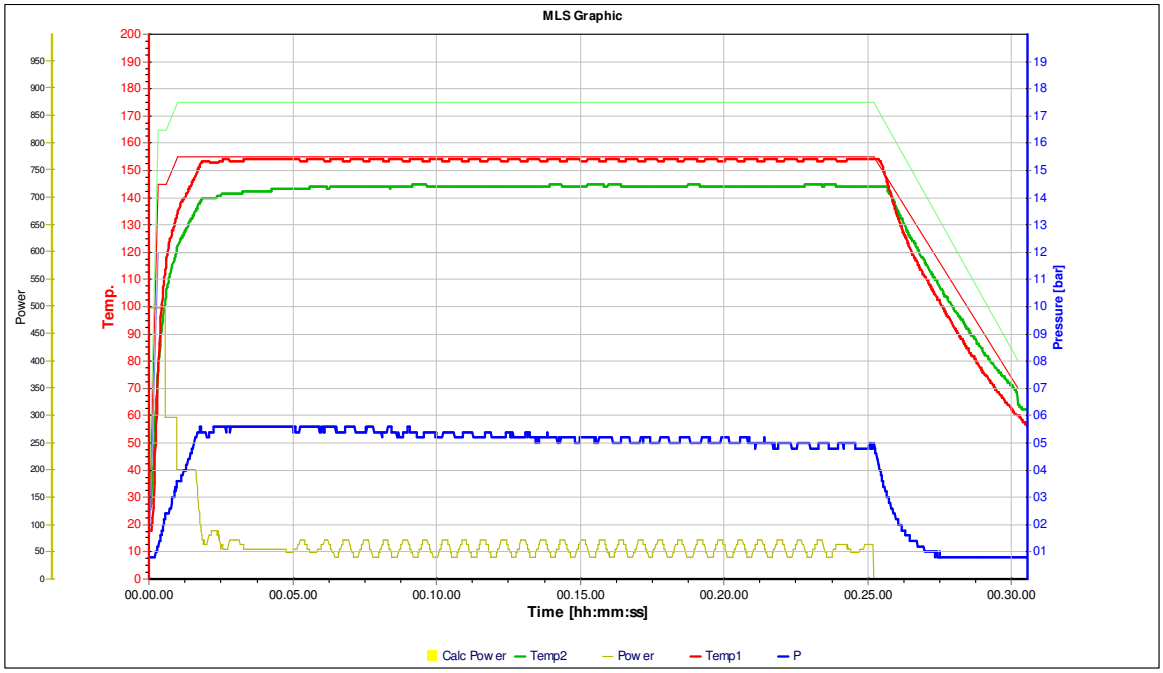
It takes 1'32" (92 s) to reach T = 148°C.



- 155 °C (conversion: 71 %)

t (s)	Max W (W)	T_{OF} (°C)	T_{IR} (°C)	Max p (bar)
20	500	145	165	12
15	500	145	165	12
25	300	155	175	12
24'13"	200	155	175	12

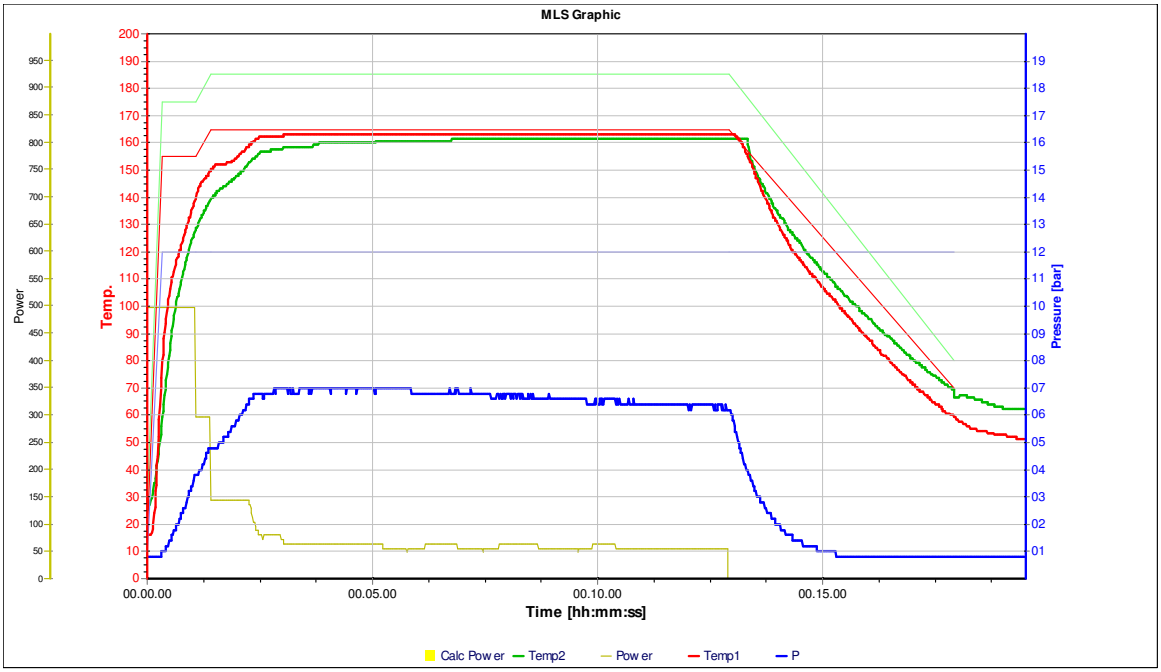
It takes 1'55" (115 s) to reach T = 155 °C.



- 165 °C (conversion: 69 %)

t (s)	Max W (W)	T_{OF} (°C)	T_{IR} (°C)	Max p (bar)
20	500	155	175	12
45	500	155	175	12
20	300	165	185	12
11'30"	200	165	185	12

It takes 2'37" (157 s) to reach T = 163 °C.



- 180 °C (conversion 70 %)

t (s)	Max W (W)	T_{OF} (°C)	T_{IR} (°C)	Max p (bar)
20	500	170	190	12
50	500	170	190	12
20	300	180	200	12
6'10"	200	180	200	12

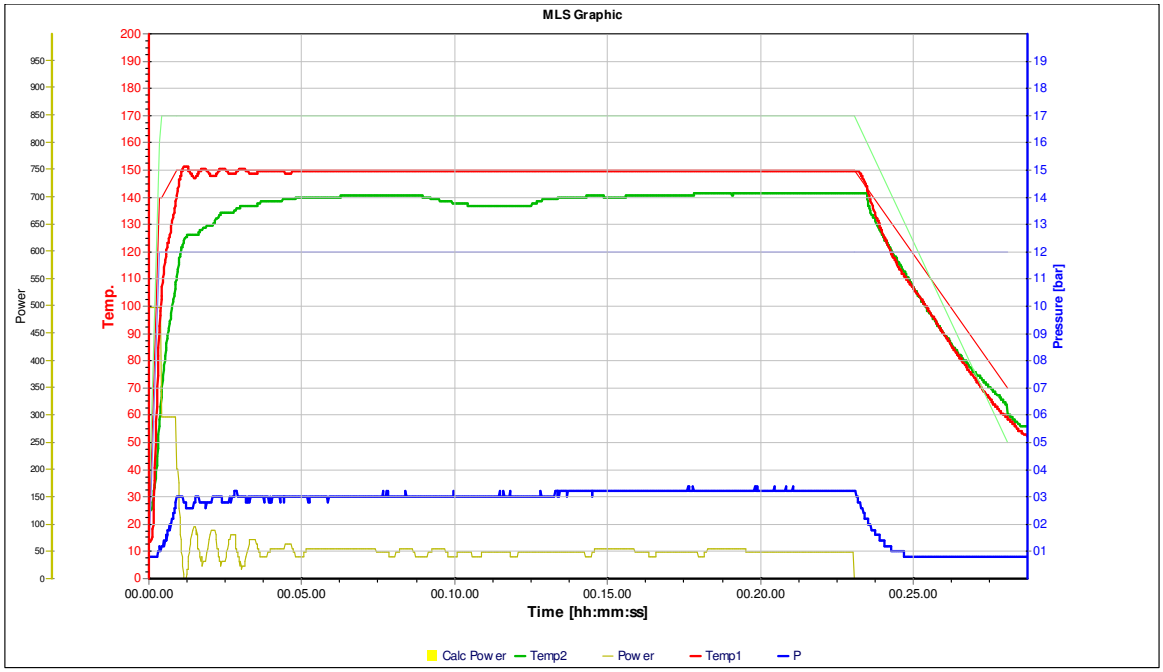
It takes 2'40" (160 s) to reach T =180 °C.

4. [C_8mim]Cl in CH_3CN

- 150 °C (conversion: 61 %)

t (s)	Max W (W)	T_{OF} (°C)	T_{IR} (°C)	Max p (bar)
20	500	140	160	12
5	500	140	160	12
30	300	150	170	12
22'10"	200	150	170	12

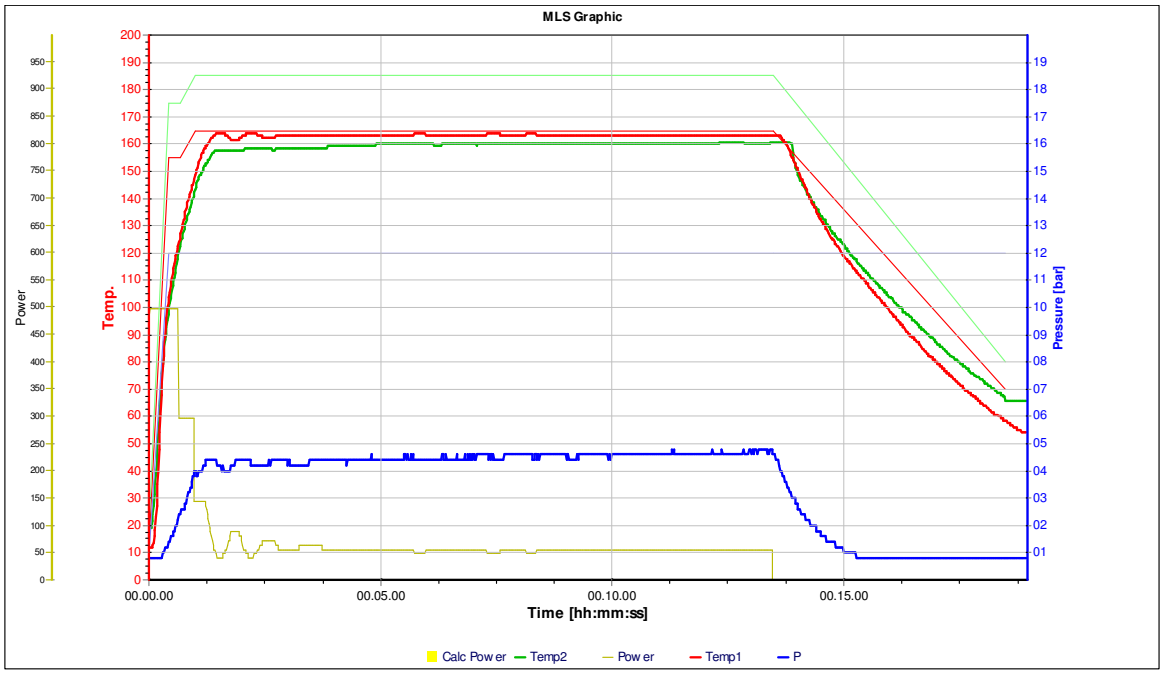
It takes 1'05" (65 s) to reach T = 150 °C.



- 165 °C (conversion: 66 %)

t (s)	Max W (W)	T_{OF} (°C)	T_{IR} (°C)	Max p (bar)
25	500	155	175	12
20	500	155	175	12
20	300	165	185	12
729	200	165	185	12

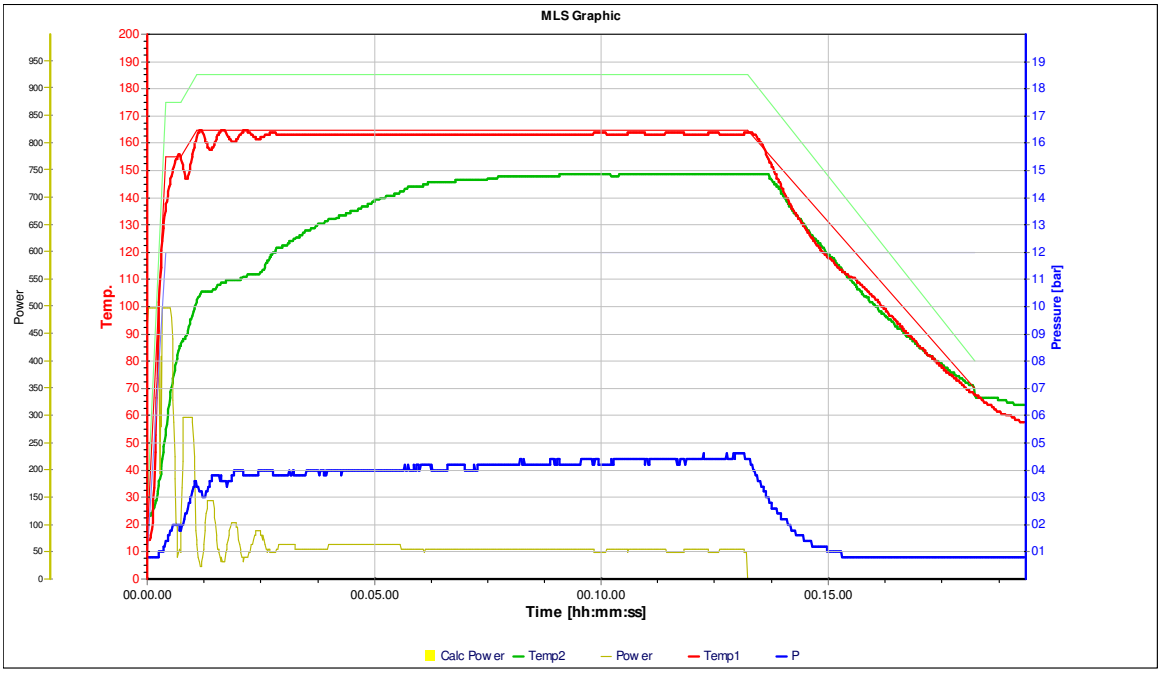
It takes 1'04" (64 s) to reach T = 165 °C.



- 180 °C (conversion: 66 %)

t (s)	Max W (W)	T_{OF} (°C)	T_{IR} (°C)	Max p (bar)
20	500	170	190	12
25	500	170	190	12
25	300	180	200	12
5'00"	200	180	200	12

It takes 1'10" (70 s) to reach T = 180 °C



5 [C_8mim]Cl in EtOH

- 120 °C (conversion: 68 %)

t (s)	Max W (W)	T_{OF} (°C)	T_{IR} (°C)	Max p (bar)
25	500	110	130	12
10	300	120	140	12
2h 10'12"	150	120	140	12

It takes 47 s to reach T =118 °C.

- 135 °C (conversion: 60 %)

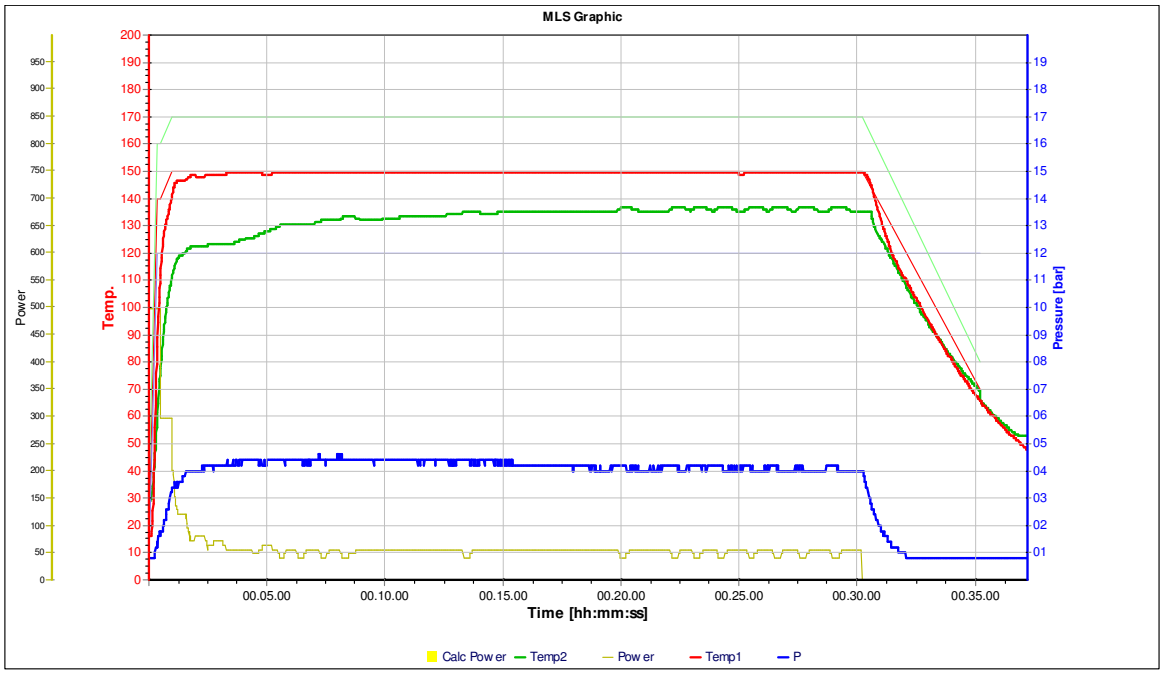
t (s)	Max W (W)	T_{OF} (°C)	T_{IR} (°C)	Max p (bar)
30	500	125	145	12
10	500	125	145	12
20	300	135	155	12
1h 16'54"	200	135	155	12

It takes 54 s to reach T =134 °C.

- 150 °C (conversion: 69 %)

t (s)	Max W (W)	T_{OF} (°C)	T_{IR} (°C)	Max p (bar)
20	500	140	160	12
10	500	140	160	12
30	300	150	170	12
30'07"	200	150	170	12

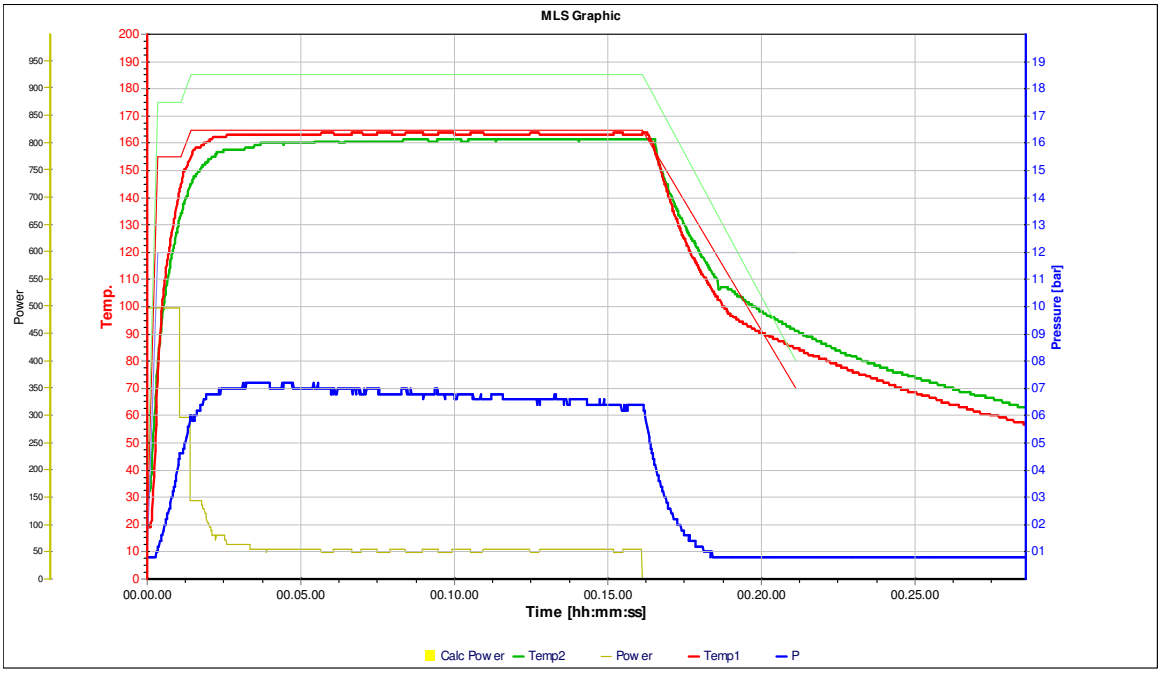
It takes 2'07" (127 s) to reach T =148 °C.



- 165 °C (conversion: 69 %)

t (s)	Max W (W)	T_{OF} (°C)	T_{IR} (°C)	Max p (bar)
20	500	155	175	12
45	500	155	175	12
20	300	165	185	12
14'43"	200	165	185	12

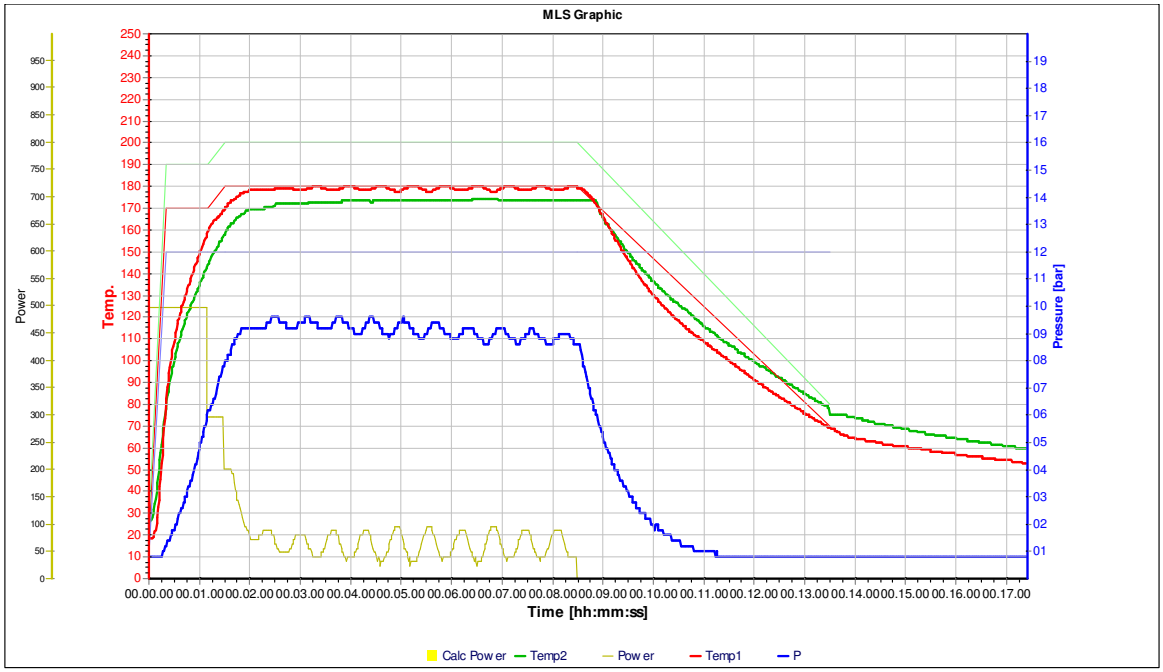
It takes 2'20" (140 s) to reach T = 163 °C.



- 180 °C (conversion: 72 %)

t (s)	Max W (W)	T_{OF} (°C)	T_{IR} (°C)	Max p (bar)
20	500	170	190	12
50	500	170	190	12
20	300	180	200	12
7'00"	200	180	200	12

It takes 2'00" (120 s) to reach T = 179 °C.

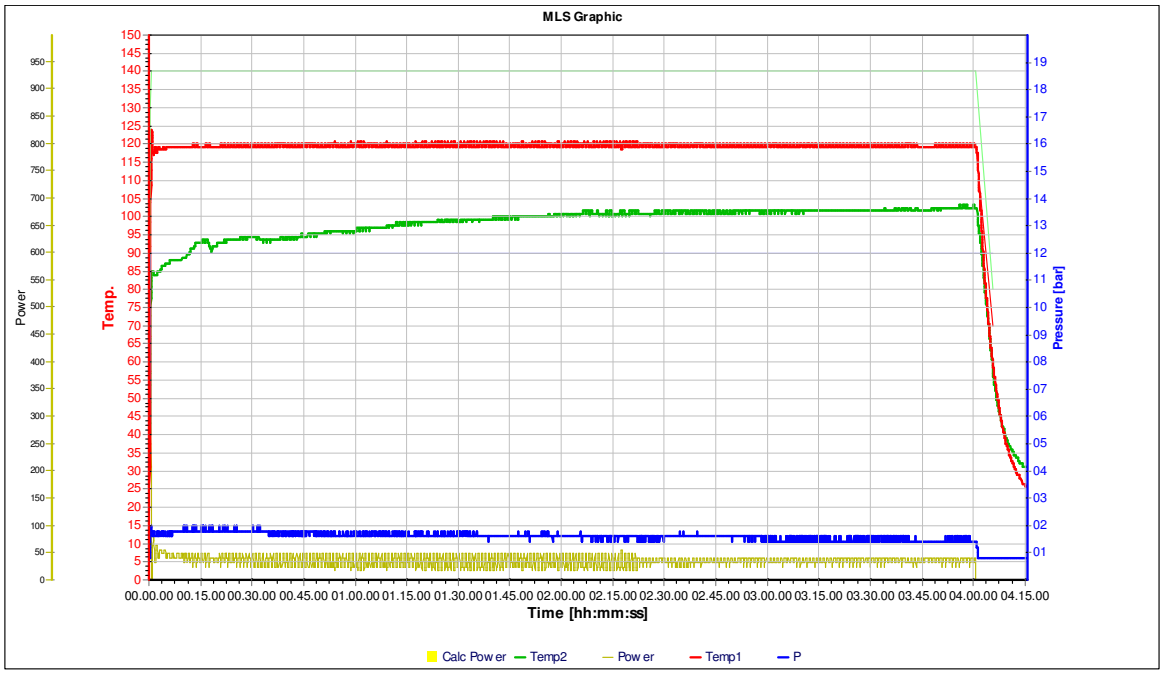


6. [C_{12}mim]Cl in EtOH

- 120 °C (conversion: 54 %)

t (sec)	Max W (W)	T_{OF} (°C)	T_{IR} (°C)	Max p (bar)
30	500	110	130	12
10	300	120	140	12
4 h 40'04"	150	120	140	12

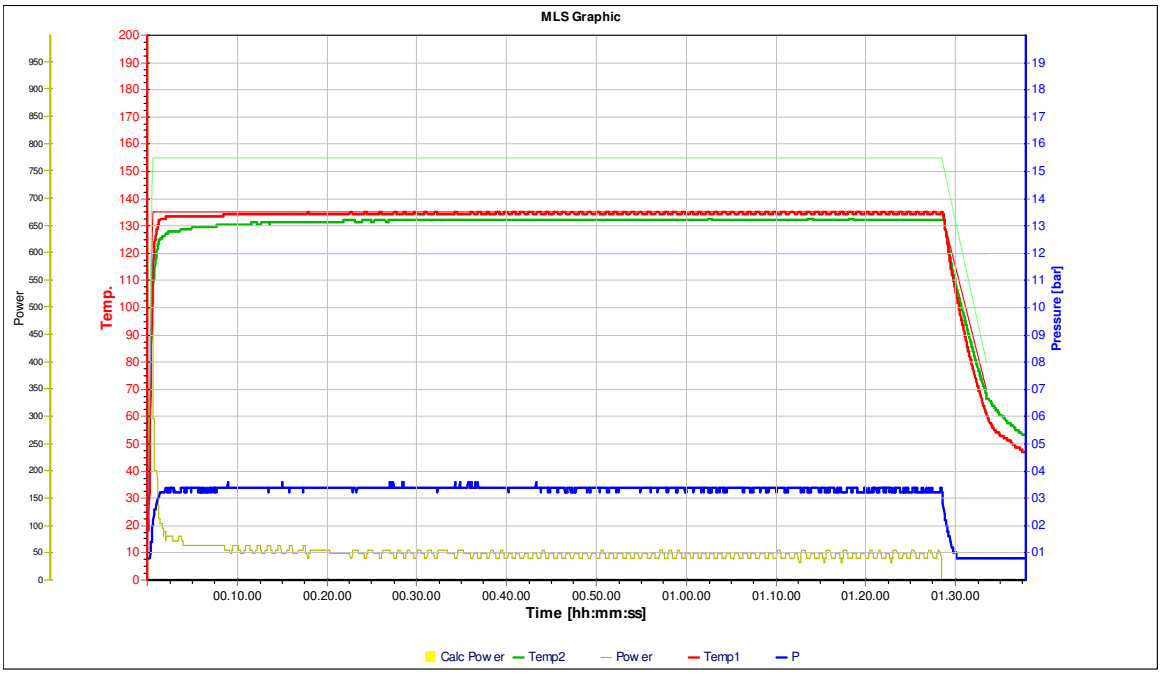
It takes 40 s to reach T = 120 °C.



- 135 °C (conversion: 59 %)

t (sec)	Max W (W)	T_{OF} (°C)	T_{IR} (°C)	Max p (bar)
30	500	125	145	12
10	500	135	155	12
20	300	135	155	12
1h 27'36"	200	135	155	12

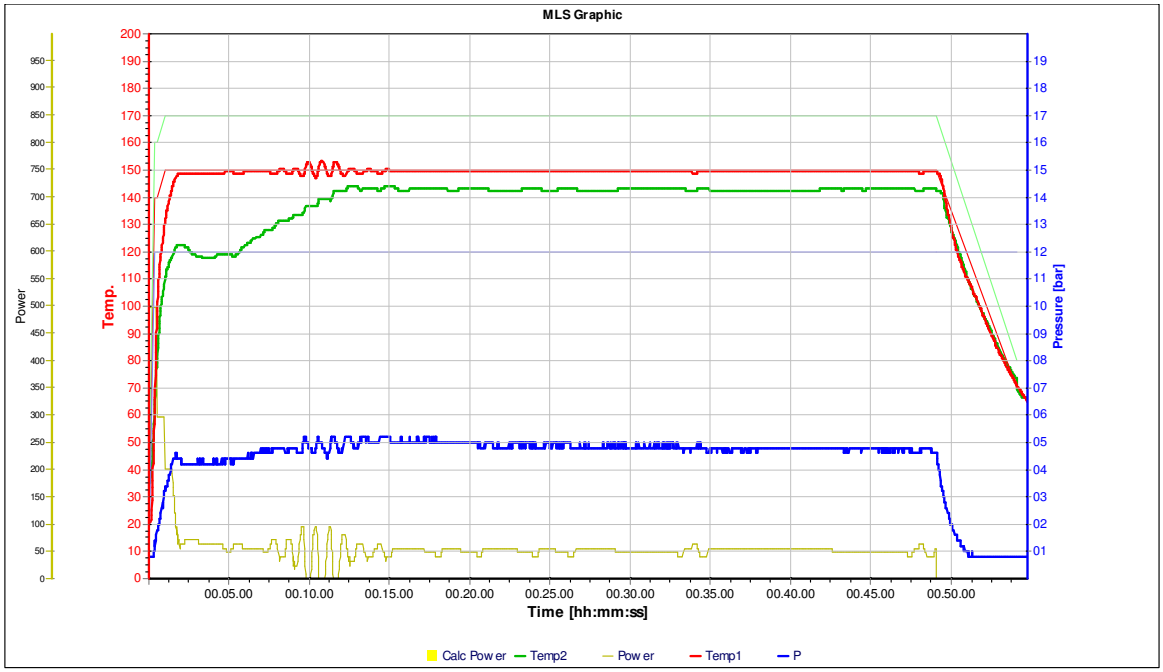
It takes 1'36" (96 s) to reach T = 133 °C.



- 150 °C (conversion: 68 %)

t (sec)	Max W (W)	T_{OF} (°C)	T_{IR} (°C)	Max p (bar)
30	500	140	160	12
10	500	140	160	12
30	300	150	170	12
28'07"	200	150	170	12

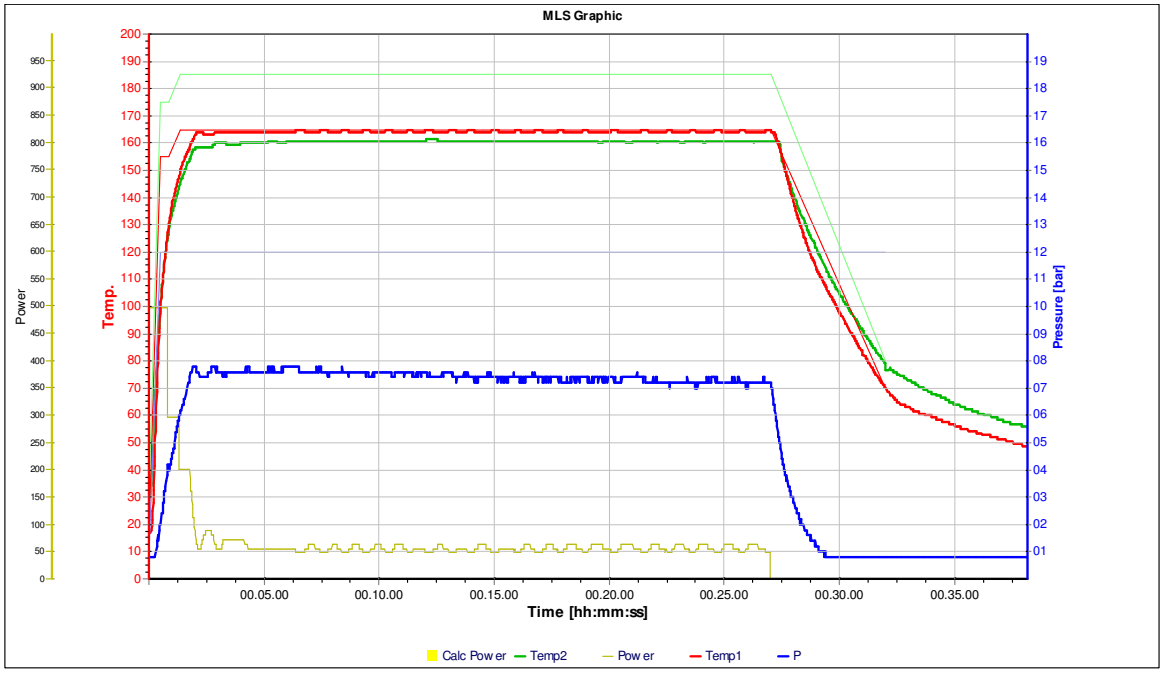
It takes 1'47"(107 s) to reach T = 149 °C.



- 165°C (conversion: 73 %)

t (s)	Max W (W)	T_{OF} (°C)	T_{IR} (°C)	Max p (bar)
30	500	155	175	30
20	500	155	175	30
30	300	165	185	30
25'42"	200	150	170	12

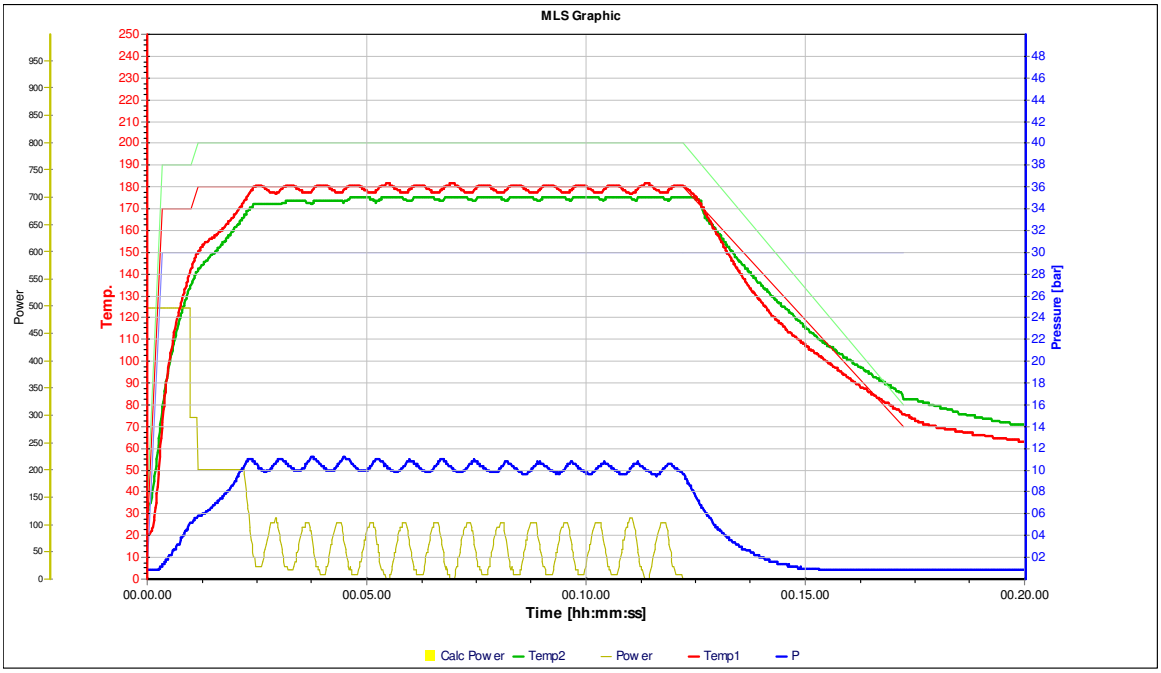
It takes 2'02" (122 s) to reach T= 165 °C.



- 180 °C (conversion: 75 %)

t (s)	Max W (W)	T_{OF} (°C)	T_{IR} (°C)	Max p (bar)
20	500	170	190	30
25	500	170	190	30
25	300	180	200	30
12’59”	200	180	200	30

It takes 1’09” (69 s) to reach T = 180 °C.

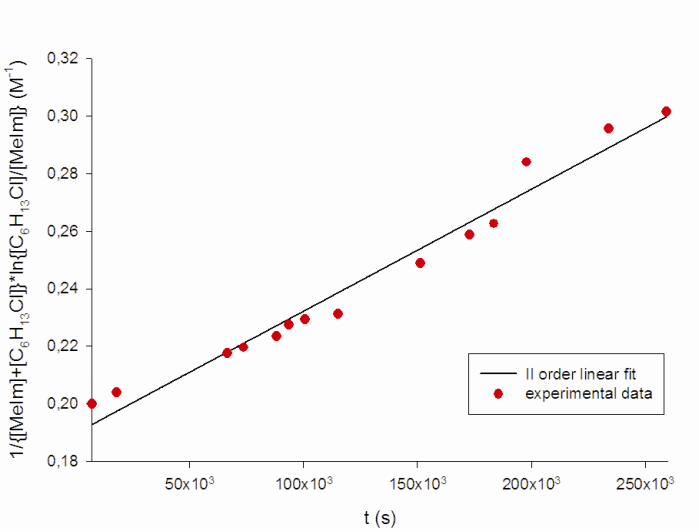


Appendix B

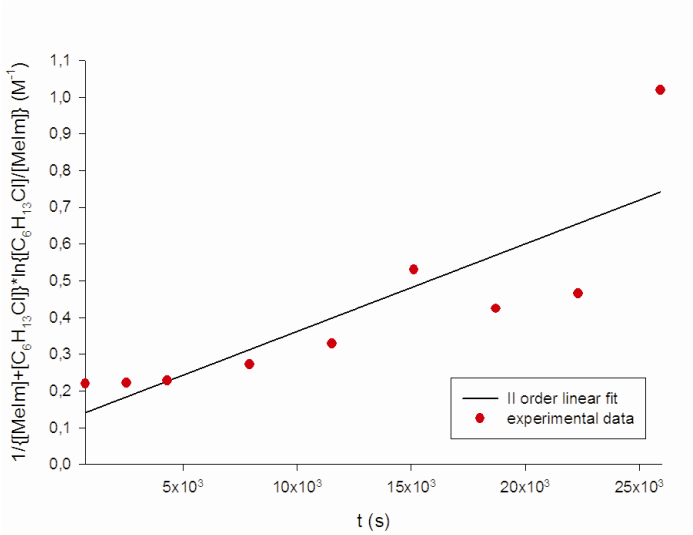
Kinetics measurements in pressurised containers

1. Synthesis of [C₆mim]Cl in CH₃CN

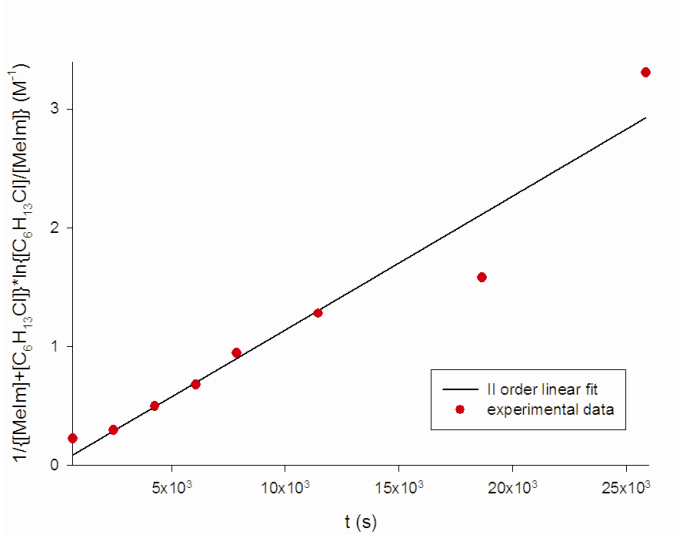
- Stem Block, 60 °C, 72 h



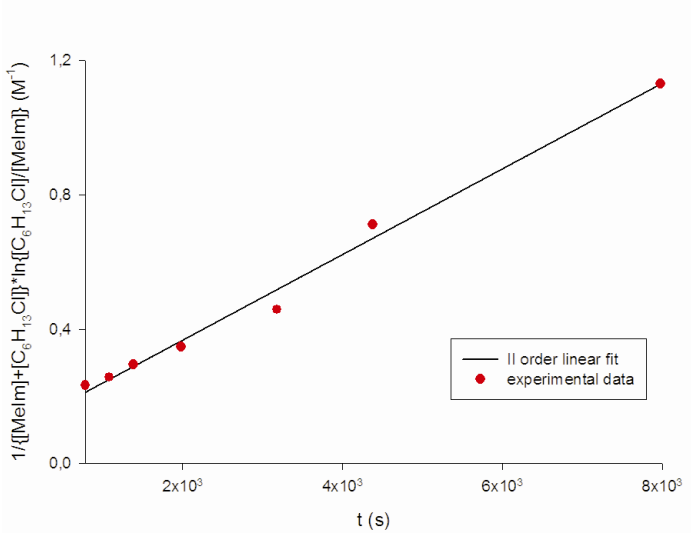
- Autoclave, 110 °C, 8 h



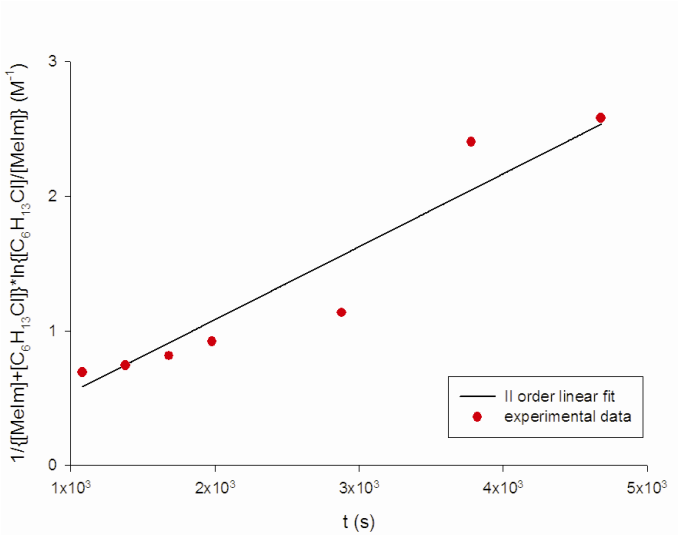
- Autoclave, 120 °C, 9 h



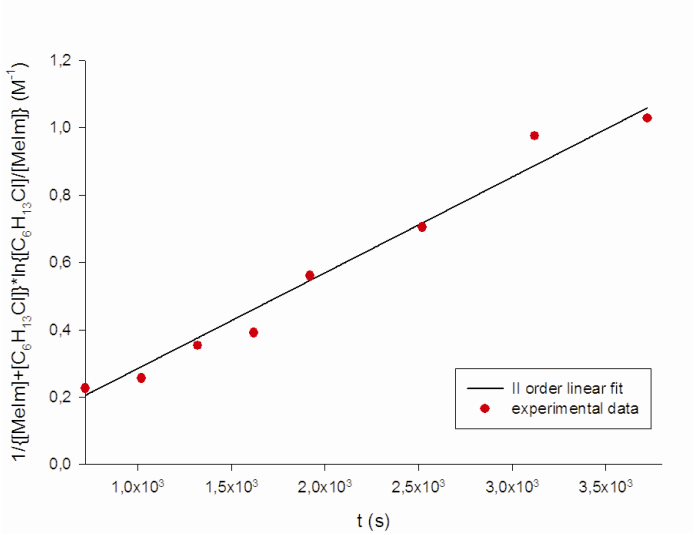
- Autoclave, 140 °C, 3 h



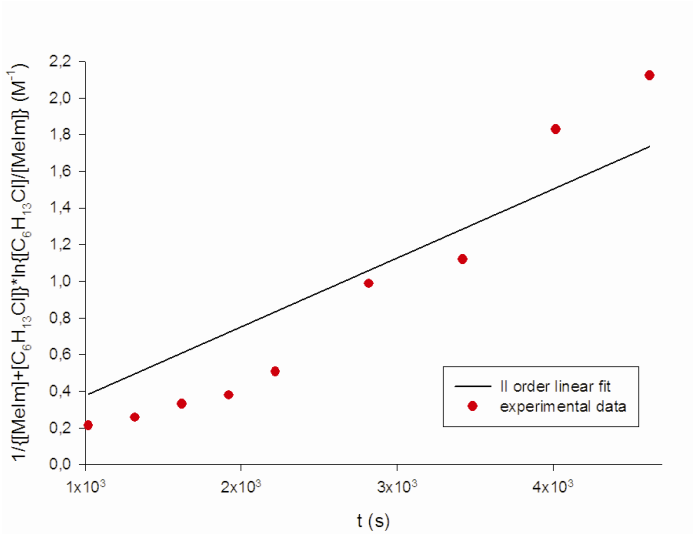
- Autoclave, 150 °C, 1 h



- Autoclave, 150 °C, 1 h, ratio MeIm:$C_6H_{13}Cl$ 1.00:1.01

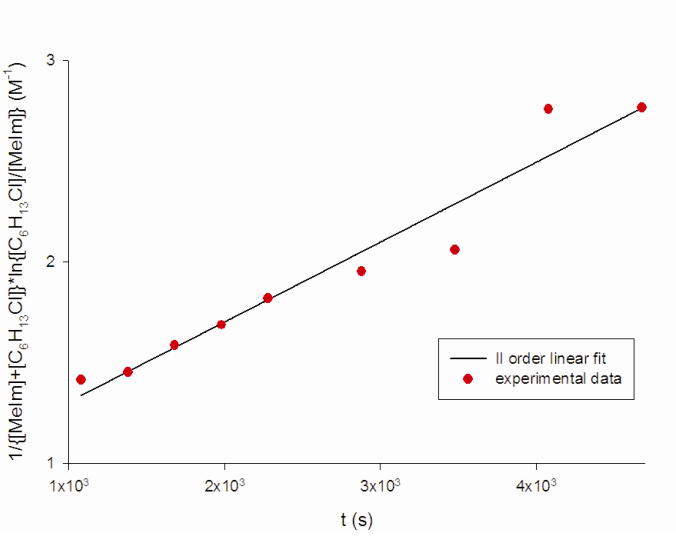


- Autoclave, 150 °C, 1 h, ratio MeIm:$C_6H_{13}Cl$ 1.00:1.10



2. Synthesis of [C_6mim]Cl in EtOH

- Autoclave, 150 °C, 1 h



Appendix C

^{1}H NMR chemical shift of synthesised compounds

1–methylnaphthalene [110]: δ_H (400 MHz, $CDCl_3$): 8.05 (d, 1H, J = 8.0; Ar*H*); 7.90 (d, 1H, J = 7.5; Ar*H*); 7.75 (d, 1H, J = 8.0; Ar*H*); 7.59–7.51 (m, 2H; Ar*H*); 7.42 (t, 1H, J = 8.0; Ar*H*); 7.37 (d, 1H, J = 8.0; Ar*H*); 2.75 (s, 3H; *Me*).

2–methylnaphthalene [110]: δ_H (400 MHz, $CDCl_3$): 7,82 (d, 1H, *J*=8.0 Hz; Ar*H*); 7.78 (d, 1H, *J*=8.0 Hz; Ar*H*); 7.77 (d, 1H, *J*=8.0 Hz; Ar*H*); 7.64 (s, 1H; Ar*H*); 7.49–7,41 (m, 2H; Ar*H*); 7.34 (dd, 1H, *J*=8.0 Hz; Ar*H*); 2.55 (s, 3H; *Me*).

1–methyl–2–nitrobenzene [110]: δ_H (400 MHz, $CDCl_3$): 7.96 (d, 1H, *J*=12.0 Hz; Ar*H*); 7.50 (d, 1H, *J*=8.0 Hz; Ar*H*); 7.32–7.36 (m, 2H; Ar*H*); 2.60 (s, 3H; *Me*).

1–methyl–4–methoxybenzene [110]: δ_H (400 MHz, $CDCl_3$): 7.09 (d, 2H, *J*=8.0 Hz; Ar*H*); 6.81 (d, 2H, *J*=8.5 Hz; Ar*H*); 3.78 (s, 3H, O*Me*); 2.30 (s, 3H; *Me*).

1–methyl–2–methoxybenzene [110]: δ_H (400 MHz, $CDCl_3$): 7.18 (dd, 1H, *J*=7.5 Hz; Ar*H*); 7.16 (dd, 1H, *J*=7.5 Hz; Ar*H*); 6.87 (dd, 1H, *J*=7.5 Hz; Ar*H*); 6.83 (dd, 1H, *J*=7.5 Hz; Ar*H*); 3.84 (s, 3H, O*Me*); 2.23 (s, 3H; *Me*).

1–methyl–4–nitrobenzene [110]: δ_H (400 MHz, $CDCl_3$): 8.11 (d, 2H, *J*=5.6 Hz; Ar*H*); 7.32 (d, 2H, *J*=8.4 Hz; Ar*H*); 2.46 (s, 3H; *Me*).

4,4'–dinitrobiphenyl [155]: δ_H (400 MHz, $CDCl_3$): 8.36 (d, 4H, *J*=8.8 Hz; Ar*H*); 7.32 (d, 4H, *J*=8.8 Hz; Ar*H*).

1,3–dimethylbenzene [110]: δ_H (400 MHz, $CDCl_3$): 7.15 (t, 1H, *J*=7.2 Hz; Ar*H*); 6.98 (t, 3H, *J*=6.0 Hz; Ar*H*); 2.32 (s, 6H; *Me*).

4–methylphenol [110]: δ_H (400 MHz, $CDCl_3$): 7.03 (d, 2H, *J*=4.4 Hz; Ar*H*); 6.73 (dt, 2H, *J*=6.4 Hz; Ar*H*); 2.75 (s, O*H*); 2.27 (s, 3H, *Me*).

4–methylbenzaldehyde [110]: δ_H (400 MHz, $CDCl_3$): 9.96 (s, 1H, C*H*O); 7.77 (d, 2H, *J*=6.4 Hz; Ar*H*); 7.33 (d, 2H, *J*=8.0 Hz; Ar*H*); 2.44 (s, 3H; *Me*).

1–methyl–4–(trifluoromethyl)benzene [110]: δ_H (400 MHz, $CDCl_3$): 7.51 (d, 2H, *J*=8.0 Hz; Ar*H*); 7.28 (d, 2H, *J*=8.0 Hz; Ar*H*); 2.41 (s, 3H; *Me*).

4,4'–bis(trifluoromethyl)biphenyl [156]: δ_H (400 MHz, $CDCl_3$): 7.75–7.69 (m, 8H, Ar*H*).

List of publications and chemistry schools attended

Publications:

“Metal–Catalyzed Electrophilic Processes in Ionic Liquids” Conte, V.; Fiorani, G.; Floris, B.; Galloni, P.; Mirruzzo, V. in *Green Chemistry Research Trends*; Pearlman, J. T. (Ed.) Nova Science Publisher, Inc.; New York, **2009**, pp. 131-160.

"Improvements of ferrocene acylation. Conventional *vs.* Microwave heating for scandium–catalyzed reaction in alkylmethylimidazolium–based ionic liquids" Berardi, S.; Conte. V.; Fiorani, G.; Floris, B.; Galloni, P. *J. Organomet. Chem.* **2008**, *693*, 3015-3020.

Chemistry Schools attended:

January 2007: Winter School of Physical Organic Chemistry, WISPOC 2007, Bressanone (TN), Italy.

June 2007: XXXII "A. Corbella" Summer School – Seminars in Organic Synthesis, Gargnano (BS), Italy.

October 2008: Summer School on Green Chemistry, 10th event, Venice, Italy.

January 2009: European Winter School on Physical Organic Chemistry, E–WISPOC 2009, Bressanone (TN), Italy.

September 2009: VII International School of Organometallic Chemistry, ISOC 2009, Camerino (MC), Italy.

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