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INNOVATIVE GREEN METHODOLOGIES FOR C-C, C-N AND C-O BOND FORMING REACTIONS

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Tesi di dottorato di MASSIMO FABRIS, matricola 955502

Direttore della Scuola di dottorato	Tutore del dottorando
prof. Paolo Ugo	prof. Maurizio Selva
Paolo Ugo	Maurizio Selva

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Scientific-disciplinary sector of pertinence: Organic Chemistry

PhD thesis of MASSIMO FABRIS, matriculation number 955502

Director of the PhD School

prof. Paolo Ugo

Paolo Ugo

Supervisor

prof. Maurizio Selva

Maurizio Selva

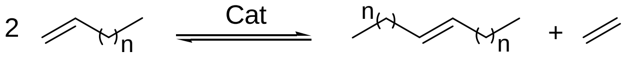
Abstract

In this PhD thesis it is presented the use of some Green Chemistry Tools such as an alternative solvent like supercritical carbon dioxide ($scCO_2$), catalysts like ionic liquids (ILs), and alternative alkylating reagents like dialkyl carbonates, for the set up of new green methodologies for C-C, C-N and C-O bond forming reactions. Two high atom economy C-C forming reactions have been considered: *i*) the self-metathesis of α-olefins has been carried out using dense CO_2 as reaction solvent and supported Re oxide as heterogeneous catalyst. With respect to the use of conventional organic solvents, $scCO_2$ allowed to achieve higher reaction conversion and productivity in both batch and continuous flow conditions; *ii*) the Michael addition of nitroalkanes and β-diketones to α,β-unsaturated ketones catalyzed by task specific phosphonium based ionic liquids. In this study, basic ionic liquids proved to be more effective catalysts than conventional organic bases [for example, DBU, DMAP, DABCO and phosphazene base P_1-*t*-Bu]. Three different reactions of dialkyl carbonates with anilines, have been explored for the formation of C-N bonds: *i*) the selective mono-hydroxyalkylation of anilines with glycerol carbonate catalysed by alkali metal exchanged Y- and X- faujasites, for the synthesis of *N*-(2,3-dihydroxy)propyl anilines; *ii*) the selective bis-*N*-methylation of anilines carried out by dimethyl carbonate prepared *in situ* via the transesterification of alkylene carbonate with methanol catalysed by alkali metal exchanged faujasites; *iii*) the alkylation of primary aromatic amines with alkylene carbonates, such as ethylene- and propylene- carbonates, catalysed by phosphonium based ionic liquids, for the selective synthesis of bis-*N*-(2-hydroxy)alkyl anilines. All these reactions proceeded with high conversion and selectivity. Finally, two classes of reactions have been explored for the formation of C-O bonds: *i*) the decarboxylation reaction of dialkyl carbonates catalyzed by different heterogeneous systems like K_2CO_3, alkali metal exchanged faujasites and hydrotalcite. The selective formation of dialkyl ethers has been observed for light dimethyl- and diethyl-carbonates, while for higher homologues (dipropyl- and dioctyl carbonate), the decarboxylation reaction occurred along with side-process producing alcohols and olefins; *ii*) the reaction of glycerol carbonate with phenol, in the presence of faujasites as catalysts, for the synthesis of *O*-(2,3-dihydroxy)propyl phenol. Under the conditions tested, the reaction was not selective to the formation of the desired product.

Estratto della tesi in lingua italiana (abstract of the thesis in Italian)

Questo lavoro di tesi è stato sviluppato presso il Dipartimento di Scienze Ambientali dell'Università Ca' Foscari, Venezia, nel laboratorio del Gruppo di Sintesi Organiche "Green", e ha riguardato la messa a punto di metodologie innovative a ridotto impatto ambientale per reazioni di formazione di legami C-C, C-N e C-O. La linea guida del lavoro è stata la volontà di sviluppare dei processi di sintesi che rispettassero i principi della green chemistry, area di interesse del gruppo di ricerca, e per questo sono stati impiegati alcuni degli "strumenti caratteristici" di questa branca della chimica. In particolare, l'utilizzo di un solvente alternativo come la CO_2 densa, l'impiego di reagenti non pericolosi o tossici come i carbonati dialchilici, e l'utilizzo di catalizzatori riciclabili eterogenei, come le zeoliti, ed omogenei, come i liquidi ionici, sono stati gli strumenti utilizzati maggiormente in questa tesi. Le reazioni studiate sono state le seguenti:

- *Sintesi di legami C-C via metatesi di olefine in $scCO_2$*: è stata sviluppata una procedura per condurre la reazione di metatesi dell' 1-ottene (schema 1) utilizzando catalizzatori eterogenei a base di Re ossido supportato e la CO_2 densa come solvente.

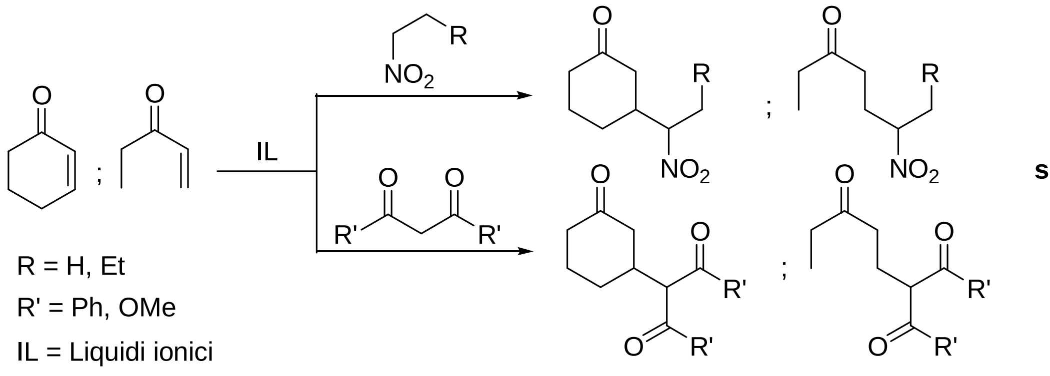


schema 1

Cat = Re_2O_7 supportato
n = 5

La reazione è stata studiata sia in condizioni batch che in flusso continuo. Il set-up dell'apparecchiatura, l'ottimizzazione dei parametri operativi (T, P) e l'individuazione del miglior supporto per il sistema catalitico sono stati l'aspetto chiave dell'indagine, che ha rilevato che l'uso della $scCO_2$ rispetto ai solventi organici convenzionali (*n*-esano) permette di condurre la reazione con conversioni, ed anche produttività, più elevate.

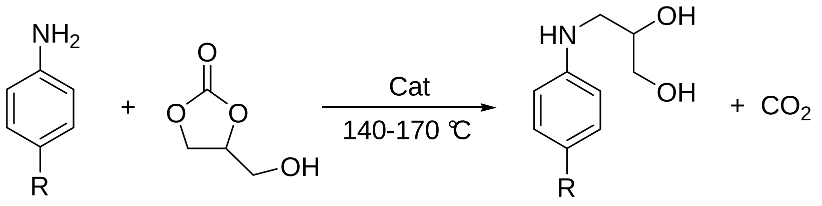
- *Sintesi di legami C-C via razioni di Michael catalizzate da liquidi ionici*: è stata messa a punto una nuova metodologia di sintesi "green" di liquidi ionici per reazione di metilazione con dimetil carbonato (DMC) di trialchil fosfine. Attraverso dei semplici scambi metatetici, da questi liquidi ionici se ne possono ottenere altri, con differenti caratteristiche basiche, che sono stati impiegati come catalizzatori per reazioni di Michael tra composti carbonilici α-β insaturi come accettori e composti CH_2 attivi come donatori (schema 2). Questi liquidi ionici si sono dimostrati esser catalizzatori molto attivi per queste reazioni, mostrando attività catalitiche anche superiori alle comuni basi forti organiche (DBU, DMAP, DABCO e fosfazene base P_1-*t*-Bu).



R = H, Et
R' = Ph, OMe
IL = Liquidi ionici

schema 2

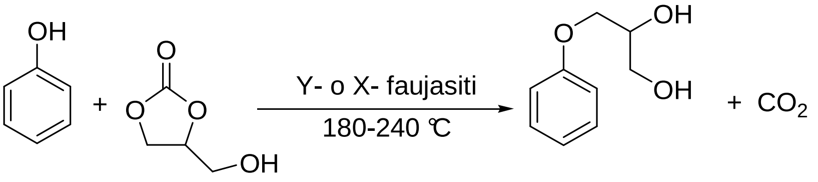
- <u>*Sintesi di legami C-N e C-O attraverso l'impiego di reagenti rinnovabili*</u>: è stata studiata la reazione di un derivato della glicerina, la glicerina carbonato (GlyC), con differenti ammine aromatiche primarie del tipo *p*-$XC_6H_4NH_2$ (con X= H, OMe, Cl, OH) in presenza di faujasiti tipo X e Y come catalizzatori (schema 3).



schema 3

Cat = Y- o X- faujasiti ; R = H, OCH_3, Cl, OH

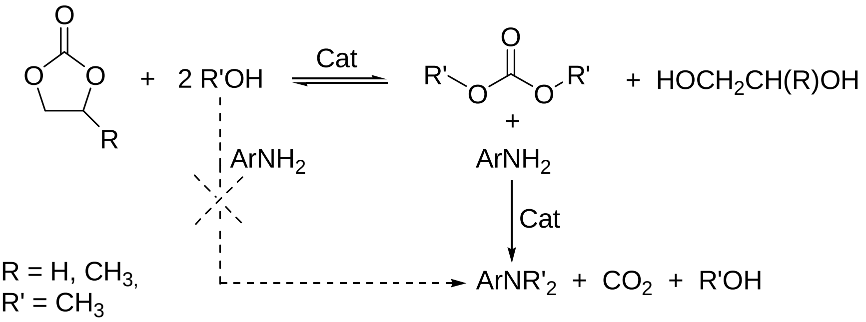
Per le reazioni studiate, la GlyC si è dimostrata un ottimo agente alchilante "green" dando reazioni ad alta conversione (~90%) e selettività (80-90%). Sono stati studiati anche il meccanismo di reazione e il riciclo del catalizzatore. E' stata studiata inoltre la medesima reazione con nucleofili all'O tipo il fenolo (schema 4).



schema 4

Nelle condizioni studiate la GlyC non si è dimostrata essere un buon agente alchilante nei confronti del fenolo, e la reazione procede con basse conversioni e selettività.

- <u>*Formazione di legami C-N via bis-N-metilazione di aniline con carbonati ciclici e MeOH*</u>: è stata messa a punto una procedura, denominata "green domino", in cui la bis-*N*-metilazione di aniline, formalmente condotta dal metanolo, avviene invece per mezzo del dimetil carbonato (DMC) prodotto direttamente nell'ambiente di reazione per reazione di transesterificazione di un carbonato ciclico, l'etilene carbonato, con il metanolo (schema 5). I catalizzatori in grado di promuovere entrambe le reazioni di transesterificazione/metilazione sono la faujiasiti di tipo X o Y. L'ottimizzazione dello step di transesterficazione, lo studio della reattività relativa del DMC e del EC nei confronti dell'anilina, e l'influenza delle variabili operative (T, natura del solvente, ecc.) sono stati oggetto di indagine.

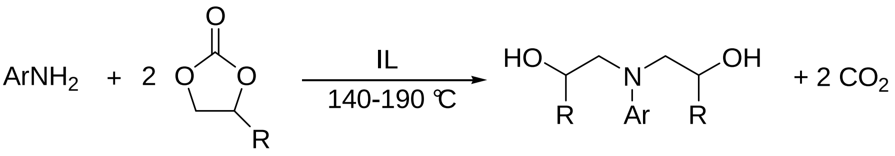


schema 5

R = H, CH_3,
R' = CH_3
Cat = faujasiti
Ar = Ph, *p*-MeC_6H_4, *p*-$MeOC_6H_4$, *p*-ClC_6H_4, *p*-$NO_2C_6H_4$

Si è studiato anche l'utilizzo di altri alcoli (EtOH, *n*-PrOH e glicerina) e di altri carbonati ciclici (propilene e glicerina carbonato), tuttavia senza buoni risultati.

- <u>*Bis-N-idrossi alchilazione di aniline con carbonati ciclici catalizzata da liquidi ionici*</u>: è stata studiata la reazione di alchilazione di ammine aromatiche primarie con carbonati organici ciclici come l'etilene e il propilene carbonato, per la sintesi selettiva di bis-*N*-(2-idrossi)alchil-aniline (schema 6).

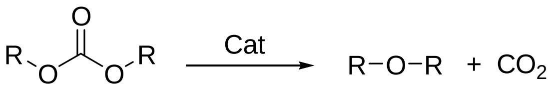


schema 6

IL = liquidi ionici basici
Ar = *p*XC_6H_4-; X = OCH_3, CH_3, H, Cl
R = H, CH_3

Come catalizzatori sono stati impiegati i liquidi ionici già descritti per la reazione di Michael: la reazione procede con alte rese e selettività ed è stato condotto uno studio di scale-up.

- <u>*Formazione di legami C-O via decarbossilazione di dialchil carbonati*</u>: è stato condotto uno studio dettagliato sulla reazione di decarbossilazione dei carbonati dialchilici in presenza di differenti sistemi eterogenei, come K_2CO_3, le faujasiti X e Y e l'idrotalcite (schema 7).



schema 7

Cat = K_2CO_3, X o Y faujasiti, idrotalcite
R = Me, Et, *n*-Pr, Octil

E' stata osservata la selettiva formazione dei corrispondenti dialchileteri nel caso dei carbonati leggeri (dimetil- e dietil- carbonato), mentre nel caso degli omologhi superiori (dipropil- e diottil- carbonato) la reazione di decarbossilazione è accompagnata da reazioni secondarie che portano alla formazione di alcoli ed olefine.

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CHAPTER 1. Introduction

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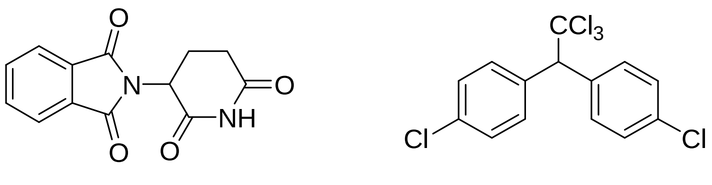
Introduction

1.1 Green Chemistry

1.1.1 Historical Overview

It is from the early 1960s that the issue of the "environmental impact" of chemical substances has come into the public dialogue and has been fully recognized as a problem. Before those years there were little or no environmental regulations on chemicals production, use and disposal, and it was not uncommon for chemical substances to be released directly to the air, water and land. Moreover, there was a deep lack of knowledge about the hazard of chemicals and their effects on the environment and human health. It was in this scenario that the first negative, and sometimes tragic, consequences due to a misuse of chemicals emerged, causing public outcries that resulted in laws and regulations to control the manufacture, treatment or disposal of chemicals.[1]

As an example of undesired and unexpected effects of chemicals on human health, significant is the case of thalidomide (figure 1.1). This synthetic drug was commercialized in Europe during the 1950s and was it used by women to lessen the nausea during pregnancy. The side complication of the use of thalidomide emerged in 1961, when the drug was found to have severe teratogenic (malformation-inducting) side effects. Children of women taking the drug suffered acute birth defects, in many cases in the form of missing or grossly deformed limbs.[1] This was one of the biggest medical disasters of modern times: more than 10.000 such children were born world-wide causing great fear in the general public about the effects that synthetic chemicals could have on human health. The tragedy lead to stringent governmental regulations for testing new drugs for teratogenic hazards before they can be licensed.



thalidomide DDT

Figure 1.1

Another example is the case of the 1,1,1-trichloro-2,2-bis(4-chlorophenyl)ethane (DDT, figure 1.1). This pesticide was used since 1939, but at beginning of 1960s, it was found to be a harmful biopersistent substance suspected to be a carcinogen compound. In the United States Rachel Carson wrote the book *Silent Spring* (1962),[2] which illustrated how the use of DDT and other pesticides could spread throughout the food chain, causing irreparable and unanticipated harm. As a final result, stringent regulatory controls on pesticide manufacturing and use were promulgated.

Other environmental disasters/issues occurred since 1960s that resulted in new, and specific, laws being enacted. A few examples: in the late 1960s the Cuyahoga River in Ohio was so acutely polluted by the waterfront industries that it caught fire. The image of a river in flames because of chemical pollution prompted calls for legislation to ensure clean water controls through regulation. In the 1980s, as the effect of chlorofluorocarbons (CFCs) on the stratospheric ozone layer become clearer, the Montreal Protocol was adopted. In the same period, the emerging effects of global warming resulted in the Kyoto Protocol, adopted in 1997, for the regulation and reduction of greenhouse gases emission (GHG; carbon dioxide, methane, nitrous oxide, sulphur hexafluoride) to prevent dangerous anthropogenic interference with the climate system.

Moreover, accidental chemical disasters also pointed out the need of regulations for chemicals (storage, handling, use, release and disposal) and lead a large part of public opinion to view chemicals and chemistry as something to be afraid of, curtailed, and avoided wherever possible. Two emblematic cases come to mind: the Seveso disaster (Italy) in 1976, where the accidental release of the toxic dioxin 2,3,7,8-tetrachlorodibenzodioxin (TCDD) from the ICMESA plant induced such a high air/land contamination that the surrounding area needed to be evacuated, and the tragedy at Bhopal (India) in 1984, where hundreds of people were killed by the accidental release of the extremely toxic methyl isocyanate from a plant of Union Carbide. Those disasters generated the Seveso Directive of 1982 and the Emergency Planning and Community Right-to-Know Act of 1986, respectively.

A major consequence of all these misuses and accidents was that from 1960s to nowadays environmental statutes and regulations have proliferated at an exponential rate (figure 1.2).[3]

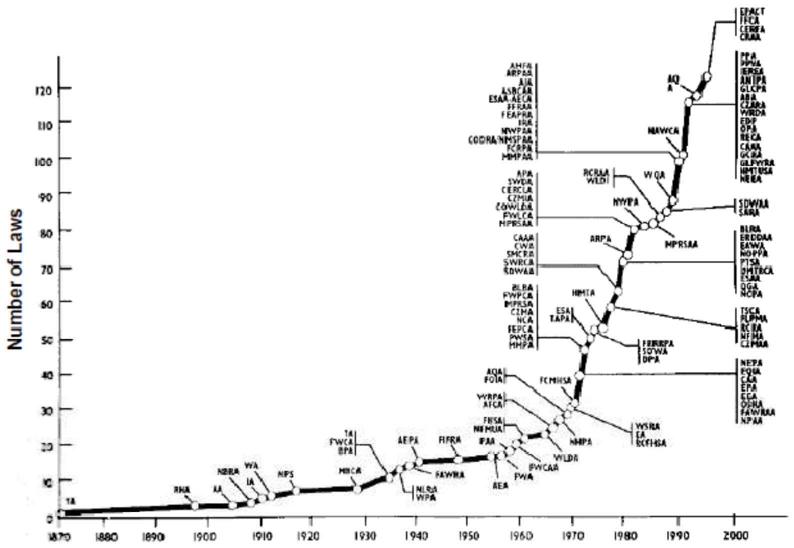


Figure 1.2. Proliferation of environmental laws and regulations (USA)

The toxicity testing required by many of these regulations generated new knowledge and a new awareness about the type and degree of hazard associated with many chemicals. As toxicity end-points and environmental effects became better known, environmental laws became more stringent as well to control the amounts of chemicals released to the environment.[1]

The progress of environmental regulations produced an increased emphasis on either treatment of wastes prior to their release, or abatement of the wastes subsequent to their release, in order to mitigate the risks to human health and the environment. Many different ways were developed to reduce pollution, like the use of treatment technologies ranging from neutralization of acids, to scrubbers for air stack emissions or to incineration. These are mainly "end-of-pipe" controls that do not solve radically the pollution, but deal with the issue of transforming wastes into more innocuous forms in order to minimize the impacts of chemicals.

Nonetheless, the increased restrictions on the use of certain compounds also provided powerful incentives for industry [confronted by tremendous pressure, not only to reduce the release of toxic product to the environment, but also to reduce the use of hazardous chemicals] and chemists to find replacements, substitutes, or alternatives.[3] In particular, at the beginning of 1990s, chemists started facing the issue of the "environmental impact" trying to find a way not only to reduce pollution, but to prevent it already at the stage of synthetic pathway design.

This new approach, that provides a fundamental methodology for changing the intrinsic nature of a chemical product or process to make it inherently of less risk to human health and the environment, was named later with the term "*green chemistry*".[4,5,6]

1.1.2 Definition and Concepts of Green Chemistry

Since the very beginning of the chemical industry, the traditional approach of synthetic chemists was dictated by economical aspects: target molecules had to be produced at the lowest possible cost irrespective to the synthetic strategy that was used. In other words, the environmental/health issue was not- or only very limitedly considered. A different and innovative standpoint to address the environmental impact of chemical productions started to grow in the middle 1990s under the general philosophy of green chemistry. Today, green chemistry has become an internationally recognized focus area of chemical science and it is defined by IUPAC as "*the invention, design and application of chemical products and processes to reduce or to eliminate the use and generation of hazardous substances*".[1,3] Looking closely at the definition, it is possible to highlight some important aspects that form the concept of green chemistry.

The first is the use of the words "*invention*" and "*design*". The impacts of chemical products and chemical processes are included as design criteria, so green chemistry is a way to prevent pollution already at the stage of synthetic pathway design.

Another aspect is found in the phrase “*use and generation*”. To prevent pollution and health hazard green chemistry focuses on all substances that are part of the process, not only on those undesirable substances that might be inadvertently produced. Not only the waste issue, but also the significant consequences of the use of hazardous substances, ranging from regulatory, handling and transport, and liability issues, to name a few, must be considered.

Finally, the definition includes the term “*hazardous*”. Green chemistry is a hazard-based approach to risk reduction and pollution prevention by minimizing the intrinsic hazards of the substances, rather than focusing on those circumstances and conditions of their use that might increase their risk. This is a very important aspect, and to understand it there is the need to introduce the concept of risk. At its most basic level, risk can be described as the product of hazard and exposure:[3]

Risk = **Hazard** x **Exposure**

The traditional approaches to risk reduction focus on reducing exposure to hazardous substances. Regulations often require increases in control technologies and treatment technology, and in personal protective equipments in order to reduce risk by restricting/limiting exposure. But these approaches may fail because they rely on either equipment or human activity: equipments can rupture, air scrubbers can break down, etc. When failure occurs, risk is maximized because the resultant is an exposition to a constant hazard. The green chemistry approach, on the other hand, imposes to reduce risk by reducing hazard associated to chemical products and transformations. This conceptually different method makes green chemistry intrinsically invulnerable to failure, since there is no way for an innocuous reagent/solvent to become arbitrarily dangerous.

Moreover, the definition of green chemistry also illustrates another important point about the use of the term “*hazard*”. This term is not restricted to physical hazards such as explosiveness, flammability and so on, but it includes also acute and chronic toxicity, carcinogenicity, and ecological toxicity. Nowadays a lot about the hazards of chemicals is known, so it is possible for chemists to translate this knowledge into powerful tools for structure–activity relationships that correlate hazard with molecular construction. Furthermore, for the purposes of this definition, hazards must include global threats such as global warming, stratospheric ozone depletion, resource depletion and bioaccumulation, and persistent chemicals.

1.1.3 Green Chemistry Principles

The objective of green chemistry is the development of chemical technology and processes that are designed to be safe for the environment and human health. The twelve principles of green chemistry, as articulated by Anastas and Warner,[1] can guide chemists towards fulfilling their unique and vital role in achieving sustainable development. These principles are listed and shortly described below:

I. *It is better to prevent waste than to treat or clean up waste after it is formed.*

This principle is "the first" of green chemistry as it is clear that the aim to pollution prevention is represented in the words "*better to prevent waste*". Beyond the environmental implication, there is also an economic aspect that should be pointed out. With the proliferation of environmental statutes and regulations the cost of treatment and disposal of chemical substances has become of significant importance. Often the cost of waste disposal may be many times the cost of starting material. This principle is therefore also a way to minimize this cost.

II. *Synthetic methods should be designed to maximize the incorporation of all materials used in the process into the final product.*

This principle basically states that the time-honored concept of "yield" as a standard to measure the efficiency of a synthetic methodology must be replaced by more modern metrics such as "atom economy".[7] Yield in fact, is the percentage of moles of the desired product obtained with respect to the theoretical moles of desired product obtainable. By its definition, yield does not consider the use or generation of undesirable by-products that may be an intrinsic part of a synthetic process. It is possible to achieve 100% yield and generate wastes that could be far greater in mass and volume than that of the desired product. On the other hand, atom economy is the ratio between the molecular weight of the desired product and the sum of all the molecular weights of reactants. Atom economy measures the degree to which each of the reactant is incorporated into the final product: only a reaction where all atoms contained in the reactants are incorporated into the product completely is 100% atom economical.

III. *Wherever practicable, synthetic methodologies should be designed to use and generate substances that possess little or no toxicity to human health and the environment.*

As aforementioned, one of the fundamental bases of green chemistry is to reduce chemical risks by lowering or eliminating the use of hazardous compounds throughout all the steps of the synthetic strategy. The main goal is the development of safe processes for human health and the environment. This principle however, puts forward also an economical benefit. The upfront capital costs of exposure controls (from engineering controls through protective gear) can be reduced/eliminated by achieving risk reduction through hazard reduction.

IV. Chemical products should be designed to preserve efficacy of function while reducing toxicity.

In recent years, a great progress has been done in the understanding of the chemical toxicity, and of the mechanism of action of substances on the body and in the environment. Thanks to this knowledge, it is now possible for chemists to design safer compounds. By changing the physical and chemical properties of a molecule (*e.g.* water solubility and polarity) it is possible to minimize its bioavailability and capability of being absorbed through biological membranes and tissue, making the toxic substances innocuous.

V. The use of auxiliary substances (e.g., solvents, separation agents, etc.) should be made unnecessary wherever possible and innocuous when used.

In a chemical process, the auxiliary substances are those that aid the reaction but do not appear incorporated in the product. The most widely used auxiliary substances are organic solvents which pose a number of concerns. For instance, halogenated solvents and aromatic hydrocarbons are often used because of their excellent solvency proprieties in a wide range of application, though they have long been identified as suspected human carcinogens. Moreover, as most of these solvents are quite volatile compounds, they are often involved in environmental issues like the stratospheric ozone depletion or the formation of smog in the atmospheric pollution. Green procedures aim to the elimination of the use of solvents, and if not possible, clean reactions should enhance the use of innocuous alternative media such as supercritical CO_2 and water, etc.

VI. 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.

As energy generation and consumption has long been known to include adverse environmental effects, chemists must consider the need for energy in the synthetic pathway design, and strive to reduce it. It is well known that both heating (*e.g.* to accelerate reaction) and cooling (*e.g.* to control reactivity) involve additional costs, as well as purification/separation procedures like distillation, recrystallization or ultrafiltration in which energy is needed. This principle prompts to include energy requirements of all the stages of a synthetic process as evaluation process criteria, and to minimize them.

VII. *A raw material or feedstock should be renewable, rather than depleting, wherever technically and economically practicable.*

This principle stresses how the purpose of green chemistry, beyond pollution prevention, is the "sustainability". This latter can be defined as the ability to maintain the development of the quality of life while not compromising the ability of our progeny to do the same. The use of depleting resources like petroleum violate the goals of sustainability, and the use of renewable feedstocks like biological and plant-based starting material should be adopted according to ethical guidelines implying the use of non-food renewables.

VIII. *Unnecessary derivatization (blocking group, protection/deprotection, temporary modification of physical/chemical processes) should be avoided whenever possible.*

The use of blocking/protecting groups is a quite common practice especially in organic chemical synthesis. Nonetheless, any molecular modification to produce a new derivative by adding a functional group and then replacing it is an intrinsically undesirable process from the green chemistry standpoint: it not only generate wastes, but it usually requires a solvent per each of the involved steps, and it involves costly purification procedures.

IX. *Catalytic reagents (as selective as possible) are superior to stoichiometric reagents.*

Catalysts by definition, facilitate chemical transformations without being consumed or incorporated in the final product, and very often they can be recycled and reused many times before they lose their activity. In addition, catalysts allow general enhancement of reaction selectivity and energy usage minimization. Overall, they can improve the utilization of the starting-material and reduce the production of waste. Thanks to all these aspects, catalysis represents a fundamental pillar of green chemistry.

X. *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.*

This principle is related to the so-called "persistent chemicals" or "persistent bioaccumulators" substances like plastics or organohalogen-based pesticides. These compounds represent a major concern in terms of pollution of the environment. In this contest, clean compounds should be designed so that, at the end of their use, they are degraded by the environment itself. For example, the biodegradability of a chemical can be enhanced by placing functional groups in the molecular structure sensitive to hydrolysis, photolysis or other cleavage reactions occurring spontaneously in the environment. This facilitates the disassembly of the original compounds into innocuous degradation products.

XI. *Analytical methodologies need to be further developed to allow for real-time in-process monitoring and control prior to the formation of hazardous substances*.

This principle is quite straightforward: by using in-process and real-time analytical methodologies, a chemical process can be monitored for the generation of hazardous by-products and side reactions. If the sensors are interfaced directly with process parameters controls, the hazard minimization can be automated, and the waste production minimized as well.

XII. *Substances and the 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*.

Green chemistry aims at the development of chemical processes that in first place, are safe. Therefore, the importance of accident prevention cannot be overstated. Approaches to the design of safer chemistry can include for example the use of solids or low vapor pressure substances rather than volatile liquids or gases.

The 12 principles have become a widely accepted set of criteria for the rapid assessment of the "greenness" of a chemical route. Yet, they are not certainly exhaustive,[8] since they do not directly settle practical parameters that chemists can use to evaluate and compare the greenness of different processes. Also, they do not provide a quantitative measure of environmental performance.

1.1.4 Green Chemistry Metrics and Tools

In the development of a sustainable chemical route, the above described principles of green chemistry are useful to set the theoretical approach that chemists should adopt. But for the practical and quantitative evaluation of a chemical process, the formulation of straightforward numerical operative parameters is needed. For this reason a large number of parameters to measure the eco-compatibility and economic sustainability of a chemical process have been proposed by different authors.[9] All these parameters are named "*green chemistry metrics*". While the principles of green chemistry are criteria answering to the question "*How to do it?*", the use of green chemistry metrics gives a means to answer the question "*How much green is it?*". Some examples of the more widely used metrics are reported in table 1.1.

Table 1.1. Examples of green chemistry metrics

Metric	Formula
Environmental factor (**E**)	$E = \dfrac{\text{total waste [kg]}}{\text{product [kg]}}$
Atom economy (**AE**)	$AE = \dfrac{\text{m.w. product}}{\Sigma\ \text{m.w. reagents}} \text{ x } 100$
Reaction mass efficiency (**RME**)	$RME = \dfrac{\text{mass of product [kg]}}{\Sigma\ \text{mass reagents [kg]}} \text{ x } 100$
Carbon efficiency (**CE**)	$CE = \dfrac{\text{carbon mass in product [kg]}}{\Sigma\ \text{carbon masses in reagents [kg]}} \text{ x } 100$
Effective mass yield (**EMY**)	$EMY = \dfrac{\text{mass of products [kg]}}{\text{mass of non-benign reagents [kg]}} \text{ x } 100$
Mass index (**S^{-1}**)	$S^{-1} = \dfrac{\Sigma\ \text{reagents + catalysts + solvents [kg]}}{\text{product [kg]}}$
Cost index (**CI**)	CI = € / kg of product

The environmental factor (E) measures the greenness of a process considering the amount of waste that is generated for each kg of desired product: the main limit of this metric is the difficulty of define a boundary for what must be considered as waste.[10] The atom economy (AE), as already written above, measures the degree of incorporation of reactants in the desired product but does not consider the yield or the nature of wastes.[7] The reaction mass efficiency (RME) and the carbon efficiency (CE) join together the concept of atom economy and yield, considering the mass or the carbon content respectively, but still the wastes are not considered.[11] The effective mass yield (EMY), defined as the percentage of the mass of desired product relative to the mass of all non-benign materials used in the synthesis, is a metric that considers the toxicity of the substances used in a chemical route: here the main limit is the definition and quantification of whatever is non-benign.[12] The mass index (S^{-1}) is a metric that defines the overall mass flow in a chemical process, by taking into account the degree of incorporation of all the substances used in a process into the final desired product.[11] Finally, the cost index (CI) is a parameter that sets if a synthetic procedure is economically viable once all costs (upstream and downstream) are considered. It should be stressed here that in the design/evaluation of a process, the consideration of only one of these metrics does not give a complete information about the greenness of the procedure. Let's consider for example AE: this is a good parameter for a preliminary evaluation of the greenness of a synthetic transformation, but it is not suitable as a standalone green chemistry metric, since it does not consider the yield and the wastes of a process. Other metrics often give a more realistic assessment of a reaction: for instance, RME examines the process in terms of yield and molar quantities involved. The mass index, S^{-1} considers the overall mass flow of the chemical process.

The perfect green synthesis process should respect all the twelve green chemistry principles and pass the test of green chemistry metrics, but this is a hard goal. So the solutions/tools proposed by chemists for green chemistry have been once by once, influenced by the principles/aspects selected as the most relevant. From the chemical synthetic point of view, if we think that a generic reaction can be represented by the sentence "*a starting material set to react with a reagent in presence of a catalyst and a solvent*", it is quite clear that the green chemistry tools can be broken down into the following categories: *i*) alternative feedstocks/starting material; *ii*) alternative reagents; *iii*) alternative catalysts; *iv*) alternative solvents.

For what specifically concerns the green chemistry tools adopted in this PhD thesis work, a more in depth analysis of alternative solvents such as supercritical carbon dioxide ($scCO_2$), catalysts like ionic liquids (ILs), and alternative reagents like dialkyl carbonates is addressed.

1.2 Supercritical CO_2: a Green Solvent for Organic Synthesis

An important area in green chemistry deals with the design of environmentally benign media to replace the common organic solvents used in chemical processes. As already mentioned in paragraph *1.1.3.V*, the use of organic solvents poses a number of concerns: many of these substances in fact are inherently dangerous due to their flammability, carcinogenicity, toxicity, and/or volatility, etc. The overall relevance of this issue can be better understood if one considers the quantities of solvents manipulated by the chemical industry. As shown in figure 1.3, in recent years the worldwide consumption of organic solvents can be estimated around 20 million tons per year.[13]

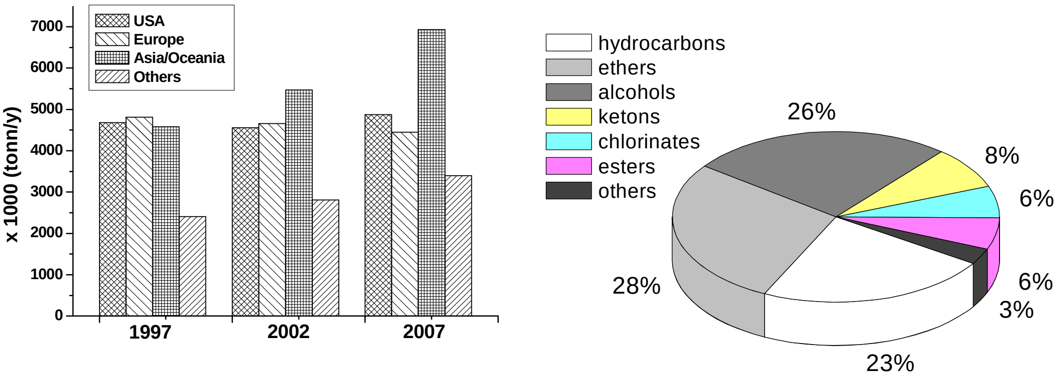


Figure 1.3. The worldwide consumption of organic solvents until 2007 (left). The distribution of the major classes of organic solvents used in the US market in 2002 (right)

Another remarkable example is reported in figure 1.4 which shows the trend of European market of light chlorinated hydrocarbons, such as dichloromethane and perchloroethene. These compounds have been long identified as highly toxic compounds, suspected to be human carcinogens. Although a general tendency to reduce the use of such products can be appreciated, the consumption in 2007 still reached the considerable amount of around 180 thousand tons per year (figure 1.4).[14]

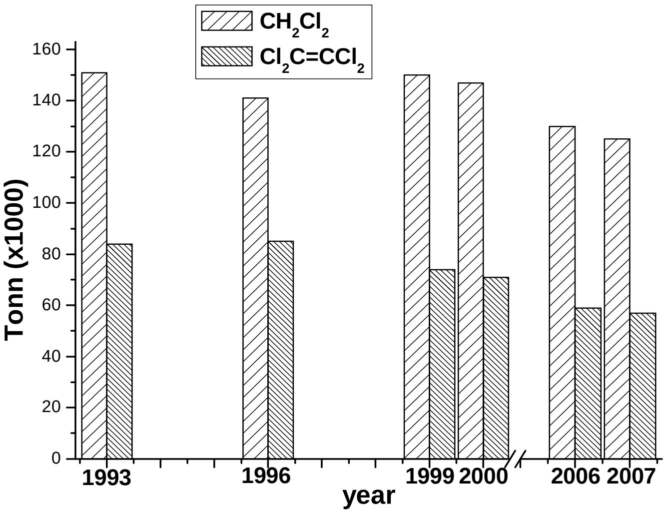


Figure 1.4. The European consumption of light chlorinated hydrocarbons from 1993 to 2007

These impressive numbers show the size of the problem: the development and selection of appropriate alternative solvents is becoming one of the crucial aspects to decrease environmental, health and safety impacts of industrial processes.

In this context, chemists have looked at several green alternatives during the past two decades. Among them the use of dense CO_2 as solvent in new eco-friendly synthetic methodologies design is very attractive. CO_2 is not only an intrinsically eco-compatible and a not flammable compound, but it is also very abundant in wildlife reserve of our planet and it is a by-product in many industrial processes (synthesis of NH_3, EtOH, H_2)[15] as well. Moreover, CO_2 is relatively inexpensive[16] and, as a general rule, it can be quickly and completely separated from the reaction mixture through easy depressurization.[17] As a solvent, CO_2 is mostly employed in its supercritical state ($scCO_2$) that its rather low energy intensive as critical temperature and pressure are 31 °C and 74 bar respectively (figure 1.5).[18]

As a supercritical fluid (SCF), $scCO_2$ can be considered a dense-phase gas, which in principle, can solvate a mixture of gases, liquids, and solids into a single homogeneous phase occupying the whole volume of a reaction vessel. Increasing the pressure increases the density of the $scCO_2$ reaching a liquid-like density, but a distinct gas-liquid boundary layer is not observed.[19] To appreciate the potential of $scCO_2$ as a solvent in synthetic chemistry, the tuneability of its solvent properties must be considered.

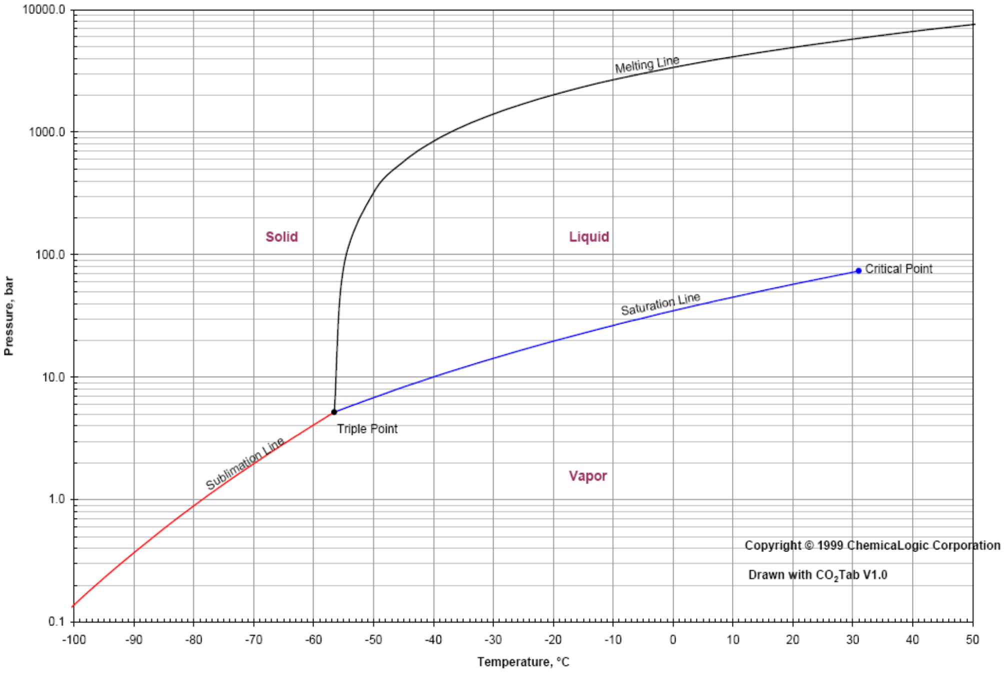
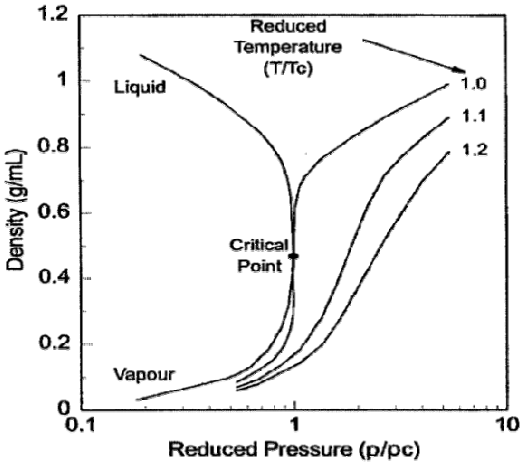


Figure 1.5. Phase diagram of CO_2

$ScCO_2$ has a solvent capability roughly comparable to apolar organic compound like cyclohexane, CCl_4 and fluorocarbons. In this context, the main aspect is its density, that close to its critical point can be greatly manipulated by small pressure and temperature variations. In figure 1.6 is reported the behavior of the density of CO_2 as function of reduced pressure, at different reduced temperatures.[16] At the reduced temperature $T_r = 1.1$ ($T_r = T/T_c$), the increase of the reduced pressure ($P_r = P/P_c$) from 1 to 3, increases the density of CO_2 of ~80%.



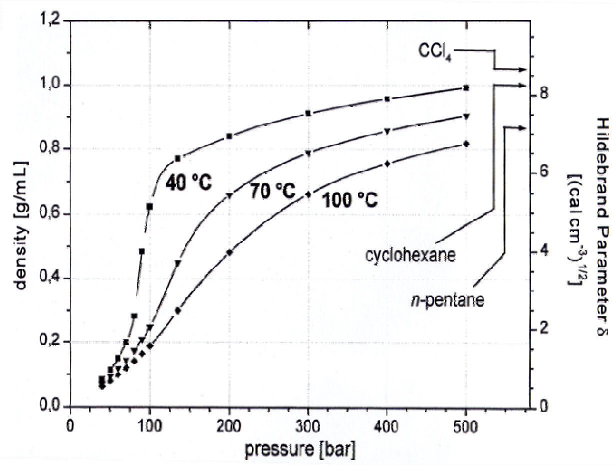


Figure 1.6 **Figure 1.7**

Moreover, the density of CO_2 continuously increases by increasing the pressure, and decreases when the temperature increases, showing a normal liquid-like behavior as reported in figure 1.7. The possibility to modulate the density affects the dissolution power of the CO_2. This property, although not clearly defined, can be experimentally expressed by the Hildebrand approach. According to this approach, for liquid solvents, the Hildebrand parameter δ is defined as:[20]

$$\delta = \left(\frac{E}{V} \right)^{\frac{1}{2}}$$

with V = molar volume of the solvent, and E = vaporization energy ($E = \Delta H_V - RT$, with ΔH_V = vaporization enthalpy).

The δ parameter allows to predict that the solvent capability of a liquid increases at a high cohesive energy (of which the vaporization energy E is a direct measure) and at a low molecular volume. A practical example is the case of solvents for polymers: although having similar polarity, methanol and acetone are usually better solvents for polymers than *i*-propanol and methyl isobutyl ketone, as they have higher molecular volumes.[20]

In the case of SCFs, it has been experimentally observed that the Hildebrand parameter δ is directly proportional to the density of the supercritical fluids.[16] This aspect is clearly shown in figure 1.7 for $scCO_2$: the increase of the pressure of the supercritical fluid increases the density and the δ parameter as well; if the reduced density d_r ($d_r = d/d_c$; $d_c = 0.466$ g/mL) is higher than 1, $scCO_2$ is comparable to apolar organic media like cyclohexane, CCl_4 and *n*-pentane. This feature of dense CO_2 is utilized both in application processes like dry cleaning, natural product extraction like caffeine and hops, microchip cleaning,[21] high value products purification (drugs, vitamins), and in organic synthesis to carry out a number of reactions such as hydrogenations and hydroformylations (even enantioselective ones),[22] Diels-Alder cycloadditions, oxidations and photochemical reactions.[16] In all of these applications, the main aspect is the possibility to tune the solvent capability of the supercritical phase (by T and P variations) according to the solubility of the products to be extracted, and of the reactants/products or of the catalysts to be used.

Another aspect that makes $scCO_2$ an attractive solvent for synthesis is related to its mass transfer parameters. As reported in table 1.2, $scCO_2$, and in general all supercritical fluids, show physic-chemical properties of particular interest. Although SCFs have liquid-like density, their mass transfer parameters are well in between liquids and gases: their diffusivity (D) is about two orders of magnitude higher and their viscosity is about one order of magnitude lower than those of conventional liquids.[16] This means that mass transport phenomena are highly favoured in

SCFs with respect to liquid media: not only the diffusion rate of a solute is higher in SCFs, but also the mass transfer of reactants and products are enhanced in porous frameworks as for example, those of meso and micro-porous materials widely used as supports for heterogeneous catalysts.

Table 1.2. Average values of some properties for gases, liquids and SCFs

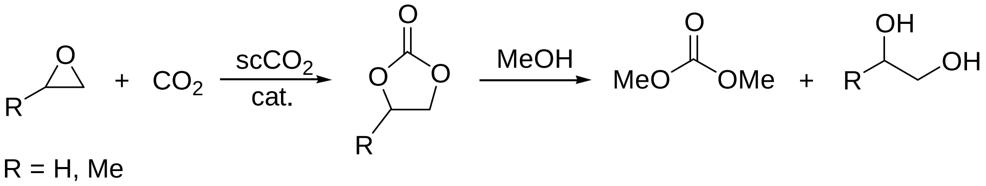
Properties	GAS	SCF	LIQUIDS
Density (ρ) [g/mL]	10^{-3}	0.3	1
Viscosity (η) [Pa s]	10^{-5}	10^{-4}	10^{-3}
Diffusivity (D) [$cm^2 s^{-1}$]	0.1	10^{-3}	$5x10^{-6}$

In other words, the kinetics of solid catalyzed reactions can be often greatly improved by the use of supercritical fluids. In particular, $scCO_2$ has been widely investigated as a solvent for different heterogeneously catalyzed reactions such as alkylations, esterifications, hydrogenations and oxidations.[22,23] For these reactions both higher rates and selectivities have been described with respect to traditional liquid solvents, due to the enhanced mass transfer and the higher solubility of reactants (in particular, gases like H_2 and O_2) in $scCO_2$.

Noteworthy are the studies by the group of Martin Poliakoff's at the University of Nottingham, on Friedel-Crafts alkylation reactions,[24] synthesis of chetal or ethers,[25] and hydrogenation and hydroformylation reactions,[26] carried out under continuous flow conditions, using $scCO_2$ as a solvent/carrier. Besides the enhanced mass transfer, Poliakoff introduced the idea that the kinetic and selectivity improvements observed using $scCO_2$ could be due also to the moderate polarity of the solvent (CO_2), which promoted and favored the interactions between the polar reactants and the catalysts.[25]

Other works reported on the hydroformylation of α-olefins catalyzed by heterogeneous Rh catalyst under batch conditions, and claimed that a high reaction selectivity was achieved due to the combined use of $scCO_2$ and MCM-type mesoporous supports.[27]

Finally, examples on the use of $scCO_2$ simultaneously acting as solvent and a reactant, can be found in green procedures for the synthesis of dialkyl carbonates, most of all dimethyl carbonate, by the reaction of ethylene or propylene oxides with methanol in presence of solid bases as catalysts (scheme 1.1).[28]



Scheme 1.1. Green synthesis of dimethyl carbonate

When describing $scCO_2$ properties, another significant aspect that should be mentioned is the solute-solvent clustering phenomenon, which is promoted by the high compressibility of $scCO_2$.[29] This phenomenon arises from a non-uniform spatial distribution of the solvent molecules surrounding the solute that, close to the critical point, induces a notable increase of the density around the solute molecules with respect to the bulk of the sc-phase (LDE: local density enhancement). This is another effect that can have an influence on the kinetic profile and selectivity of chemical reactions.[30]

1.3 Ionic Liquids: Green Designer Solvents and Catalysts

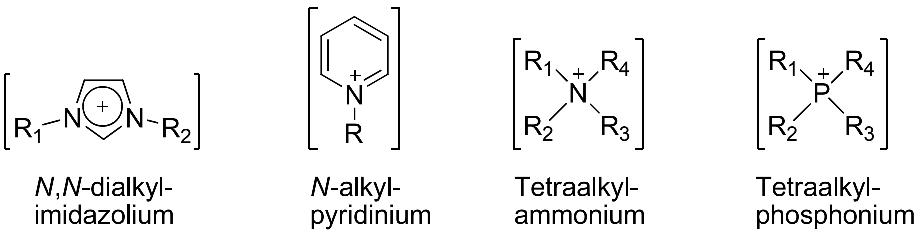
Ionic liquids (ILs) represent today one of the most fascinating area of research to develop alternative eco-friendly synthetic methodologies.

Although synthesis and applications of ionic liquids have shown an exponential growth only in the last 15 years,[31] ILs have been known for a long time: the first observation of these compounds is historically dated 1914, when Paul Walden reported the physical properties of ethylammonium nitrate ($[EtNH_3][NO_3]$).[32]

As their name suggests, ILs are materials composed entirely of cations and anions which, by definition, melt below or around 100 °C.[33] In the past, ionic liquids were considered to be rare, but now a large number of these compounds are known and are commercially available as either organic salts or mixtures consisting of at least one organic component.

Figure 1.8 reports the most common ionic liquids in use. *N*,*N*-dialkylimidazolium, *N*-alkylpyridinium, alkylammonium and alkylphosphonium are the most conventional organic cations, and ionic liquids displaying consistently different physical properties can be obtained by the combination of these cations with a number of different organic and inorganic anions.

MOST COMMONLY USED CATIONS



$R_{1,2,3,4}$= CH_3; $CH_3(CH_2)_n$, (*n*=1, 3, 5, 7, 9); aryl; *etc.*

SOME POSSIBLE ANIONS

water-immiscibile ——————→ water-miscible

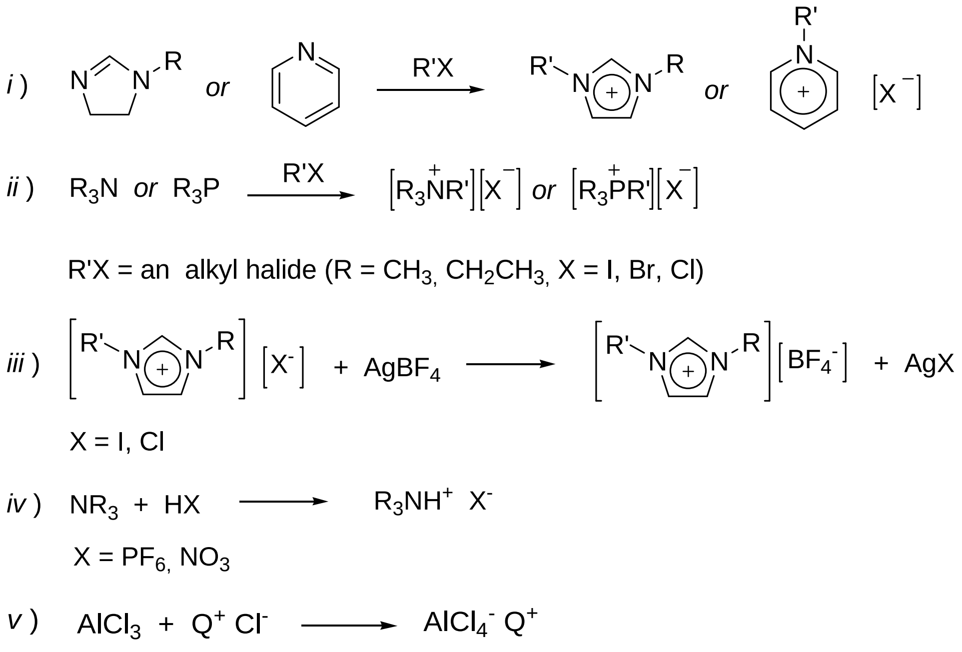
$[PF_6]^-$
$[NTf_2]^-$
$[BR_4]^-$

$[BF_4]^-$
$[OTf_2]^-$
$[N(CN)_2]^-$

$[CH_3CO_2]^-$
$[CF_3CO_2]^-$, $[NO_3]^-$
Br^-, Cl^-, I^-

Figure 1.8. Some commonly used ionic liquids[34]

The preparation of ionic liquids takes place by diverse methodologies which can be grouped in five basic categories (scheme 1.2): *i*) alkylation of *N*-alkylimidazoles and pirydines; *ii*) quaternarization of amines and phosphines; *iii*) inorganic methatesis of halide salts with, for instance, silver salts of the desired anion; *iv*) acid-base neutralization reactions; *v*) direct combination of a halide salt with a metal halide.[35]



Scheme 1.2. Preparation of ionic liquids

The intriguing physical-chemical properties of ILs accounts for their large interests in green chemistry. First of all, ILs have a negligible vapour pressure at near ambient conditions: many of them show no signs of distillation below the temperature of their thermal decomposition, and for a long time, it was almost universally believed that ionic liquids could not evaporate at all.[36] This feature allows to minimize the risks of atmospheric contamination and it remarkably reduces health and environmental concerns. Accordingly, ILs have been named “green solvents” and they can efficiently replace conventional volatile organic media in developing new synthetic methodologies.

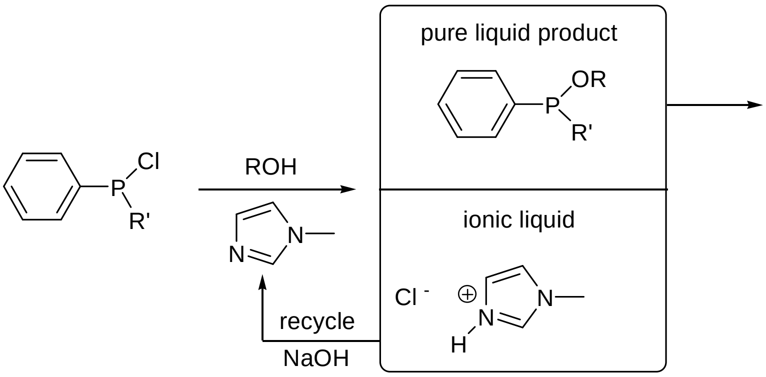
Secondly, ILs display properties such as the dissolution power, polarity and hydro/lipo-philicity, which are rather peculiar and different to those of conventional organic liquids. These features depend on the nature of the cation and the anion that compose the ionic liquid. In a first approximation, cations are responsible for the physical properties, whereas anions control chemical properties and reactivity.[34] For this reason, ILs have been named “designer solvents”, as either the cation or the anion can be changed in order to tune their properties as solvents for chemical reactions. It is possible, at least in principle, to design ionic liquids able to optimize the relative solubilities of reactants and products, the reaction kinetics, the liquid range of the solvent, and even the intrinsic catalytic behaviour of the media and the air-stability of the system.[37]

A lot of studies have been conducted to determine correlations between the chemical structures of both cations and anions and the properties of ILs, in order to predict those properties already at the stage of ionic liquid design. Even if general quantitative methods are still not available, some general trends have been observed. The melting point of ionic liquids is affected by both the asymmetry and the size of cations,[38] as well as by the occurrence of hydrogen bonds between cations and anions.[39] Also, the ability of ions to act as hydrogen-bond donors and/or acceptors influences the polarity of ionic liquids (see water miscibility scale in figure 1.8), while the increase of the chain length of alkyl substituents on both cations and anions leads to a greater lipophilicity of these materials.

For these reason, ILs can be good solvents for a wide range of both inorganic and organic compounds: unusual combinations of reagents/catalyst can be brought into the same phase by using ILs, or thanks to the immiscibility of ILs with polar or nonpolar solvents, innovative two-phase or multiphase systems can be originated to facilitate either the recovery of final reaction products or of the catalyst.

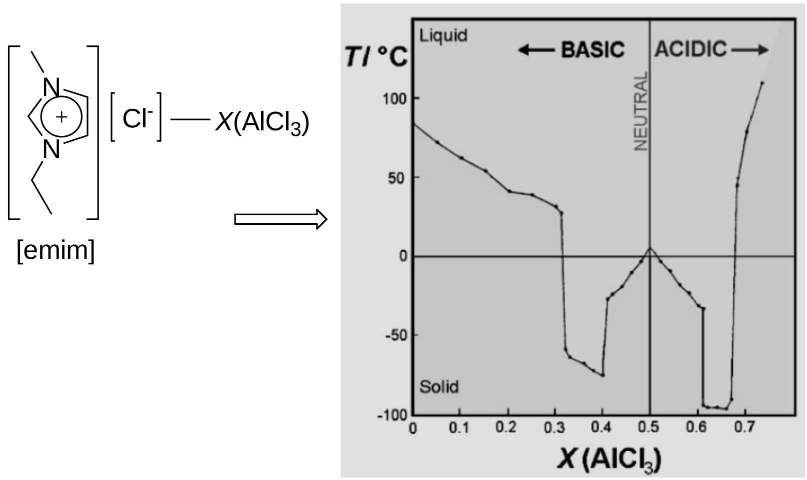
Ionic liquids have been investigated as solvents for a number of synthetic purposes. For example, ILs have been examined as substitutes for water in Diels-Alder reactions,[40] or substitutes for organic solvents in alkylation reactions of indole and β-naphtol,[41] for the immobilization of homogeneous catalysts in biphasic reaction systems for hydrogenation reactions (even asymmetric),[42] for hydroformylation reactions,[42a,43] Heck reactions,[44] olefin dimerizations (butadiene,[45] propene,[46] butene[47] and ethene[48]) and polymerization processes.[49]

Today, ILs find also industrial applications in a lot of processes, like cellulose dissolution, aluminum plating, hydrosilylation and so on, which have been recently reviewed by Seddon and Plechkova.[31] Among others, the BASIL™ process setup by BASF for the production of alkoxyphenylphospynes as photoinitiator precursors, is probably the most successful example of an industrial process using an ionic liquid based-technology.[50]



Scheme 1.3. The BASIL™ process

Ionic liquids are not only good solvents, but they can be used as effective acid-base catalysts as well. A relevant example is the case of chloroaluminate ionic liquids. Figure 1.9 shows the phase behaviour of a model binary system [emim]Cl/AlCl$_3$.



$[Al_2Cl_6] + Cl^- \longrightarrow [Al_2Cl_7]^-$

$2[AlCl_4]^- \rightleftharpoons [Al_2Cl_7]^- + Cl^-$

$2[Al_2Cl_7]^- \rightleftharpoons [Al_3Cl_{10}]^- + [AlCl_4]^-$

Figure 1.9. The experimental phase diagram for the [emim]Cl-AlCl$_3$ system

Depending on the mole fraction of $AlCl_3$ [$X_{(AlCl_3)}$], different anionic species such as Cl^-, $[Al_2Cl_7]^-$ and $[Al_3Cl_{10}]^-$ are present in the mixture (figure 1.9, right). This feature allows to manipulate the acid/base character of the ionic liquid by altering its composition: since Cl^- is a Lewis base while $[Al_2Cl_7]^-$ and $[Al_3Cl_{10}]^-$ are both Lewis acids, the binary ILs displays acid [$X_{(AlCl_3)}>0.5$], basic [$X_{(AlCl_3)}<0.5$], or neutral [$X_{(AlCl_3)}=0.5$],[51] properties.[52] Thanks to this adjustable behaviour and to the good solubility for simples arenes, chloroaluminate ILs have been used simultaneously as solvents and catalysts for electrophilic aromatic substitutions reactions,[53] particularly for Friedel-Crafts acylation and alkylation reactions of aromatic compounds.[54]

1.4 Organic Carbonates: Alternative Green Reactants

As mentioned in an earlier paragraph (*1.1.3*) the substitution of hazardous reagents with innocuous compounds in synthetic chemistry is considered a major target for the modern chemical industry.[55] Nonetheless, a number of conventional reagents are still employed for the production of chemicals. These compounds are usually parts of well-established and relatively old methodologies that have been designed only thinking about the process yield and selectivity, without any other consideration of the environmental and the health impact of such products. Remarkable examples inherent to the content of this work, are the cases of two classes of organic reactions such as alkylation and carboxylation reactions. Both transformations are of a broad scope and widely used in organic synthesis. According to conventional methodologies reported in literature,[56] alkylation reactions are usually carried out using alkyl halides (RX, X = I, Br, Cl; R = Me, Et, Bu, Allyl, ...) or dialkyl sulfates ($ROSO_3R$) as alkylating agents, while carboxylation reactions are commonly performed using phosgene ($COCl_2$),[56e] or phosgene-derivatives such as di- and tri-phosgene,[57] and alkyl chloroformates ($ClCO_2R$),[56f] as carboxylating agents. In scheme 1.4, a few general examples of these reactions using alcohols and phenols as model substrates are reported.[56a-c]

$$PhOH + R_2SO_4 + NaOH \longrightarrow PhOR + NaRSO_4 + H_2O \quad (1)$$

$$PhOH + R'X + NaOH \longrightarrow PhOR' + NaX + H_2O \quad (2)$$

$$2\ R''OH + COCl_2 + 2\ NaOH \longrightarrow R''OCOOR'' + 2\ NaCl + 2\ H_2O \quad (3)$$

R = R'' = Alkyl
R' = Me, Et, Bu, allyl, etc.
X = I, Br, Cl

Scheme 1.4. Conventional alkylation (eq. 1-2) and carboxylation (eq. 3) reactions

These reactions usually allow to obtain very good yields of alkylated/carboxylated products, though for several reasons, they exemplify the antithesis of green methods: *i*) the alkylating and carboxylating reactants are highly toxic and corrosive compounds; *ii*) the reactions require the use of stoichiometric amounts of bases, thereby producing stoichiometric amounts of salts as by-products which need to be disposed of; *iii*) most of these processes are exothermic reactions, and an accurate control of the reaction parameters is needed; *iv*) the use of organic solvents is generally required for both homogeneity and heat-control reasons. Eco-friendly alternatives to these hazardous reactants and procedures can be devised with the use of organic carbonates.[58]

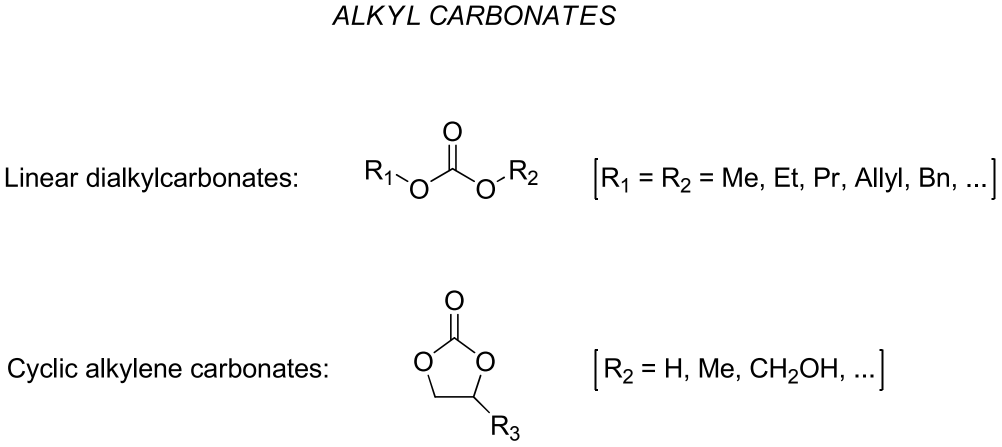
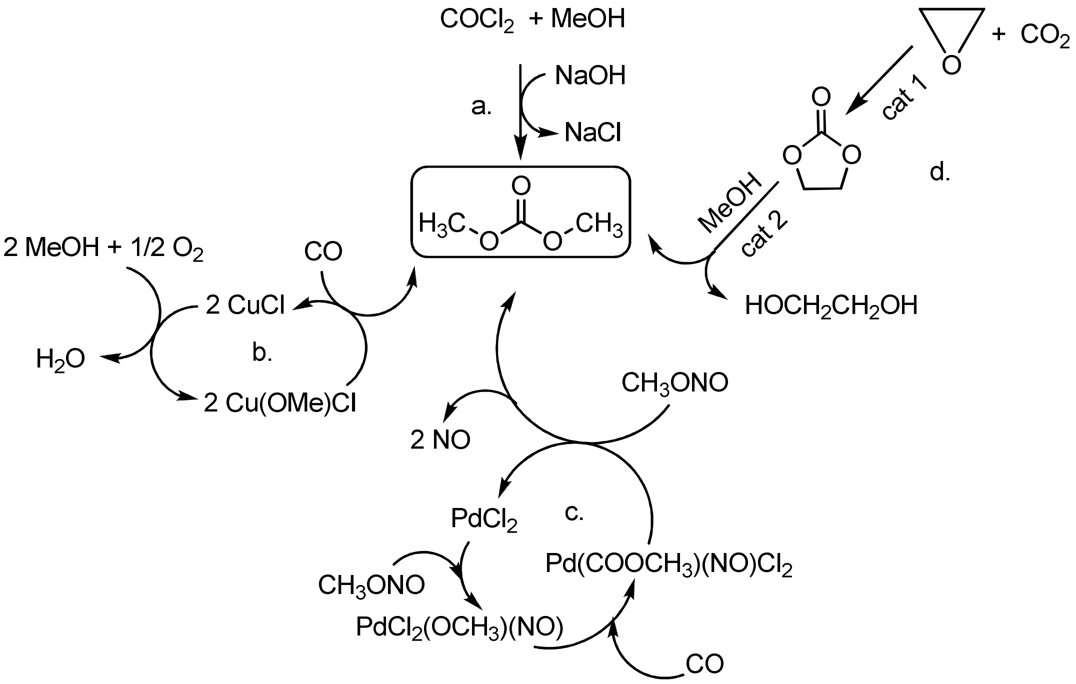


Figure 1.10. Examples of commonly used organic carbonates

Currently, a number of reasons justify the use of dialkyl carbonates (DAlCs) for clean syntheses. A first remarkable green aspect concerns the method of industrial synthesis of DAlCs. Consider for example, the model case of dimethyl carbonate (scheme 1.5).

Although DMC is still produced from phosgene (eq. a),[59] this method is highly undesirable: not only it uses the extremely toxic phosgene, but it also requires a stoichiometric amount of a base generating a stoichiometric amount of a polluted salt to be disposed of. Alternative industrial synthesis may operate with different green strategies. Among them: *i*) The oxycarbonylation of methanol catalyzed by copper salts (eq. b), represents the first ever reported green and industrially viable alternative for the production of DMC.[60] This process was patented by Enichem in the early 80's and until a few years ago, an Italian plant in Ravenna produced up to 12000 t/y. Key advantages of this synthesis are the high safety improvement with respect to the phosgenation of MeOH, the high selectivity (and therefore, purity of the final product), and the sole formation of water as a by-product. *ii*) The carbonylation of methyl nitrite over a Pd-catalyst (eq. c), developed by UBE Industries in 1993, is also a recognized eco-friendly method.[61]



Scheme 1.5. Industrial synthesis of DMC

In this case, methyl nitrite, which is one of the substrates for the formation of DMC, acts simultaneously as an efficient oxidant of the metallic catalyst. This expedient guarantees the catalytic cycle and further enhances the process safety since the direct introduction of O_2 (as in the Enichem route), is no longer necessary. UBE plants operate on a 3000 t/y capacity. *iii*) A second industrial approach is the two-stage process of insertion of CO_2 into ethylene oxide, followed by a transesterification reaction with MeOH (eq. d).[62] This is the most recent breakthrough in the production of DMC, and it represents by far, the greener and more promising solution stemming from cheap and safe carbon dioxide. The two reactions (path d) are presently carried out in separate units through established procedures; though, many efforts are underway to set up a one-pot catalytic method. Once prepared according to methods *i*)-*iii*), DMC is classified only as a flammable liquid with non toxic properties (table 1.3).[63]

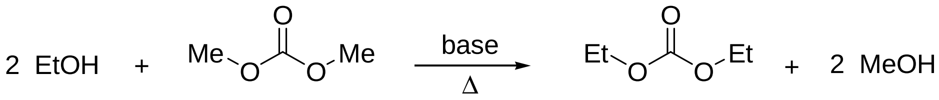
Therefore, DMC can be handled without special precautions required for phosgene or methyl halides and dialkyl sulfates as well. It is clear how these alternative synthesis of DMC are genuine examples which actually allow to avoid the use of harmful chemicals and to prevent pollution at the source.

Table 1.3. Toxicological and ecotoxicological profile of DMC

property	**DMC**
oral acute toxicity (rats)	LD_{50} 13.8 g/Kg
acute toxicity per contact (cavy)	LD_{50} >2.5 g/Kg
acute toxicity per inhalation (rats)	LD_{50} 140 mg/L; (4 h)
mutagenic properties	none
irritating properties (rabbits, eyes, skin)	none
biodegradability (OECD 301 C)	> 90% (28 days)
acute toxicity (fish) (OECD 203)	NOEC[a] 1000 mg/L
acute toxicity on aerobial bacteria of wastewaters (OECD 209)	EC_{50} > 1000 mg/L

[a] NOEC = Concentration which does not produce any effect.

Other light DAlCs, for example diethyl carbonate (DEC), can be obtained by base-catalyzed transesterification of the non toxic DMC with ethanol (scheme 1.6).



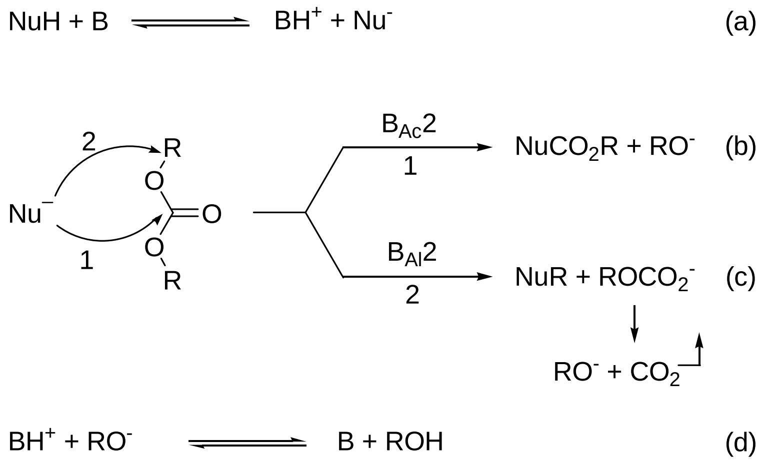
Scheme 1.6. Transesterification of DMC with ethanol to give DEC

Alike to DMC, DEC possesses an interesting toxicological profile, being classified as an irritant, but non toxic compound.

The case of alkylene carbonates also deserves some consideration. Compounds such as ethylene and propylene carbonate (EC and PC, respectively) represent perhaps, the best green replacements for ethylene and propylene oxides to carry out high yield and selective hydroxyalkylation reaction of several nucleophiles.[64] Although the catalytic insertion of CO_2 on alkylene oxides still represents the most important route for the preparation of both EC and PC (eq. d, scheme 1.5), nonetheless the latter offer a number of practical benefits over their parent oxides. Among them: *i*) EC and PC are classified as irritant but non-toxic products; *ii*) EC is a low-melting solid (35 °C), while PC is a liquid, and both products are not flammable; therefore, they can be used as stoichiometric reagents without added solvents; *iii*) when EC or PC serve as hydroxyalkylating agents, CO_2 is the only by-product. Thus, alkylene carbonates can be safely used even for large scale preparations, as documented by the extensive literature reported over the years.[65]

In addition to the methods of synthesis and their toxicological profiles, the versatile reactivity of DAlCs represents another remarkable green feature for the development of new and safer synthetic protocols. It should be noted that: *i*) reactions with organic carbonates are always catalytic processes, producing no wastes except for alcohols which can be recycled to the synthesis of DAlCs, and CO_2 which does not involve disposal problems; *ii*) very often, light organic carbonates can be used not only as reactants, but also as reaction solvents. Scheme 1.7 helps to detail these aspects by examining the reaction of a generic nucleophilic substrate (NuH) with DAlCs.

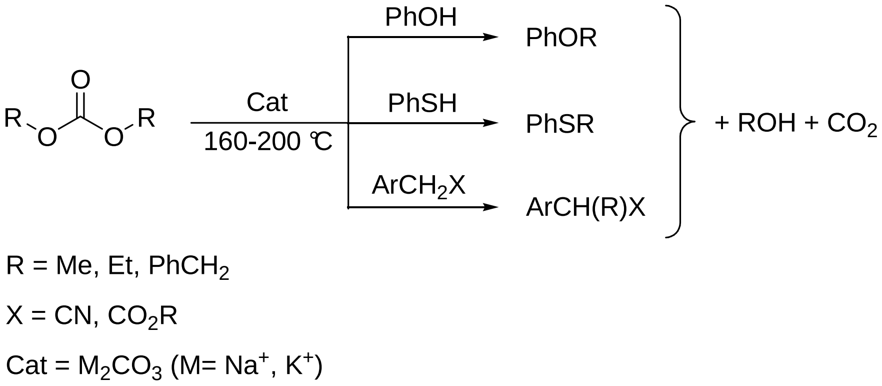
At first, the base (B) catalyst promotes the formation of a nucleophilic anion (Nu^-) (eq. a). Due to the double electrophilic reactivity of DAlCs, two different reaction pathways may follow: *i*) a nucleophilic attack of Nu^- to the carbonylic group of the organic carbonate, producing the carboxyalkylated product and the corresponding alcoholate anion RO^- (path 1, $B_{Ac}2$ type mechanism, eq. b). Under such conditions DAlCs behave as a replacement for the toxic phosgene in carboxylation reactions. *ii*) A nucleophilic attack of Nu^- to the alkyl carbon of the carbonate with the formation of the alkylated product and of the alkyl carbonate anion $ROCO_2^-$ (path 2, $B_{Al}2$ type mechanism, eq. c). The latter anion is a rather unstable specie which easily undergoes decomposition to RO^- and CO_2. Under such conditions, DAlCs behave as safe replacements for alkyl halides or dialkyl sulphates in alkylation reactions. In both cases, the protonated moiety BH^+ can be neutralised by the reaction with an alcoholate anion, producing the corresponding alcohol ROH as by-product, and restoring the catalytic base B (eq. d). Additional solvents are not usually required for both alkylation and carboxyalkylation processes.



Scheme 1.7. Double reactivity of dialkyl carbonates as alkylating (b) and carboxyalkylating (c) agents

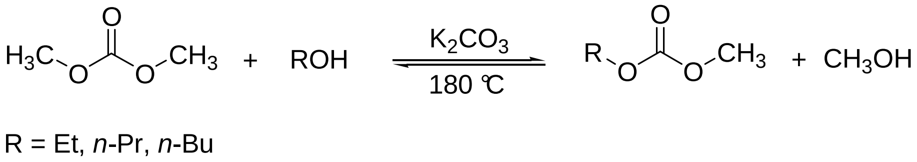
Although a clear cut-off between these two pathways is not always possible, reaction conditions, more specifically the temperature and the nature of the catalyst, often allow to discriminate between the carboxyalkylation and the alkylation reactions. For the specific interest of this PhD thesis, a brief overview on this subject is now considered. As an example, the model case of dimethyl carbonate is detailed.

The effect of the temperature. In the past fifteen years, the reactivity and the use of dialkyl carbonates, with emphasis on dimethyl carbonate ($MeOCO_2Me$), have been extensively investigated by our research group.[66] When an alkaline carbonate (M_2CO_3, M = Na, K) is used as a catalyst, it is generally observed that below or at the reflux temperature of DMC ($T \leq 90$ °C), a methoxycarbonylation reaction takes place almost exclusively. A $B_{Ac}2$ (bimolecular, base-catalyzed, acyl cleavage, nucleophilic substitution) mechanism operates: the nucleophile attacks the carbonyl carbon of DMC, giving the transesterification product. At higher temperatures instead (usually at $T \geq 120$ °C), DMC acts primarily as a methylating agent through a $B_{Al}2$ (bimolecular, base-catalyzed, alkyl cleavage, nucleophilic substitution) mechanism: the nucleophile attacks the methyl group of DMC, giving the methylation product.[66] Solvation phenomena can be accounted for this behaviour: as described in literature for the hydrolisis of methyl esters in gas phase,[67] the reduced (or absent) solvation of nucleophiles makes the attack to the less hindered (even though less electrophilic) alkyl carbon preferred with respect to the carbonyl carbon of DMC. At high temperature, the $B_{Al}2$ mechanism becomes the major reaction pathway. Accordingly, highly selective alkylation reactions of several nucleophiles can be carried out using DMC as the methylating agent.[66] Higher homologues of DMC, such as diethyl carbonate (DEC) and dibenzyl carbonate (DBnC) display an analogue reactivity (scheme 1.8).



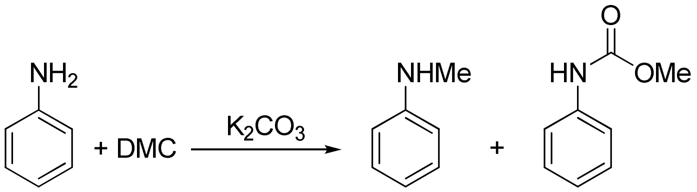
Scheme 1.8. Selective alkylation reactions with dialkyl carbonates

In the presence of alkaline carbonates as catalysts, at 160-200 °C the reaction of CH_2-active compounds (e.g. arylacetonitriles, arylacetoesters, sulphones bearing α-CH_2 groups, etc.), phenols and thiols with dialkyl carbonates gives the corresponding alkyl derivatives with a very high selectivity (up to 99% at complete conversion).[66a,b] However, under basic catalysis, there are relevant examples in which the temperature cannot modulate the double reactivity of dialkyl carbonates. In the case of alcohols for instance, even operating at high temperature (180 °C), the reaction proceeds with the predominant formation of the carboxyalkylated products (scheme 1.9).[68]



Scheme 1.9. Alkali carbonate catalysed trasesterification of alcohols with DMC

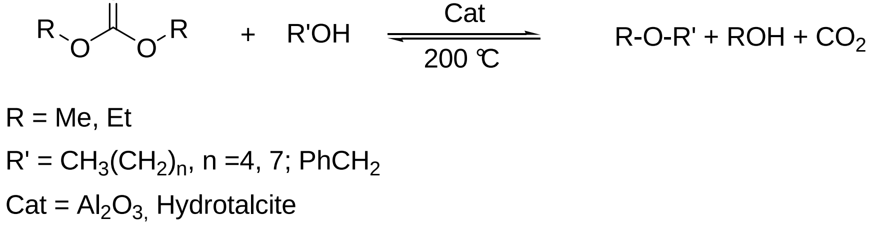
The same holds true with primary aromatic amines whose reaction with DMC in the presence of K_2CO_3 provides a mixture of mono-*N*-methyl amines and methyl carbamates (scheme 1.10).[69] These side products (carbamates) form even at high temperature (180 °C).



Scheme 1.10. Reaction of aniline with DMC catalysed by K_2CO_3

In such cases however, selective alkylation is still possible on conditions that different catalysts are used.

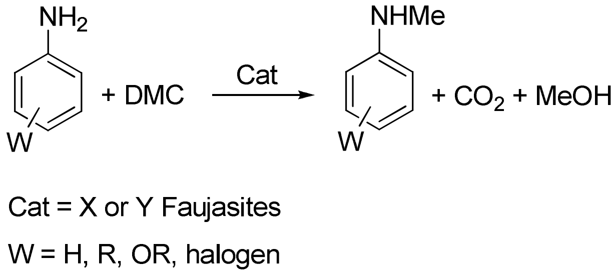
The effect of the catalyst. Operating at 200 °C, the reaction of alcohols with both DMC and DEC produces the corresponding ethers in very good yields (97-100%) using basic alumina or hydrotalcite as the catalysts (scheme 1.11).[70]



Scheme 1.11. Synthesis of ethers via the *O*-alkylation of alcohols with dimethyl- and diethyl- carbonate

Other efficient catalysts are a class of zeolites, namely alkali metal exchanged faujasites. The best example to describe the performance of such systems is the methylation of primary aromatic amines and aminophenols.

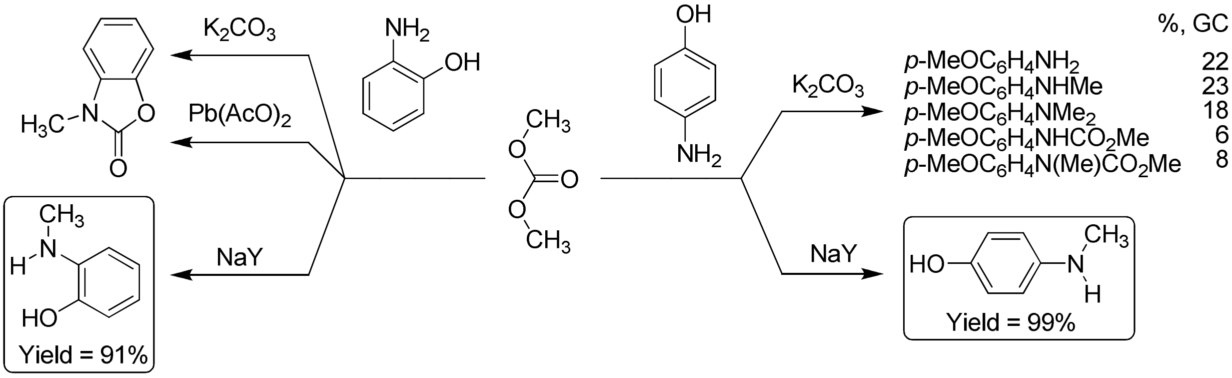
Alkali metal exchanged X or Y faujasites (MY or MX, M = Li, Na, K) allow to carry out a very selective *N*-methylation reactions of anilines even when deactivated by both steric or electronic effects (scheme 1.12).[71]



Scheme 1.12. Reaction of anilines with DMC catalysed by faujasites

As a further added value, the reaction produces exclusively mono-*N*-methyl derivatives (ArNHMe), avoiding the concurrent formation of bis-*N*-methyl products ($ArNMe_2$).

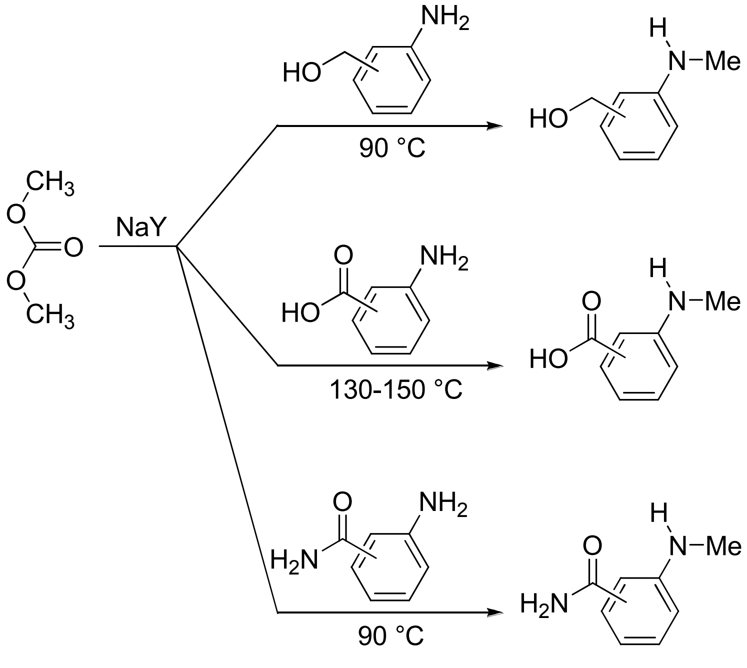
In this context, another relevant case is that of ambident nucleophiles, more specifically of amines bearing other functional groups which can in principle, react with DMC. Aminophenols exemplify the situation (scheme 1.13). [72,66e,f]



Scheme 1.13

In the presence of K_2CO_3 as a catalyst, when *p*-aminophenol reacts with DMC, a plethora of products are observed. They originate from several competitive reactions: the methylation at the oxygen, the mono and bis-methylation at the nitrogen, the carboxymethylation at the nitrogen, and so on. These products reflects known aspects of the reactivity of DMC under basic catalysis. By contrast, the use of commercial NaY zeolites as a catalyst allows not only a selective mono-methylation, but also a very highly chemoselective reaction: the exclusive methylation at the *N*-atom is observed and, in particular, only the mono-*N*-methyl derivative is isolated in substantially quantitative yield (99 %) while, the OH group does not react at all. A similar situations holds true for *o*-aminophenol: in the presence of basic or even Lewis acidic catalysts such as K_2CO_3 and lead acetate respectively, a cyclic product, namely a *N*-methylbenzoxazole, is isolated.[66f] This product is originated from simultaneous *N*-methylation and *O*-carboxymethylation reactions occurring at the *N*- and *O*-atoms of the reagent. Instead, in the presence of NaY, DMC and *o*-aminophenol react to give only the mono-*N*-methylated products in a 91% yield. For both *o*- and *p*-aminophenols, the use of faujasite catalysts allows to fully preserve OH functions from any possible concomitant *O*-methylation or transesterification reaction.

This result is even more general since Na-exchanged faujasites catalyze the reaction of DMC with several ambident nucleophiles such as aminobenzylic alcohols, aminobenzamides and aminobenzoic acids, towards the formation of the corresponding mono-*N*-methyl derivatives with a selectivity up to 99 % (scheme 1.14).[66h] In all cases, a complete chemoselectivity toward the amino group is achieved, the other functionalities (OH, hydroxyl; CO_2H, carboxylic group; and $CONH_2$, amide group) being fully preserved from possible alkylation and/or transesterification reactions.



Scheme 1.14

Since alkali metal exchanged X and Y faujasites have been widely used as catalysts during this PhD thesis, a brief overview of their properties and morphological characteristics is now given.

Metal exchanged X and Y faujasites. Metal exchanged X- and Y-faujasites are a type of natural zeolites, which can be also synthetized on an industrial scale by hydrothermal processes.[58b] These solids are crystalline aluminosilicates whose general formula is:

$$M_{x/n}[(AlO_2)_x(SiO_2)_y] \bullet mH_2O$$

where n is the valence of the cation M (n=1, M= Na^+, Li^+; n=2, M= Ca^{2+}, Mg^{2+}). The difference between X and Y faujasites consists in the Si/Al ratio of the crystal structure: this ratio is between 1.5 and 3 for the Y type, while it varies between 1 and 1.5 for the X type.[73] Accordingly, model faujasites such as NaX and NaY, have the following compositions:

$$X: \quad Na_{86}[(AlO_2)_{86}(SiO_2)_{106}] \bullet 264\ H_2O$$

$$Y: \quad Na_{56}[(AlO_2)_{56}(SiO_2)_{136}] \bullet 250\ H_2O$$

This feature, as we will see later on this paragraph, reflects different acid-base properties of the two types of solids. Faujasites posses a regular tridimensional structure where the framework of the aluminosilicate is built up starting from a primary unit of 24 tetrahedrons of silica and alumina bound together, in which four or six member rings alternate each other. This primary (base) unit, in the shape of a truncated octahedron, is called sodalite unit or β-cage (figure 1.11, a). The assembly of β-cages allows the formation of some of the more common zeolites, like the sodalite (figure 1.11, b), the zeolite A (figure 1.11, c) and the faujasite (figure 1.11, d).[73]

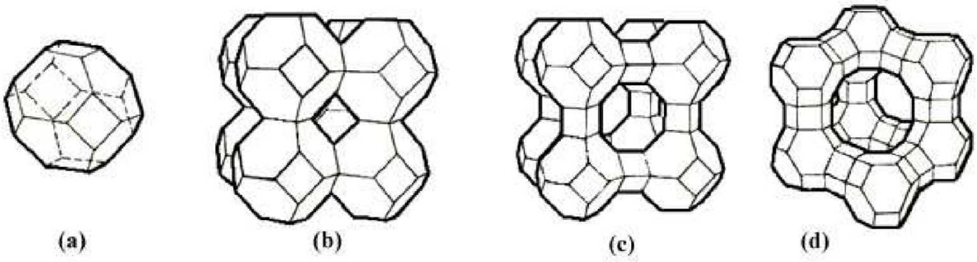


Figure 1.11. β-cage (a) and some crystal aluminosilicates: the sodalite (b), the zeolite A (c) and the faujasite (d)

As shown in figure 1.11 (d), the faujasite is formed by the assembly of the β-cages through the hexagonal faces in which oxygen atoms are the bridging atoms. Faujasites posses relatively large internal cavities named *supercavities* (11.8 Å in diameter) that are accessible through channels whose diameter is 7.4 Å. Cations (more often alkali metal cations) neutralize the negative charge generated in faujasites by the presence of a trivalent aluminum [Al(III)] in a tetrahedral coordination. The nature of the cations modifies not only the size of the windows which provide access to the internal cavities, but also the acid-base properties of the solid. In this context, alkali metal exchanged X and Y faujasites are often described as amphoteric solids:[74] oxygen atoms of the aluminosilicate (those atoms distributed on the *supercavity* surface) act as Lewis basic sites, while metal cations act as weak Lewis acid sites. A general trend of the acid-base features of faujasites has been described by using IR-techniques: *i*) as far as the effect of the metal cation is considered, the basicity of faujasites follows the order $Li^+ < Na^+ < K^+ < Rb^+ < Cs^+$. This behavior reflects the decrease of electronegativity of the metal (from Li^+ to Cs^+) which enhances the availability of negative charge on oxygen atoms of the aluminosilicate; *ii*) if the cation does not change, an increase of the Si/Al ratio decreases the basicity of the faujasite, as Si is more electronegative than Al. This is the reason why Y type faujasites (Si/Al = 1.5 ÷ 3) show a lower basicity than X type (Si/Al = 1 ÷ 1.5).[74] Thanks to the availability of different morphologies and acid-base properties, the modes of adsorption of a number of inorganic/organic substrates can be tuned over faujasites. This versatility along with a excellent thermal and chemical stability, make zeolites powerful adsorbents/catalysts for several applications/processes, including the selective adsorption of water/organic molecules from both gaseous and liquid mixtures,[75] ion exchange,[76] the use as catalysts for remarkable industrial transformations such as alkylations, isomerization, and cracking reactions.[75] In the present work, alkali metal exchanged faujasites have been used to catalyse alkylation reactions mediated by both linear and cyclic organic carbonates.

To close this paragraph, the use of dialkyl carbonates not only as green reactants, but also as green solvents, should be briefly mentioned. The use of a number of DAlCs, including dimethyl carbonate, diethyl carbonate, ethylene carbonate, propylene carbonate, butylene carbonate and glycerol carbonate, as solvents for organic reactions and for technical, electrochemical, and extractive applications has been recently reviewed by Börner et al.[77] The general conclusion of these Authors is that DAlCs posses solvency properties that should always be taken into consideration to replace conventional media in organic synthesis.

1.5 Aim and Summary of the Work

This work has been carried out at the Dipartimento di Scienze Ambienti dell’Università Ca’ Foscari, Venezia, in the *Green Organic Synthesis Group* (GOSyG). The group has a long-standing interest in the green chemistry area. In particular, among the research activities of GOSyC, an important field includes the setup of organic syntheses with low environmental impact reagents and solvents, mostly CO_2 and safe chemicals such as dialkyl carbonates, and green catalysts including solid heterogeneous systems (zeolites) and homogeneous systems (ionic liquids). Among dialkyl carbonates, the attention is mainly focused on the lightest term of the series, dimethyl carbonate, and more recently, also on a higher alicyclic compound such as glycerol carbonate which is becoming an attractive biomass derived building block.

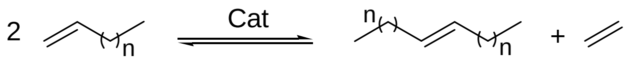
Such interests and the consolidated expertise of the group in these research activities have inspired the project for this PhD work, whose general aim has been the development of new eco-friendly methodologies for the formation of C-C, C-N and C-O bonds. Both the experimental conditions and the reactions here investigated have been chosen according to the principles of green chemistry. In particular catalytic processes with high atom economy and carbon efficiency have been considered with the objective to improve the existing methodologies for these reactions by improving the mass index and the overall environmental factor (E). To this purpose, the preferred green tools have been those described in the previous paragraphs, including the use of eco-solvents, catalysts and reagents such as CO_2, ionic liquids and dialkyl carbonates.

The work has been articulated in three main sections, dedicated to C-C, C-N and C-O bond forming reactions, respectively, and thoroughly described in chapters 2, 3 and 4. A brief summary follows.

1.5.1 Green Solvents and Catalysts for C-C Bond Forming Reactions

Two high atom economy reactions such as the self-metathesis of α-olefins and the Michael addition were considered.

In the first case -the metathesis of α-olefins- the attention was focused on the reaction solvent, in particular on the use of dense CO_2 to replace conventional organic solvents for this process (hydrocarbons and light chlorinated). The combination of dense CO_2 and supported Re oxide as heterogeneous catalytic system was investigated for the self-metathesis of a model α-olefin such as 1-octene (scheme 1.15).



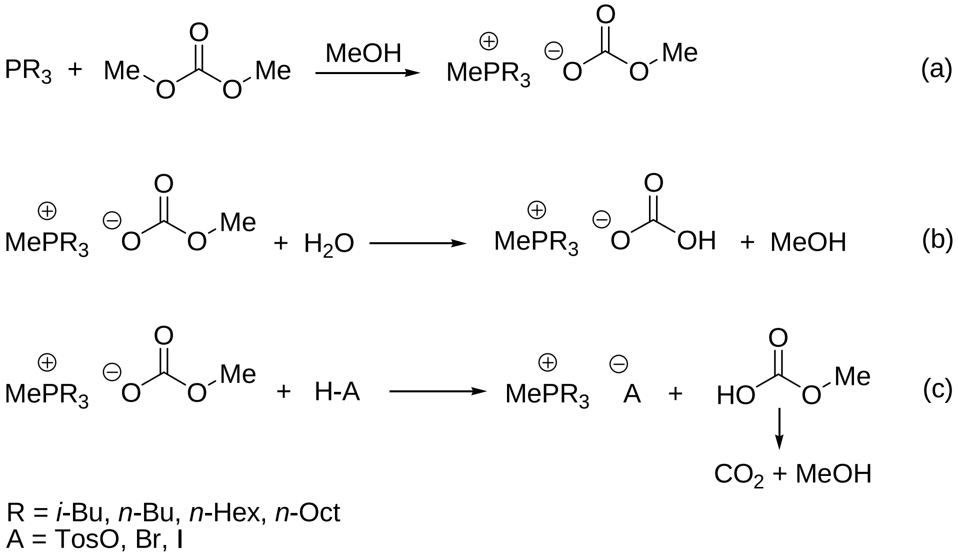
Cat = supported Re_2O_7
n = 5

Scheme 1.15. Self-metathesis of 1-octene

The work was developed in two stages [(a) and (b)]. In the first one (a), different Re-oxides supported catalysts were prepared in collaboration with the group of Prof. T. Maschmeyer at the Laboratory for Advanced Catalysis and Sustainability, University of Sidney. These systems were explored as catalysts for the self-metathesis of 1-octene carried out under batch conditions in the presence of supercritical CO_2 as solvent.

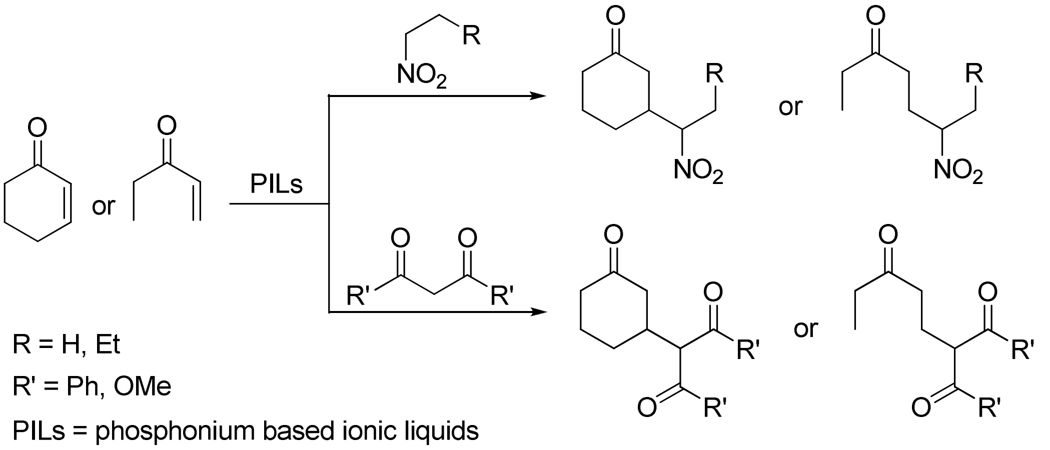
In the second one (b), the most effective catalyst selected from the first stage, was used to compare supercritical CO_2 and a conventional organic liquid (*n*-hexane) as solvent for the metathesis reaction under continuous flow conditions. Continuous flow reactions have been carried out at the Laboratory of the Clean Technology Group, University of Nottingham, in collaboration with Prof. P. Licence. In both the stages (a and b), the setup of the batch and continuous flow systems for the metathesis and the optimization of the reaction parameters were examined.

For the second investigated C-C bond forming reaction, the Michael addition, the attention was focused on the use of catalytic systems belonging to the class of ionic liquids. A new green synthesis of task specific phosphonium based ionic liquids (PILs) was followed *via* the methylation of trialkylphosphines with dimethyl carbonate. Thus, a set of methoxycarbonylated phosphonium salts [$R_3P^+\ ^-OCO_2CH_3$] were prepared (scheme 1.16, eq. a). These products were set to react with both water and protic acids to produce ionic liquids possessing different acid base properties (scheme 1.16, eq. b and c).



Scheme 1.16. Synthesis of task specific ILs: the quaternarization of trialkyl phosphines (a) is followed by the reaction with water (b) or the metathetic anion exchange (c)

Once prepared, PILs exchanged by methoxycarbonyl and bicarbonate anions have been used as base catalysts to condense different Michael acceptors of the class of α,β-unsaturated ketones, with -CH_2- active compounds such as nitroalkanes and β-diketones (scheme 1.17).



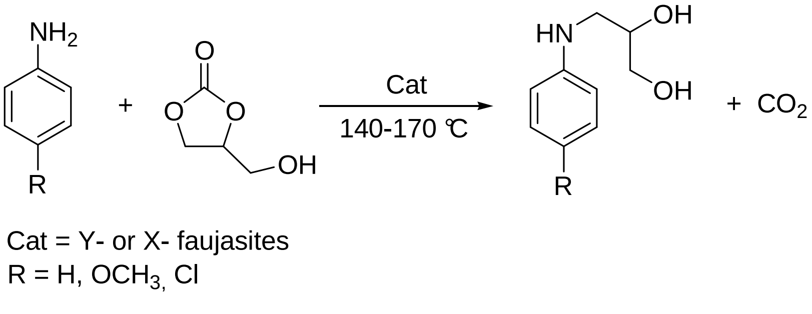
Scheme 1.17. Michael reactions catalysed by PILs

In this study, basic ionic liquids as catalysts have been compared to conventional organic base catalysts [for example, diazabicycloundecene (DBU), dimethylaminopyridine (DMAP), diazobicyclooctane (DABCO) and phosphazene base P_1-*t*-Bu]. Experiments have been performed under solvent free conditions.

1.5.2 Organic Carbonates as Green Reactants for C-N Bond Forming Reactions

Both linear and cyclic organic carbonates have been widely used in this work. In particular, three different reactions (a, b and c) of DAlCs with anilines, have been explored for the formation of C-N bonds.

a) The first process has been the selective mono-hydroxyalkylation of anilines with glycerolcarbonate catalysed by alkali metal exchanged Y- and X- faujasites, for the synthesis of *N*-(2,3-dihydroxy)propyl anilines (scheme 1.18).

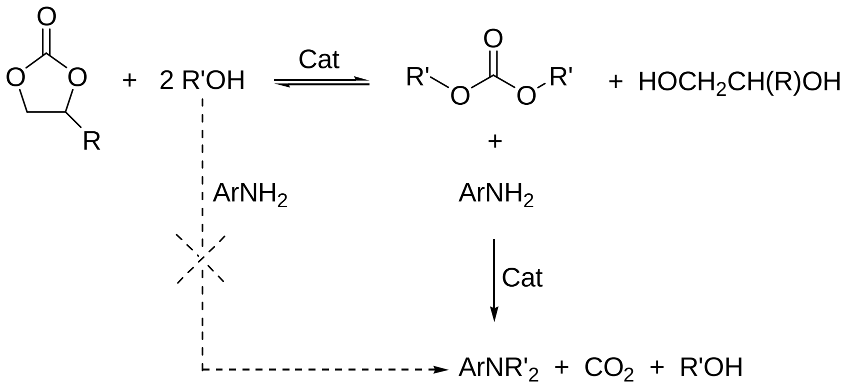


Scheme 1.18. Selective synthesis of *N*-(2,3-dihydroxy)propyl anilines

The influence of reaction conditions (T, solvent, molar ratios, etc.), of the nature and loading of the catalyst and the catalyst recycling as well, have been described. Also a mechanistic study and a plausible mechanistic hypothesis have been reported.

b) The second process has been the selective bis-*N*-methylation of anilines carried by dimethyl carbonate prepared *in situ* via the transesterification of alkylene carbonate with methanol. The overall process has been described as a sequential coupling of a transesterification with an alkylation reactions both catalysed by alkali metal exchanged faujasites. Thanks to these features, this sequence has been named as "green domino" (scheme 1.19).

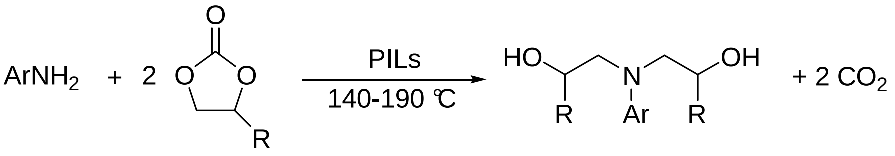
The optimization of the transesterification step, the relative reactivity of DMC and EC with anilines, and the influence of other reaction conditions (T, solvent, etc.) have been examined. Also, the use of other alcohols (EtOH, *n*-PrOH and glycerol) and other cyclic carbonates (propylene- and glycerol- carbonate) have been investigated.



R = H, CH_3,
R' = CH_3
Cat = faujasites
Ar = Ph, *p*-MeC_6H_4, *p*-$MeOC_6H_4$, *p*-ClC_6H_4, *p*-$NO_2C_6H_4$

Scheme 1.19. "Green domino" project for the bis-*N*-alkylation of anilines

c) The third process has been the alkylation of primary aromatic amines with alkylene carbonates, such as ethylene- and propylene- carbonates, for the selective synthesis of bis-*N*-(2-hydroxy)alkyl anilines (scheme 1.20). Efficient catalysts for this reaction have been phosphonium based ionic liquids (PILs), prepared according to the procedure earlier mentioned in scheme 1.16.



PILs = phosphonium based ionic liquids
Ar = pXC_6H_4-; X = OCH_3, CH_3, H, Cl
R = H, CH_3

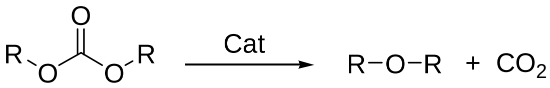
Scheme 1.20. Selective synthesis of bis-*N*-(2-hydroxy)alkyl anilines

The general scope of the procedure has been evaluated through the isolation of reaction products.

1.5.3 Organic Carbonates as Green Reactants for C-O Bond Forming Reactions

Two classes of reactions have been explored for the formation of C-O bonds.

The first process has been a detailed investigation of the decarboxylation reaction of dialkyl carbonates catalyzed by different heterogeneous systems like K_2CO_3, alkali metal exchanged faujasites and hydrotalcite (scheme 1.21).

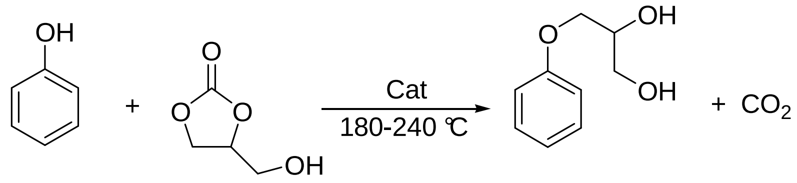


Cat = K_2CO_3, X or Y faujasites, hydrotalcite
R = Me, Et, *n*-Pr, Octyl

Scheme 1.21. Organic carbonate decarboxylation for the synthesis of ethers

Accordingly, the selective formation of dialkyl ethers has been observed for light DAlCs (DMC and DEC); while, for higher homologues (dipropyl- and dioctyl- carbonate), the decarboxylation reaction always occurs along with side-process producing alcohols and olefins. The effect of reaction conditions, mostly the temperature, and the nature and the loading of catalysts, have been investigated.

In analogy to the above mentioned alkylation of amines with glycerolcarbonate previously illustrated (scheme 1.18), the second investigated process has been the reaction of glycerolcarbonate with phenol, in the presence of faujasites as catalysts, for the synthesis of *O*-(2,3-dihydroxy)propyl phenol (scheme 1.22).



Cat = Y- or X- faujasites

Scheme 1.22. Selective synthesis of *O*-(2,3-dihydroxy)propyl phenol

A study on the effect of the reaction parameters (T, t, molar ratios) and the catalyst loading has been considered.

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CHAPTER 2

Green Solvents and Catalysts for C-C Bond Forming Reactions

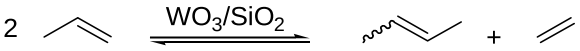
- Metathesis Reaction -

2.1 The Metathesis of α-Olefins over Supported Re-Catalysts in Supercritical CO_2

2.1.1 Introduction

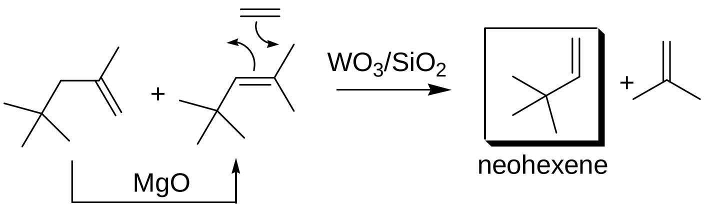
The olefin metathesis reaction is a powerful, elegant, clean, and atom economical means of constructing complex carbon frameworks.[1] As such it has undergone tremendous development since its discovery in the 1950s,[2] culminated in the Nobel Prize in Chemistry awarded to Chauvin, Grubbs, and Schrock in 2005. In that occasion the metathesis of alkenes has been described as an archetype green chemistry reaction for clean syntheses with reduced emissions of hazardous wastes to the environment:[3] the Academy stated "…[Metathesis] represents a great step forward for green chemistry, reducing potentially hazardous waste through smarter production. Metathesis is an example of how important basic science has been applied for the benefit of man, society and the environment".[4] The attention/interest to the metathesis reaction is not limited to academia, but it extends to chemical industry as well. In fact, the applications of the reaction span from petrochemistry, to polymer chemistry, to fine chemistry. In the matter of metathesis reaction applications, a few significant examples are here recalled briefly.[1a]

The historic Phillips triolefin process for the production of ethene and 2-butene from propene using a WO_3/SiO_2 catalyst (scheme 2.1),[5] that was shut down in 1972 after six years of operation due to increased demand for propene, and later reutilized in the reverse direction to produce propene.



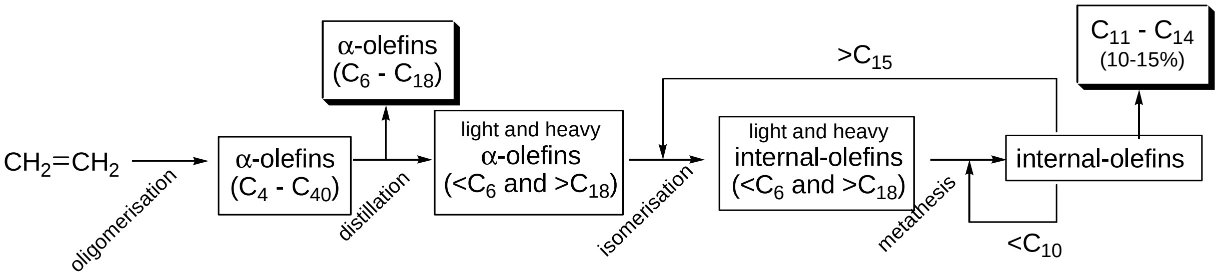
Scheme 2.1. Phillips triolefin process

Another industrial example by Phillips Petroleum Co. is the production of 3,3-dimethyl-1-butene (neohexene: an intermediate for musk) from ethene and a mixture of 2,4,4-trimethyl-2-pentene and 2,4,4-trimethyl-1-pentene (the latter is isomerised *in-situ* with MgO, scheme 2.2).[6]



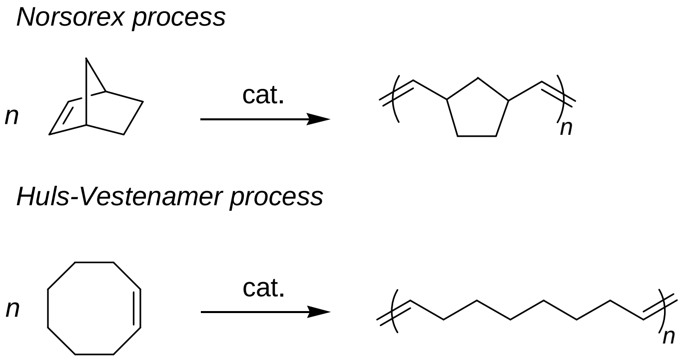
Scheme 2.2. The Neohexene process

A large-scale industrial metathesis process is the Shell Higher Olefin Process (SHOP) for the production of C_{11}-C_{14} olefins, en route to detergents.[7] Ethene is first oligomerized to a mixture of C_4-C_{40} alkenes, these are then fractionally distilled to isolate the C_6-C_{18} fraction comprised almost entirely of terminal alkenes. These are then further fractionated to obtain individual α-olefins. The lighter ($<C_6$) and heavier ($>C_{18}$) alkenes are subsequently isomerised to the corresponding mixture of internal olefins. The third stage involves metathesis of the olefins mixture that produces a statistical distribution of linear internal alkenes. Distillation yields the desired fraction of C_{11}-C_{14} olefins (10-15% yield per-pass, on a scale of over one million tons per year)[8] which are then converted into detergent alcohols *via* hydroformylation. The remaining $<C_{10}$ and $>C_{15}$ fractions are recycled (scheme 2.3).



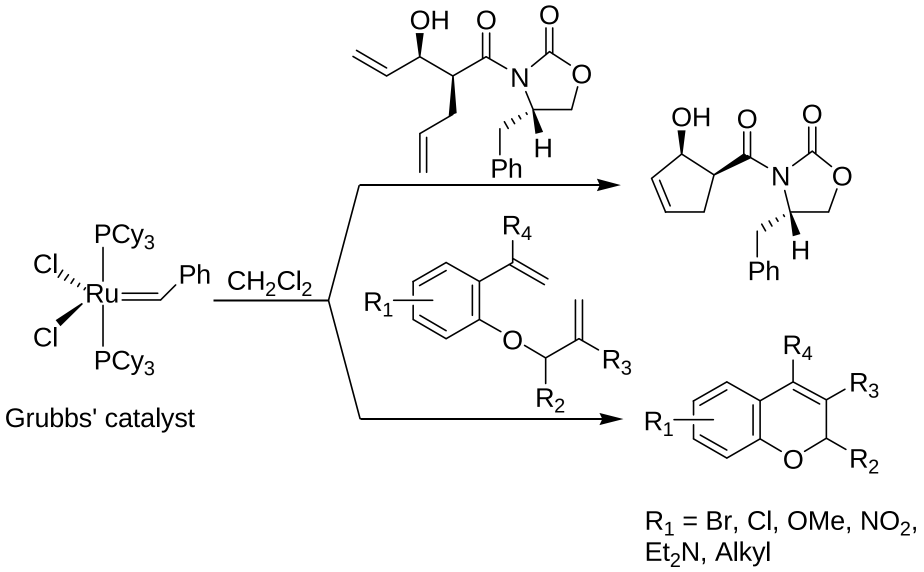
Scheme 2.3. Shell's Higher Olefin Process

For what concerns polymer chemistry, industrial processes such as the Norsorex process, of CD-F Chemie,[9] and the Hüls-Vestenamer[1a] process are examples for the production of elastomers *via* ring-opening-metathesis-polymerization (ROMP) of norbornene and cyclooctene respectively (scheme 2.4).



Scheme 2.4. Norsorex and Hüls-Vestenamer processes

The huge versatility of olefin metathesis along with the increasing demand for safer and more efficient synthetic procedures has spurred a great deal of research towards the synthesis of new catalysts able to operate under milder conditions, to improve the reaction selectivity, and to extend the synthetic scope of the metathetic process in general. In the field of homogeneous catalysts, excellent examples were developed by Grubbs *et al.*,[3,10,11] based on Ru- and Mo-carbene complexes capable of tolerating a variety of polar and protic groups for the ring-closing metathesis (RCM) of functionalized dienes to produce valuable cyclic intermediates for fine chemistry (scheme 2.5).



Scheme 2.5. Grubb's catalyst and fine chemistry application of RCM

As far as heterogeneous catalysis is concerned, the research over the past 20 years has focused mainly on Re supported on refractory materials such as alumina and – to a lesser extent – silica.[12] Metals such as Mo and Ru have also been supported[13] or immobilized[14] on solid supports and used for the metathesis reaction, as have bimetallic Mo-W ones.[15] However, effective heterogeneous catalysts for the metathesis of olefins are usually transition metal oxides such as Re_2O_7 and MoO_3 supported on inorganic matrices such as SiO_2, Al_2O_3, ZrO_2 and TiO_2. While many of the earlier publications relate to gas-phase processes, where the olefins were passed through a catalyst bed, applications of the heterogeneous reaction system have been widened to the liquid-phase metathesis, involving liquid olefins such as among others: pentene,[13] α,ω-olefins,[16] unsaturated nitriles,[17] octane[15,18] and oleochemicals.[19] In this context one of the limitations of using solid catalyst for the liquid-phase metathesis reaction is mass transfer. Further improvements not only of the synthetic potential and scope, but also of eco-compatibility of the reaction lie in the use of alternative safer and greener solvents able to replace conventional media, typically hydrocarbons (hexane and toluene) or light chlorinated compounds (dichloromethane and carbon tetrachloride).[3,13,16,17,18,20]

This is a largely unexplored area: only a few recent patents and papers report on the application of dense CO_2 or ionic liquids as solvents for RCM and ROMP processes.[21,22] In all cases however, either a Grubbs complex (scheme 2.5) or transition metal salts [$RuCl_3$, $Ru(H_2O)_6(tos)_2$, and WCl_6/Ph_4Sn] are reported as catalysts.

Compressed CO_2 as a solvent is perfectly suited for metathesis applications, especially if combined with the use of heterogeneous catalysts. First of all its solvating power towards alkenes is high.[23] Secondly, dense carbon dioxide is very efficient at penetrating meso- and micro-porous supports used for solid catalysts, thanks to its low viscosity (η) and high diffusivity (D) (0.01-0.03 mPa s and ~0.07 x 10^{-6} m^2 s^{-1}, respectively).[24] Liquid and supercritical CO_2 as a solvent/carrier can therefore improve the mass transfer (and the reaction rate) for a variety of different processes catalysed by solid materials.[25] Yet, to the best of our knowledge, the combined use of heterogeneous catalysts and CO_2 solvent has not been investigated for the metathesis of olefins.

These observations, in conjunction with the interest of this thesis work for green syntheses using CO_2 and its derivatives,[26] have inspired the present work. Different Re-oxides supported catalysts were prepared. These systems were explored as catalysts for the model self-metathesis reaction of 1-octene carried out under batch and continuous flow conditions with supercritical CO_2 ($scCO_2$) as solvent/carrier. The use of supercritical CO_2 was compared to that of conventional organic liquid (*n*-hexane) as reaction solvent. Catalysts have been prepared in collaboration with the group of Prof. T. Maschmeyer at the Laboratory for Advanced Catalysis and Sustainability, University of Sydney, while continuous flow reactions have been investigated at the Lab. of the Clean Technology Group, University of Nottingham, under the supervision of Prof. P. Licence.

The setup of the batch and continuous flow systems for the metathesis and the optimization of the reaction parameters have been examined. For clarity the results of this investigation are presented in two separate parts (paragraphs 2.1.2 and 2.1.4, respectively), the first related to batch conditions, while the second one devoted to continuous flow conditions.

2.1.2 Batch Conditions: Results

Foreword. Under batch conditions, the investigation of the olefin metathesis catalysed by a conventional heterogeneous system (Re_2O_7 on γ-Al_2O_3) in $scCO_2$ was reported by us in a previous work.[27] This investigation included not only the comparison of $scCO_2$ with other liquid solvents (*n*-heptane and toluene), but also the effect of the catalysts amount and its recycling, and of the CO_2 pressure. The salient features (*i-iv*) of this study are briefly summarized here:

i) Heterogeneous catalysts, prepared by impregnation of Re on commercial alumina supports, were shown to be active for the metathesis of 1-octene when combined with the use of compressed CO_2 as a solvent. In particular, the use of $scCO_2$ allowed higher conversion (on overage, over 30%) compared to conventional liquid solvents. That represented an improvement towards greening the overall process. The properties of the supercritical medium such as the gas-like diffusivity and viscosity and the liquid-like density of $scCO_2$, as well as the elimination of interphases, offered a significant improvement of the mass transfer which plausibly accounted for the observed behavior.

ii) The outcome of the self-metathesis was sensitive to the concentration of the olefin: the more diluted the substrate, the lower the conversion. However, when the pressure of CO_2 was increased in the range of 80-150 bar, thereby diluting the reactant olefin, the expected drop of conversion was not observed. This apparent inconsistency was explained by considering that like many other reported reactions,[22,28] the enhancement of the pressure (*i.e.* the density) could have a beneficial influence. However, this seemed to be counterbalanced by the pressure effect on the metathesis equilibrium where the release of stoichiometric amounts of ethylene could prove disadvantageous for the process.

iii) As far as the amount of the catalyst, in the presence of a relatively low metal loading (7%), a convenient olefin:Re molar ratio was in the range of 20–25. Under these conditions, in supercritical CO_2 (90 bar, 35 $^\circ$C, d = 0.66 g/mL), the substrate conversion reached an equilibrium value of ~ 70% after the first 120 min. Also the catalytic system could be recycled – at least for three subsequent runs – with no loss of activity or selectivity.

iv) In the combined system $Re_2O_7/\gamma\text{-}Al_2O_3$ and $scCO_2$, different α-olefins including 1-octene, 1-heptene, and 1-hexene underwent the self-metathesis towards the corresponding 7-tetradecene, 6-dodecene, and 5-decene with very similar reactivity. In all cases, after 2 hours at 35 °C, conversions and selecitivities were in the range of 65-70% and 93-97%, respectively.

Based on these results, different aspects of the metathesis in $scCO_2$ were examined in this PhD thesis. In particular, under batch conditions, a more in-depth analysis of the nature of the catalyst was undertaken.

I. Catalysts. Heterogeneous catalysts for the metathesis of olefins are basically oxides of transitions metals such as Re_2O_7 and MoO_3 supported on several inorganic matrixes (SiO_2, Al_2O_3, ZrO_2 and TiO_2)[1]. Among them, the most investigated and efficient system is Re_2O_7 on $\gamma\text{-}Al_2O_3$: literature data indicate that the metal content usually ranges from 5 to 18%.[29]

In this work, a set of six catalytic systems were prepared by supporting Re_2O_7 on different refractory materials including alumina and silica. Four samples supported on alumina were labelled as Re-A_1, Re-A_2, Re-A_3 and Re-A_4. A sample supported on an alumino-silicate was labelled as Re-AS_1, and a last sample supported on silica was labelled as Re-S_1. All but one of these materials were prepared by wet impregnation,[30] using commercial ammonium perrhenate (NH_4ReO_4) as the precursor of the active phase.[31] One catalyst (Re-S_1) was instead prepared by a sol-gel technique using the same metal precursor (NH_4ReO_4) which was introduced into the template solution prior to addition of the silica source (tetraethoxysilane). This allowed to incorporate directly the metal into the silica matrix.

Each sample was calcined in dry air at 550 °C for 4 h, and immediately before use, activated in dry N_2 at the same temperature. The final metal content (by weight) was determined by optical ICP, and it ranged from 5.5 to 11.8% for the alumina samples, while the sol-gel Re-SiO_2 had a value of 2.8 wt.%. The catalysts on Al_2O_3 (Re-A_1, Re-A_2, Re-A_3 and Re-A_4), the Si:Al-TUD-1 (Re-AS_1), and the sol-gel Re-SiO_2 (Re-S_1) were characterised by TEM after the calcination step. Major features of the catalysts are listed in table 2.1.

Table 2.1. Supported Re_2O_7 catalysts

#	% Re (wt) [a]	Support			Cat. Label	Particle size (nm)[c]
		type	S_A [m^2/g][b]	Source		
1	6.8	γ-Al_2O_3	257	Puralox-Condea	Re-A_1	< 1
2	7.0	γ-Al_2O_3	200	Alfa-Aesar	Re-A_2	< 1
3	6.4	γ-Al_2O_3	257	Puralox-Condea	Re-A_3	< 1
4	11.8	Meso-porous Al_2O_3	362	Ref. 30a	Re-A_4	< 1
5	7.7	Si:Al-TUD-1[d]	298	Ref. 30b	Re-AS_1	< 1
6	2.7	sol-gel Re-SiO_2	696	This work	Re-S_1	< 1

[a] The metal content was determined by optical ICP. [b] Surface area of the support. (Typically, the S_A for metathesis catalysts is ≥ 200 m^2/g; Ref. 1) [c] Determined by TEM. [d] Si:Al = 1:3.35.

II. Self-metathesis of 1-octene in supercritical CO_2 with different catalytic systems. The metathesis of 1-octene was performed in dense CO_2 according to a procedure previously reported by us.[27] Heterogeneous catalysts available for this study were those of table 2.1.

Figure 2.1 shows a schematic diagram of the apparatus used for such reactions. A Schlenk system was assembled to perform multiple operations under an inert (N_2) atmosphere. In particular: *i*) the high-temperature activation of the catalyst in a glass flask;[32] *ii*) the charge of the catalyst and of the reactant olefin in a stainless-steel reactor (a 30-mL autoclave); *iii*) the reaction step in the autoclave, at CO_2 pressures $\geq$ 90 bars (further details are reported in the experimental section).

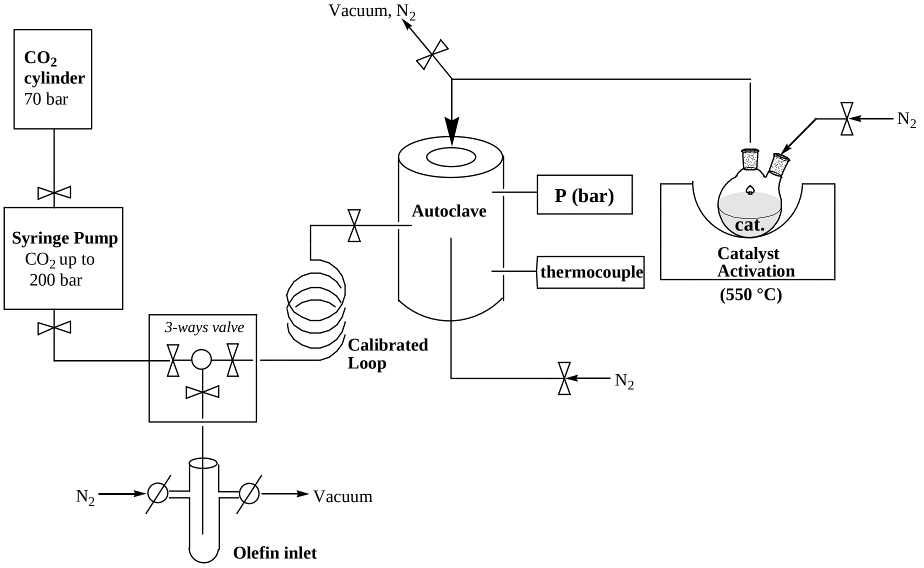
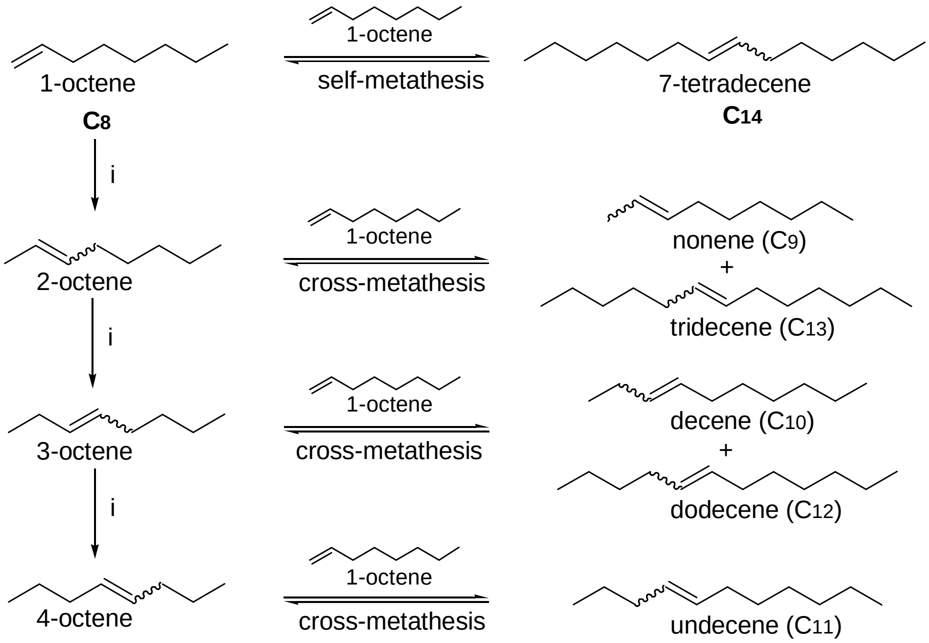


Figure 2.1. Schematic diagram of the apparatus used to carry out the metathesis of 1-octene in dense CO_2

In a typical experiment, the catalyst was activated at 550 °C as described above. Then, under a N_2 atmosphere, it was conveyed into a 30-mL stainless steel autoclave thermostated at 35 °C. By a high pressure syringe pump, a mixture of **C_8** (5 mmol) in scCO_2 was delivered to the reactor until a final pressure of 90 bars was reached. Previous tests showed that under these conditions (35 °C, 90 bar), 1-octene was completely solubilized in the supercritical phase.[33] Experiments were run for 2 h, sufficient to reach the equilibrium composition of metathesis products, as indicated by the fact that conversion did not increase further for longer reaction times. After venting the autoclave, the reaction mixture was analyzed by GC/MS.

Regardless of the catalyst used, the formation of the expected product of self-metathesis (7-tetradecene, **C_{14}**) was accompanied by different co-products which were identified as isomers of 1-octene (2-, 3-, and 4-octene) and linear olefins C_9-C_{13} (scheme 2.6). This behaviour was in line with that already reported for the metathesis of α-olefins carried out in liquid phase.[29,30,34] In particular, the isomerisation reaction of the starting alkene could occur either due to the acidic sites of the support, [34b] or by an addition-elimination sequence mediated by a metal-hydride species as observed elsewhere for Ru.[35] Higher internal olefins (C_9-C_{13}) derived from the cross-metathesis of the reagent $\mathbf{C_8}$ and of its isomers.[36]



Scheme 2.6. Self- and cross-metathesis reactions were catalysed by supported Re_2O_7. The isomerization (i) of 1-octene was promoted by the support (γ-Al_2O_3) or by metal hydride specie

Results are reported in table 2.2.

Table 2.2. The self-metathesis of 1-octene in $scCO_2$ with different Re_2O_7 supported catalysts [a]

#	Cat.	Support (S_A, $m^2 g^{-1}$)	Conv (%,GC) [b]	Products (%, GC)			Selectivity (%) [f]
				iso [c]	Cross [d]	C_{14} [e]	
1	Re-A_1	γ-Al_2O_3 (257)	74	1	2	71	96
2	Re-A_2	γ-Al_2O_3 (200)	37	1	2	34	92
3	Re-A_3	γ-Al_2O_3 (257)	71	1	2	68	96
4	Re-A_4	Meso-porous Al_2O_3 (362)	33	2	3	28	84
5	Re-AS_1	Si:Al-TUD-1[d] (298)	< 1	< 1			
6	Re-S_1	Re-SiO_2 (696)	< 1	< 1			

[a] All reactions were carried out for 2 h, at 35 °C, using 1-octene (5 mmol) and the catalyst (0.56 g) in the molar ratio olefin:Re = 23.7. [b] The reaction conversion (% by GC) was referred to all metathesis (olefins C_9-C_{14}) and isomerization compounds (scheme 2.6). [c] Total amount (% by GC) of isomerization by-products (2-, 3- and 4-octene). [d] Total amount (% by GC) of products of the cross-metathesis reaction (olefins C_9-C_{13}). [e] Total amount (% by GC) of 7-tetradecene: the *trans*/*cis* ratio was 3.8-4.0. [f] Selectivity towards the product of self-metathesis: [$\mathbf{C_{14}}$ (Area %, GC)/conversion (%)] x 100.

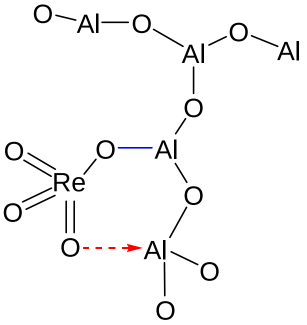
Alumina emerged as the optimal support for the Re-oxide active phase. In particular, catalysts Re-A_1 and Re-A_3 prepared from γ-Al_2O_3 (Puralox alumina, S_A = 257 m^2/g), proved to be the best ones, yielding conversions of 74 and 71%, respectively, after 2 h (entries 1 and 3).

The reaction conversion was lower (33-37%) on both Re-A_2 (on γ-Al_2O_3 Alfa-Aesar, S_A = 200 m^2/g) and Re-A_4 (mesoporous Al_3O_2, S_A = 362 m^2/g) (entries 2 and 4).

Remarkably, catalysts Re-AS_1 and Re- S_1 supported on alumina-silica and on silica, respectively, were not active at all (entries 5 and 6).

2.1.3 Batch Conditions: Discussion and Conclusions

Under the examined conditions, the nature of supports (γ-Al_2O_3, mesoporous alumina, mesoporous silica-alumina, and Re-incorporated silica) plays a critical role in the efficiency of catalytic systems used in this work. It is generally agreed that a monomeric tetrahedral structure of ReO_4^- species, is stabilized over the alumina surface: the metal centre forms three equivalent Re=O moieties and a Re-O-Al bond with an acidic OH group on the support (blue line, scheme 2.7).[30,37]



Scheme 2.7. Pictorial view of possible Rhenium oxide interaction with the alumina surface

Although the nature of these interactions are still not fully understood, it is plausible that the higher the surface area (S_A) of the solid alumina, the better the dispersion of the active phase and the corresponding catalytic performance.[8] This reason may account for the results of entries 1-3 of table 2.2. In the presence of $scCO_2$ as a solvent, the Re-A_1 sample supported on a γ-Al_2O_3 of 257 m^2/g, allows a higher conversion with respect to the Re-A_2 catalyst prepared on a γ-Al_2O_3 of 200 m^2/g. However, definite conclusions on metal dispersion and particle size cannot be drawn. The TEM analysis of Re-A_1 and Re-A_2 shows the γ-phase in the shape of grains of 5-6 nm, while the Re-oxide particles are not clearly distinguishable, their size being less than 1 nm. Oikawa *et al.* have reported a similar result.[30]

As far as the mesoporous alumina support is concerned, the higher activity reported in the literature for mesoporous Al_2O_3 was obtained with high-surface area supports (560 m^2/g).[30] In our case the mesoporous Re-A_4 catalyst (S_A=362 m^2/g, entry 4, table 2.1) was not as active, and is comparable to that of Re-A_2 (compare entries 2 and 4, table 2.2), probably due to the surface area being not sufficiently large.

The surface area, but mainly effects of the acidity of supports, should be considered to discuss the behavior of other catalysts in table 2.2. The ReO_4^- supported on Si:Al-TUD-1 (Re-AS_1) and inserted directly into the sol-gel matrix of the catalyst (Re-S_1), show no activity (entries 5-6). The Si:Al-TUD-1 has a relatively low surface area (298 m^2/g), while Re-S_1 has a very large surface area, though the amount of Re in the silica matrix is low (2.8 wt.%) due to the method of incorporation: the active phase is therefore likely less available on the surface. However, effects of the solid acidity appear even more important in this case as silica supports possess a lower surface acidity with respect to alumina.[38] This difference has been claimed to explain the generally poorer activity of silica-supported Re-oxide in the metathesis of olefins.[12,18b,39]An example is the metathesis of 1-butene which is reported to take place at temperatures not below 75 ◦C, in the presence of a Re_2O_7/SiO_2 (6%) catalyst.[40]

To conclude, in the presence of $scCO_2$ as a solvent, different catalysts based on Re-oxide are active for the self-metathesis of 1-octene. Though only alumina, preferably in the γ-phase, is a convenient support. The use of other solid materials such as alumina-silica or silica as such, kill the metal activity. This fact seems mainly attributable to the lower Brønsted and Lewis acidity of the supports compared to alumina.

2.1.4 Continuous Flow Conditions: Results

The experimental test on the continuous flow reactions has been carried out in a period of four months, at the Lab. of the Clean Technology Group, University of Nottingham. This short period did not permit an in-depth investigation, and some aspects have not been deepened/clarified as hoped. For this reason, results presented in this work, although promising, remained at a preliminary stage and it was not possible to continue the investigation further back in Venezia, due to the lack of the appropriate apparatus to carry out reactions under such conditions.

I. System set up. Continuous flow (CF) reactions have been carried out at the Laboratory of the Clean Technology Group of Prof. M. Poliakoff, University of Nottingham, under the supervision of Prof. P. Licence. Figure 2.2 shows a schematic diagram of the automated $scCO_2$ continuous flow apparatus used for the experiments.

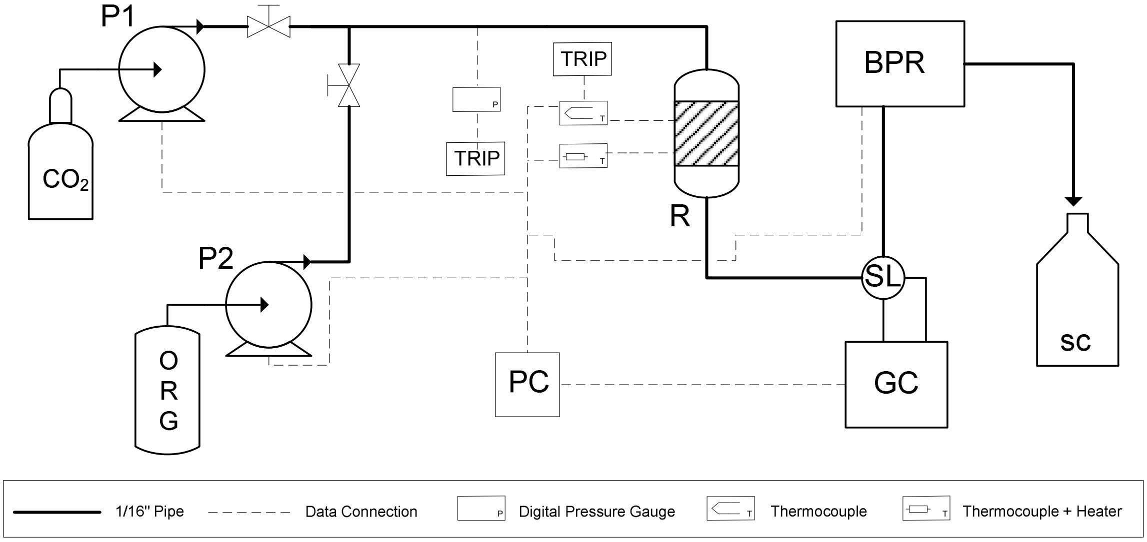


Figure 2.2. Piping diagram of the automated apparatus for CF reactions using $scCO_2$

Some key features of the system are briefly summarized. *i*) Two reciprocating pumps (P1 and P2) are dedicated to the delivery of CO_2 and the organic substrate to the reactor R. Both pumps can be programmed to control separately the flow rates of the solvent and of the substrate. Accordingly, a virtually indefinite number of different compositions of the substrate/solvent mixture can be pumped to the reactor. *ii*) The pressure of the system is checked continuously by an automated back pressure regulator (BPR). The use of the expansion system (BPR) to control the pressure, and of the CO_2 pump to control the flow rate makes the apparatus more stable and reliable with respect to the common approach for continuous $scCO_2$ flow apparatus.[41] *iii*) A small volume reactor (R), usually an 1/4" pipe, is used in order to decrease the time required to reach a thermal steady state. The reactor is heated at the desired temperature by means of cartridge heaters placed inside an aluminum block controlled by a programmable heating controller. *iv*) A high pressure sample loop (SL), placed between the base of the reactor and the BPR, allows to inject aliquots of the reaction mixture from the outflow of the reactor bed directly into the gas chromatograph (GC). In this way "*on-line real time*" analyses of the reaction outcome can be performed at the operating pressure of the reactor. This also specifically allows the collection and analysis of gaseous and volatile products. *v*) The pressure and temperature are logged at several points throughout the system on a computer (PC). So, a continuous monitoring of these parameters throughout the reaction is achievable.

Compared to batch processes, the CF conditions using $scCO_2$ have a number of synthetic and environmental advantages. Among others it is possible to: *i*) control and tune the reaction parameters (P,T, flow) to optimize the reaction outcome; *iii*) recover products and unconverted reagents on exit, and remove the gaseous by-products (*e.g.* ethylene in the metathesis), at the same time avoiding depressurization (and the related energy costs) and CO_2 recycle; *iv*) in general, reduce reactor volume (process-intensification) compared to batch processes with the same productivity. In addition, a critical issue of batch metathesis in $scCO_2$, that partly limited our previous investigation, is the high sensitivity of the supported Re-oxide catalysts to traces of oxygen or water.[1] This complicates the experimental setup due to the need to operate under a rigorously inert atmosphere and at the same time, to link a high temperature (550 °C) activation of the catalysts with their use at 35 °C under CO_2 pressure in an autoclave. Lengthy procedures are therefore required to achieve good reproducibility. By contrast, CF conditions allow the practical advantage of activating and using the catalysts in a single reactor without discontinuity, under a controlled atmosphere (inert or CO_2) to avoid Re-oxide deactivation. To do so, the apparatus of figure 2.2 was slightly modified by the introduction of a secondary line for the activation gas (N_2). Also, an additional line for air was implemented. This was used to re-activate the catalytic bed at the end of the reaction in order to study the possibility of a *in-situ* recycling of the catalyst.

II. Self-metathesis of 1-octene over $Re_2O_2/\gamma\text{-}Al_2O_3$. Based on the results of our previous batch experiments, the self-metathesis of 1-octene **C_8** (scheme 2.6) was chosen as a model reaction, while Re_2O_7 on γ-Al_2O_3 was selected as a catalyst. In particular, γ-Al_2O_3 from Puralox-Condea (As = 257 m^2g^{-1}, see table 2.1), was the support. A new catalytic sample (Re-A_5) was prepared according to the same procedure described for catalysts Re-A_1 and Re-A_3 (table 2.1). The a metal content was 7%.

Initial experiments were carried out to verify the suitability of the designed apparatus (figure 2.2), and to standardize the steps of the procedure. In a first test, a tubular reactor (1/4" pipe: volume = 1.67 cm^3, h = 15.2 cm, ø = 0.375 cm) was totally filled with the Re-A_5 sample (1.50 g). The catalyst was activated at 550 °C (1.5 h) under a N_2 stream. Then, it was cooled to 35 °C, and fed with a mixture of **C_8** in $scCO_2$: CO_2 was delivered at a pressure of 90 bar with a volumetric flow rate (F_{CO_2}) of 1.0 mL min^{-1}, while the olefin was pumped at a volumetric flow rate (F_{C_8}) of 0.1 mL min^{-1} (Further details of the procedure are in the experimental section). Under these conditions, the molar fraction of 1-octene (X_{C_8}) in the 1-octene/$scCO_2$ flow was $2.8x10^{-2}$.[42] After 8 min, the conversion of 1-octene was 18.5% (by GC). The self-metathesis product 7-tetradecene (**C_{14}**) was obtained with a 97% selectivity. Other products were cross-metathesis compounds (linear olefins C_9-C_{13}, scheme 2.6), and isomers of 1-octene (iso, 2-, 3-, and 4- octene, scheme 2.6). Ethylene and light cross-metathesis alkenes (linear olefins C_2-C_7)

were also observed. However, as for batch conditions (par. 2.1.2), the reaction conversion and selectivity were calculated by omitting the formation of ethylene and light cross-metathesis products.

At the end of the reaction (420 min), the catalyst was kept in the reactor and reactivated through a two-step thermal treatment: *i*) a calcination at 550 °C, 4 h, in an air stream followed by *ii*) a further heating at 550 °C, 1.5 h, in a N_2 stream. Then, the Re-A_5 was re-used to carry out an additional metathesis reaction according to conditions described above (35 °C, 90 bar, $F_{CO_2} = 1.0$ mL min^{-1}, $F_{C_8} = 0.1$ mL min^{-1}). After 8 min, both conversion (20%) of 1-octene and selectivity (96%) towards 7-tetradecene were very similar to the first experiment.

These two preliminary tests indicated that continuous flow (CF) conditions were suitable for the metathesis reaction and apparently, the catalyst could be recycled with no loss of efficiency.

III. The effect of the reaction temperature. In order to improve the reaction conversion, the temperature effect was investigated. Two experiments [(a) and (b)] were run under the conditions described above (90 bar, $F_{CO_2} = 1.0$ mL min^{-1}, $F_{C_8} = 0.1$ mL min^{-1}): in the first (a) the reactor temperature was kept constant at 35 °C, while in the second test (b) the catalytic bed was heated, from 35 to 100 °C, with a rate of 0.2 °C min^{-1} during the reaction.

In both reactions, the reactor outflow was sampled and analyzed by GC every 22 min. Figure 2.3 shows the two reaction profiles, where the amount of 1-octene, 7-tetradecene, iso (2-, 3- and 4-octene) and cross (linear olefins C_9-C_{13}), along with the reactor temperature, are plotted *vs* time.

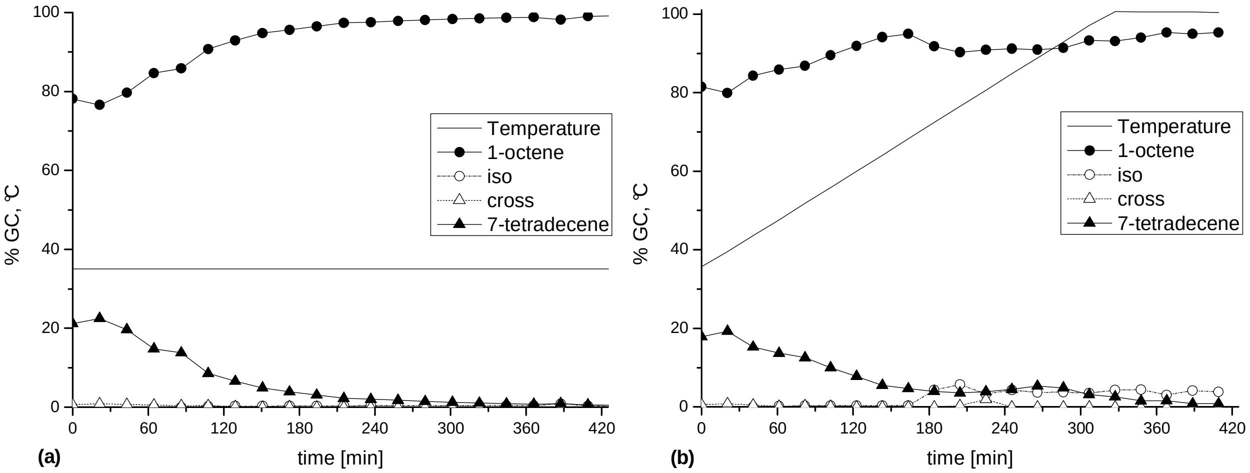


Figure 2.3. Reaction profiles for the self-metathesis of 1-octene: (a) isothermal conditions (35 °C); (b) heating ramp temperature conditions (35-100 °C)

Similar reaction profiles were obtained: in the first 45 minutes, the (initial) conversion of 1-octene was ~20%, and it dropped to less than 5% within 3 hours of reaction. Apparently, the increase of the temperature had no remarkable effect on the reaction outcome, except for a slight increase of the isomerization by-products (~8% in total) over 80 °C [figure 2.3 (b)].

This was a rather unexpected result. To gather more information on it, the behavior of the conversion had to be consider at the very beginning of the reaction. Accordingly, a set of five isothermal experiments was carried out: keeping all the other parameters unaltered (90 bar, F_{CO_2} = 1.0 mL min^{-1}, F_{C_8} = 0.1 mL min^{-1}), the reaction temperature was set to 35, 100, 110, 120 and 150 °C, respectively, and the mixture at the outlet of the reactor was sampled after the first 5-8 minutes of reaction.[*] Figure 2.4 reports the initial conversion and the product distribution as a function of the temperature.

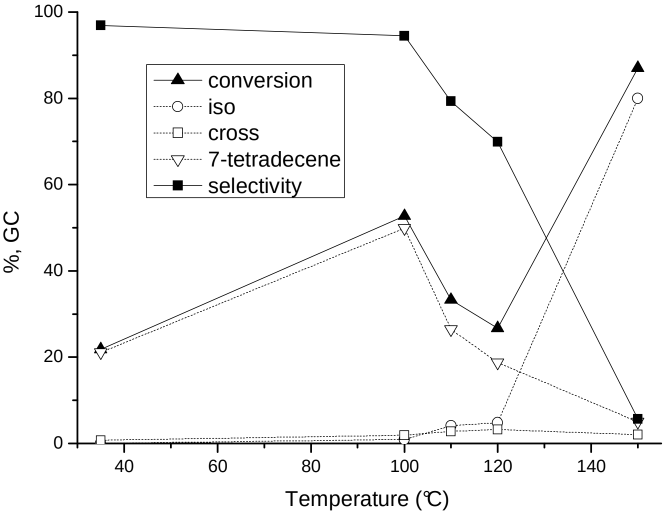


Figure 2.4. The effect of the reaction temperature on the initial outcome of the CF metathesis of 1-octene

The increase of the temperature from 35 to 100 °C improved the conversion of 1-octene from 20 to 50%, while the selectivity towards 7-tetradecene remained good at > 95%. However, a further enhancement of the temperature to 110-120 °C produced a significant drop of both the initial conversion and the selectivity. This latter due to a higher formation of isomerization and cross-metathesis products. Finally, at 150 °C, the isomerization of the starting alkene became the major (if not exclusive) observed transformation. Under such conditions, an almost quantitative conversion of 1-octene was obtained, though less than 5% of 7-tetradecene was detected.

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[*] As described in the experimental section, the first GC analysis was started only when a regular flow of organic solution was visually detected by the operator in the sample collector (SC). This, and the plausible time difference to reach a steady state of the system in each reaction, led to a fluctuation of the time of the first GC analysis in the range of 5-8 min after the start of the organic pump (P2). For this reason, the data presented in this work are to be considered as preliminary results.

Overall, a positive effect on the self metathesis of 1-octene was manifested up to 100 °C; then, an additional temperature increase highly disfavored the reaction. This aspect certainly deserved a more in-depth analysis which, however, was not possible due to time limitation of the investigations carried out at the University of Nottingham.

IV. The effect of the pressure. At 100 °C, under the same conditions used for the previous experiments (F_{CO_2} = 1.0 mL min^{-1}, F_{C_8} = 0.1 mL min^{-1}), three reactions were carried out at different pressures, setting the BPR (figure 2.2) at 60, 90 and 150 bar, respectively. Figure 2.5 reports the composition of the mixtures sampled at the reactor outflow, after the first 5-8 minutes of reaction.

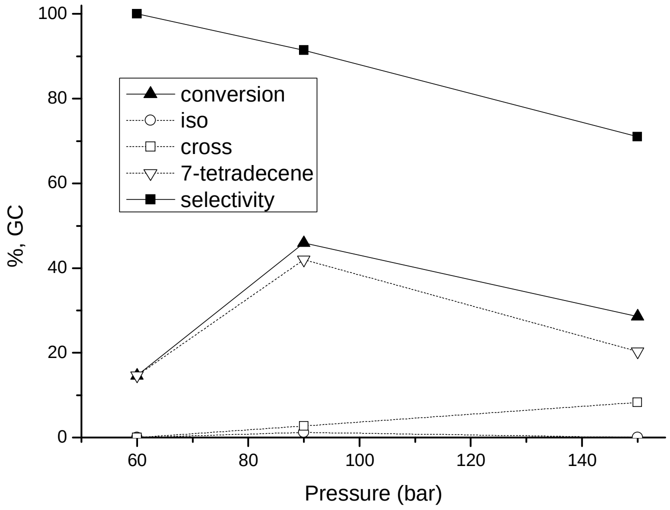


Figure 2.5. The effect of the pressure on the initial conversion

In the presence of subcritical CO_2 (60 bar, d_{CO2} = 0.099 g/mL, vapor phase,[43]), the initial conversion was low (15%), though 7-tetradecene was the sole product. The increase of the pressure up to 90 bar (supercritical conditions, d_{CO2} = 0.16 g/mL,[43]), almost tripled the conversion (46%) with only slight effects on the self-metathesis selectivity (93%). However, a higher pressure of 150 bar (supercritical conditions, d_{CO2} = 0.33 g/mL,[43]), had a negative effect on the reaction outcome: the conversion decreased (30%) and the formation of by-products of cross-metathesis (8%) was favored.

V. The influence of the volumetric flow rate of 1-octene. Under the (relative) best conditions of temperature and pressure identified by the previous tests (100 °C and 90 bar, respectively), possible effects due to variations of the volumetric flow rate of the reactant 1-octene (F_{C_8}) were investigated.

Three experiments were run by setting the F_{C_8} at 0.04, 0.1 and 0.5 mL min^{-1}, respectively. Under these conditions, the flow rate of CO_2 was kept constant at F_{CO_2} = 1.0 mL min^{-1}. This meant a change of the molar fraction of 1-octene in the 1-octene/scCO_2 flow to the reactor: the X_{C_8} were 1.1, 2.8 and 14.1 x10^{-2} operating at flow rates of 0.04, 0.1 and 0.5 mL min^{-1}, respectively. Figure 2.6 reports the composition of the mixtures sampled at the reactor outflow, after the first 5-8 minutes of reactions, *vs* the molar fraction X_{C_8}.

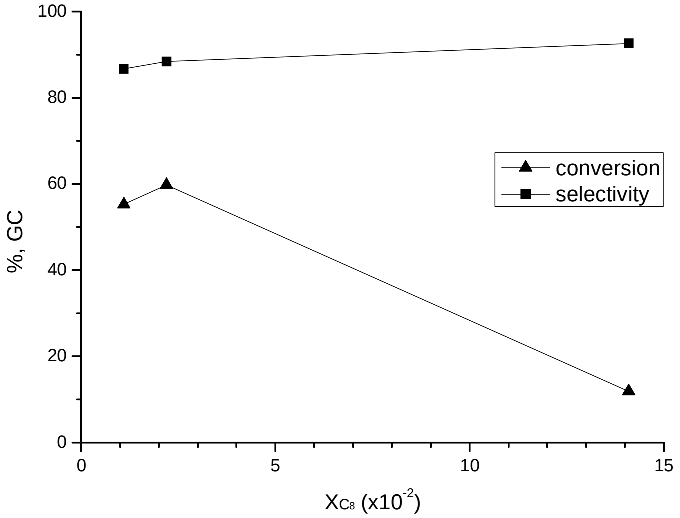


Figure 2.6. The effect of the volumetric flow rate of 1-octene on the initial conversion/selectivity

In the range of lower flow rate (X_{C_8} = 1.1÷2.8x10^{-2}), the conversion was of 50-60%, while it dropped to 12% at a higher flow rate (X_{C_8} = 14.1x10^{-2}). The self-metathesis selectivity was always rather constant (87÷92%).[44] Overall, the five-fold increase of the volumetric flow rate of the starting alkene (from 0.1 to 0.5 mL min^{-1}) produced a corresponding five-fold decrease of the initial conversion (from 60 to 12%).

VI. Reactivation of the catalyst. As mentioned before, a general advantage of CF conditions with respect to batch ones, is the option of activating and using catalysts in a single reactor without discontinuity, even operating under a controlled atmosphere. In the specific case of metathesis, CF modes would allow to minimize any Re-oxide deactivation caused by accidental contacts of the catalytic system with air and moisture. For this reason, CF conditions would appear also suitable to recycle the same catalytic bed without removing it from the reactor. These considerations were proved true and viable by the experiments: an effective re-activation method was set up according to a two-step thermal treatment in which the metathesis catalyst was first heated at a high temperature (550 °C), in an air stream (for 4 h), and then, at the same T, in a N_2

stream (1.5 h). For example, this procedure allowed the same reactor bed of $Re_2O_7/\gamma\text{-}Al_2O_3$ (ReA_5) to be used and recycled for all the experiments reported in figures 2.3-6.

An additional investigation of the catalyst reactivation was carried out. A new reactor (same size of the previous one: volume = 1.67 cm^3, h = 15.2 cm, ø = 0.375 cm) was filled with a fresh sample of the Re-A_5 catalyst (1.50 g). Then, seven subsequent reactions were run. Each experiment was performed at 100 °C, 90 bar, with a F_{CO_2} = 1.0 mL min^{-1}, and a F_{C_8} = 0.1 mL min^{-1}. Conversions and product distributions were determined by GC, after the first 15 minutes of reaction. At the same time, also isolated yields of 7-tetradecene collected at the BPR out flow, were evaluated. Results are reported in figure 2.7.

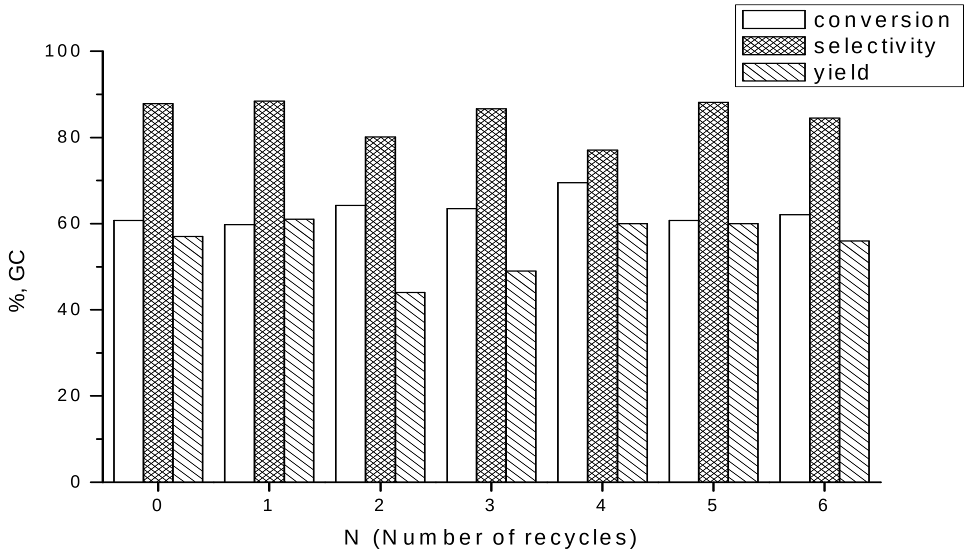


Figure 2.7. The reactivation of the catalyst

The initial catalytic activity was preserved throughout the set of reactions: after the sixth reactivation of the catalyst, no substantial variations of the reaction conversion, selectivity, and isolated yield of the self-metathesis product 7-tetradecene, were appreciable.

VII. Comparison between different solvents: $scCO_2$ vs n-hexane. $ScCO_2$ as a solvent/carrier for the metathesis reaction under CF conditions was compared with a conventional liquid medium for such a reaction. *n*-Hexane was used a model hydrocarbon solvent. ReA_5 was the catalyst. Although the molar concentration was a convenient parameter to compare kinetic profiles in liquid solvents, this was not suitable for supercritical solvents as pressure effects and the related significant solvation effects, were not accounted for. The mole fraction of 1-octene $\mathbf{C_8}$ $\{X_{C_8}$ = $[\mathbf{C_8}]/([\mathbf{C_8}]+[\text{solvent}])\}$ appeared like a more appropriate parameter for a coherent comparison. Therefore, the molar fraction of 1-octene (X_{C_8}) in the 1-octene/$scCO_2$ mixture (X_{C_8} = $2.8\text{x}10^{-2}$) was the same of that used in the 1-octene/*n*-hexane solution.[45]

Three experiments (*i*, *ii*, *iii*) were performed: *i*) in the presence of $scCO_2$, the reaction was carried out at 100 °C, 90 bar, with a F_{CO_2} = 1.0 mL min^{-1}, and a F_{C_8} = 0.1 mL min^{-1}. Under these conditions, the reactor was fed with a molar flow rate of 1-octene (MF_{C_8}) of 0.6 mmol min^{-1}; *ii*) in the presence of *n*-hexane as a solvent, the reaction was carried out at 100 °C, 90 bar, and with a volumetric flow rate of the organic solution (F_{Sol}) of 3.05 mL min^{-1}. This allowed a molar flow rate of 1-octene (MF_{C_8}) equal to 0.6 mmol min^{-1}, the same used with $scCO_2$; *iii*) in the presence of *n*-hexane as a solvent, the reaction was carried out under the same conditions of experiment *ii*, except for F_{Sol} which was reduced by a factor of 6, and set to 0.5 mL min^{-1} (the corresponding MF_{C_8} was 0.1 mmol min^{-1}). The composition of mixtures sampled at the reactor outflow were determined by GC after the first 5-8 minutes of reaction. Also, isolated yields of 7-tetradecene collected at the BPR outflow were evaluated after the first 15 minutes of reaction. Results are reported in table 2.3.

Table 2.3. Comparison between the use of $scCO_2$ and *n*-hexane [a]

#	Solvent	MF_{C_8} [mmol min^{-1}] [b]	Conv (%) [c]	Products (%, GC) [d]			Sel. (%) [e]	Yield (%) [f]
				Iso	Cross	C_{14}		
1	CO_2	0.6	53		7	46	87	57
2	*n*-hexane	0.6	-					
3	*n*-hexane	0.1	36		8	28	78	27

[a] All reactions were carried out at 90 bar, 100 °C, in the presence of Re-A_5 as the catalyst. Experiments were run under the following conditions: entry 1, F_{CO_2} = 1.0 mL min^{-1} and a F_{C_8} = 0.1 mL min^{-1}; entry 2, F_{Sol} = 3.05 mL min^{-1}; entry 3, F_{Sol} = 0.5 mL min^{-1}. [b] Molar flow rate of reactant 1-octene to the catalytic bed. [c] The initial reaction conversion was determined by GC after the first 5-8 minutes. [d] Products. Iso: total amount of isomers of 1-octene (2-, 3- and 4-octene); Cross: total amount of products of cross metathesis of 1-octene (olefins C_9-C_{13}); **C_{14}**: amount of the product of self-metathesis 7-tetradecene. [e] The selectivity was defined towards the product of self-metathesis **C_{14}**: [**C_{14}** (Area %, GC)/conversion (%)] x 100. It was evaluated after the first 5-8 minutes. [f] Isolated yield of crude 7-tetradecene collected at the BPR out flow after the first 15 minutes.

Two important aspects emerged. First, when the reactor was fed at the same MF_{C_8} of 0.6 mmol min^{-1} (entries 1-2), the conversion was 53% using $scCO_2$ as solvent/carrier (entry 1), while the reaction did not proceed at all in the presence of *n*-hexane (entry 2). Second, only operating at a lower flow rate (F_{Sol} = 0.5 mL min^{-1}; MF_{C_8} = 0.1 mmol min^{-1}), the metathesis took place in *n*-hexane (entry 3); though, the conversion (36%) was lower than that achieved in $scCO_2$.

VIII. The reaction profile and the deactivation of the catalyst. Figures 2.4-2.6 report the initial outcome of the self-metathesis of 1-octene, *i.e.* the trend of conversion and selectivity in the first few minutes (from 5 to 8 min) of the reaction, as a function of the most representative parameters such as T, P and F_{C_8}. However, if the process was followed at different time intervals, then the corresponding reaction profile was similar to those reported in figure 2.3 (a) and (b): in other words, a rapid catalyst deactivation occurred.

As an example, figure 2.8 shows the profile obtained for an experiment of 4 hours carried out at 100 °C, 90 bar, with a F_{CO_2} = 1.0 mL min^{-1} and a F_{C_8} = 0.1 mL min^{-1}.

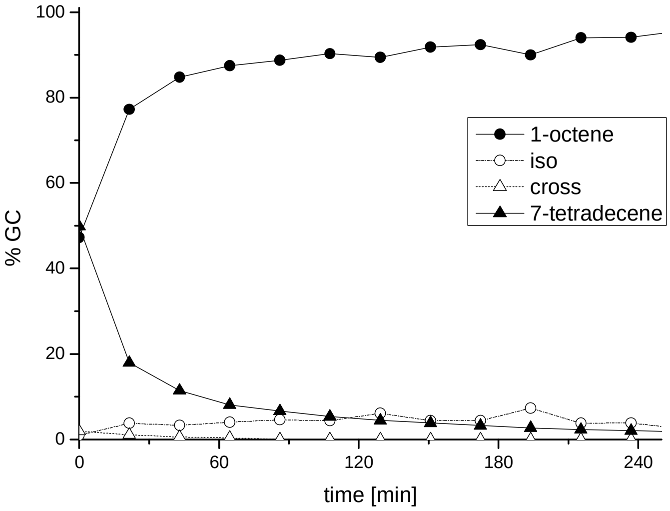


Figure 2.8. The profile of the CF reaction of 1-octene at 100 °C and 90 bar (F_{CO_2} = 1.0 mL min^{-1} and a F_{C_8} = 0.1 mL min^{-1})

The **C_8** conversion rapidly decreased within the first hour: in particular, after 20 min, it was more than halved (from 48 to 18%), and in 1 hour, it dropped dramatically to 1/6 of its initial value. The catalyst was no longer active after the first 3 hours.

As a first hypothesis, traces of O_2 or H_2O in the stream fed to the reactor seemed a plausible cause for a such fast deactivation of the catalytic system.[46] Accordingly, a set of experiments was run by replacing the Food grade CO_2 (purity = 99.97%) used as a carrier/solvent for the CF reactions of figure 2.3-2.8, with a higher CO_2 grade (SFC grade; purity = 99.99%). Moreover, degassed 1-octene was also used. Results are reported in table 2.4.

The results clearly showed that the use of a different CO_2 grade (SFC), even in combination with degassed 1-octene, did not improve significantly the life of the catalyst: regardless of conditions/quality of reactant/solvent, conversion and selectivity were similar at comparable reaction times. The deactivation of the catalyst had therefore other reasons. Some of them, are given in the discussion section.

Table 2.4. The use of different CO_2 types and of degassed 1-octene [a]

#	CO_2 grade	1-octene treatment	t (min)	Conv (%) [b]	Products (%, GC) [c]			Sel. (%) [d]
					Iso	Cross	C_{14}	
1	Food	none	5-8	56		4	52	93
			60	12	3	1	9	75
2	SFC	none	5-8	61		7	54	88
			60	3	1		2	67
3	SFC	degassed	5-8	60		7	53	88
			60	21	5	2	14	67

[a] All reactions were carried out at 90 bar, 100 °C, in the presence of Re-A_5 as the catalyst. Experiments were run under the conditions of figure 2.8, F_{CO_2} = 1.0 mL min^{-1} and a F_{C_8} = 0.1 mL min^{-1}. [b] The reaction conversion was determined by GC. [c] Products. Iso: total amount of isomers of 1-octene (2-, 3- and 4-octene); Cross: total amount of products of cross metathesis of 1-octene (olefins C_9-C_{13}); **C_{14}**: amount of the product of self-metathesis 7-tetradecene. [d] The selectivity was defined towards the product of self-metathesis **C_{14}**: [**C_{14}** (Area %, GC)/conversion (%)] x 100.

It should be noted that catalyst deactivation was observed also operating with *n*-hexane as a solvent. As an example, figure 2.9 shows the profile obtained for an experiment of 4 hours in *n*-hexane, carried out at 100 °C, 90 bar, and with a volumetric flow rate of the organic solution (F_{Sol}) of 0.5 mL min^{-1} (condition of entry 3, table 2.3).

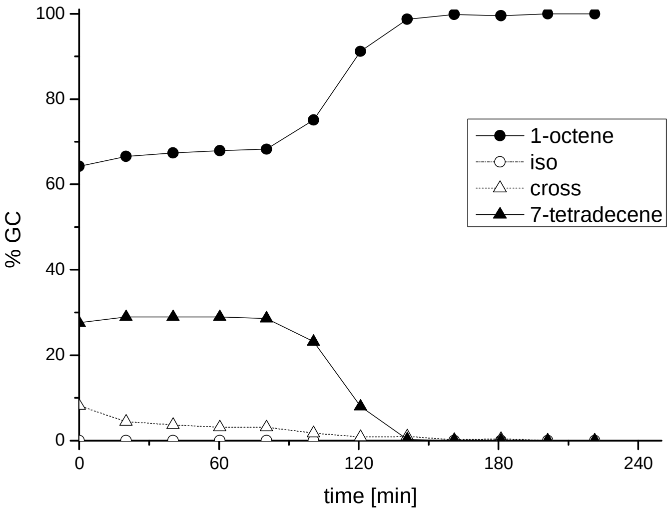


Fig 2.9. The reaction profile using *n*-hexane as solvent

In *n*-hexane, the overall behavior looked different with respect to $scCO_2$ (figure 2.8). The reaction conversion (and therefore the catalytic activity) remained rather steady at its initial value

(~30%) for the first 90 min of reaction (~30% by GC). Then, in the subsequent 60 min (a total of 150 min of reaction) the conversion rapidly decreased to zero. The catalyst deactivated also in *n*-hexane as a solvent, though apparently, its life was longer than in $scCO_2$. It should be noted however, that conditions of figure 2.9 were not comparable to figure 2.8: in the presence of $scCO_2$ a much higher molar flow rate of 1-octene (MF_{C_8}) was used (0.6 mmol min^{-1} *vs* 0.1 mmol min^{-1}), implying a higher reactant loading per time unit over the catalyst. Therefore, a faster deactivation in $scCO_2$ seemed a logical consequence.

2.1.5 Continuous Flow Conditions: Discussion

Our results on the self-metathesis of 1-octene under continuous flow (CF) conditions show both analogies and differences with the same reaction under batch conditions. Although preliminary, some salient aspects are here considered:

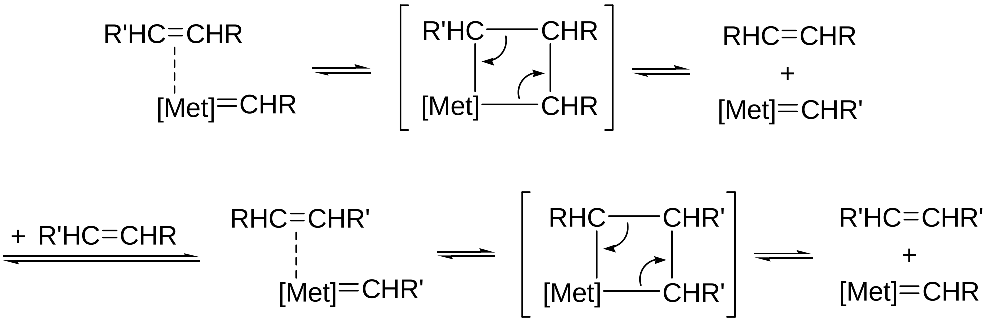
i) As for the batch process, $scCO_2$ proves to be a suitable solvent (carrier) for the reaction when Re-oxide supported on γ-Al_2O_3 is used as a catalyst. In particular, at 100 °C, figure 2.5 demonstrates that the CO_2 phase transition from vapor (60 bar) to its supercritical state (90 bar), remarkably improves the reaction outcome. However, by contrast to batch conditions, the CF process is sensitive also to higher CO_2 pressures (and densities): a further increase from 90 to 150 bar provokes a reduction on the conversion of the starting alkene (figure 2.5). Although this behavior has presently no clear reasons, at least two aspects should be considered. For one, the occurrence of local density enhancements (LDEs), whereby the density and the composition of the local environment around the solute molecules are modified with respect to the bulk of the supercritical solvent,[22,28] may offer an explanation for the improvement observed as the supercritical conditions are reached. On the other hand, the release of ethylene and other light gaseous olefins as co/by-products of self- and cross-metathesis equilibria could be disfavored by a high pressure of CO_2. Dynamic conditions of the CF operating mode may account for the sensitivity to the CO_2 pressure which is not observed under the batch mode.

ii) As for the batch process, the CF metathesis in $scCO_2$ proceeds with a higher conversion, yield and productivity compared to a conventional liquid solvent such as *n*-hexane (table 2.3). The gas-like diffusivity and the liquid-like density of the supercritical medium that have been described in previous chapters (chapt. 1, par 1.2) are the most plausible reasons for this behavior.

iii) At 35 °C, the highest possible conversion is of only 23% under CF conditions. A value by far lower than that achieved (65-70%) under the batch mode. Once again, the different reaction environment of dynamic *vs* static conditions likely accounts for such a result.

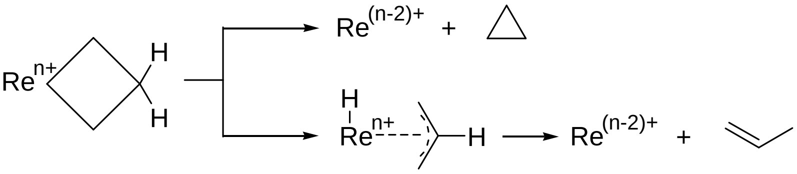
The temperature has a dramatic effect on the outcome of the CF process (figure 2.4). At 100 °C, the conversion of 1-octene increases up to 60% with a self-metathesis selectivity of ~90%. Though, a further enhancement to 150 °C, completely depresses the desired reaction in favor of the isomerization of the starting alkene. This behavior well matches literature data reporting that at a high temperature (usually over 100 °C), metathesis catalysts, particularly $Re_2O_7/\gamma\text{-}Al_2O_3$, become efficient for the C-C double bond isomerisation thanks to the Brønsted acid sites (*i.e.* the hydroxyl group on the catalytic surface) of the support.[12,34,47]

iv) An advantage of the CF operating mode is that the catalytic system ($Re_2O_7/\gamma\text{-}Al_2O_3$) selected for metathesis reactions can be activated and used in a single reactor, thereby avoiding its exposure to traces of air or moisture. The latter are known to produce a severe deactivation of Re-oxide. Notwithstanding this, CF experiments show that at 100 °C, even after a short initial period (~ 20 min), the reaction conversion is halved and eventually, it drops to almost zero in the next two hours. This result is hardly ascribable to the quality of both the reactant and the carrier: the use of SFC grade CO_2 or Food grade CO_2, and of degasses 1-octene do not improve the catalyst performance. Other facts should be considered: a) in the presence of *n*-hexane as a solvent (figure 2.9), when the catalyst is fed with a molar flow rate of 1-octene much lower than that used with $scCO_2$ (0.1 mmol min^{-1} *vs* 0.6 mmol min^{-1}), a steady conversion (30%) is maintained for the first 90 min of reaction. This suggests that the catalyst deactivation is controlled by the rate of saturation of the active metal sites by the organic reactant pumped through the reactor bed. b) The recycle and reuse of the catalyst is possible only on condition that a high temperature treatment of the system is carried out, including a (re)calcination step (550 °C, 4 h) in an air stream. On the contrary, if the catalyst is only heated at 550 °C, in an inert flow (N_2), then the re-activation fails. This demonstrates that oxidative conditions are crucial to restore the active metal sites, suggesting that also the formation of oligomers and/or of carbonaceous residues (coke) cannot be ruled out during the reaction.[48] It should be noted however that catalyst deactivation is observed even at 35 °C (figure 2.3) where the onset of side reactions (oligomerisation and coke formation) is less probable. In this case, a plausible explanation for catalyst deactivation can be given considering the reaction mechanism. For both homogeneous and heterogeneous catalysis, it is generally accepted that the metathesis reaction proceeds *via* the metal-carbene mechanism (scheme 2.8).[49]



Scheme 2.8. The metathesis mechanism *via* metal-carbene

Although the route of formation of the metal-carbene (*e.g.* [Met]=CHR) is not fully clarified,[50] this mechanism describes the metathesis through the coordination (*via* π) of the olefin at the vacant site of the transition metal of the metal-carbene moiety, followed by the formation of a metallacyclobutane intermediate. This metallacycle is unstable and cleaves to form a new metal-carbene and a new olefin.[49] In the case of rhenium oxide based catalysts, which are well know to deactivate, it is generally accepted that a reductive elimination of the metallacyclobutane intermediate may occur (scheme 2.9).[12] This intrinsic deactivation mechanism is probably the main cause of deactivation of these systems, and seems always operative.[51]



Scheme 2.9. The reductive elimination on Re based catalysts

In our case, the reduction of Re below its optimum oxidation state by this deactivation mechanism is a plausible explanation for the deactivation of the catalysts. However, the reasons why this deactivation process is so effective under the condition investigated in this work are not clear to us. Overall, these aspects require a more in depth investigation which will the object of future studies.

v) If the initial reaction outcome is considered (first 5-8 min of reaction), figure 2.6 shows that at 100 °C and 90 bar, a five-fold increase of the volumetric flow rate of 1-octene (F_{C_8}) corresponds to an equivalent (five-fold) decrease of the reaction conversion. In other words, under the investigated CF conditions, the rate of consumption of 1-octene per mass unit of the catalyst does not vary. This suggests that regardless of the flow rate, the catalytic system is always operating at its maximum allowed activity.

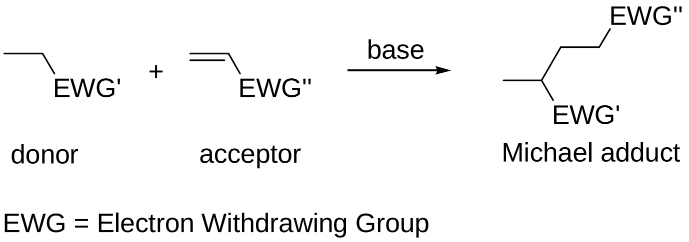
2.1.6 Continuous Flow Conditions: Conclusions

Although the use of $scCO_2$ as a metathesis solvent in place of traditional organic solvents represents an improvement towards greening the process, by itself it is not necessarily an innovation. It becomes such only when $scCO_2$ contributes to enhance other aspects of the chemical transformation as well, particularly if it makes the reaction faster compared to traditional conditions, or if it overcomes a technological barrier towards more efficient operation. One such instance where $scCO_2$ has a significant advantage over traditional solvents, is suggested by the results of this preliminary investigation. As in the batch mode, CF metathesis reactions catalysed by $Re_2O_7/\gamma\text{-}Al_2O_3$ proceed with both higher conversion and productivity in $scCO_2$ than in *n*-hexane. Under such conditions, the catalytic system can also be re-used: after 6 recycles, no loss of efficiency is appreciable. A concern however, is posed by the relatively fast deactivation of the catalyst. This behavior has presently no clear reasons and it will be the object of further studies.

2.2 Green Methodologies for the Michael Reaction

2.2.1 Introduction

The Michael reaction[52] is the conjugate addition of nucleophilic carbon species to electron deficient olefins (scheme 2.10).[53]

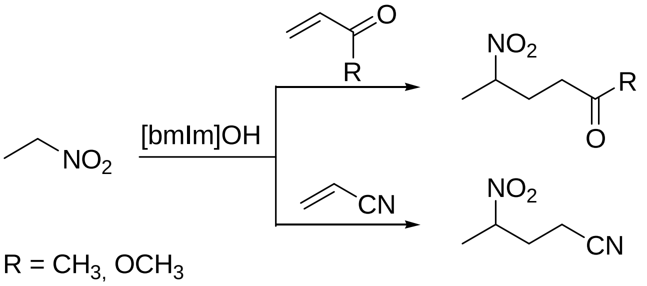


Scheme 2.10. The Michael Addition. EWG'= COR, COOR, NO_2, etc. ; EWG"= COR, COOR, CN, NO_2, SO_2Ph, etc.

Thanks to its versatility, the process is recognised among the fundamental pillars of carbon-carbon bond forming reactions, and it finds a number of applications in organic synthesis.[54]
Scheme 2.10 clearly shows that the Michael addition has also a great potential from the green chemistry standpoint: in fact, it is a catalytic process with no by-products, *i.e.* with a 100% atom economy. This green perspective however, is hardly noticed under the conventional conditions used for such a reaction, for a number of reasons. Among them, *i*) traditional base catalysts for the Michael addition, both organic and inorganic ones, such as NaOH, DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) and alkylamines, often lead to the formation of undesirable side-products, such as polymerization-, bis-addition- and self condensation- by-products; *ii*) classical solvents are irritating/toxic/carcinogenic compounds such as aromatic hydrocarbons, tetrahydrofuran (THF), dichloromethane (CH_2Cl_2) and acetonitrile (MeCN). In this context, a lot of efforts have been done in the past 20 years to improve the eco-compatibility of the Michael addition, especially by developing new homogeneous and heterogeneous catalysts able to enhance the reaction selectivity. For what specifically concerns the work presented in this PhD thesis, a brief overview follows on the Michael reaction carried out using nitroalkanes as carbonucleophiles.

Nitroalkanes are important starting materials in the formation of carbon-carbon bonds. Since the nitro group can be transformed into a variety of functionalities,[55] the Michael addition of nitroalkanes to electron-poor olefins provides a convenient method for the preparation of a number of synthetic intermediates.[56] Different classes of both homogeneous and heterogeneous systems have been used for such a reaction.

In the presence of homogeneous organic base catalysts such as tetramethylguanidine,[57] diisopropylamine,[57b,58] tri-*n*-butylphosphine[59] and DBU,[60] multiple Michael adducts are often formed in significant amounts.[61] Remarkable results for the synthesis of mono-substituted compounds have been obtained by using basic (task-specific) ionic liquids such as 3-butyl-1-methylimidazolium hydroxide, [bmIm]OH.[62] In this case the reaction is highly selective towards the formation of Michael monoadducts using nitroalkanes with both α,β-unsaturated -ketons -esters and -nitriles (scheme 2.11). The process takes place under solventless conditions and very good isolated yields (up to 90%) are achieved.



Scheme 2.11. The Michael addition using [bmIm]OH

Monosubstituted compounds have been obtained also by using solid bases (*e.g.* K_2CO_3) in combination with an ionic liquid such as Aliquat® 336.[63] In this case, the Michael addition of nitroalkanes to α,β-unsaturated esters produces γ-nitro esters, under rather green conditions, that is in the absence of solvents and under ultrasonic irradiation.[64]

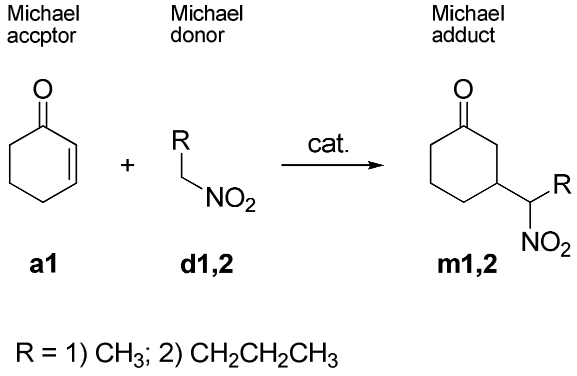
A number of different heterogeneous catalysts have been employed for the Michael reaction of nitroalkanes; though, these methods often show important drawbacks. For example: *i*) KF can be applied as such but its low activity imposes the use of a large excess of nitroalkane;[65] *ii*) the adsorption of KF on neutral[66] or basic[67] alumina greatly enhances the efficiency of the base catalyst, yet, an excess of nitroalkane is required, and low to moderate yields of Michael products are obtained;[68] *iii*) weakly basic macroreticular resins[69] and different types of alumina[67,70] can be used but their activity is limited to a rather restricted class of Michael acceptors such as α,β-unsaturated esters[69] or conjugated enones.[67,70] Among heterogeneous systems, good results have been instead reported using supported alkylamine catalysts, such as Amberlist A-27[71] or KG-60-NEt_2:[72] these solids catalyze the Michael addition of both primary and secondary nitroalkanes with a number of α,β-unsaturated ketons, esters, sulphones and nitriles with good to excellent isolated yields of monoadducts.

In light of these results, in this PhD thesis the investigation of the Michael reaction with nitroalkanes as donors, has been articulated through two different lines [(a) and (b)], based on the use of heterogeneous (a) and homogeneous (b) catalysts.

2.2.2 Heterogeneous Catalysis: Results

Our previous successful experience on the alkene metathesis (paragraphs 2.1) where the use of dense CO_2 as a solvent was coupled to heterogeneous catalysts, prompted us to consider whether the same concept could be applied to the case of the Michael additions. The literature analysis showed that this was a substantially unexplored area: no references were available on the combined use of $scCO_2$ and heterogeneous catalysis for the use of nitroalkanes as Michael donors.

In particular, the additions of nitroethane and nitrobutane to cyclohexenone were chosen as model reactions (scheme 2.12). Conventional solid catalysts for Michael reactions were used for our investigation: different bases such as basic alumina and KF supported on alumina fitted our scope.



Scheme 2.12. Michael additions of nitroalkanes over solid catalysts

Under these conditions, supercritical carbon dioxide as a solvent was compared to solvent-free conditions and to two traditional organic liquid media such as THF and *n*-heptane.

I. Catalysts. Four different heterogeneous catalysts were used (table 2.5): two basic aluminas from different commercial sources, Baker and Macherey Nagel, labeled as $[Al_2O_3]_B$ and $[Al_2O_3]_M$ respectively; KF supported on Macherey Nagel alumina, labeled as $[KF/Al_2O_3]_M$, and a mesoporous alumina, labeled as $[Al_2O_3]_{meso}$. The sample of supported KF (KF loading = 0.35 mmol g^{-1}) was prepared according to a standard impregnation technique.[73] Mesoporous alumina was prepared according to a procedure described in the literature.[30a]

Table 2.5. Basic solids used as catalysts

Material type	**Source**	**Label**
Al_2O_3	Baker	$[Al_2O_3]_B$
Al_2O_3	Macherey Nagel	$[Al_2O_3]_M$
KF over Al_2O_3	Macherey Nagel and ref.73	$[KF/Al_2O_3]_M$
mesoporous Al_2O_3	Ref. 30a	$[Al_2O_3]_{meso}$

II. Michael reaction of nitroethane and cyclohexenone under solvent-free conditions. Initial experiments were run in the absence of solvents. Experimental conditions were chosen according to previously reported Michael additions of nitrolalkanes to α,β–unsaturated ketones.[72]

In a typical reaction, a glass reactor shaped as a test tube, was charged with cyclohexenone (**a1**: 0.1 g, 1.04 mmol), nitroethane (**d1**: 0.156 g, 2.08 mmol), and the catalyst $[Al_2O_3]_B$ (0.2 g). Then, the reactor was heated at the desired temperature (40 °C) and the mixture was kept under magnetic stirring throughout the reaction. Samples of the reaction mixture were analysed by GC/MS at different time intervals. At the end of the reaction, the Michael adduct was isolated and its structure was confirmed by MS and ^{1}H NMR spectra. Results are reported in figure 2.10, were the conversion of cyclohexenone (**a1**) and the selectivity towards the Michael product 3-(1-nitroethyl)cyclohexanone (**m1**, scheme 2.12) are plotted against the reaction time.

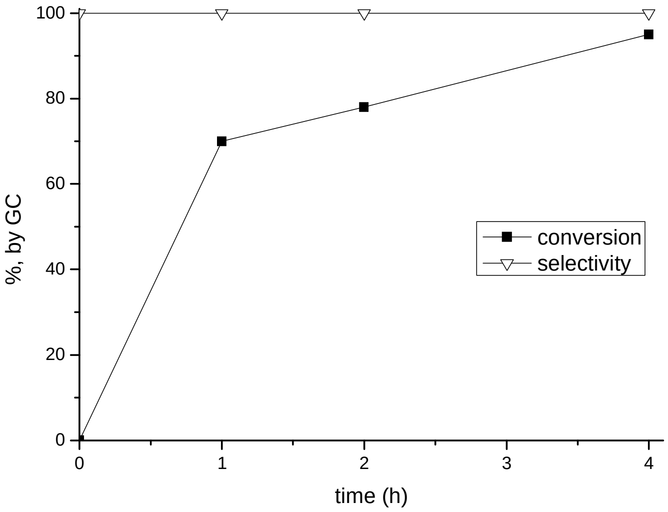


Figure 2.10. Michael reaction of **a1** with **d1** catalysed by basic $[Al_2O_3]_B$, 40 °C

A substantially quantitative conversion (95% by GC) was reached after 4 hours with the exclusive formation of the Michael product 3-(1-nitroethyl)cyclohexanone (**m1**). Once the reaction was complete, the catalyst was filtered, and the crude compound **m1** was isolated with a 90% yield.

According to this procedure, catalysts of table 2.5 ($[Al_2O_3]_M$, $[KF/Al_2O_3]_M$ and $[Al_2O_3]_{meso}$) were compared. Reactions were carried at 40 °C, and analyzed (by GC/MS) after 2 hours. Figure 2.11 shows the results. For a more complete comparison, the behavior of $[Al_2O_3]_B$ as a catalyst (figure 2.10, 2 h) is also reported.

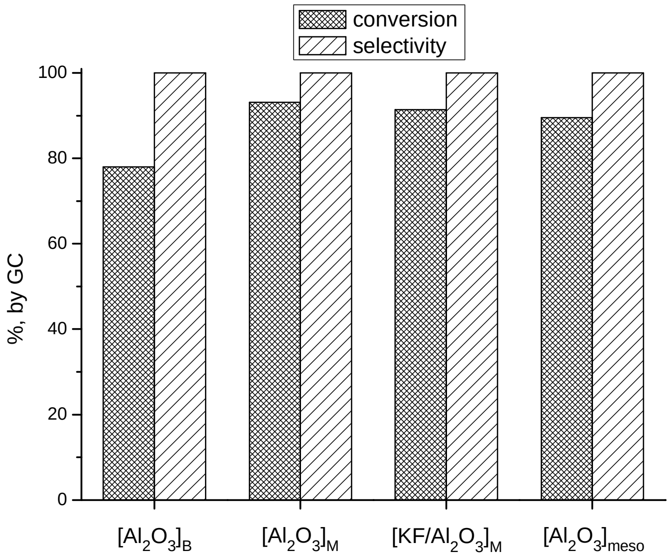


Figure 2.11. Michael reaction of **a1** with **d1** catalysed by basic materials

Under solvent-free conditions, different aluminas as well as $[KF/Al_2O_3]_M$ showed a comparable performance: high conversions (~80-90%, by GC) and 100% selectivity towards the product **m1** were obtained in all cases.

Two additional experiments [(a) and (b)] were carried out to examine whether the catalysts could be recycled. $[Al_2O_3]_B$ and $[KF/Al_2O_3]_M$ were used to this scope. Conditions were those described above (40 °C, 2 h). At the end of a first reaction, catalysts were filtered, washed with Et_2O, re-activated at 400 °C for 2 h in a dry air flow, and then reused. This recycling procedure was repeated once more. Figure 2.12 reports the results: the conversion of cyclohexenone (**a1**) and the selectivity to the Michael product 3-(1-nitroethyl)cyclohexanone (**m1**) are plotted against the number of recycles.

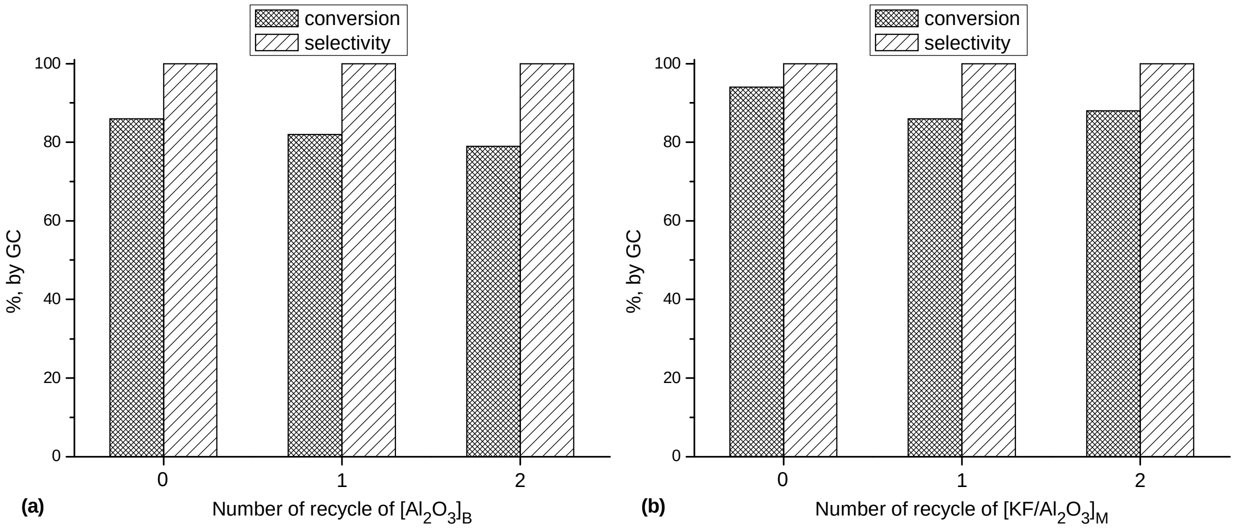


Figure 2.12. The recycle of catalysts $[Al_2O_3]_B$ (a, left) and $[KF/Al_2O_3]_M$ (b, right)

The reaction outcome did not show significant variations with both catalysts. After two recycles, the conversion was on average 80% for $[Al_2O_3]_B$, and 90% for $[KF/Al_2O_3]_M$, respectively, while the selectivity towards **m1** was 100% in all reactions. Notwithstanding the relatively high catalyst loading (the weight ratio Q = catalyst:**a1** = 2), $[Al_2O_3]_B$, and $[KF/Al_2O_3]_M$ could be re-activated and re-used with no substantial loss of activity. However, it should be mentioned that due to the nature of alumina, each recycle step brought to a loss of ~20% of the initial weight of the catalyst during the filtration/re-activation sequence (details are in the experimental section). This posed a practical limitation to the number of recycles.

III. Comparison between solvent-free conditions and $scCO_2$ as a solvent. The next step of the investigation on the Michael reaction of cyclohexenone (**a1**) and nitroethane (**d1**) was devoted to a comparison between the use of supercritical CO_2 as a solvent and solvent-free conditions as described in the previous paragraph. $[Al_2O_3]_B$ and $[Al_2O_3]_{meso}$ were used as the catalysts. Reactions in $scCO_2$ were carried out in an autoclave (V = 5.3 mL), at 40 °C. The reactor was charged with cyclohexenone (**a1**: 0.1 g, 1.04 mmol), nitroethane (**d1**: 0.156 g, 2.08 mmol) and catalyst (0.2 g). The CO_2 pressure was set at 90 bar corresponding to a molar fraction ($X_{\mathbf{a1}}$) of cyclohexenone in the CO_2 solution equal to $1.8x10^{-2}$. Under these conditions, previous experiments showed that both cyclohexenone and nitroethane were completely soluble in $scCO_2$. The reaction mixture was magnetically stirred for 2 hours. Then, the reactor was depressurized and the mixture was analysed by GC/MS. Results are shown in figure 2.13: the conversion of cyclohexenone obtained both in the presence of $scCO_2$ and under solventless conditions (data of figure 2.11), is reported using $[Al_2O_3]_B$ and $[Al_2O_3]_{meso}$ as catalysts.

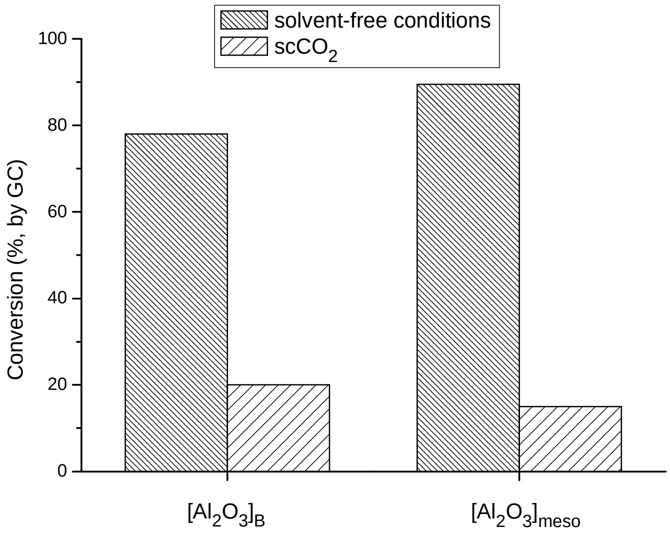


Figure 2.13. Michael reaction of **a1** and **d1** at 40 °C (W = 2). The conversion of cyclohexenone under solvent free conditions and in the presence of $scCO_2$ (90 bar) as a solvent

With respect to the solvent-free conditions, the use of $scCO_2$ induced a dramatic drop of the reaction conversion which decreased from 80% to 20% on $[Al_2O_3]_B$, and from 91% to 16% on $[Al_2O_3]_{meso}$ catalysts, respectively. A dilution effect appeared a plausible reason for this result.
In all reactions, the selectivity was 100% towards the Michael product **m1**.

IV. The comparison of $scCO_2$ with different organic solvents. The use of $scCO_2$ as a solvent for the Michael reaction of scheme 2.12 was compared to that of conventional organic liquid media such as *n*-heptane and THF. As for the metathesis of alkenes (par. 2.1), the molar fraction of the limiting reactant ($X_{\mathbf{a1}}$ of cyclohexenone) appeared like the more appropriate parameter for a coherent comparison between the supercritical and the liquid solutions used for the reactions.
Initial experiments were carried out at 40 °C for 2 h, using $[KF/Al_2O_3]_M$ as a catalyst, with a molar ratio (W) **a1**:**d1** = 2, and a weight ratio (Q) catalyst:**1a** = 2. For each of the chosen solvents ($scCO_2$, *n*-heptane and THF), four reactions were run operating at four different values of $X_{\mathbf{a1}}$ of 3.1, 1.8, 1.2 to 1.1 x 10^{-2}, respectively. Three sets of experiments were performed.
$ScCO_2$. According to the procedure above described for figure 2.13, reactions in $scCO_2$ were carried out by setting the CO_2 pressure at 80, 90, 120 and 150 bar, respectively. At 40 °C, this corresponded to a CO_2 density of 0.278, 0.485, 0.718 and 0.780 g mL^{-1}, respectively.
n-Heptane. Experiments were carried out by adjusting the procedure used under solvent-free conditions. Four solutions of cycloexenone in *n*-heptane (d = 0.683 g mL^{-1}) were prepared at different molar concentration of cyclohexenone ($M_{\mathbf{a1}}$) of 0.07, 0.08, 0.12 and 0.21 mol L^{-1}, respectively, and then used in different amounts (13.8, 12.7, 8.5 and 5.0 mL, respectively) to carry out the reactions.

THF. Reactions in THF were carried out under the same conditions used for *n*-heptane. Four solutions of cyclohexenone in THF (d = 0.889 g mL^{-1}) were prepared at different molar concentration of cyclohexenone ($M_{\mathbf{a1}}$) of 0.13, 0.15, 0.22 and 0.37 mol L^{-1}, and then used in different amounts (7.7, 7.1, 4.8 and 2.8 mL, respectively) to carry out the reactions.

Figure 2.14 reports the results. The reaction conversion of each experiment is plotted *vs* the molar fraction ($X_{\mathbf{a1}}$) of cyclohexenone.

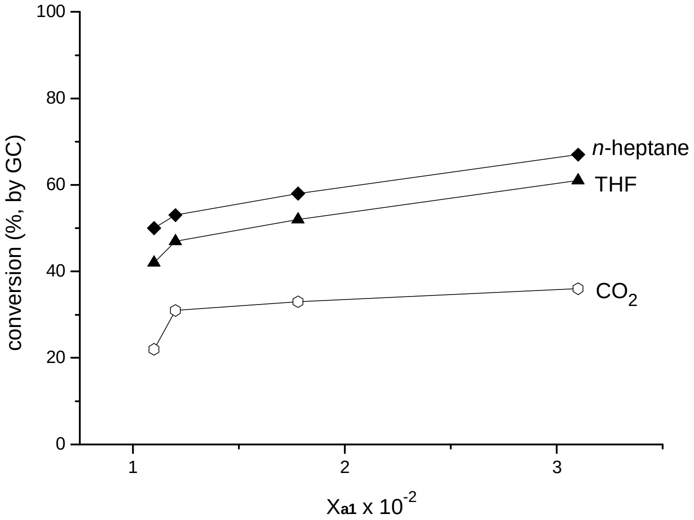


Figure 2.14. The Michael reaction of **a1** and **d1** catalysed by [KF/Al_2O_3]$_M$, in presence of different solvents at different concentrations

Main aspects emerging from this investigation were: *i*) for all the solvents tested, the conversion was slightly sensitive to the variation of the molar fraction of **a1**. A three-fold increase of $X_{\mathbf{a1}}$ (from 1.1 to 3.1 x 10^{-2}) did not remarkably enhanced the reaction conversion, that ranged from 50 to 67% in *n*-heptane, from 42 to 61% in THF and from 22 to 36% in scCO_2. *ii*) Regardless of the molar fraction $X_{\mathbf{a1}}$, the conversion was considerably lower in scCO_2 than in liquid solvents; also, a higher conversion was always obtained in *n*-heptane with respect to THF. *iii*) under all conditions of figure 2.14, the conversion was always lower than in the absence of solvents (compare to figure 2.11).

These results confirmed the negative effect of dilution on the reaction rate. Also, if one considered only liquid solvents, figure 2.14 showed that the reaction was slower in THF than in *n*-heptane even when molar concentrations were comparable (in the range of 0.12-0.22 mol L^{-1}). In all reactions, the selectivity was 100% towards the Michael product **m1**.

To further compare scCO_2 with organic solvents, an additional set of experiments was run using [Al_2O_3]$_{meso}$ as a catalyst. Reactions were carried out in scCO_2 (90 bar), *n*-heptane and THF, under the same conditions of figure 2.14 (40 °C, 2 h), and using a molar fraction $X_{\mathbf{a1}}$ of $1.8x10^{-2}$. Results are reported in figure 2.15.

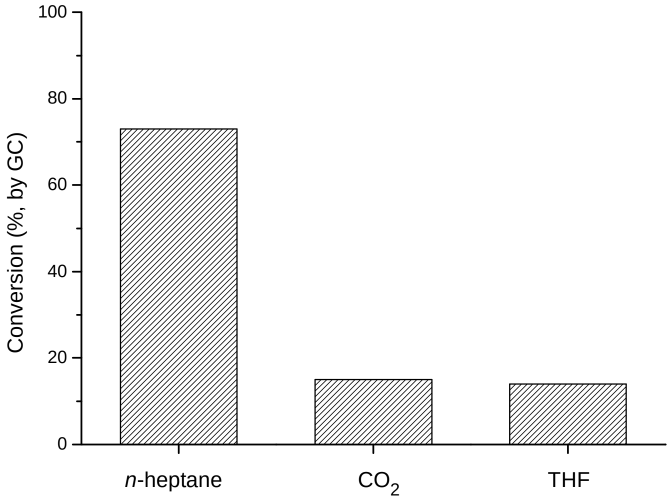


Figure 2.15. The Michael reaction of **a1** and **d1** catalysed by $[Al_2O_3]_{meso}$, at $X_{\mathbf{a1}} = 1.8x10^{-2}$, in the presence of different solvents

As for previous experiments (figure 2.14), *n*-heptane turned out to be the better solvent: in the presence of $[Al_2O_3]_{meso}$ as the catalyst, the conversion (73%) was even improved with respect to $[KF/Al_2O_3]_M$. Yet, it (conversion) was still lower than under solvent-free conditions (90%, figure 2.11). The outcome of reactions carried out in $scCO_2$ and in THF was comparable and by far, worse with respect to heptane (the conversion was 15 and 14%, respectively).

In all cases, the selectivity was 100% towards the Michael product **m1**.

V. Comparison of different solvents in the Michael reaction of nitrobutane and cyclohexenone. The Michael reaction of nitrobutane (**d2**) and cyclohexenone (**a1**) was investigated under solvent-free conditions, and by comparison, in the presence $scCO_2$, *n*-heptane and THF as solvents.

$[KF/Al_2O_3]_M$ and $[Al_2O_3]_{meso}$ were used as catalysts. Reaction conditions were those of figure 2.15, except for the fact that nitrobutane (**d2**: 0.214 g; 2.08 mmol) was used in place of nitroethane. The results are reported in figure 2.16.

A general trend could be inferred from the comparative analysis of figures 2.14, 2.15, and 2.16: regardless of the Michael donor [nitroethane (**d1**) or nitrobutane (**d2**)], solventless conditions always promoted higher conversion of cyclohexenone; among the solvent used, *n*-heptane was better than THF and $scCO_2$, these latter offering a somewhat comparable performance.

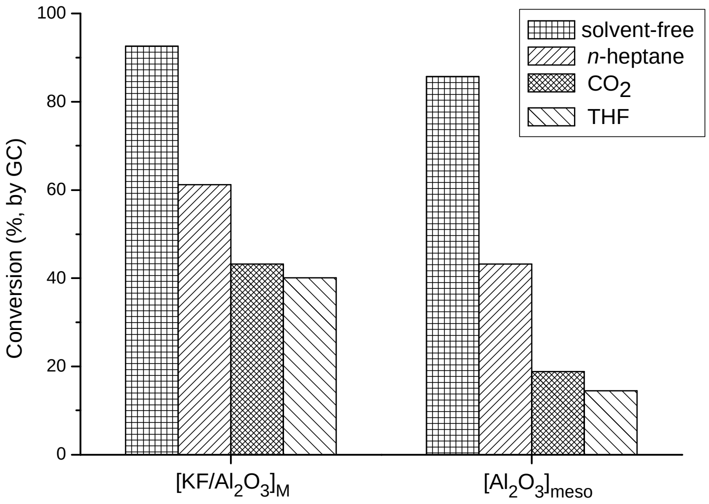


Figure 2.16. The Michael reaction of **a1** and **d2** (40 °C, 2 h, $X_{\mathbf{a1}} = 1.8 \times 10^{-2}$) under solventless conditions and in the presence of different solvents

Under solvent-free conditions in the presence of $[KF/Al_2O_3]_M$, once the reaction was complete, the catalyst was filtered and the product 3-(1-nitrobutyl)-cyclohexanone (**m2**) was obtained in 89% isolated yield. The structure of the product was assigned through MS and ^{1}H NMR spectra.

Less clear was the behavior of the catalysts. In the first studied reaction (**a1**+**d1**), $[KF/Al_2O_3]_M$ showed a higher activity than $[Al_2O_3]_{meso}$ in both THF and $scCO_2$, the reverse occurring in *n*-heptane (figures 2.14, 2.15). In the second studied reaction (**a1**+**d2**), $[KF/Al_2O_3]_M$ gave always better results than $[Al_2O_3]_{meso}$ both in the presence and in the absence of solvents. On the other hand, if one considered the two carbonucleophiles (nitroethane and nitrobutane), no remarkable differences (of the conversion) were observed when $[KF/Al_2O_3]_M$ was used (figures 2.14 and 2.16, left). While, in *n*-heptane only, $[Al_2O_3]_{meso}$ allowed a higher conversion of **d1** (73%, figure 2.15) with respect to **d2** (43%, figure 2.16, right).

Overall, there were no obvious advantages in using $scCO_2$ compared to other organic liquids as solvents for the investigated Michael additions. Solventless conditions always allowed the best results.

2.2.3 Heterogeneous Catalysis: Discussion

A dilution effect probably accounts for the lower conversion observed for the investigation reaction carried out in the presence of solvent with respect to solvent-free conditions. This appears in line with previous results reported for the solvent effect of the Michael addition on α,β-unsaturated ketones.[74] These papers also offer an interpretation for the different behaviour between polar and apolar solvents. According to these Authors, the catalytic activity involves the absorption of the reactants on the catalytic surface of the polar solid materials. When a solvent is added, the decrease in the effective concentration of the reactants on the catalyst surface, resulting from competition between the reactants and the solvent for the surface, is thought to be, among other factors, the reason for the sharp decline in yield. Moreover, this consideration on the competitive absorption on the catalyst surface gives an explanation to why less polar solvents show relatively better yields compared to polar solvents. This explanation fits our results when *n*-heptane is compared to THF: in all cases, regardless of the catalyst, the less polar medium, the higher the conversion.

In lights of these considerations, $scCO_2$ looked like a promising solvent for the Michael reaction: it is in fact an apolar solvent, with a polarity comparable to light hydrocarbons (such as *n*-heptane), and together with its low viscosity and high diffusivity, $scCO_2$ was expected to favor even more than *n*-heptane the absorption of the reactants on polar catalysts. Unfortunately the behavior of the supercritical fluid was not as expected, and the use of $scCO_2$ did not improve the reaction rate and conversion. Apparently, the weak Lewis acidity of CO_2[75] plays an important role in our case, when solid materials such as basic aluminas are used as catalysts. In particular, under the conditions investigated here for the Michael reaction, CO_2 is certainly chemisorbed over the basic sites of solid Al_2O_3.[76] This acid-base interaction between acid CO_2 and the basic catalyst results in a decrease of the catalytic activity.

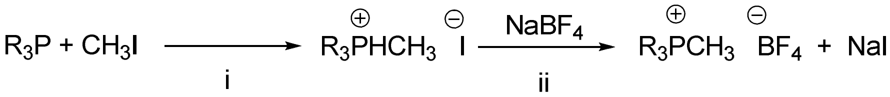
2.2.4 Heterogeneous Catalysis: Conclusions

The Michael addition of primary nitroalkanes to cyclohexenone in the presence of various basic aluminas as catalyst, is not improved by the use of supercritical CO_2 as a solvent, with respect to conventional solvents such as *n*-heptane and THF. Moreover, the highest reaction conversions were achieved under solvent-free conditions. However, from the environmental standpoint, solventless conditions are particularly appealing, but the procedure here reported suffered the drawback of the use of stichiometric excess of nitroalkanes. The heterogeneous catalysts tested (table 2.5) were effective catalyst for the reactions investigated, allowing to carry out the reaction under solvent-free conditions with 100% selectivity towards the Michael addition products, and with conversion on average ~90%.

2.2.5 Homogeneous Catalysis: Results

As mentioned in chapter 1 (par. 1.3), ionic liquids (ILs) have elicited phenomenal interest, in particular among chemists who develop novel systems for clean catalysis.[77] However, a degree of controversy still exists concerning their absolute greenness: a limitation of ionic liquids often lies in their manufacturing process, that is frequently un-green. For what specifically concerns the work presented in this PhD thesis, a brief overview is now considered for the case of phosphonium based ionic liquids.

Phosphonium based ionic liquids, that have been known and used for a long time as phase transfer catalysts,[78] are particularly appealing,[79] owing to their ease of preparation with high purity, to their transparency, and to their higher stability toward thermal and chemical degradation compared with the homologous ammonium salts. Their conventional synthesis, however, involves two potentially environmentally adverse steps: quaternarization of a phosphorous atom, usually by alkylation with hazardous alkyl halides, followed by a halogen anion metathesis step that produces equimolar amounts of an inorganic salt.[80] An example is given in scheme 2.13.



Scheme 2.13. Synthesis of a phosphonium based ionic liquids: (i) phosphine quaternarization and (ii) anion metathesis

In addition, the materials thus prepared inevitably contain residual undesirable halide ions. Although the overall synthesis can be optimized in a number of ways, for example by halide-free transformations,[81] they still often use hazardous and highly toxic reagents such as dimethylsulfate (DMS),[82] and generate unwanted by-products.

Looking for a greener synthetic route to these materials, Proionic (Production of Ionic Substances GmbH) has recently patented and commercialized a method for the quaternarization of phosphines[83] using dialkyl carbonates, that yields an alkylcarbonate or hydrogencarbonate anion.[84] The second steps involve metathesis of the anion with a Brønsted acid. These ionic liquids are commercialized as water-methanol solutions with the trademark CBILS©.[85] We found this methodology interesting, but the patent was rather cryptic on the synthetic conditions, the characterization, the stability, and regarding the storage of these ionic liquids.

These reasons along with the long-standing interest of the research group in the use of dialkylcarbonates as green alkylating agents (par. 1.4)[26c-d,86] prompted us to begin an investigation focused on two activities: *i*) the synthesis of ionic liquids via methylation of phosphines with dimethyl carbonate (DMC),[87] to obtain methycarbonate- or hydrogencarbonate-exchanged phosphonium salts; *ii*) the use of these task-specific (basic) ILs as catalysts for the Michael additions involving mainly nitroalkanes as donors.

I. Catalysts preparation: a green synthesis of phosphonium based ionic liquids. Two basic phosphonium ionic liquids were prepared through the methylation of a trialkyl phosphine followed by an inorganic anion methatesis.

A mixture of trioctylphosphine (TOP) and DMC was set to react in a sealed steel autoclave at 140 °C. The experimental conditions for the reaction were chosen according to the previous knowledge of the research group on the methylating reactivity of DMC:[26f] different phosphine to DMC molar ratios, different reaction temperatures, and the addition of co-solvents were tested. Attempts to carry out the reaction in the absence of added solvents, *i.e.* simply by heating a mixture of TOP and a 5-fold molar excess of DMC, proved impractical and yielded unidentified side products, probably due to the immiscibility of the reagents. However, by adding equal volumes of methanol and DMC, the reaction of TOP went to completion in 20 hours under N_2 atmosphere. The synthesis was carried out on a 20 g batch of TOP, with a 6-fold molar excess of DMC (details are reported in the experimental section). The resulting clear solution was simply stripped of methanol and DMC under vacuum to yield quantitatively the pure trioctylmethylphosphonium methylcarbonate salt: TOMP(OCO_2Me). The product was perfectly clear and colourless and stable in air up to over 150 °C, and was fully characterised by ^1H- and ^{13}C-NMR spectra of the neat liquid. The ^{13}C-NMR spectra provided a wealth of information relative to the carbon backbone, and on the purity of the compounds. In addition, quantitative integration of the ^{13}C resonance peaks allowed to confirm cation to anion equimolarity.

The synthesis of the second ionic liquid was carried out by reaction of trioctylmethylphosphonium methylcarbonate salt TOMP(OCO_2Me) with water (scheme 1.16, eq. b, R = *n*-Oct). Ionic liquid TOMP(OCO_2Me) was stirred under air with water (8.5-fold molar excess) at 40 °C for 2 hours. Excess water and methanol were removed under reduced pressure to quantitatively yield the pure trioctylmethylphosphonium hydrogencarbonate salt TOMP(OCO_2H). The product was a deliquescent white solid, at room temperature, and was fully characterised by ^1H- and ^{13}C-NMR spectra.

Overall, this first part of the investigation allowed us to standardize simple reaction conditions for the use of DMC as a green methylating agent in the synthesis of basic phosphonium salts.

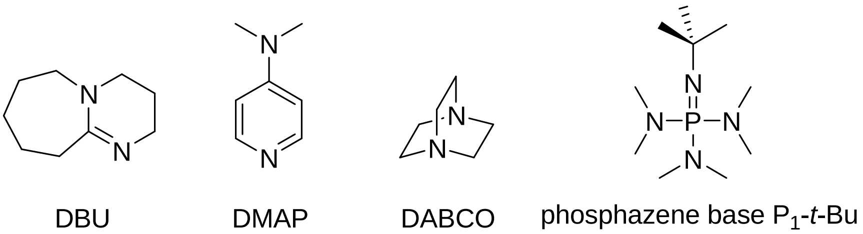
II. Michael reaction of nitroethane and cyclohexenone catalysed by ionic liquids under solvent-free conditions. As both the (OCO_2Me) and (OCO_2H) anions were expected to impart medium to good basicity to TOMP(OCO_2Me) and TOMP(OCO_2H), these ionic liquids were investigated as basic homogeneous catalysts for the Michael addition of nitroethane (**d1**) with cyclohexenone (**a1**) (scheme 2.12).

Experiments were carried out in a glass reactor shaped as a test tube and equipped with a side screw-capped neck for the withdrawal of samples and a condenser. The reactor was charged with a mixture of cyclohexenone (**a1**: 1.00 g, 10.4 mmol) and nitroethane (**d1**: 0.937 g, 12.5 mmol) and thermostated at 40 °C. Different amounts of TOMP(OCO_2H) were used: initially, the molar ratio (W') between IL and cyclohexenone was varied in the range from 0.02 to 0.11.

Under such conditions, TOMP(OCO_2H) showed an extraordinary high activity as a base catalyst for the reaction. A quantitative conversion was reached in a few minutes with the sole formation of the expected Michael adduct **m1** (scheme 2.12).

In order to conveniently follow the reaction, the amount of TOMP(OCO_2H) was decreased by one order of magnitude. Additional experiments were carried out using a W’ (IL:cyclohexenone) molar ratio of 0.004. Under these conditions, also the activity of TOMP(OCO_2Me) was investigated.

The results were eventually compared to those obtained using conventional basic organo-catalysts able to generate carbonucleophiles from Michael donors: sterically hindered tertiary organic amines such as DBU, DMAP, DABCO, and phosphazene base P_1-*t*-Bu were considered. Also sodium bicarbonate and sodium hydroxide were used for comparison.



Scheme 2.14

All reactions were run without solvent. A mixture of cyclohexenone (**a1**: 1.00 g, 10.4 mmol) and nitroethane (**d1**: 0.937 g, 12.5 mmol) was set to react at 40 °C for 2 hours in the presence of a base catalyst (either an IL or compounds of scheme 2.14) used in 0.004 molar equivalents with respect to cyclohexenone. At the end of each reaction, a sample of the reaction mixture (~0.01 mL) was purified through a small column of silica gel (~0.25g of silica, eluent diethyl ether, ~2 mL), and analysed by GC/MS. Table 2.6 reports the results.

TOMP(OCO_2Me) and TOMP(OCO_2H) proved to be more efficient catalysts, yielding reaction conversions of 87 and 86%, respectively (entries 1 and 2). Based on these (conversion) data, the efficiency of phosphonium salts was comparable to that of the very strong phosphazene base (pKa = 27, entry 3, conv. 82%), and superior to that of DBU (pKa = 24, entry 24, conv. 77%). Moreover, IL and phosphazene base allowed the exclusive formation of the desired product **m1**, while DBU promoted minor side-reactions with an overall selectivity not exceeding 92%.

Other organic/inorganic bases showed a negligible, if any, activity for the investigated Michael addition (entries 5-8).

Table 2.6. Michael reaction of nitroethane with cyclohexenone using different bases [a]

#	**Catalyst**	**pKa**	**Conv** (%, GC)	**Selectivity**[b]
1	TOMP(OCO_2Me)		87	100
2	TOMP(OCO_2H)		86	100
3	Phosphazene base P_1-*t*-Bu	27 [88,c]	82	100
4	DBU	24 [89,c]	77	92
5	DMAP	18 [89,c]		
6	NaOH	15.7 [d]	7	100
7	DABCO	8.5 [90,c]		
8	$NaHCO_3$	6.4 [d]		

[a] Conditions: 40 °C, 2 hours, no solvent, catalyst:cyclohexenone molar ratio = 0.004. [b] Selectivity (%, by GC) towards Michael addition product 3-(1-nitroethyl)-cyclohexanone **m1**. [c] pKa's of entries 3, 4, 5, 7 refer to acetonitrile solutions. [d] pKa's of entries 6, 8 refer to aqueous solution.

A more in-depth analysis of reactions of entries 1, 2, 3 and 4 was carried out by monitoring the processes during their first 60 min. In particular, GC analyses of the reaction mixture were performed at time intervals of 10-20 min.

The relative reaction profiles are shown in figure 2.17, where the consumption of cyclohexenone and the selectivity towards the Michael addition product 3-(1-nitroethyl)-cyclohexanone (**m1**) are plotted versus the reaction time.

All reactions showed a similar behavior: they proceeded to a large extent (conversions of 50-70%) in the first five minutes. Then, they slowed down to reach an almost constant conversion (75-85%) after 30 min. Despite this analogy, the comparative analysis of figure 2.17 also indicated that TOMP(OCO_2H) gave (slightly) better results in terms of reaction rate and final with respect to the corresponding methylcarbonate salt TOMP(OCO_2Me), P_1-*t*-Bu and DBU. To improve this comparison, other tests would have been necessary on a larger scale, to further reduce the amount of the catalysts, and so the reaction rate. However, due to time limitations, this study was not addressed.

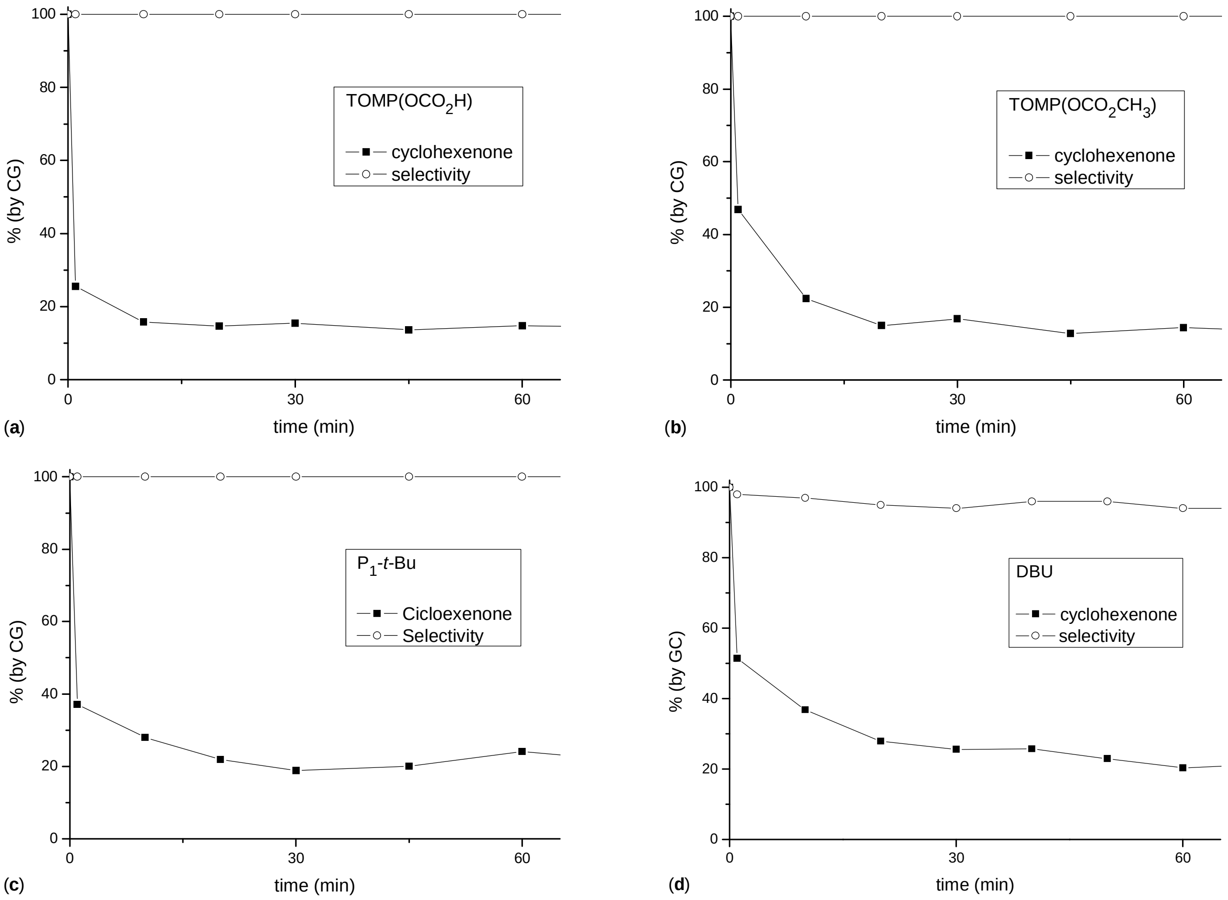
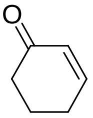
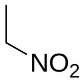
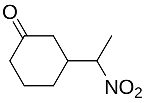
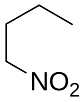
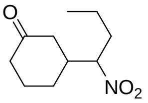
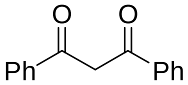
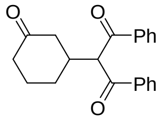
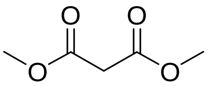
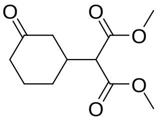
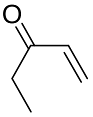
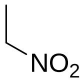
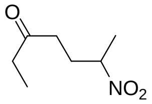
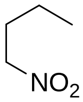
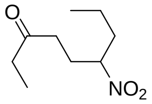
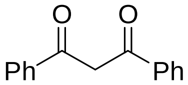
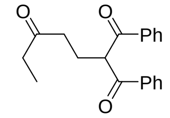
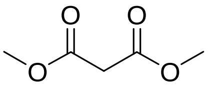
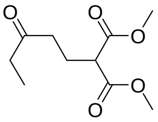


Figure 2.17. The Michael addition of **a1** and **d1**. Reaction profiles using different catalysts

III. Michael reactions of other donors and acceptors catalysed by ionic liquid TOMP(OCO$_2$H). The very promising results obtained with the use of TOMP(OCO$_2$H) as a catalyst for the Michael additions with nitroethane, prompted us to examine the activity of this phosphonium salt in the presence of other carbonucleophilic precursors. In particular, other nitroalkanes such as nitrobutane (**d2**) and β-dicarbonyl compounds such as dibenzoylmethane (**d3**: $C_6H_5COCH_2COC_6H_5$) and dimethylmalonate (**d4**: $CH_3OCOCH_2COOCH_3$) were chosen as Michael donors. Cyclohexenone (**a1**) and ethylvinylketone (**a2**: $CH_3CH_2COCH{=}CH_2$) were used as acceptors: thanks to the abundant literature on the use of compound **a2** for Michael reactions, this seemed a convenient substrate to test and compare new reaction conditions. Scheme 1.17 reports the reaction.

Experiments were run in the absence of solvent, at T ranging from 4 to 40 °C, and by using a molar ratio TOMP(OCO$_2$H):Michael acceptor of 0.01-0.004, the onium salts being a genuine catalyst. The results are collected in table 2.7 where isolated yields are reported for each of the shown product after FCC purification. For a more complete comparison, the table indicates also the reaction of **a1** with nitroethane discussed in the previous paragraph.

Table 2.7. TOMP(OCO_2H) catalysed Michael addition reactions [a]

#	Michael acceptor	Michael donor	W' [b] (mol:mol)	Time (h)	T (°C)	Product	Yield [c] (**m**, %)
1	 **a1**	 **d1**	0.004	2	40	 **m1**	81
2		 **d2**	0.01	14	40	 **m2**	88
3		 **d3**	0.02	72	40	 **m3**	55
4		 **d4**	0.01	2	40	 **m4**	82
5	 **a2**	 **d1**	0.004	2	4	 **m5**	94
6		 **d2**	0.004	2	4	 **m6**	95
7		 **d3**	0.01	2	4	 **m7**	90
8		 **d4**	0.01	2	4	 **m8**	81

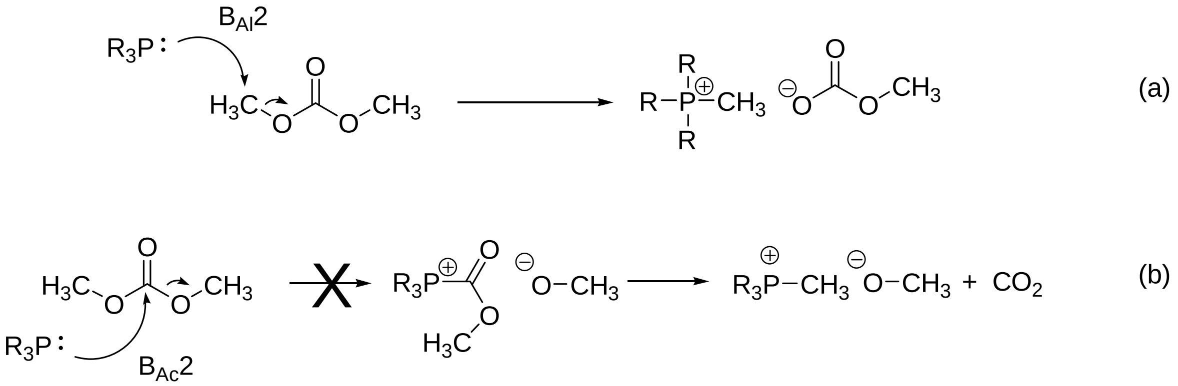
[a] All reactions were carried out under solvent-free conditions. [b] Molar ratio W' = TOMP(OCO_2H):enone. [c] Isolated yields of Michael addition products **m**.

The Michael adducts (compounds **m1-m8**) were fully characterised by MS and ^1H NMR (details are in the experimental section). The use of TOMP(OCO_2H) catalyst was clearly not limited to nitroethane, but it could be extended to nitrobutane and to β-dicarbonyl compounds **d3** and **d4**, as well. Also, ethyl vinyl ketone was a practicable acceptor.

In the presence of cyclohexenone, at 40 °C, all reactions gave good yields (>80%) of mono-adduct derivatives, except when dibenzoylmethane was used: in this case, a rather long reaction time was necessary (72 h) and the corresponding product was isolated in a 55% yield (entry 3). The results were even better with ethyl vinyl ketone: this ketone, perhaps due to a reduced steric hindrance with respect to cyclohexenone, allowed the reaction to proceed at a lower temperature (4 °C) and with excellent yields in all cases (81-95%; entries 5-8). The Michael addition of **d1-d4** to **a2** was also tested at rt: under such conditions, a mixture of mono- and bis-adducts was instantaneously formed (results are not reported).

2.2.6 Homogeneous Catalysis: Discussion

I. Green synthesis of phosphonium based ionic liquids. The quaternarisation of trioctylphosphine (TOP) with DMC yields the trioctylmethylphosphonium methylcarbonate ionic liquid TOMP(OCO_2Me). As already described in chapter 1 (par. 1.4), DMC can act both as a methylating and a carboxymethylating agent (scheme 1.7). In the present case however, the reaction temperature and the related solvation effects,[91] offer the conditions to discriminate the dual reactivity of DMC. At 140 °C, the reaction between the aliphatic nucleophilic phosphine and DMC plausibly occurs through a direct nucleophilic attack of the phosphine to the DMC methyl group (scheme 2.15, eq. a).[92] The competitive mechanism yielding the carboxymethyltrialkylphosphonium methoxide salt (scheme 2.15, eq b), followed by elimination of CO_2, do not take place; alternatively, even if the carboxymethylation step is possible, it would be masked by the reversibility of such a reaction.



R = *n*-Oct

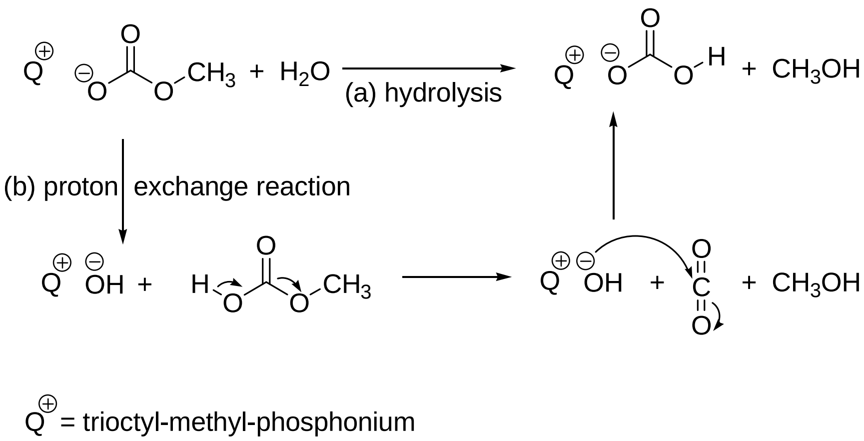
Scheme 2.15

Albeit the reaction is somewhat energy intensive, the procedure shows remarkable synthetic and environmental advantages: not only it proceeds with a quantitative yield, but it represents a

100% atom economic process, it avoids the use of toxic and dangerous methyl halides and of DMS, it is totally halogen free, and it does not require work-up with additional solvents to isolate and purify the products.

It should be here pointed out that the general environmental issue associated with the preparation of most ionic liquids begins upstream with the starting phosphorous compounds that are often toxic. For example, tertiary phosphines are prepared from toxic and dangerous PH_3 and α-olefins.[93] It should also be noted that the methylation of phosphines with DMC has a few recent, scarcely described, precedents in the literature: the preparation of CBILS©.[85] Commercial CBILS© are sold as water-methanol solutions, for a reason that is not clear to us, but maybe due to the degradation of the methylcarbonate anion (OCO_2Me) under their reaction conditions. Nonetheless, in our case, the ionic liquid is perfectly stable as such, and it is certainly preferable to isolate it in its pure liquid form.

The treatment of TOMP(OCO_2Me) with water affords the trioctyl-methyl-phosphonium hydrogencarbonate ionic liquid TOMP(OCO_2H) (scheme 1.16, eq. b, R = *n*-Oct). This transformation of the methylcarbonate anion into the hydrogencarbonate anion may take place either (a) by direct hydrolysis of the methylcarbonate anion with water acting as a nucleophile (top reaction, scheme 2.16), or (b) by an acid-base reaction with water acting as an acid in analogy to scheme 1.16 (eq. c), followed by methyl-hydrogencarbonate decomposition,[94] and CO_2 sequestration by hydroxide (bottom, scheme 2.16).



Scheme 2.16. Pathways for transformation of methylcarbonate into hydrogencarbonate anion

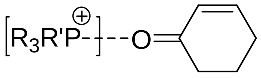
Although this mechanism has not been investigated and available data do not permit a choice between path (a) and (b) of scheme 2.16, the methylcarbonate anion is probably basic rather than electrophilic, thus favouring the bottom pathway.

II. Michael reactions. TOMP(OCO_2Me) and TOMP(OCO_2H) are expected to be somewhat basic, but in fact their behavior exceeded our expectations, as they catalyse the Michael addition of nitroethane to cyclohexenone more efficiently than any of the other strong organic and inorganic bases tested, even when used in a mere 0.4 mol% with respect to cyclohexenone (table 2.6).

Comparison of the pKa's (measured in CH_3CN) of sterically hindered tertiary organic amines (DBU, DMAP, DABCO) and phosphazene base P_1-t-Bu, plus sodium bicarbonate and sodium hydroxide, indicates that phosphazene (pKa = 27) is the most basic together with DBU (pKa = 24), followed by DMAP (pKa = 18), NaOH, DABCO, and $NaHCO_3$.[95] Table 2.6 shows that this basicity scale parallels the catalytic activity trend observed for the Michael addition of nitroethane to cyclohexenone, with phosphazene yielding the highest conversion (82%, entry 3, table 2.6) after 2 hours. The ionic liquid catalysts TOMP(OCO_2Me) and TOMP(OCO_2H), on the other hand, reach > 85% conversion with 100% selectivity with respect to the substrates under the same conditions. These conversions are even higher than with phosphazene base P_1-t-Bu and DBU. DABCO and DMAP are completely inactive, as is sodium bicarbonate.

The comparison of the catalytic activities of the trioctylmethylphosphonium bicarbonate TOMP(OCO_2H) and of $NaHCO_3$ (entry 8, table 2.6) is particularly striking, since TOMP(OCO_2H) behaves as a base approximately 2 orders of magnitude stronger (pKa > 25) than bicarbonate, suggesting that the basic properties of the (OCO_2H) anion are tremendously enhanced when coupled to the phosphonium cation. The reason for the high basicity of the methylcarbonate and bicarbonate anions is still not clear, and may depend on the lypophilic environment surrounding the anions and on solvation effects, as well as on the orientation of the negative charge with respect to the cation.

Comparison of the (OCO_2Me) and (OCO_2H) anions, indicates that the reaction catalysed by TOMP(OCO_2Me) is slightly slower than with the corresponding hydrogencarbonate (figure 2.17), implying that TOMP(OCO_2H) is more basic than the methylcarbonate analogue, notwithstanding the pKa's of the acid base reactions of their respective anions (5.6 and 3.6 respectively).[96] However, not only the basicity of anions, but also the role of the trioctylmethylphosphonium cation should be considered. It is well-known that phosponium cations possess a weak Lewis acidity,[97] and that a great affinity exists between phosphorous and oxygen atoms.[98] In our case, a plausible hypothesis is the coordination the P center of the catalyst acid to the carboxylic oxygen of the reacting α,β-unsaturated ketone (cyclohexenone, **a1** of scheme 2.17), with the formation of an acid-base adduct. This would enhance the electron withdrawing character of the carbonyl group, thereby increasing the electrophilicity of the double bond, and the reaction rate of the Michael addition as well.



R = *n*-Oct
R' = CH_3

Scheme 2.17

The above considerations likely hold true for different carbonucleophile precursors and other electrophilic C=C bonds: TOMP(OCO_2H) in fact, proves to be an efficient catalyst for the Michael addition of both nitroalkanes and β-dicarbonyl compounds to the two α,β-unsaturated ketones (cyclohexenone and ethyl vinyl ketone, **a1** and **a2**, respectively). Table 2.7 however, shows remarkable differences of reactivity. For example, in the reaction with cyclohexenone, nitrobutane is a poorer nucleophile than nitroethane (entries 1-2), and so is dibenzoylmethane with respect to dimethylmalonate (entries 3-4). By contrast, ethyl vinyl ketone (entries 5-8) is a much better Michael acceptor than cyclohexenone (entries 1-4), the former and the latter requiring reaction temperatures of 4 °C and 40 °C, respectively. Steric effects acting on both the nucleophilic and the electrophilic terms of the investigated processes offer an explanation for such a behavior.

2.2.7 Homogeneous Catalysis: Conclusions

A green two-step procedure has been developed for the preparation of ionic liquids starting from phosphines and DMC. In the first step, a clear colourless halide-free ionic liquid precursor TOMP(OCO_2Me) is isolated quantitatively and pure from the reactor (autoclave) simply by vacuum stripping of methanol and excess DMC. Although the reaction conditions using DMC as methylating agent are more energy intensive (T = 140 °C, sealed reactor) than those required with highly toxic dimethylsulfate (DMS) and methyl halides (CH_3X) as alkylating agents, this apparent limitation appears largely compensated by the gain in greenness,[86] including safety, handling, and absence of wastes. In the second step, TOMP(OCO_2Me) can be simply anion exchanged using water (and no solvents) to yield the corresponding phosphonium hydrogencarbonate salt TOMP(OCO_2H) in high purity and quantitative yield, without any workup.

The ionic liquids TOMP(OCO_2Me) and TOMP(OCO_2H) showed very striking basicity, and catalyze the Michael addition of different nucleophiles precursors such as nitroalkanes and β-dicarbonyl compounds, to electron poor C=C bonds of α,β-unsaturated ketones. In all cases, the reaction proceeds with high yield and selectivity, even just in the presence of 0.4 mol% of ionic liquids with respect to the Michael acceptor. Moreover, especially TOMP(OCO_2H) proves to be more active than known strong hindered bases conventionally used for such reactions.

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[31] It should be noted that he alumino-silicate support was obtained via a sol-gel technique (see experimental section for details).

[32] It was not advisable (and also particularly difficult) to perform the activation step directly in the autoclave. Possible thermal shocks due to a rapid heating (at 550 °C) and a subsequent cooling (at rt) could be a danger for the steel reactor.

[33] The visual inspection of the mixture $\mathbf{C_8}$/CO_2 was possible thanks to sapphire windows fixed on both head and bottom covers of the autoclave (see experimental).

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[36] All reactions of scheme 2.6 were formal equilibria whose reversibility depended on the availability of reactant olefins, and consequently, on the reaction conditions. It should be noted that beyond 7-tetradecene ($\mathbf{C_{14}}$), the self-metathesis of 1-octene yielded also ethylene. Likewise, the formation of olefins C_9-C_{13} was accompanied by lower alkenes C_3-C_5. These volatile compounds however, were not observed by GC/MS.

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[41] Usually, to carry out $scCO_2$ reactions and extractions under continuous flow conditions, the system pressure is controlled by the CO_2 pump, whilst the flow rate is controlled through manually adjusted expansion valves at the outflow of the reactor.

[42] The CO_2 pump operated at T = -10 °C with a cylinder pressure of 60 bar. Under these conditions the CO_2 density was d_{CO_2} = 0.995 g mL^{-1} (see http://webbook.nist.gov). The HPLC pump for the delivery of the olefin, operated at room temperature (25 °C), and at the system pressure (90 bar). No data were available for the isothermal behavior of density (d_{C_8}) of 1-octene as a function of pressure. However, for octane, it was reported that the enhancement of the pressure from 1 bar to 90 bar produced a density change from 0.698 to 0.706 g mL-1, at room temperature, with an overall variation of ~1.1%. Accordingly, a calculation was done using the

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d_{C_8} value at standard conditions (rt, 1 atm; d_{C_8} = 0.715 g mL^{-1}). (see http://webbook.nist.gov). The mass flow rates (MassFR) of the substances were calculated as MassFR = F · d (flow per density), while the corresponding molar flow rates were (MassFR)/(m.w.), being m.w. the molecular weight of the used substances.

[43] http://webbook.nist.gov

[44] It should be noted that at F_{C_8} = 0.1 mL min^{-1} the initial conversion and selectivity were 60 and 87%, respectively. Under the same conditions, figure 2.5 reports a conversion and selectivity of 47 and 92%, respectively. This fluctuation was plausibly due to the variation of the time corresponding to the initial GC analysis (from 5 to 8 minute). See note p. 57.

[45] A 0.21 M solution of 1-octene in *n*-hexane was used as feed of the organic pump (P2, figure 2.2).

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CHAPTER 3

Organic Carbonates as Green Reactants for C-N Bond Forming Reactions

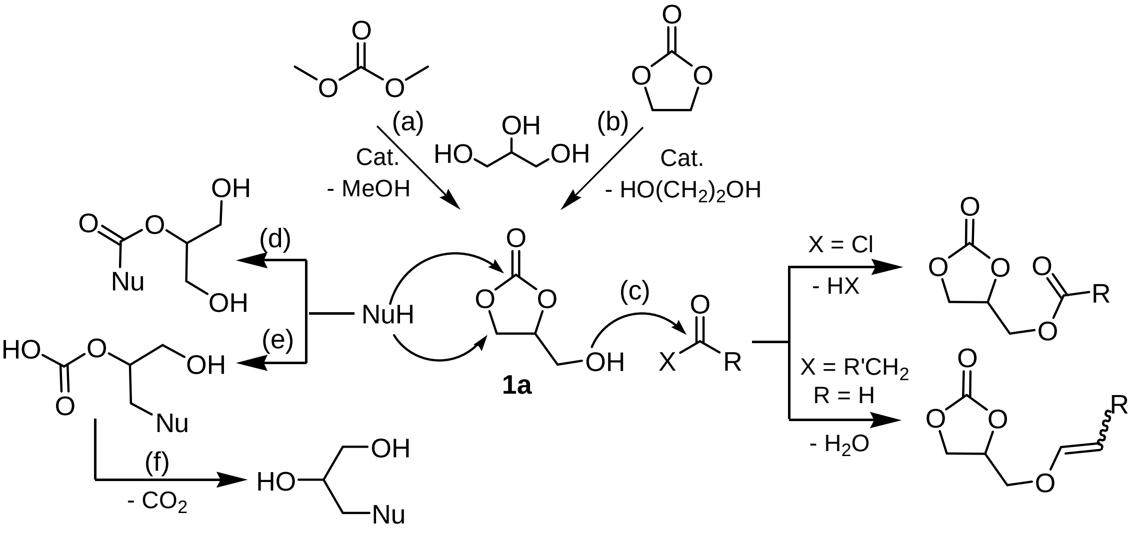
- Glycerol Carbonate -

3.1 The Reaction of Glycerol Carbonate with Primary Aromatic Amines in the Presence of Y- and X-Faujasites

3.1.1 Introduction

In the past two decades, the increasing demand for biofuels, particularly biodiesel, has stimulated a great deal of research devoted to the chemistry of glycerol, and generally speaking, to its conversion to high added value chemicals.[1] Glycerol in fact, is a natural source of C_3 building block and the major co-product in the industrial production of biodiesel:[2] according to a recent estimate, the sole European market will receive some additional 1.0×10^6 tonn/y of pure glycerol in the current year, 2010.[3] This impressive number (almost tripled since 2005),[4] means an urgent need to discover and develop innovative methods for the use of glycerol itself or of its derivatives.

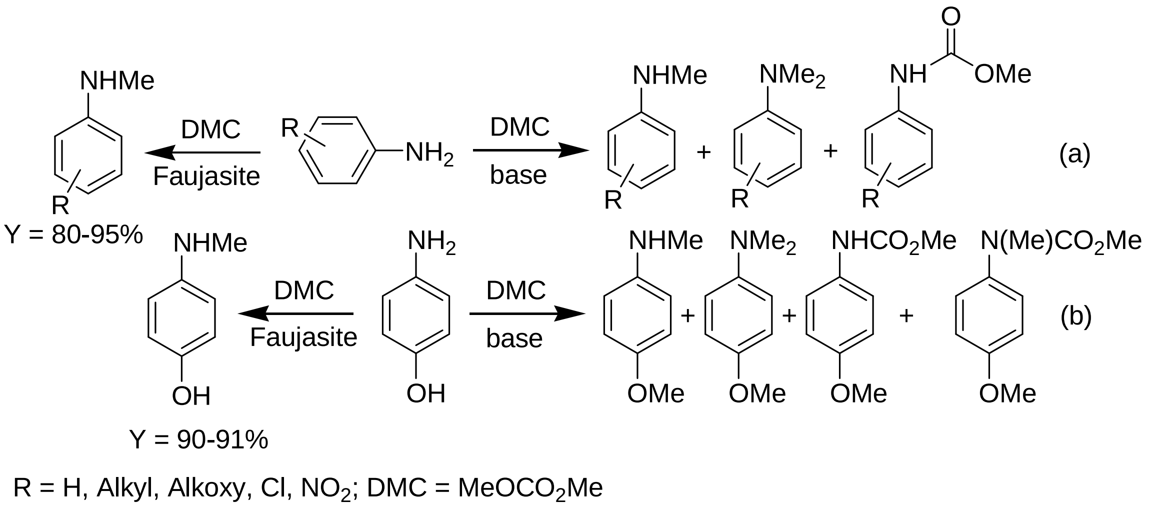
In this context, due to the long standing interest of our group for eco-friendly reagents and solvents of the class of organic carbonates,[5] the attention was caught by glycerol carbonate (GlyC, **1a**: 4-hydroxy methyl-1,3-dioxolan-2-one, scheme 3.1).



Scheme 3.1. The synthesis and the multiple reactivity of GlyC[6]

This compound is prepared through the transesterification of dimethyl carbonate (DMC) or ethylene carbonate with glycerol [scheme 3.1, paths (a) and (b), respectively].[2,6c] In particular, path (a) represents a genuine green synthesis where the reaction of a renewable material (glycerol) and a non toxic compound (DMC[7]) is performed catalytically and in the absence of added solvents. Methanol is the only co-product. GlyC finds applications in different sectors. It is used as a solvent for varnishes, colours, cosmetics, and pharmaceuticals,[3,8] while its prominent role as a reagent, is in the fabrication of multi-functional carbonate-based polymers.[6-9] Paths (c)-(f) of scheme 3.1 illustrate the multiple reactivity of GlyC. The oxygen atom of the hydroxymethyl function of GlyC serves as a nucleophile, while both carbonyl and alkyl carbon atoms (C2 and C5, respectively) show a typical electrophilic character.[10] For example, GlyC reacts with carboxylic acid derivatives or aldehydes (XCOR) to yield the corresponding esters or enol ethers [path (c)];[11] on the other hand, the reactions of different nucleophiles (NuH: phenols, alcohols, aliphatic amines) with GlyC form both carboxyalkylated and alkylated products [paths (d) and (e), respectively], which, eventually, may lose CO_2 [path (f)].

Although this versatile reactivity opens a variety of synthetic perspectives, it poses the problem to control the product distribution. As already mentioned in chapter 1 (paragraph 1.4), an analogous situation is observed also with light dialkyl carbonates: scheme 3.2 exemplifies the case of the reaction of dimethyl carbonate ($MeOCO_2Me$, DMC) with primary aromatic amines.[5]

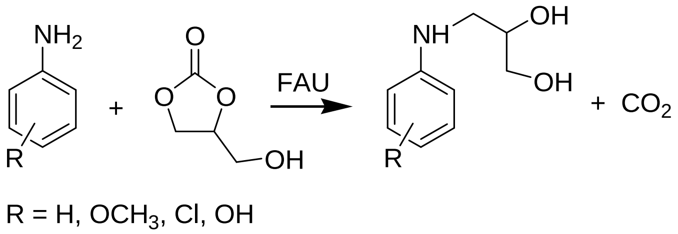


Scheme 3.2. The product distribution for base- and zeolite-catalysed reactions of DMC with primary aromatic amines

In the presence of a base catalyst (*e.g.* an alkaline carbonate), anilines react with DMC to produce mixtures of methylanilines and carbamates [scheme 3.2, path (a), top right]. The reaction selectivity is even less satisfactory if an ambident nucleophile such as *p*-aminophenol, is used [path (b), bottom right]: not only methylation and carboxymethylation take place at the amine function, but the OH group is methylated as well.[5d] This outcome however, is dramatically affected by the nature of the catalyst used. When the transformations of scheme 3.2 are carried out over alkali metal exchanged faujasites (*e.g.*

NaY or NaX, FAU) as catalysts,[12] the exclusive formation of mono-*N*-methylanilines is observed [scheme 3.2, paths (a) and (b): up and bottom left, respectively].[13] Both the alkylation selectivity and the chemoselectivity of the overall process are efficiently controlled by faujasites: neither bis-*N*-methylations nor side-reactions of other nucleophilic terms of ambident amines, take place.

These results prompted us to investigate whether NaY and NaX zeolites could be used to exploit the electrophilic reactivity of glycerol carbonate as well. Accordingly, the reaction of GlyC with primary aromatic amines was investigated in the presence of faujasites as catalysts. We found that this class of zeolites are not only efficient catalysts for the process, but they are also able to direct the reaction chemoselectivity towards the formation of *N*-alkyl derivatives, namely *N*-(2,3-dihydroxy)propyl anilines (scheme 3.3).

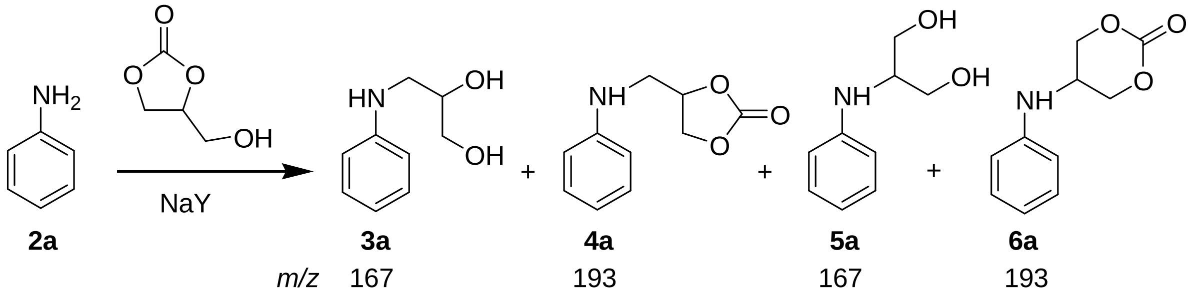


Scheme 3.3

The reaction however, does not proceed exclusively as a direct nucleophilic substitution at the C5 position of GlyC: evidence proves that an intermediate species is formed and that both transesterification and hydrolysis reactions are involved to obtain the final product. A mechanism has been proposed to discuss this reactivity scheme.

3.1.2 Results

I. GlyC as an alkylating agent of aniline. The reaction of GlyC with aniline (**2a**) was chosen as a model to begin the study. Four different faujasites (FAU) were used as catalysts: three of them, namely NaY_A, NaY_S and NaX_A were commercially available compounds (from Aldrich and Strem), while the fourth specimen was a LiY zeolite prepared through an ionic exchange reaction from NaY_A.[14] The relative amounts of reactants and of the catalysts were defined according to our previously reported procedures on the alkylation of primary aromatic amines with dialkyl carbonates.[5] Initially, a mixture of aniline (0.5 g, 5.4 mmol), and GlyC (0.76 g, 6.5 mmol) was set to react at different temperatures (90, 110, 140, and 160 °C), in the presence of the NaY_A faujasite (the weight ratio, Q = NaY_A:**2a** was 1.5). Due to relatively high viscosity of GlyC, diethyleneglycol dimethylether [$MeO(CH_2)_2O(CH_2)_2OMe$, diglyme: 2 mL] was used as a co-solvent, to allow an uniform stirring of the reacting slurry.[15] The same procedure was repeated at 140 °C with the other catalysts, NaY_S, LiY, and NaX_A (the weight ratio, Q = FAU:**2a** was of 1.5). All experiments were run twice, at ambient pressure, in an open vessel. The reaction mixtures were analyzed by GC/MS, after 2 and 4 hours, respectively. Four products were observed (**3a-6a**, **s**cheme 3.4): the two major derivatives (**3a** and **4a**) were isolated and fully characterised by ^{1}H and ^{13}C NMR, while the structure of minor compounds **5a** and **6a**, was assigned from their MS spectra.[16] Results are reported in table 3.1.



Scheme 3.4

Table 3.1. The reaction of aniline with GlyC in the presence of different faujasites [a]

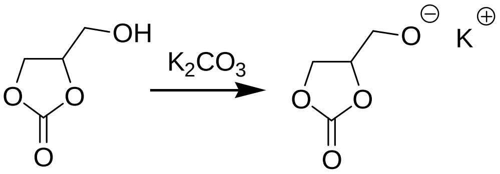
#	FAU	S_A (m^2/g)[b]	T (°C)	t (h)	Conv (%) [c]	Products (%, GC) [c]			
						3a	**4a**	**5a**	**6a**
1	NaY_A	748	90	2	18	11	7		
2			110	2	50	23	22	4	1
3			140	2	79	47	31		1
4				4	93	64	27	1	1
5			160	2	92	66	24	2	
6				4	96	74	18	2	2
7	NaY_S	900	140	2	85	45	33	4	3
8				4	89	58	23	4	4
9	LiY	[d]	140	2	84	51	29	3	1
10[e]				4	94	54	24	6	2
11	NaX	n.a. [f]	140	2	13		12		
12				4	22		20		2

[a] All reactions were carried out in presence of diglyme (2 mL) as the solvent. The molar ratio GlyC: **2a** was of 1.2, while the weight ratio FAU:**2a** was of 1.5. [b] Surface area of faujasites reported by suppliers. [c] Each experiment was repeated twice; the values for conversions and amounts of products (%, determined by GC) were the average of two runs that not differed more than 5-7%. [d] LiY was obtained by an ion exchange reaction, from NaY_A. [e] Entry 10: an unidentified product (8%, GC) was observed. [f] Not available.

In the presence of the NaY_A faujasite, by raising the temperature from 90 to 160 °C, the reaction conversion increased smoothly up to a substantially quantitative value (96%, entry 6). *N*-(2,3-dihydroxy)propyl aniline (**3a**) was always the main product up to a maximum of 74% at 160 °C (4h: entry 6). The formation of compound **4a** was also significant: at a moderate conversion (50%), **4a** was present in an amount comparable to that of **3a** (**3a** and **4a**: 23 and 22%, respectively; entry 2). As the reaction proceeded further, the ratio **4a**:**3a** dropped considerably (entries 4-6: **4a**:**3a** = 0.24-0.42). In all cases, the total quantity of compounds **5a** and **6a** was in the range of 1-5% (entries 1-6). At 140 °C, an additional experiment was carried out for 4 h under an inert (N_2) atmosphere: both the conversion (91%) and the product distribution (**3a**: 62%; **4a**: 27%) were not substantially different to those reported in table 3.1 (entry 4).

The activity of other Y zeolites (NaY_S and LiY) was similar to NaY_A: after 4 hours at 140 °C, the range of aniline conversions was 89-94% (entries 8 and 10). These reactions however, yielded a higher formation of both compounds **5a** and **6a** (8%, in total), and in the case of LiY, of an unidentified by-product (8%, footnote e, table 3.1). Under the same conditions, the NaX zeolite was much less efficient: the conversion was only 22%, and a mixture of **4a** and **6a** (20 and 2%, respectively) was obtained (entry 12).

An additional experiment was carried out by using K_2CO_3 as a base catalyst:[17] under conditions analogous to those reported in entries 3-4 (table 3.1), aniline (0.5 g, 5.4 mmol) and GlyC (0.76 g, 6.5 mmol) were set to react at 140 °C, in the presence of K_2CO_3 (0.75 g, 5.4 mmol) and diglyme (2 mL). The mixture rapidly turned to a white thick slurry plausibly due to the precipitation of a GlyC-derived alcoholate (scheme 3.5).[18]



Scheme 3.5

Then, a very sluggish reaction was observed: after 4 hours, the conversion of aniline was 12% and compound **4a** was the sole product.

The investigation was continued with the use of only NaY_A as a catalyst. In order to clarify the product distribution, an additional reaction was carried out at 140 °C, and it was monitored (by GC/MS) at different time intervals. Conditions were those of entries 3-4 of table 3.1, except for the Q ratio (NaY$_A$:**2a**) which was slightly diminished from 1.5 to 1.[19] Figure 3.1 reports the results.

The analysis of the kinetic profile showed three main aspects: *i*) a good selectivity (up to 90%) could be achieved towards the alkyl derivative **3a**: the amount of this compound increased progressively with time, until it reached a rather constant value (~ 85%) after 430 min; *ii*) products **4a** and **6a** followed a typical intermediate-like behaviour: their concentrations went up to a maximum (**4a**: ~ 50%, **6a**: 15%) in the first 60 min, and then dropped to less than 10% (**4a**) and 3% (**6a**), as the reaction proceeded further; *iii*) the amount of **5a** was always very low (1-3%).

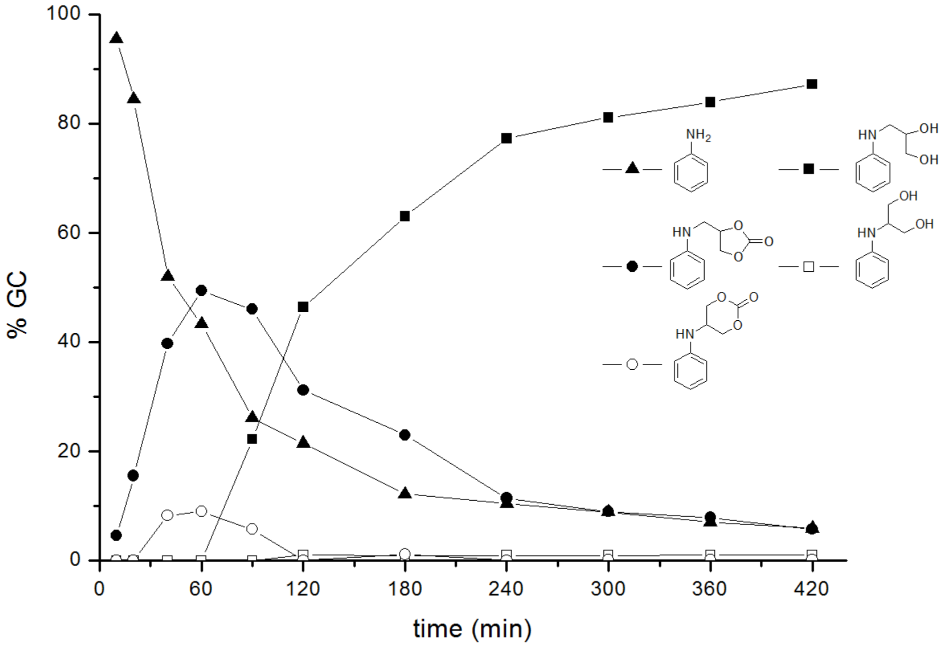
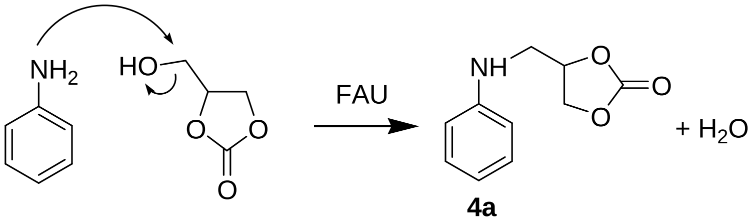


Figure 3.1. The profile of the reaction of aniline with GlyC carried out at 140 °C in the presence of NaY$_A$ as a catalyst (Q = 1)

Figure 3.1 therefore suggested that the desired product (**3a**) was not obtained through an exclusive nucleophilic substitution of aniline at the C5 position of GlyC. The intriguing feature was the presence of compounds **4a** and **5a**, particularly **4a**, which apparently formed and disappeared in favour of *N*-(2,3-dihydroxy)propyl aniline (**3a**). Accordingly, a set of new experiments was devised to study the reactivity of **4a**, **5a** and **6a** as such, and of other plausible co-products in the reaction mixture.

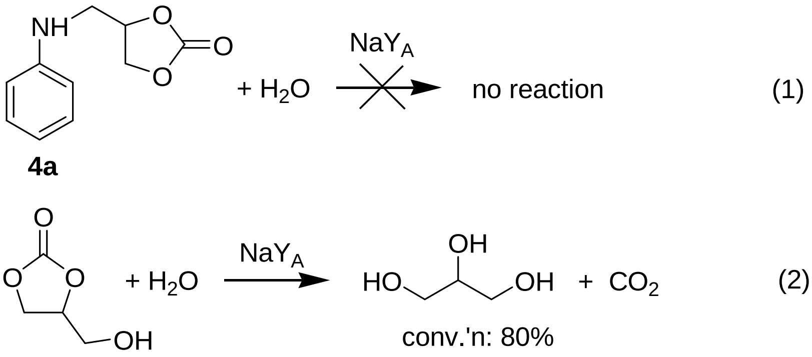
II. The investigation of the reaction mechanism. At first, compounds **4a**, **5a** and **6a** had to be isolated. Aniline (0.5 g, 5.4 mmol) was set to react with GlyC under the conditions of figure 3.1 (140 °C, Q =1). After 90 min, the reaction was stopped at a 71% conversion, when

4a, **5a** and **6a** were present in 48, 13 and 4% amounts, respectively. Separation of the mixture was performed by flash column chromatography (FCC) on silica gel, using a gradient elution with petroleum ether/ethyl acetate solutions. Compound **4a** (0.42 g, 2.17 mmol) was isolated in a 40% yield. Unfortunately, both **5a** and **6a** were not obtained, not even in trace amounts; all subsequent experiments carried out to separate these derivatives by FCC with eluants of different polarity, were always unsuccessful. Compound **4a** was plausibly formed by the direct condensation of aniline with GlyC (scheme 3.6): this hypothesis was corroborated by the fact that very similar reactions were catalysed by alkali metal exchanged faujasites. For example, the dehydration of benzyl alcohol to dibenzyl ether took place at a high temperature (200 °C) over NaY.[20] This observation prompted us to examine the role of the co-product water (scheme 3.6) to promote hydrolytic processes of carbonate-like derivatives **4a** and **6a**, and of GlyC itself, in the presence of faujasites as catalysts.



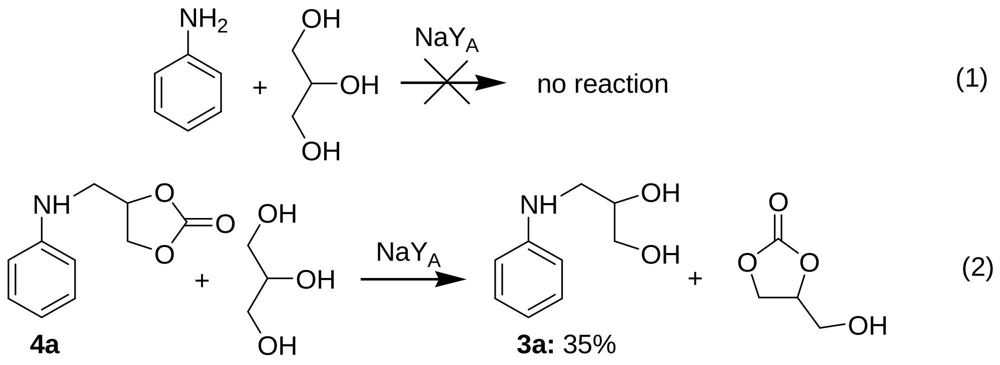
Scheme 3.6

The reactions of both **4a** and GlyC with water were carried out under conditions similar to those reported on entries 3-4 of table 3.1: at 140 °C, a mixture of **4a** or GlyC (**4a**: 0.2 g, 1.0 mmol; GlyC: 0.76 g, 6.5 mmol), was set to react with water (20-120 µL; the molar ratio H_2O:**4a** and H_2O:GlyC was 1), in the presence of NaY_A faujasite (the weight ratio NaY_A:substrate was 1.5), and diglyme (1 mL) as a solvent. Experiments were run for 5 hours. Results are reported in scheme 3.7.



Scheme 3.7

Compound **4a** proved to be quite stable to hydrolysis: the GC/MS analysis of the mixture showed no reaction (eq. 1). On the contrary, glycerine carbonate was substantially hydrolysed to glycerol (eq. 2): the ^{1}H NMR spectrum of the mixture indicated that the reaction proceeded with a conversion of 80%. This last finding along with scheme 3.6, suggested that glycerol was a plausible co-product of the reaction of aniline with GlyC.[21] If so, the investigation of the direct reactions of glycerol (Gly) with both aniline and **4a**, appeared worthwhile. At 140 °C, a mixture of aniline or **4a** (aniline: 0.5 g, 5.4 mmol; **4a**: 0.2 g, 1.0 mmol), was set to react with glycerol (0.58-0.32 g; the molar ratio Gly:aniline and Gly:**4a** was 1.1 and 3.5 respectively), in the presence of NaY_A faujasite (the weight ratio NaY_A:substrate was 1.5), and diglyme (1 mL) as a solvent. Experiments were run for 5 hours. Results are reported in scheme 3.8.



Scheme 3.8

Although the NaY zeolite was plausibly able to catalyse the dehydrative condensation of aniline with GlyC (scheme 3.6), the analogous reaction of aniline with glycerol was not allowed, the amine being recovered unaltered (eq. 1, scheme 3.8). Instead, compound **4a** gave a clean transesterification reaction to produce *N*-(2,3-dihydroxy)propyl aniline (**3a**) in a 35% amount (eq. 2, scheme 3.8). This last result suggested to examine whether an external addition of glycerol affected the outcome of the reaction of aniline with GlyC.

Accordingly, at 140 °C, aniline was set to react with GlyC under the conditions of figure 3.1: after 60 min, glycerol (0.25 g, 2.7 mmol; this amount was adjusted to have a Gly:**4a** molar ratio of ~1) was introduced in the reaction mixture. The reaction profile is reported in figure 3.2.

The addition of glycerol had two significant effects: *i*) the conversion of aniline stopped abruptly at ~60%. Aniline did not react further even after a prolonged reaction time (7.5 h);[22] *ii*) the concentration profiles of **3a** and **4a** showed an initial sharp increase and decrease, respectively (between 60 and 120 min). Then, the further slow consumption of **4a** was the mirror image of the formation of the product **3a**. In other words, once Gly was added, the transesterification of **4a** to **3a** (scheme 3.8, eq. 2) was the sole observed process.

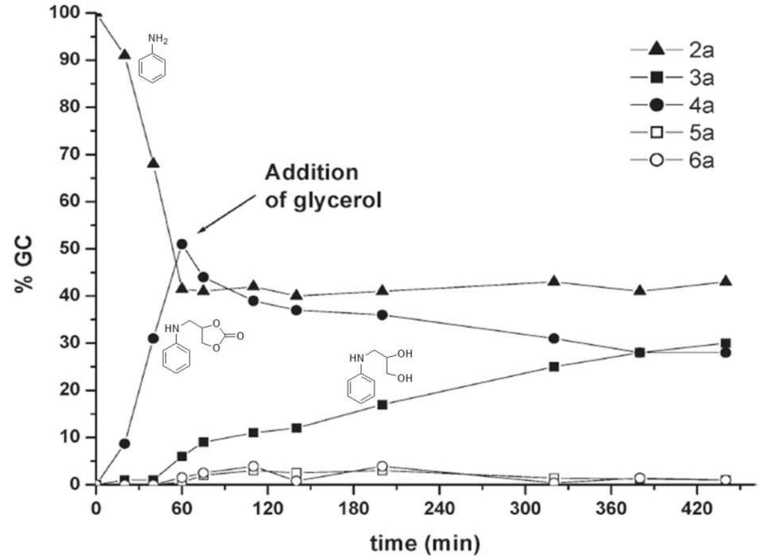


Figure 3.2. The reaction of aniline and GlyC with added glycerol

Overall, this analysis indicated that faujasites, particularly NaY, were not only effective catalysts for the desired process, but they also controlled the final selectivity by tuning the distribution of products in the reactions of schemes 3.6, 3.7 and 3.8.

III. The loading and the recycle of the catalyst. To detail the effect of the catalyst loading, the reaction of aniline with GlyC was examined in the presence of different amounts of NaY_A. Other conditions being equal to those of entries 3-4 of table 3.1 [140 °C, GlyC:aniline molar ratio (W) = 1.2, diglyme (2 mL) as the solvent], the experiments were carried out for 5 hours, by varying the NaY_A:aniline (Q) weight ratio in the range of 0.2-2. The results are reported in figure 3.3 in which the conversion of aniline and the selectivity towards product **3a**,[23] both determined through GC/MS analyses, are plotted *versus* the Q ratio.

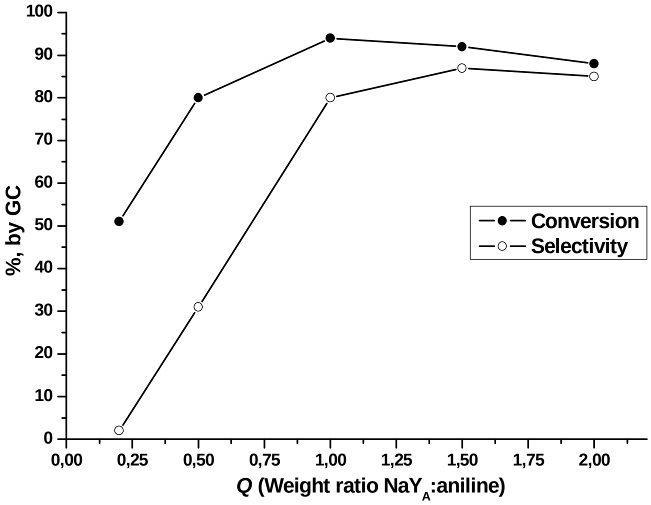


Figure 3.3. Trends for conversion and selectivity towards product **3a**, in the presence of different amounts of NaY_A catalyst

The conversion (C) of aniline and the selectivity for **3a** (S_{3a}) showed a similar trend. Both parameters increased substantially (C from 50 to 92%; S_{3a} from 2 to 80%) as the Q ratio was augmented from 0.2 to 1. Then, a further increase of the catalyst amount ($1.5<Q<2$) had only minor effects: the conversion remained rather constant at ~90% and the selectivity slightly increased up to 85%. Apparently, after 5 hours, the rate of consumption of both aniline and compound **4a** (to produce the final product **3a**) were not significantly improved at $Q \geq 1$.

Finally, two sets (A and B) of recycling experiments were carried out. In the first set (A), the reaction of aniline with GlyC was run under the conditions of entries 3-4 of table 3.1 (140 °C, W = 1.2, Q = 1.5) for 4 hours. Then, the catalyst (NaY_A) was filtered, thoroughly washed with MeOH, and dried under vacuum (70 °C, 18 mbar, overnight). The recovered zeolite was re-used under the conditions above described (entry 3, table 3.1). The cycle of activation/reaction was repeated once more. In the second set (B), the operating conditions were identical to those of set (A), except for the fact that both the fresh and the recycled faujasite were calcined at 400 °C in an dried air stream, before use. All reaction mixtures were analysed by GC/MS, after 4 hours.
Figures 3.4A and 3.4B report the results for experiments of sets (A) and (B), respectively. The conversion of aniline and the % amounts of major products (**3a** and **4a**) are plotted against the number of recycles (N). To complete the view, figures 3.4A and 3.4B also illustrate the data related to the fresh catalyst (N = 0).

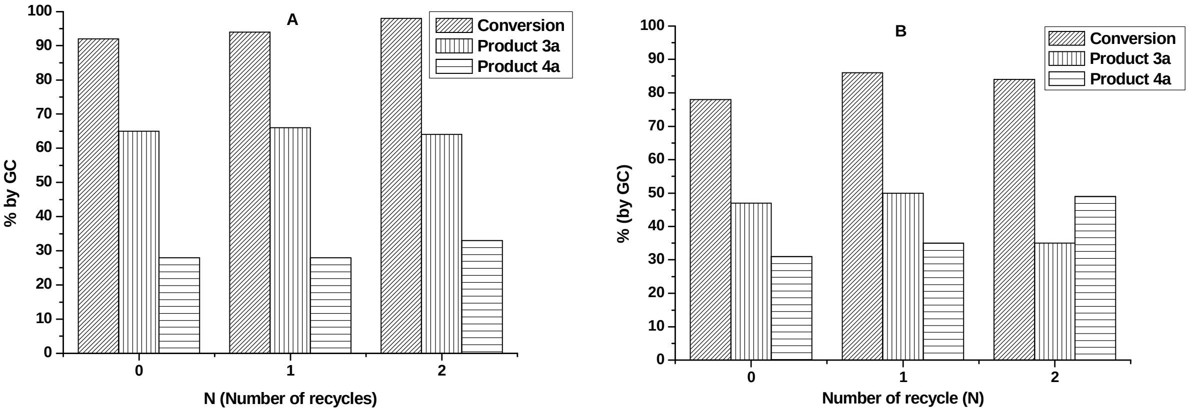


Figure 3.4. The recycle of the NaY_A faujasite. (A): data refer to a not calcined catalyst (set A). (B): data refer to a calcined catalyst (set B). All reactions were carried out for 4 hours at 140 °C

The reaction conversion (C) did not change appreciably with the number of recycles, but it was affected by the thermal treatment of the catalyst: the C values ranged between 92-97% for experiments of the set (A) (not calcined faujasite, figure 3.4A) and 80-85% for set (B) (calcined faujasite, figure 3.4B).

The product distribution was even more sensitive to the handling of the zeolite before the reaction: the ratio **3a**:**4a** was rather constant (2.0-2.3) during the recycle of the not calcined catalyst (figure 3.4A), while it dropped considerably from 1.5 to 0.6 (with the increase of N) in the case of the calcined zeolite (figure 3.4B).

Additional experiments were carried out to further investigate these aspects. Since the calcination was expected to remove large amounts of water adsorbed on the catalyst,[24] a gravimetric analysis was carried out on two identical fresh samples of NaY_A (3.0 g): it was found that the water loss (by weight) was 23 % and 9% after the solids were calcined (400 °C, dried air, 4h, 80 mL/min) and evacuated at 70 °C (18 mbar, overnight), respectively.

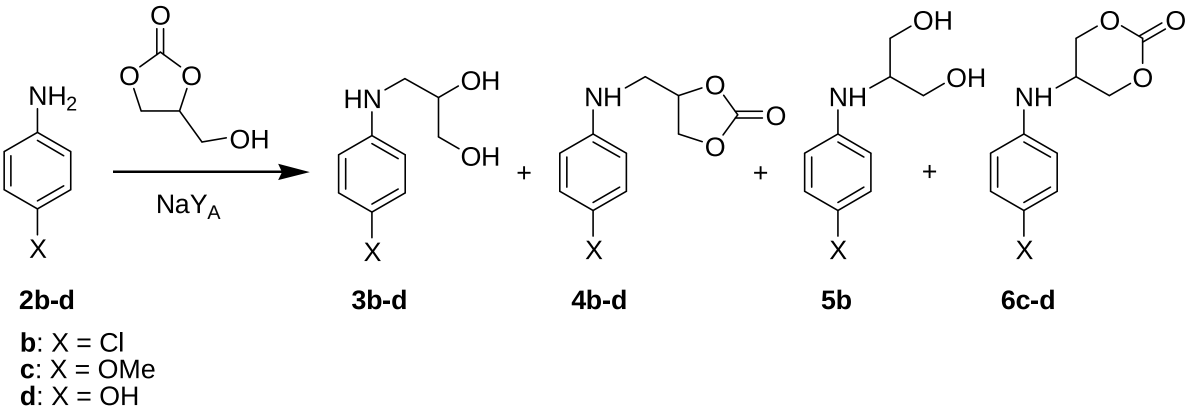
The calcined sample was then allowed to stand in the open air (rt, 8 h), until it recovered its original weight. The solid was dried mildly under vacuum (70 °C, 18 mbar, overnight), and finally, it was re-used to catalyse the reaction of aniline and GlyC under the conditions of entry 3, table 3.1. After 4 h at 140 °C, the conversion was 90% and the ratio **3a**:**4a** was 1.9, in line with the results of figure 3.4A.

In summary, two facts emerged: *i*) the calcination of the faujasite produced a negative effect on both the reaction conversion and on the disappearance of the intermediate compound **4a**; however, *ii*) if the calcined solid was allowed to recover its original degree of hydration, then the catalytic activity was substantially restored.

IV. The reactivity of other anilines and the isolation of the corresponding N-(2,3-dihydroxy)propyl-derivatives. The reaction of GlyC with other primary aromatic amines such as *p*-chloroaniline, *p*-anisidine, and *p*-aminophenol (*p*-$XC_6H_4NH_2$; **2b**: X = Cl, **2c**: X = MeO, **2d**: X = OH), was examined in the presence of the NaY_A faujasite.

The reaction conditions were similar to those used for aniline (table 3.1, entry 4), except for the temperature and the reaction time: these parameters were chosen after a preliminary screening of the reactivity of compounds **2b-d**.

In addition, to test whether these transformations could be scaled up, all experiments were carried out starting from both ~0.6 and ~2.5 g of each amine. Accordingly, a mixture of the primary amine (5.4 or 21.5 mmol; **2b**: 0.69 or 2.64 g, **2c**: 0.66 or 2.71 g, **2d**: 0.59 or 2.39 g), GlyC [the molar ratio (W) GlyC:**2** was 1.2], was set to react in the presence of NaY_A [the weight ratio (Q) NaY_A:**2** was 1.5] and diglyme (2 or 8 mL) as a solvent. The temperature was 170, 160, and 140 °C for **2b**, **2c**, and **2d**, respectively. The reaction mixtures were analyzed by GC/MS. Up to three products were observed for each of the reactant substrates (**3-6**, scheme 3.9).



Scheme 3.9

Once the reactions on the larger scale (21. 5 mmol of **2b-d**) were complete, the major derivatives (**3b-d**) and compound **4c** were isolated by FCC. These products were fully characterised by ^{1}H and ^{13}C NMR. The structure of other compounds **4b-5b**, **6c**, **4d**, and **6d** was assigned from their MS spectra.[25] To complete this investigation, also the reaction of aniline with GlyC was carried out on a 2.0 g scale (**2a**: 21.5 mmol), at 140 °C. The corresponding derivative **3a** was isolated by FCC. Results are reported in table 3.2.

Table 3.2. The reaction of GlyC with different amines **1a-d** catalyzed by the faujasite NaY$_A$ [a]

#	Substrate		T (°C)	time (h)	Conv (%) [b]	Products (%, CG)				Yield (3, %) [c]
	p-XC$_6$H$_4$NH$_2$	Initial amount (mmol)				3	4	5	6	
1	**2b**: X = Cl	5.4	170	22	69	65	3	1		
2		21.5	170	72	45	34	9			13
3	**2c**: X = OMe	5.4	160	6	90	73	10		7	
4		21.5	170	7	86	64	22			61
5[d]	**2d**: X= OH	5.4	140	5	88	75	8		1	
6[d]		21.5	140	22	78	65	7		1	61
7[e]	**2a**: X = H	5.4	140	7	93	84	6	1		
8		21.5	140	16	88	80	8			65

[a] All reactions were carried out in presence of diglyme (2 mL: entries 1, 3, and 5; 8 mL: entries 2, 4, and 6) as the solvent. The molar ratio GlyC: **2a-d** was 1.2, while the weight ratio NaY$_A$:**2a-d** was 1.5. [b] The reaction conversion was determined by GC/MS analyses. [c] The isolated yields of crude products **3a-d** were evaluated after the FCC separation. [d] Entries 5 and 6: 4 and 5% of unidentified by-products, respectively. [e] Data taken from figure 3.1, Q=1.

All the tested amines gave the corresponding *N*-(2,3-dihydroxy)propyl-derivatives **3a-d**. However, *p*-anisidine (**2b**) and especially, *p*-chloroaniline (**2c**) required more severe conditions (entries 1-4): both higher temperatures (160-170 °C) and longer reaction times were necessary with respect to *p*-aminophenol (**2d**) and aniline (**2a**) (entries 3-4). For example, in the reaction of **2b** (5.4 mmol), the conversion was of only 69%, after 22 hours, at 170 °C (entry 1). The reaction time was also dependent upon the starting amount of the amines: regardless of the temperature, the large-scale transformations were considerably longer than the low-scale ones (amines: 21.5 and 5.4 mmoles, respectively; compare entries 1-2, 5-6, and 7-8).

Finally, the isolated yields of compounds **3a-d** did not exceed 65% (entries 2, 4, 6, and 8). During the flash-column chromatography (gradient elution: petroleum ether/ethyl acetate, from 9:1 to 1.9 v/v), the desired products were partly co-eluted with the residual GlyC and glycerine. Experimental conditions to optimize the separation technique were not further investigated.

3.1.3 Discussion

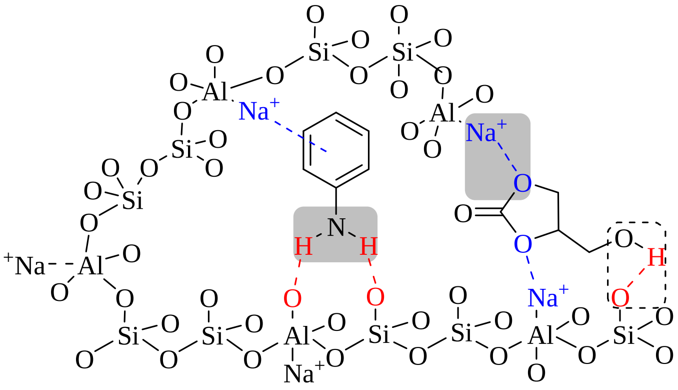
I. The comparison of different catalysts. Table 3.1 and figure 3.1 clearly indicate that alkali metal-exchanged faujasites, especially of the Y type, are good catalysts for the investigated reaction. This is the first ever reported case in which zeolites are claimed to promote the *N*-alkylation reaction of aromatic amines with glycerol carbonate.

As already mentioned in chapter 1 (paragraph 1.4), faujasites are often described as amphoteric solids whose acid-base features are tuned by both the Lewis acid character of their metal ions (usually Na^+, Li^+, K^+, and Cs^+) and the basic nature of the oxygen atoms of the aluminosilicate framework.[12,26] In particular, the basicity of oxygen atoms is controlled by the Si/Al ratio (ranging from 1.0-1.5 to 1.5-3.0 for X and Y type, respectively) of the solid: in the presence of the same cation, X faujasites result more basic than the Y ones. This behaviour plausibly accounts for the striking differences shown in table 3.1, where NaY is by far, more active than NaX (entries 3-4 and 11-12).[27] The trend seems further substantiated by the use of $K_2CO_{3:}$ this base catalyst is even less efficient than NaX (scheme 3.5).[28]

Finally, the minor differences observed between the Y-type zeolites (NaY_A, NaY_S, and LiY: entries 3-4, 7-8, and 9-10) may be attributed to a slight variation of both the Lewis acidity and the surface area (748-900 m^2/g) of the solids.

II. The reaction mechanism. Anilines and dialkyl carbonates diffuse within the polar cages (supercavities) of zeolites, and they are adsorbed primarily through two modes of interaction: *i*) H-bonds between NH_2 groups and oxygen atoms of the lattice, and *ii*) acid–base reactions of the metal cations on the surface of the solid catalyst with both the aromatic rings of amines and the carbonate fragments of dialkyl carbonates.[29] In a similar fashion, also the OH functions of alcohols undergo H-bonds with faujasites to form alcoholate-like species.[30]

Scheme 3.10 depicts the overall pattern of adsorption for the model case of aniline and glycerine carbonate on a Na-faujasite: both H-bonds (red) and acid-base reactions (blue) are highlighted.[31]



Scheme 3.10. Pictorial view of the adsorption of aniline and glycerol carbonate over a Na-faujasite

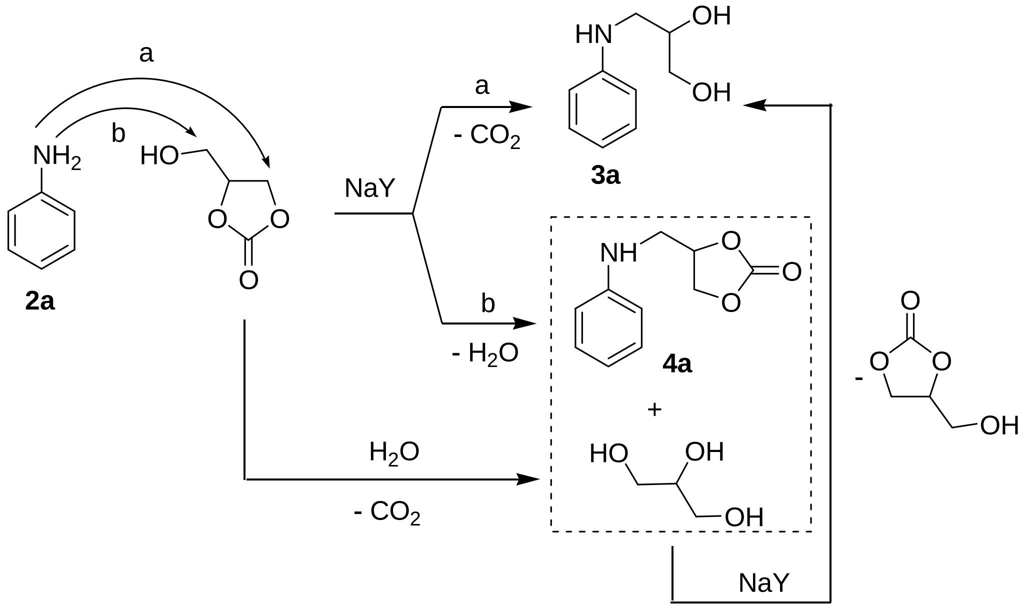
This complex network of interactions implies that the aromatic amine and GlyC experience a nucleophilic (shaded section, left) and an electrophilic (shaded section, right) activation, respectively.

Accordingly, two reactions are favoured: *i*) the NH_2 group is assisted to attack GlyC through a S_N2 reaction occurring preferably at the less hindered C5 position of the cyclic carbonate.[32] Compound **3a** and CO_2 are directly produced (scheme 3.3); *ii*) water, co-adsorbed on the faujasite,[33] initiates the hydrolysis of GlyC at its C2 position (carbonyl carbon), to form glycerol (scheme 3.7, eq.2). The difference in the size and possibly in the requisites of adsorption of aniline and water mostly account for the fact that the reaction of aromatic amines at the carbonyl carbon of GlyC is forbidden. This reflects an even more general trend observed in the reactions of anilines with dialkyl carbonates catalyzed by faujasites: these transformations never produce carbamates ($ArNHCO_2R$).[5,34]

Water entrapped in the catalyst can play a further role: it may allow the protonation of the alcoholate-like moiety derived from GlyC (dashed section, scheme 3.10), to favour the S_N2 process for the formation of compound **4a** (scheme 3.6). This compound (**4a**) in turn, displays a peculiar reactivity: *i*) despite a carbonate structure, its hydrolytic cleavage does not occur, in contrast to what observed for GlyC (scheme 3.7: compare eq.1 and 2). This behaviour has presently no clear reasons, though different modes of adsorption of the two carbonates (**4a** and GlyC) at the catalyst surface, might be considered. *ii*) Compound **4a** acts as the typical intermediate species: once formed, it is consumed through its reaction with glycerol, to produce *N*-(2,3-dihydroxy)propyl aniline (**3a**) as the final derivative (scheme 3.8, eq. 2).

It should be noted here that faujasites are catalysts for transesterification processes even when bulky electrophiles (*i.e.* triglycerides) and different alcohols including glycerol, are used.[35] Nonetheless, figure 3.2 clearly indicates that the direct addition of glycerol to the reacting mixture of aniline and GlyC, does not contributed the overall process. Rather, the competitive adsorption of glycerol at the polar surface of the faujasite catalyst,[36] inhibits the conversion of aniline.

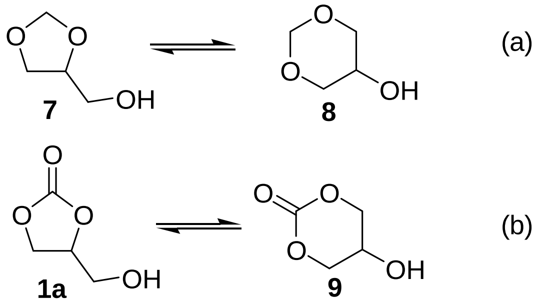
Finally, the lack of direct condensation between aniline and glycerol (scheme 3.8, eq. 1) is plausibly due to relatively modest reaction temperature: in the presence of zeolites or acid solids as catalysts, the dehydration of glycerol usually takes place at T ≥ 250°C, preferably over 300 °C.[37] The reaction mechanism of scheme 3.11 combines all these considerations.



Scheme 3.11. The reaction mechanism

This hypothesis should also assume that the rates for the formation and the consumption of glycerol are balanced to avoid its accumulation in the reaction mixture. Otherwise, the conversion of aniline would stop (figure 3.2).

III. Other reaction intermediates/products. The structure of compounds **5a** and **6a** has been proposed from the analysis of MS spectra (scheme 3.4 and figure 3.1). A further support to the formation of these products can be offered by the behaviour of glycerol formal (GlyF). It is well known that GlyF exists as an equilibrium mixture of two cyclic acetal alcohols: 4-hydroxymethyl-1,3-dioxolane and 5-hydroxy-1,3-dioxane (**7** and **8**, respectively) (scheme 3.12, eq. a).[38]



Scheme 3.12

The similarity between the structures of GlyF and GlyC suggests the occurrence of an analogous equilibrium also for the case of GlyC, involving a six-membered cyclic isomer of **1** (compound **9**: scheme 3.12, eq. b). If so, the reaction of such a carbonate (**9**) with aniline would substantiate the presence of both products **5a** and **6a**. A more in-depth NMR investigation of commercial samples of GlyC is currently under progress to corroborate this hypothesis.[39] Once the structures of **5a** and **6a** will be confirmed, their reactivity, particularly the unexpected intermediate-like behaviour of **5a** (figure 3.1), will be examined.

IV. The catalytic activity and the recycle of the faujasite. In the presence of NaY$_A$, figure 3.3 shows that the conversion (C) of aniline and the selectivity for compound **3a** (S_{3a}) reach rather constant values (~90% and ~80%, respectively), once the weight ratio (Q) NaY$_A$:aniline is ≥ 1. One may conclude that at $Q \geq 1$, reactants no longer saturate all active sites of the zeolite, and consequently, both the decay of aniline and the reactions involving other species (scheme 3.11), plausibly proceed at the maximum rate allowed by the reaction conditions. Hence, the conversion and the selectivity must level off.

The comparison of figures 3.4A and 3.4B clearly indicates that the NaY$_A$ faujasite can be re-used after a mild thermal treatment (heating at 70 °C, under vacuum, figure 3.4A), but the activity of the zeolite drops if it is recycled after calcination at 400 °C (figure 3.4B). All faujasites are rather thermally stable materials: therefore, no morphological-structural variations are induced by thermal treatments below or at 400 °C.[40] In addition, experimental evidence proves that the efficiency of the calcined catalyst is significantly restored once the solid is allowed to recover its original level of hydration.[41] These observation give a further support to the mechanism proposed in scheme 3.11: the extensive removal of water from the catalyst (calcination) affects both the hydrolytic cleavage of GlyC and the formation of the intermediate **4a**, so that the overall process is disfavoured. Doetschman *et al.* have observed a similar behaviour also in the hydrolytic decomposition of phosphonate esters catalysed by a NaX faujasite: in this case, an increase of the catalytic activity was obtained once a controlled amount of water was available at the zeolite surface.[40]

V. Other anilines. Three major aspects emerge from table 3.2. *i*) The reactivity trend shown by aniline and *p*-substituted primary aromatic amines (*p*-Cl<<*p*-OMe<<H~*p*-OH) does not follow the nucleophilicity scale (*p*-Cl<H<*p*-OMe<*p*-OH) expected by the electronic properties of the aromatic substituents. Although the electron-withdrawal effect of the Cl^- group may account for the slowest reaction of *p*-chloroaniline, steric reasons offer a good explanation for the faster alkylation of aniline with respect to *p*-anisidine:[42] the bulkier the substituent (OMe *vs* H) the more difficult the diffusion of the amine within the catalytic pores, and consequently, the lower the reaction rate. A similar behaviour was observed also in the methylation of primary aromatic amines with methyl alkyl carbonates in the presence of faujasite catalysts.[5c] Finally, the adsorption modes of the reactants should be considered: in the case of *p*-aminophenol (**2d**), despite the moderate steric hindrance of the *p*-OH group, the capability of the hydroxyl substituent to form extra H-bonds over the catalytic surface (scheme 3.10) along with its strong electrondonating character, may account for the comparable reactivity of **2d** and aniline. *ii*) Multi-gram scale processes (entries 2, 4, 6, and 8) require a significantly longer reaction time with respect to small-scale reactions (entries 1, 3, 5, and 7). The high viscosity of GlyC and the physical nature of the catalyst (fine powder) are the most plausible reasons for this behaviour: on the larger scale, the reaction mixtures are thick slurries whose difficult stirring may favour the onset of mixed chemical- and diffusion-controlled regimes. *iii*) The moderate yields of products **3a**-**d** suffer from the difficult separation of the unreacted GlyC and of the by-product glycerine. It should be noted however, that alternative routes for the synthesis of compounds **3** are not always more efficient (average yields: 36-90%), and most of all, compared to the safe glycerine carbonate,[43] they are based on the use of very toxic and carcinogenic reagents such as glycidol [(oxiran-2-yl)methanol] and aryl halides.[44]

3.1.4. Conclusions

The catalytic reaction of primary aromatic amines with GlyC offers a genuine green route for the synthesis of *N*-(2,3-dihydroxy)propyl anilines (**3**), in which the use of a glycerol-derived and innocuous alkylating agent such as glycerine carbonate, is coupled to eco-safe solid catalysts such as alkali metal exchanged faujasites. Among the investigated zeolites, NaY_A has been the most efficient catalyst. Although NaY_A must be used in a relatively high amount, it allows a fine control of the selectivity towards the desired compounds **3**, and it can be recovered and recycled without any loss of its performance.

Experimental evidence suggests that at least two consecutive reactions account for the formation of *N*-(2,3-dihydroxy)propyl anilines. Accordingly, a mechanistic hypothesis has been formulated through four major steps catalyzed by the faujasite: *i*) the nucleophilic attack of anilines at the C5 position of GlyC, followed by a decarboxylation process, which yields directly compounds **3**; *ii*) the dehydrative condensation of anilines with GlyC, which generates water and carbonate-like species (compounds **4**) as intermediates; *iii*) the hydrolysis of GlyC to glycerine and CO_2; *iv*) the transesterification of compounds **4** with glycerine, which also ends up in the formation of compounds **3**. The recycling experiments corroborate the role of water adsorbed over the polar catalytic surface: faujasites can be re-used without any loss of activity and/or selectivity, only if they are activated under mild conditions (70 °C, 18 mbar) which avoids an extensive removal of water from the catalysts.

The nucleophilicity scale of the investigated anilines (*p*-Cl<H<*p*-OMe<*p*-OH) does not account for the observed trend of reactivity (*p*-Cl<<*p*-OMe<<H~*p*-OH). This latter is better explained through the combined effects of both electronic and steric properties of substituents, which alter not only the amine nucleophilicity, but also the diffusion/adsorption of reagents within the catalytic pores of the faujasites.

Although these alkylation reactions are rather energy intensive, an added value is the possibility to scale up the processes to multi-gram preparations with isolated yields (~65%) of compounds **3** comparable to those reported for more conventional methods based on highly toxic starting materials (glycidol and aryl halides).

Future studies will be devoted to a more in-depth investigation of other by-products/ intermediates, in particular compounds **5** and **6** (schemes 3.4 and 3.9), whose isolation and structural definition will possibly improve the mechanistic interpretation.

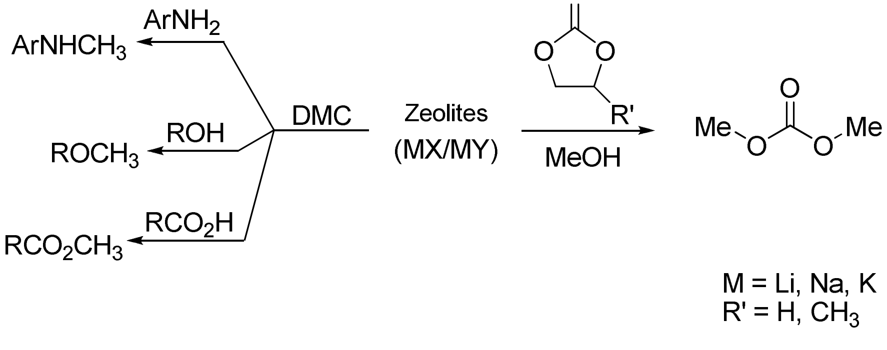
3.2 Sequential Coupling of the Transesterification of Cyclic Carbonates with the Selective *N*-Methylation of Anilines Catalysed by Faujasites: a "Green Domino"

3.2.1 Introduction

Chapter 1 (paragraph 1.4) of this PhD thesis has been devoted to the discussion and properties of dialkylcarbonates and to their role as eco-friendly reagents in the greening of synthetic organic transformations. In particular the use of light organic carbonates such as DMC and DEC has been considered in place of conventional highly noxious alkyl halides, dialkyl sulfates, and phosgene, in both alkylation and carbonylatin reactions.[5a]

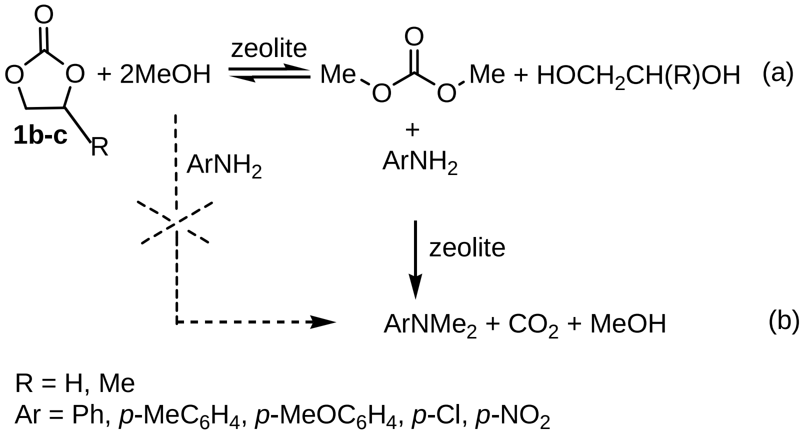
As a reminder, some of the most relevant green aspects related to the use of dimethyl carbonate are: *i*) DMC is a safe non-toxic reagent which very often may act simultaneously as a reaction solvent, *ii*) both methylation and carboxymethylation involving DMC are catalytic processes, *iii*) the only co-products are MeOH (recyclable in principle to the synthesis of DMC) and CO_2, and *iv*) reactions of DMC are slightly, if at all, exothermic.[45]

A more in-depth analysis of the catalytic systems involved in these transformations shows another potentially valuable aspect: when X- and Y-zeolites (alkali metal exchanged faujasites) are used,[12] these solids are not only able to catalyze methylation and esterification reactions of several nucleophiles with DMC (scheme 3.13, left), but they also promote the transesterification of ethylene and propylene carbonates (EC and PC, respectively) with methanol to yield DMC (scheme 3.13, right).[46]



Scheme 3.13. The use of zeolites as catalysts for the chemistry of dialkyl carbonates

These considerations inspired a novel investigation aimed to exploiting the dual reactivity of the zeolites for a sequential reaction, *i.e.* in succession: the synthesis of DMC, followed by its reaction with a nucleophile to yield the methylation and esterification products. The concept has been named “green domino” in this work and employs faujasites, preferably of the X-type, to catalyze the reactions illustrated in scheme 3.14.



Scheme 3.14

In particular, when a slurry of a cyclic carbonate (EC, **1b**; PC, **1c**), methanol, a primary aromatic amine ($ArNH_2$), and a solid zeolite is heated to 180 °C in a batch reactor, two sequential reactions occur: a transesterification process [scheme 3.14, path (a)] which generates the active methylating agent dimethyl carbonate, followed by the selective methylation of the amine [path (b)] which forms the corresponding bis-*N*-methyl derivative ($ArNMe_2$) in yields up to 98%. Experimental evidence confirms that methanol is not involved in the alkylation step (scheme 3.14: dashed path) and that the transformation is unequivocally mediated by DMC. Interestingly, it is also highly chemoselective: in fact, the competitive reaction of anilines with cyclic carbonates **1b-c** to yield the *N*-(β-hydroxy)alkyl derivatives [$ArNHCH_2CH(R)OH$, R = H, CH_3], is not observed. Overall, the faujasite catalyst significantly intensifies the process since DMC is formed and its alkylating capability exploited *in situ*.

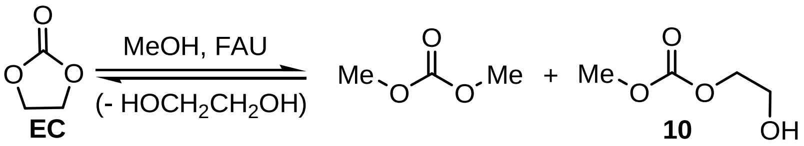
Under the same conditions, the use of higher alcohols (ethanol, *n*-propanol and glycerol) is not successful to produce the corresponding *N*-alkylamines. In these cases, diethyl, dipropyl and glycerol carbonates form, but anilines react also with the starting ethylene carbonate, to give mixture of *N*-alkyl and *N*-(β-hydroxy)ethyl derivatives ($ArNHCH_2CH_2OH$).

3.2.2 Results

I. The transesterification of ethylene carbonate with methanol. The initial experiments were carried out to test the activity of faujasites in the transesterification of ethylene carbonate (EC) with methanol (scheme 3.14, a: R = H). Five different zeolites, namely MX

(M = Li, Na, K) and MY (M = H, Na) were used as catalysts. Four of them were either commercially available (NaX and NaY) or synthesized (LiX and KX) by ion exchange using LiCl or KCl.[14] HY instead, was obtained by calcination of a commercial NH_4Y solid.[47] The main features of these materials are reported in the experimental section.

The transesterification reactions were performed at temperatures of 110-150 °C, in a stainless steel autoclave (150 mL) charged with ethylene carbonate (EC: 2.2 g, 25 mmol), methanol (8-30 mL), and the faujasite catalyst [the weight ratio Q = EC:FAU was ranged from 4.8 to 31.4]. After 5 hours, the reactor was rapidly cooled to rt and vented, and the reaction mixture was analyzed by GC/MS. Results are reported in table 3.3. In all cases, major products were dimethyl carbonate and 2-(hydroxy)ethyl methyl carbonate (**10**) (scheme 3.15).[48]



Scheme 3.15

The reaction outcome however, was greatly affected by the nature of the catalysts. At 110 °C (Q = 4.8), alkali metal exchanged faujasites of the X-type (MX, M = Li, Na, K) generally afforded both higher conversions (81-97%) and higher yields of dimethyl carbonate (50-80%) with respect to the NaY zeolite (compare entries 1-3 and 4), and to the more acidic HY solid, by far the least effective catalyst (entry 5).

Accordingly, the commercial NaX zeolite was chosen to continue the investigation. Additional experiments were carried out at higher temperatures and with different NaX loadings. At 130 and 150 °C (Q = 4.8, entries 6-7), the conversion of ethylene carbonate was substantially quantitative, but the product distribution was not improved.

At 110 °C, the zeolite proved to be efficient even at lower loadings: when the Q ratio was increased in the range of 7.8-15.7 (entries 8-9), a conversion of 96% was attained, while the proportion between DMC and compound **10** did not substantially change compared to previous tests.

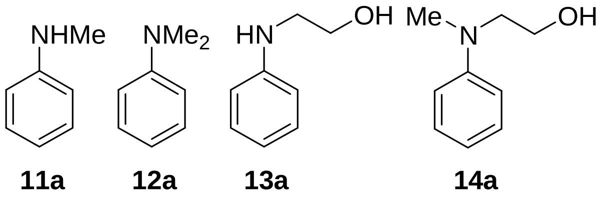
Table 3.3. The transesterification of ethylene carbonate with MeOH in presence of different faujasites [a]

#	FAU (g)	MeOH (mL)	EC:FAU (Q, wt:wt)[b]	T (°C)	Conv (%)[c]	Products (%, GC)[c]		
						DMC	**10**	**Others[d]**
1	NaX (0.45)	30	4.8	110	93	73	12	8
2	LiX (0.45)	30	4.8	110	81	50	26	5
3	KX (0.45)	30	4.8	110	96	80	6	10
4	NaY (0.45)	30	4.8	110	79	17	57	5
5	HY (0.45)	30	4.8	110	26	8	14	4
6	NaX (0.45)	30	4.8	130	97	80	7	10
7	NaX (0.45)	30	4.8	150	96	74	7	15
8	NaX (0.28)	30	7.8	110	96	78	10	8
9	NaX (0.14)	30	15.7	110	96	82	10	4
10	NaX (0.07)	30	31.4	110	86	65	20	1
11	NaX (0.14)	15	15.7	110	83	70	12	1
12	NaX (0.14)	8	15.7	110	71	48	23	-

[a] All reactions lasted 5 hours. [b] Q was the weight ratio between ethylene carbonate and faujasite. [c] Both conversion of ethylene carbonate and the product distribution were determined by GC. [d] Others: unidentified products detected by GC/MS analyses.

However, a further decrease of the catalyst quantity as well as of the volume of methanol (8-15 mL) resulted in a drop of both conversion and selectivity towards the formation of DMC (entries 10-12).

II. The N-methylation of aniline. The next step of the investigation was to test whether DMC, once prepared through the reaction of scheme 3.15, could be used as a methylating agent *in situ*, without isolating it from the mixture. Aniline (**2a**) was chosen as a model nucleophile. Experiments were performed at temperatures of 130-180 °C, in a stainless steel autoclave (150 mL) charged with aniline (**2a**: 0.5 g, 5.4 mmol), ethylene carbonate (EC: 2.0-4.0 g, 23-46 mmol), methanol (30-50 mL), and the NaX faujasite catalyst. In particular, four sets of conditions were used: *i*) molar ratio (W) EC:**2a** = 4, methanol 30 mL; *ii*) W = 8.5, methanol 30 mL; *iii*) W = 4, methanol 50 mL; *iv*) W = 8.5, methanol 50 mL. The weight ratio Q’ = **2a**:FAU was ranged from 1 to 3. After different time intervals (4-24 h), the reactor was cooled to rt and vented, and the reaction mixture was analyzed by GC/MS. Two additional tests (a-b) were carried out in the absence of a) ethylene carbonate and of b) the zeolite. Four main products were identified: their structure was assigned by GC/MS and by comparison to authentic samples (scheme 3.16). Results are reported in table 3.4.



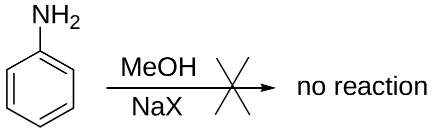
Scheme 3.16

Table 3.4. The reaction of aniline (**2a**) with ethylene carbonate and methanol, catalyzed by NaX zeolite

#	MeOH (mL)	2a:FAU, Q' (wt:wt)[a]	EC:2a, W (mol:mol)[b]	T (°C)	t (h)	Conv (%)[c]	Products (%, GC)[d]				
							11a	12a	13a	14a	Others
1	30	-[e]	4	150	8	-					
2	30	1	4	120	20	43	18	5	16	4	
3	30	1	4	150	8	65	17	22	11	15	
4	30	1	4	180	8	82	26	36	7	10	3
5	30	1	8.5	165	8	88	21	44	7	15	
6	30	1	8.5	180	8	97	8	64	3	19	3
7	30	2	4	180	8	96	5	40	26	20	5
8	30	3	4	180	8	99	9	13	35	30	11
9	50	1	4	150	8	24	20	4			
10	50	1	4	180	8	64	35	29			
11	50	1	4	180	24	88	24	64			
12	50	1	8.5	180	8	82	21	61			
13	50	1	8.5	180	16	99	5	89		5	

[a] Q' was the weight ratio between aniline and the NaX faujasite. [b] Molar ratio between ethylene carbonate and aniline. [c] Conversion of aniline. [d] The structure of products **11**-**14a** was assigned by GC/MS and by comparison to authentic samples of **11a**, **12a** and **13a**. Others were unidentified compounds detected by GC/MS analyses. [e] In the absence of faujasite.

At 150 °C, aniline was recovered unaltered in the absence of faujasite (entry 1). By contrast, in presence of NaX, (Q' = 1), conversions of 65 and 82% were measured after 8 h, at 150 and 180 °C, respectively (entries 3-4). Under these conditions, a moderate conversion was observed even at 120 °C (entry 2: conv. 43%, 20 h). The formation of both compounds **11a** and **12a** (*N*-methylaniline and *N*,*N*-dimethylaniline) proved that a methylation process occurred in all cases. By using methanol in the absence of ethylene carbonate at 150-200 °C for the methylation of aniline in the presence of the faujasite, no conversion was observed, thereby confirming that DMC was the active methylating agent (scheme 3.17).[49]



T = 150-200 °C
MeOH: 30 mL
NaX: Q = 1
No ethylene carbonate

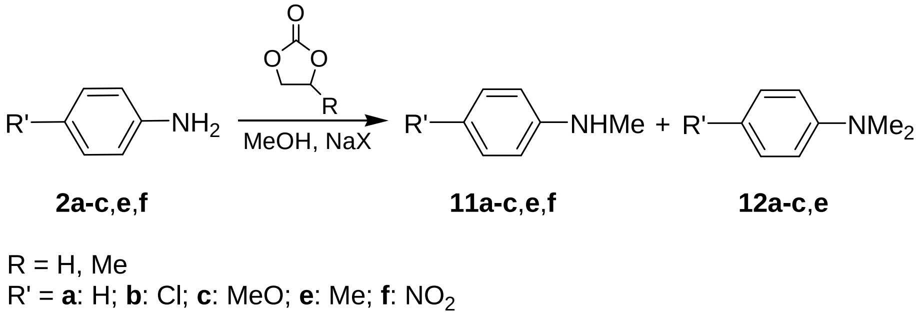
Scheme 3.17

However, under the conditions of entries 2-4, the selectivity was never satisfactory: the presence of sizeable amounts (17-26%) of products **13a** and **14a** indicated that competitive methylation and (β-hydroxy)ethylation reactions, mediated by DMC and ethylene carbonate respectively, took place to comparable extents. A higher loading of ethylene carbonate [conditions *ii*): W = 8.5], improved aniline conversion (88-97%, entries 5-6), but it did not produce significant changes of the methylation selectivity: the total amount of methylamines (**11a** + **12a** = 65-72%) remained less than three times the amount of **13a** and **14a** (22-23%). The formation of the latter compounds was in fact favored by the use of higher catalyst loadings (Q' = 2-3, entries 7-8; **13a** + **14a** = 46-65%).

Although methanol did not take part in the alkylation reaction (scheme 3.17) it played a crucial role on the reaction outcome: the increase of its volume (from 30 to 50 mL), had two effects: a) it lowered the conversion (tables 3.4, compare entries 4 and 10, and 6 and 12);[50] and b) it greatly improved the selectivity towards the exclusive formation of methylamines (entries 9-13). Under these conditions, when the molar ratio ethylene carbonate/aniline (W) was augmented from 4 to 8.5, the reaction became faster and the bis-methylation process predominated (entries 9-11 and 12-13). At 180 °C, over a NaX zeolite catalyst, the green domino of scheme 3.14, produced dimethylaniline (**12a**) in very high selectivity and yield (89%, 16 h: entry 13). Compound **12a** was purified by FCC (petroleum ether/diethyl ether, 95:5 v/v), and it was isolated in a 85% yield.

III. The N-methylation of primary aromatic amines with alkylene carbonates. To extend the scope of the green domino procedure, different anilines ($R'C_6H_4NH_2$: 0.5 g; **2b**: R' = *p*-Cl; **2c**: R' = *p*-MeO; **2e**: R' = *p*-Me; **2f**: R' = *p*-NO_2) were set to react with both ethylene and propylene carbonates [EC (**1b**) and PC (**1c**), respectively]. Experiments were run under conditions *iii*) and *iv*) previously described for aniline (W = 4-8.5, Q' = 1, T = 180-200 °C, MeOH = 50 mL). In all cases, the structures of products were assigned by GC/MS and by comparison to authentic samples (scheme 3.18).

The reaction of aniline (**2a**) with propylene carbonate was also investigated. Finally, two further experiments were aimed at improving the overall mass index of the green domino.[51] The reactions of aniline and *p*-anisidine (**2c**), were performed by decreasing the amounts of both the catalyst and ethylene carbonate: Q' and W ratios were set to 0.1 and 3, respectively. In these cases, the temperature was increased to 190 °C. Results are reported in table 3.5.



Scheme 3.18

Table 3.5. The reaction of different anilines (**2a-c**, **e**, **f**) with alkylene (ethylene and propylene) carbonates, and methanol, catalyzed by NaX zeolite[a]

#	Alkyl Carb.	$R'C_6H_4NH_2$ R':	2:NaX (Q')[b]	1:2[c] (mol:mol)[c]	T (°C)	t (h)	Conv (%)[d]	Products (%, GC)[e]			Yield (%)[f]
								11	12	Others	
1	EC	**2c:** *p*-MeO	1	4	180	16	95	9	86		
2	EC	**2c:** *p*-MeO	1	8.5	180	8	100		100		98
3	PC	**2c:** *p*-MeO	1	8.5	180	8	96	9	87		
4	EC	**2e:** *p*-Me	1	4	180	24	92	12	80		
5	EC	**2e:** *p*-Me	1	8.5	180	8	95	8	83	4	78
6	PC	**2e:** *p*-Me	1	8.5	180	8	90	12	78		
7	EC	**2b:** *p*-Cl	1	8.5	180	28	99	9	90		87
8	PC	**2b:** *p*-Cl	1	8.5	180	28	91	23	68		
9	EC	**2f:** *p*-NO_2	1	8.5	200	24	16	16			
10	PC	**2a:** H	1	8.5	180	24	97	8	86	3	
11	EC	**2a:** H	0.1	3	190	24	81	25	51	5	
12	EC	**2c:** *p*-MeO	0.1	3	190	24	87	18	69		

[a] All reactions were carried out using 0.5 g of the substrate (**2a-c**, **e**, **f**), and 50 mL of MeOH. [b] Q' ratio was in the range of 0.1-1. [c] Molar ratio between alkylene carbonate and aniline. [d] Conversion of the substrate. [e] The structure of products ArNHMe and $ArNMe_2$ was assigned by GC/MS and by comparison to authentic samples. Others were unidentified compounds detected by GC/MS analyses. [f] Isolated yields of compounds **12b**, **12c**, and **12e**.

Five main features emerged from this investigation:

a) No competitive formation of *N*-(β-hydroxy)ethyl derivatives due to the reaction of ethylene or propylene carbonates with the amine was observed. The *N*-methylation reaction promoted by DMC was the sole observed process for each of the tested amines.

b) Different aryl substituents on the anilines affected the final outcome. A reactivity scale was clearly evident: *p*-anisidine > *p*-toluidine ≥ aniline > *p*-chloroaniline >> *p*-nitroaniline. For example, after 8 hours at 180 °C (W = 8.5), in presence of ethylene carbonate, the reactions of *p*-anisidine (**2c**) and *p*-toluidine (**2e**) showed comparable conversions (100 and 95%, respectively) and *N*,*N*-dimethyl *p*-anisidine **12c** was obtained in a 100% yield (entry 2), while **2e** gave a mixture of mono- and bis-*N*-methyl derivatives (**11e** + **12e**) in 8 and 83%, amounts (entry 5). Under the same conditions, the reaction of *p*-chloroaniline (**2b**) required a considerably longer time: a conversion of 91% was reached after 28 h (entry 7). The corresponding products of mono- and di-methylation (**11b** + **12b**) were observed in 9 and 90% quantities, respectively. Finally, *p*-nitroaniline (**2f**) reacted only at 200 °C: after 24 h, notwithstanding the high temperature, a modest conversion of 16% was attained (entry 9).

c) As in the case of aniline, the increase of the W ratio from 4 to 8.5 improved the methylation rate for both *p*-anisidine and *p*-toluidine (compare entries 1-2, and 4-5).

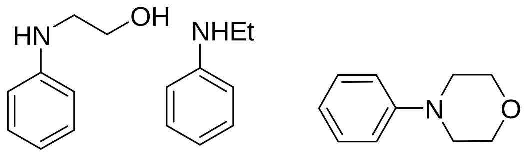
d) Both ethylene- and propylene-carbonate (EC and PC) could be used to produce DMC and to methylate amines **2a**-**c**, **e**, **f**. However, the use of EC allowed faster reactions with respect to PC. For example, after 8h at 180 °C, compound **12c** (*p*-$MeOC_6H_4NMe_2$) was obtained in 100 and 87% GC yields using EC and PC, respectively (entries 2 and 3). Likewise, in the case of *p*-toluidine and *p*-chloroaniline, the amounts of products **12e** and **12b** (*p*-$MeC_6H_4NMe_2$ and *p*-$ClC_6H_4NMe_2$) were higher with EC than with PC (compare entries 5-6 and 7-8). A similar behavior held also for aniline, whose reaction with propylene carbonate (entry 10, table 3.5: conv. 97%, 24 h) was slower than that with ethylene carbonate (entry 13, table 3.4: conv. 99%, 16 h).

e) The green domino proceeded even when NaX was used in a catalytic amount (Q' = 0.1) and ethylene carbonate was slightly over the stiochiometric quantity (W = 3) (entries 11 and 12). Although a temperature of 190 °C was necessary to allow sufficiently rapid conversions of both aniline and *p*-anisidine, these results proved not only the catalytic role of the faujasite, but also that the overall flow of materials involved in the process, could be improved to make the transformation more green and economic. However, further optimization of the conditions/ parameters will be the object of future studies.

Once reactions of entries 2, 5 and 7 were completed, *N*,*N*-dimethyl- *p*-anisidine, *p*-

toluidine and *p*-chloroaniline were purified by FCC (petroleum ether/diethyl ether, 95:5 v/v): they were isolated in 98%, 78%, and 87% yields, respectively.

IV. The reaction of aniline with ethylene carbonate and light alcohols (ethanol and n-propanol). The reaction of aniline and ethylene carbonate (scheme 3.14) was carried out also with ethanol and *n*-propanol in place of methanol. Experiments were performed at 180 and 200 °C under the conditions of table 3.5 (W = 8.5, Q' = 1). Three products were identified by GC/MS and by comparison to authentic samples (scheme 3.19).[52] Results are reported in table 3.6.



13a **15a** **16a**

Scheme 3.19

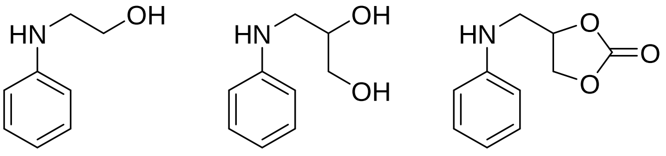
Table 3.6. The reaction of aniline (**2a**) with ethylene carbonate, in presence of ethanol or *n*-propanol, and NaX zeolite catalyst [a]

#	Alcohol [b] (mL)	T (°C)	t (h)	Conv (%) [c]	Products (%, GC) [d]			
					13a	**15a**	**16a**	**Others**
1	EtOH (50)	180	15	93	80	2	11	
2	EtOH (70)	200	15	96	39	2	38	17
3	EtOH (90)	200	15	94	50	3	11	10
4	EtOH (110)	200	15	89	43	4	34	8
5	*n*-PrOH (90)	200	15	92	55		32	5

[a] All reactions were carried out using 0.5 g of the aniline, 0.5 g of NaX (Q' = 1), and 4.0 g of ethylene carbonate (W = 8.5). [b] Different volumes of EtOH were used (entries 1-4: 50 to 110 mL). Entry 5: 90 mL of *n*-PrOH. [c] Conversion of aniline. [d] The structure of products **13**, **15** and **16a**, was assigned by GC/MS and by comparison to authentic samples. Others were unidentified compounds detected by GC/MS analyses.

In the presence of ethanol, the conversion was high (89-96% after 15 h), but the selectivity was elusive: mixtures of **13a** and **16a** (total of 77-81%) were always obtained along with minor amounts of **15a** (2-4%) and other unidentified by-products (8-17%) (entries 1-4). A larger volume of ethyl alcohol (from 50 to 110 mL) did not substantially improve the product distribution. Products **13a** and **16a** were observed also in presence of *n*-propanol (entry 5): in this case, not even a trace of *N*-propylaniline (PhNHPr) was detected.

V. The reaction of aniline with ethylene carbonate and glycerol. In a previous paragraph (3.1) a synthetic route to glycerol carbonate (GlyC) was described through the transesterification of ethylene carbonate (EC) with glycerol (Gly) [scheme 3.1, path (b)].[6] Moreover, it was demonstrated that GlyC acted as a (2,3-dihydroxy)alkylating agent of aromatic amines, in the presence of faujasites as catalysts. These results prompted us to investigate if the green domino was still possible when aniline was set to react with ethylene carbonate and glycerol, in place of methanol (scheme 3.14). Reaction conditions were chosen accordingly to the results presented in paragraph 3.1. A mixture of aniline (**2a**, 0.5 g, 5.4 mmol), ethylene carbonate (EC, 0.5 g, 5.75 mmol; molar ratio EC:**2a** W ~ 1.1) and zeolite [NaX or NaY, 0.5 g; weight ratios **2a**:FAU (Q') and EC:FAU (Q) were equal to 1] was set to react at 140 °C with different quantities of glycerol (Gly; 3 g, 32.5 mmol; 5g, 54.2 mmol; molar ratio Gly:EC W' = 5.6 and 9.4, respectively). Due to relatively high viscosity of glycerol, some experiments were also carried out in the presence of dense CO_2 (120 bar, see experimental for details) as a dispersing agent, to allow a more uniform stirring of the reaction slurry. Three products were identified by GC/MS (scheme 3.20). Results are reported in table 3.7.



13a **3a** **4a**

Scheme 3.20

Two main features emerged from this investigation: *i*) the NaY zeolite was a more efficient catalyst than NaX, consistent with results presented in table 3.1. Both in the absence or in the presence of CO_2 as a dispersing agent, the reaction conversion and the yield of **3a** were higher using NaY instead of NaX (compare: entries 1 and 5, 4 and 7); *ii*) the increase of the glycerol amount did not improve the reaction selectivity significantly: when the molar ratio Gly:EC (W') was raised from 5.6 to 9.4, only a slight increase on the yield of **3a** was observed (compare entries 2-3 and 6-7). Although compound **3a** was plausibly due to the formation of glycerol carbonate, thereby proving the occurrence of green domino reactions, the maximum yield and the selectivity of **3a** did not exceed 47% and 62%, respectively (entry 5). The increase of the reaction temperature showed some benefit: in an additional experiment carried out at 170 °C (conditions of entry 5), the conversion was 69% and the yield of **3a** was 48%.

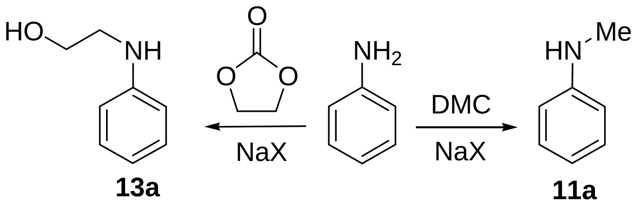
Table 3.7. The reaction of aniline (**2a**), EC and Gly at 140 °C in the presence of faujasites catalyst [a]

#	**FAU**	**Gly:EC (W’) (mol:mol)** [b]	**Solvent** [c]	**t (h)**	**Conv (%)** [d]	**Products (%, GC)** [e]			
						13a	**3a**	**4a**	**Others**
1	NaX	5.6	none	3	33	7	21		5
2			CO_2	3	44	17	14	13	
3		9.4	CO_2	3	30	13	16		1
4				6	65	20	25	18	2
5	NaY	5.6	none	3	76	18	47	5	6
6			CO_2	6	72	30	26	13	3
7		9.4	CO_2	6	74	26	38	7	3

[a] All reactions were carried out using 0.5 g of the aniline, 0.5 g of zeolite (NaX, NaY, Q’ = 1), and 0.5 g of ethylene carbonate (W = 1.1). [b] Molar ratio Gly:EC. [c] CO_2 (120 bar) was used as dispersing agent; see experimental session for details. [d] Conversion of aniline. [e] The structure of products **13a**, **3a** and **4a**, was assigned by GC/MS. Others were unidentified compounds detected by GC/MS analyses.

Nonetheless, the overall results were not encouraging and the reaction of aniline with ethylene carbonate in presence of glycerol was not further investigated.

VI. The relative reactivity of dialkyl carbonates. The results of tables 3.4 and 3.5 showed that when methanol was present in a relatively large amount, the competition between DMC and ethylene carbonate as methylating and hydroxyethylating agents of primary aromatic amines was suppressed, and the *N*-methylation reaction proceeded with a selectivity up to 100%. By contrast, the corresponding reactions carried out with ethanol and propanol, took place with the exclusive formation of products derived from ethylene carbonate (table 3.6). To investigate these aspects, the relative reactivity of DMC and ethylene carbonate was tested in competitive reactions with aniline. Two sets of experiments were performed at 90 °C (refluxing temperature of DMC) and at 140 °C, respectively. In both cases, a mixture of aniline (0.5 g, 5.4 mmol), DMC (10 g, 111 mmol), and NaX (0.5 g, Q’ = 1), was set to react with different amounts of ethylene carbonate (EC). In particular, the molar ratio DMC:EC was increased from 1 to 5, 10, 20, and 40, respectively. GC/MS analyses showed that major products were mono-*N*-methylaniline (**11a**) and mono-*N*-(β-hydroxy)ethylaniline (**13a**) (scheme 3.21),[53] whose total amount (**11a** + **13a**) corresponded to 97-99% of all the observed products.



13a **11a**

Scheme 3.21

Results are reported in figure 3.5, where the ratio of anilines **13a**:**11a** (GC amounts) is plotted against the molar ratio DMC:EC. For a coherent evaluation, each set of data was calculated at comparable conversions.

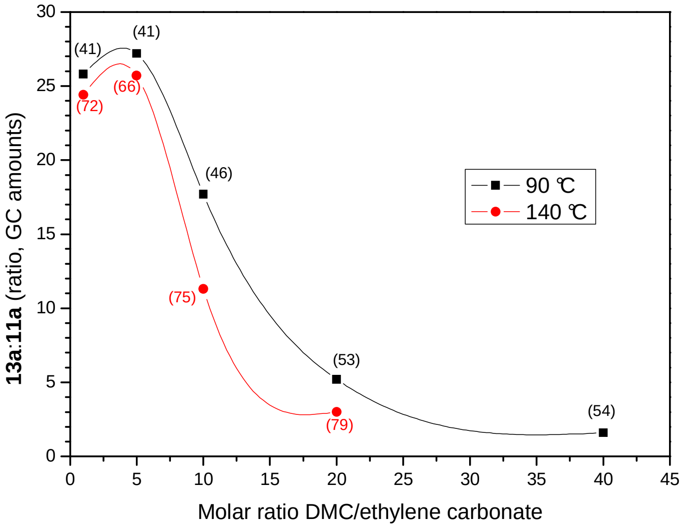


Figure 3.5. Ratio of *N*-(β-hydroxy)ethylaniline (**13a**)/*N*-methylaniline (**11a**) as a function of the DMC:EC molar ratio. Conversions of aniline are shown in parethesis. Black profile: reactions at 90 °C; red profile: reactions at 140 °C

At 90 °C, in the range of conversions of 41-54%, *N*-(β-hydroxy)ethylaniline (**13a**) was always the main product even though ethylene carbonate (EC) was used in a considerably lower amount with respect to DMC (black curve). The ratio **13a**:**11a**, decreased smoothly from ~27 to 5 while the molar ratio DMC:**1a** increased from 5 to 20. Remarkably, the quantity of **13a** was 1.5 times higher than that of *N*-methyl aniline, even when DMC was present in a 40 molar excess over ethylene carbonate: under these conditions, ethylene carbonate was understoichiometric with respect to aniline.

An analogous behavior was observed at 140 °C. In the range of conversions of 66-79%, the ratio **13a**:**11a** varied between 3 and 26 (red curve). Apparently, the reaction temperature had a limited effect on the relative rates of hydroxyethylation and methylation of aniline. Ethylene carbonate was by far, more reactive than DMC, and the formation of **13a** was favored at all times, with respect to **11a**.

Other experiments were run at 140 °C, in the presence of co-solvents of different polarity: cyclohexane, 1,2-dimethoxyethane (DME), and *N*,*N*-dimethylformamide (DMF). A mixture of aniline (0.5 g, 5.4 mmol) dimethylcarbonate (13.11 g, 111 mmol), ethylene carbonate (0.97 g, 11.1 mmol) (molar ratio DMC:EC = 10), and NaX (0.5 g), was set to react in presence of these solvents (20-40 mL).[54]

Results are reported in table 3.8. For a convenient comparison, the table includes also the reaction carried out without added solvents.

Table 3.8. The reaction of aniline (**2a**) with ethylene carbonate and DMC, in presence of NaX and different co-solvents [a]

#	Solvent (mL)	ε [b]	DMC:EC (mol:mol) [c]	T (°C)	t (h)	Conv (%) [d]	Products [e]			Ratio 13a:11a
							11a	13a	Others	
1	DMC (10)	3.08	10	140	1	75	6	69		11.5
2	CyH (20)	2.02	10	140	1	56	2	54		27
3	CyH (40)		10	140	2	61		61		∞
4	DME (20)	7.2	10	140	1	68	4	61	3	15.3
5	DMF (20)	38.3	10	140	1	60	3	47	10	15.6
6	DMF (40)		10	140	3	59	8	41	10	5.1

[a] All reactions were carried out using aniline (0.5 g, 5.4 mmol), NaX (0.5 g, Q' = 1), DMC (10 g, 111 mmol), ethylene carbonate (0.98 g, 10.8 mmol), and the solvent (20 or 40 mL of cyclohexane, of DME, and of DMF in entries 2-6, respectively). [b] Dielectric constants were taken from ref. 54. [c] Molar ratio between DMC and ethylene carbonate. [d] Conversion of aniline. [e] The structure of products **4a** and **6** was assigned by GC/MS and by comparison to authentic samples. Others were unidentified compounds detected by GC/MS analyses.

Despite the excess of DMC used in all reactions, β-hydroxyethyl aniline (**13a**) was always the preferred product, particularly in the presence of the apolar cyclohexane (40 mL) where **13a** was the only observed product (entry 3). In the more polar DME and DMF (20 mL), the ratio **13a**:**11a** was ~ 15 (entries 4-5), comparable to that reported using only DMC as a solvent (11.5, entry 1). A larger volume of DMF (40 mL) resulted in a considerable decrease of the ratio **13a**:**11a** to 5.1 (entry 6). Higher dilution also caused longer reaction times for both cyclohexane and DMF: conversions of ~ 60% were reached after 2 and 3 hours, respectively (entries 3 and 6).

Finally, at 140 °C, a mixture of aniline (0.5 g, 5.4 mmol), diethylcarbonate (13.11 g, 111 mmol) and ethylene carbonate (0.48 g, 5.4 mmol) (molar ratio DEC:EC = 20), was set to react in the presence of NaX (0.5 g). After 2 h, the conversion was of 60%, and *N*-(β-hydroxy)ethyl aniline (**13a**) was the sole product. No competition was observed between ethylene carbonate and diethyl carbonate.

3.2.3 Discussion

I. The catalytic activity of faujasites. In analogy to the reaction of GlyC described in the previous paragraph (3.1), acid-base properties of faujasites affect the outcome of both the transesterification of ethylene carbonate and the green domino as well. According to the acid-base scale proposed by Barthomeuf,[26b] table 3.3 shows that more basic MX systems (entries 1-3) offer better performances than NaY and HY zeolites (entries 4-5) in the synthesis of DMC by transesterification of ethylene carbonate with methanol. Even more specifically, a comparison among X-type faujasites indicates that KX (entry 3) is more active than NaX and LiX (entries 1 and 2, respectively), thanks to the milder acidic character of K^+ with respect to Na^+ and Li^+. These results match those observed by other Authors[46] in the study of the transesterification of cyclic carbonates over zeolites. In general, this reaction is reported to be rather sensitive to the basic properties of the catalysts involved.[55]

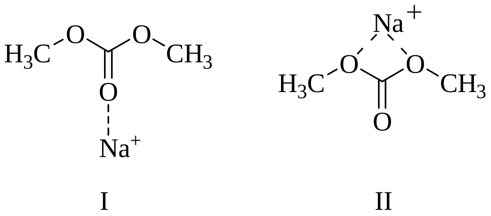
II. The "green domino". The results of table 3.4 show that in presence of the NaX faujasite catalyst a mixture of aniline, ethylene carbonate, and methanol react to produce mono-*N*- and bis-*N*-methyl anilines (**11a** and **12a**) as major products. In addition, in the absence of ethylene carbonate, aniline is recovered fully unreacted (scheme 3.17). This is evidence of the fact that methanol does not act itself as the methylating agent of the amine. The most plausible explanation for the occurrence of compounds **11a**-**12a**, is through two sequential processes: the transesterification of ethylene carbonate to yield dimethyl carbonate, which in turn methylates aniline (scheme 3.14). This domino reaction may suffer from the competition between the two organic carbonates for the nucleophile (scheme 3.21), and the formation of *N*-(β-hydroxy)ethyl anilines (**13a** and **14a**) is described accordingly.[56] Yet, 100% methylation selectivity can be achieved by increasing the volume of methanol from 30 to 50 mL (table 3.4, entries 4 and 11). This beneficial effect is not likely to be due to the shift in the transesterification equilibrium of ethylene carbonate towards the formation of DMC (scheme 3.14, path a). In fact, the ratio of the equilibrium concentrations does not vary significantly between the lowest MeOH:EC molar ratio (= 27.0) calculated with 50 mL of methanol, and the highest MeOH:EC molar ratio (= 34.5) calculated with 30 mL of methanol (table 3.9).

Table 3.9. The excess of methyl alcohol over ethylene carbonate

#	Methanol (mL)	EC:2a (mol:mol) [a]	MeOH:EC (mol:mol) [b]
1	30	4	34.5
2	30	8.5	16.2
3	50	4	57.4
4	50	8.5	27.0

[a] Molar ratio between ethylene carbonate (EC) and aniline (**2a**), [b] Molar ratio between methanol and ethylene carbonate.

Why then the exclusive formation of methyl anilines **11a** and **12a** with respect to hydroxyethyl amines **13a** and **14a**? Reason may be that a further consequence of the increase of methanol is the reduction of the reaction rate (for instance, compare entries 6 and 13 of table 3.4). This result parallels the behavior reported for several liquid-phase processes catalyzed by faujasites:[50] in general, the more polar the solvent, the more it competes with organic reagents for the adsorption on active sites of the polar surface of zeolites, and consequently, the lower the reaction rates. In our case, a strong MeOH/faujasite interaction may also play a further role on the adsorption of dialkyl carbonates over the catalytic surface. In fact, IR and Raman investigations demonstrate that DMC (and likely ethylene carbonate as well) is adsorbed over zeolites through the formation of acid-base complexes (I and II) with weak Lewis acidic sites (e.g. Na^+ cations) of the framework of the aluminosilicate (scheme 3.22).[29b,57]



Scheme 3.22. Interactions of DMC with Na^+ of faujasites

These modes of adsorption of dialkyl carbonates are plausibly altered when methanol is itself co-adsorbed over the catalytic surface. Although the nature (and entity) of such a perturbation is not presently clear, its effect may modify the relative reactivity of DMC and ethylene carbonate, favoring the former (DMC). This behavior becomes unpredictable if the two organic carbonates are compared in the competitive alkylation of aniline catalyzed by NaX (figure 3.5). In fact, in the formation of *N*-(β-hydroxy)ethyl anilines (**13a** and **14a**, scheme 3.16), the relief of some ring strain in ethylene carbonate likely accounts for its higher reactivity with respect to DMC.[58] Under these conditions however, a moderate effect on the reaction selectivity is observed if co-solvents are used (table 3.8). In polar solvating media such as DMF, the methylation of aniline is less disfavored than in apolar cyclohexane, where the reaction may not take place at all. This evidence further corroborates the results above discussed: a large excess of polar MeOH alters the reaction environment to the point that the *N*-methylation of aniline occurs on an exclusive basis.

The outcome of reactions carried out with ethanol and *n*-propanol (table 3.6), is also explained through the competitive reactivity of dialkyl carbonates. The alkylation rate of several nucleophiles, drops by 1-2 orders of magnitude by simply substituting DMC with diethyl carbonate (DEC).[5,53a-c,59] Accordingly, both diethyl- and dipropyl- carbonates, which form under the conditions of table 3.6,[60] cannot vie with the more reactive ethylene carbonate.

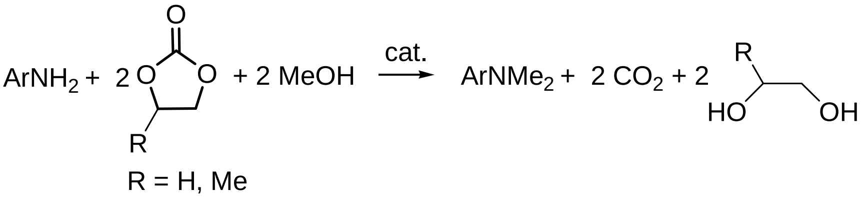
Table 3.7 shows that the "green domino" sequence accurs also in the presence of glycerol producing glycerol carbonate as an alkylating agent of aniline. Yet, the selectivity of the reaction is not satisfactory. The relative high viscosity of the reaction slurry, the adsorbtion of glycerol over the catalyst and the different activation/adsorbton of both EC and GlyC, should be considered to explain such result. These aspects will be object of future studies.

III. Different anilines and different cyclic carbonates. Table 3.5 shows that the green domino sequence is effective for different primary aromatic amines. The reactivity scale of these compounds, leaves few doubts about the effect of aryl substituents: the *N*-methylation reaction is accelerated by electron-donating groups, while it becomes difficult with scantly nucleophilic amines such as *p*-chloro- and particularly, *p*-nitro-aniline. This closely follows a result previously described by this research group, for the alkylation of aromatic amines with DMC catalyzed by faujasites.[5,53a-c,59]

Table 3.5 indicates that also propylene carbonate (PC) promotes the selective methylation of different anilines; though, the overall reaction rate drops with respect to the use of ethylene carbonate (EC). A plausible explanation comes from the study of the transesterification of cyclic carbonates with methanol: Arai *et al.*,[61] have reported that when ethylene carbonate is replaced with propylene carbonate, the different steric hindrance of the two carbonates accounts for a sharp decrease of reactivity. For the same reason, the availability of DMC, and consequently the *N*-methylation rates decrease in the green domino promoted by PC.

3.2.4 Conclusions

An innovative and selective synthesis of bis-*N*-methyl anilines is described through the reaction of aromatic amines, methanol and a cyclic carbonate. Although in the formal stoichiometry of the process, methanol is the alkylating agent (scheme 3.23), the overall transformation proceeds *via* the coupling of two sequential processes, both catalysed by alkali metal exchanged faujasites.



Scheme 3.23

In particular, ethylene or propylene carbonate react preferably in the presence of a NaX zeolite, with methanol, to produce dimethyl carbonate (DMC) which *in situ*, acts as an efficient methylating agent of anilines. This green domino sequence, offers an original approach from both synthetic and environmental standpoints: in fact, the transesterification of cyclic carbonates with MeOH is the preferred eco-friendly solution for the production of the non toxic DMC, that itself possesses much better and greener alkylation performances than methanol. *N,N*-dimethylanilines can be isolated in good to excellent yields (78-98%), starting from *p*-substituted amines with both electron-donating and -withdrawing groups; though, the more nucleophilic the substrates (*e.g. p*-anisidine and *p*-toluidine), the faster the reaction. In addition, steric reasons likely account for the higher reactivity of ethylene carbonate with respect to propylene carbonate.

The study of competitive reactions of aniline with mixtures of ethylene carbonate and DMC, unequivocally proves that the cyclic carbonate is the better *N*-alkylating agent. This notwithstanding, under the *green domino* conditions, a methylation selectivity up to 99%, is achieved. This intriguing and unpredictable result is explained mainly by the presence of MeOH as a reagent/solvent, whose polar protic features alter the modes of adsorption (and the reactivity) of dialkyl carbonates over the surface of the faujasites catalysts. The effects observed in the presence of other polar and apolar co-solvents (DMF, DME and cyclohexane), further support these considerations.

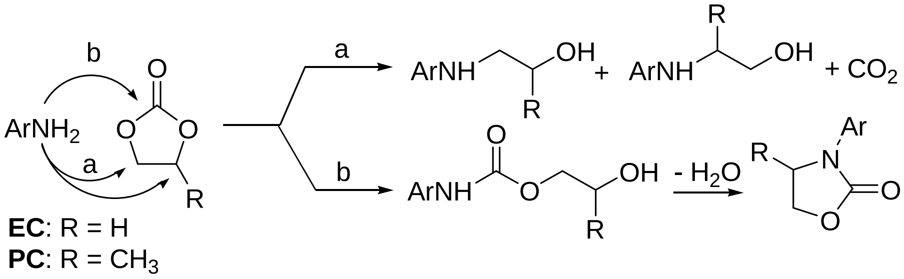
3.3 The Reaction of Primary Aromatic Amines with Alkylene Carbonates in the Presence of Phosphonium-based Ionic Liquids as Catalysts

3.3.1 Introduction

In the previous paragraph (3.2), the hydroxyalkylation of anilines with ethylene- and propylene- carbonate in the presence of zeolites was briefly described. A more in depth analysis of this reaction has been carried out by using phosphonium-based ionic liquids as catalysts. Before discussing the results of this investigation, a short overview on the hydroxyalkylation of anilines and a summary of the work done in this field are given.

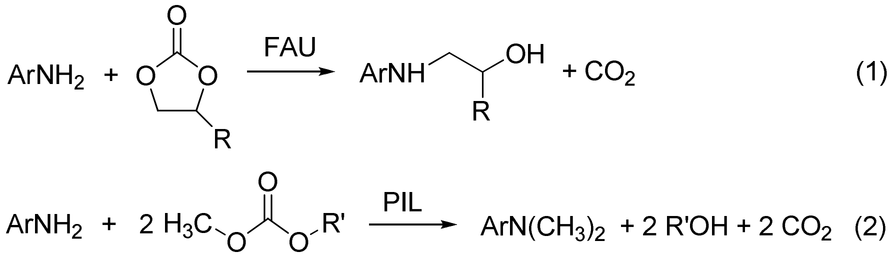
The hydroxyalkylation of primary aromatic amines is extensively used, especially in medicinal chemistry, for the synthesis of aminoalcohols as intermediates.[62] Despite the broad scope, the reaction poses a major concern from both safety and environmental standpoints: conventional *N*-hydroxyalkylation methods are based on ethylene and propylene oxides which are highly toxic and carcinogenic compounds.[63] Moreover, the flammability of these oxides imposes low reaction temperatures or sealed reactors.[62,64] Alternative reagents such as ethylene and propylene halohydrins [$X(CH_2)_2OH$, $XCH_2CH(OH)CH_3$; X = Cl, Br] do not reduce the overall impact of the procedure;[62a,65] halohydrins are also very toxic and corrosive products and their use generates stoichiometric amounts of halogenated salts which must be disposed of.[66]

In this context, alkylene carbonates (ethylene carbonate and propylene carbonate: EC and PC, respectively) offer a valuable option for new hydroxyalkylation protocols of anilines. Although the catalytic insertion of CO_2 on alkylene oxides still represents the most important route for the synthesis of both ethylene and propylene carbonates,[61,67] nonetheless the latter offer a number of practical benefits over their parent oxides as well as over halohydrins. Among them: *i*) EC and PC are classified as irritant but non-toxic products; *ii*) EC is a low-melting solid (35 °C), while PC is a liquid, and both products are not flammable; therefore, they can be used as stoichiometric reagents without added solvents; *iii*) when EC or PC serve as hydroxyalkylating agents, CO_2 is the only by-product. Thus alkylene carbonates can be safely used even for large scale preparations, as documented by the extensive literature over the years.[68] Only few papers however, claim the application of EC and PC for the hydroxyalkylation of primary aromatic amines (scheme 3.24, path a).[53, 69] In the presence of different catalysts, the efficiency of the reaction is limited by the dual electrophilic character of the cyclic carbonates EC and PC which may cause competitive acylation (possibly followed by cyclization)[5,20,29b,53a-c,59] (scheme 3.24, path b).



Scheme 3.24. Competitive reactions of anilines with alkylene carbonates

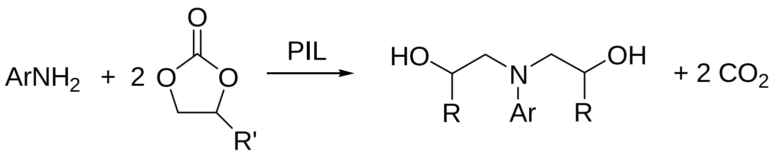
This behaviour is quite general for the reaction of anilines with both linear and cyclic dialkyl carbonates, where mixtures of *N*-alkyl derivatives and carbamates are often obtained.[5d-e,34a-b,70] Effective solutions to improve the selectivity toward alkylation have been recently proposed by us through the use of two classes of catalysts: *i*) zeolites such as alkali metal exchanged faujasites (FAU,[12,26] see previous paragraph 3.1 and 3.2) and more recently, *ii*) phosphonium-based ionic liquids (PILs). FAU and PILs however, thanks to their different acid-base properties and steric requisites, promote different reaction outcomes. FAU catalyze the formation of mono-*N*-alkyl amines, while the more active PILs steer the reaction towards the formation of bis-*N*-alkyl derivatives. Scheme 3.25 describes some relevant examples: in the presence of FAU, eq. 1 shows the mono-*N*-alkylation of anilines with EC and PC,[53] and with glycerol carbonate;[71] while, eq. 2 refers to the PIL-promoted *N*,*N*-dimethylation of primary aromatic amines with different methylalkyl carbonates.[72]



FAU: faujasites of Y- and X-type
PIL: ionic liquids based on phosponium salts
Ar = XC_6H_4-; X = OH, OCH_3, CH_3, H, Cl, CO_2R'', NO_2
R = H; CH_3, CH_2OH
R' = $CH_3O(CH_2)_2O(CH_2)_2O(CH_2)_2$; $CH_3O(CH_2)_2O(CH_2)_2$; $CH_3O(CH_2)_2$

Scheme 3.25. Selective *N*-alkylation reactions catalysed by FAU and PILs

Excellent alkylation selectivities (up to 98 %, at complete substrate conversion) are achieved in all cases, although, the reactions show a high activation energy irrespective of the catalyst (FAU or PILs), which usually implies a temperature greater than 140 °C. A more in-depth analysis of this scenario indicates that the potential of cyclic alkylene carbonates as alkylating agents of anilines is still largely unexplored; particularly, the use of PILs as catalysts for this process, has been hardly investigated. In this work, we report that at temperatures in the range of 140-170 °C, phosphonium-based ionic liquids catalyze the reaction of different primary aromatic amines (pX-$C_6H_4NH_2$; X = H, OCH_3, CH_3, Cl) with both EC and PC, towards the formation of the corresponding bis-*N*-hydroxyalkyl derivatives [pX-$C_6H_4N(CH_2CH(R)OH)_2$; R = H, CH_3] with a high selectivity (up to 97%) at complete conversion (scheme 3.26).



PIL: 13 different phosponium ionic liquids
Ar = XC_6H_4-; X = p-OCH_3, p-CH_3, H, p-Cl
R= H, CH_3;

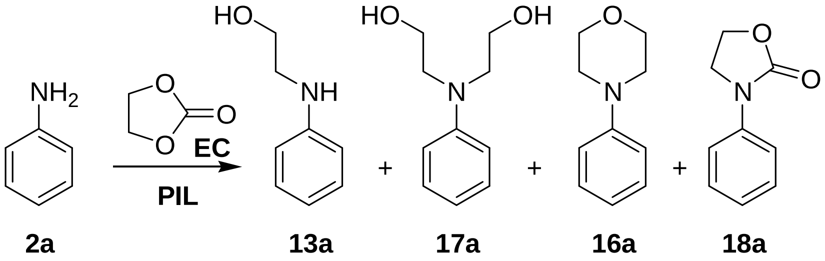
Scheme 3.26. Selective bis-*N*-hydroxyalkylations of anilines by ethylene and propylene carbonates in the presence of PILs catalysts

Interestingly, at 140 °C, the model reaction of aniline with ethylene carbonate proceeds to near quantitative formation of the bis-*N*-hydroxyethyl derivative, even without the assistance of any catalyst/promoter.

Up to 13 different phosphonium salts have been used. They have been prepared in order to guarantee an accessible synthesis with high purity and high thermal and chemical stability, or selected from commercial sources. In particular, the combination of four cations such as tri-*i*-butyl methylphosphonium [(i-Bu)$_3$PMe], tri-*n*-butylmethyl phosphonium [(n-Bu)$_3$PMe], tri-*n*-hexylmethylphosphonium [(n-Hexyl)$_3$PMe], tri-*n*-octylmethylphosphonium [(n-Octyl)$_3$PMe], with bromide (Br), tosylate (TosO), methyl carbonate (OCO_2Me), chloride (Cl) and iodide (I) anions, has been explored. Bromide exchanged PILs have proven to be the most efficient catalysts; while, the variation of the cation structure presented a moderate, if any, effect. A mechanistic hypothesis was formulated to rationalise the performance of the examined catalysts.

3.3.2 Results

I. The bis-N-(2-hydroxy)ethylation of aniline. The reaction of aniline (**2a**) with EC was selected as a model to begin the investigation. Previously reported results[72] on the *N*-methylation of primary aromatic amines with dialkyl carbonates (scheme 3.25, eq. 2) suggested the use of tri-isobutylmethylphosphonium tosylate [(*i*-Bu)$_3$PMe]TosO (**PIL1**) as a catalyst for a preliminary screening: this salt was stable at a high temperature, commercially available (in high-purity) and inexpensive. Two sets (a and b) of experiments were carried out by varying the loading of both the catalyst and ethylene carbonate, as well as the reaction temperature. In the first set (a), a mixture of aniline (**2a**, 0.80 g, 8.6 mmol), and ethylene carbonate (EC, in a two molar excess over aniline), was set to react at 150 °C, in the presence of different amounts of **PIL1** (the molar ratio Q = **PIL1**:**2a** was varied between 0.05 and 0.75). All reactions were stopped after 2 hours and analysed by GC/MS. In the second set (b), a mixture of aniline (0.8 g, 8.6 mmol), and **PIL1** (0.1 molar equiv. with respect to aniline, Q=0.1), was set to react with increasing amounts of ethylene carbonate (the molar ratio EC:**2a** was 2, 2.2, and 4), at two different temperatures of 150 and 170 °C. The reactions were monitored by GC-MS at time intervals of 2, 6, and 8 hours. For both sets (a) and (b), the major products were the mono- and the bis-*N*-(hydroxy)ethyl derivatives of aniline (scheme 3.27: compounds **13a** and **17a**, respectively).



Scheme 3.27. Products observed in the reaction of aniline with ethylene carbonate catalysed by **PIL1**

Traces (~1%) of *N*-phenylmorpholine (**16a**) and 3-phenyloxazolidin-2-one (**18a**) along with other unidentified by-products (total amount 1-5%) were also detected. Compound **17a** was isolated and fully characterised by ^{1}H and ^{13}C NMR, while the structures of **13a**, **16a** and **18a** were assigned from their MS spectra and by comparison to authentic commercial samples. An experiment was also conducted in the absence of the salt **PIL1**. The results of sets (a) and (b) are reported in figure 3.6 and table 3.10, respectively. In the figure, the red profile refers to the overall *N*-alkyl selectivity ($S_{N\text{-alk}}$) expressed as: $S_{N\text{-alk}}$ = [(**13a**+**17a**)/Conversion]x100 (left ordinate), while the blue profile is the ratio of bis- to mono-*N*-alkyl products, *i.e.* (**17a**/**13a**) (right ordinate).

Set (a), figure 3.6. At 150 °C, the reaction proceeded even without catalyst (Q=0): the conversion of aniline was of 48% and the mono-*N*-alkyl derivative **13a** was formed almost quantitatively (46%).[73]

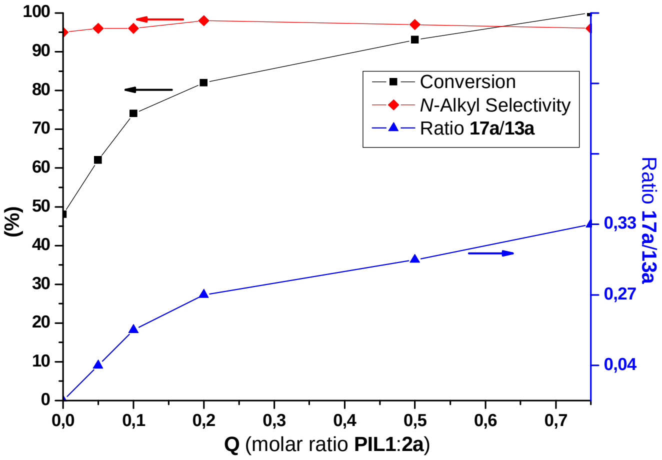


Figure 3.6. The reaction of aniline with ethylene carbonate (150 °C, 2h): effects of the amount of **PIL1**

However, the reaction outcome was improved by the ionic liquid: the conversion was significantly larger (up to 73%) with the addition of even small quantities of **PIL1** (molar ratio **PIL1**:**2a** Q = 0.05 – 0.1) and, by further increasing the Q ratio from 0.1 to 0.75, the conversion finally rose up to a quantitative value.

With respect to the uncatalysed process, the presence of the ionic liquid promoted the formation of both the mono- and the bis-*N*-alkyl derivatives of aniline (compounds **13a** and **17a**). Although the overall *N*-alkyl selectivity was very high ($S_{N\text{-alk}}$= [(**13a**+**17a**)/conversion]x100 = 96-98%), mixtures of products **13a** and **17a** were always obtained. At Q≥0.1, the (**17a**/**13a**) ratios were in the range of 0.2-0.33 (blue profile, right ordinate).

Set (b), table 3.10. Experiments were continued at a constant Q ratio (**PIL1**:**2a**) of 0.1,[74] by varying the temperature and EC:**2a** ratio. At 150 °C, going from 2 to 6 h reaction times, a substantially quantitative conversion (95-97%) was observed with an excellent *N*-alkyl selectivity ($S_{N\text{-alk}}$: 95-98%; entries 1-2 and 3-4).

The ratio of bis-*N*- to mono-*N*-alkyl compounds (**17a**/**13a**) also increased significantly, but it was still in favour of the product **13a** (50-51%; entries 2 and 4). The reaction outcome was greatly improved at 170 °C. Aniline was detected in trace amounts (3-4%) after only 2 hours (entries 5, 7 and 10), and, as the reaction proceeded further, compound **13a** was efficiently transformed in the bis-*N*-alkyl product **17a** with yields of 86-95% (by GC, entries 9 and 12).

Table 3.10. The reaction of aniline (**1a**) with EC in the presence of [MeP(*i*-Bu)$_3$]TosO [a]

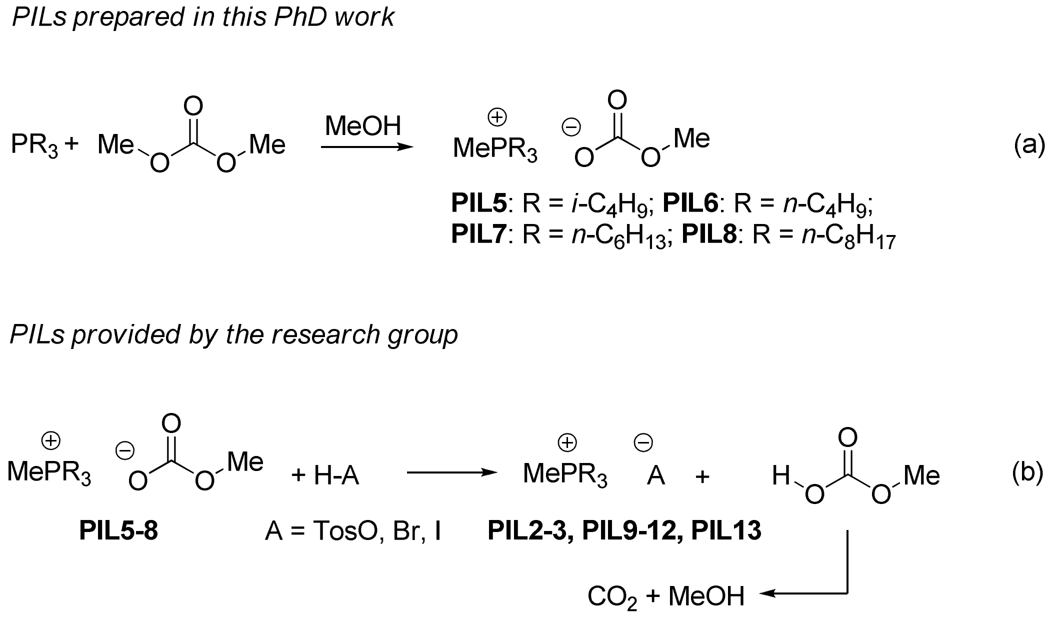
#	EC:2° (mol: mol) [b]	T (°C)	t (h)	Conv (%, by GC) [c]	Products (%) [c]					Yield (17a, %)
					13a	17a	16a	18a	Others [d]	
1	2	150	2	74	67	5			2	
2			6	95	51	38		1	5	
3	4	150	2	72	64	6			2	
4			6	97	50	45	1		1	
5	2	170	2	97	49	46	1	1		
6			6	99	23	74			2	
7	2.2	170	2	97	46	48		1	2	
8			6	98	17	79		1	1	
9			8	98	9	86	2	1		74
10	4	170	2	96	52	41	2			
11			6	99	15	81	1		2	
12			9	98		95	2	1		61

[a] All reactions were carried out using a mixture of aniline (**2a**, 0.8 g) and compound **PIL1** in a 1:0.1 molar ratio. [b] The molar ratio ethylene carbonate:aniline. [c] The reaction conversion and the amounts of products were determined by GC/MS analyses (columns 5 and 6, respectively). The conversion was referred to aniline (the limiting reagent). [d] Total amounts of unidentified by-products.

At both 150 °C and 170 °C, the increase of the EC:**2a** molar ratio (from 2 to 4) moderately favoured the conversion of **13a** to the desired final product **17a** (compare entries 1-2 to 3-4, and entries 5-6 to 7-8 and 10-11). Nonetheless, when the reaction mixtures were purified by FCC (gradient elution: MeOH/diethyl ether/petroleum ether; from 0:1:4 to 1:7.5:1.5 v/v, total of 650 mL), EC was partly co-eluted with compound **17a**; hence, the higher the amount of ethylene carbonate, the lower the final isolated yields (entries 9 and 12: yields of 74% and 61%, respectively).[75]

II. The synthesis of phosphonium based ionic liquids (PILs). The reaction of aniline with EC was examined by using a total of 13 PILs. Four of them were prepared according to the new green protocol developed in this PhD thesis and described in chapter 2 (paragraph 2.2). Four alkylphosphines (R_3P; R= *n*-octyl, *n*-hexyl, *i*-butyl, and *n*-butyl) were set to react with dimethyl carbonate ($MeOCO_2Me$) as a green methylating agent, to obtain methyltrialkylphosphonium methylcarbonate salts **PIL5-8** [scheme 3.28, (a)]. Other PILs were provided by the research group: these compounds were obtained through an anion-exchange reaction of **PIL5-8** with

Brønsted acids [H–A, A= TosO, Br, and I; (scheme 3.28, (b)] to yield the corresponding tosylate, bromide, and iodide salts (**PIL2-4**, **PIL9-12**, and **PIL13**, respectively) along with methyl hydrogen carbonate (*i.e.*, the half-ester of carbonic acid). The latter was unstable above -36 °C[76] and immediately decomposed to form methanol and CO_2, thus providing its built-in removal.



Scheme 3.28. The synthesis of PILs

The structures of all PILs used in this work are summarized in table 3.11. These products were obtained on a 2-3 g scale. They were fully characterized by ^1H and ^{13}C NMR.

Table 3.11. List of Ionic Liquids utilized in this work

Cation	**Anion**			
	[TosO]	[OCO_2Me]	[Br]	[I]
[*i*-Bu_3PMe]	[a]	**PIL5**	**PIL9**	
[*n*-Bu_3PMe]	**PIL2**	**PIL6**	**PIL10**	
[*n*-Hex_3PMe]	**PIL3**	**PIL7**	**PIL11**	
[*n*-Oct_3PMe]	**PIL4**	**PIL8**	**PIL12**	**PIL13**

[a] [*i*-Bu_3PMe][TosO] was commercially available (Aldrich).

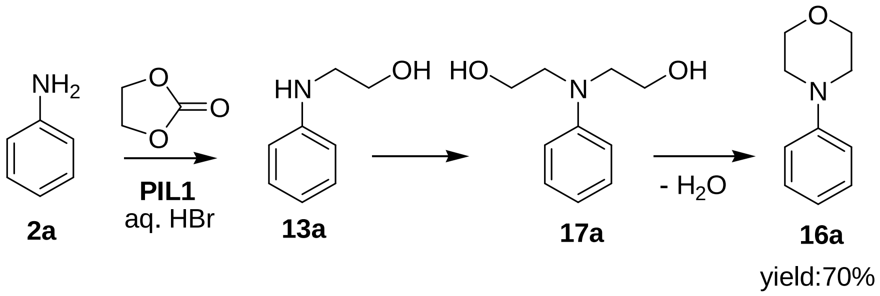
III. The bis-N-(2-hydroxy)ethylation of aniline in the presence of different ionic liquids. Preliminary experiments on the reaction of aniline with ethylene carbonate were carried out with strongly basic IL such as [*i*-Bu_3PMe][OCO_2Me] and [*n*-Oct_3PMe] [OCO_2Me] (**PIL5** and **PIL8**). Complex mixtures of products were always obtained. For this reason, the use of the methylcarbonate exchanged PILs (**PIL5-8**) was not further examined. Based on the results of table 3.10, tosylate and bromide-exchanged salts (**PIL2-4** and **PIL9-12,** respectively), were then used. The complete combination of four cations (from C4 to C8: [*i*-Bu_3PMe], [*n*-Bu_3PMe], [*n*-Hex_3PMe], and [*n*-Oct_3PMe] was available for these anions (TosO and Br, table 3.11). A mixture of aniline (**2a**, 0.8 g, 8.6 mmol), ethylene carbonate (EC) and a **PIL** (the molar ratio **2a**:EC:**PIL** was 1:2:0.1, respectively) was set to react at 170 °C and the progress of the reaction was monitored by GC-MS at time intervals in the range of 2-4 hours. Analogously to the commercial **PIL1**, the major products were the desired mono- and the bis-*N*-(hydroxy)ethyl derivatives of aniline (compounds **13a** and **17a** of scheme 3.27). *N*-phenylmorpholine (**16a**) and 3-phenyloxazolidin-2-one (**18a**) were also detected along with other unidentified by-products (total amount 3-12%). The results are reported in table 3.12 which, for a more complete comparison, includes also the data related to compound **PIL1** (entries 5-6 of table 3.10).

Table 3.12. The reaction of aniline with ethylene carbonate at 170 °C, in the presence of different PILs [a]

#	**PIL**	**t (h)**	**Conv (%)[b]**	**Products (%)[b]**				
				13a	**17a**	**16a**	**18a**	**Others**
1	**PIL1**	2	97	49	46	1	1	
2	MeP(*i*-Bu)$_3$TosO	4	99	25	68	1		5
3	**PIL2**	2	80	57	17		1	5
4	MeP(*n*-Bu)$_3$TosO	4	96	42	41	3	1	8
5	**PIL3**	2	85	56	18	4		7
6	MeP(*n*-Hex)$_3$TosO	4	91	45	34	2	1	9
7	**PIL4**	2	97	48	51			
8	MeP(*n*-Oct)$_3$TosO	4	100	36	58	1		5
9	**PIL9** MeP(*i*-Bu)$_3$Br	2	98	13	64	9	4	7
10	**PIL10** MeP(*n*-Bu)$_3$Br	2	98	9	61	12	3	12
11	**PIL11** MeP(*n*-Hex)$_3$Br	2	100	12	80	5		3
12	**PIL12** MeP(*n*-Oct)$_3$Br	2	100	18	77	4	1	

[a] All reactions were carried out at 170 °C, using a mixture of aniline (**2a**, 0.8 g), ethylene carbonate, and PIL in a 1:2:0.1 molar ratio, respectively. [b] The reaction conversion and the amounts of products were determined by GC/MS analyses. Others were unidentified by-products.

At 170 °C, after 2 hours, the comparison of our model PILs showed that: *i*) high aniline conversions (80-100%) were reached in all cases; *ii*) bromide salts (**PIL9-12**) were by far more efficient than tosylate ones (**PIL1-4**) for the transformation of the mono-*N*-alkyl derivative **13a** into the final desired bis-*N*-alkyl product **17a**. The ratio **17a**/**13a** was 4-6.5 for bromides **PIL9-12**, (entries 9-12), while it ranged between 0.3 and 1 for tosylates **PIL1-4** (entries 1, 3, 5, and 7). Overall, the bromide-catalysed processes were substantially over after 2 hours, while the tosylate-catalysed reactions were far from complete even after 4 hours (entries 2, 4, 6, and 8). In the case of **PIL9** and **PIL10**, an apparent drop of the *N*-alkyl selectivity ($S_{N\text{-alk}}$) was observed (entries 9-10). This was mainly due to the formation of *N*-phenylmorpholine **16a** (9-12%). Two additional experiments explained this result: under the conditions of entry 1 (table 3.12), aniline was set to react with ethylene carbonate in the presence of water or of aq. HBr (both H_2O and HBr were used in 10% mol with respect to aniline). While the addition of water had no appreciable effects on the reaction outcome, a catalytic amount of aq. HBr prompted the transformation of compound **17a** into **16a** in 70% GC yield, after 18 hours (scheme 3.29).[77]



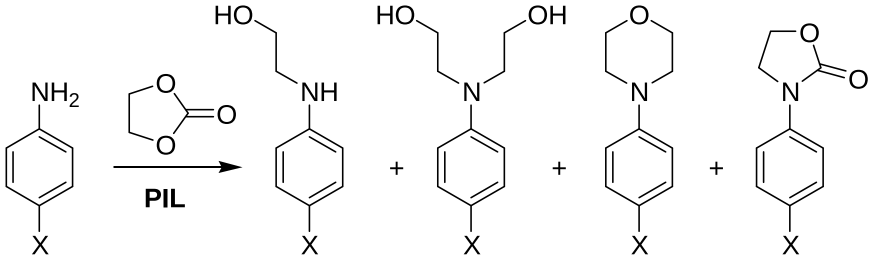
Scheme 3.29. The reaction of aniline and ethylene carbonate with added water or aq. HBr

Traces of residual acidity (HBr) from the synthesis of ionic liquids (scheme 3.28), reasonably accounted for the presence of the by-product **16a** in table 3.12. However, any attempt to purify **PIL9** and **10** to improve their performance, was not successful.

IV. The reaction of different anilines with ethylene carbonate. **PIL1** and **PIL12** [MeP(*i*-Bu)$_3$TosO and MeP(*n*-Oct)$_3$Br, respectively] were chosen as catalysts for the reaction of primary aromatic amines (*p*-chloroaniline, *p*-anisidine and *p*-toluidine: compounds **2b**, **2c** and **2e**, respectively) with ethylene carbonate (EC).

A mixture of the primary amine (8.6 mmol), ethylene carbonate, and a PIL in a 1:2.2:0.1 molar ratio, respectively, was set to react at temperatures in the range of 150-170 °C. All reactions were followed by GC/MS at different time intervals. Major products were the mono- and the bis-*N*-(2-hydroxy)ethyl derivatives of the reactant amines (scheme 3.30: compounds **13** and **17**, respectively). *N*-[(*p*-substituted)phenyl]morpholines (**16:** 1-4%) and *N*-[(*p*-substituted)phenyl]-oxazolidin-2-ones (**18**: 2-4%) along with other unidentified by-products (total amount 2-8%)

were also detected. Compounds **17** (**b**, **c** and **e**) were isolated and fully characterised by ^{1}H and ^{13}C NMR, while the structures of **13**, **16** and **18** (**b**, **c** and **e**), were assigned from their MS spectra.



2b,c,e **13b,c,e** **17b,c,e** **16b,c,e** **18b,c,e**

b: X = Cl; **c**: X = MeO; **e**: X = Me

Scheme 3.30. The products observed in the reaction of different anilines with ethylene carbonate catalysed by **PIL1** and **PlL12**

The results are reported in table 3.13 where, for a more complete comparison, also the data related to aniline (tables 3.10 and 3.12) are included.

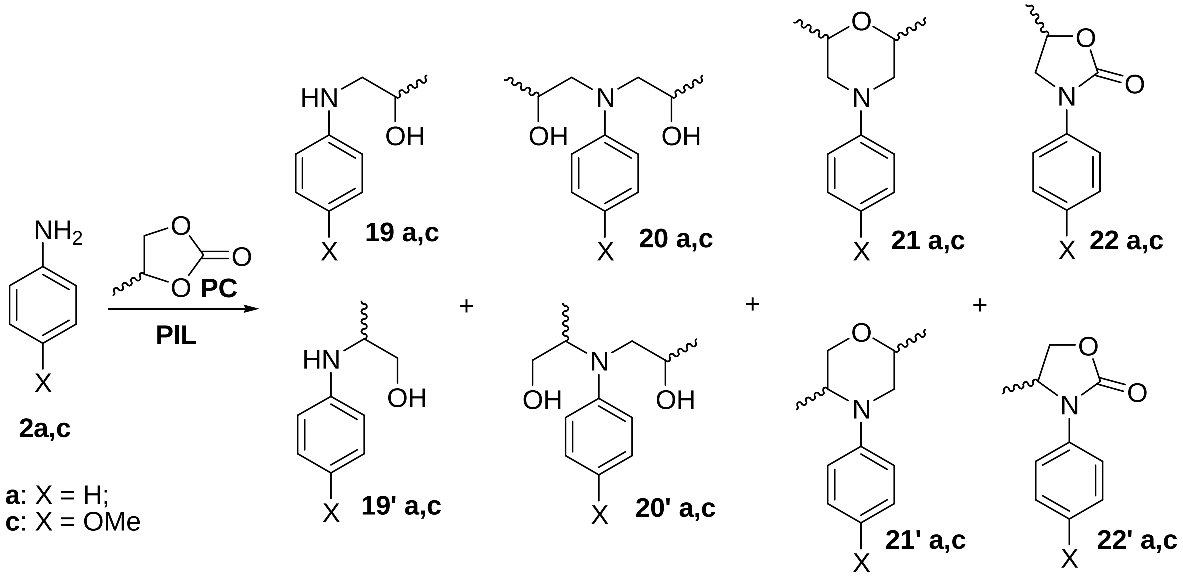
Table 3.13. The reaction of different anilines with ethylene carbonate catalysed by **PIL1** and **PlL12** [a]

#	$XC_6H_4NH_2$	Catalyst	T (°C)	t (h)	Conv (%)[b]	Products (%) [b]					17 (Yield, %) [c]
						13	17	16	18	Others	
1	**2a** X = H	**PIL1**	170	6	99	23	74			2	
2			150	6	95	51	38		1	5	
3	**2c** X = *p*-MeO		170	4	100	21	72	1	2	4	
4			150	15	100	3	86	1	4	6	74
5	**2e** X = *p*-CH_3		150	18	100	9	87		2	2	70
6	**2b** X = *p*-Cl		170	14	100	17	72	4	3	4	62
7	**2a** X = H	**PIL12**	170	2	100	18	77	4	1		
8	**2c** X = *p*-MeO		150	4	99	16	71	2	2	8	
9	**2e** X = *p*-CH_3		150	7	99	13	74	4	1	7	

[a] All reactions were carried out using a mixture of the primary amine (8.6 mmol), ethylene carbonate, and a **PIL** in a 1: 2.2: 0.1 molar ratio, respectively. [b] The reaction conversion was referred to the primary amine. Both the conversion and the amounts of products were determined by GC/MS analyses. Others: total amounts of unidentified by-products. [c] Isolated yields of bis-*N*-alkyl derivatives **17b**, **c** and **e**.

Three main considerations emerged: *i*) the bromide exchanged PIL was more active than the tosylate salt. At 150 °C for example, both *p*-anisidine and *p*-toluidine were completely converted in 4-7 hours and in 15-18 hours, using **PIL12** [MeP(*n*-Oct)$_3$Br] and **PIL1** [MeP(*i*-Bu)$_3$TosO], respectively (entries 8-9 and 4-5); *ii*) the reaction was of a general scope for different amines. On average, *p*-anisidine (entries 3-4, and 8) was more reactive than *p*-toluidine (entries 5 and 9), aniline (entries 1-2 and 7), and *p*-chloroaniline (entry 6); *iii*) as for the case of aniline, the FCC-purification of bis-*N*-alkyl derivatives **17b**, **c** and **e** was rather difficult: these compounds however, were isolated in reasonably good yields (62-74%; entries 4-6).

V. The reaction of primary aromatic amines with propylene carbonate. Three different PILs, namely tri-*i*-butylmethylphosphonium tosylate and bromide [**PIL1** and **PIL9**: MeP(*i*-Bu)$_3$TosO and MeP(*i*-Bu)$_3$Br), respectively] and tri-*n*-octylphosphonium bromide [**PIL12**: MeP(n-Oct)$_3$Br)], were selected as catalysts for the reaction of primary aromatic amines (aniline and *p*-anisidine, **2a** and **2c** respectively) with propylene carbonate (PC). A mixture of the primary amine (8.6 mmol), racemic propylene carbonate, and the chosen PIL in a 1:2.2:0.1 molar ratio, respectively, were set to react at temperatures in the range of 150-190 °C. An additional experiment was carried out also in the absence of PILs. All reactions were followed by GC/MS. The asymmetry of PC implied the formation of a number of products whose structures are outlined in scheme 3.31.



Scheme 3.31. The products observed in the reaction of different anilines with propylene carbonate catalysed by **PIL1**, **PlL9**, and **PIL12**

Major products derived from the *N*-alkylation of the reactant amines. The double nucleophilic attack of the amine at the C in position 5 of PC gave rise to bis-*N*-(2-hydroxy)propyl derivatives (compounds **20a**, **20c**) as a pair of diastereoisomers in a 1:1 ratio. A non-negligible amount of other bis-*N*-alkylated compounds originated also from the reaction of the amine at the highly hindered C in position 4 of PC (compounds **20'a**, **20'c**): the ratio **20/20'** was ~ 4-5.[78]

Two isomeric morpholines, *i.e.* 2,6-dimethyl- and 2,5-dimethyl-*N*-[(*p*-substituted)phenyl] morpholines (compounds **21a**, **21c** and **21'a**, **21'c**, respectively; total of 3-11%), as well as two isomeric oxazolidin-2-ones, *i.e.* 5-methyl- and 4-methyl-*N*-[(*p*-substituted)phenyl]-oxazolidin-2-ones (compounds **22a**, **22c** and **21'a**, **22'c**, respectively; total of 1-7%) were also detected.

Finally, pairs of isomeric unidentified by-products were observed (m/z = 193 in the reaction of aniline; m/z = 223 in the reaction of *p*-anisidine) in 11-25% yields. The isomeric ensemble **20/20'** was isolated and fully characterised by ^{1}H and ^{13}C NMR, while the structures of **19**, **21** and **22** were assigned from their MS spectra. The results are reported in table 3.14.

Table 3.14. The reaction of different anilines with propylene carbonate in the presence of PILs catalysts [a]

#	$XC_6H_4NH_2$	Catalyst	T (°C)	t (h)	Conv (%) [b]	Products (%) [b]					20 (Yield, %) [c]
						19	20	21	22	others	
1	X = H	None	170	16	1					1	
2			190	10	3					3	
3		**PIL1**	190	54	98	41	36	10	1	11	
4		**PIL9**	170	35	96	9	63	11		13	58
5		**PIL12**	170	40	99	6	65	15	4	9	
6	X = *p*-MeO	**PIL1**	170	21	89	48	18	4	1	18	
7		**PIL9**	150	29	100	6	60	3	6	25	55
8		**PIL12**	150	24	100	6	58	6	7	23	

[a] All reactions were carried out using a mixture of the primary amine (8.6 mmol), propylene carbonate, and a **PIL** in a 1: 2.2: 0.1 molar ratio, respectively. [b] The reaction conversion was referred to the primary amine. Both the conversion and the amounts of products were determined by GC/MS analyses. Others: unidentified by-products were constituted by two isomers (m/z = 193). [c] Isolated yields of bis-*N*-alkyl derivatives **20a**, **c**.

In the absence of PILs, the conversion of aniline was negligible even at high temperature (190 °C, entry 2). This remarkable difference with respect to ethylene carbonate, was likely due to the weaker electrophilic character of PC. However, the use of a catalytic amount of PILs allowed the reaction of aniline with propylene carbonate to proceed up to completion.

Bromide exchanged salts (**PIL9** and **12**) were also able to promote the transformation of mono-*N*-alkyl products **19** to bis-*N*-alkyl derivatives **20** (entries 4-5 and 7-8). This process instead, was rather sluggish in the presence of the tosylated **PIL1**: for example, in the reaction of aniline, the ratio **19a**/**20a** was in favor of the mono-alkyl compound (**19a**) even after 54 h at 190 °C (entry 3). A similar situation held true for *p*-anisidine (entry 6).

In any case, the poorer reactivity of PC implied long reaction times (>20 hours). This increased the formation of by-products at the point that the overall *N*-alkyl selectivity ($S_{N\text{-alk}}$ = [(**19**+**20**)/ Conversion]x100) could not exceed 75%. A value, by far, lower than that achieved with ethylene carbonate (up to 97%, table 3.13).

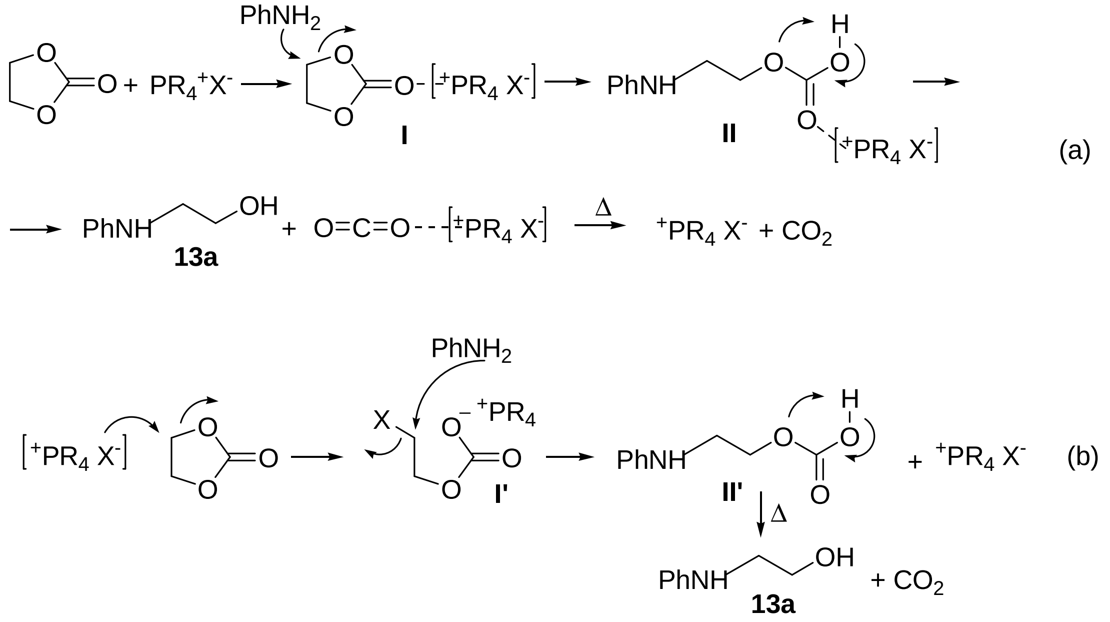
However, to the best of our knowledge, this was the first ever reported reaction in which organocatalysts, particularly PILs, were able to activate PC as an alkylating agent of primary aromatic amines. Bis-*N*-alkyl derivatives **20** were purified by FCC and the corresponding isolated yields were in agreement to their GC amounts (entries 4 and 7).

3.3.3 Discussion

I. The reaction of aniline with alkylene carbonates: the effects of PILs. A first significant feature of the reaction of aniline with ethylene carbonate comes from the analysis of figure 3.6. At 140-150 °C, the process not only proceeds in the absence of catalysts but, under such conditions, it yields selectively the bis-*N*-(2-hydroxy)ethyl derivatives of the amine with no concurrent formation of carbamates. This behaviour is rather unexpected, especially if compared to the literature data discussed in the introduction (scheme 3.24).[5,34,69] Aniline is perfectly capable, as a nucleophile, of discriminating between the two electrophilic centres of ethylene carbonate (the alkyl and the carbonyl carbons, respectively), with a preference for the β carbon. This preference is not altered by the action of the PIL catalysts. The cyclic structure of EC offers two plausible reasons for this result: *i*) on one hand, the *N*-alkylation selectivity would be favoured by the rigid 5-membered ring of EC which hinders access to the carbonyl carbon; *ii*) on the other hand, the relief of some ring strain consequent to the alkylation of aniline with EC, would allow even the non-catalytic reaction to proceed. It should be noted that this last effect is often offered to explain the higher reactivity of ethylene carbonate with respect to linear dialkyl carbonates.[5h,58]

Figure 3.6 and table 3.12 however, leave few doubts about the catalytic action of PILs. In general, the alkylation rate of aniline with EC is doubled by the use of tosylate salts (**PIL1-4**), while the reaction is up to eight-fold accelerated by the more efficient bromide exchanged PILs (**PIL9-12**). This effect is even more pronounced when propylene carbonate is the alkylating agent (table 3.14): *N*-(2-hydroxy)propyl derivatives of aniline (**19a** and **20a**) form only in the presence of catalytic amounts of PILs, otherwise no reaction takes place at all. Also in this case, bromide salts (**PIL9** and **12**) offer a better performance than the tosylated **PIL1**.

A plausible reaction mechanism should consider the action of both the cationic and the anionic parts of the PILs. Scheme 3.32 illustrates two hypotheses [for simplicity, only the mono-*N*-(2-hydroxy)ethylation of aniline is shown].



Scheme 3.32. Mechanistic hypotheses for the mono-*N*-(2-hydroxy)ethylation of aniline with EC

Hpothesis (a) stands on the weak Lewis acidity of phosponium cations,[79] and the great affinity between phosphorous and oxygen.[80] An initial coordination of the P^+ center of the catalyst to the carboxylic oxygen of EC, produces the acid-base adduct (**I**); a similar structure, with pentavalent phosphorus, has been described in the literature.[81]

Although the carboxylic carbon of the complex (**I**) undergoes electrophilic activation, no reaction occurs at this position because of the rigid structure of EC (see above), and of the steric crowding imposed by the bulky phosphonium cation.[82] Aniline directs its nucleophilic attack to the β-alkyl carbons (in positions 3 and 4) of EC: both these atoms are rather accessible, and they experience an activating inductive effect caused by the strong polarisation of the C=O bond in the complex (**I**). An intermediate amino carbonic acid (**II**) forms, which is unstable[83] and quickly releases CO_2 to give the final product **13a**. Path a) hardly explains why halide salts, more specifically bromides, are remarkably more active than tosylate PILs. However it is plausible that the size, the polarisability, and the stability of anions alter the strength of ionic pairs in PILs and therefore, the Lewis acidity of the corresponding cations. A crucial role is plausibly also played by the nucleophilic properties of bromides and tosylates. Path b) accounts for this last aspect in analogy to a mechanism previously proposed for the reaction of EC with carboxylic acids in the presence of tetraalkylammonium halides ([$NR_4^+X^-$]) as catalysts.[84] The following steps are considered: *i*) the aperture of the ethylene carbonate ring takes place through the attack of a halide anion (X^-) to one β-alkyl carbon, and **I'** is formed; *ii*) then, aniline displaces the X-group and the carbamic acid **II'** is obtained; *iii*) finally, the evolution of CO_2 from **II'** brings to the final derivative **13a**. The greater nucleophilic strength of bromide or iodide anions with respect to the tosylate anions, makes path b) especially valid for **PIL 9-12** and **13**, but not for the poor nucleophilic tosylate catalysts (**PIL 1-4**).[85] This may account for the activity displayed by the two types of PILs: paths (a) and (b) may simultaneously operate with halides, while only path (a) is active for tosylates.

II. The reaction of different anilines with ethylene- and propylene-carbonate. Tables 3.13 and 3.14 show that both activated and scantly nucleophilic amines react with alkylene carbonates to yield mainly the corresponding bis-*N*-alkyl derivatives. Three major observations emerge: *i*) on average, the reactivity of different aromatic amines is consistent with the electron-donating properties of their ring substituents, *i.e.* p-OCH_3 > p-CH_3> H >> Cl; *ii*) PC is by far less reactive than EC. As reported by different Authors and by us,[61,79,86] the steric hindrance of the methyl group in PC, likely accounts for its poor electrophilicity with respect to EC; *iii*) the higher activity of bromide exchanged salts (**PIL9** and **12**) over the tosylate (**PIL1**) in the alkylation of *p*-anisidine and *p*-toluidine with both EC and PC, suggests that the mechanism of scheme 3.32 discussed for aniline, holds for *p*-substituted anilines as well.

3.3.4 Conclusions

The reaction of primary aromatic amines with alkylene carbonates is a rather unexplored transformation. This investigation describes an advantageous methodology to carry out the bis-*N*-hydroxyalkylation of anilines with EC and PC. Although the methodology is rather energy intensive, several advantages can be recognized from both synthetic and environmental standpoints: *i*) the reaction is of a general scope for different anilines and for PC and EC; *ii*) non toxic alkylene carbonates replace very harmful hydroxyalkylating agents such as alkylene oxides or halohydrins; *iii*) the reactions are chemoselective, occurring almost exclusively at the β carbons of EC and PC. The competitive formation of carbamate products is ruled out; *iv*) the reaction setup is very simple and it allows truly catalytic processes using robust systems based on phosphonium salts (PILs). In particular, bromide exchanged PILs have proven to be the most efficient organocatalysts; *v*) a catalyst is not always required for the reaction: the quantitative formation of bis-*N*-(2-hydroxy) ethylaniline is achieved at a reasonable temperature by merely mixing stoichiometric amounts of aniline and EC; *vi*) no additional solvents are required.

Two mechanistic hypothesis are proposed to account for the efficiency of the PILs organocatalysts: the Lewis acidic phosphonium cations may electrophilically activate the alkyl carbons of alkylene carbonates, while nucleophilic halide anions (but not tosylates) assist the aperture of the carbonate ring through a direct attack at the alkyl positions.

Propylene carbonate is a weaker electrophile than ethylene carbonate: primary aromatic amines react with PC only in the presence of catalytic amounts of bromide or tosylate onium salts.

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[7] Today, DMC can be obtained as a non toxic compound via phosgene-free routes (see chapter 1 of this work and M. Selva, *Pure Appl. Chem.*, 2007, **79**, 1855–1867).

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[10] To the best of our knowledge, the steric crowding at C4 of GlyC prevents reactions on this position.

[11] (a) G. Grahe, EP Patent 0328150 A2, DaiNippon Ink & Chemicals (Aug. 16, 1987); (b) M. Pallavicini, E. Valoti, L. Villa and O. Piccolo, *J. Org. Chem.*, 1994, **59**, 1751-1754; (c) A. Behr and M. Becker, *Dalton Trans.*, 2006, **267**, 4607-4613; (d) A. Behr, P. Bahke, B. Klinger and M.

Becker, *J. Mol. Cat.*, 2007, **267**, 149, 156; (e) H. R. Pfandler and F. X. Müller, *Synthesis*, 1992, 350-352.

[12] Alkali metal exchanged faujasites are alumino-silicates belonging to the general class of zeolites: see: F. Schwochow and L. Puppe, *Angew. Chem. int. Edit.*, 1975, **14**, 620.

[13] It should be noted here that in the presence of faujasites, a number of ambident aromatic amines such as amino-phenols, amino-benzoic acids, amino-benzamides, and amino-benzyl alcohols, react with DMC to produce only the corresponding mono-*N*-methylanilines. See reference 5d and M. Selva, P. Tundo, INCA, EP 1431274 (June 23, 2004).

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[15] The viscosity of GlyC is 61.0 cst at 25 °C (see www.huntsman.com, JEFFSOL® Glycerine Carbonate). Diglyme was already described by us as a good solvent for zeolite-catalysed alkylations of amines with dialkylcarbonates (see ref. 5c).

[16] FCC was used to purify the final reaction mixtures. Efforts to isolate both compounds **5a** and **6a** were always unsuccessful: these products were eluted together with a mixture of glycerol and (unreacted) glycerol carbonate.

[17] K_2CO_3 is often the base of choice to catalyse alkylation reactions mediated by dialkyl carbonates (see reference 5).

[18] L. P. Kyrides, S. Carswell, E. Pfeifer and R. S. Wobus, *Ind. Eng. Chem.*, 1932, **24**, 795-797. Also, ref. 6 reports the formation of such an alcoholate.

[19] With respect to table 3.1, the lower Q ratio allowed a slower reaction whose monitoring with time, was facilitated.

[20] M. Selva, E. Militello and M. Fabris, *Green Chem.*, 2008, **10**, 73–79.

[21] It should be noted that both GlyC and glycerol gave no good responses at the GC/MS analysis. On the other hand, the ^{1}H NMR analysis of the crude mixture of the reaction of aniline with GlyC, was useless to determine the presence of glycerol whose signals (if present) were overlapped to those of compounds **3a**, **4a**, and of GlyC itself.

[22] Under the conditions of figure 3.1, an additional experiment was also carried out by adding glycerol (0.25 g, 2.7 mmol) at the very beginning of the reaction: after 120 min, no reaction took place.

[23] The selectivity towards compound **3a** was calculated using the expression: [(**3a**)/Σ(all products)]x100, where (**3a**) and Σ(all products) were the % amount, determined by GC, of compound **3a** and of all reaction products, respectively.

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[25] Unfortunately, during FCC separation, compounds **4b**-**5b**, **6c**, **4d**, and **6d** were eluted together with glycerol and (unreacted) glycerol carbonate (see also ref. 16).

[26] Alkali metal-exchanged Y- and X-faujasites are a class of zeolites in which the negative charge of the aluminosilicate framework is counterbalanced by an alkali metal cation. For example, NaY and NaX faujasites possess the same 3D-structure, but they differ for the Si/Al content: their general formulas are $Na_{56}[(AlO_2)_{56}(SiO_2)_{136}]\cdot 250H_2O$ and $Na_{86}[(AlO_2)_{86}(SiO_2)_{106}]\cdot 264H_2O$, respectively. For morphological details and other properties, see: (a) G. C. Bond, *Heterogeneous Catalysis Principles and Applications*, Clarendon Press, Oxford, 2nd edn, 1987; (b) D. Barthomeuf, *J. Phys. Chem.*, 1984, **88**, 42–45.

[27] Such a different performance between X- and Y-faujasites has been observed by us in several reactions involving dialkyl carbonates as alkyalting agents: see for example, references 5.

[28] By contrast to the reaction of primary aromatic amines with dimethyl-, diethyl-, dibenzyl-, and ethylene-carbonate, the K_2CO_3-catalysed reaction of aniline and GlyC does not afford the corresponding carbamate ($PhNHCO_2R$). The formation of an insoluble alcoxide salt (scheme 3.5) is likely to account for this behavior.

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[31] References 27 and 29 detail the adsorption of aniline and dimethyl carbonate (DMC), and of primary alcohols, respectively, over a NaY faujasite. Scheme 3.10 offers a plausible hypothesis for the case of an higher homologue of DMC, such as GlyC.

[32] Ref. 6 reports a similar reaction: the attack of an anionic nucleophile (an alkoxide) to the C5 of GlyC is described.

[33] Alkali metal faujasites of both X- and Y-type, are rather hygroscopic solids; see: F. Toda in *Organic Solid State Reactions*, Kluwer Acad. Pub., 2002.

[34] (a) M. Selva, A. Bomben and P. Tundo, *J. Chem. Soc., Perkin Trans 1*, 1997, 1041-1045; (b) M. Selva, P. Tundo and A. Perosa, *J. Org. Chem.*, 2001, **66**, 677-680.

[35] (a) E. Leclercq, A. Finiels and C. Moreau, *J. Am. Oil Chem. Soc.*, 2001, **78**, 1161-1165; (b) M. J. Ramos, A. Casas, L. Rodrıguez, R. Romero and A. Perez, *Appl. Catal. A: General*, 2008, **346**, 79–85.

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[36] Polar protic molecules, particularly alcohols, strongly interact with polar surfaces of aluminosilicates (as zeolites are). See, refs. 5c and 30.

[37] (a) J.-M. Clacens, Y. Pouilloux, J. Barrault, C. Linares and M. Goldwasser, *Stud. Surf. Sci. Catal.*, 1998, **118**, 895–902; (b) J.-M. Clacens, Y. Pouilloux and J. Barrault, *Applied Catalysis, A: General*, 2002, **227**, 181–190; (c) L. Ott, M. Bicker and H. Vogel, *Green Chem.*, 2006, **8**, 214–220; (d) S.-H. Chai, H.-P. Wang, Y. Liang and B.-Q. Xu, *J. Catal.*, 2007, **250**, 342–349; (b) L. Ning, Y. Ding, W. Chen, L. Gong, R. Lin, Y, Lü and Q. Xin, *Chin. J Catal.*, 2008, **29**, 212–214; (d) Y. K. Krisnandi, R. Eckelt , M. Schneider, A. Martin and M. Richter, *ChemSusChem.*, 2008, **1**, 835-844.

[38] (a) Z. Wu, M. Razzak , I. G. Tucker and N. J. Medlicott, *J. Pharm. Sci.*, 2005, **94**, 983-993; (b) H. Kilambia, E. R. Beckela, K. A. Berchtoldb, J. W. Stansburyc and C. N. Bowman, *Polymer*, 2005, **46**, 4735–4742.

[39] The ^{1}H NMR (400 MHz) analysis of commercial GlyC shows the presence of minor signals not belonging to the structure of compound **1a**. At the moment however, the resolution of such peaks is not sufficient for a structural characterization.

[40] (a) R. Szostak in *Handbook of Molecular Sieves: Structures*, Springer, 1992, p. 281; (b) U. Lohse, I. Pitsch, E. Schreier, B. Parlitz and K.-H. Schnabel, *Appl. Catal. A: General*, 1995, **129**, 189-202. In particular, under our calcination conditions (dried air), the dealumination of the faujasites is not expected since this process requires a highly-rich steam atmosphere (see: (c) T. H. Fleisch, B. L. Meyers, G. J. Ray, J. B. Hall and C.L. Marshall, *J. Catal.*, 1986, **99**, 117-125; (d) V. Semmer-Herledan, L. Heeribout, P. Batamack, C. Doremieux-Morin, J. Fraissard, A. Gola and E. Benazzi, *Microporous Mesoporous Mater.*, 2000, **34**, 157–169).

[41] Once the zeolites are handled through standard procedures for both their thermal treatment and their re-use in the reactions of GlyC, the level of the hydration of the catalysts should be reproducible for each set of solids (calcined and evacuated, respectively). A more in-depth investigation would require the evaluation of the kinetics of the water diffusion into zeolites [see: (a) C. Parravano, J. D. Baldeschwieler and M. Boudart, *Science*, 1967, **155**, 1535-1536; (b) H. Paoli, A. Methivier, H. Jobic, C. Krause, H. Pfeifer, F. Stallmach and J. Karger, *Microporous Mesoporous Mater.*, 2002, **55**, 147–158]. This last aspect however, is rather beyond the scope of this work.

[42] Steric effects should be considered also for *p*-chloroaniline: however, the steric and electronic contributions of the Cl^{-} substituent are hardly distinguishable.

[43] http://www.sigmaaldrich.com

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[44] (a) W. A. Gregory, D. R. Brittelli, C. L. J. Wang, M. A. Wuonola, R. J. McRipley, D. C. Eustice, V. S. Eberly, A. M. Slee, M. Forbes, and P. T. Bartholomew, *J. Med. Chem.*, 1989, **32**, 1673-1681; (b) M. G. Ladona, J. Bujons, A. Messeguer, C. Ampurdanés, A. Morató, and J. Corbella, *Chem. Res. Toxicol.*, 1999, **12(12)**, 1127-1137; (c) Z. Lu and R. J. Twieg, *Tetrahedron Lett.*, 2005, **46**, 2997–3001.

[45] By contrast, it should be noted that methylations with methyl halides or dimethyl sulfate, and carbonylations with phosgene always generate stoichiometric amounts of inorganic salts to be disposed of, they usually require additional solvents, and their exothermal outcome often needs a careful control.

[46] (a) T. Kondoh, Y. Okada, F. Tanaka, S. Asaoka, S. Yamamoto and A. Sachio (Chiyoda Corporation), USP 5436362 (July 25, 1995); (b) J. F. Knifton and R. G. Duranleau, *J. Mol. Catal.*, 1991, **67**, 389-399.

[47] Z. Kui, H. Changhua, Z. Huaibin, X. Shouhe, L. Shangyuan, X. Dong and L. Hexuan, *Appl. Catal.*, 1998, **166**, 89-95.

[48] Other compounds, whose total amount was usually less than 10%, were detected by GC/MS analyses: their structures were not assigned. The co-product ethylene glycol was also observed, but its GC signal showed poor intensity and resolution. It was excluded from the integration. The formation of 2-(hydroxy)ethyl methyl carbonate (**10**) was reported also in the transesterification of ethylene carbonate with MeOH, catalyzed by bases (see ref. 46).

[49] In the presence of different heterogeneous catalysts, methanol is often reported as a good *N*-methylating agent of aniline. (see, for example: (a) N. Nagaraju and G. Kuriakose, *New J. Chem.*, 2003, **27**, 765 – 768; (b) M. A. Aramendia, V. Borau, C. Jimenez, J. M. Marinas and F. J. Romero, *Appl. Catal. A: General*, 1999, **183**, 73-80; (c) T. Oku, Y. Arita, H. Tsuneki and T. Ikariya, *J. Am. Chem. Soc.*, 2004, **126**, 7368 – 7377). However, high reaction temperatures of 250-500 °C are usually required.

[50] Methanol and more generally, polar protic solvents strongly interact with polar surfaces of aluminosilicates (as zeolites are). Consequently, organic reactions catalysed by faujasites, are often inhibited in this media (see, for example ref. 5c).

[51] M. Selva and A. Perosa, *Green Chem.*, 2008, **10**, 457-464.

[52] Compound **16a** (*N*-phenylmorpholine) was plausibly formed by the dehydration of the bis-*N*-alkyl derivative [$PhN(CH_2CH_2OH)_2$] of aniline. Zeolites are reported to catalyse the dehydration of diols: (a) W. Hoelderich, M. Schwarzmann, U S Pat. 4904806, February 27, 1990; (b) C. Moreau, M. Naceur Belgacemb and A Gandini, *Top. Catal.*, 2004, **27**, 11-30.

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[53] In presence of faujasites, primary aromatic amines react with dialkyl carbonates to yield selectively the corresponding mono-*N*-alkyl amines (ArNHR). Good examples for both the case of DMC and of ethylene carbonate, are reported in refs 34a and by: (a) M. Aresta and E. Quaranta, *Chemtech*, 1997, 32-40; (b) P. Tundo, M. Selva and A. Bomben, *Org. Synth.*, 1999, **76,** 169-177; (c) A. Bomben, M. Selva, P. Tundo and L. Valli, *Ind. Eng. Chem. Res.*, 1999, **38**, 2075-2079; (d) A. B. Shivakar, S. P. Gupte and R. V. Chaudari, *Synlett*, 2006, **9**, 1374-1378.

[54] The polarity of cyclohexane, 1,2-dimethoxyethane, and *N*,*N*-dimethylformamide was determined by the values of the corresponding dielectric constants (ε, table 3.8) taken from *Handbook of Chemistry and Physics*, D. R. Lide, Ed; 75th Ed., CRC Press, 1994.

[55] (a) Y. Watanabe and T. Tasumi, *Micr. Mes. Mat.*, 1998, **22**, 399-407; (b) M. S. Han, B. G. Lee, B. S. Ahn, K. Y. Park and S. I. Hong, *React. Kinet. Catal. Lett.*, 2001, **73**, 33-38; (c) H. Cui, T. Wang, F. Wang, C. Gu, P. Wang and Y. Dai, *Ind. Eng, Chem. Res.*, 2003, **42**, 3865-3870; (d) B. M. Bhanage, S.-I. Fujita, Y. Ikushina and M. Arai, *Appl. Catal. A.: General*, 2001, **219**, 259-266.

[56] The possible reaction of aniline at the carbonyl carbon of both ethylene carbonate and DMC, which would produce urethanes, is ruled out by the nature of faujasites. The acid-base features and steric requisites of these catalysts, allow the exclusive *N*-alkylations of aromatic amines (see also refs. 5 and 53a-c).

[57] T. Beutel, *J. Chem. Soc., Faraday Trans.*, 1998, **94**, 985.

[58] A similar trend of reactivity has been found also in the reaction of mixtures of ethylene carbonate / dimethyl carbonate with $LiPF_6$: S. E. Sloop, J. K. Pugh, S. Wang, J. B. Kerr and K.Kinoshita, *Electrochem. Solid-State Lett.*, 2001, **4**, A42-A44.

[59] (a) M. Aresta and E. Quaranta, *Tetrahedron*, 1991, **47**, 9489-9502; (b) M. Selva, C. A. Marques and P. Tundo, *J. Chem. Soc. Perkin Trans. 1*, 1994, 1323-1328; (c) Y. Ono, *J. Mol. Cat.*, 1994, **91**, 399-405; (d) A. Bomben, C. A. Marques, M. Selva and P. Tundo, *Tetrahedron*, 1995, **51**, 11573-11580; (e) A. Perosa, M. Selva, P. Tundo and F. Zordan, *Synlett*, 2000, **2**, 272-274; (f) M. Selva, P. Tundo, A Perosa and F. Dall'Acqua, *J. Org. Chem.*, 2005, **70**, 2771-2777.

[60] GC/MS analyses of reactions of table 3.6, unequivocally prove the formation of both diethyl and dipropyl carbonates. These compounds have been identified by comparison to authentic samples.

[61] B. M. Bhanage, S.-I. Fujita, Y. Ikushina and M. Arai, *Appl. Catal. A.: General*, 2001, **219**, 259-266.

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[62] (a) P. Chin-Min Mao, J. F. Mouscadet, H. Leh, C. Auclair and L. F. Hsu, *Heterocycles*, 2001, **55**, 1263-1270; (b) S. Heilporn, F. Broeders, D. Daloze and Breakman, *Bull. Soc. Chim. Belg.*, 1994, **103**, 309-319; (c) B. D. Palmer, W. R. Wilson, S. M. Pullen and W. A. Denny, *J. Med. Chem.*, 1990, **33**, 112-121; (d) M. H. Benn, L. N. Owen and A. M. Creighton, *J. Chem. Soc.*, 1958, 2800-2810.

[63] www.sigmaaldrich.com: the safety sheets (MSDS) of ethylene and propylene oxide report T labels.

[64] T. Yoshino, S. Inaba, H. Komura and Y. Ishido, *J. Chem. Soc., Perkin Trans. I*, 1977, 1266-1272.

[65] (a) Z. Y. Sun, E. Botros, A. D. Su, Y. Kim, E. Wang, N. Z. Baturay and C. H. Kwon, *J. Med. Chem.*, 2000, **43**, 4160–4168; (b) F. Jourdain and J. C. Pommelet, *Tetrahedron Lett.*, 1994, **35**, 1545-1548; (c) H. Adkins and R. M. Simington, *J. Am. Chem. Soc.*, 1925, **47**, 1687-1689.

[66] The safety sheets (MSDS) of ethylene bromo- and chloro-hydrin report a T and T+ labels, respectively (www.sigmaaldrich.com).

[67] (a) B. Denise and R. P. A. Sneeden, *Chemtech*, 1982, **108**; (b) M. Lichtenwalter and J. Cooper, U.S. Patent 2,773,070, 1956. It should be noted that also the addition of CO_2 to glycol has been examined for the synthesis of EC ((c) J. I. Kadokawa, H. Habu, S. Fukamachi, M. Karasu, H. Tagaya and K. Chiba, *J. Chem. Soc., Perkin Trans. 1*, 1999; 2205 – 2208). At the moment however, the method has only a speculative interest.

[68] (a) J. H. Clements, *Ind. Eng. Chem. Res.*, 2003, **42**, 663-674; (b) A. A. G. Shaikh and S. Sivaram, *Chem. Rev.*, 1996, **96**, 951-976.

[69] E. Gulbins and K. Hamann, *Chem. Ber.*, 1966, **99**, 55-61.

[70] M. Selva, *Synthesis*, 2003, **18**, 2872-2876.

[71] M. Selva and M. Fabris, *Green Chem.*, 2009, **11**, 1161 – 1172.

[72] (a) A. Loris, A. Perosa, M. Selva and P. Tundo, *J. Org. Chem.*, 2004, **69**, 3953-3956; (b) M. Selva, A. Perosa, P. Tundo and D. Brunelli, *J. Org. Chem.*, 2006, **71**, 5770-5773.

[73] In the presence of tryglime as solvent, at 160 °C, the same uncatalysed process was reported to proceed to a much lower extent (the yield of **13a** was 4% after 2 hours; ref. 53). While, at 176 °C and under solventless conditions, the reaction of aniline and ethylene carbonate catalysed by LiCl, proceeded through competitive *N*-alkylation and *N*-carboxyalkylation processes, to produce mixture of compounds **13a** and **18a** (ref. 69).

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[74] Although the increase of the amount of **PIL1** (figure 3.6), favoured the reaction rate, the Q ratio was set 0.1 for practical reasons: the separation of the IL from the reaction products was easier and interferences in the GC/MS analyses were greatly limited.

[75] FCC however, was not optimised.

[76] G. Gattow and W. Behrendt, *Angew. Chem., Int. Ed.*, 1972, **11**, 534-535.

[77] Plausibly, HBr assisted the dehydration of **17a** via an initial *O*-protonation followed by an internal nucleophilic displacement releasing water.

[78] In principle, an additional couple of diastereoisomers was expected, coming from the double attack of the amine at the C4 of PC. However, plausibly for steric reasons, these compounds were never observed.

[79] (a) O. Sereda, S. Tabassum and R. Wilhelm in *Asymmetric Organocatalysis, Topics in Current Chemistry,* Springer, Berlin-Heidelberg, 2009; (b) M. Terada and M. Kouchi, *Tetrahedron,* 2006, **62**, 401–409; (c) X. Wang and S.-K. Tian, *Tetrahedron Lett.,* 2007, **48**, 6010–6013.

[80] (a) A. J. Kirby and S. G. Warren In *The Organic Chemistry of Phosphorus*, Elsevier: Amsterdam, London, New York, 1967; (b) J. Chen, Y. Chen, Y.-L. Niu, H. Fu and Y.-F. Zhao, *J. Mass Spectrom.*, 2002, **37**, 934–939.

[81] H. Schmidbaur, W. Buchner and F. H. Kohler, *J. Am. Chem. Soc.*, 1974, **96**, 6208-6210.

[82] The size of the catalyst appears rather important to control the chemoselectivity: for instance, if a small Lewis acid such as LiCl is used as a catalyst (see ref. 69), anilines are able to attack both alkyl and carboxyl carbons of EC.

[83] D. Belli Dell'Amico, F. Calderazzo, L. Labella, F. Marchetti, and G. Pampaloni, *Chem. Rev.*, 2003, **103**, 3857-3897.

[84] T. Yoshino, S. Inaba, H. Komura and Y. Ishido, *J. Chem. Soc., Perkin Trans 1*, 1977, 1266-1272.

[85] E. V. Anslyn and D. A. Dougherty In *Modern Physical Organic Chemistry,* University Science Books, 2006, Capt. 8.

[86] D. Aurbach, Y. Gofer, M. Ben-Zion and P. Aped, *J. Electroanal. Chem.,* 1992, **339**, 451-47.

CHAPTER 4

Organic Carbonates as Green Reactants for C-O Bond Forming Reactions

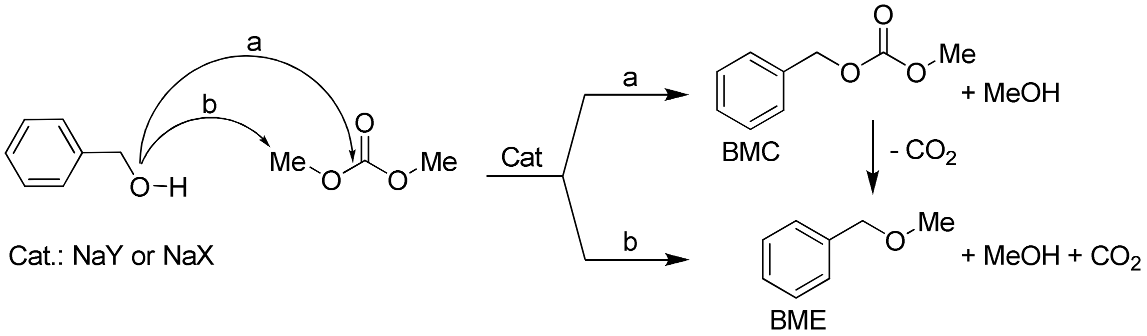
- Dialkyl Carbonates -

4.1 Decarboxylation of Dialkyl Carbonates to Dialkyl Ethers over Alkali Metal-exchanged Faujasites

4.1.1 Introduction

As mentioned in previous chapters (1 and 3), light dialkyl carbonates ($ROCO_2R$, DAlCs, R = C1-C3), especially dimethyl carbonate (DMC), are excellent green substitutes of toxic reagents and solvents.[1] In particular, the combination of DAlCs with a class of zeolites, namely alkali metal exchanged faujasites as catalysts,[2] has proven to be successful to improve the outcome of several *O*- and *N*-alkylation reactions of different nucleophiles.[3] Schemes 1.13, 1.14, 3.2 and 3.13 detail examples of highly selective and chemoselective alkylation processes carried out in the presence of NaY or NaX faujasites.

The investigation of these reactions indicates that the formation of the desired alkylation products may take place through two concurrent mechanisms. This is especially true for alcohols whose etherification with DAlCs over faujasites, proceeds through a sequence of tetrahedral and S_N2-type intermediates followed by a decarboxylation reaction.[3d] Scheme 4.1 describes the reaction of benzyl alcohol with DMC.



Scheme 4.1

Initially, benzyl methyl carbonate (BMC) and benzyl methyl ether (BME) originate from the attack of benzyl alcohol at both the carbonyl and methyl carbons of DMC [paths (a) and (b), respectively]. Then, if the mixture is allowed to react further, BMC undergoes a quantitative decarboxylation and BME is obtained as a sole product in isolated yields up to 96%. An intriguing question arises from this example: if reaction conditions allow BMC to lose CO_2, then would the decarboxylation of DMC be possible as well? In addition, this opens a rather more general window on the scope and limitations of the combined use of dialkyl carbonates and faujasites: in fact, higher homologues such as DEC and DPrC, would be expected to react similarly to DMC.

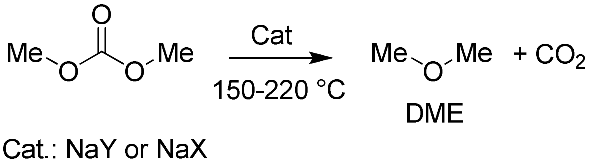
It should be noted that the decarboxylation of organic carbonates is documented in the literature: for example, Pd-complexes catalyze the transformation of allyl alkyl carbonates to unsaturated esters and ketones,[4] thermal treatment and/or basic/radical initiators induce the loss of CO_2 from carbonate polymers and alkyl aryl carbonates to produce mixtures of olefins, alcohols and polyether diols,[1a,5] hydrotalcite or alumina catalysts allow the synthesis of dialkyl ethers from heavy (C_{10}-C_{21}) dialkyl carbonates.[6] However, to the best of our knowledge, an investigation of the behavior of light dialkyl carbonates with respect to the decarboxylation reaction, has never been reported particularly in the presence of zeolite systems. The investigation presented here details a systematic study of such a reaction using dimethyl, diethyl-, and dipropyl- carbonates (DMC, DEC, and DPrC, respectively) as substrates and alkali metal-exchanged Y and X faujasites (NaY and NaX) as catalysts. The corresponding ethers have been observed in all cases though the onset of the decarboxylation is affected by the structure of the carbonate and the nature of the zeolites. For a more complete comparison, also different catalysts such as hydrotalcite and K_2CO_3, and reagents such as dioctyl- and glycerol- carbonates have been examined. A mechanistic hypotheses has been formulated on the basis of the adsorption of DMC over the NaY surface.

4.1.2 Results

I. Reaction of dimethyl carbonate over faujasites, hydrotalcite, and K_2CO_3. Four different faujasites, namely MY (M = Li, Na, Cs) and NaX were used as catalysts. Two of them, NaY and NaX were commercially available samples. LiY and CsY were prepared through conventional ion exchange reactions, starting from NaY and LiCl or CsCl as precursors.[7] Hydrotalcite (HT: KW2000, $Mg_{0.7}Al_{0.3}O_{1.15}$) and K_2CO_3 were also from commercial suppliers.

DMC was used as a model substrate to begin the investigation. Before each reaction, the catalysts (faujasites, hydrotalcite, and K_2CO_3) were dried under vacumm (8 mbar) at 70 °C, overnight. Initial experiments were carried out in a 120 mL-autoclave charged with a mixture of DMC (10 mL, 119 mmol) and the faujasite (0.6 g of NaY or NaX; the weight ratio, Q, catalyst:DMC was 0.056), and heated under stirring, for 6 hours at different temperatures of 150-220 °C.[8] Under these conditions, hydrotalcite (HT: 0.6 g) was also tested as a catalyst.[9] Once cooled to rt, a residual pressure up to 20 bar was measured inside the reactor.

In order to recover the gaseous products of the reaction, the autoclave was purged by a low temperature trap-to-trap apparatus (see experimental for further details). The gaseous mixture was collected in an air-tight drechsel bottle (200 mL) and weighed. Both the gas phase and residual liquid in the autoclave were analysed by GC/MS. In the first one (gas), only two products, CO_2 and dimethyl ether (DME), were observed.[10] This unambiguously proved that the DMC underwent a decarboxylation reaction (scheme 4.2).



Scheme 4.2

The progress of such a reaction was evaluated from the total (weighed) amounts of CO_2 and DME: this allowed to calculate the conversion of DMC in each experiment. The results are reported in figure 4.1.

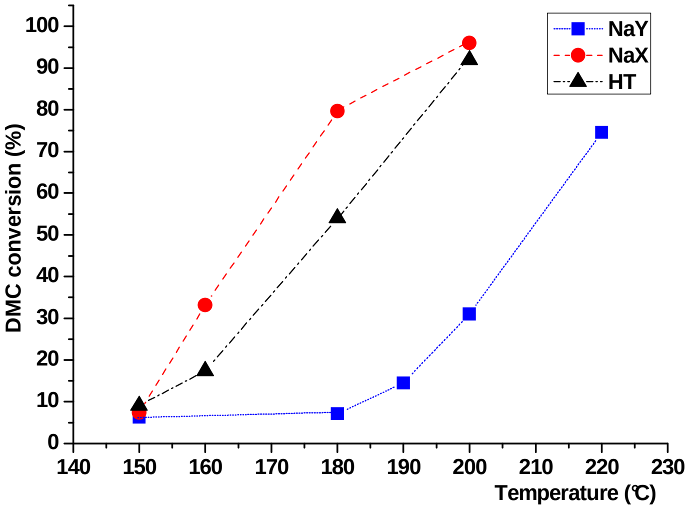


Figure 4.1. Decarboxylation of DMC over sodium faujasites (NaY and NaX) and hydrotalcite (HT) at different temperatures, and after 6 hours

Although the three catalysts were all effective for the decarboxylation of DMC, their performance was quite different. For example, at 180 °C, the reaction conversion was 80%, 54%, and 7%, over NaX, HT, and NaY, respectively. In the same order, at 200 °C, the unreacted DMC was 4%, 8%, and 31%. These results indicated a preliminary trend of catalytic activity: NaX>HT>NaY.

The GC/MS analysis of the residual DMC in the autoclave showed traces of methanol whose amount did not exceed 3% even at high conversions (up to 90%). The presence of the alcohol was ascribed to hydrolysis of the starting carbonate, due to water adsorbed on the catalysts.[6]

The comparison of different catalysts was then extended to Li- and Cs-exchanged Y faujasites and K_2CO_3.[11] Under the conditions above described (DMC: 10 mL; weight ratio Q = cat/DMC = 0.056), reactions were performed at 200 °C for 6 hours. An additional experiment was carried out in the absence of any catalyst. The results are reported in figure 4.2 where for a more complete view, also the cases of NaY, NaX and HT are included.

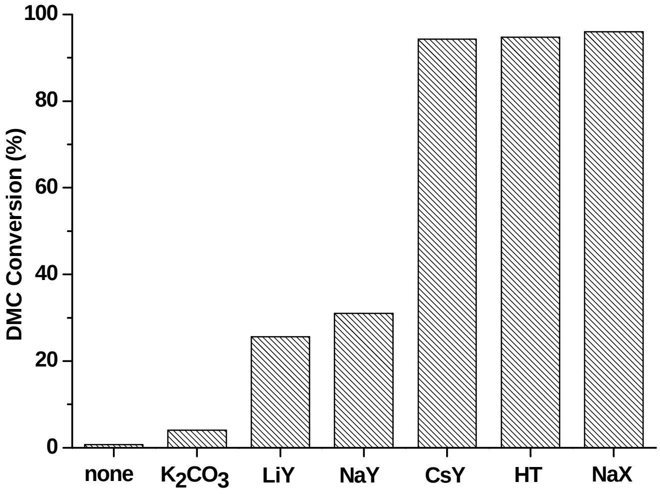


Figure 4.2. Decarboxylation of DMC over different catalysts, at 200 °C

DMC by itself was rather stable to the decarboxylation. The reaction was observed only in the presence of a catalyst, and in all experiments, CO_2 and dimethyl ether were the sole detected products (scheme 4.2). However, the outcome was greatly affected by the nature of the added solid: the conversion of DMC was very modest (4%) on K_2CO_3, while it progressively raised from 26% to 94% with the increase of the basic character of Y-faujasites, *i.e.* from LiY to NaY and to CsY, respectively. This latter (CsY) offered an activity comparable to that of NaX and HT.

II. Effect of the faujasite amount and of the reaction time on the decarboxylation of DMC. Commercial NaY and NaX catalysts were chosen to continue the investigation. Two sets of experiments [(a) and (b)] were carried out: (a) at 200 °C and for 6 hours, DMC (10 mL, 119 mmol) was set to react with increasing quantities of both NaY and NaX, by varying the weight ratio Q = cat:DMC from 0.015 to 0.084; (b) at 200 °C, a mixture of DMC (10 mL, 119 mmol) and the catalyst (NaY or NaX; Q = 0.056), was set to react at different times, from 1 to 18 hours, respectively. The results are shown in figure 4.3 (a) and (b), respectively. Both sets of reactions confirmed that NaX was by far, a more active catalyst than NaY.

Figure 4.3a [left; set (a)] proved that the decarboxylation of DMC was a truly catalytic process affected by the zeolite loading: the reaction conversion smoothly increased from 7 to ~ 50% as the NaY amount was augmented by a factor of 6 (Q = 0.084). By contrast, even with a modest Q ratio of 0.028, the use of NaX allowed a substantially quantitative conversion. Figure 4.3b [right; set (b)] showed the effect of the reaction time: at a Q ratio of 0.056, the decarboxylation process was complete in ~ 3 hours in the presence of NaX (red profile), while even after 18 hours, 20% of the initial DMC was still unreacted when NaY was the catalyst (blue profile). The conversion of DMC was always determined by the weighed amounts of the reaction products (CO_2 and DME).

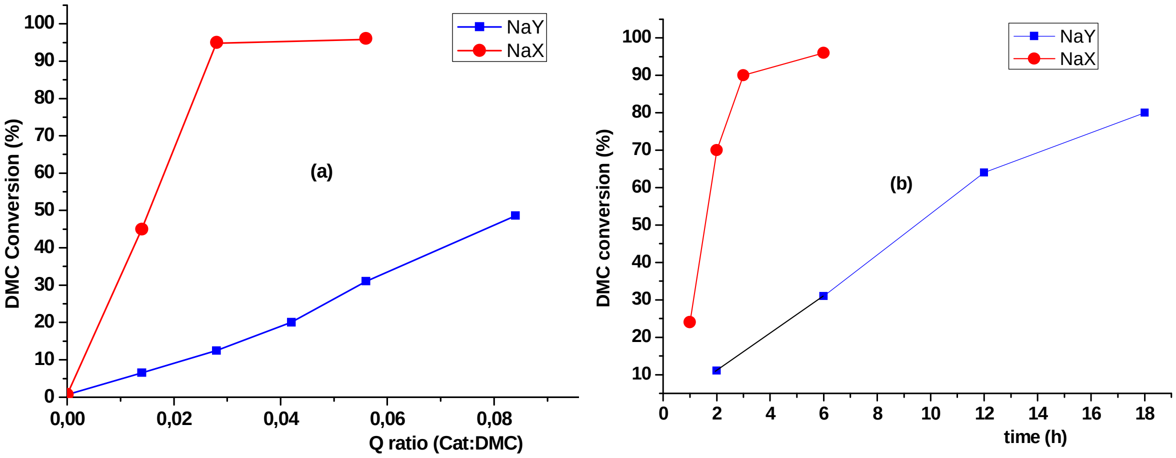


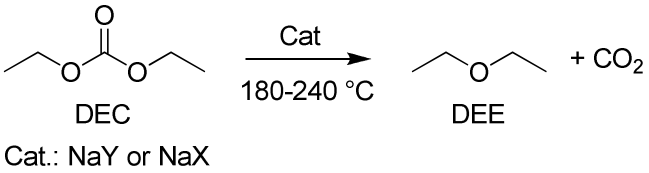
Figure 4.3. The decarboxylation of DMC carried out at 200 °C, over NaY and NaX.(a) Effect of the catalyst amount; (b) effect of the reaction time (Q = 0.056)

In order to test whether the thermal activation of faujasites affected their performance, two aliquots of NaY were heated in a stream of dry air (10 mL/min), at 200 and 400 °C, respectively, for 4 hours. Then, these samples were used as catalysts to carry out two additional reactions with DMC at 200 °C, for 6 hours. The weight ratio Q= NaY:DMC was set to 0.056. In both cases, the reaction conversion (~ 30%) did not appreciably differ from that evaluated when the catalyst was simply dried at 70 °C (compare figures 4.1, 4.2, and 4.3a).

III. Competitive methylation and decarboxylation reactions over NaX. Figures 4.1-3 and table 4.1 proved that extensive decarboxylation of DMC took place under the same conditions used to carry out several methylation reactions mediated by DMC and catalyzed by faujasites (scheme 4.1). This led to the plausible hypothesis that dimethyl carbonate could exhibit its methylating activity while, simultaneously, it underwent a decarboxylation reaction. An experiment was performed to verify such an aspect. A mixture of benzyl alcohol (5.0 mL, 48.4 mmol), DMC (15.0 mL, 178.2 mmol), and NaX (0.52 g; Q = cat:DMC = 0.032) was set to react at 200 °C, in a 120 mL-autoclave, for 12 hours. Once cooled to rt, the reactor was purged according to the procedure above mentioned (figure 4.1): a mixture of gaseous products (13.3 g) composed of CO_2 and DME, was recovered. The GC/MS analysis of the residual slurry content of the reactor revealed that the starting benzyl alcohol was totally converted as shown in scheme 4.1.[12] These results confirmed the competitive occurrence of the decarboxylation of DMC and the *O*-methylation of the alcohol: the two processes consumed ~70% and 25%, respectively, of the initial DMC amount.

IV. Reaction of diethyl- and dipropyl-carbonates over Na-faujasites. The reactions of higher homologues of DMC such as diethyl- and dipropyl- carbonates (DEC and DPrC, respectively), were investigated in the presence of NaX and NaY faujasites. Before each run, both catalysts were carefully dried under vacumm (8 mbar) at 70 °C, overnight. Experiments were carried out in the same 120 mL-autoclave used for DMC.

In the case of DEC, a mixture of the carbonate (10 mL, 83 mmol) and the faujasite (0.55 g of NaY or NaX; the weight ratio, Q, catalyst:DEC was 0.056), was set to react for 6 hours at different temperatures of 180-240 °C. Once cooled to rt, the reactor was dipped in a cooling bath at -55 °C, and vented. A GC/MS analysis of the released gas showed the sole presence of CO_2. The autoclave was allowed to return gradually to ambient temperature, and the reaction mixture was analyzed by GC/MS. Diethyl ether (DEE) was observed as the main product (90-93%), confirming that also the decarboxylation of DEC took place over Na-faujasites (scheme 4.3).



Scheme 4.3

Minor amounts (3-5%) of ethanol were detected as a by-product. Figure 4.4 reports the conversion of DEC and the selectivity towards the formation of DEE (both parameters evaluated by GC/MS), *vs* the reaction temperature.

Two aspects emerged: *i*) the performance of the two faujasites resembled that shown for DMC. At comparable conditions, the DEC conversion was always higher over NaX with respect to NaY (black profiles); *ii*) the onset of the decarboxylation of DEC required a temperature of ~ 30 °C higher than that for DMC (compare figure 4.1). In other words, diethyl carbonate appeared less prone than DMC, to the loss of CO_2. The selectivity to DEE was on average, very good

(>90%, blue profiles); however, as for DMC, a minor hydrolysis of DEC due to water adsorbed on the faujasites, yielded ethanol as a co-product.

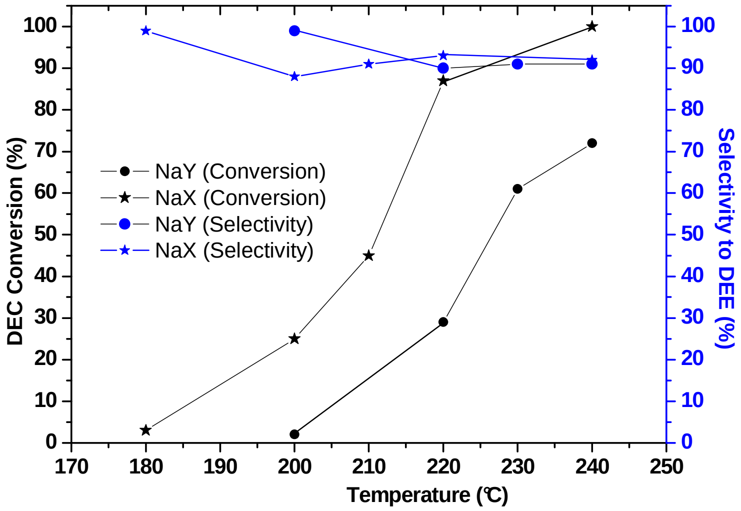
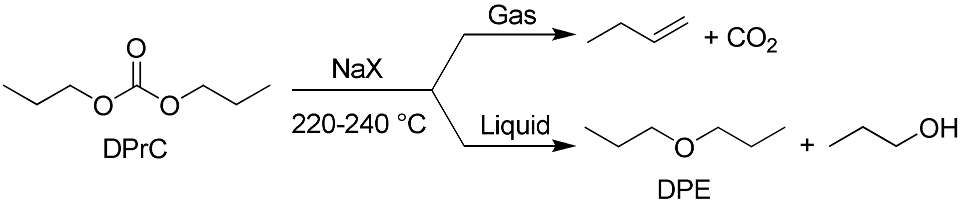


Figure 4.4. Decarboxylation of DEC over NaY and NaX faujasites

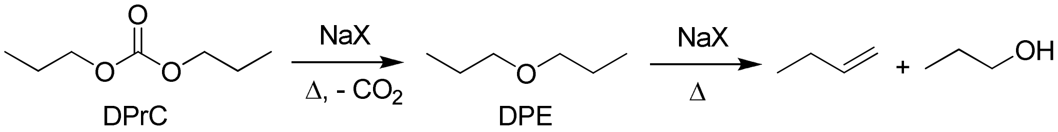
Dipropyl carbonate (DPrC) was prepared by adjusting a general procedure reported for the synthesis of dialkyl carbonates.[13] The reaction of DPrC was carried out using the procedure above described for DEC, only in the presence of the more active NaX as the catalyst: the carbonate (8.8 mL, 56 mmol) and the faujasite (0.3 g of NaX; the weight ratio, Q, catalyst:DPrC was 0.036), was set to react at temperatures of 220 and 240 °C for 6 and 12 hours, respectively. The GC/MS analysis of the reaction products showed that the outcome of these experiments was remarkably different from that of DMC and DEC. DPrC underwent the expected decarboxylation reaction, though, the process was no longer selective on formation of the corresponding ether. Regardless of the conversion of DPrC, the gas vented from the autoclave was a mixture of CO_2 and propylene, while liquid products were *n*-propanol and di-*n*-propyl ether (DPE) (scheme 4.4).



Scheme 4.4

At 220 °C, after 6 hours, the liquid phase contained unreacted DPrC (61%) along with comparable amounts of *n*-PrOH and DPE (22 and 17%, respectively). The gas phase (2.0 g) was composed by CO_2 and propylene.[14] Both propylene and *n*-PrOH formed even at a moderate conversion of the starting carbonate.

At 240 °C, the conversion of DPrC was complete after 12 hours: a gaseous mixture (3.70 g) of propylene and CO_2, and a liquid mixture of *n*-propanol (62%) and of DPE (38%) were recovered. A first observation was that the presence of such a remarkable amount *n*-propanol hardly derived from the hydrolysis of DPrC. If so, the required quantity of water (0.31 g, 17 mmol) adsorbed on the catalyst would have been comparable to the weight of the catalyst itself. A plausible explanation for the formation of both propanol and propylene was instead, the cracking of DPE according to scheme 4.5:[15]



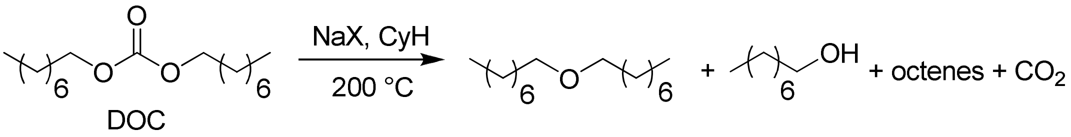
Scheme 4.5

This hypothesis was substantiated by the following considerations. The full decarboxylation of DPrC corresponded to the release of 56 mmol (2.45 g) of CO_2 which, from the total weight of gaseous products, allowed to calculate the formation of 30 mmol (1.25 g) of propylene. The stoichiometry of scheme 4.5 indicated that the same molar amount (30 mmol) of *n*-propanol had to be present in the liquid products, thereby implying a residual (liquid) DPE quantity of 26 mmol. Accordingly, a propanol:DPE ratio of 65:35 was obtained in good agreement with the GC ratio (62:38) observed for these two compounds.

V. Other dialkyl carbonates. To verify whether the decarboxylation over Na-faujasites occurred also for high molecular weight and/or viscous organic carbonates, two model compounds such as dioctyl carbonate (DOC) and glycerine carbonate (GlyC) were chosen.[16]

The reactions of DOC (2.0 g, 10.8 mmol) and GlyC (2.0 g, 17.0 mmol) were explored at 200 °C for 6 hours, in the presence of NaX faujasite (the weight ratio, Q, catalyst:carbonate, was 0.06). In both cases, the viscosity of the reagents required the use of a solvent: cyclohexane (9 mL) and dimethoxyethane (9 mL) were used for DOC and GlyC, respectively. Experiments were carried out according to the procedure detailed for DEC.

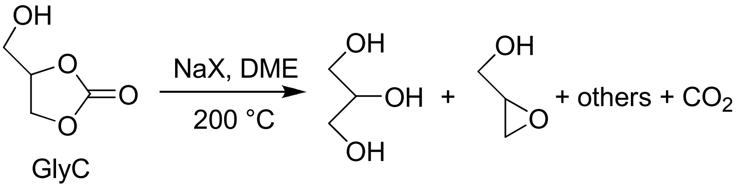
In the case of DOC, the GC/MS analysis of the reaction mixture showed the presence of unreacted carbonate (42%), dioctyl ether (7%) and comparable amounts of *n*-octanol and isomeric octenes (28 and 23%, respectively,[17]) (scheme 4.6).



Scheme 4.6

The good analogy with the behavior of DPrC (scheme 4.4) indicated that also the decarboxylation of DOC took place along with the plausible decomposition of the corresponding dioctyl ether to octanol and octenes.

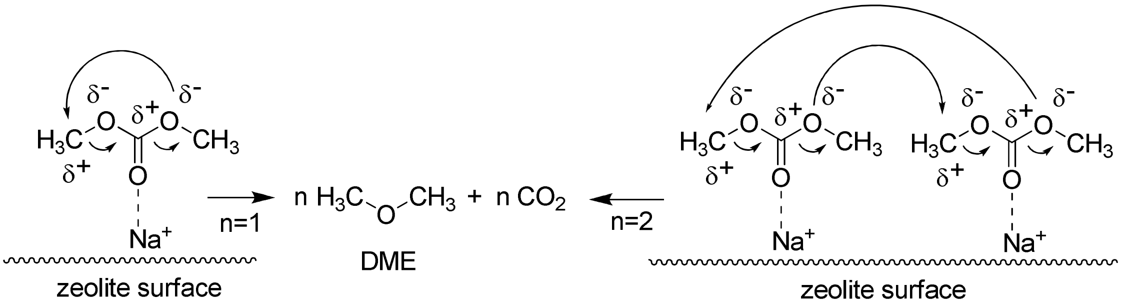
The reaction of GlyC instead, did not offer any clear interpretation: a complex mixture of several products was observed, most of them remained unidentified compounds. However, glycerol and trace amounts (5%) of glycidol were detected (scheme 4.7).



Scheme 4.7

4.1.3 Discussion

I. Decarboxylation of DMC and the nature of the catalyst. As described previously in chapter 3 (par. 3.2) the adsorption of DMC over Na-faujasites takes place via the formation of acid-base complex between oxygens of DMC and the Lewis acidic sites (Na^+) of the catalyst (scheme 3.22). Accordingly, both O-CH_3 and C-OCH_3 bonds of the carbonate are weakened. This fact implies an electrophilic activation of DMC after adsorption over faujasites, and in the last instance, it can explain the catalytic activity of such solids in methylation/carboxymethylation reactions (chapter 1 and 3). The mode of adsorption of DMC also offers an interpretation for the decarboxylation reaction here examined. Scheme 4.8 shows a plausible mechanistic hypothesis via polar intra- and inter-molecular reactions (left and right, respectively).



Scheme 4.8

The elongation of both O-CH_3 and C-OCH_3 bonds in the adsorbed DMC, favours their cleavage with the extrusion of CO_2; the recombination (through a nucleophilic attack) of $^{-\delta}OCH_3$ and $^{+\delta}CH_3$ groups produces dimethyl ether.

Whatever the mechanism, results of figures 4.1-3 leave no doubts about the superior catalytic efficiency of NaX with respect to NaY, for the decarboxylation of DMC. More specifically, according to the acid-base scale proposed by Barthomeuf *et al.*,[18] figure 4.2 shows that the increase of the reaction conversion is in good agreement with the trend of basic strength of faujasites: the more basic the zeolite (NaX~CsY>NaY≥LiY), the better its performance. The capacity of CO_2 adsorption by zeolites should be considered among the factors responsible for this behaviour. Alkali metal exchanged faujasites, particularly the cheap and safe NaX and NaY, are claimed as some of the most effective adsorbents for CO_2 storage,[19] whose affinity for CO_2 (under moderate pressures) has been demonstrated to increase with the basicity of the solids.[19,20] In our case, this feature is plausibly reflected on the ability of the catalyst to facilitate the release of carbon dioxide from DMC (scheme 4.2), thus favouring the overall process.

It should be noted however, that the basicity *per se* is not a sufficient requisite for a rapid decarboxylation reaction. Solid K_2CO_3 in fact, is a rather poor catalyst (figure 4.2) probably because of its inefficiency in the adsorption of DMC. By contrast, the good result with hydrotalcite (HT, figure 4.2) is ascribable to the moderate amphoteric properties exhibited by this material.[21]

II. The decarboxylation of higher dialkyl carbonates. In the case of diethyl- and dipropyl-carbonate, their adsorption over faujasites, their decarboxylation mechanism, as well as the relative catalytic activity of NaX and NaY (figure 4.4 for DEC), can be explained according to the discussion proposed for DMC.[22] The same holds for the selectivity in the reactions of DMC and DEC: the presence of alcohols (MeOH and EtOH) is compatible with minor hydrolysis of the two carbonates due to residual water adsorbed on the catalysts.[23] Major differences concern two aspects. *i*) The loss of CO_2 from both DEC and DPrC is more energy intensive than for DMC. The corresponding decarboxylation reactions take place conveniently at 240 and 200 °C, respectively (compare figures 4.1 and 4.4). This result is consistent with the general trend observed for a number of alkylation and carboxyalkylation processes mediated by dialkyl carbonates, where a dramatic drop of reactivity always occurs if DMC is replaced with heavier DAlCs (except for dibenzyl carbonate).[1,24] An increase of the steric hindrance around both alkyl and carbonyl carbons of the reacting carbonates accounts for this behavior. *ii*) The decarboxylation of DPrC is not a selective process. The expected product, dipropyl ether (DPE), forms along with two side compounds such as *n*-propanol and propylene (scheme 4.5). Although some hydrolysis of DPrC is possible, this reaction hardly accounts for the sizable amount of the alcohol (up to 62%) detected in the liquid mixture. Instead, the cracking of DPE catalyzed by NaX offers the most reasonable pathway to explain the presence of both *n*-propanol and propylene (scheme 4.5).[25] It should be noted that the conversion of C_5-C_{12} dialkyl ethers to the corresponding olefins has been claimed in the literature, by using alkali- and alkali earth-metal exchanged faujasites.[15]

This analysis is corroborated by the behavior of dioctyl carbonate (DOC). Although the presence of a reaction solvent (CyH) does not allow a direct comparison with DPrC, the reaction of DOC catalyzed by NaX yields dioctyl ether, *n*-octanol and isomeric octenes (scheme 4.7). At 180-250 °C, the decarboxylation of DOC has been described also with a hydrotalcite catalyst.[6] In this case however, reaction products were only dioctyl ether and *n*-octanol: Authors did not observe octene(s) and the formation of the alcohol (up to 20% at complete conversion) was attributed to the hydrolysis of the reactant carbonate.

4.1.4 Conclusions

The combined use of dialkyl carbonates (DAlCs) and alkali metal exchanged faujasites is a powerful synthetic tool to promote the alkylation of a number of *N*-, *O*-, and *S*-nucleophiles with excellent selectivities, above 95%, at quantitative conversions. However, this investigation demonstrates that the experimental conditions, especially the high temperature often required for such processes, may also trigger important side reactions: in the range of 150-240 °C, a decarboxylation of the reactant dialkyl carbonates may take place followed by other processes whose occurrence is strictly dependent on the nature of DAlCs. In particular, dimethyl- and diethyl-carbonate undergo the loss of CO_2 to produce the corresponding dimethyl- and diethyl-ethers in a very high yield. Heavier carbonates instead, give different products: dipropyl carbonate provides a mixture of dipropyl ether, *n*-propanol and propylene; likewise, dioctyl carbonate provides dioctyl ether, *n*-octanol, and octene(s), respectively. The mechanism of adsorption of DMC over Na-faujasites offers a rationale to discuss the onset of the decarboxylation reaction, while the acid-base properties of zeolites allow an interpretation for the catalytic activity of the tested catalysts: the more basic the faujasite, the better its capability to favor the release of CO_2 during the reaction, the better its performance. In the case of dipropyl- and dioctyl-carbonate, once decarboxylation takes place, cracking of the corresponding dialkyl ethers catalysed by Na-faujasites is a plausible pathway to explain the presence of alcohols and alkenes as co-products.

Overall, the results reported in this work, highlight two significant aspects: they elucidate the possible limitations of the use of dialkyl carbonates in the presence of faujasite catalysts and they offer boundaries to the reaction conditions, *i.e.* temperature and nature of the catalysts, in order to avoid side reactions by which an extensive consumption of DAlCs may take place, and to control the efficiency of the whole alkylation procedure. Finally, the formation of highly flammable ethers such as DME and DEE, may also pose a safety concern.

- Glycerol Carbonate -

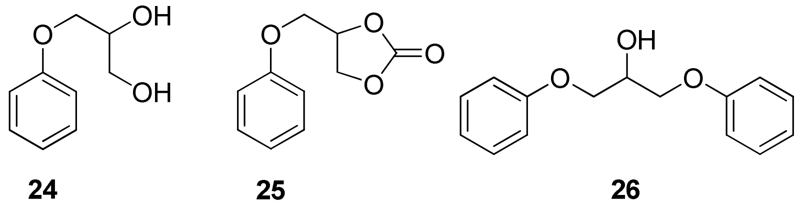
4.2 The Reaction of Glycerol Carbonate with Phenol in the Presence of NaY Zeolite

4.2.1 Introduction

As already stated in chapter 3 (par. 3.1), the market surplus of glycerol from biodiesel production, [26] is going to have a remarkable resonance on the development of new synthetic routes from renewables.[27] In this context, non toxic derivatives of glycerol such as glycerol carbonate (GlyC) are becoming attractive building blocks.[28] Scheme 3.1 has already described the multiple reactivity of GlyC: the oxygen atom of the hydroxymethyl function of GlyC serves as a nucleophile, while both carbonyl and alkyl carbon atoms (C2 and C5, respectively) show a typical electrophilic character.[29] As an example of the latter behaviour, the *N*-alkylation of anilines with GlyC carried out over faujasite catalysts, has been previously reported in this PhD thesis (chapter 3, par. 3.1). These results prompted us to extend the investigation to the reaction of GlyC with other nucleophiles. Phenol was chosen as a model compound.

4.2.2 Results

I. GlyC as an alkylating agent of phenol. Initial experimental conditions for the reaction of phenol (**23**) with GlyC in the presence of NaY_A as the catalyst, were defined according to the procedures, previously reported in chapter 3 (par. 3.1), for the alkylation of primary aromatic amines. A mixture of phenol **23** (0.5 g, 5.3 mmol), and GlyC (0.76 g, 6.5 mmol; the molar ratio W = GlyC:**23** = 1.2) was set to react at different temperatures (140, 150, and 200 °C), in the presence of the NaY_A faujasite (the weight ratio, Q = NaY_A:**23** was 1.5). Due to relatively high viscosity of GlyC, triethyleneglycol dimethylether [$MeO(CH_2)_2O(CH_2)_2O(CH_2)_2OMe$, triglyme: 2 mL] was used as a co-solvent, to allow an uniform stirring of the reacting slurry.[30] All experiments were run at ambient pressure, in an open vessel. The reactions were stopped after 6 hours, and the reaction mixtures were analyzed by GC/MS. Three major products were observed, whose structures were assigned from their MS spectra (scheme 4.9). Also some unidentified by-products (total amount 4%) were detected. Results are reported in table 4.1.



Scheme 4.9

Table 4.1. The reaction of GlyC with phenol catalyzed by the faujasite NaY_A [a]

#	T (°C)	Conv (%) [b]	Products (%, GC)			
			24	**25**	**26**	**Others** [c]
1	140	13		10	1	2
2	200	42	7	28	3	4

[a] All reactions were carried out for 6 hours in the presence of triglyme (2 mL) as the solvent. The molar ratio GlyC:**23** was 1.2, while the weight ratio NaY_A:**23** was 1.5. [b] The reaction conversion and the amounts of products were determined by GC/MS analyses. [c] Total amounts of unidentified by-products.

The increase of the reaction temperature (from 140 °C to 200 °C) produced an increase of the reaction conversion (from 13% to 42%) (entries 1 and 2). Compound **25** was always the major product (10-28%); though, at 200 °C, the desired alkylation derivative **24** was observed in a 7% amount. The latter conditions (200 °C) were then used to continue the investigation.

II. Effect of amounts of faujasite and GlyC. Three different sets (a-c) of experiments were carried out.

In the first set (a), different catalyst loadings were considered. A mixture of phenol (0.5 g, 5.3 mmol), and GlyC (1.77 g, 15.0 mmol; the molar ratio W = GlyC:**23** = 2.8) was set to react at 200 °C in the presence of different amounts of the NaY_A faujasite (0.375, 0.75, 1.5 to 2.0 g; the weight ratio, Q = NaY_A:phenol was 0.75, 1.5, 3 and 4, respectively). As described above, triethyleneglycol dimethylether (triglyme, 2 mL) was used as a co-solvent. The reactions were stopped after 18 hours, and mixtures were analyzed by GC/MS. Results are reported in figure 4.5, where the reaction conversion and selectivity towards the alkyl derivative **24**, are plotted *vs* the weight ratio Q.

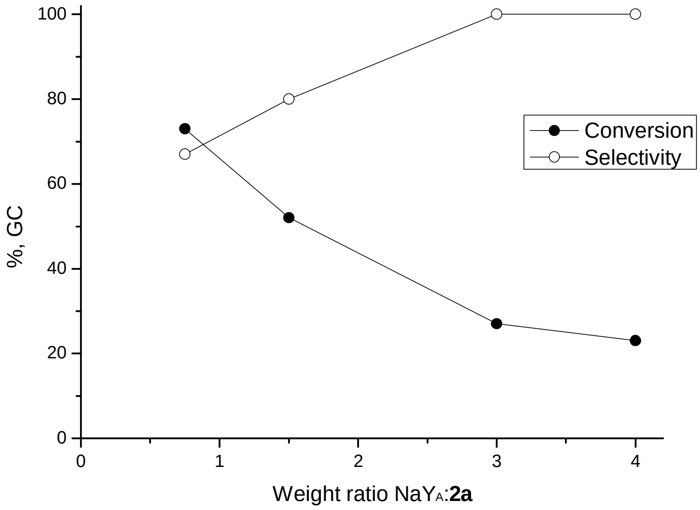


Figure 4.5. Effect of the NaY_A amount

At low Q ratios (Q≤1.5), the conversion was rather good (50-70%), but the selectivity for **24** ($S_{\%}$ = [**24**]/conversion x 100) did not exceed 80% along with unidentified by-products. The increase of the catalyst loading (Q≥3) produced a remarkable drop of the reaction conversion (from ~70% to ~20%), though the process reached a selectivity ($S_{\%}$ = [**24**]/conversion x 100) up to 100% towards the alkyl derivative **24**.

In the second set of experiments (b), different amounts of GlyC, from 1.77, 2.51 to 3.14 g (15, 21.3 and 22.6 mmol, respectively), were considered. A mixture of phenol (0.5 g, 5.3 mmol), and GlyC was set to react at 200 °C, in the presence of NaY_A faujasite (the weight ratio, Q, NaY_A:phenol was 1.5). The corresponding molar ratios W (GlyC:phenol) ranged from 2.8, 4.0 to 5.0. Triethyleneglycol dimethylether (triglyme, 2 mL) was used as a co-solvent. The reactions were stopped after 18 hours, and mixtures were analyzed by GC/MS. Results are reported in table 4.2.

Table 4.2. The effect of GlyC loading in the reaction with phenol and NaY_A catalyst [a]

#	GlyC:2a, W (mol:mol) [b]	Conv (%) [c]	Products (%, GC) [c]				Sel. (24, %) [e]
			24	25	26	Others [d]	
1	2.8	52	39	3	8	2	75
2	4.0	74	52	6	13	3	70
3	5.0	80	50	7	20	3	62

[a] All reactions were carried out for 18 h, at 200 °C, in the presence of triglyme (2 mL) as the solvent. The weight ratio, Q, NaY_A:**23** was 1.5. [b] Molar ratio W= GlyC:**23**. [c] The reaction conversion and the amounts of products were determined by GC/MS analyses. [d] Total amounts of unidentified by-products. [e] Selectivity towards product **24**.

The increase of the molar ratio W from 2.8 to 5.0 enhanced the reaction conversion (from 52 to 80% by GC, entries 1 and 3, respectively). In addition, the desired alkylated compound **24** was the major product, with a selectivity up to 70-75% at rather good conversions (52-74%) (entries 1 and 2). However, a further increase of the GlyC amount (W=5) slightly increased the conversion (80%) with no benefits on the selectivity (62%) (entry 4).

The third set of experiments (c) was carried out under the same conditions used for the set (b) except for the catalyst amount which was lowered at 0.375 g. The corresponding Q ratio (NaY_A:phenol) was 0.75. As for set (b), results of set (c) showed that the increase of the GlyC quantity from 0.76, 2.51 to 3.14 g (W = 1.2, 4.0 and 5.0) increased the conversion of phenol from 23, 65 and 77, respectively. However, the selectivity for **24** decreased progressively from 87, 75 and 67%, respectively. Other products were unidentified by-products.

III. Temperature and time dependence of the reaction outcome. Possible effects of the reaction temperature were investigated according to the results of figure 4.5 and table 4.2. In particular, conditions were chosen to obtain the best compromise in terms of conversion and selectivity. A mixture of phenol (0.5 g, 5.3 mmol), and GlyC (3.14 g, 26.6 mmol; the molar ratio W = GlyC:phenol = 5.0) was set to react at different temperatures (180, 200 and 220 °C), in the presence of the NaY_A faujasite (0.75 g, the weight ratio, Q = NaY_A:**23** was 1.5). Triglyme (2 mL) was used as a co-solvent. The reactions were stopped after 18 hours, and mixtures were analyzed by GC/MS. Results are reported in figure 4.6, where the reaction conversion and selectivity (see table 4.1 for definitions) are plotted *vs* the reaction temperature.

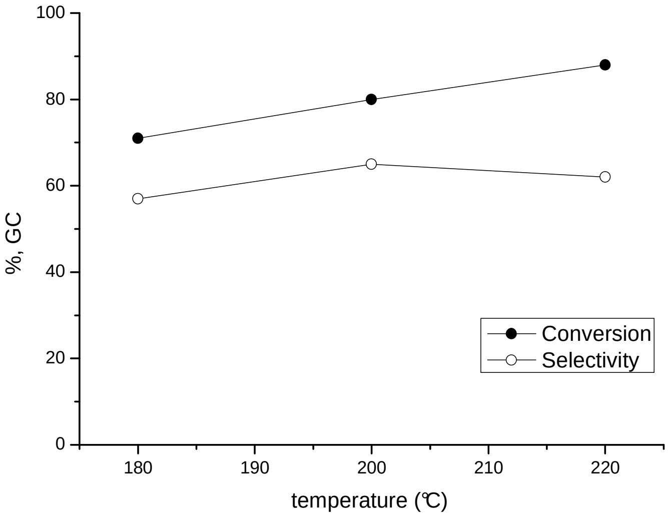


Figure 4.6. The effect of the reaction temperature

The increase of the reaction temperature from 180 to 220 °C, increased the conversion (from 71 to 88%, respectively), while the selectivity for **24** remained almost unaltered around 60%. The experiment carried out at 220 °C was monitored (by GC/MS) at different time intervals. Figure 4.7 shows the corresponding reaction profile.

This analysis showed that after the first hour, the conversion and the formation of products **24** and **25** boosted up to 66% , 42%, and 18%, respectively. Then, the reaction slowed dramatically: only after 18 hours, the conversion reached 90% and compound **24** slowly increased up to the final amount of 55%.

Product **25** followed a typical intermediate-like behaviour: after an initial maximum, its concentration dropped progressively to less than 1%, as the reaction proceeded further. Compound **26** increased progressively with time up to a rather high value of 33%, while unidentified by-products (others) were almost constant throughout the reaction (~3%).

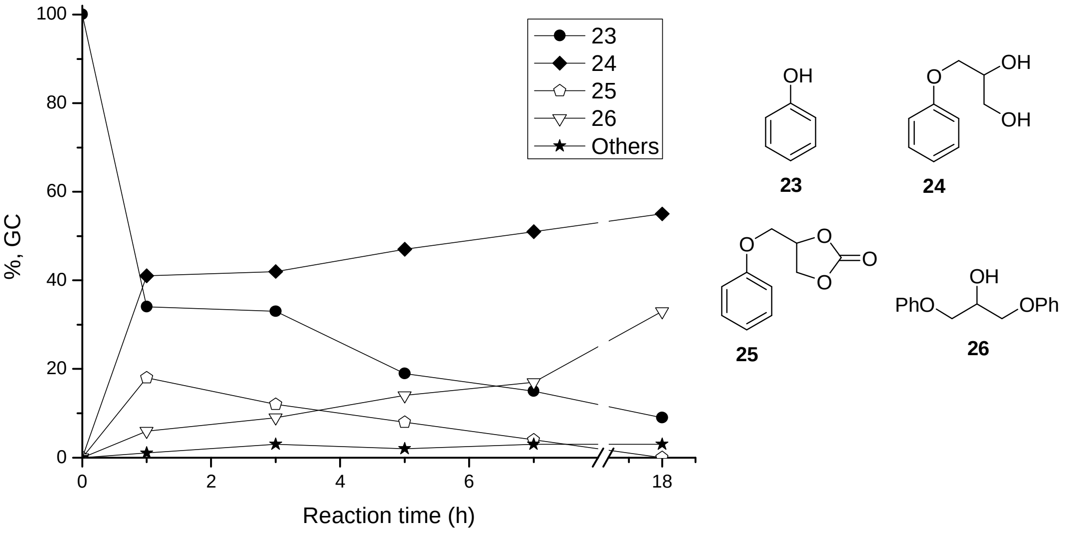
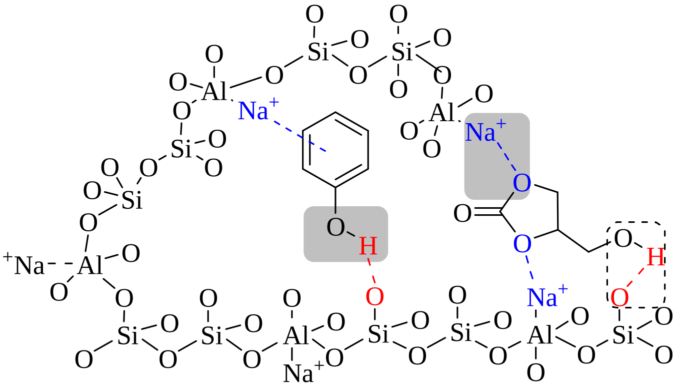


Figure 4.7. The profile of the reaction at 220 °C (Q = 1.5, W = 5.0)

4.2.3 Discussion

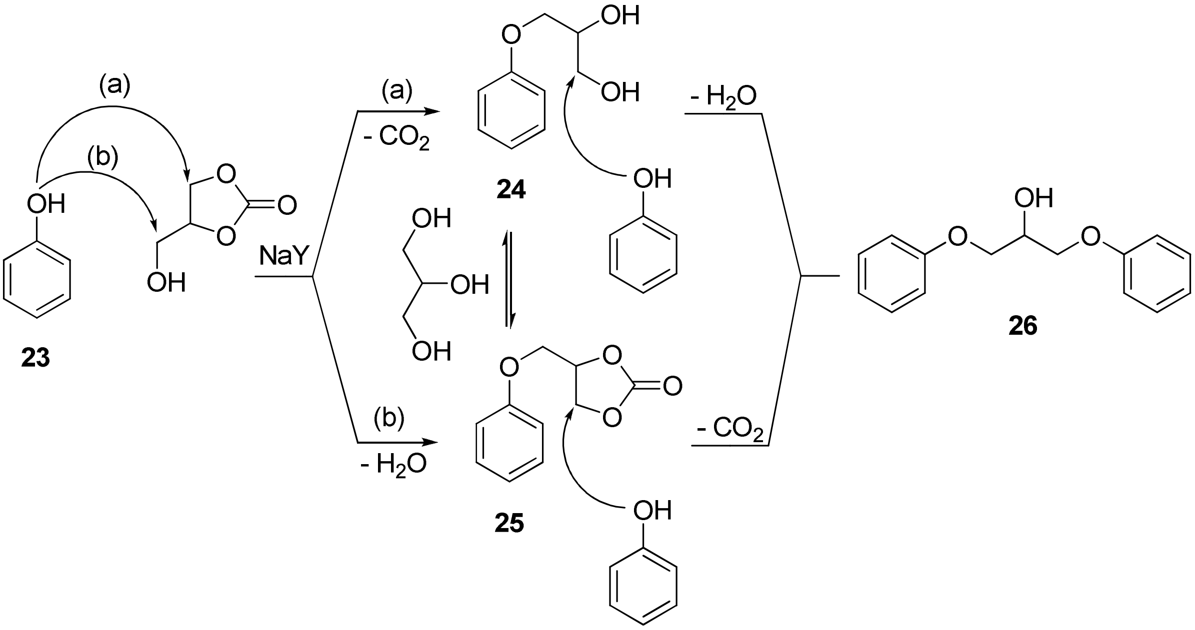
Results of tables 4.1-2 and figures 4.5-6 indicate that the faujasite NaY$_A$ is able to catalyze the formation of the desired alkylation product **24** where glycerol carbonate acts as an *O*-alkylation agent of phenol. Even if this investigation is still at a preliminary stage, some analogies and differences can be highlighted with respect to the reaction of aniline (**2a**) with GlyC presented in chapter 3 (par. 3.1).

As for aniline, the adsorption of phenol on faujasites has been described through two modes of interaction,[31] involving *i)* H-bonds between OH groups of phenol and oxygen atoms of the lattice, and *ii)* acid–base reactions of metal cations on the catalytic surface with the aromatic ring of phenol. Similar interactions explain the adsorption of glycerol carbonate over faujasites: these have been previously discussed by analogy with the behaviour of DMC and primary alcohols adsorbed on zeolites (scheme 3.10). The overall picture can be sketched out as shown in scheme 4.10.



Scheme 4.10. Pictorial view of the adsorption of phenol and glycerol carbonate over a Na-faujasite

Phenol and GlyC experience a nucleophilic (shaded section, left) and an electrophilic (shaded section, right) activation, respectively. In this way, the OH group of phenol is assisted to attack GlyC through a S_N2 reaction occurring preferably at the less hindered C5 position of the cyclic carbonate,[32] and product **24** and CO_2 are directly produced (scheme 4.11, path a).



Scheme 4.11. The reaction of GlyC with phenol: the formation of products **24**, **25**, and **26**

Other similarities to aniline are: *i*) the reaction of phenol at the carbonyl carbon of GlyC do not occur; *ii*) the presence of some water entrapped by the catalyst,[23] allows the protonation of the alcxide-like moiety derived from GlyC (dashed section, scheme 4.10), to favour the S_N2 process for the formation of product **25** (scheme 4.11, path b); *iii*) the latter compound (**25**) is likely to act as an intermediate species (figure 4.7) producing the desired product **24**.[33]

However, by contrast to the case of aniline, **25** can plausibly lead also to compound **26** through a nucleophilic attack of phenol (scheme 4.11, bottom). Moreover, the alkyl derivative **24** can itself undergo a nucleophilic attack of phenol to produce compound **26** (scheme 4.11, top). This side reactions mainly account for the lower selectivity observed for phenol with respect to aniline. The nature of the substrates as well the operating conditions may offer an explanation for such a behavior. Phenol is certainly a poorer nucleophile than aniline,[34] and temperatures (up to 220 °C) required for the alkylation of phenol are higher than those for aniline (140 °C). Overall, at high reaction conversion (>70%), the selectivity towards *O*-(2,3-dihydroxy)propyl phenol (**24**) do not exceed 80%. Future investigations should be addressed to a more in-depth analysis of the catalyst loading and to the use of different co-solvent to avoid possible mass-transfer limitations and improve the product distribution.

4.2.3 Conclusions

The investigated reaction couples the use of eco-safe faujasite catalysts to a glycerol-derived and innocuous reagent such as glycerol carbonate. Notwithstanding these remarkable green features, the study performed up to now shows that the reaction is not selective towards the formation of the desired alkyl derivative, *O*-(2,3-dihydroxy)propyl phenol (**24**). The mechanistic hypothesis formulated for the case of aniline seems to hold true even for the reaction of phenol, but in the latter situation, side reactions also occur producing mainly 1,3-diphenoxypropan-2-ol (**26**) as a by-product. This drop of selectivity is plausibly due to a poor nucleophilicity of phenol with respect to aniline and to the more severe reaction conditions.

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[2] Alkali metal exchanged Y- and X-faujasites are a class of zeolites in which the negative charge of the aluminosilicate framework is counterbalanced by an alkali metal cation. For example, NaY and NaX faujasites possess the same 3D-structure, but they differ for the Si/Al content. Their general formulas are $Na_{56}[(AlO_2)_{56}(SiO_2)_{136}]\cdot 250H_2O$ and $Na_{86}[(AlO_2)_{86}(SiO_2)106]\cdot 264H_2O$, respectively. For morphological details and other properties, see: (a) F. Schwochow and L. Puppe, *Angew. Chem., Int. Ed. Engl.*, 1975, **14**, 620-628; (b) G. C. Bond in *Heterogeneous Catalysis Principles and Applications*, Oxford University Press, NewYork, USA, 2nd edn, 1987, pp. 104–110

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[8] The temperature range (150-200 °C) was chosen according to the operating conditions usually employed for DMC mediated methylation reactions.

[9] Hydrotalcite is an aluminium-magnesium hydroxycarbonate. Natural hydrotalcite possesses the general formula $Mg_6Al_2(OH)_{16}CO_3$ x $4H_2O$. However, both Mg^{2+} and Al^{3+} can be

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isomorphously substituted by other metal ions, forming new hydrotalcite-like materials of general formula $[\mathrm{M}_{1-x}^{2+}\,\mathrm{M}_x^{3+}\,(\mathrm{OH})_2]^{x+}\mathrm{A}_{x/n}^{n-}$ x $m\mathrm{H_2O}$, where M denotes metal ions, A denotes exchangeable anions with valence *n*, and *x* is within 0.17–0.33. See, for example: A. Bhattacharyya, V. W. Chang and D. J. Schumacher, *Appl. Clay Sci.*, 1998, **13**, 317–328.

[10] It should be noted for clarity that at rt, a refluxing liquid was visible at the bottom of the drechsel bottle. Once the bottle was opened, its content was completely released to the atmosphere. The liquid was compressed dimethyl ether (bp = 24.8 °C), as confirmed by the GC/MS analysis. In addition, this also explained why the GC response of the gaseous mixture showed a slight excess of CO_2: the ratio of CO_2/DME signals was on average, 1.2.

[11] K_2CO_3 was reported as a catalyst for a number of DMC-mediated alkylations (ns Accounts). Therefore, the knowledge of the behavior of K_2CO_3 as a catalyst for the decarboxylation of DMC was rather important.

[12] A 9:1 mixture of benzyl methyl ether and dibenzyl ether [$(PhCH_2)_2O$; DBE] was obtained. The small amount (10%) of dibenzyl ether plausibly derived from two reactions, both catalyzed by the NaX faujasite: the dehydration of benzyl alcohol (see ref. 3d), and/or the transesterification of benzyl alcohol to dibenzylcarbonate ($PhCH_2OCO_2CH_2Ph$) followed by a decarboxylation process. In our case, the presence of DBE as a side-product left a minor uncertainty on the final conversion of DMC.

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[22] To the best of our knowledge, the interactions of faujasites with dialkyl carbonates other than DMC, have not been investigated so far. However, the adsorption of DEC, DPrC, and DOC on such catalysts, is expected to proceed as for DMC, via the formation of acid-base complexes similar to those shown in scheme 4.8.

[23] Alkali metal faujasites of both X- and Y-type are hygroscopic solids, see: *Organic Solid State Reactions*, ed. F. Toda, Kluwer Academic Publishers, Dordrecht, The Netherlands, 2002, pp. 160-161.

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[30] The viscosity of GlyC is 61.0 cst at 25 °C (see www.huntsman.com, JEFFSOL® Glycerine Carbonate). Triglyme was already described by us as a good solvent for zeolite-catalysed alkylations of amines with dialkylcarbonates (see ref. 7b).

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[33] As discussed in chapter 3 (par. 3.1), water co-adsorbed on the faujasite initiates the hydrolysis of GlyC to form glycerol (scheme 3.7, eq.2). Then, the transesterification of **25** with glycerol may take place to form product **24**. This is supported by the fact that faujasites are catalysts for transesterification processes even when bulky electrophiles (*i.e.* triglycerides) and different alcohols including glycerol, are used. See: (a) E. Leclercq, A. Finiels and C. Moreau, *J. Am. Oil Chem. Soc.*, 2001, **78**, 1161-1165; (b) M. J. Ramos, A. Casas, L. Rodrıguez, R. Romero and A. Perez, *Appl. Catal. A: General*, 2008, **346**, 79-85.

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CHAPTER 5

Concluding Remarks

As presented in the introduction, the aim of this PhD thesis was to develop new eco-friendly organic synthesis for the formation of C-C, C-N and C-O bonds. To this purpose, the work was carried out following the green chemistry principles fundamentally: "*the invention, design and application of chemical products and processes to reduce or to eliminate the use and generation of hazardous substances*" (see chapter 1). Thus, catalytic reactions with high atom economy (AE) and carbon efficiency (CE) were considered, in order to incorporate as much of the substrate as possible in the product and avoid the formation of wastes. The use of eco-solvents, catalysts and reagents such as CO_2, ionic liquids and dialkylcarbonates, has been investigated with the objective to improve the environmental factor (E) of the existing methodologies. In this chapter, a brief summary of the conclusions for each reaction investigated is given along with some concluding remarks on the work.

As far as C-C bond forming reactions are concerned, chapter 2 of this work describes the first example of self-metathesis of α-olefins (1-octene) catalysed by heterogeneous Re-based catalysts, in presence of supercritical carbon dioxide as the solvent, under both batch and continuous flow conditions. Although an additional “compression” energy (and costs) must be provided with respect to traditional solvent systems, in this case, beyond the environmentally benign character of $scCO_2$, a remarkable improvement of the reaction outcome has been observed. Under both operating modes (batch and continuous flow) in fact, the use of $scCO_2$ allows to carry out the metathesis reaction with higher conversion, selectivity and also productivity with respect to conventional organic solvents, thereby improving both the effective mass yield (EMY) and the mass index (S^{-1}) of the process.

Moreover, two others features make this methodology "green": the heterogeneous catalyst is easily separable and recyclable, so that it does not influence S^{-1}; the work-up of the reaction is very simple, as the product of self-metathesis is obtainable via simple depressurization of the system followed by vacuum removal of unreacted substrate (1-octene). Future studies will be dedicated to the catalyst development, especially under continuous flow conditions, in order to improve the reaction conversion and productivity further.

The use of $scCO_2$ as reaction solvent has been investigated also for the Michael addition of primary nitroalkanes to cyclohexenone, in presence of various basic aluminas as heterogeneous catalyst. In this case however, the reaction outcome is not improved by the use of supercritical CO_2 with respect to conventional solvents such as *n*-heptane and THF. This is an unexpected result if the properties of the $scCO_2$ are considered (*e.g.* higher diffusivity and enhanced mass transfer). However, the highest reaction conversions for the Michael addition are achieved under solvent-free conditions, which are particularly appealing from the environmental standpoint: the problem of the solvent disposal is so intrinsically solved. Moreover, also in this case, an additional improvement of S^{-1} is given by the possibility of recycling the catalysts.

For the Michael reaction, also the use of homogeneous catalysts belonging to the class of ionic liquids (ILs) has been investigated. The green features of ionic liquids are described in chapter 1 (par. 1.3). However, we would like to stress here that these materials are mostly prepared via un-green processes (scheme 1.2), which is clearly a contradiction in terms. For this reason, we have investigated a green synthetic procedure of ionic liquids, carrying out the quaternarization of a trialkylphosphine with a green methylating agent such as dimethyl carbonate (DMC) in place of highly toxic dimethyl sulfate (DMS) and methyl halides (CH_3X, X=I, Br, Cl). Although the reaction conditions are energy intensive (T=140 °C), our method gained in greenness, including safety, handling and absence of wastes, with respect to conventional methods.

The phosphonium based ionic liquids (PILs) prepared according to this process, catalyse the solvent-free Michael addition not only of nitroethane to cyclohexenone, but also of different nitroalkanes and β-dicarbonyl compounds to other α,β-unsaturated ketones. In all cases, the reaction proceeds with high yield and selectivity with respect to known strong hindered organic bases conventionally used as catalysts for such process. Notwithstanding the good synthetic results obtained, the reaction procedure developed in this PhD thesis lacks in greenness in some of its steps. No toxicological data on the investigated PILs are available. Though, alike to many phosphonium salts, also our PILs are plausibly toxic compounds. Even if these materials are used in very small amounts (even just in 0.4 mol%), their separation from the reaction mixture requires additional materials, such as silica gel and solvents (see experimental section), that negatively contributed on the overall S^{-1} and E of the process. These aspects will be object of future investigation, in order to optimize the Michael reaction procedure based on the combined use of PILs, in truly catalytic amount, and solvent-free conditions, that looked promising in this preliminary stage.

For what concerns C-N forming reactions, three processes based on the use of safe reactants such as dialkyl carbonates (DAlCs) have been studied. The green features of this class of compounds, and in particular of the lightest term of the series, DMC, has been extensively described in chapter 1 (par 1.4). Although DAlCs are valuable green alkylating reactants, relatively high temperatures are usually required (*e.g.* over 120 °C for DMC). This energetic drawback is usually compensated by the high selectivity and chemoselectivity that can be achieved when suitable catalytic systems are adopted. These considerations hold true in the cases of the reactions presented in this PhD thesis (chapter 3). All of them have been carried out at temperatures > 100 °C and up to 200 °C, but it was possible to obtain the desired products with high selectivity and good isolated yields. Each of the three investigated methodologies has some peculiar green features.

In the first case presented in chapter 3, for example, a synthesis of *N*-(2,3-dihydroxy)propyl anilines (starting from anilines) has been developed by replacing a conventional highly toxic reactant, such as glycidol, with an innocuous alkylating agent such as glycerol carbonate (GlyC). Alkali metal exchanged faujasites, particularly NaY, have proven to be effective catalysts for these reactions, and even if used in a relatively high amount, the catalysts can be recovered and recycled without any loss of their performance. Moreover, the use of GlyC allows to develop a genuine green synthesis not only because of the gain in safety, but also because this carbonate is a chemical derived from a renewable resource such as glycerol.

In the case of the *green domino*, we have developed an innovative and selective synthesis of bis-*N*-methyl anilines, *via* the coupling of two sequential processes, both catalysed by alkali metal exchanged faujasites: the transesterification of cyclic carbonates with MeOH for the *in situ* production of DMC, and the subsequent methylation reaction of anilines with DMC in the same reaction batch. This process is an original approach from both the environmental and synthetic standpoints: in fact, in the formal stoichiometry of the process, methanol is the alkylating agent, but the reaction is actually carried out by DMC, that itself possesses much better and greener alkylation performances than methanol.

In the third case, we have developed an advantageous green methodology to carry out the bis-*N*-hydroxyalkylation of anilines, by replacing harmful hydroxyalkylating agents such as alkylene oxides or halohydrins with non toxic alkylene carbonates such as ethylene- and propylene-carbonate, and using phosphonium based ionic liquids (PILs) as catalysts.

It should be noted however that a general environmental drawback of all these C-N bond forming reactions is posed by the purification technique (flash column chromatography, FCC) used to isolate the products. FCC in fact is a conventional technique that requires additional volumes of solvents, usually volatile organic ones, which should be avoided in the development of a green method of synthesis. The optimization of FCC conditions, for example by recycling of the solvent, or the investigation of other greener purification/isolation procedures will be object of further studies to enhance the overall greenness of these methodologies.

In chapter 4, the use of organic carbonates as green reactants has been investigated also for the setup of C-O bond forming reactions. In this field, two processes have been investigated.

The first process has been the decarboxylation reaction of dialkyl carbonates catalyzed by different heterogeneous systems like K_2CO_3, alkali metal exchanged faujasites and hydrotalcite (such catalysts are those conventionally used to promote alkylation reactions carried out with

DAlCs). The selective formation of dialkyl ethers (dimethyl- and diethyl-ether) has been observed for light DAlCs (DMC and DEC); while, for higher homologues (dipropyl- and dioctyl-carbonate), the decarboxylation reaction always occurs along with side-process producing alcohols and olefins. This investigation however, has not been intended to claim a green method for the synthesis of dialkyl ethers (and CO_2 as co-product). Rather, the general purpose of the work has been to establish the boundaries of the reaction conditions for the use of DAlCs. The reported experiments identify the temperature range that according to the nature of the catalysts, avoids the extensive consumption of DAlCs through a decarboxylation reaction, and the related formation of highly flammable ethers that may also pose a safety concern. Overall, the work defines how (light) DAlCs should be used productively for alkylation reactions.

The last investigation has been on the reaction of phenol with glycerol carbonate (GlyC) in the presence of faujasite catalysts. As reported in chapter 4 (par 4.2), the motivation for this study has been the good results obtained for the analogue reaction of anilines and GlyC, that produces *N*-(2,3-dihydroxy)propyl anilines. The reaction of phenol is not as selective as for primary aromatic amines: the overall yield of the desired derivative, *O*-(2,3-dihydroxy)propyl phenol does not exceed 50%. However, experiments indicate that a different compound, *i.e.* 1,3-diphenoxypropan-2-ol can perhaps be obtained as a major product through a concurrent mechanism of alkylation/condensation followed by nucleophilic displacement (scheme 4.11). A further investigation in the future will be devoted to this subject.

In light of these considerations, the general conclusion is that the initial objectives of this PhD thesis have been achieved for the most part: new processes have been setup according to green/sustainable methodologies whose novelties open new perspectives in fields which are still largely unexplored. Due to time limitations however, some aspects of the work have certainly to be analyzed in the future.

Overall, topics investigated during this PhD thesis lead to the publication of seven papers on international scientific journal. A list follows:

- C-C bonds forming reactions -

- M. Fabris, C. Aquino, A. J. Ward, A. Perosa, T. Maschmeyer and M. Selva, "Self-metathesis of 1-octene using alumina-supported Re_2O_7 in supercritical CO_2", *Top. Catal.*, 2009, **52**, 315-321.

- M. Fabris, V. Lucchini, M. Noè, A. Perosa and M. Selva, “Ionic Liquids Made with Dimethyl Carbonate: Solvents as well as Boosted Basic Catalysts for the Michael Reaction”, *Chem. Eur. J.*, 2009, **15**, 12273-12282.

- C-N bonds forming reactions -

- M. Selva and M. Fabris, “The reaction of glycerol carbonate with primary aromatic amines in the presence of Y- and X-faujasites: the synthesis of *N*-(2,3-dihydroxy)propyl anilines and the reaction mechanism”, *Green Chem.*, 2009, **11**, 1161-1172.
- M. Selva, A. Perosa and M. Fabris, “Sequential Coupling of The Transesterification of Cyclic Carbonates with The Selective *N*-Methylation of Anilines Catalysed by Faujasites”, *Green Chem.*, 2008, **10**, 1068-1077.
- M. Selva, M. Fabris, V. Lucchini, A. Perosa and M. Noè, “The Reaction of Primary Aromatic Amines with Alkylene Carbonates for the Selective Synthesis of bis-N-(2-hydroxy)alkylanilines: the Catalytic Effect of Phosphonium-Based Ionic Liquids”, *Org. Biomol. Chem.*, 2010, **8**, 5187-5198.
- V. Lucchini, M. Fabris, M. Noè, A. Perosa and M. Selva, “Kinetic Parameter Estimation of Solvent Free Reactions Monitored by ^{13}C NMR Spectroscopy. A Case Study: Mono- and Di-(hydroxy)ethylation of Aniline with Ethylene carbonate”, *Int. J. Chem. Kinet.*, 2010, in the press.

- C-O bonds forming reactions -

- M. Selva, M. Fabris and A. Perosa, “The Decarboxylation of Dialkyl Carbonates to Dialkyl Ethers over Alkali Metal-exchanged Faujasites”, *Green Chem.*, 2011, in the press.

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Massimo Fabris

CHAPTER 6

Experimental Part

6.1 The Metathesis of α-Olefins over Supported Re-Catalysts in Supercritical CO_2 [Ch. 2, par. 1]

6.1.1 General

1-octene $\mathbf{C_8}$ was ACS grade and was employed without further purification. *n*-Hexane as a solvent was used as such or purified through known methods.[1] Ammonium perrhenate (NH_4ReO_4, ≥99%) was from Aldrich. γ-Al_2O_3 was from two different sources: Puralox-Condea and Alfa-Aesar [surface area (A_s) of 257 and 200 m^2/g, respectively]. Wherever used, water was of milli-Q grade. ^1H NMR spectra were recorded on a 300 MHz spectrometer, using $CDCl_3$ as solvent.

I. Batch conditions. GC/MS (70 eV) analyses were run using a HP5/MS capillary column (30 m). The gaseous N_2 used throughout the activation of catalysts and the general procedure for the reaction (see below), was of a R-grade and it was further purified by drierite®/13X filters (Aldrich). CO_2 was of a SFC/SFE grade (purity 99.998 %).

II. Continuous flow condition. GC analyses were run using a HP5/MS capillary column (30 m). Gaseous air and N_2 used throughout activation of catalysts were of R-grade. CO_2 was of used both Food grade (purity 99.97%) and SFC/SFE grade (purity 99.998%).

6.1.2 Preparation of the Catalysts

I. Wet impregnation technique. Catalysts Re-A_1, Re-A_2, Re-A_3, Re-A_4, Re-AS_1 (used under batch conditions) and ReA_5 (used under continuous flow conditions) were prepared by a wet-impregnation technique described in the literature.[2] A 25-mL round bottomed flask was charged with an aqueous solution (1.7×10^{-1} M, 12 mL) of NH_4ReO_4 (555 mg, 2.1 mmol) and with the chosen support (γ-Al_2O_3; meso-porous Al_2O_3, Al:Si-TUD-1, 5 g). The slurry was kept under magnetic stirring for 1 hour at rt, and then dried under vacuum (50 °C, 36 mbar). The solid residue was further wet with water (8 mL), stirred for 15 min at rt, and finally, dried again (50 °C, 2 mbar). The solid sample was calcined at 550 °C (10 °C/min), for 4 h, in a stream of dried air (~80 mL/min).

Supporting materials for catalysts Re-A_4 and Re-AS_1 have been prepared by the group of Prof. T. Maschmeyer at the Laboratory for Advanced Catalysis and Sustainability, University of Sidney. In particular, meso-porous Al_2O_3[3] and Si:Al-TUD-1,[4] supports for catalysts Re-A_4 and Re-AS_1 respectively, were prepared according to previously published methods.[3,4]

Catalyst Re-S_1 has been prepared in collaboration with the Laboratory for Advanced Catalysis and Sustainability by the following procedure. A solution of ammonium perrhenate (0.62 g, 2.32 mmol), water (45 mL) and triethanolamine (15 mL, 0.11 mol) was stirred until the solution was homogeneous. To the resulting solution was added tetraethoxysilane (50 mL, 0.22 mol) over 10 min with stirring. After this time triethanolamine (15 mL, 0.11 mol) and tetraethylammonium hydroxide (20 wt.%, 48.6 g, 66 mmol) were added. The resulting solution was stirred for 2 h, then left to stand for 24 h. The resulting viscous solution was dried at 98 ^oC for 24 h. The template was eventually removed from the resulting solid by extraction with ethanol in a Soxhlet extractor. The solid residue was calcined at 550 °C for 10 h under a stream of air (~80 mL min^{-1}) to obtain a white powder.

II. Characterization of the catalysts. Catalytic systems reported in table 2.1 were characterized by optical ICP and TEM.

In order to perform ICP analyses, solid samples were digested through the following procedure: a Teflon-lined autoclave (200 mL) was charged with the catalyst (0.05 g), water (5 mL), aq HF (40%, 1.5 mL), and a mixture of aq HCl/HNO_3 (3:1 v/v; 3 mL). The autoclave was then closed with a Teflon-lined cap, and heated in a microwave digestion rotor (MDS 2000) at 170 °C, for 1 hour. After being cooled to rt, the clear solution was transferred into a volumetric flask and diluted with water to 50 mL. Then, ICP analyses were carried out at 197.248 nm (power of 1400 W). The Re content of the catalysts Re-A_{1-4}, ReAS_1 and ReS_1 was of 6.8, 7.0, 6.4, 11.8, 7.7 and 2.7, respectively (table 2.1).

TEM analysis was carried out with JEM 3010 (JEOL) electron microscope operating at 300 kV, point to point resolution at Scherzer defocus of 0.17 nm. A suspension of the catalytic sample (20 mg) in *i*-propanol was sonicated for 5 min. Then, an aliquot (5 µL) was poured on a copper grid coated with amorphous carbon. At rt, once *i*-propanol was evaporated, the sample was ready for the analysis. TEM measures showed the presence of grains of γ-Al_2O_3 with an average size of 5-6 nm. Instead, the particles of Re-oxide were not clearly visible, their dimensions being lower than 1 nm.

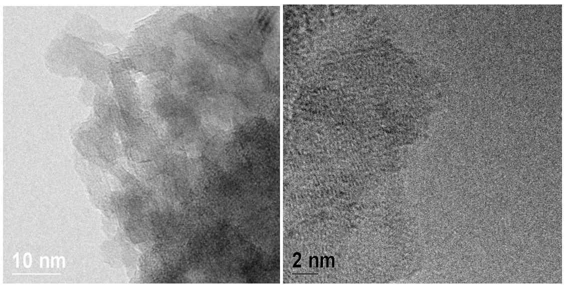

Figure 6.1. TEM images of the ReA_1 catalyst

In the case of meso-porous Al_2O_3 (support for catalyst Re-A_4), nitrogen adsorption-desorption isotherms at 77 K revealed a BET surface area of 362 m^2 g^{-1}, a single-point pore volume of 0.580 cm^3 g^{-1}, and an average pore width of 66.7 Å. In the case of Si:Al-TUD-1 (support for catalyst Re-AS_1), nitrogen adsorption-desorption isotherms at 77 K revealed a BET surface area of 298 m^2 g^{-1}, a single-point pore volume of 0.855 cm^3 g^{-1}, and an average pore width of 114.7 Å. In the case of sol-gel prepared Re-SiO_2 (Re-S_1), nitrogen adsorption-desorption isotherms at 77 K revealed a BET surface area of 696 m^2 g^{-1}, a single-point pore volume of 0.516 cm^3 g^{-1}, and an average pre width of 34.2 Å.

6.1.3 Batch Conditions: Metathesis of α-olefins

I. Reaction procedure. Figure 6.2 illustrates the apparatus specifically designed to carry out metathesis reaction reported in table 2.2.

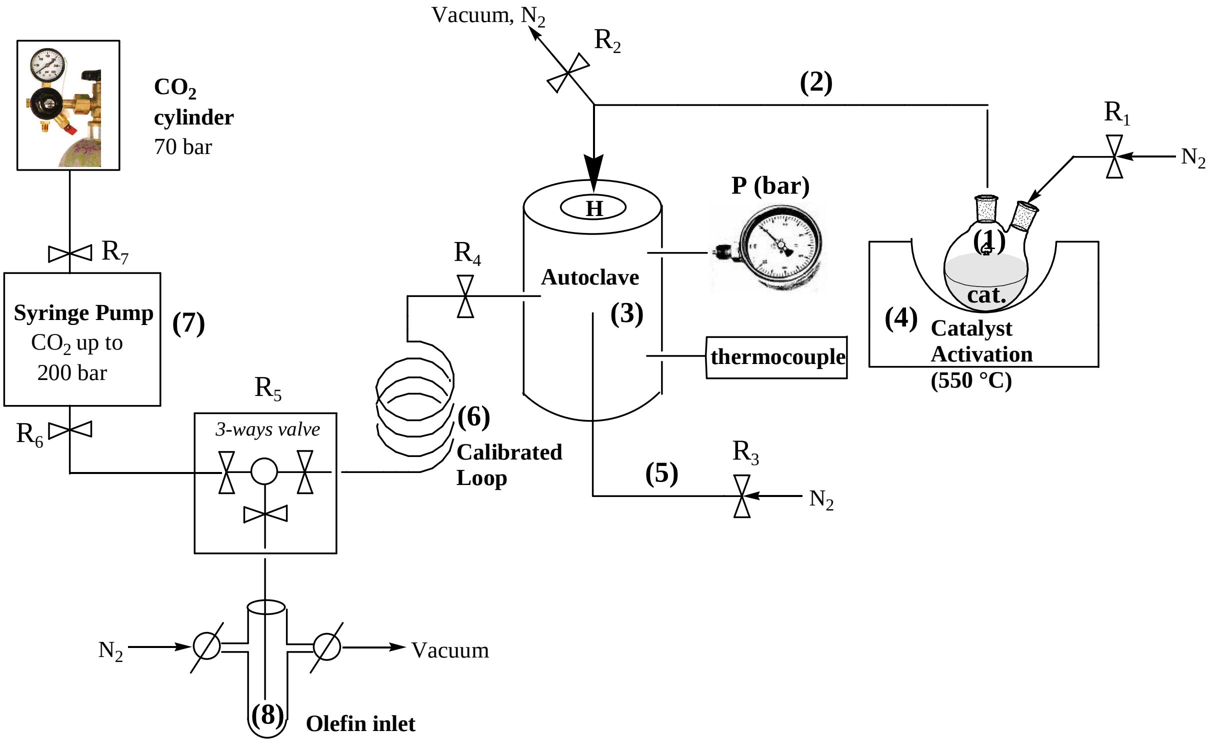

Figure 6.2. Schematic diagram of the apparatus used to carry out the metathesis of olefins in dense CO_2

A flask charged with 0.56 g of the desired catalyst (**1**) was connected to a glass adapter (**2**) sealed at the autoclave top aperture (**H**), by a rubber conic ring. At rt, three N_2/vacuum cycles were done, and the system was kept under a N_2 stream of 50 mL/min. The N_2 stream coming out from the flask, was conveyed directly in the autoclave (**3**) throughout the activation step by **2** and **H**. The flask was placed in an electric oven and heated up to 550 °C. This temperature was reached through a ramp of 10 °C/min, and it was maintained for 1.5 hours. The heating operation was checked by a thermocouple placed at the bottom of the flask. During the activation step, the colour of the catalyst showed some peculiar changes: the white powder (initially charged in the flask) turned to a gray tonality around 400 °C, then a black color was persistent at 550 °C. After 1 h at this temperature, the powder began to fade until a pale yellow solid was obtained at the end of the heating time. This was the final color of the catalyst used in the reaction.

Once this operation was concluded, at rt, the flask was rotated along the axis of the adapter (**2**), to let the catalyst slide in the autoclave. Thanks to a supplementary gas line (**5**), the N_2 flow was enhanced up to 150 mL/min, the adapter (**2**) was rapidly removed, and the reactor was finally closed. The reactant olefin $\mathbf{C_8}$ (1-octene, 0.56 g, 5 mmoles), preliminary charged in a 4-mL vial (**8**), was degassed under vacuum and loaded in a 1-mL calibrated loop (**6**). From here, the olefin was transferred in the 30 mL autoclave under a CO_2 stream generated through a syringe pump (ISCO 260D, **7**). The reactor was pressurized at approximately 60 bar and electrically heated at the desired temperature (35 °C). The final pressure, 90 bar, was reached by slowly adding the remaining CO_2. Under these conditions, the 1-octene molar fraction $X_{\mathbf{C8}}$ was of 1.1×10^{-2}. The mixture was magnetically stirred at ~ 500 rpm and its visual inspection was possible thanks to two sapphire windows assembled on both head and bottom of the autoclave. The reaction was allowed to proceed for 2 h. Then, after cooling at rt, CO_2 was slowly vented by bubbling it into a 5-mL vial of acetone. The content of the reactor was washed with additional acetone (5 mL), and the combined organic solutions were analyzed by GC/MS.

II. Isolation and characterization of 7-tetradecene. Since heterogeneous catalysts for the metathesis of alkenes are rather delicate systems, the mass balance of the reaction was never evaluated by addition of internal standards. However, at the end of reaction of table 2.2, entries 1 and 3, the product of self-metathesis of 1-octene (7-tetradecene, $\mathbf{C_{14}}$) was obtained in yields of 70 and 65%, respectively, which well-matched conversions measured by GC/MS. Product $\mathbf{C_{14}}$ was simply isolated by filtration of the catalyst and removal of the unreacted 1-octene under vacuum (50 °C/200 mbar). The crude product was obtained as a pale-yellow liquid and it was characterized as such by GC/MS and ^1H NMR.

5.1.4 Continuous Flow Conditions: Metathesis of 1-octene

I. Equipment description. To carry out the experiments under continuous flow (CF) conditions an automated $scCO_2$ continuous flow apparatus was used. Figure 6.3 shows a piping diagram of the equipment used.

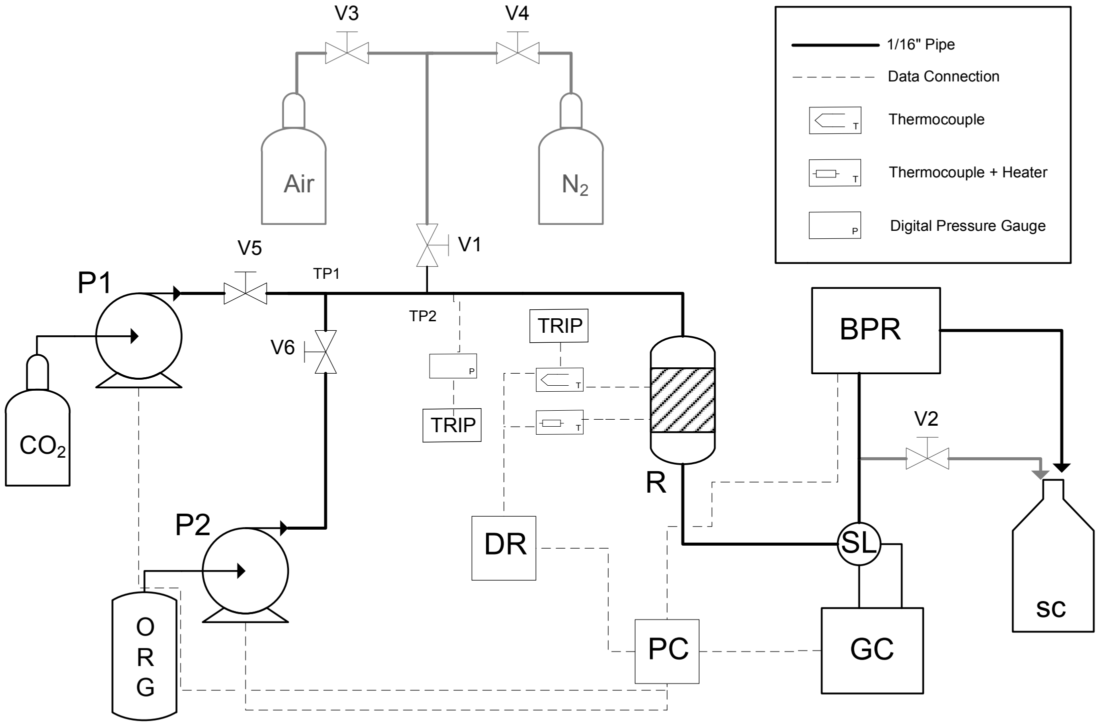

Figure 6.3. The piping diagram of the automated apparatus used to carry out the metathesis reaction under CF conditions

A Jasco PU-1580-CO_2 CO_2 pump (P1) was connected to a tee-piece (TP1) to a Jasco PU980 HPLC pump (P2) used to deliver the organic substrate, 1-octene. Both pumps were interfaced with a computer (PC) and could be programmed either by using the in-built menu or by the computer. From the safety standpoint, pumps had in-built pressure monitors, which could be set to stop the pump if the system went over a set pressure. Pumps P1 and P2 could be excluded from the system using valves V5 and V6, respectively. In order to carry out the activation/re-activation of the catalyst, a supplementary gas line was connected to the main pipeline via a tee-piece (TP2). Thanks to valves V3 and V4, it was possible to switch the activation/re-activation gas from air to N_2. The supplementary gas line could be excluded from the system using valve V1. The reactor (R) was a 1/4" pipe (Volume = 1.67 cm^3, h = 15.2 cm, ø = 0.375 cm), heated to activation/reaction temperature by means of cartridge heaters and a brass heating block. The temperature of the reactor heaters could be controlled over time via a programmable heating controller, while the temperature of the catalytic bed was monitored via a coaxial thermocouple placed inside the reactor. On the top of the reactor, a tee piece used to connect reactor, thermocouple and the in-pipe, was filled with sand and used as mixing/pre-heating zone. For on-line analysis of mixture of products purpose, the out-pipe from the reactor was connected to a HPLC 4-port sample loop, SL, VICI 4 port micro-volume sample loop. The loops injects the sample into the carrier gas flow of a Shimadzu GC 17-a v3 (GC), where the products analysis were carried out. The system pressure was maintained by a Jasco BP-1580-81 back pressure regulator (BPR) which was interfaced with the PC and could be programmed to maintain different pressure profiles at a given time. The BPR was designed to not trip or shutoff under any circumstances, so as to avoid venting of the CO_2 gas cylinder. Products were collected from the outflow of the BPR in the sample collecting round flask (SC). A supplementary vent line was added before the BPR, to allow the outflow of the activation/re-activation gases (N_2 and air). This supplementary vent line could be closed using valve V2. Temperature and pressure were logged at different point of the system on a computer, PC, via a picoTC-08 data recorder, DR.

II. Reaction procedure using $scCO_2$ as a solvent. The standard reaction procedure for the metathesis of 1-octene under continuous flow conditions, using $scCO_2$ as solvent, is described below.

-Preliminary Operations-

i) the reactor (a 1/4" pipe, Volume = 1.67 cm^3, h = 15.2 cm, ø = 0.375 cm) was filled with 1.5 g of ReA_5. The catalyst bed was placed between two thin layers of glass wool at the top and the bottom of the reactor. Once filled, the reactor was fitted in the apparatus.
ii) the PC was booted up and GC solutions (the Shimadzu GC controller software) and Pico log software were loaded.
iii) the GC was switched on.
iv) pumps P1 and P2, the BPR, and the sample loop were turned on, and P1 was allowed to cool down.

These were the preliminary operations for the very first reaction, when the reactor was filled with "fresh" catalyst. With the same reactor and catalytic bed, it was possible to carry out multiple reactions that required only operations *ii*-*iv*.

-Activation of the Catalyst-

i) with all the valve closed, the BPR was set to 90 bar.
ii) valves V1, V2 and V3 were opened, the air flow was regulated to ~10 mL min^{-1}, and the reactor was heated at 550 °C [at 10 °C min^{-1}] and kept at this temperature for 4 hours.
iii) valve V3 was closed and then valve V4 was opened, switching the gas from air to N_2. The flow rate and the reactor temperature were kept to 10 mL min^{-1} and 550 °C, respectively, for 1.5 h. *iv*) under N_2 stream, the reactor heater was set to the reaction temperature, typically 100 °C, and the reactor was allowed to cool.

-Reaction-

i) with the reactor at the reaction temperature, 100 °C, and the BPR set to 70 bar, valves V2, V1 and V4 were closed (in this order). Then, valve V5 was opened and CO_2 was fed into the system at CO_2 cylinder pressure (~56 bar at room temperature) and the apparatus was leak-tested.
ii) with valve V6 still closed, pump P2 was primed with 1-octene.
iii) the BPR was set to the desired reaction pressure, typically 90 bar.
iv) pump P1 was started at the required flow rate of CO_2, 1.0 mL min^{-1}, and the system was allowed to reach the set pressure.
v) after about 5 min from the prime operation, the pump P2 was started at the desired flow rate, typically 0.1 mL min^{-1}, and valve V6 opened.
vi) when organic solution was detected in the sample collecting round flask (SC), usually after 5-8 min, the ramp of reaction temperature and the GC analysis were started via the reactor heater controller and the GC solutions software for controlling the sample loop.

In figure 2.3 [(a) and (b)] of chapter 2, the reaction profiles have been obtained keeping the reactor temperature constant at 35 °C throughout the reaction [figure 2.3(a)], or heating the catalytic bed from 35 to 100 °C (0.2 °C min^{-1}) throughout the reaction [figure 2.3(b)]. Results reported in figure 2.4 were obtained using the procedure described above, but the reaction temperature was set to 35, 100, 110, 120 and 150 °C. For results reported in figure 2.5, being all the other operations unchanged, the BPR was set to 60, 90 and 150 bar during the reactions. Figure 2.6 shows results obtained by setting the flow rate of the 1-octene pump (P2) at 0.04, 0.1 and 0.5 mL min^{-1} (molar fraction of 1-octene in the 1-octene/scCO_2 flow to the reactor: X_{C_8} = 1.1, 2.8 and 14.1x10^{-2}, respectively). The result of entry 2, table 2.4, was obtained carrying out the reaction using a SFC CO_2 cylinder. The result of entry 3, table 2.4, was obtained carrying out the reaction using SFC CO_2 and degassed 1-octene.[5]

-Turn off and Venting Operations-

i) at the end of the reaction, the 1-octene flow from pump P2 was stopped and valve V6 was closed.
ii) after 1 hours the reactor heater was turned off, allowing the reactor to cool down.
iii) at room temperature, the CO_2 flow from pump P1 was stopped and valve V5 was closed.
iv) the system was slowly depressurized by gradual decrements in set pressure at the BPR.
v) GC and all remaining equipment were turned off.

III. Reaction procedure using n-hexane as a solvent. To carry out the metathesis reaction of 1-octene under continuous flow conditions, using *n*-hexane as a solvent, a 0.21 M solution of 1-octene in *n*-hexane (X_{C_8} = $2.8x10^{-2}$) was prepared and used as feed for the organic pump P2. Results reported in table 2.3 and figure 2.9 were obtained using a the following procedure.

The preliminary operations and activation of the catalyst were carried by using the same procedure described for CF conditions.

-Reaction-

i) with the reactor at the reaction temperature, 100 °C, and the BPR set to 90 bar, valves V2, V1 and V4 were closed (in this order).
ii) with valve V6 still closed, pump P2 was primed with the 1-octene/*n*-hexane solution.
iii) the pump P2 was started at the desired flow rate and valve V6 opened. The system was allowed to reach the set pressure. For reaction of entry 2, table 2.3, the flow rate was set to 3.05 mL min^{-1}, while for reaction of entry 3, table 2.3, and figure 2.9 the flow rate was set to 0.5 mL min^{-1}.
vi) when organic solution was detected in the sample collecting round flask (SC), usually after 5-8 min, the ramp of reaction temperature and the GC analysis were started via the reactor heater controller and the GC solutions software for controlling the sample loop.

-Turn off and Venting Operations-

i) at the end of the reaction, the organic pump (P2) was stopped, and the reactor heater was turned off, allowing the reactor to cool down.
ii) at room temperature, the pump (P2) feed was switched from the 1-octene/*n*-hexane solution to acetone, then P2 was turned on, and the flow rate set to 1.0 mL min^{-1}.
iii) the apparatus was washed with acetone for 1 hour. Then the pump P2 was stopped and valve V6 was closed. Valve V5 was opened and pump P1 was started at the flow rate of 1.0 mL min^{-1} of CO_2.
iv) after 1.5 hours, the CO_2 flow from pump P1 was stopped and valve V5 was closed.
v) the system was slowly depressurized by gradual decrements in set pressure at the BPR.
vi) GC and all remaining equipment were turned off.

IV. Isolated yields of 7-tetradecene. The isolated yields reported in figure 2.7 and table 2.3 were obtained by the following procedure. Once the reaction was started, the organic mixture was collected at the outflow of the BPR during the first 15 minutes. Then, the product 7-

tetradecene (**C_{14}**) was simply isolated by removal of the unreacted 1-octene and other (light) cross-metathesis products under vacuum (65 °C/10 mbar). The crude **C_{14}** (on average 93 % pure, by GC) was obtained as a pale-yellow liquid.

6.2 Green Methodologies for the Michael Reaction

[Ch. 2, par. 2]

6.2.1 General

Reagents were ACS grade and, if not specified, used as received without any further purification. Basic Al_2O_3 was from two sources: $[Al_2O_3]_B$ was from Baker; $[Al_2O_3]_M$ was from Macherey Nagel. KF and ethanol were from Carlo Erba. Supported KF (KF loading = 0.35 mmol g^{-1}) was prepared according to a standard impregnation technique,[6] and mesoporous alumina was prepared according to a procedure described in the literature.[3] DMC, methanol, 1-propanol, *n*-heptane, 1-penten-3-one (**a2**), dimethylmalonate (**d4**), dibenzoylmethane (**d3**), nitroethane (**d1**), 1,4-diazabicyclo[2.2.2]octane (DABCO), lauric acid, water (milli-Q grade) and Al(O-*s*-Bu)$_3$ were from Sigma-Aldrich. Tri-*n*-octylphosphine (TOP, >98%) was from Strem Chemicals. Cyclohexenone (**a1**), 1-nitrobutane (**d2**), phosphazene base P_1-*t*-Bu, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), 4-(dimethylamino)pyridine (DMAP), NaOH and $NaHCO_3$ were from Fluka. THF was from Sigma-Aldrich, and was purified accordingly to known methods.[1] CO_2 was of a SFC/SFE grade (purity 99.998 %).

^1H and ^{13}C NMR spectra of ionic liquids were collected neat at 60 °C on a Varian Unity 400 MHz spectrometer by locking the sample on DMSO-d_6 placed in a sealed capillary blocked in a coaxial position by means of a Teflon insert in the NMR tube. INADEQUATE experiments were used to assign all the ^{13}C-NMR signals in TOMP[OCO_2Me] and, HMBC experiments were used to assign the peak of residual MeOH in the same samples, and HMQC to assign all ^1H peaks based on the correlation with the ^{13}C signals. The ^{13}C satellites were used, where possible, as internal standards to calculate the amount of impurities.[7] Since however the ^1H NMR spectra were acquired in the neat phase, the vast majority of all the resonance bands was rather broad, making integration very tricky and subject to a large error. A conservative estimate indicates that the purity of the ionic liquids was greater than 95%. ^1H NMR spectra of Michael products were collected in $CDCl_3$ solution at 25 °C on a Varian Unity 400 MHz spectrometer. Chemical shifts were reported in δ values downfield from TMS. GC/MS (EI, 70 eV) analyses were run using a HP5/MS capillary column (30 m).

6.2.2 Heterogeneous Catalysis

I. Catalysts preparation. Catalyst labeled $[KF/Al_2O_3]_M$ (table 2.5) was prepared through a standard impregnation tecnique.[6] A 25-mL round bottomed flask was charged with an aqueous solution (3.5×10^{-1} M, 10 mL) of KF (206 mg, 3.5 mmol) and with basic Al_2O_3 (10 g) from

Macherey Nagel. The slurry was kept under magnetic stirring for 1 hour at rt. Then, it was concentrated under vacuum (50 °C, 36 mbar) and dried (150 °C, 2 mbar, overnight). The final KF loading of the catalyst was 0.35 mmol g^{-1}.

Mesoporous alumina $[Al_2O_3]_{meso}$ (table 2.5) was prepared according to a procedure described in the literature.[3] In a 500 mL polypropylene reactor a mixture of Al(O-*s*-Bu)$_3$ (45.6 mL, 43.8 g, 178 mmol) and 1-propanol (450 mL, 360 g, 6 mol) was stirred for 10 min, and then H_2O (10.3 mL, 10.3 g, 572 mmol) was added. The solution was kept under magnetic stirring for 60 min at rt. then, a solution of lauric acid (10.8 g, 54 mmol) in 1-propanol (43.5 mL, 34.8 g, 580 mmol) was added. The mixture was stirred for 24 h at rt. After that, the reactor was sealed and the mixture was aged at 110 °C for 48 h without stirring. The solid was separated from the solution by centrifugation (6000 rmp), washed with ethanol (100 mL), centrifuged again and left drying in an open vessel at rt for 28 h. The white solid material was calcined at 600 °C (1 °C/min), for 4 h, in a stream of dried air (~10 mL/min).

All catalysts $[Al_2O_3]_B$, $[Al_2O_3]_M$, $[KF/Al_2O_3]_M$ and $[Al_2O_3]_{meso}$ (table 2.5) were stored under vacuum (70 °C, 18 mbar, overnight) before each reaction.

II. Michael reactions under solvent-free conditions. Reactions of figures 2.10, 2.11 and 2.13 were carried out accordingly to the following procedure. A 7 mL glass reactor equipped with a side screw-capped neck for the withdrawal of samples and a condenser, was charged with cyclohexenone (**a1**: 0.1 g, 1.04 mmol) and nitroethane (**d1**: 0.156 g, 2.08 mmol). Then the chosen catalyst {0.2 g, $[Al_2O_3]_B$, $[Al_2O_3]_M$, $[KF/Al_2O_3]_M$ and $[Al_2O_3]_{meso}$, see figures 2.10, 2.11 and 2.13 for details} was loaded and the reactor was heated at the desired temperature (40 °C). The mixture was kept under magnetic stirring throughout the reaction. Under these conditions the molar ratio **d1**:**a1** (W) was = 2, while the weight ratio catalyst:**a1** (Q) was = 2. For reaction of figure 2.10, samples (~0.01 mL) of the reaction mixture were withdrawn at 1, 2 and 4 hours, diluted with Et_2O (~2 mL), centrifuged and then analysed by GC/MS. All other reactions were carried out for 2 h and then analysed by GC/MS in the same way. The above described procedure was adapted for the following experiments [(i), (ii) and (iii)].

(i) recycling of catalyst $[Al_2O_3]_B$ (figure 2.12, a): a first experiment was carried out according to the above described procedure. At the end of the reaction catalysts was filtered, carefully washed with Et_2O (10 mL) and then transferred in a tubular quartz reactor. The re-activation was carried out at 400 °C (10 °C/min), for 2 h, in a stream of dried air (~80 mL/min). The solid was weighted: of the starting 200 mg, only 185 mg of $[Al_2O_3]_B$ were recovered. For the first recycling experiment conditions were adjusted to the amount of catalyst available: cyclohexenone (**a1**: 93 mg, 0.96 mmol) and nitroethane (**d1**: 144 mg, 1.92 mmol) were used

according to a molar ratio **d1**:**a1** (W) = 2 and a weight ratio catalyst:**a1** (Q) = 2. At the end of the reaction, the procedure of filtration/washing/calcination of the catalyst was repeated as described above, and 113 mg of $[Al_2O_3]_B$ were recovered. For the second recycling reaction, conditions were adjusted to the amount of catalyst: accordingly, **a1** (56 mg, 0.59 mmol) and **d1** (88 mg, 1.17 mmol) were used with W = 2 and Q = 2.

(ii) recycling of catalyst $[KF/Al_2O_3]_M$ (figure 2.12, b): the procedure was the same as described above for $[Al_2O_3]_B$. After the first reactivation of the catalyst, 140 mg of $[KF/Al_2O_3]_M$ were recovered. The corresponding reaction was carried out with cyclohexenone (**a1**: 70 mg, 0.73 mmol) and nitroethane (**d1**: 109 mg, 1.46 mmol) to have a molar ratio **d1**:**a1** (W) = 2 and a weight ratio catalyst:**a1** (Q) = 2. After the second reactivation of the catalyst, 135 mg of $[KF/Al_2O_3]_M$ were recovered and the reaction was carried out with **a1** (67 mg, 0.70 mmol) and **d1** (105 mg, 1.40 mmol), at W = 2 and Q = 2.

(iii) Michael reaction of nitrobutane and cyclohexenone (figure 2.16): the reactions were carried out according to the general reaction procedure, by charging the reactor with cyclohexenone (**a1**: 0.1g, 1.04 mmol), nitrobutane (**d2**: 0.214 g, 2.08 mmol), and the chosen catalyst {0.2 g, $[KF/Al_2O_3]_M$ and $[Al_2O_3]_{meso}$}.

III. Michael reaction using $scCO_2$ as a solvent. Reactions of figure 2.13 and 2.15 were carried out in a sealed steel autoclave (V = 5.3 mL) fitted with a pressure gauge and a thermocouple for temperature control. The autoclave was charged with cyclohexenone (**a1**: 0.1 g, 1.04 mmol), nitroethane (**d1**: 0.156 g, 2.08 mmol) and the chosen catalyst {0.2 g, $[Al_2O_3]_B$ and $[Al_2O_3]_{meso}$}. Under these conditions the molar ratio (W) **d1**:**a1** was = 2, the weight ratio (Q) catalyst:**a1** was = 2. The reactor was pressurized with CO_2 at approximately 60 bar[8] and electrically heated at the desired temperature (40 °C). The final pressure, 90 bar, was reached by slowly adding the remaining CO_2. Under these conditions, the molar fraction ($X_{\mathbf{a1}}$) of cyclohexenone in the CO_2 solution was $1.8x10^{-2}$. The reaction mixture was stirred throughout the reaction and after 2 h, after cooling at rt, the reactor was depressurized by bubbling CO_2 into a 5-mL vial of Et_2O. The content of the reactor was washed with additional Et_2O (5 mL), and the combined organic solutions were analyzed by GC/MS. This procedure was adapted for the experiments [(i) and (ii)] below described.

(i) reaction at different pressure of CO_2 (figure 2.14): these reactions were carried out using $[KF/Al_2O_3]_M$ as catalyst. Being all the other condition unaltered, the CO_2 pressure was set 80, 90, 120 and 150 bar (at 40 °C, CO_2 density d = 0.278, 0.485, 0.718 and 0.780 g mL^{-1}, respectively). Under these conditions, the molar fraction $X_{\mathbf{a1}}$ ranged from 3.1, 1.8, 1.2 to $1.1x10^{-2}$, respectively.

(ii) Michael reaction of nitrobutane and cyclohexenone in $scCO_2$ (figure 2.16): the reactions were carried out according to the general reaction procedure, charging the autoclave with cyclohexenone (**a1**: 0.1 g, 1.04 mmol), nitrobutane (**d2**: 0.214 g, 2.08 mmol), and the chosen catalyst {0.2 g, $[KF/Al_2O_3]_M$ and $[Al_2O_3]_{meso}$}.

IV. Michael reaction in conventional solvents. Reactions of figure 2.14 were carried out according to the following procedure. A 25 mL glass reactor equipped with a side screw-capped neck for the withdrawal of samples and a condenser, was charged with nitroethane (**d1**: 0.156 g, 2.08 mmol) and the catalyst {0.2 g, $[KF/Al_2O_3]_M$}. Then, a solution of cyclohexenone (**a1**) in the desired solvent (*n*-heptane or THF) was added. In all experiments the molar ratio **d1**:**a1** (W) was = 2, while the weight ratio catalyst:**a1** (Q) was = 2.

In the presence of *n*-heptane (d = 0.683 g mL^{-1}) as a solvent, four solutions at different molarity of cyclohexenone ($M_{\mathbf{a1}}$) were used. $M_{\mathbf{a1}}$ ranged from 0.21, 0.12, 0.08 to 0.07 mol L^{-1}. Accordingly, 5.0, 8.5, 12.7 and 13.8 mL of these solutions, respectively, were charged in the reactor. The corresponding molar fraction $X_{\mathbf{a1}}$ ranged from 3.1, 1.8, 1.2 to $1.1x10^{-2}$, respectively.

In the presence of THF (d = 0.889 g mL^{-1}) as a solvent, $M_{\mathbf{a1}}$ ranged from 0.37, 0.22, 0.15 to 0.13 mol L^{-1}. Thus, 2.8, 4.8, 7.1 and 7.7 mL of these solutions, respectively, were charged in the reactor. The corresponding molar fraction $X_{\mathbf{a1}}$ ranged from 3.1, 1.8, 1.2 to $1.1x10^{-2}$, respectively.

The reactor was heated at the desired temperature (40 °C) and the mixture was kept under magnetic stirring throughout the reaction. All reactions were carried out for 2 h and then analysed by GC/MS. This procedure was adapted for the experiments [(i) and (ii)] below described.

(i) reaction catalysed by $[Al_2O_3]_{meso}$ (figure 2.15): being all the other quantities and conditions unaltered, these reactions were carried out using catalyst $[Al_2O_3]_{meso}$ (0.2 g), and charging the reactor with 8.5 mL of a solution 0.12 M of **a1** in *n*-heptane, and 4.8 mL of a solution 0.22 M of **a1** in THF. Under these conditions, the molar fraction $X_{\mathbf{a1}}$ was = $1.8x10^{-2}$ (W = 2 and Q = 2).

(ii) Michael reaction of nitrobutane and cyclohexenone in conventional solvents (figure 2.16): these reactions were carried out at 40 °C, for 2 h, using 0.2 g of the chosen catalyst {$[KF/Al_2O_3]_M$ and $[Al_2O_3]_{meso}$}, 0.214 g of nitrobutane (**d2**: 2.08 mmol), and charging the reactor with 8.5 mL of a solution 0.12 M of **a1** in *n*-heptane, and 4.8 mL of a solution 0.22 M of **a1** in THF. Under these conditions, the molar fraction $X_{\mathbf{a1}}$ was = $1.8x10^{-2}$ (W = 2 and Q = 2).

6.2.3 Homogeneous Catalysis

I. Synthesis of phosphonium based ionic liquids. The synthesis of ionic liquid tri-*n*-octylmethylphosphonium methylcarbonate TOMP(OCO_2Me) was carried out according to the following procedure. 25 mL of TOP (20.8 g, 56 mmol), 30 mL of DMC (32.1 g, 356 mmol), and 30 mL of methanol were combined (two phases) in a sealed 200 mL steel autoclave fitted with a pressure gauge and a thermocouple for temperature control. Three freeze-pump-thaw cycles were carried out to ensure complete degassing of the mixture and air removal, the empty volume was then filled with nitrogen. The autoclave was heated for 20 h at 140 °C with magnetic stirring, after which time it was cooled and vented. Methanol and residual DMC were removed from the mixture by rotary evaporation (10^{-2} bar, 25 °C), to give 27.5 g of TOMP(OCO_2Me) (100% yield) as a viscous clear colorless liquid (mp < 0 °C). TOMP(OCO_2Me) was fully characterized by ^{1}H- and ^{13}C NMR spectra. A small amount (< 1 eq.) of methanol may remain incorporated even after prolonged high vacuum. It can be identified in the ^{1}H-NMR spectrum by an HMBC experiment.

The synthesis of ionic liquid tri-*n*-octylmethylphosphonium hydrogencarbonate TOMP(OCO_2H) was carried out by reaction of the precursor TOMP(OCO_2Me) with water. A 25-mL round bottomed flask was charged with TOMP(OCO_2Me) (3.0 g, 6.5 mmol) and 1 mL of water. The mixture was stirred under air at 40 °C for 2 hours. Excess water and methanol were removed under reduced pressure (10^{-3} bar, 60 °C) to yield 2.9 g (100 %) of TOMP(OCO_2H) as a viscous clear liquid that tends to solidify with time (mp ~ 25 °C). TOMP(OCO_2H) was fully characterized by ^{1}H- and ^{13}C NMR spectra.

II. General procedure for Michael reaction. For experiments reported in table 2.6 and figure 2.17, the following procedure was used. A 7-mL glass reactor equipped with a side screw-capped neck for the withdrawal of samples and a condenser, was charged with cyclohexenone (**a1**: 1.00 g, 10.4 mmol) and nitroethane (**d1**: 0.937 g, 12.5 mmol). Under these conditions the molar ratio **d1**:**a1** (W) was = 1.2.

Then, the catalyst [4.16 x 10^{-2} mmol: TOMP(OCO_2Me) (20 mg), TOMP(OCO_2H) (19 mg), phosphazene base P_1-*t*-Bu (10 mg), DBU (6 mg), DMAP (5 mg), NaOH (2 mg), DABCO (5 mg), $NaHCO_3$ (3 mg)] was loaded. The molar ratio catalyst:**a1** (W') was ~0.004.

The reactor was heated at the desired temperature (40 °C) and the mixture was kept under magnetic stirring throughout the reaction. For reactions of figure 2.17, at intervals, samples of the reaction mixture (~0.01 mL) were withdrawn, passed through a small column of silica gel (~0.25g of silica, eluent diethylether, ~2 mL) for catalyst removal, and then analysed by GC/MS.

All reactions were carried out for 2 h. At the end of each reaction, samples of the reaction mixtures were analysed by GC/MS as before.

The same equipment and reaction procedure were used to carry out the experiments reported in table 2.7. In all cases, TOMP(OCO_2H) was the catalyst. The other conditions were: *entry 1),* cyclohexenone (**a1**: 1.00 g, 10.4 mmol), nitroethane (**d1**: 973 mg, 12.5 mmol, W=1.2), catalyst (19 mg, 0.04 mmol, W'=0.004), 40 °C, 2 h; *entry 2),* cyclohexenone (**a1**: 1.00 g, 10.4 mmol), nitrobutane (**d2**: 1.287 g, 12.5 mmol, W=1.2), catalyst (50 mg, 0.1 mmol, W'=0.01), 40 °C, 14 h; *entry 3),* cyclohexenone (**a1**: 0.4 g, 4.16 mmol), dibenzoylmethane (**d3**: 448 mg, 2 mmol, W=0.5), catalyst (50 mg, 0.1 mmol, W'=0.02), 40 °C, 72 h; *entry 4),* cyclohexenone (**a1**: 1.00 g, 10.4 mmol), dimethylmalonate (**d4**: 1.650 g, 12.5 mmol, W=1.2), catalyst (50 mg, 0.1 mmol, W'=0.01), 40 °C, 2 h; *entry 5),* ethylvinylketone (**a2**: 874 mg, 10.4 mmol), nitroethane (**d1**: 937 mg, 12.5 mmol, W=1.2), catalyst (19 mg, 0.04 mmol, W'=0.004), 4 °C, 2 h; *entry 6),* ethylvinylketone (**a2**: 874 mg, 10.4 mmol), nitrobutane (**d2**: 1.287 g, 12.5 mmol, W=1.2), catalyst (19 mg, 0.04 mmol, W'=0.004), 4 °C, 2 h; *entry 7),* ethylvinylketone (**a2**: 0.5 g, 5.9 mmol), dibenzoylmethane (**d3**: 448 mg, 2 mmol, W=0.3), catalyst (25 mg, 0.05 mmol, W'=0.01), 4 °C, 2 h; *entry 8),* ethylvinylketone (**a2**: 874 mg, 10.4 mmol), dimethylmalonate (**d4**: 1.650 g, 12.5 mmol, W=1.2), catalyst (50 mg, 0.1 mmol, W'=0.01), 4 °C, 2 h.

6.2.4 Isolation and Characterization of Michael Adducts

Compound **m1** was isolated from both the experiments of figure 2.10 and entry 1 of table 2.7. In the case of experiment of figure 2.10, at the end of the reaction the catalyst $[Al_2O_3]_B$ was filtered and washed with diethylether (10 mL). The resulting solution was rotary evaporated and stripped of ether and residual reactants under vacuum (34 mbar, 45 °C). The crude product 3-(1-nitroethyl)-cylclohexanone (**m1**) was obtained with an isolated yield of 90%. The product was characterized by ^1H NMR.

Michael products **m1**, **m2**, **m4**, **m5**, **m6**, **m8** were isolated from experiments of table 2.7 (entries 1, 2, 4, 5, 6 and 8, respectively). At the end of reactions the catalyst was removed by filtration on silica gel (weight ratio silica: catalyst = 80, eluent diethylether, 30 mL). The resulting solution was rotary evaporated and stripped of ether and residual reactants under high vacuum. The products 3-(1-nitroethyl)-cylclohexanone (**m1**: colourless oil, yield 81%), 3-(1-nitrobutyl)-cyclohexanone (**m2**: pale yellow oil, yield 88%), 2-(3-oxocyclohexyl)malonic acid dimethyl ester (**m4**: pale yellow oil, yield 82%), 6-nitroheptane-3-one (**m5**: colourless oil, yield 94%), 6-nitrononane-3-one (**m6**: light brown oil, yield 95%) and 2-(3-oxopentyl)malonic acid dimethyl ester (**m8**: yellow oil, yield 81%) were characterized by GC/MS, ^{1}H NMR, and by comparison with literature data.

Michael addition products **m3** and **m7** were isolated from experiments of table 2.7 (entries 3 and 7, respectively) by flash-column chromatography (FCC) on silica gel, using petroleum ether (PE) and ethyl acetate (EA) as eluents (PE:EA = 2:1 v/v). The products 2-(3-oxocyclohexyl)-1,3-diphenylpropane-1,3-dione (**m3**: brown solid, yield 55%) and 2-benzoyl-1-phenylheptane-1,5-dione (**m7**: pale yellow solid, yield 90%) were characterized by GC/MS and ^{1}H NMR.

6.3. The Reaction of Glycerol Carbonate with Primary Aromatic Amines in the Presence of Y- and X-Faujasites

[Ch. 3, par. 1]

6.3.1 General

Anilines **2a-d** (p-$XC_6H_4NH_2$: **2a**: X=H; **2b**: X=Cl; **2c**: X=OMe; **2d**: X=OH), glycerine carbonate (GlyC), glycerine (Gly) and diglyme (diethylen glycol dimethyl ether) were ACS grade and were employed without further purification. Wherever used, water was of milli-Q grade. Zeolites were all of the faujasite (FAU) type: NaY_A, NaX were from Aldrich, while NaY_S was from Strem. Zeolite LiY was synthesized from NaY_A by an ion exchange reaction using LiCl.[9] Unless otherwise stated, the zeolites were dried under vacuum (70 °C, 18 mbar, overnight) before each reaction. GC/MS (EI, 70 eV) analyses were run using a HP5/MS capillary column (30 m). ^1H NMR were recorded at 400 MHz, ^{13}C NMR spectra at 100 MHz. Chemical shifts were reported in δ values downfield from TMS; $CDCl_3$ or CD_3OD were used as solvents.

*6.3.2 General Procedure for the Reaction of GlyC with Anilines **2a-d** (tables 3.1; table 3.2: entries 1, 3, 5, and 7)*

A glass reactor (7 mL) shaped as a test tube and equipped with a side screw-capped neck for the withdrawal of samples and a condenser, was charged with the chosen substrate (**2a-d**, 5.4 mmol; **2a**: 0.50 g, **2b**: 0.69 g, **2c**: 0.66 g, **2d**: 0.59 g), GlyC (0.76 g, 6.5 mmol, molar ratio GlyC:**2** was 1.2), diglyme (2 mL) and the faujasite NaY_A as a catalyst (the weight ratio FAU:**2** was 1.5). The reactor was then immersed in an oil bath thermostated at the desired temperature (90-170 °C, see tables 3.1-2 and figures 3.1-3 for details) and the mixture was kept under magnetic stirring throughout the reaction. At intervals, samples (~0.01 mL) of the reaction mixture were withdrawn, diluted with Et_2O and MeOH (~2 and 1 mL, respectively), centrifuged and then analysed by GC/MS.

The same procedure was used to run a single experiment under an inert atmosphere. In this case, once the mixture was charged in the reactor, air was carefully removed by 3 vacuum/N_2 cycles. The system was then equipped with a N_2-filled rubber reservoir (2 L) and kept under a static inert atmosphere throughout the reaction.

The above described procedure was adapted for the following experiments [(i) and (ii)].

(i) reactions with different catalyst loadings (figure 3.3): being all other conditions unaltered, the weight ratio Q=NaY_A:**2a** was set to 0.2, 0.5, 1, 1.5, and 2, respectively

(NaY_A=0.1, 0.25, 0.5, 0.75 and 1 g).

(ii) scale-up of the reactions (table 3.2: entries 2, 4, 6, 8): a round-bottomed glass flask (50 mL) equipped with a condenser and a side screw-capped neck for the withdrawal of samples, was charged with the chosen substrate (**2a-d**, 21.5 mmol; **2a**: 2.00 g, **2b**: 2.64 g, **2c**: 2.71 g, **2d**: 2.39 g), GlyC (3.04 g, 25.8 mmol, molar ratio GlyC:**2** was 1.2), diglyme (8 mL) and the faujasite NaY_A as a catalyst (the weight ratio FAU:**2** was 1.5). The reactor was then thermostated (oil bath) at the desired temperature (140-170 °C), with magnetic stirring. At intervals, samples of the reaction mixture were withdrawn and analysed by GC/MS.

*I. The reactions of water with 4-[(phenylamino)methyl]-1,3-dioxolan-2one (**4a**) and with glycerine carbonate [scheme 3.7, eqn. (1) and (2), respectively].* A cylindrical glass reactor (7 mL) equipped with a condenser, was charged with compound **4a** (0.20 g, 1.0 mmol), diglyme (1 mL) and dried faujasite NaY_A (0.3 g; the weight ratio FAU:**4a** was 1.5). The reactor was immersed in an oil bath thermostated at 140 °C, and the slurry was kept under magnetic stirring. Water (20 μL; the molar ratio H_2O:**4a** was 1) was added at once, by a microsyringe, to the mixture. After 5 hours, compound **4a** was recovered unaltered. An analogous procedure was used for the reaction of water with GlyC: a mixture of GlyC (0.76 g, 6.5 mmol), water (120 μL; the molar ratio H_2O:GlyC was 1), NaY_A faujasite (1.15 g; the weight ratio NaY_A:GlyC was 1.5), and diglyme (1 mL) was set to react at 140 °C. After 5 hours, GlyC was substantially hydrolysed to glycerine (conversion 80%, by ^{1}H NMR).

II. The reactions of glycerol with aniline or with 4-[(phenylamino)methyl]-1,3-dioxolan-2one [scheme 3.8, eqn. (1) and (2), respectively]. A cylindrical glass reactor (7 mL) equipped with a condenser, was charged with aniline (0.5 g, 5.4 mmol), glycerol (0.58 g, 6.3 mmol; the molar ratio Gly:aniline was 1.1), diglyme (1 mL), and dried faujasite NaY_A (0.75 g; the weight ratio FAU:aniline was 1.5). The reactor was immersed in an oil bath thermostated at 140 °C, and the slurry was kept under magnetic stirring. After 5 hours, the mixture was analysed by GC/MS: no reaction took place. An analogous procedure was used for the reaction of glycerol with compound **4a**: a mixture of **4a** (0.2 g, 1.0 mmol), glycerol (0.32 g, 3.5 mmol; the molar ratio Gly:aniline was 3.5), NaY_A faujasite (0.3 g; the weight ratio NaY_A:**4a** was 1.5), and diglyme (1 mL) was set to react at 140 °C. After 5 hours, the transesterification of **4a** with glycerol produced *N*-(2,3-dihydroxy)propyl aniline (**3a**) in a 35% amount (by GC/MS).

III. Recycle of the catalyst. Two sets (A and B) of recycling experiments were carried out by using the same catalyst (NaY_A) for three subsequent reactions (figures 3.4A and 3.4B, respectively). At the end of each reaction, the catalyst was filtered, thoroughly washed with methanol (100 mL) and then reactivated. In the first set (A), NaY_A was re-activated by drying it at 70 °C, under vacuum (18 mbar), overnight. In the second set (B), NaY_A was first dried overnight at room temperature. Then, the solid was placed in a tubular quartz reactor and calcined in a stream of dried air (~80 mL/min). The final calcination temperature (400 °C) was reached through a ramp of 10 °C/min, and it was kept for 3.5 hours. The catalyst was cooled to room temperature and directly used.

IV. The water loss from the catalyst. Two samples A and B (3.00 g each) of NaY_A were weighted as received, on an analytical balance: A was placed in a quartz reactor and calcined in dried air (400 °C, 4h, 80 mL/min), while B was dried at 70 °C, under vacuum (18 mbar), overnight. After the thermal treatment, both samples were cooled to room temperature (in dried air and under vacuum, respectively), and rapidly re-weighted three times in 1.0 min. The final weight values for both A and B were the average of the three measures.

6.3.3 Isolation and Characterization of the Products

All products **3a-d**, **4a-d**, **5a-c**, **6a** and **6c, d** were characterized by GC/MS. Compounds **3a-d**, **4a** and **4c** were isolated by flash-column chromatography (eluant: petroleum ether (PE) and ethyl acetate (EA), gradient elution: initial PE:EA= 9:1 v/v, final PE:EA= 1:9 v/v) and further characterized by ^{1}H and ^{13}C NMR.

6.4 Sequential Coupling of the Transesterification of Cyclic Carbonates with the Selective *N*-Methylation of Anilines Catalysed by Faujasites: a "Green Domino"

[Ch. 3, par. 2]

6.4.1 General

Anilines (R'$C_6H_4NH_2$; **2a**: R' = H, **2b**: R' = *p*-Cl, **2c**: R' = *p*-MeO, **2e**: R' = *p*-Me, **2f**: R' = *p*-NO_2), cyclic carbonates (**1b**: ethylene-; **1c**: propylene-carbonate), and dimethyl carbonate were ACS grade and were employed without further purification. Zeolites NaY and NaX were from Aldrich. The metal content of MX (M = Li, Na, K) and NaY catalysts was determined according to a procedure previously reported by us.[10] Table 6.1 summarizes the composition of these solids.

Table 6.1. Faujasite catalysts

Starting zeolite (Na, %) [a]	**Product**	**Ion exchange (%)** [b]
NaX (7.5)	LiX	71
NaX (7.5)	KX	92
NaY (8.1)		

[a] The Na content was evaluated through atomic adsorption (AA). [b] Percentage of ionic exchange (from NaX) was evaluated by AA (K) and emission (Li).

Before each reaction, all the faujasites were dried by heating at 70 °C, under vacuum (10 mmHg) overnight. MS (EI, 70 eV) analyses were run using HP5/MS capillary columns (30 m), respectively. ^1H NMR spectra were recorded on a 300 MHz spectrometer, using $CDCl_3$ as solvent.

6.4.2 Reactions Carried Out in Autoclave (tables 3.3, 3.4, 3.5, 3.6, and 3.8)

I. General. A stainless-steel autoclave (150 mL of internal volume) equipped with a pressure gauge, a thermocouple, and two needle valves, was charged with the mixture of reagents and the catalyst. At room temperature and before each reaction, air was purged with a N_2 stream. The autoclave was then heated by an electric oven, while the reaction mixture was kept under magnetic stirring. After the desired time interval, the autoclave was cooled to rt, vented and opened. The reaction mixture was analysed by GC/MS.

II. The transesterification of ethylene carbonate with methanol (table 3.3). A mixture of ethylene carbonate (EC: 2.2 g, 25 mmol), methanol (the volume was ranged from 8 to 30 mL), and the catalyst (MX; M = Li, Na. K; NaY, and HY; the weight ratio EC:faujasite was ranged from 4.8 to 31.4), was set to react at different temperatures (110-150 °C) for 5 hours. Major products were dimethyl carbonate and 2-(hydroxy)ethyl methyl carbonate (**10**). Both compounds were not isolated: they were identified by GC/MS. The structure of DMC was confirmed also by comparison to an authentic sample.

III. The methylation of aniline (table 3.4). A mixture of aniline (**2a**: 0.5 g, 5.4 mmol), ethylene carbonate (EC**:** the weight amount was ranged from 2.0 to 4.0 g; 23-46 mmol), methanol (the volume was ranged from 30 to 50 mL), and NaX (the weight ratio **2a**:NaX was ranged from 1 to 3), was set to react at temperatures of 130-180 °C, for different time intervals (4-24 h). Two additional tests were carried out in the absence of: a) ethylene carbonate; b) the zeolite. Products **11a** (mono-*N*-methyl aniline), **13a** [*N*-(2-hydroxyethyl)aniline], and **14a** [*N*-(2-hydroxyethyl),*N*-methylaniline] were not isolated: they were identified by GC/MS and by comparison to authentic samples (only for **11a** and **13a**). Product **12a** (bis-*N*-methylaniline) was isolated as reported below.

IV. The methylation of primary aromatic amines (table 3.5). A mixture of a primary amine ($R'C_6H_4NH_2$: 0.5 g; **2b**: R' = *p*-Cl; **2c**: R' = *p*-MeO; **2e**: R' = *p*-Me; **2f**: R' = *p*-NO_2), ethylene carbonate (1.4-3.5 g; the molar ratio EC:**2** was ranged from 4 to 8.5), methanol (50 mL), and NaX (0.5 g), was set to react at temperatures of 180-200 °C, for different time intervals (8-28 h). Under the same conditions, reactions of *p*-anisidine, *p*-toluidine, *p*-chloroaniline, and aniline were carried out using propylene carbonate (PC: 3.5-4.0g; the molar ratio PC:**2** was of 8.5) in place of ethylene carbonate.

At 190 °C, the reaction of aniline and *p*-anisidine (0.5 g, 5.4 and 4.1 mmol, respectively) were also performed by decreasing the amounts of both NaX (0.1 g) and ethylene carbonate (1.1-1.4 g; the molar ratio EC:**2** was 3).

V. The reaction of aniline with ethylene carbonate in presence of ethanol or of n-propanol (table 3.6). A mixture of aniline (**2a**: 0.5 g, 5.4 mmol), ethylene carbonate (4.0 g; 45.5 mmol), ethanol or *n*-propanol (the volume was ranged from 50 to 110 mL), and NaX (0.5 g), was set to react at temperatures of 180-200 °C, for 15 hours. Products **15a** (mono-*N*-ethylaniline), **13a** [*N*-(2-hydroxyethyl)aniline], and **16a** (*N*-phenylmorpholine) were not isolated: they were identified by GC/MS and by comparison to authentic commercial samples.

VI. The reaction of aniline with ethylene carbonate in presence of glycerol (table 3.7). A stainless steel autoclave (45 mL) was charged with a mixture of aniline (0.5 g, 5.4 mmol), ethylene carbonate (0.5 g, 5.75 mmol), zeolite (NaX, 0.5 g, entries 1-4; NaY, 0.5 g, entries 5-7), and glycerol (whose amount was ranged from 3g, 32.5 mmol, entries 1-2 and 5-6, to 5 g, 54.2 mmol, entries 3, 4 and 7). Before each reaction, at room temperature, the autoclave was degassed under a moderate vacuum (20 mm), and purged with a N_2 stream. In the reactions carried out in presence of CO_2 (entries 2-4 and 6-7), at rt, the autoclave was pressurized up to 60 bar with the gas. The reactor was electrically heated at 140 °C (in one experiment the temperature was set to 170 °C), and in the reactions carried out in presence of CO_2, the pressure was set to 120 bar adding more CO_2 through the valve on the head of the autoclave. High pressure CO_2 was available thanks to the syringe pump described in paragraph 6.1. The reaction mixture was kept under a magnetic stirring throughout the reaction. After the desired time, the autoclave was cooled to rt, vented and opened. The mixture was analysed by GC/MS.

6.4.3 Isolation and Characterization of N,N-dimethyl Anilines (R'$C_6H_4NMe_2$: R' = H, p-MeO, p-Me, p-Cl)

Under the conditions of entry 13 in table 3.4, and of entries 2, 5, 7 in table 3.5, once reactions were completed (8-28 h), final mixtures were filtered, and methanol was removed by rotary evaporation. The viscous residues were purified by flash-chromatography on silica gel (F60; eluant: petroleum ether/diethyl ether, 95:5 v/v). *N*,*N*-dimethyl- aniline, *p*-anisidine, *p*-toluidine, and *p*-chloroaniline, were obtained in isolated yields of 85% (0.55 g), 98% (0.60 g), 78% (0.49 g), and 87% (0.53 g), respectively. All *N*,*N*-dimethyl anilines were known products, whose characterization was carried out by ^{1}H NMR and GC/MS, and by comparison to commercial authentic samples. The spectroscopic/physical properties were in full agreement to those reported in the literature.[11]

6.4.4 The Competitive Reactions of Aniline with Ethylene Carbonate and Dimethyl Carbonate (figure 3.5)

Two sets of experiments were performed at 90 °C and at 140 °C, respectively. At 90 °C (refluxing temperature of DMC; method A), reactions were carried out using standard laboratory glassware. At 140 °C (method B), reactions were run in an autoclave.

I. Method A. A two-necked, round-bottomed, 50-mL flask fitted with a reflux condenser, a magnetic stirring bar, and an adapter for the withdrawal of samples, was charged with a mixture of aniline (0.5 g, 5.4 mmol), DMC (10 g, 111 mmol), NaX (0.5 g), and ethylene carbonate (9.7 g, 111 mmol). The mixture was placed under a nitrogen atmosphere at room temperature, and then heated in an oil bath at 90 °C. At intervals, aliquots (0.2 mL) of the mixture were analyzed by GC/MS, and products **11a** (mono-*N*-methylaniline) and **13a** [*N*-(2-hydroxyethyl)aniline] were identified accordingly. Four subsequent experiments were carried out with the same procedure: being other conditions unaltered, the amount of ethylene carbonate was decreased to 1.9, 0.97, 0.48, and 0.24 g (21.6, 11.0, 5.5, and 2.7 mmol), respectively.

II. Method B. A stainless steel autoclave (45 mL) was charged with a mixture of aniline (0.5 g), DMC (10 g), NaX (0.5 g), and ethylene carbonate (whose amount was ranged from 9.7, 1.9, 0.97, and 0.48 g). Before each reaction, at room temperature, the autoclave was degassed under a moderate vacuum (20 mm), and purged with a N_2 stream. The reactor was electrically heated at 140 °C, while the mixture was kept under a magnetic stirring throughout the reaction. After the desired time interval, the autoclave was cooled to rt and opened. The mixture was analysed by GC/MS.

III. The competitive reactions of aniline with ethylene carbonate and dimethyl carbonate, in presence of different co-solvents (table 3.8). The experiments were performed according to the procedure described for method B. A 45-mL autoclave was charged with aniline (0.5 g,), DMC (10 g), NaX (0.5 g), and ethylene carbonate (0.97g), in presence of a co-solvent. In particular, cyclohexane (20 and 40 mL), dimethoxyethane (20 mL), and *N,N*-DMF (20 and 40 mL) were used in five subsequent tests carried out at 140 °C.

6.5 The Reaction of Primary Aromatic Amines with Alkylene Carbonates in Presence of Phosphonium-based Ionic Liquids as Catalysts

[Ch. 3, par. 3]

6.5.1 General

Anilines **2a-c**, **e** (*p*-$XC_6H_4NH_2$: **2a**: X=H; **2b**: X=Cl; **2c**: X=OMe; **2e**: X=Me), ethylene carbonate (EC), propylene carbonate (PC) and tri-isobutylmethylphosphonim tosylate (**PIL1**) were ACS grade and were employed without further purification. **PIL2-13** were prepared accordingly to the method described in paragraph 6.2.3. GC/MS (EI, 70 eV) analyses were run using a HP5/MS capillary column (30 m). ^1H NMR were recorded at 400 MHz, ^{13}C NMR spectra at 100 MHz, ^{31}P NMR spectra were recorded at 200 MHz. Chemical shifts were reported in δ values downfield from TMS; $CDCl_3$ or CD_3OD were used as solvents. ^{31}P chemical shifts were referenced with respect to 85% orthophosphoric acid (as external standard).

6.5.2 Reaction Procedure

I. The bis-N-(2-hydroxy)ethylation of aniline in the presence of different ionic liquids (table 3.12). A glass reactor (7 mL) shaped as a test tube and equipped with a side screw-capped neck for the withdrawal of samples and a condenser, was charged with aniline (**2a**, 0.80 g, 8.6 mmol), ethylene carbonate (EC, 1.51 g, 17.2 mmol, molar ratio EC:**2a** was 2), and a PIL (0.86 mmol, molar ratio **PIL**:**2a** was 0.1). The chosen catalysts were **PIL**s **1-4** and **9-12**. The reactor was then immersed in an oil bath thermostated at the desired temperature (170 °C) and the mixture was kept under magnetic stirring throughout the reaction. At intervals, samples of the reaction mixture were withdrawn and analysed by GC/MS. The procedure was used to run an experiment also in the absence of PILs. The above described procedure was adapted for the following experiments [(*i*)-(*v*)]:

(i) reactions with different catalyst loadings (figure 3.6): being all other conditions unaltered, the molar ratio Q=**PIL1**:**2a** was set to 0.05, 0.1, 0.2, 0.5 and 0.75, and the reaction temperature was set to 150 °C;

(ii) reactions with different ethylene carbonate loadings (table 3.10): being all other conditions unaltered, the molar ratio EC:**2a** was set to 2.2 and 4, and the reaction temperature was set to 150 or to 170 °C;

(iii) reactions with added water or aq. HBr (scheme 3.29): being all other conditions unaltered, water (0.015 g, 0.86 mmol, molar ratio H_2O:**2a** was 0.1) or an aqueous solution of HBr [48%] (0.1 mL, HBr 0.88 mmol, molar ratio HBr:**2a** was 0.1) were added. The reaction

temperature was set to 170 °C;

(iv) reactions of different anilines with ethylene carbonate (table 3.13): the glass reactor was charged with the amine (**2b**, **c** and **e**, 8.6 mmol; **2b**: 1.09 g, **2c**: 1.06 g, **2e**: 0.92 g), ethylene carbonate (EC, 1.66 g, 18.9 mmol, molar ratio EC:**2** was 2.2), and a PIL (0.86 mmol, molar ratio PIL:**2** was 0.1). The chosen catalysts were **PIL1** and **PIL12**. The reactor was then immersed in an oil bath thermostated at the desired temperature (150-170 °C);

(v) reactions of different amines with propylene carbonate (table 3.14): the glass reactor was charged with the amine (**2a**, **c**, 8.6 mmol; **2a**: 0.8 g, **2c**: 1.06 g), propylene carbonate (PC, 1.93 g, 18.9 mmol, molar ratio PC:**2** was 2.2), and a PIL (0.86 mmol, molar ratio **PIL**:**2** was 0.1). The chosen catalysts were **PIL1, PIL9**, and **PIL12**. The reactor was then immersed in an oil bath thermostated at the desired temperature (150-190 °C).

6.5.3 Synthesis of PILs (table 3.11)

*I. Synthesis of methyltrialkylphosphonium methylcarbonate salts **PIL5-8.*** According to the procedure previously described in paragraph *6.2.3.I*, a sealed 200 mL steel autoclave fitted with a pressure gauge and a thermocouple for temperature control was charged with a trialkylphosphine (R_3P, 56 mmol; R= *i*-butyl, 15 mL, 12.2 g; R= *n*-butyl, 15 mL, 12.2 g; R= *n*-hexyl, 20 mL, 16.2 g; R= *n*-octyl, 25 mL, 20.8 g), dimethyl carbonate (30 mL, 32.1 g, 356 mmol) and methanol (30 mL). Three freeze–pump–thaw cycles were carried out to ensure complete degassing of the mixture and air removal. The empty volume was then filled with nitrogen. The autoclave was heated for 24 h at the desired temperature (140 °C: R= *n*-octyl, *n*-hexyl, *n*-butyl; 170 °C: R= *i*-butyl) with magnetic stirring. Then, the reactor was cooled to rt and vented. Methanol and the residual DMC were removed from the mixture by rotary evaporation. A small amount (<1 equiv) of methanol could remain incorporated in the sample even after a prolonged high vacuum was applied. Isolated yields were: **PIL6** (17.4 g) 96%; **PIL7** (21.5 g) 94%; **PIL8** (27.5 g) 100%. These salts were fully characterized as such, by ^{1}H and ^{13}C NMR, and used without further purifications. **PIL5** (15.8 g, 87 %) was washed with *n*-hexane (3x15 mL) to remove some unreacted phosphine; then, it was characterized and used.

II. General anion exchange reaction procedure. **PIL2-4** and **PIL9-13** were provided by the research group. They were prepared according to the following procedure. A 50-mL round-bottomed flask was charged with an equimolar mixture of methyltrialkylphosphonium methylcarbonate (**PIL5-8;** 6 mmol, 1.75-2.76 g) and of a Brønsted acid (H–A: A= TosO, Br, or I), and methanol (5 mL) as a co-solvent. TosOH·H_2O (1.14 g) was used as a solid, while both HBr (0.68 mL) and HI (0.79 mL) were used as aqueous commercial solutions (48% and 57%, respectively). The mixture was kept under magnetic stirring for 1 h at 40 °C. Then, water and methanol were removed by rotary evaporation. The desired **PIL2-4** and **PIL9-13** were obtained in quantitative yields and fully characterized as such, by ^{1}H and ^{13}C NMR. They were used without further purifications.

6.5.4 Isolation and Characterization of the Products

All the reaction products **13**, **17**, **16** and **18** (**a-c** and **e**), and **19**, **20**, **21** and **22** (**a** and **c**) were characterized by GC/MS. Compounds **17** (**a-c** and **e**) and **20** (**a** and **c**) were isolated and fully characterized by ^{1}H and ^{13}C NMR.

Bis-*N*-(2-hydroxy)ethyl aniline, **17a**.[12] The product was isolated from the reactions carried out under the conditions of entries 9 and 12 of table 3.10. The final mixtures were purified by flash column chromatography (FCC) on silica gel, using a gradient elution with methanol/diethyl ether/petroleum ether (PE) solutions (initial MeOH:Et_2O:PE = 0:1:4 v/v, final MeOH:Et_2O:PE = 1:7.5:1.5 v/v). Compound **17a** was a dark yellow oil (74 and 61% respectively, table 3.10).

Bis-*N*-(2-hydroxy)ethyl *p*-anisidine, **17c**.[12a,13] The product was isolated from the reaction carried out under the conditions of entry 4 of table 3.13. The final mixture was purified by flash column chromatography (FCC) on silica gel, using a ethyl acetate (EA)/petroleum ether (PE) solution (EA:PE = 3:1 v/v). Compound **17c** was isolated as brown solid (74%).

Bis-*N*-(2-hydroxy)ethyl *p*-toluidine, **17e**.[13] The product was isolated from the reaction carried out under the conditions of entry 5 of table 3.13. The final mixture was purified by flash column chromatography (FCC) on silica gel, using a gradient elution with EA/PE solutions (initial EA:PE = 1:1 v/v, final EA:PE = 3:1 v/v). Compound **17e** was a dark brown solid (70%).

Bis-*N*-(2-hydroxy)ethyl *p*-chloroaniline, **17b**.[13] The product was isolated from the reaction carried out under the conditions of entry 6 of table 3.13. The final mixture was purified by flash column chromatography (FCC) on silica gel, using a EA/PE solution (EA:PE = 1:1 v/v). Compound **17b** was a pale brown solid (62%).

Bis-*N*-(2-hydroxy)propyl aniline, 20a. The product was isolated from the reaction carried out under the conditions of entry 4 of table 3.14. The final mixture was purified by flash column chromatography (FCC) on silica gel, using a gradient elution with EA/PE solutions (initial EA:PE = 7:3 v/v, final EA:PE = 3:7 v/v). Compound **20a** (sum of diastereoisomers) was isolated as a pale yellow oil (58%).

Bis-*N*-(2-hydroxy)propyl *p*-anisidine, 20c.[14] The product was isolated from the reaction carried out under the conditions of entry 6 of table 3.14. The final mixture was purified by flash column chromatography (FCC) on silica gel, using a gradient elution with EA/PE solutions (initial EA:PE = 7:3 v/v, final EA:PE = 3:7 v/v). Compound **20c** was a brown oil (55%).

6.6 Decarboxylation of Dialkyl Carbonates to Dialkyl Ethers over Alkali Metal-exchanged Faujasites

[Ch. 4, par. 1]

6.6.1 General

All reagents used [K_2CO_3, dimethylcarbonate (DMC), diethylcarbonate (DEC), glycerine carbonate (GlyC), dimethoxyethane, cyclohexane, *n*-propanol, propyl chloroformate, and *n*-octanol] were ACS grade and were employed without further purification. GlyC was a generous gift from Huntsman Corporation. Faujasites NaY and NaX were commercial samples from Aldrich (art. # 334448 and 28,359-2); LiY and CsY were synthesized from NaY by an ion exchange using LiCl and CsCl precursors.[15] Hydrotalcite KW2000 was from Kyowa Chemical Industry Co. Tokyo, ($Mg_{0.7}Al_{0.3}O_{1.15}$) with a specific surface area 202 m^2 g^{-1}. The catalysts (faujasites, hydrotalcite, and K_2CO_3) were stored under vacumm (8 mbar) at 70 °C. In two additional experiments, two samples of NaY were activated in a stream of dry air (10 mL/min), at 200 and 400 °C, respectively. GC/MS (EI, 70 eV) analyses were run using a HP5/MS capillary column (30 m). The infrared spectra have been recorded on a Bruker Vertex 70 FTIR spectrometer equipped with a Ge/KBr beamsplitter, a Globar source, and a DTGS detector.

I. Dipropyl carbonate (DPrC). DPrC was prepared by adjusting a general method for the synthesis of dialkyl carbonates:[16] a 250-mL 2-necked flask equipped with a condenser and a dropping funnel, was charged with a mixture of *n*-propanol (0.33 mmol, 20 g) and pyridine (0.34 mmol, 27 g). The flask was cooled at 0 °C and propyl chloroformate (0.31 mmol, 38 g) was added dropwise under vigorous stirring. The mixture was allowed to reach rt. Then, aq. HCl (5%, 30 mL) was added. The organic phase was extracted with diethyl ether (2x120 mL), and dried over Na_2SO_4. The product DPrC was distilled (bp = 83°C at 86 mbar; Y= 35 g, 77%) and characterized by GC/MS and ^{1}H NMR.

II. Dioctylcarbonate (DOC). DOC was prepared by the transesterification reaction of *n*-octyl alcohol with DMC, accordingly to a procedure already reported.[17] Starting from 26 g (0.2 mol) of *n*-octanol, DOC was isolated in a 68% yield (20 g) and characterized by GC/MS and ^{1}H NMR.

6.6.2 Reaction Procedure

I. The decarboxylation of DMC: general procedure. A 120-mL stainless steel autoclave fitted with two valves, a pressure gauge and a thermocouple for temperature control, was charged with

DMC and the catalyst. The autoclave was closed and, after a careful air removal by 3 vacuum/N_2 cycles, it was electrically heated at the desired temperature. The reaction mixture was kept under magnetic stirring throughout the experiments. The following conditions and amounts of DMC/catalyst were used:

(i) figure 4.1: 10 mL (10.7 g, 119 mmol) of DMC and 600 mg of the catalyst (weight ratio, *Q*, catalyst: DMC = 0.056). Catalysts were NaX and NaY faujasites, and hydrotalcite (HT: KW2000). The reaction temperature was in the range of 150-220 °C, and the reaction time was 6 hours.

(ii) figure 4.2: 10 mL (10.7 g, 119 mmol) of DMC and 600 mg of the catalyst (weight ratio, *Q*, catalyst: DMC = 0.056). Six catalysts were used: LiY, NaY, CsY and NaX faujasites, hydrotalcite (HT: KW2000), and K_2CO_3. The reaction temperature was 200 °C and the reaction time was 6 hours.

(iii) figure 4.3(a): 10 mL (10.7 g, 119 mmol) of DMC were set to react with increasing quantities (from 160 to 900 mg) of both NaY and NaY. The weight ratio, *Q*, catalyst:DMC was ranged from 0.015 to 0.084. The reaction temperature was 200 °C and the reaction time was 6 hours.

(iv) figure 4.3(b): 10 mL (10.7 g, 119 mmol) of DMC and 600 mg of the catalyst (weight ratio, *Q*, catalyst: DMC = 0.056). Catalysts were NaY or NaX faujasites. The reaction temperature was 200 °C, and the reaction time was in the range of 1-18 hours.

At the end of each experiment, the autoclave was cooled to room temperature. In order to recover the gaseous products of the reaction, CO_2 and dimethyl ether (DME), the autoclave was purged by a low temperature trap-to-trap apparatus. The system is outlined in figure 6.4.

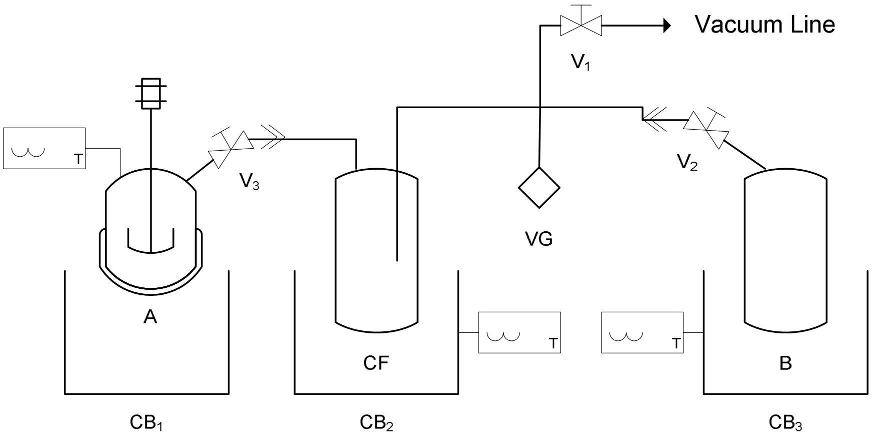

Figure 6.4. The apparatus used for the recovery of gaseous CO_2 and dimethyl ether.
A: autoclave; CB: cooling bath; CF: cold finger; B: air-tight Drechsel bottle; V: valve; VG: vacuum gauge; T: temperature control

A vacuum line was equipped with a cold finger (250 mL, CF) and a drechsel bottle (250 mL, B). By valves V_1-V_2, the whole system was set to a pressure $\leq$ 1 torr. This was continuously monitored by a vacuum gauge (VG). Then, the autoclave (A) containing the reaction mixture, the finger CF, and the bottle B were simultaneously dipped in three cooling baths (CB_1, CB_2, and CB_3) set at -60 °C, -196 °C, and -196 °C, respectively. The valves V_1-V_2 were closed and the autoclave was connected to CF by opening V_3: once the pressure of the system reached a constant value (~ 150 torr), V_1 was opened to vent N_2 charged in the reactor at the beginning of the experiment. Then, V_1 was closed and the bath CB_1 was brought to -20 °C. At this temperature, V_3 allowed to purge the reaction products, CO_2 and DME, from the autoclave. Both compounds were condensed in CF along with a very small fraction ($\leq$ 0.5 mL) of the residual DMC. V_3 was closed and acetone was added to the bath CB_2 until it reached –50 °C. Then, V_2 was opened to convey selectively CO_2 and DME from CF to the bottle B, while DMC remained in CF. Eventually, V_3 was closed. The bottle B was disconnected from the vacuum line, allowed to return gradually to ambient temperature, and weighted. The gaseous mixture in the bottle was then analysed by GC/MS.

The conversion of DMC reported in figures 4.1, 4.2 and 4.3 was calculated by the total mass (and molar) amounts of CO_2 and DME, according to the stoichiometry given in scheme 4.2. MS spectra of both CO_2 and DME gave a match quality higher than 97% when compared to standard products of the Wiley-MS database.[18] The structure of DME was further confirmed by the comparison of the IR spectrum of the reaction mixture with that of an authentic sample of DME (details are given in the appendix).

II. The decarboxylation of DEC and DPrC. The decarboxylation of both DEC and DPrC were carried out according to the procedure described for DMC. The following conditions and amounts of dialkyl carbonate/catalyst were used.

DEC, figure 4.4: 10 mL (83 mmol) of DEC and 550 mg of the catalyst (weight ratio, *Q*, catalyst: DEC = 0.056). Catalysts were NaX and NaY faujasites. The reaction temperature was in the range of 180-240 °C, and the reaction time was 6 hours. The GC/MS analysis of the gas phase showed the presence of CO_2 as a sole product: its (weighted) mass amount allowed to calculate the conversion of DEC. The GC/MS analysis of the residual liquid mixture in the autoclave showed two products: diethyl ether (major, >90% at complete conversion) and ethanol (trace amounts, 3-5%). The analysis of the liquid phase also offered the possibility to determine the conversion of DEC whose values matched (within ± 3%) those calculated from the weight of

CO_2. The structure of diethyl ether and ethanol were confirmed by their mass spectra and by comparison with authentic commercial samples.

DPrC, scheme 4.4: 8.8 mL (56 mmol) of DPrC and 300 mg of the faujasite (the weight ratio, Q, catalyst:DPrC = 0.036). The temperature was set at 220 and 240 °C for 6 and 12 hours, respectively. CO_2 and propylene were detected as gaseous products. MS spectra of both compounds gave a match quality higher than 95% when compared to standard products of the Wiley-MS database.[18] However, the conversion of DPrC could not be estimated from the weighted amounts of CO_2 and propene.[19] The GC/MS analysis of the residual liquid mixture in the autoclave showed two products: dipropyl ether (17-40%) and *n*-propanol (23-60%). The structure of dipropyl ether and *n*-propanol were confirmed by their mass spectra and by comparison with authentic commercial samples.

III. The reaction of dioctyl carbonate (DOC) and glycerol carbonate (GlyC). The reaction of both DOC and GlyC were carried out with the same procedure used for DMC. However, due to the viscosity of the starting carbonates, a solvent was necessary. The following conditions and amounts of dialkyl carbonate/catalyst were used.

DOC, scheme 4.6: 2.0 g (10.8 mmol) of DOC, 120 mg of NaX faujasite (the weight ratio, Q, catalyst:carbonate, was 0.06), and cyclohexane (9 mL) as solvent. The reaction temperature was set at 240 °C, and the reaction time was 6 hours. The GC/MS analysis of the gas phase showed CO_2 as a sole product. The GC/MS analysis of the residual liquid mixture in the autoclave showed the presence of unreacted DOC (42%), dioctyl ether (7%), *n*-octanol (28%), and isomeric octenes (mixture of 1-octene, 2-octene and other octenes: total of 23%). The structure of dioctyl ether, *n*-octanol, 1-octene and 2-octene was confirmed by their mass spectra and by comparison with authentic commercial samples.

GlyC, scheme 4.7: 2.0 g (17 mmol) of GlyC, 120 mg of NaX faujasite (the weight ratio, Q, catalyst:carbonate, was 0.06), and dimethoxyethane (9 mL) as solvent. The reaction temperature was set at 240 °C, and the reaction time was 6 hours. The GC/MS analysis of the residual liquid mixture in the autoclave showed the formation of several products. Among them, glycerol (10-12%) and glycidol (3-5%) were detected. The structure of both compounds were confirmed by their mass spectra and by comparison with authentic commercial samples.

6.7 The Reaction of Glycerol Carbonate with Phenol in the Presence of NaY Zeolites [Ch. 4, par. 2]

6.7.1 General

Phenol (**23**), glycerine carbonate (GlyC) and triglyme (triethylen glycol dimethyl ether) were ACS grade and were employed without further purification. Faujasite NaY_A was from Aldrich. Unless otherwise stated, NaY_A were dried under vacuum (70 °C, 18 mbar, overnight) before each reaction. GC/MS (EI, 70 eV) analysis were run using a HP5/MS capillary column (30 m).

6.7.2 General Procedure for the Reaction of GlyC with Phenol

A glass reactor (7 mL) shaped as a test tube and equipped with a side screw-capped neck for the withdrawal of samples and a condenser, was charged with phenol (**23**, 5.3 mmol, 0.50 g), GlyC (0.76 g, 6.5 mmol, molar ratio W = GlyC:**23** was 1.2), triglyme (2 mL) and the faujasite NaY_A as a catalyst (the weight ratio Q = NaY_A:**23** was 1.5). The reactor was then immersed in an oil bath thermostated at the desired temperature (140-200 °C, see tables 4.1 for details) and the mixture was kept under magnetic stirring throughout the reaction. After 6 h, samples of the reaction mixtures were withdrawn and analysed by GC/MS.

The above described procedure was used for the experiments (i), (ii) and (iii) below described:

(i) reactions with different catalyst loadings (figure 4.5): being all other conditions unaltered, GlyC (1.77 g, 15.0 mmol, molar ratio W = 2.8) was charged and the weight ratio Q = NaY_A:**23** was set to 0.75, 1.5, 3 and 4, respectively (NaY_A = 0.375, 0.75, 1.5 and 2.0 g). Reactions were carried out for 18 h at 200 °C.

(ii) reactions with different GlyC loadings (table 4.2): being all other conditions unaltered, NaY_A (0.75 g, Q = NaY_A:**23** = 1.5) were charged and the molar ratio W = GlyC:**23** was set to 2.8, 4.0 and 5.0, respectively (GlyC = 1.77, 2.51 and 3.14 g; 15.0, 21.3 and 22.6 mmol). Reactions were carried out for 18 h at 200 °C. In another set of experiments the molar ratio W = GlyC:**23** was set to 1.2, 4.0 and 5.0, respectively (GlyC = 0.76, 2.51 and 3.14 g; 6.5, 21.3 and 22.6 mmol) and 0.375 g of NaY_A (Q = NaY_A:**23** = 0.75) were used.

(iii) reactions at different temperature (figure 4.6-7): being all other conditions unaltered, NaY_A (0.75 g, Q = NaY_A:**2a** = 1.5) was charged and the molar ratio W = GlyC:**23** was set to 5.0 (GlyC = 3.14 g, 22.6 mmol). Reactions were carried out for 18 h at 180, 200 and 220 °C.

6.7.3 Isolation and Characterization of the Products

Any attempt to isolate compounds **24**, **25** and **26** by flash column chromatography (FCC) on silica gel was unsuccessful. In all cases, the separation was not efficient, and the products were eluted together with unreacted GlyC. Ethyl acetate (EA), petroleum ether (EP), methanol (MeOH) and diethyl ether (Et_2O) were tested as eluant solutions: *i*) gradient elution with EA/PE solutions (initial EA:PE = 1:1 v/v, final EA:PE = 5:1 v/v); *ii*) gradient elution with methanol/diethyl ether/petroleum ether (PE) solutions (initial MeOH:Et_2O:PE = 0:0.5:4 v/v, final MeOH:Et_2O:PE = 1:7.5:1.5 v/v); *iii*) gradient elution with EA/PE solutions (initial EA:PE = 7:5 v/v, final EA:PE = 3:7 v/v); *iv*) ethyl acetate (EA)/petroleum ether (PE) solution (EA:PE = 2:1 v/v). The structure of compounds **24**, **25** and **26** wasassigned by GC/MS.

References

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[5] Three freeze-pump-thaw cycles were carried out to ensure complete degassing of 1-octene before the reaction.

[6] See, for example, P. Qiu, B. Yang, C. Yi and S. Qi, *Catal. Lett.*, 2010, **137**, 232-238.

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[8] CO_2 at 200 bar was available through the ISCO 260D syringe pump described in paragraph 6.1.3, for the methatesis of olefins under batch condition.

[9] M. Onaka and K. Ishikawa,Y. Izumi, *Chem. Lett.* 1982, 1783-1786.

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[12] (a) W. C. J. Ross, *J. Chem. Soc.*, 1949, 183-191 (b) M. H. Benn, L. N. Owen and A. M. Creighton, *J. Chem. Soc.*, 1958, 2800-2810; (c) A. Clerici, A. Ghilardi, N. Pastori, C. Punta, O. Porta *Org. Lett.* 2008, **10**, 5063-5066.

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[14] A. H. Sommers, U. Biermacher, S. B. Brehm and J. H. Short, *J. Med. Chem.*, 1970, **13**, 581-583.

[15] The ionic exchange reaction was carried out as described by M. Onaka, K. Ishikawa and Y. Izumi, Chem. Lett., 1982, 1783. The percentage of ion exchange was determined according to a method previously reported by us (M. Selva, P. Tundo, and A. Perosa *J. Org. Chem.* 2002, **67**, 9238-9247): based on initial Na, this was 67% and 56%, for Li and Cs, respectively.

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[18] Wiley Library of Mass Spectral Data, 2002: software of the GC/MS instrument.

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[19] Unfortunately, the GC signals of CO_2 and propylene could not be perfectly resolved and an estimation of the CO_2 amount was not possible. As a consequence, the conversion of DPrC could not be calculated from the weight of gaseous products.

APPENDIX

A.1 The Metathesis of α-Olefins over Supported Re-Catalysts in Supercritical CO_2 [Ch. 2, par. 1]

I. Metathesis of 1-octene

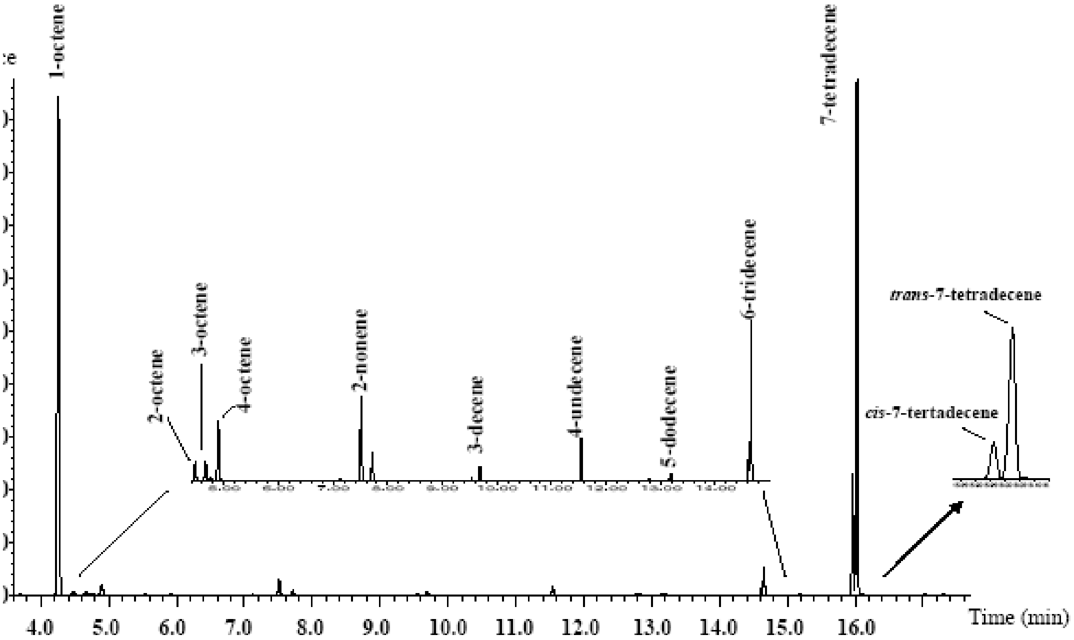


Figure A.1. Batch conditions. GC/MS of the self-metathesis of 1-octene in dense CO_2

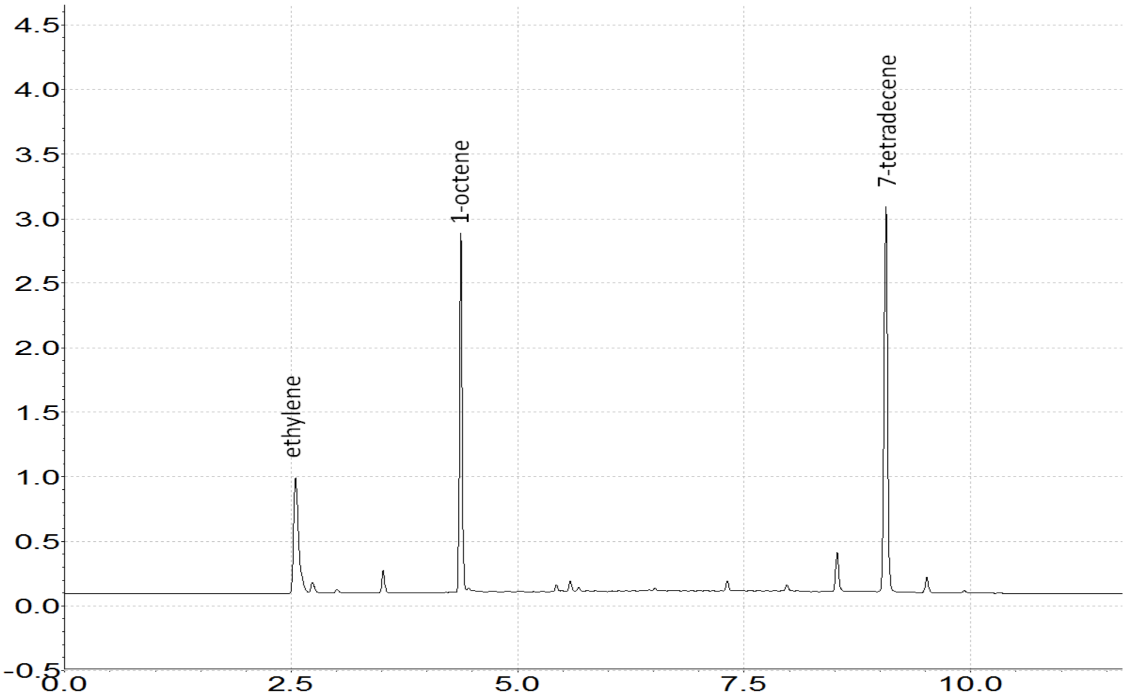


Figure A.2. Continuous flow conditions. GC of the self-metathesis of 1-octene in $scCO_2$

II. Products of self-metathesis

7-Tetradecene, C_{14}

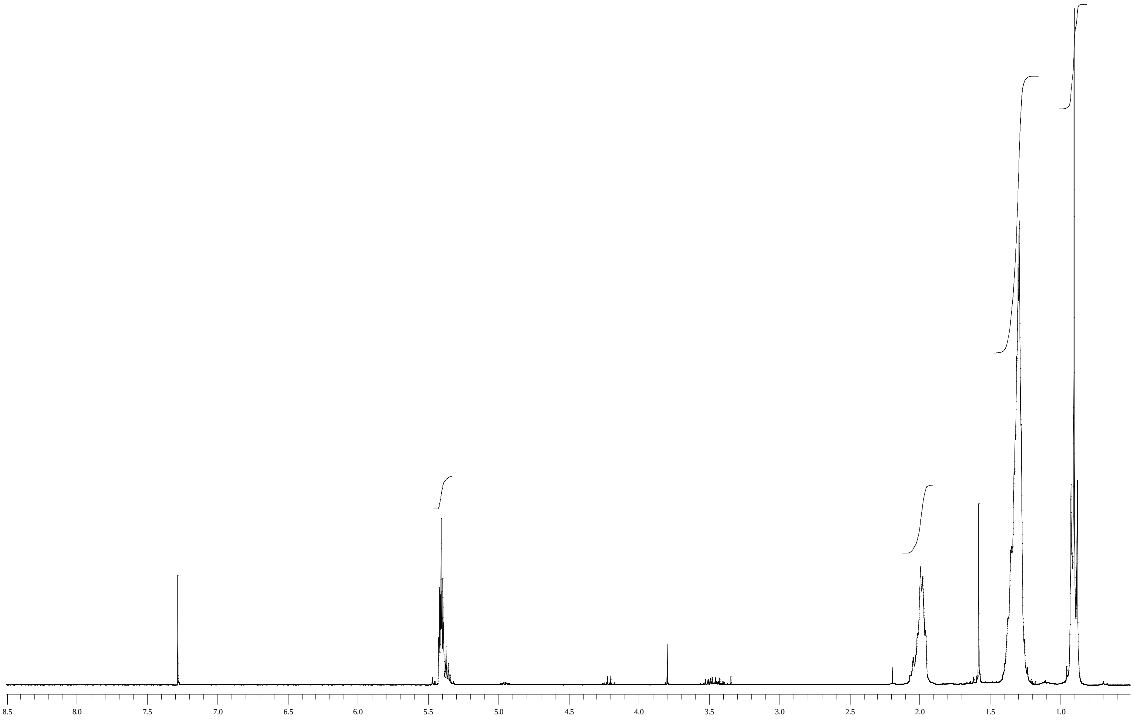


Figure A.3. ^{1}H NMR of 7-tetradecene

^{1}H NMR (300 MHz, $CDCl_3$) δ: 5.40 (2H, m), 1.99 (4H, m), 1.29 (16H, m), 0.90 (6H, t, J = 6.7 Hz). In the cis/trans mixture, vinylic hydrogens were centered at δ = 5.35 for the cis isomer, and at δ = 5.38 for the trans compound.[1] The structure was also assigned by comparison with an authentic commercial sample (Aldrich # 227560).

Trans 7-tetradecene. GC/MS (relative intensity, 70 eV) m/z: 196 ($[M]^+$, 24%), 111 (21), 98 ($[M-(CH_2)_7]^+$, 18), 97 (50), 85 (12), 84 ($[M-(CH_2)_8]^+$, 35), 83 (72), 82 (14), 71 (23), 70 ($[M-(CH_2)_9]^+$, 63), 69 (100), 68 (12), 67 (21), 57 (43), 56 ($[M-(CH_2)_{10}]^+$, 58), 55 (90), 54 (24). Database Wiley: Ref. 33342, *match quality* 97%.[2]

Cis 7-tetradecene. GC/MS (relative intensity, 70 eV) m/z: 196 ($[M]^+$, 20%), 111 (21), 98 ($[M-(CH_2)_7]^+$, 16), 97 (50), 85 (12), 84 ($[M-(CH_2)_8]^+$, 34), 83 (68), 82 (16), 81 (11), 71 (24), 70 ($[M-(CH_2)_9]^+$, 67), 69 (99), 68 (13), 67 (25), 57 (47), 56 ($[M-(CH_2)_{10}]^+$, 66), 55 (100), 54 (23). Database Wiley: Ref. 33341, *match quality* 96%.[2]

III. Products of isomerization of 1-octene and of cross-metathesis

These compounds (see scheme 2.6) were identified by GC/MS analyses, and their structures were assigned by comparison to standard products included in the Wiley Library of Mass spectral data.[2] Table A.1 reports molecular ions, the main fragmentation pattern, and the match quality obtained for each compound.

Table A.1. MS characterization of the reaction products of 1-octene

Compound	**GC/MS** **(relative intensity, 70 eV)**	**Match Quality** **(%)** *(Ref. Wiley)*
1-octene	m/z: 112 ($[M]^+$, 11%), 84 ($[M-(CH_2)_2]^+$, 23), 83 (39), 71 (12), 70 ($[M-(CH_2)_3]^+$, 88), 69 (50), 57 (16), 56 ($[M-(CH_2)_4]^+$, 86), 55 (100), 54 (11), 53 (10)	91 *(116372)*
2-octene	m/z: 112 ($[M]^+$, 40%), 84 ($[M-(CH_2)_2]^+$, 10), 83 (21), 70 ($[M-(CH_2)_3]^+$, 53), 69 (29), 57 (18), 56 ($[M-(CH_2)_4]^+$, 53), 55 (100), 54 (10)	91 *(3597)*
3-octene	m/z: 112 ($[M]^+$, 39%), 83 (19), 70 ($[M-(CH_2)_3]^+$, 55), 69 (32), 57 (19), 56 ($[M-(CH_2)_4]^+$, 52), 55 (100), 53 (10)	64 *(3598)*
4-octene	m/z: 112 ($[M]^+$, 41%), 84 ($[M-(CH_2)_2]^+$, 11), 83 (19), 70 ($[M-(CH_2)_3]^+$, 53), 69 (35), 57 (20), 56 ($[M-(CH_2)_4]^+$, 55), 55 (100), 54 (10)	80 *(116369)*
2-nonene	m/z: 126 ($[M]^+$, 33%), 97 (17), 84 ($[M-(CH_2)_3]^+$, 15), 83 (13), 70 ($[M-(CH_2)_4]^+$, 42), 69 (38), 57 (11), 56 ($[M-(CH_2)_5]^+$, 61), 55 (100), 54 (11)	83 *(6385)*
3-decene	m/z: 140 ($[M]^+$, 5%), 111 (14), 98 ($[M-(CH_2)_3]^+$, 13), 97 (32), 84 ($[M-(CH_2)_4]^+$, 26), 83 (39), 82 (11), 71 (10), 70 ($[M-(CH_2)_5]^+$, 90), 69 (70), 68 (11), 67 (12), 57 (62), 56 ($[M-(CH_2)_6]^+$, 100), 55 (89), 54 (13), 53 (10)	-
4-undecene	m/z: 154 ($[M]^+$, 32%), 97 (20), 84 ($[M-(CH_2)_5]^+$, 23), 83 (35), 71 (10), 70 ($[M-(CH_2)_6]^+$, 53), 69 (76), 67 (16), 57 (22), 56 ($[M-(CH_2)_7]^+$, 59), 55 (100), 54 (14)	94 *(15562)*
5-dodecene	m/z: 168 ($[M]^+$, 33%), 111 (11), 98 ($[M-(CH_2)_5]^+$, 12), 97 (29), 84 ($[M-(CH_2)_6]^+$, 26), 83 (45), 82 (10), 71 (12), 70 ($[M-(CH_2)_7]^+$, 53), 69 (79), 67 (15), 57 (28), 56 ($[M-(CH_2)_8]^+$, 56), 55 (100), 54 (17)	97 *(21249)*
6-tridecene	m/z: 182 ($[M]^+$, 44%), 111 (18), 98 ($[M-(CH_2)_6]^+$, 15), 97 (43), 84 ($[M-(CH_2)_7]^+$, 30), 83 (61), 82 (12), 71 (18), 70 ($[M-(CH_2)_8]^+$, 59), 69 (100), 67 (17), 57 (34), 56 ($[M-(CH_2)_9]^+$, 54), 55 (82), 54 (19)	-

A.2 Green Methodologies for the Michael Reaction [Ch. 2, par. 2]

I. Ionic Liquids

Tri-*n*-octylmethylphosphonium methylcarbonate, TOMP(OCO$_2$Me). viscous clear colourless liquid (mp < 0 °C)

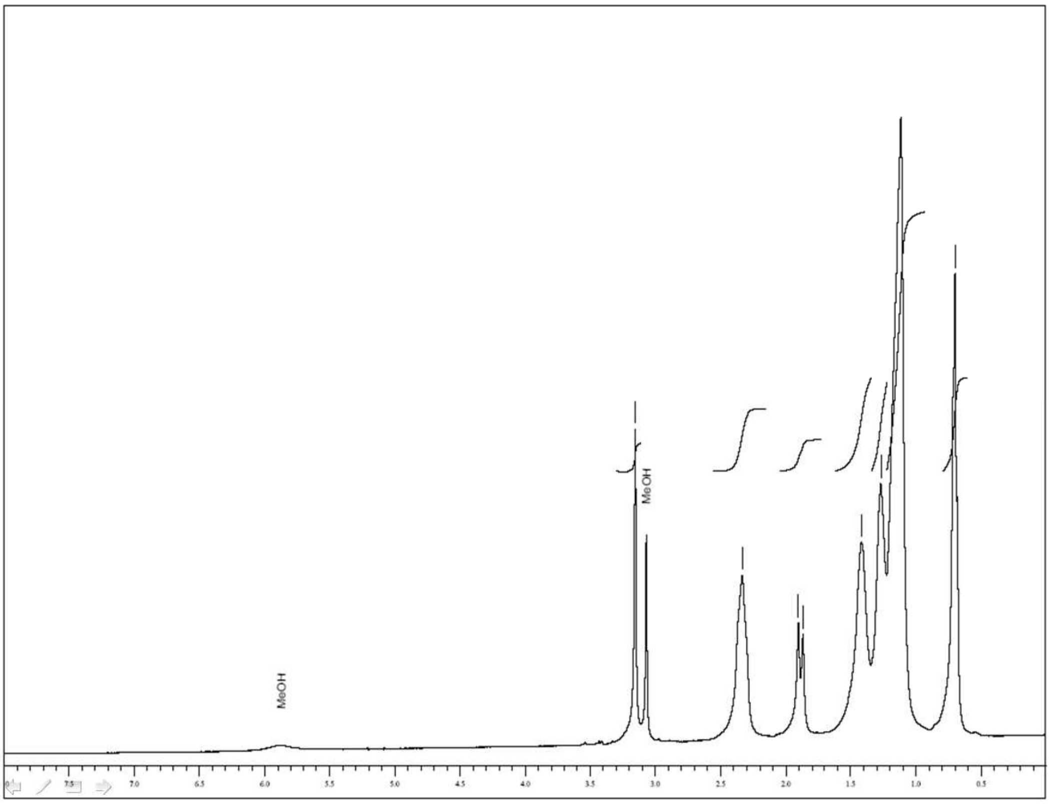


Figure A.4. ^{1}H NMR of tri-*n*-octylmethylphosphonium methylcarbonate

^{1}H NMR (neat, 60 °C, 400 MHz) (δ/ppm relative to TMS, dmso-d$_6$): 3.15 (s, 3H, C$\underline{H}_3$OCOO), 2.33 (bt, 6H, P-C$\underline{H}_2$), 1.88 (d, 3H, $J_{P\text{-}H}$ = 14 Hz, P-C$\underline{H}_3$), 1.42 (b, 6H), 1.27 (b, 6H), 1.11 (b, 24H), 0.70 (bt, 9H).

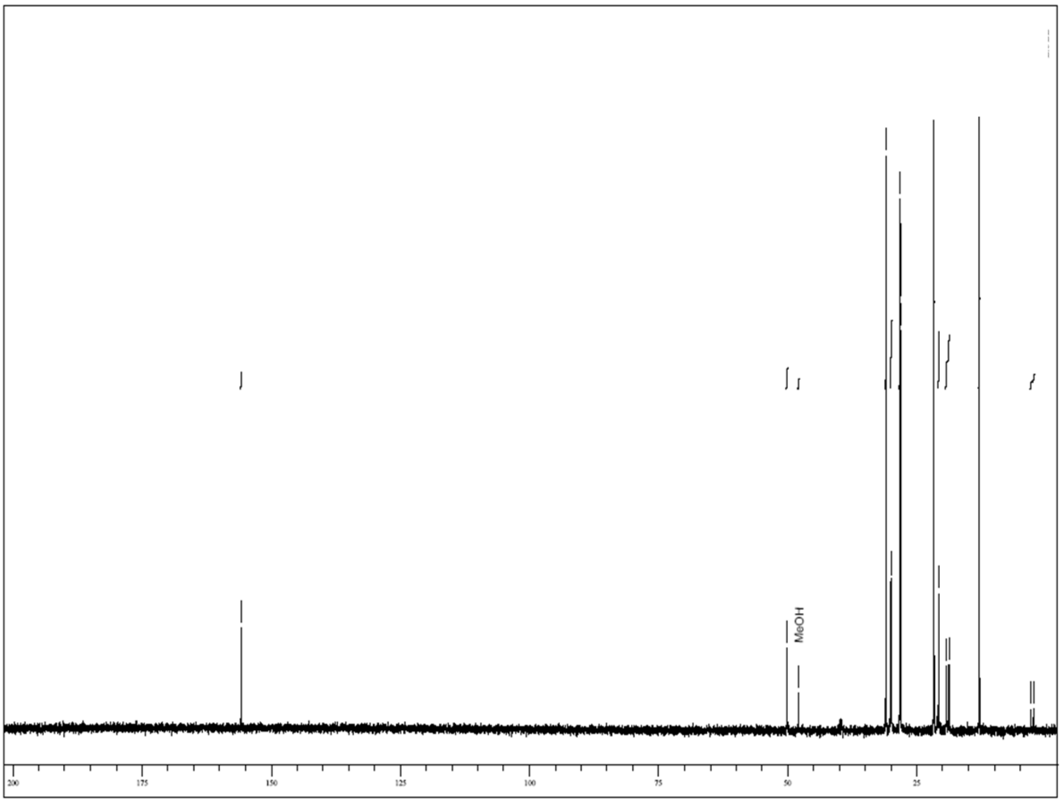


Figure A.5. ^{13}C NMR of tri-*n*-octylmethylphosphonium methylcarbonate

^{13}C NMR (neat, 60 °C, 100 MHz) (δ/ppm relative to TMS, dmso-d_6, CH_2's assigned by 2D inadequate): 155.8 (1C, $\underline{C}$=O), 50.0 (1C, $\underline{C}H_3O$), 30.9 (3C, C_6), 29.9 (d, 3C, $J_{P\text{-}C}$ = 15 Hz, C_3), 28.2 (3C, C_5), 28.0 (3C, C_4), 21.6 (3C, C_7), 20.7 (d, 3C, $J_{P\text{-}C}$ = 4 Hz, C_2), 19.0 (d, 3C, $J_{P\text{-}C}$ = 48 Hz, C_1), 12.8 (C3, C_8), 2.6 (d, 3C, $J_{P\text{-}C}$ = 53 Hz, P-$\underline{C}H_3$).

The ^{13}C NMR spectra provided a wealth of information relative to the carbon backbone, and on the purity of the compounds. In addition, quantitative integration of the ^{13}C resonance peaks allowed to confirm cation to anion equimolarity.

Tri-*n*-octylmethylphosphonium hydrogencarbonate, TOMP(OCO$_2$H). viscous clear liquid that tends to solidify with time (mp ~ 25 °C).

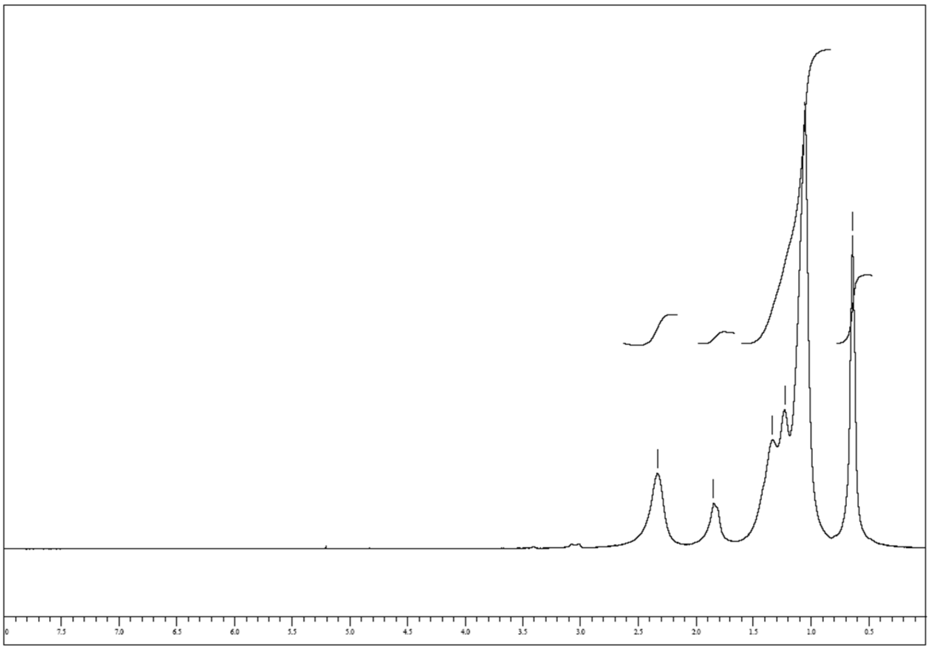


Figure A.6. ^{1}H NMR of tri-*n*-octylmethylphosphonium hydrogencarbonate

^{1}H NMR (neat, 60 °C, 400 MHz) (δ/ppm relative to TMS, dmso-d$_6$): 2.33 (b, 6H, P-C$\underline{H}_2$), 1.84 (bd, 3H, P-C$\underline{H}_3$), 1.33 (b, 6H), 1.23 (b, 6H), 1.05 (b, 24H), 0.64 (bt, 9H).

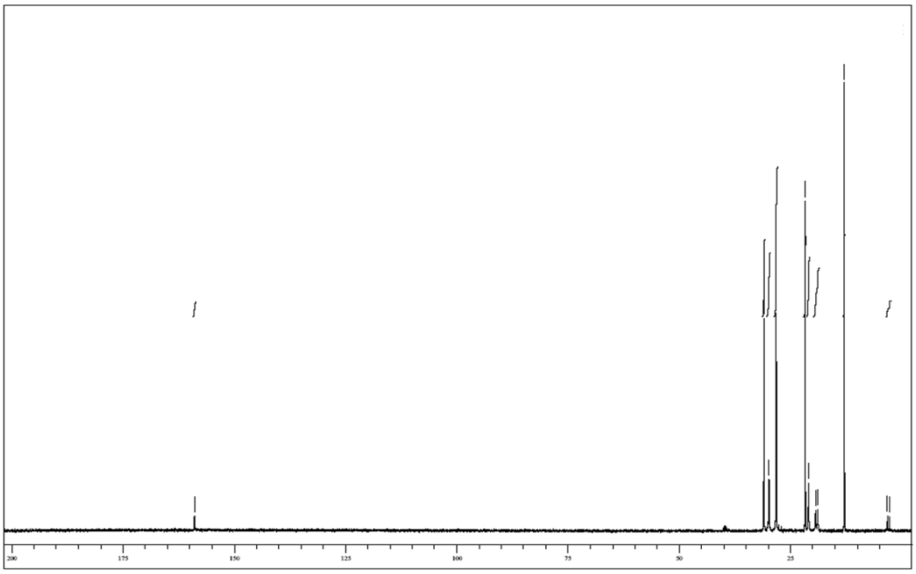


Figure A.7. ^{13}C NMR of tri-*n*-octylmethylphosphonium hydrogencarbonate

^{13}C NMR (neat, 60 °C, 100 MHz) (δ/ppm relative to TMS, dmso-d$_6$): 158.9 (1C, $\underline{C}$=O), 31.0 (3C, C$_6$), 29.8 (d, 3C, $J_{P\text{-}C}$ = 15 Hz, C$_3$), 28.2 (6C, C$_5$-C$_4$), 21.6 (3C, C$_7$), 20.9 (3C, C$_2$), 19.1 (d, 3C, $J_{P\text{-}C}$ = 49 Hz, C$_1$), 12.9 (C3, C$_8$), 2.9 (d, 3C, $J_{P\text{-}C}$ = 52 Hz, P-$\underline{C}$H$_3$).

II. Michael addition products

3-(1-nitroethyl)-cyclohexanone,[3] **m1**, CAS registry no. 59969-93-6; colourless oil, mixture of diastereomers.

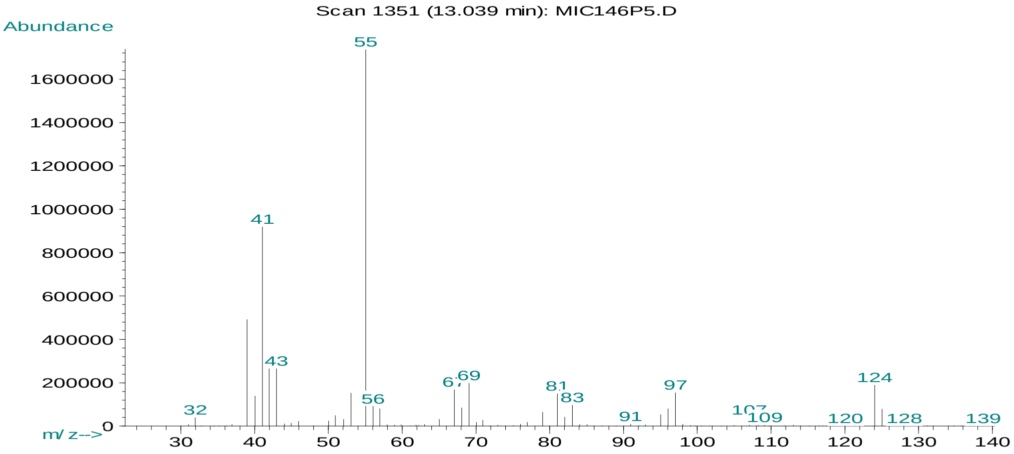


Figure A.8. MS spectrum of 3-(1-nitroethyl)-cyclohexane

GC/MS (relative intensity, 70 eV) m/z: 171 ($[M]^+$, <1%), 124 ($[M\text{-}NO_2\text{-}H]^+$, 11), 97 (9), 96 (5), 83 (6), 81 (9), 69 (11), 68 (5), 67 (10), 55 (100), 43 (15), 42 (15), 41 (52), 39 (28).

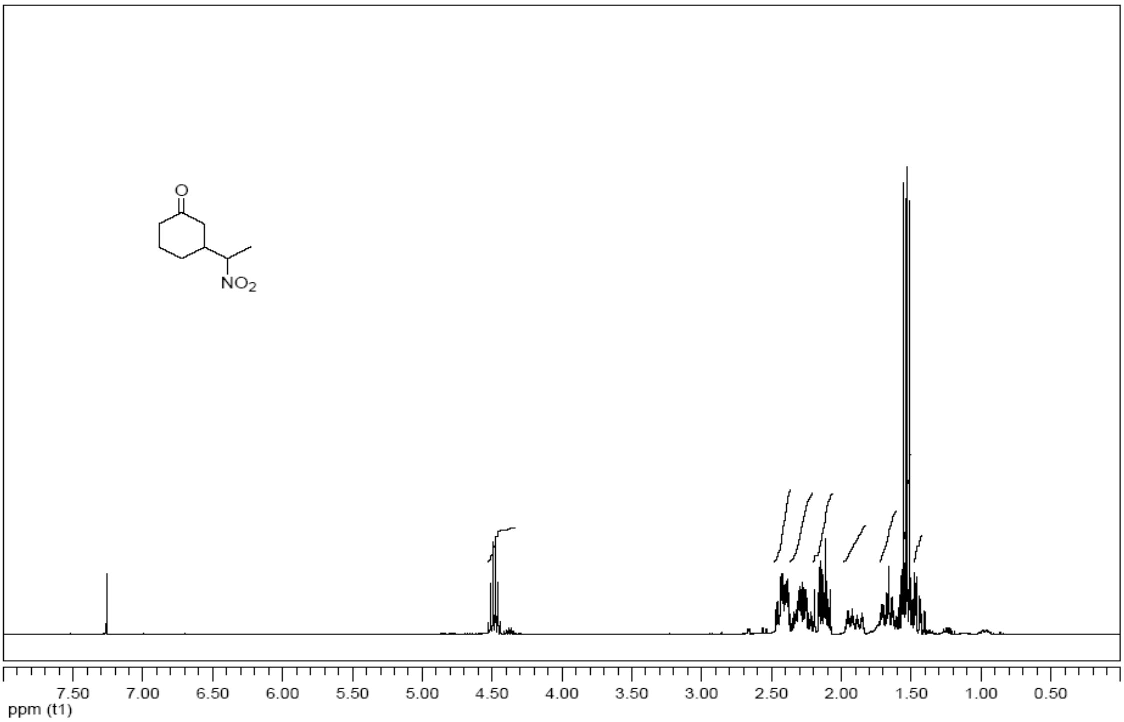


Figure A.9. ^{1}H NMR of 3-(1-nitroethyl)-cyclohexane

^{1}H NMR ($CDCl_3$, 400 MHz) (δ/ppm relative to TMS): 4.54-4.43 (m, 1H), 2.48-2.06 (mm, 6H), 1.98-1.83 (m, 1H), 1.69-1.40 (mm, 5H).

3-(1-nitrobutyl)-cyclohexanone,[4] **m2**, pale yellow oil, mixture of diastereomers.

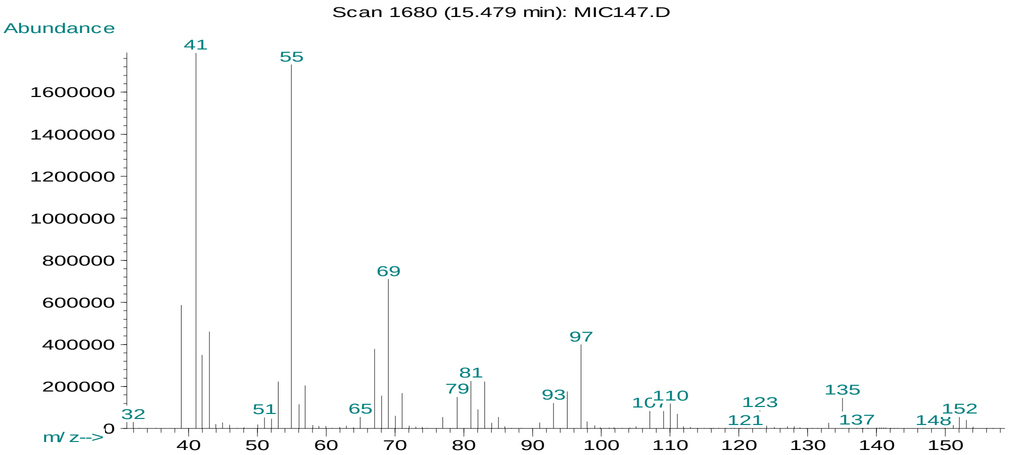


Figure A.10. MS spectrum of 3-(1-nitrobutyl)-cyclohexane

GC/MS (relative intensity, 70 eV) m/z: 199 ([M]$^+$, <1%), 152 ([M-NO_2-H]$^+$, 3), 135 (8), 123 (5), 110 (7), 109 (5), 97 (22), 95 (10), 83 (12), 81 (13), 71 (9), 69 (40), 68 (9) 67 (21), 57 (11), 55 (96), 53 (12), 43 (26), 42 (19), 41 (100), 39 (33).

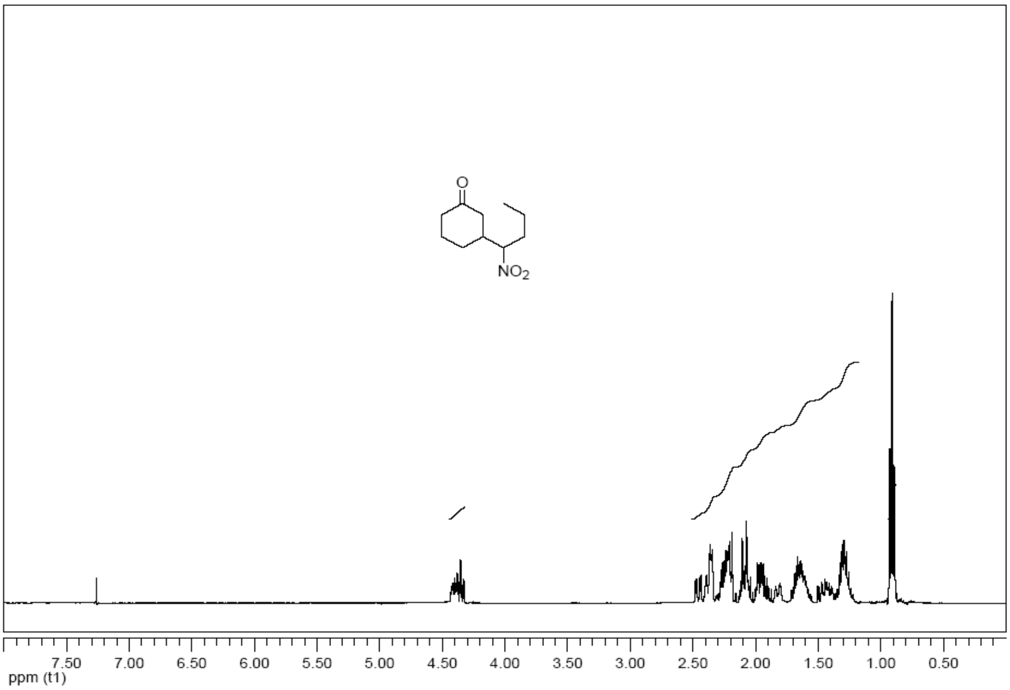


Figure A.11. ^{1}H NMR of 3-(1-nitrobutyl)-cyclohexane

^{1}H NMR ($CDCl_3$, 400 MHz) (δ/ppm relative to TMS): 4.44-4.31 (m, 1H), 2.50-1.20 (mm, 13H), 0.94-0.88 (m, 3H,).

2-(3-oxocyclohexyl)-1,3-diphenylpropane-1,3-dione, **m3**, brown solid.

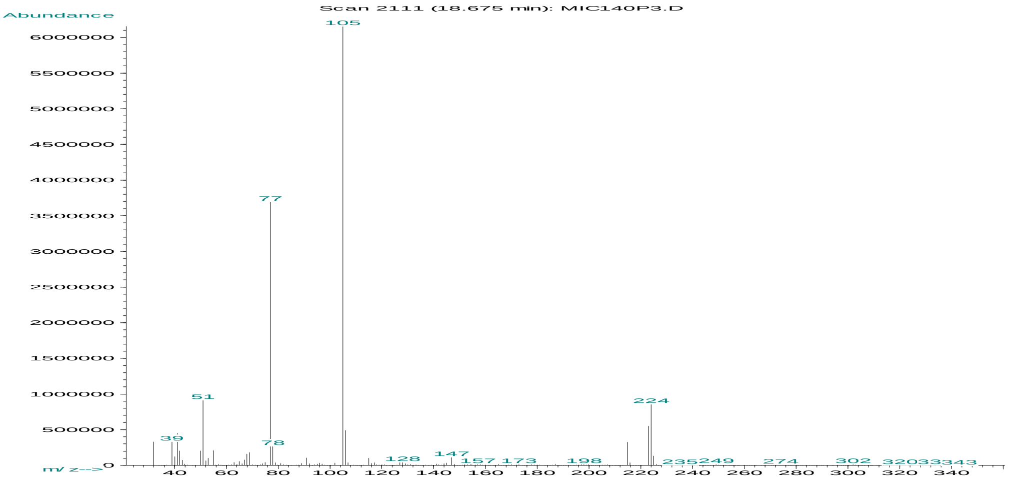


Figure A.12. MS spectrum of 2-(3-oxocyclohexyl)-1,3-diphenylpropane-1,3-dione

GC/MS (relative intensity, 70 eV) m/z: 320 ($[M]^+$, <1%), 224 (16), 223 (11), 105 ($[C_6H_5CO]^+$, 100), 77 (70), 51 (17).

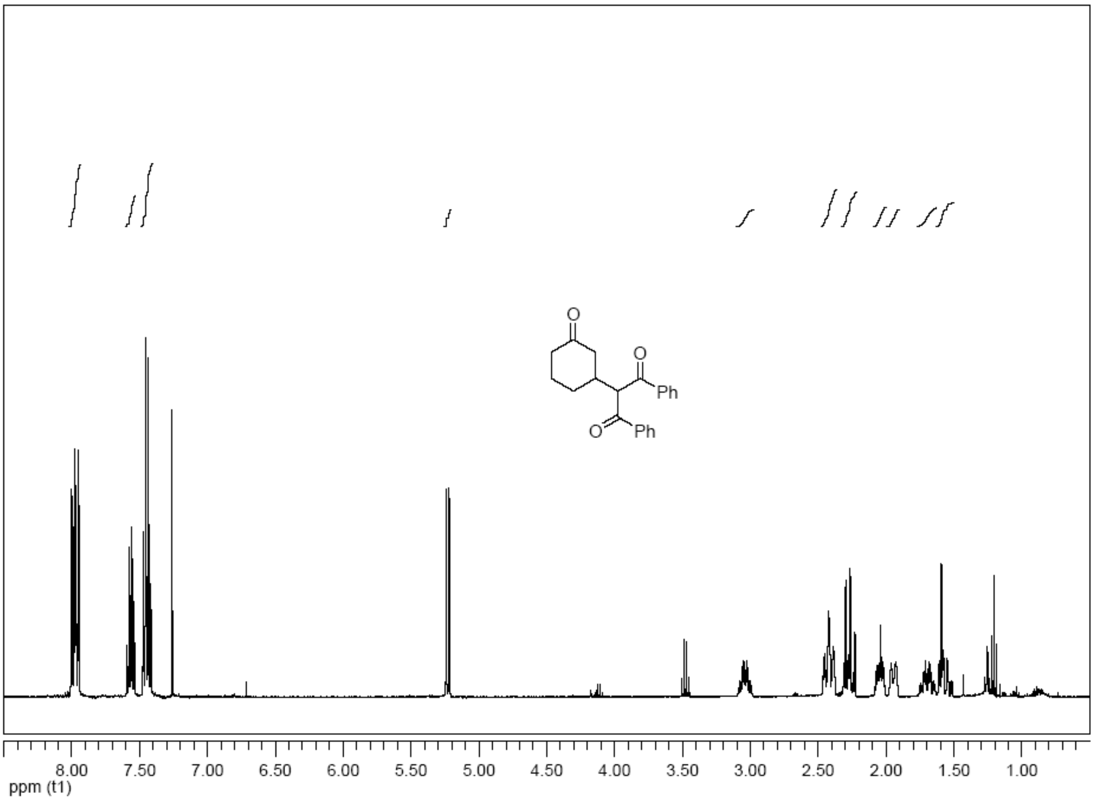


Figure A.13. ^{1}H NMR of 2-(3-oxocyclohexyl)-1,3-diphenylpropane-1,3-dione

^{1}H NMR ($CDCl_3$, 400 MHz) (δ/ppm relative to TMS): 8.02-7.93 (m, 4H), 7.60-7.53 (m, 2H), 7.49-7.40 (m, 4H), 5.23 (d, 1H, J = 8.5 Hz), 3.10-2.98 (m, 1H), 2.47-2.36 (m, 2H), 2.32-2.22 (m, 2H), 2.09-2.00 (m, 1H), 1.98-1.90 (m, 1H), 1.76-1.63 (m, 1H), 1.62-1.50 (m, 1H).

2-(3-oxocyclohexyl)malonic acid dimethyl ester,[5] **m4**, pale yellow oil.

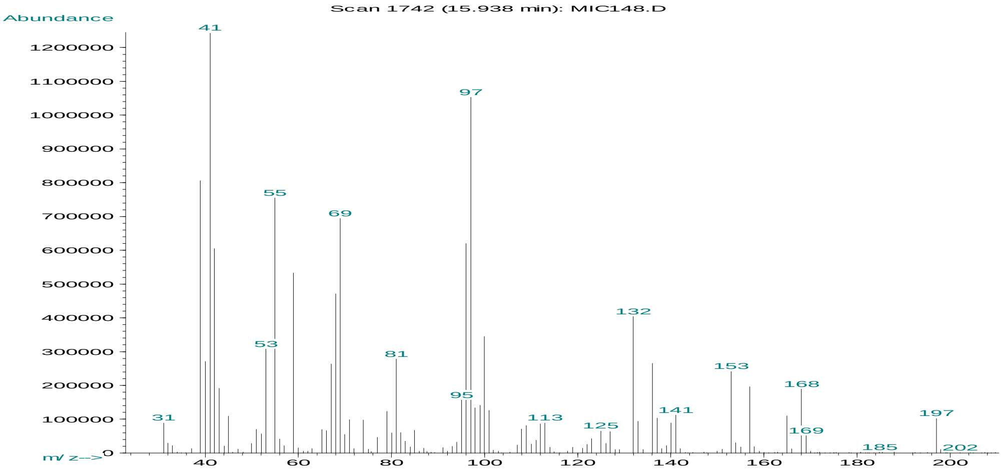


Figure A.14. MS spectrum of 2-(3-oxocyclohexyl)malonic acid dimethyl ester

GC/MS (relative intensity, 70 eV) m/z: 228 ($[M]^+$, <1%), 197 ($[M\text{-}OCH_3]^+$, 10), 169 ($[M\text{-}COOCH_3]^+$, 5), 165 (9), 157 (16), 153 (23), 141 (11), 137 (10), 136 (24), 132 (38), 131 (15), 101 (12), 100 (35), 99 (12), 98 (12), 97 (93), 96 (52), 95 (14), 81 (22), 79 (11), 69 (90), 68 (38), 67 (21), 59 (38), 55 (66), 53 (21), 43 (15), 42 (50), 41 (100), 40 (22), 39 (60).

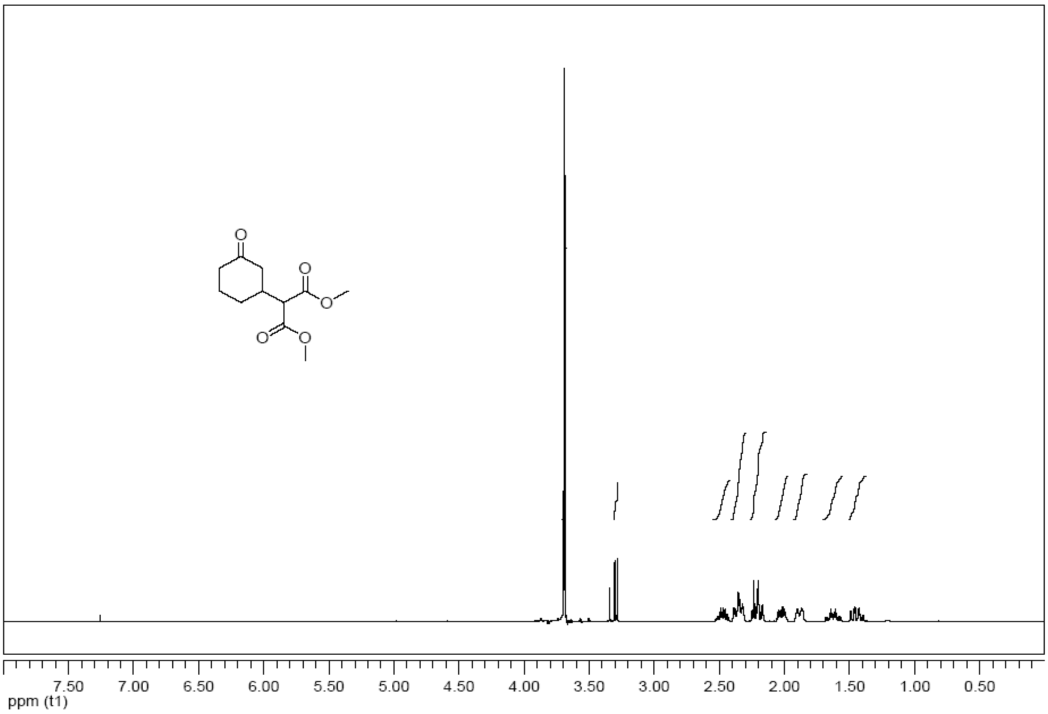


Figure A.15. ^{1}H NMR of 2-(3-oxocyclohexyl)malonic acid dimethyl ester

^{1}H NMR ($CDCl_3$, 400 MHz) (δ/ppm relative to TMS): 3.70 (s, 3H), 3.69 (s, 3H), 3.30 (d, 1H, J = 8.0 Hz), 2.54-2.42 (m, 1H), 2.41-2.30 (m, 2H), 2.27-2.15 (m, 2H), 2.07-1.98 (m, 1H), 1.93-1.85 (m, 1H), 1.70-156 (m, 1H), 1.51-1.39 (m, 1H).

6-nitroheptane-3-one,[6] **m5**, colourless oil.

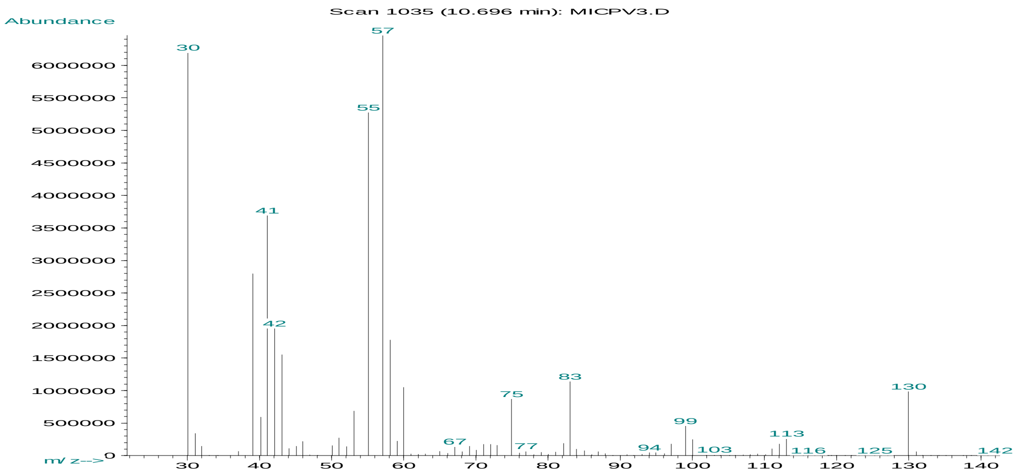


Figure A.16. MS spectrum of 6-nitroheptane-3-one

GC/MS (relative intensity, 70 eV) m/z: 159 ([M]$^+$, <1%), 130 ([M-CH_2CH_3]$^+$, 15), 113 ([M-NO_2]$^+$, 4), 99 (7), 83 (18), 75 (13), 60 (16), 58 (27), 57 (100), 55 (81), 53 (10), 43 (24), 42 (30), 41 (57), 39 (43), 30 (95).

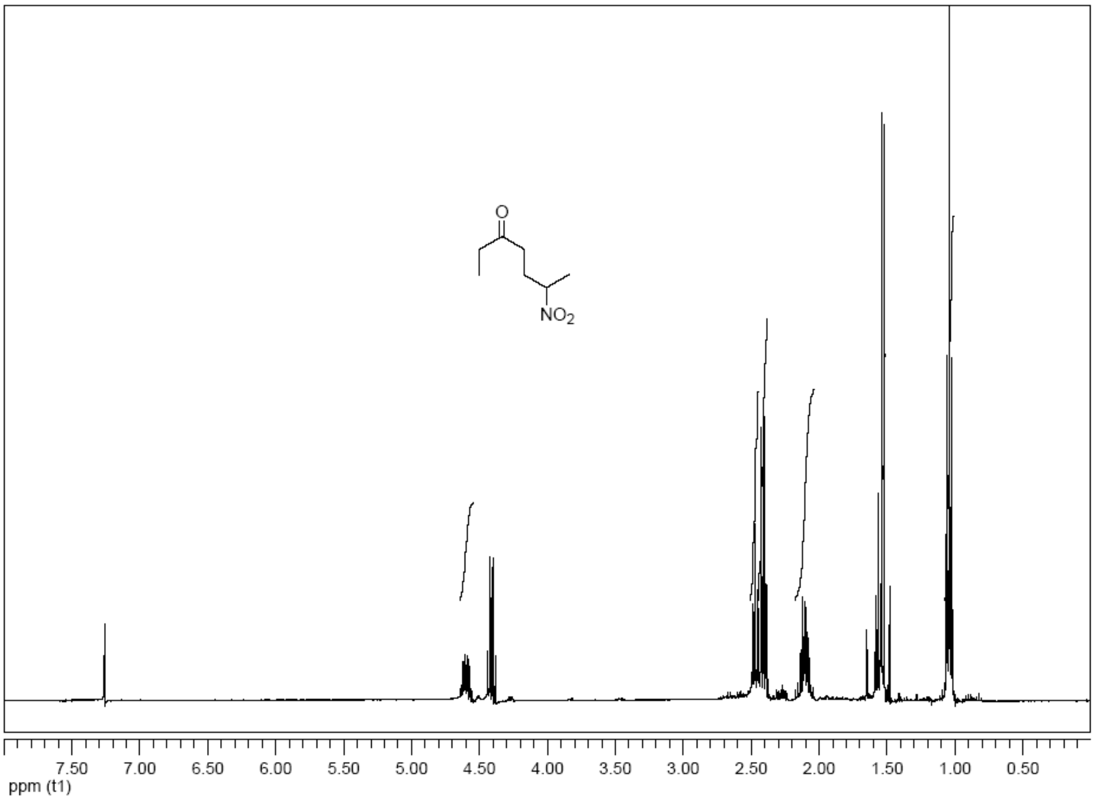


Figure A.17. ^{1}H NMR of 6-nitroheptane-3-one

^{1}H NMR ($CDCl_3$, 400 MHz) (δ/ppm relative to TMS): 4.65-4.54 (m, 1H), 2.47 (t, 2H, J = 7.0 Hz), 2.42 (q, 2H, J = 7.3 Hz), 2.15-2.06 (m, 2H), 1.53 (d, 3H, J = 6.6 Hz), 1.04 (t, 3H, J = 7.3 Hz).

6-nitrononane-3-one,[7] **m6**, light brown oil.

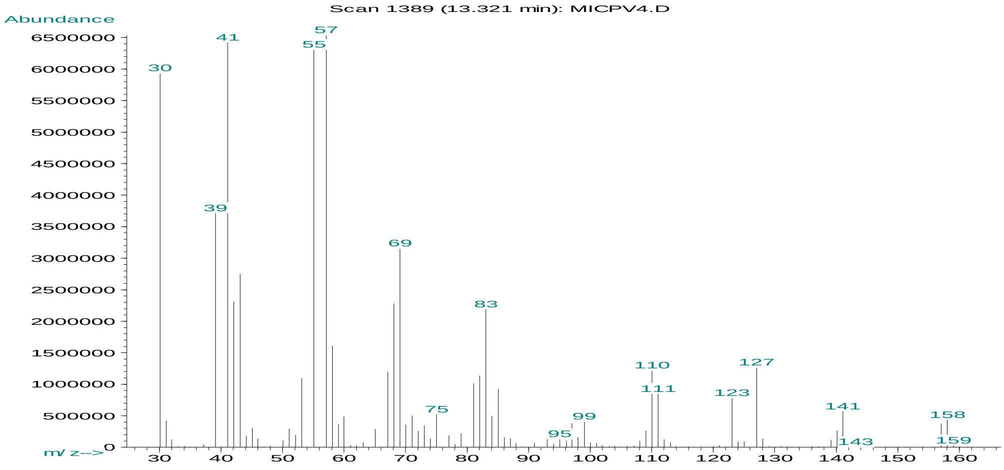


Figure A.18. MS spectrum of 6-nitrononane-3-one

GC/MS (relative intensity, 70 eV) m/z: 187 ($[M]^+$, <1%), 158 ($[M\text{-}CH_2CH_3]^+$, 7), 157 (6), 127 (19), 123 (12), 111 ($[M\text{-}NO_2\text{-}CH_2CH_3]^+$, 13), 110 (19), 85 (14), 83 (33), 82 (17), 81 (16), 69 (48), 68 (35), 67 (18), 58 (25), 57 (100), 55 (97), 53 (17), 43 (42), 42 (35), 41 (98), 39 (57), 30 (91).

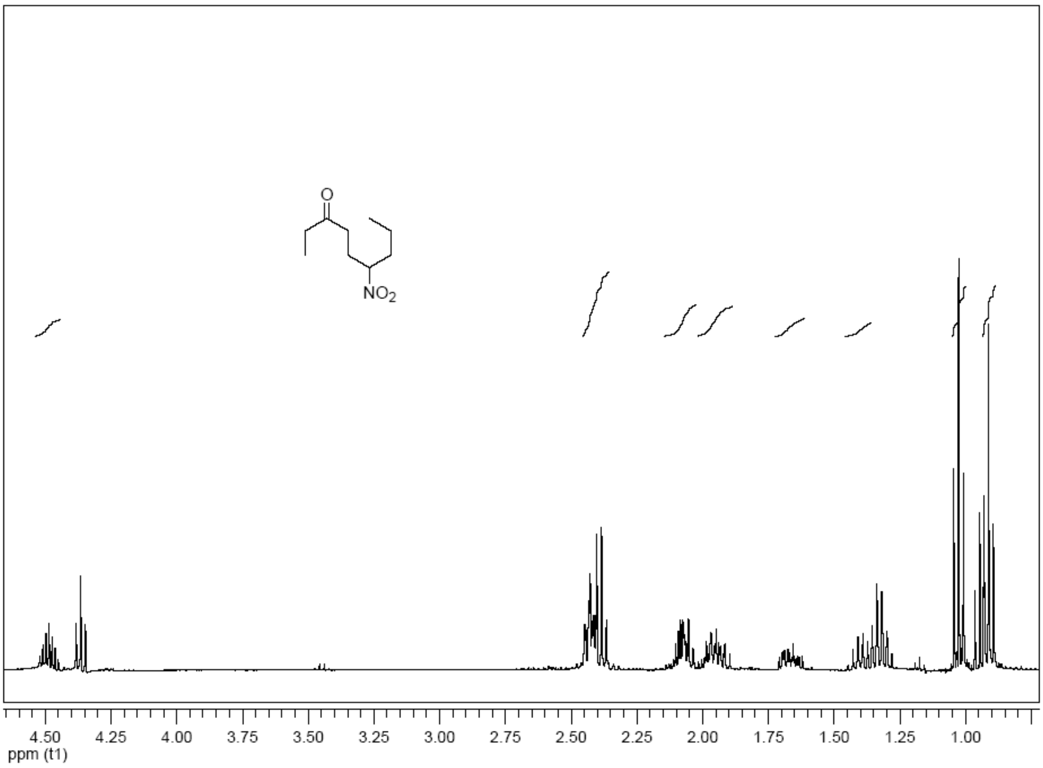


Figure A.19. ^{1}H NMR of 6-nitrononane-3-one

^{1}H NMR ($CDCl_3$, 400 MHz) (δ/ppm relative to TMS): 4.53-4.44 (m, 1H), 2.46-2.35 (m, 4H), 2.14-2.03 (m, 2H), 2.02-1.89 (m, 2H), 1.72-1.61 (m, 1H), 1.45-1.35 (m, 1H), 1.02 (t, 3H, J = 7.3 Hz), 0.91 (t, 3H, J = 7.3 Hz).

2-benzoyl-1-phenylheptane-1,5-dione, **m7**, pale yellow solid.

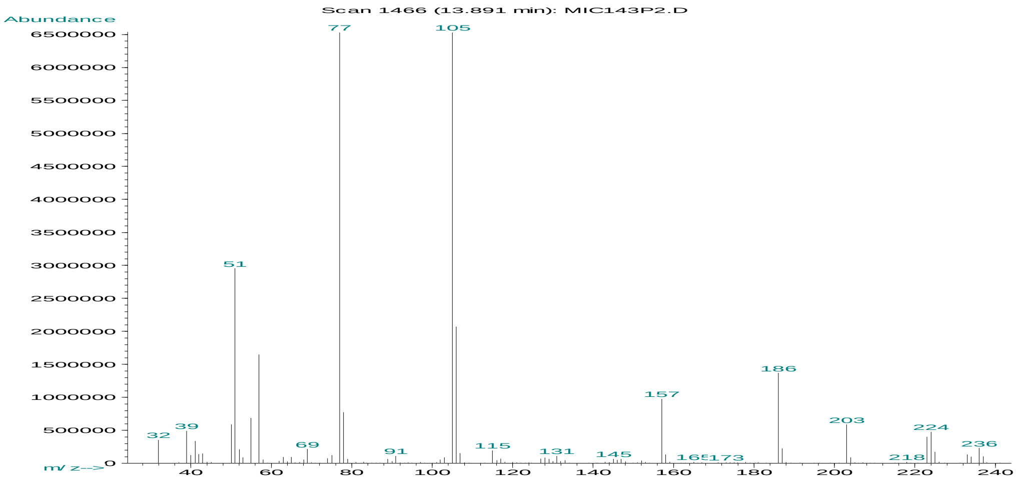


Figure A.20. MS spectrum of 2-benzoyl-1-phenylheptane-1,5-dione

GC/MS (relative intensity, 70 eV) m/z: 308 ($[M]^+$, <1%), 236 (4), 224 (7), 223 (6), 203 ($[M\text{-}COC_6H_5]^+$, 9), 186 (21), 157 (15), 106 (32), 105 ($[C_6H_5CO]^+$, 100), 78 (12), 77 (100), 57 (25), 55 (11), 51 (45), 39 (9).

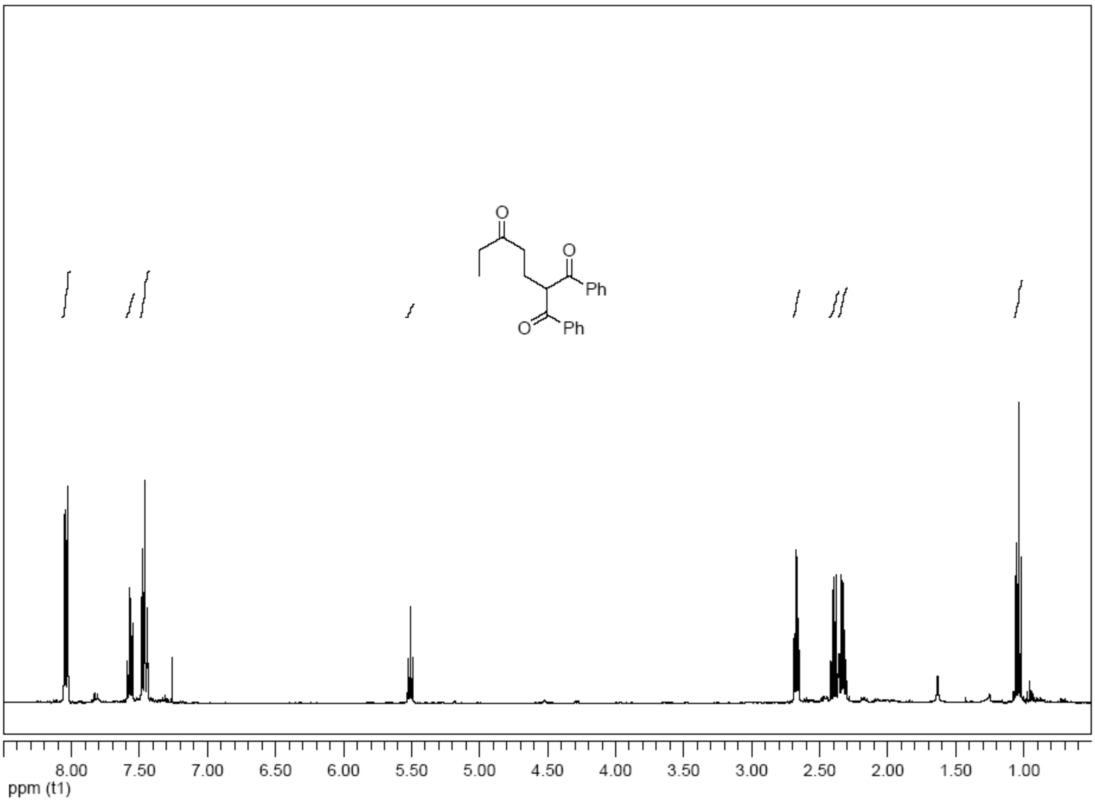


Figure A.21. ^{1}H NMR of 2-benzoyl-1-phenylheptane-1,5-dione

^{1}H NMR ($CDCl_3$, 400 MHz) (δ/ppm relative to TMS): 8.06-8.02 (m, 4H), 7.60-7.54 (m, 2H), 7.50-7.43 (m, 4H), 5.51 (t, 1H, J = 6.8 Hz), 2.67 (t, 2H, J = 6.4 Hz), 2.39 (q, 2H, J = 7.3 Hz), 2.33 (q, 2H, J = 6.5 Hz), 1.04 (t, 3H, J = 7.3 Hz).

2-(3-oxopentyl)malonic acid dimethyl ester,[8] **m8**, yellow oil.

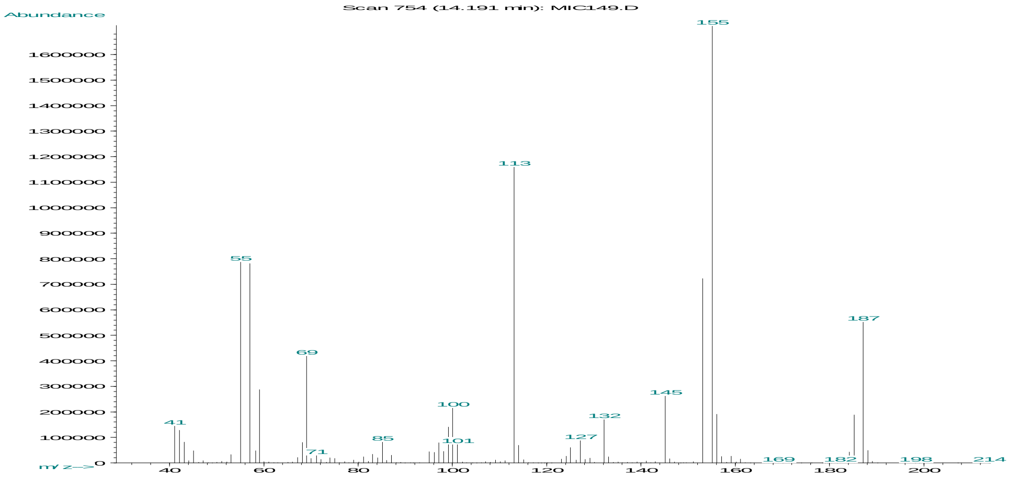


Figure A.22. MS spectrum of 2-(3-oxopentyl)malonic acid dimethyl ester

GC/MS (relative intensity, 70 eV) m/z: 216 ($[M]^+$, <1 %), 187 (20), 155 (72), 153 (28), 145 (10), 113 (57), 100 (10), 69 (25), 59 (31), 57 (100), 55 (49), 42 (18), 41 (24), 39 (22).

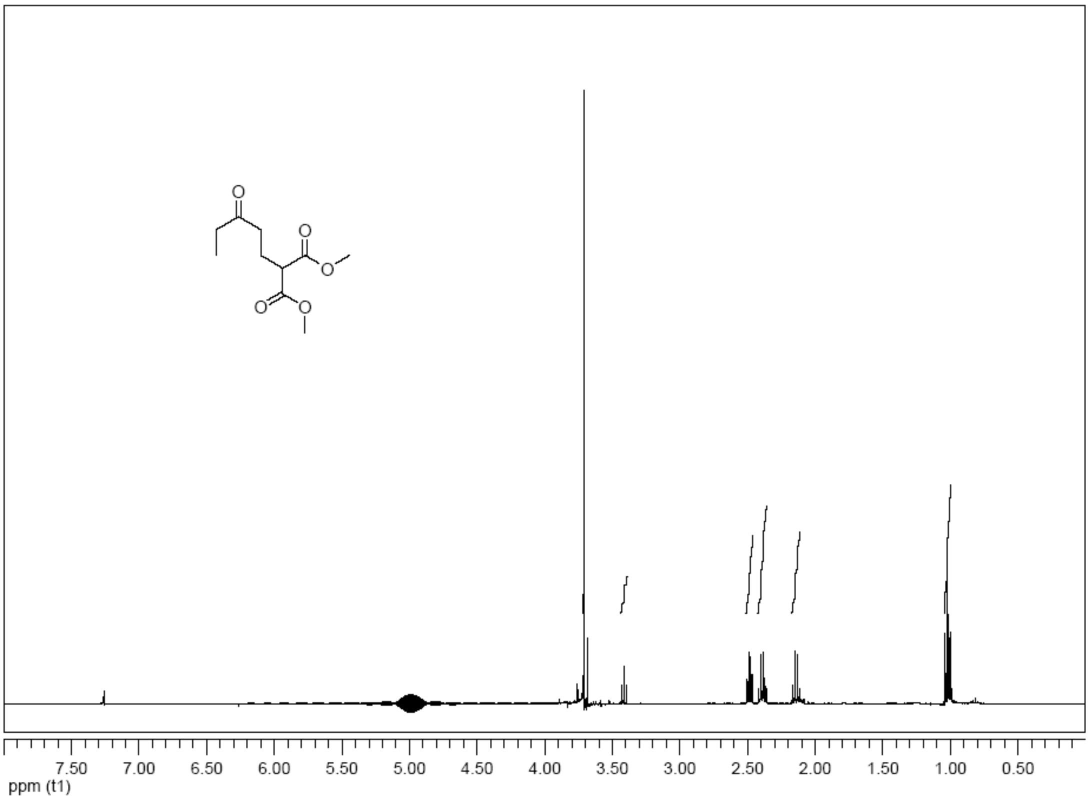


Figure A.23. ^{1}H NMR of 2-(3-oxopentyl)malonic acid dimethyl ester

^{1}H NMR ($CDCl_3$, 400 MHz) (δ/ppm relative to TMS): 3.71 (s, 6H), 3.41 (t, 1H, J = 7.3 Hz), 2.48 (t, 2H, J = 7.2 Hz), 2.39 (q, 2H, J = 7.3 Hz), 2.14 (q, 2H, J = 7.2 Hz), 1.02 (t, 3H, J = 7.3 Hz).

A.3 The Reaction of Glycerol Carbonate with Primary Aromatic Amines in the Presence of Y- and X-Faujasites [Ch. 3, par. 1]

***N*-(2,3-dihydroxy)propyl aniline, 3a**, pale yellow solid.[9] GC/MS (relative intensity, 70 eV) m/z: 167 (M^+, 12%), 136 (M^+-CH_2OH, 3), 106 (M^+-$CH(CH_2OH)OH$, 100), 77 (20).

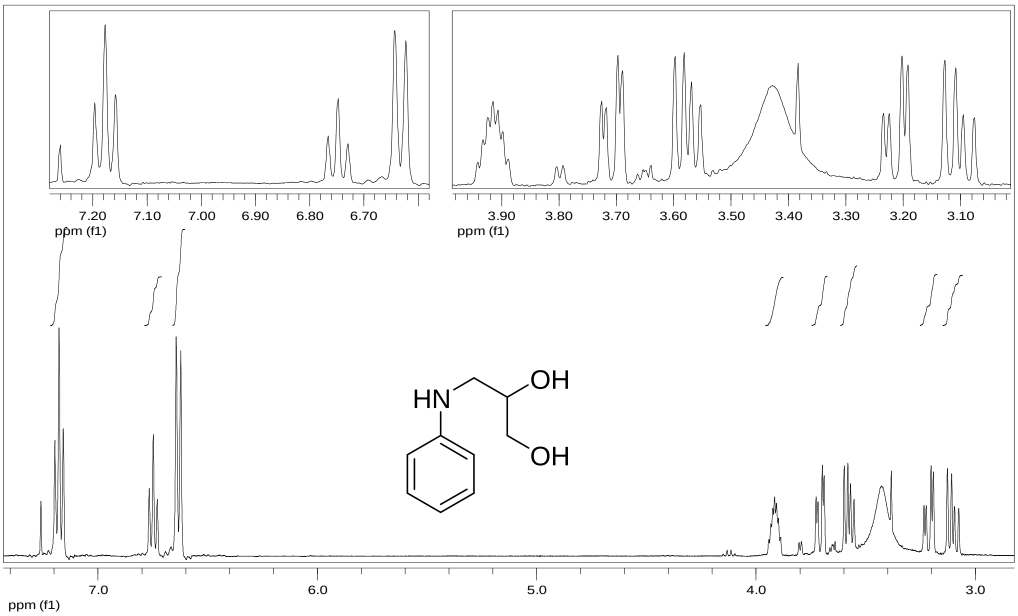


Figure A.24. ^{1}H NMR of *N*-(2,3-dihydroxy)propyl aniline

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17 (t, 2H, J = 7.7), 6.75 (t, 1H, J = 7.3 Hz), 6.63 (d, 2H, J = 8.3 Hz), 3.95-3.88 (m, 1H), 3.71 (dd, 1H, J_1 = 3.2 Hz, J_2 = 11.4 Hz), 3.58 (dd, 1H, J_1 = 6.3 Hz, J_2 = 11.4 Hz), 3.21 (dd, 1H, J_1 = 4.1 Hz, J_2 = 12.9 Hz), 3.10 (dd, 1H, J_1 = 7.6 Hz, J_2 = 12.9 Hz).

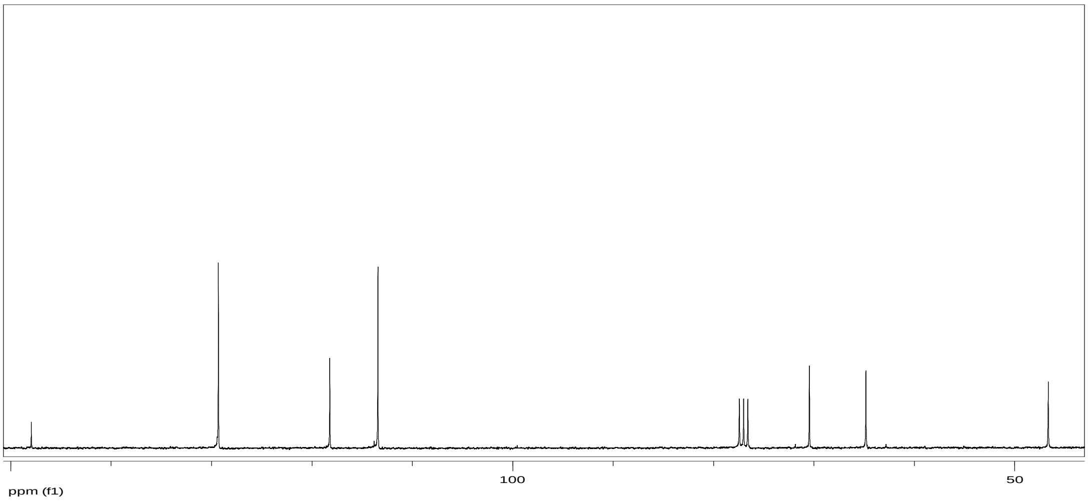


Figure A.25. ^{13}C NMR of *N*-(2,3-dihydroxy)propyl aniline

^{13}C NMR (100 MHz, $CDCl_3$) δ 147.9, 129.3, 118.2, 113.4, 70.4, 48.8, 46.6.

4-[(phenylamino)methyl]-1,3-dioxolan-2one, 4a, brown solid. GC/MS (relative intensity, 70 eV) m/z: 193 (M^+, 10%), 106 ($[PhNH{=}CH_2]^+$, 100), 77 (21).

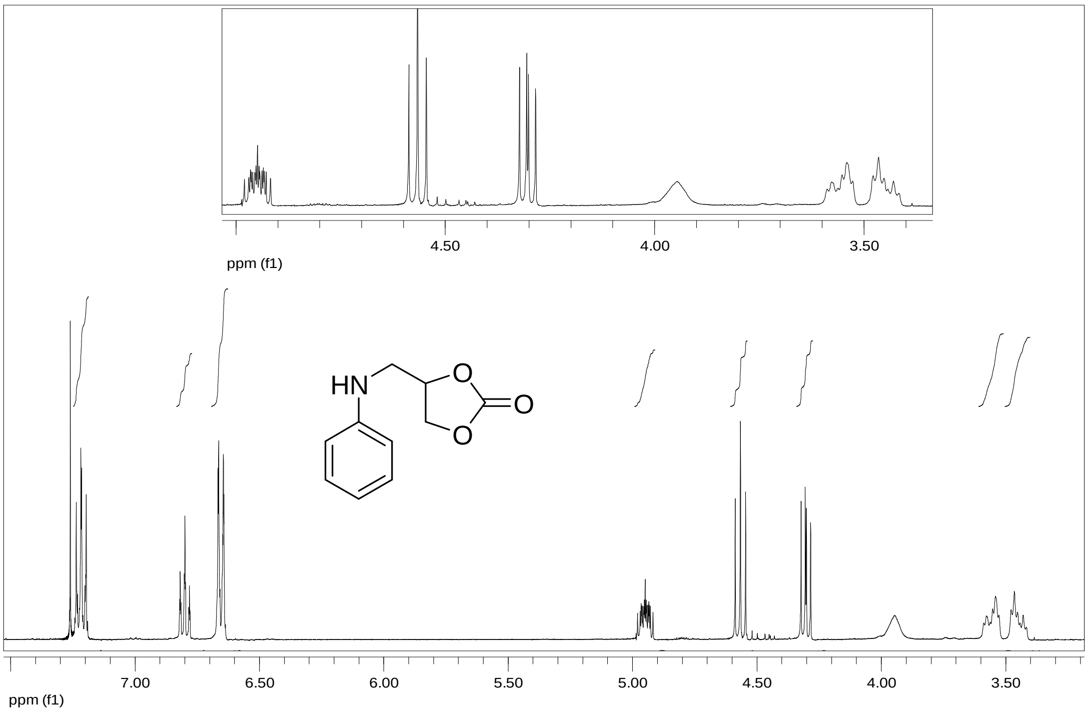


Figure A.26. ^1H NMR of 4-[(phenylamino)methyl]-1,3-dioxolan-2one

^1H NMR (400 MHz, $CDCl_3$) δ 7.24-7.19 (m, 2H), 6.83-6.77 (m, 1H), 6.67-6.64 (m, 2H), 4.98-4.91 (m, 1H), 4.57 (t, 1H, J = 8.3 Hz), 4.30 (dd, 1H, J_1 = 6.8 Hz, J_2 = 8.5 Hz), 3.95 (brs, 1H), 3.56 (dt, 1H, J_1 = 4.5 Hz, J_2 = 14.4 Hz), 3.45 (dt, 1H, J_1 = 5.2 Hz, J_2 = 14.2 Hz).

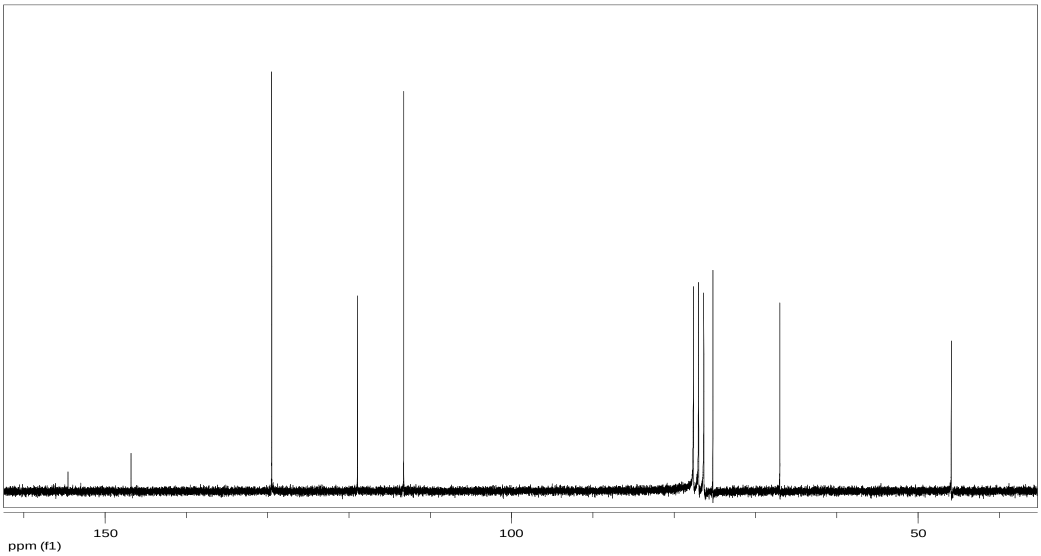


Figure A.27. ^{13}C NMR of 4-[(phenylamino)methyl]-1,3-dioxolan-2one

^{13}C NMR (100 MHz, $CDCl_3$) δ 154.6, 146.8, 129.5, 119.0, 113.3, 75.1, 67.0, 45.9.

***p*-chloro[*N*-(2,3-dihydroxy)propyl]aniline, 3b**, light brown oil.[10] GC/MS (relative intensity, 70 eV) m/z: 201 (M^+, 11%), 170 (M^+-CH_2OH, 3), 142 (32), 141 (10), 140 (M^+- $CH(CH_2OH)OH$, 100), 77 (12), 75 (11).

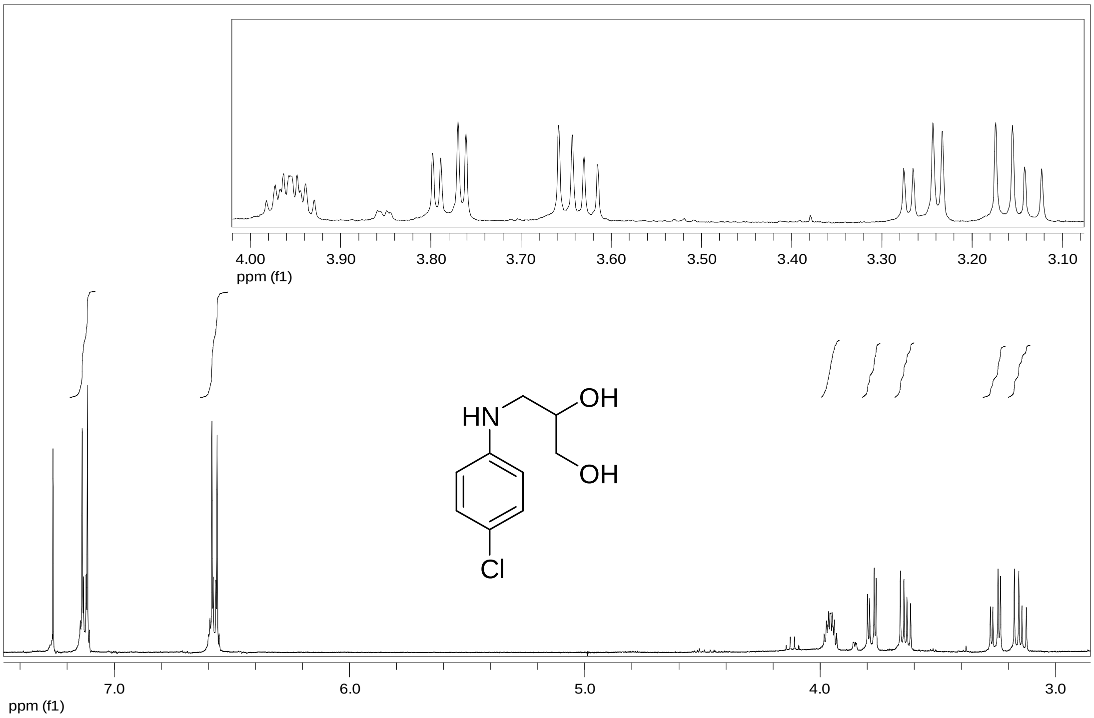


Figure A.28. ^{1}H NMR of *p*-chloro[*N*-(2,3-dihydroxy)propyl]aniline

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15-7.10 and 6.60-6.55 (m, 4H), 3.99-3.92 (m, 1H), 3.78 (dd, 1H, J_1 = 3.5 Hz, J_2 = 11.2 Hz), 3.64 (dd, 1H, J_1 = 6.0 Hz, J_2 = 11.2 Hz), 3.25 (dd, 1H, J_1 = 4.1 Hz, J_2 = 12.9 Hz), 3.15 (dd, 1H, J_1 = 7.5 Hz, J_2 = 12.9 Hz).

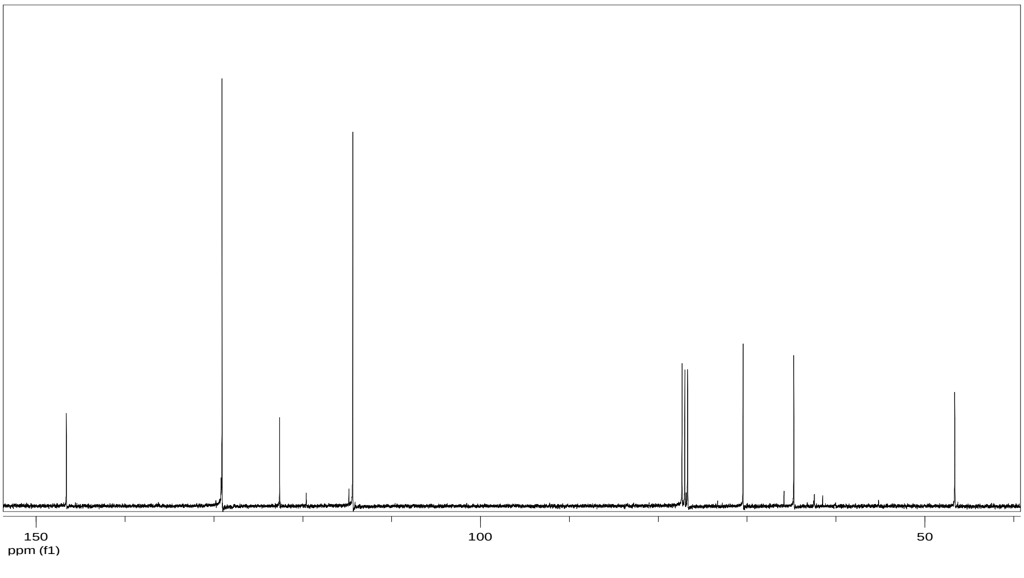


Figure A.29. ^{13}C NMR of *p*-chloro[*N*-(2,3-dihydroxy)propyl]aniline

^{13}C NMR (100 MHz, $CDCl_3$) δ 146.6, 129.1, 122.6, 114.4, 70.4, 64.7, 46.6.

***p*-methoxy[*N*-(2,3-dihydroxy)propyl]aniline, 3c**, dark brown solid.[11] GC/MS (relative intensity, 70 eV) m/z: 197 (M^+, 11%), 166 (M^+-CH_2OH, 3), 136 (M^+- $CH(CH_2OH)OH$, 100), 121 (10), 108 (13).

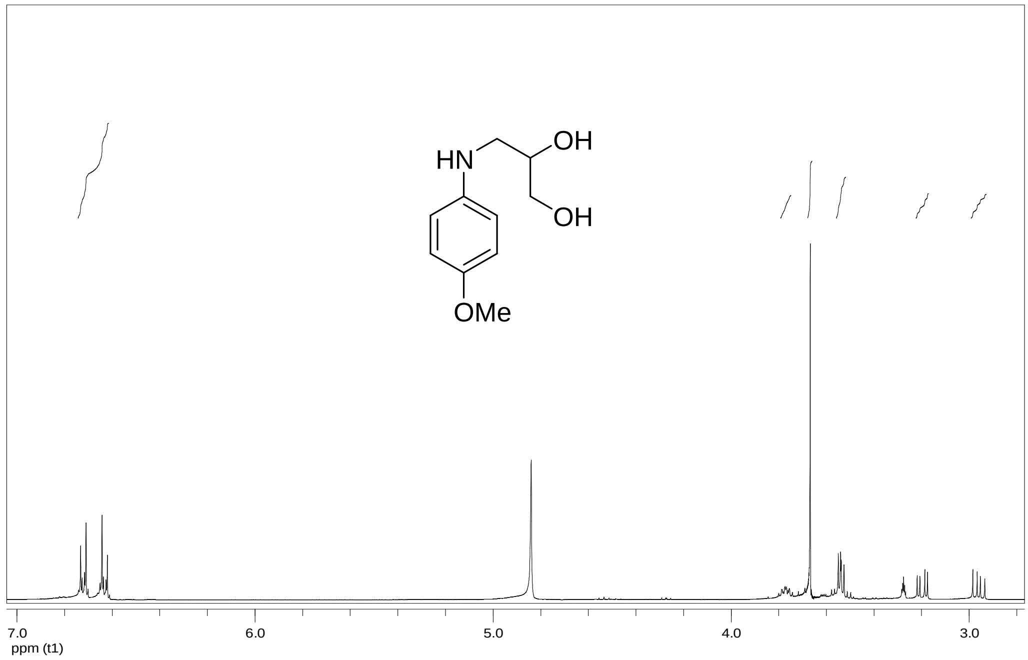


Figure A.30. ^{1}H NMR of *p*-methoxy[*N*-(2,3-dihydroxy)propyl]aniline

^{1}H NMR (400 MHz, CD_3OD) δ 6.79-6.74 and 6.70-6.65 (m, 4H), 3.84-3.78 (m, 1H), 3.71 (s, 3H), 3.62-3.53 (m, 2H), 3.24 (dd, 1H, J_1 = 4.5 Hz, J_2 = 12.7 Hz), 2.99 (dd, 1H, J_1 = 7.4 Hz, J_2 = 12.7 Hz).

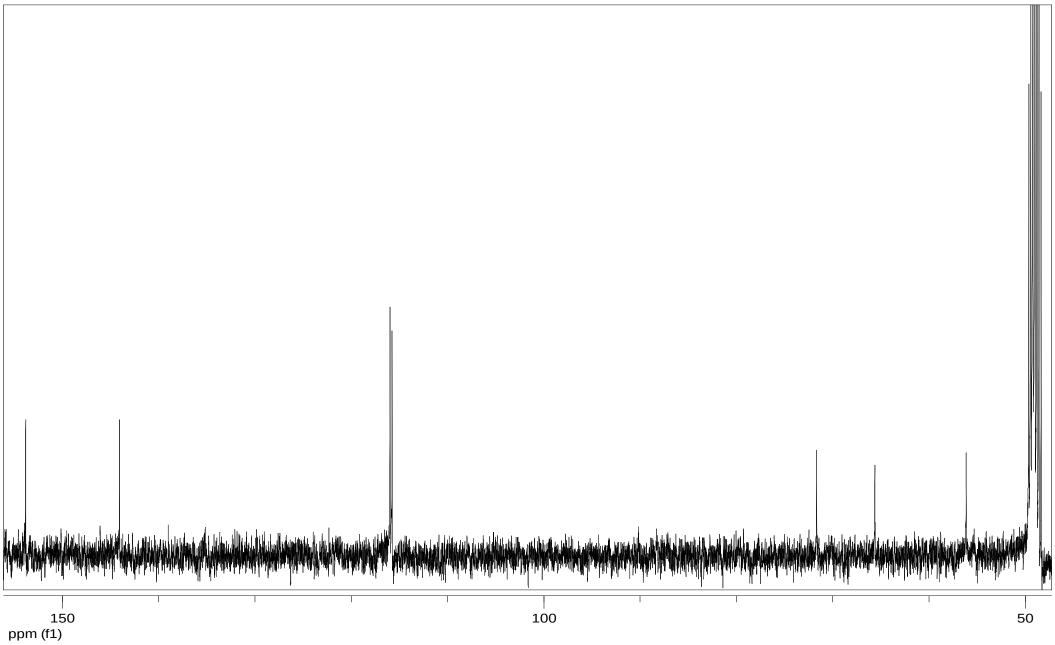


Figure A.31. ^{1}H NMR of *p*-methoxy[*N*-(2,3-dihydroxy)propyl]aniline

^{13}C NMR (100 MHz, CD_3OD) δ 153.9, 144.1, 116.0, 115.8, 71.7, 65.7, 56.2, 48.9.

4-[(4’-methoxyphenyl-amino)methyl]-1,3-dioxolan-2one, 4c, brown solid. GC/MS (relative intensity, 70 eV) m/z: 223 (M^+, 14%), 136 ($[MeOC_6H_4NH{=}CH_2]^+$, 100), 121 (10).

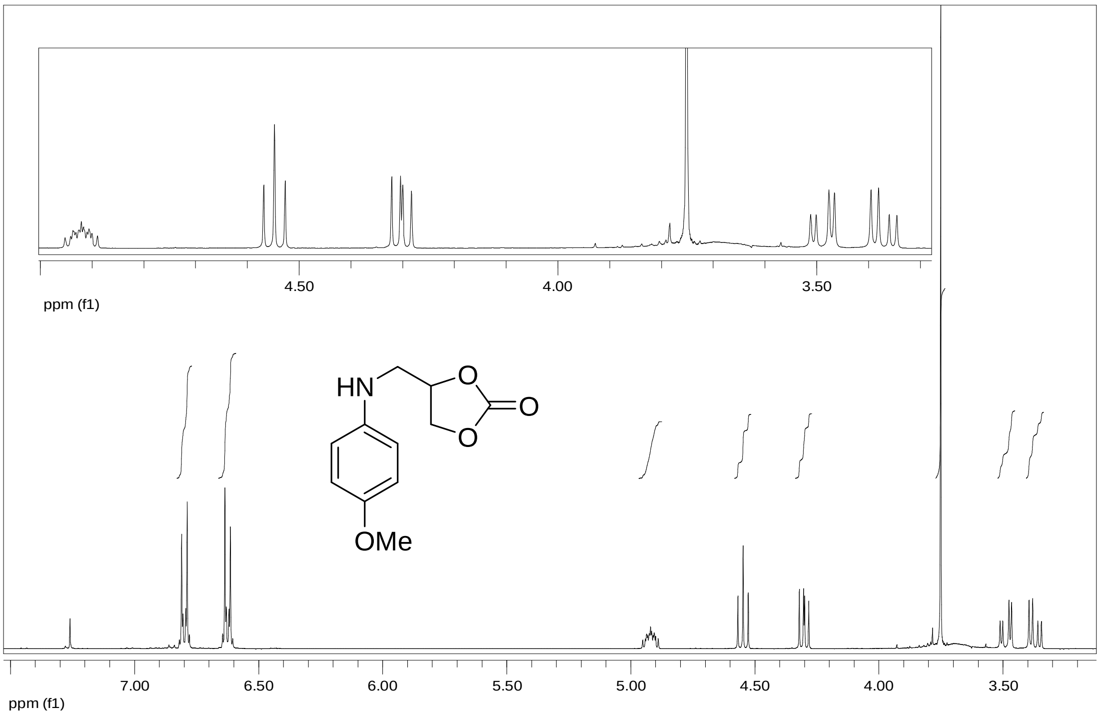


Figure A.32. ^{1}H NMR of 4-[(4’-methoxyphenyl-amino)methyl]-1,3-dioxolan-2one

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.82-6.77 and 6.66-6.60 (m, 4H), 4.96-4.89 (m, 1H), 4.55 (t, 1H, J = 8.3), 4.30 (dd, 1H, J_1 = 6.8 Hz, J_2 = 8.5 Hz), 3.75 (s, 3H), 3.49 (dd, 1H, J_1 = 4.0 Hz, J_2 = 14.1 Hz), 3.37 (dd, 1H, J_1 = 5.6 Hz, J_2 = 14.1 Hz).

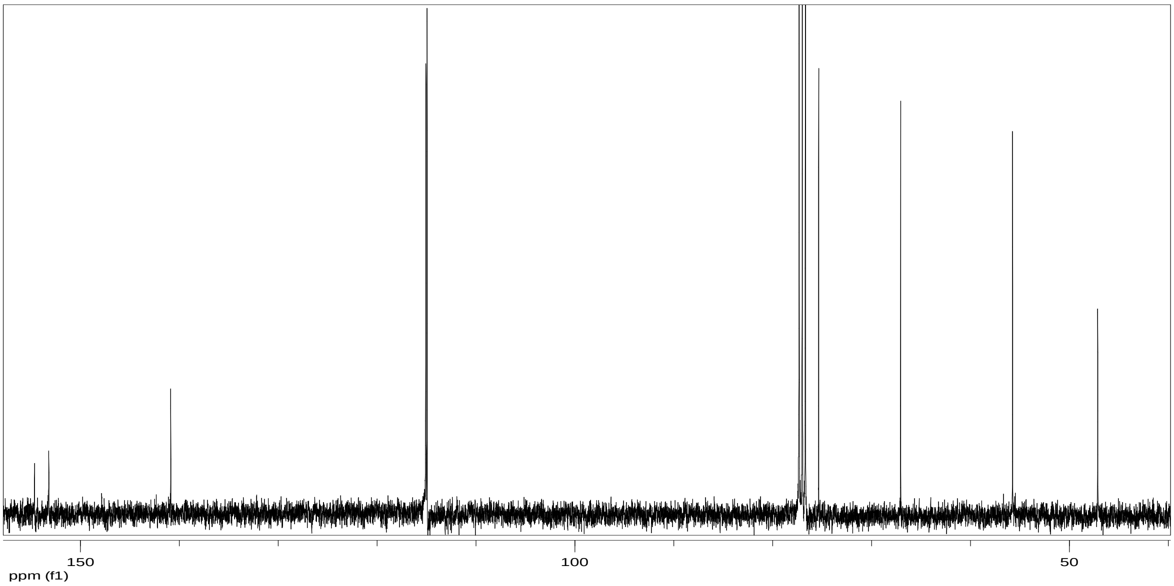


Figure A.33. ^{13}C NMR of 4-[(4’-methoxyphenyl-amino)methyl]-1,3-dioxolan-2one

^{13}C NMR (100 MHz, $CDCl_3$) δ 154.6, 153.2, 140.8, 115.0, 114.9, 75.3, 67.0, 55.7, 47.1.

***p*-hydroxy[*N*-(2,3-dihydroxy)propyl]aniline, 3d**, dark brown solid.[12] GC/MS (relative intensity, 70 eV) m/z: 183 (M^+, 12%), 152 (M^+-CH_2OH, 3), 122 (M^+- $CH(CH_2OH)OH$, 100), 94 (13).

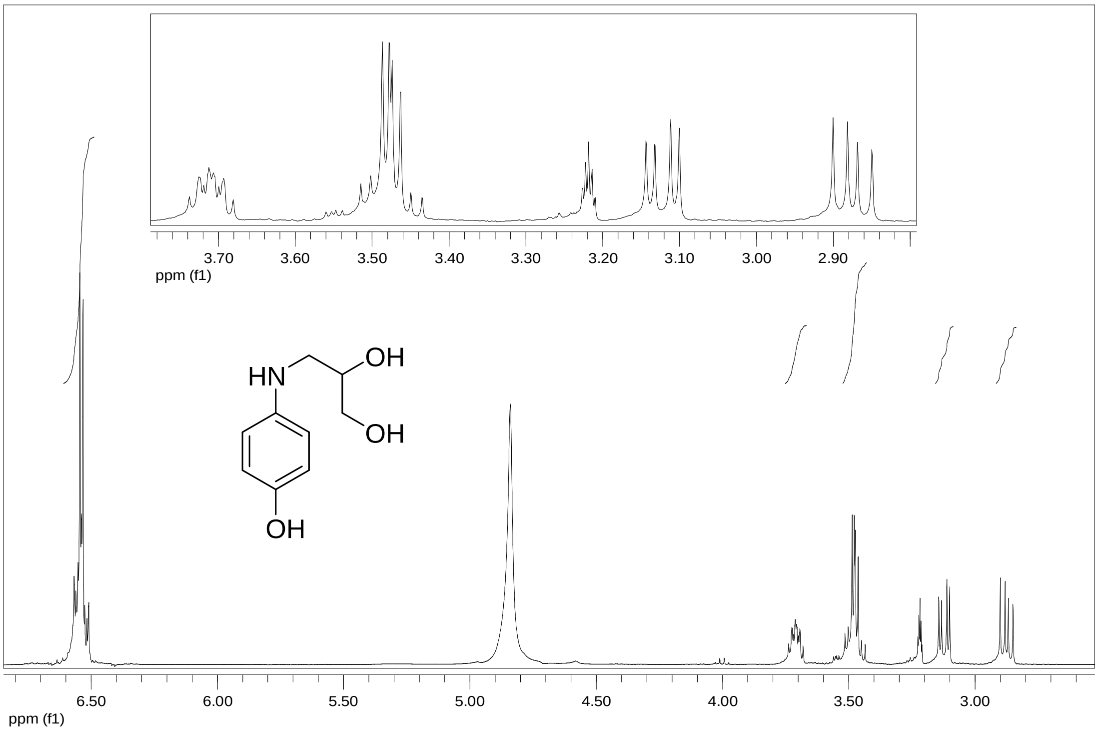


FIgure A.34. ^{1}H NMR of *p*-hydroxy[*N*-(2,3-dihydroxy)propyl]aniline

^{1}H NMR (400 MHz, CD_3OD) δ 6.67-6.59 (m, 4H), 3.84-3.76 (m, 1H), 3.61-3.52 (m, 2H), 3.21 (dd, 1H, J_1 = 4.5 Hz, J_2 = 12.7 Hz), 2.97 (dd, 1H, J_1 = 7.5 Hz, J_2 = 12.7 Hz).

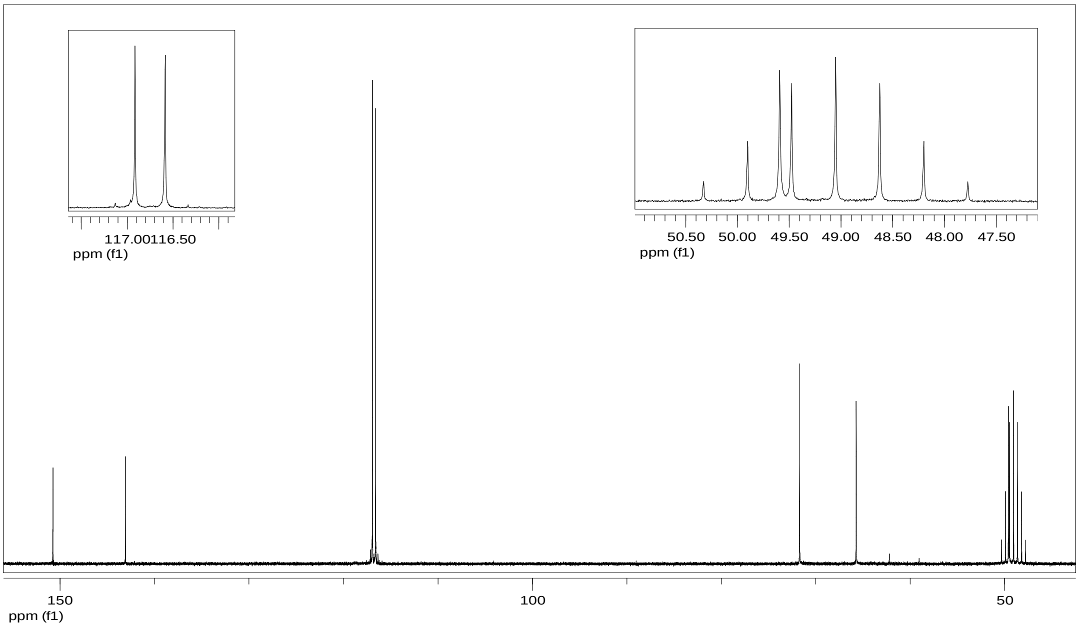


Figure A.35. ^{13}C NMR of *p*-hydroxy[*N*-(2,3-dihydroxy)propyl]aniline

^{13}C NMR (100 MHz, CD_3OD) δ 150.7, 143.0, 116.9, 116.6, 71.7, 65.7, 49.6.

Table A.2. Synopsis of MS spectra of non isolated products

Compound	**GC/MS (relative intensity, 70 eV)**
5a	*m/z*: 167 (M$^+$, 22%), 136 (M$^+$-CH$_2$OH, 99), 119 (13), 118 (M$^+$-CH$_2$OH-H$_2$O, 100), 117 (29), 106 (24), 93 (52), 91 (48), 77 (35), 65 (17), 51 (22)
6a	*m/z*: 193 (M$^+$, 63%), 148 (M$^+$-CO$_2$-H, 7), 132 (11), 130 (19), 120 (13), 119 (18), 118 (M$^+$-CH$_2$OCO$_2$, 31), 117 (11), 106 (68), 105 (34), 104 ([PhN≡CH]$^+$, 75), 93 (41), 91 (38), 78 (15), 77 (100), 51 (38)
4b	*m/z*: 227 (M$^+$, 10%), 142 (32), 140 ([ClC$_6$H$_4$NH=CH$_2$]$^+$, 100), 111 (10), 77 (11)
5b	*m/z*: 201 (M$^+$, 25%), 172 (25), 170 (M$^+$-CH$_2$OH, 25), 154 (16), 152 (M$^+$-CH$_2$OH-H$_2$O, 29), 140 (43), 127 (48), 125 (18), 118 (13), 117 (M$^+$-CH$_2$OH-H$_2$O-Cl, 100), 111 (23), 77 (17), 76 (10), 51 (13)
5c	*m/z*: 197 (M$^+$, 4%), 193 (10), 148 (M$^+$-CH$_2$OH-H$_2$O, 3) 136 (35), 106 (100), 77 (26), 51 (12)
6c	*m/z*: 223 (M$^+$, 100%), 150 (12), 149 (22), 148 (M$^+$- CH$_2$OCO$_2$, 14), 146 (12), 137 (10), 136 (54), 135 (36), 134 ([MeOC$_6$H$_4$NH≡CH]$^+$, 90), 133 (18), 123 (15), 122 (14), 121 (37), 120 (56), 117 (11), 108 (41), 107 (36), 92 (29), 78 (22), 77 (39), 65 (24), 64 (25), 63 (22), 52 (20), 51 (23)
4d	*m/z*: 209 (M$^+$, 10%), 122 ([HOC$_6$H$_4$NH=CH$_2$]$^+$, 100), 94 (13), 65 (15)
6d	*m/z*: 209 (M$^+$, 72%), 164 (M$^+$-CO$_2$-H, 4), 146 (19), 136 (13), 135 (22), 134 (M$^+$-CH$_2$OCO$_2$, 23), 122 (63), 121 (56), 120 ([OHC$_6$H$_4$NH≡CH]$^+$, 100), 109 (33), 107 (39), 94 (18), 93 (44), 65 (48), 53 (17), 52 (26)

A.4 Sequential Coupling of The Transesterification of Cyclic Carbonates with The Selective *N*-Methylation of Anilines Catalysed by Faujasites: a “Green Domino” [Ch. 3, par. 2]

***N*,*N*-dimethyl aniline, 12a,** pale yellow liquid.

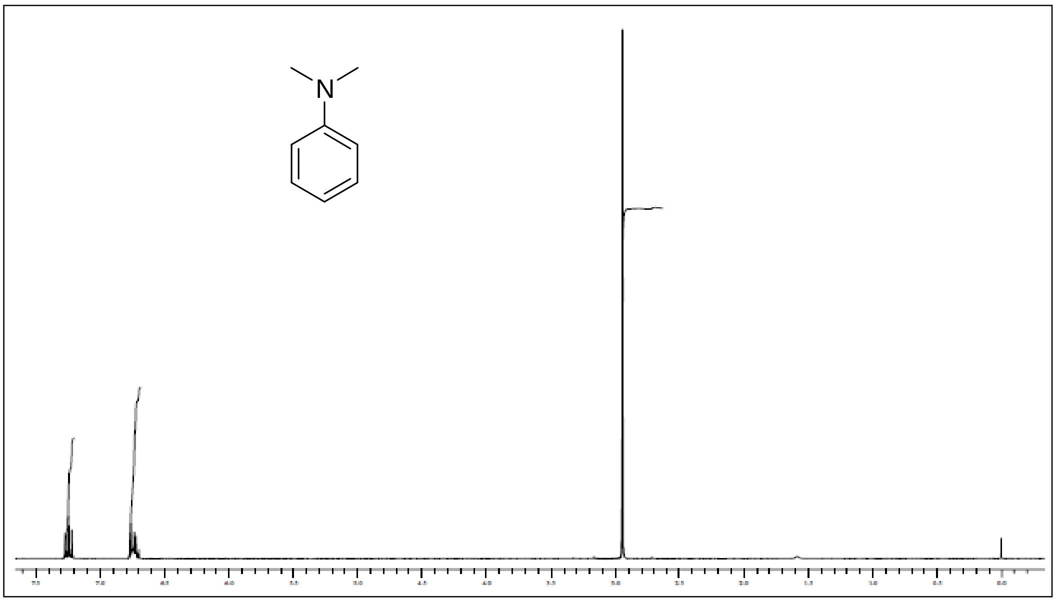


Figure A.36. ^{1}H NMR of *N*,*N*-dimethyl aniline

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28-7.20 (m, 2H), 6.77-6.68 (m, 3H), 2.94 (s, 6H).

***N*,*N*-dimethyl *p*-chloroaniline, 12b.**[13]

Figure A.37. ^{1}H NMR of *N*,*N*-dimethyl *p*-chloroaniline

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.19 (d, 2H, J = 9.23 Hz), 6.66 (d, 2H, J = 9.23 Hz), 2.94 (s, 6H).

N,N-dimethyl *p*-anisidine, 12c.[14]

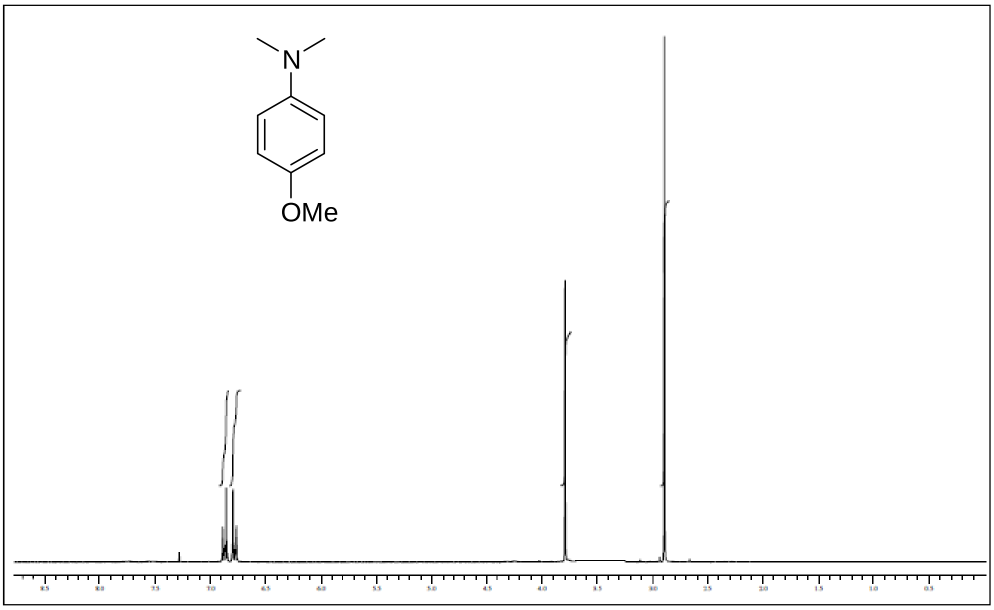


Figure A.38. ^{1}H NMR of *N*,*N*-dimethyl *p*-anisidine

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.87 (d, 2H, J = 9.04 Hz), 6.78 (d, 2H, J = 9.23 Hz), 3.80 (s, 3H), 3.79 (s, 3H), 2.89 (s, 6H).

***N*,*N*-dimethyl *p*-toluidine, 12e:** pale yellow liquid.[14]

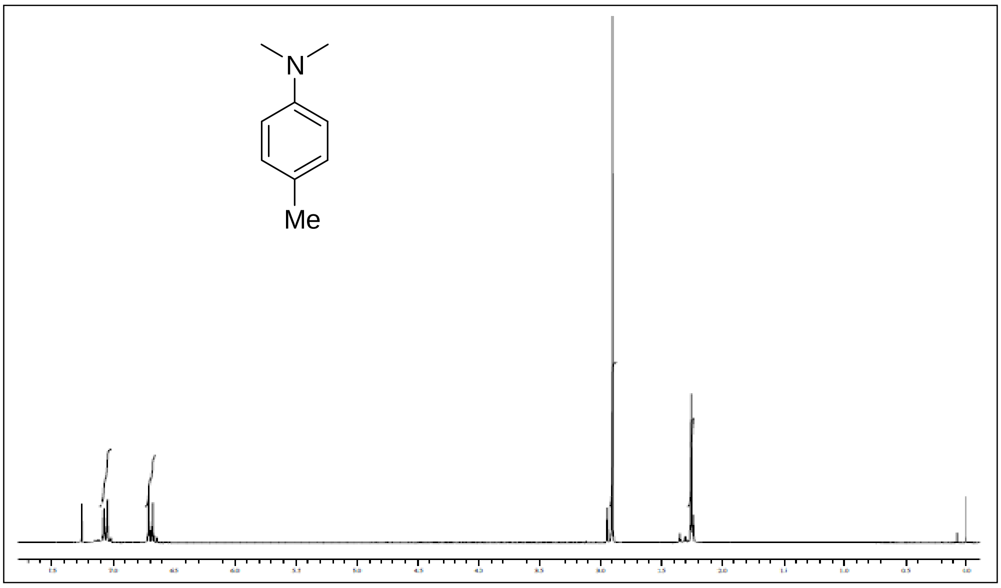


Figure A.39. ^{1}H NMR of *N*,*N*-dimethyl *p*-toluidine

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.06 (d, 2H, J = 8.85 Hz), 6.69 (d, 2H, J = 8.85 Hz), 2.89 (s, 6H), 2.25 (s, 3H).

2-(Hydroxy)ethyl methyl carbonate, 10: MS (EI), m/z (relative int.) 120 (M^+, 1%), 89 (M^+- OCH_3, 14), 59 (M^+- $O(CH_2)_2OH$, 100), 58 (51).

A.5 The Reaction of Primary Aromatic Amines with Alkylene Carbonates in the Presence of Phosphonium-based Ionic Liquids as Catalysts [Ch. 3, par. 3]

I. Ionic liquids

PIL5 [(*i*-Bu)$_3$MeP][OCO$_2$CH$_3$]: viscous pale yellow liquid.

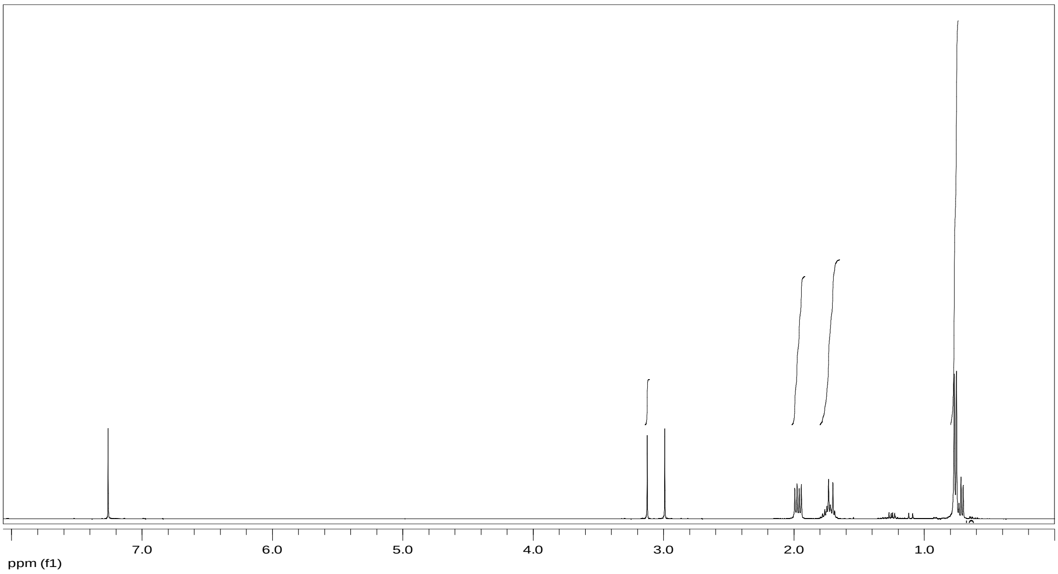


Figure A.40. ^{1}H NMR of **PIL5**

^{1}H NMR (CDCl$_3$, 25°C, 400 MHz): δ (ppm): 3.13 (s, 3H; CH_3OCOO), 1.97 (dd, J(P,H) = 13Hz, J(H,H) = 7Hz, 6H; P-CH_2), 1.78-1.68 (m, 3H; P-CH$_2$-CH(CH$_3$)$_2$), 1.72 (d, J(P,H) = 13Hz, 3H; P-CH_3), 0.76 (d, J(H,H) = 7Hz, 18H; P-CH$_2$-CH(CH_3)$_2$);

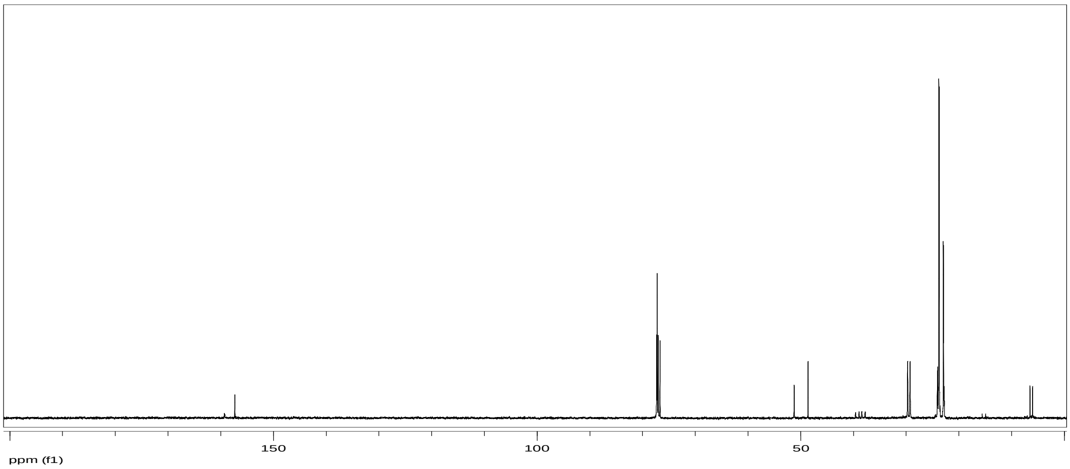


Figure A.41. ^{13}C NMR of **PIL5**

^{13}C NMR (CDCl$_3$, 25°C, 100 MHz): δ (ppm): 157.8 (1C; C=O), 51.2 (1C; CH_3O), 29.5 (d, J(P,C) = 46Hz, 3C; P-CH$_2$-CH(CH$_3$)$_2$), 23.7 (d, J(P,C) = 9Hz, 6C; P-CH$_2$-CH(CH$_3$)$_2$), 22.9 (d, J(P,C) = 5Hz, 3C; P-CH$_2$-CH(CH$_3$)$_2$), 6.2 (d, J(P,C) = 50Hz, 1C; P-CH$_3$).

PIL6 [(*n*-Bu)$_3$MeP][OCO$_2$CH$_3$]: viscous pale yellow liquid.

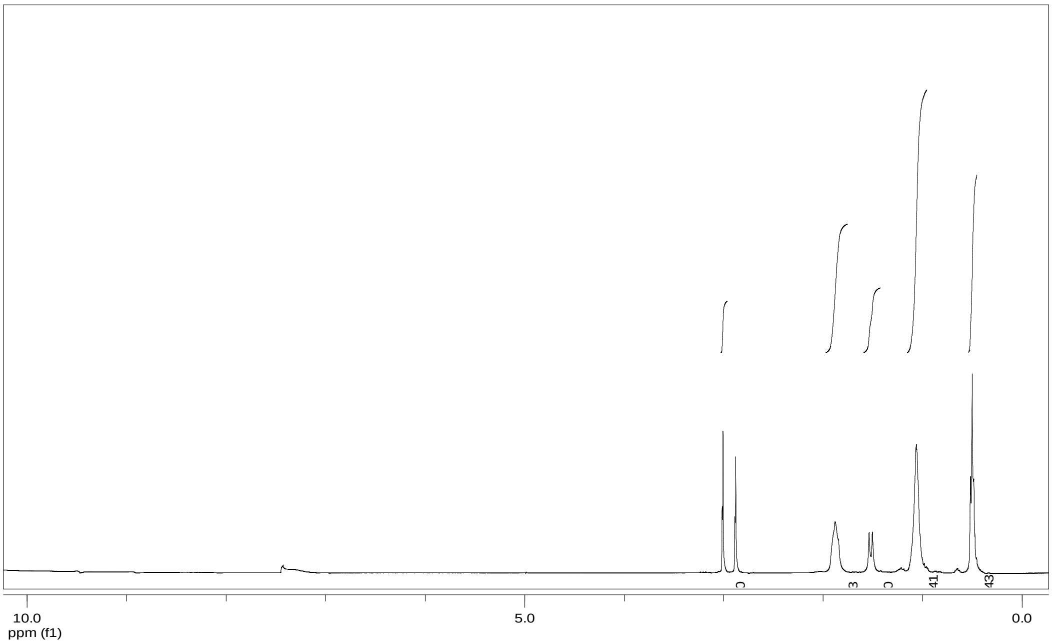


Figure A.42. ^{1}H NMR of **PIL6**

^{1}H NMR (CDCl$_3$, 25°C, 400 MHz): δ (ppm): 3.00 (s, 3H; CH_3OCOO), 1.92-1.80 (m, 6H; P-CH_2), 1.52 (d, J(P,H) = 14Hz, 3H; P-CH_3), 1.06 (brs, 12H), 0.50 (brt, 9H);

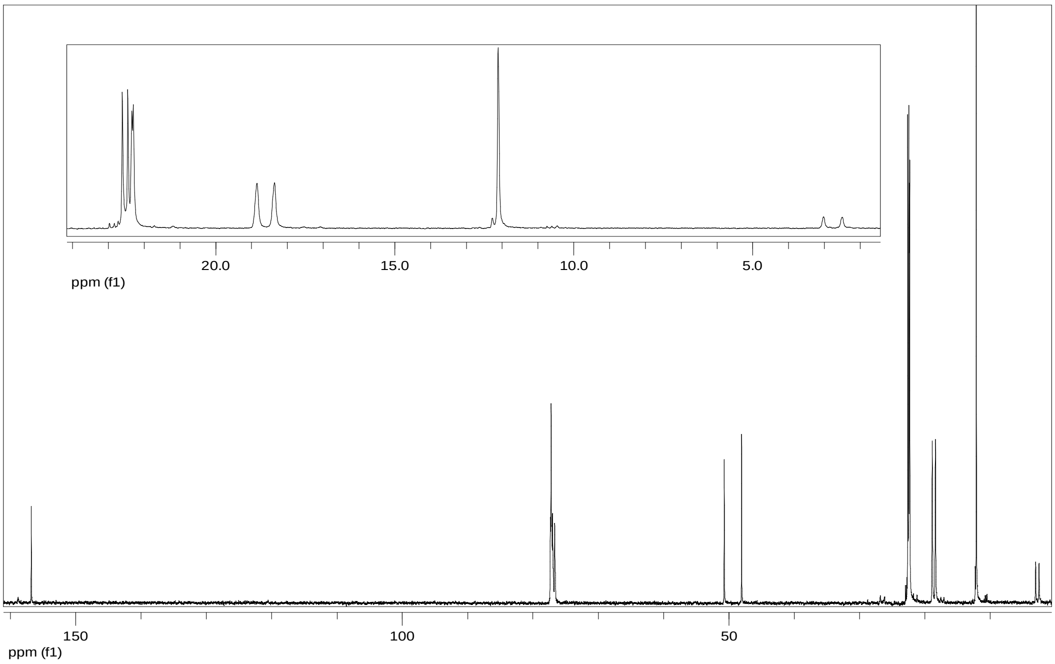


Figure A.43. ^{13}C NMR of **PIL6**

^{13}C NMR (CDCl$_3$, 25°C, 100 MHz): δ (ppm): 156.8 (1C; C=O),), 50.7 (1C; CH_3O), 22.5 (d, J(P,H) = 15Hz, 3C), 22.3(d, J(P,H) = 4Hz, 3C), 18.6 (d, J(P,H) = 49, 3C; P-*C*H2), 12.1 (3C), 2.8 (d, J(P,H) = 53Hz, 1C; P-*C*H$_3$). ^{31}P NMR (CDCl$_3$, 25°C, 200 MHz,): δ (ppm): 31.6.

PIL7 [(*n*-Hex)$_3$MeP][OCO$_2$CH$_3$]: viscous pale yellow liquid.

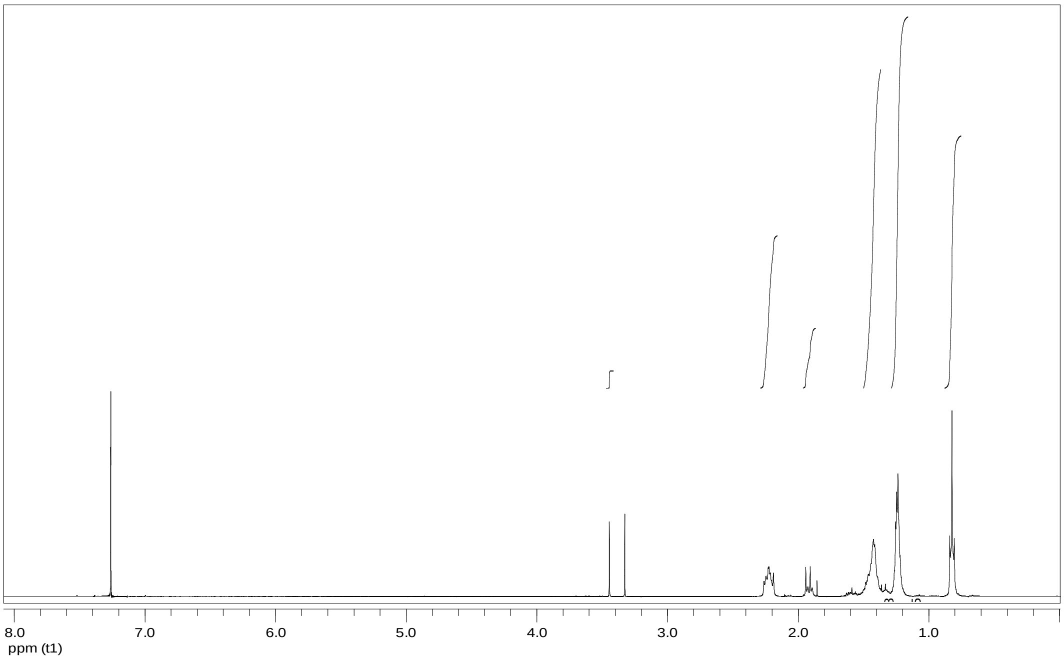


Figure A.44. ^{1}H NMR of **PIL7**

^{1}H NMR (CDCl$_3$, 25°C, 400 MHz): δ (ppm): 3.44 (s, 3H; C*H*$_3$OCOO), 2.26-2.18 (m, 6H; P-C*H*$_2$), 1.92 (d, J(P,H) = 14, 3H, P-C*H*$_3$), 1.46-1.38 (m, 12H), 1.26-1.21 (m, 12H), 0.82 (brt, 9H);

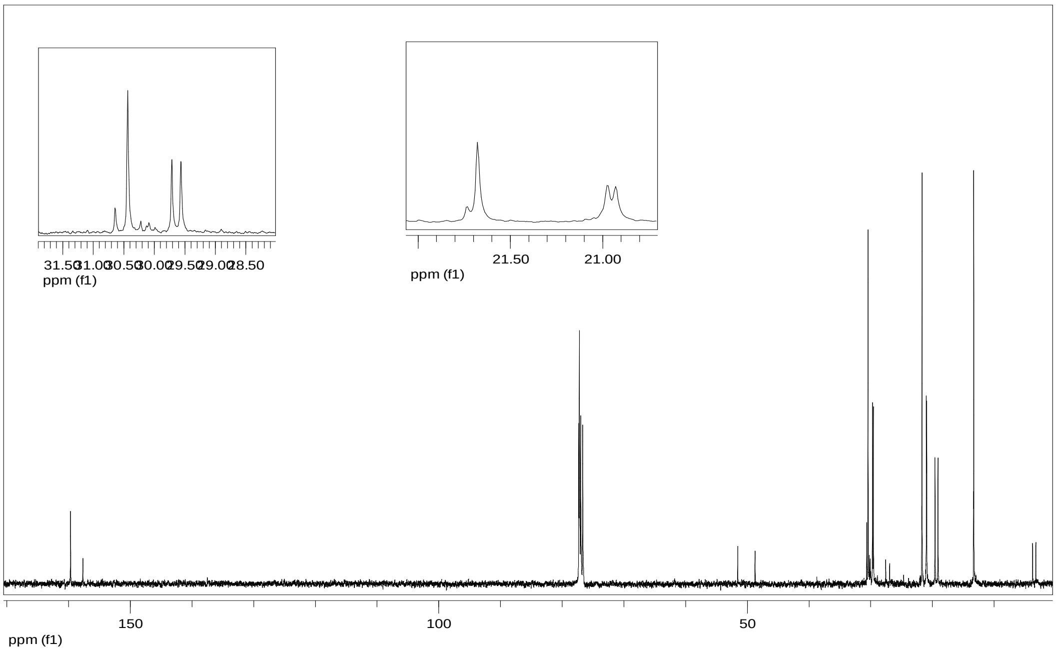


Figure A.45. ^{13}C NMR of **PIL7**

^{13}C NMR (CDCl$_3$, 25°C, 100 MHz): δ (ppm): 157.7 (1C; C=O),), 51.5 (1C; C*H*$_3$O), 30.4 (3C), 29.6 (d, J(P,C) = 15Hz, 3C), 21.7 (3C), 20.9 (d, J(P,C) = 4Hz, 3C), 19.3 (d, J(P,C) = 49Hz, 3C, P-*C*H$_2$), 13.3 (3C), 3.5 (d, J(P,H) = 52Hz, 1C; P-*C*H$_3$).

PIL8 [(*n*-Oct)$_3$MeP][OCO$_2$CH$_3$]: a complete NMR characterization has been given previously in paragraph *A.2.I*, tri-*n*-octylmethylphosphonium methylcarbonate, TOMP(OCO$_2$Me).

II. Ionic liquids provided by the research group

PIL2-4 and **PIL9-13** were provided by the research group. For semplicity, only the description of the ^{1}H and ^{13}C NMR is reported:

PIL2 [(*n*-Bu)$_3$MeP][TosO]: viscous clear colourless liquid.

^{1}H NMR (CDCl$_3$, 25°C, 400 MHz): δ (ppm): 7.61 (d, J = 8Hz, 2H), 7.00 (d, J = 8Hz, 2H), 2.21 (s, 3H; -CH_3), 2.10-2.02 (m, 6H; P-CH_2), 1.72 (d, J(P,H) = 14Hz, 3H; P-CH_3), 1.30-1.25 (m, 12H), 0.77 (brt, 9H).

^{13}C NMR (CDCl$_3$, 25°C, 100 MHz): δ (ppm): 144.1 (1C), 138.9 (1C), 128.4 (2C), 125.8 (2C), 23.7 (d, J(P,H) = 16Hz, 3C), 23.4(d, J(P,H) = 5Hz, 3C), 21.2 (1C), 19.6 (d, J(P,H) = 49, 3C), 13.4 (3C), 4.0 (d, J(P,H) = 52Hz, 1C).

PIL3 [(*n*-Hex)$_3$MeP][TosO]: viscous clear colourless liquid.

^{1}H NMR (CDCl$_3$, 25°C, 400 MHz): δ (ppm): 7.73 (d, J = 8Hz, 2H), 7.09 (d, J = 8Hz, 2H), 2.31 (s, 3H; -CH_3), 2.26-2.18 (m, 6H; P-CH_2), 1.93 (d, J(P,H) = 14, 3H, P-CH_3), 1.47-1.34 (m, 12H), 1.28-1.22 (m, 12H), 0.85 (brt, 9H).

^{13}C NMR (CDCl$_3$, 25°C, 100 MHz): δ (ppm): 144.5 (1C), 138.6 (1C), 128.3 (2C), 125.8 (2C), 31.0 (3C), 30.1(d, J(P,C) = 15Hz, 3C), 22.2 (3C), 21.4 (d, J(P,C) = 5Hz, 3C), 21.1 (1C), 19.8 (d, J(P,C) = 49Hz, 3C, P-CH$_2$), 13.8 (3C), 3.9 (d, J(P,H) = 52Hz, 1C).

PIL4 [(*n*-Oct)$_3$MeP][TosO]: white solid.

^{1}H NMR (CDCl$_3$, 25°C, 400 MHz): δ (ppm): 7.70 (d, J = 8Hz, 2H), 7.06 (d, J = 8Hz, 2H), 2.28 (s, 3H; -CH_3), 2.21-2.15 (m, 6H; P-CH_2), 1.88 (d, J(P,H) = 14, 3H, P-CH_3), 1.41-1.33 (m, 12H), 1.20 (brs, 24H), 0.83 (t, 9H).

^{13}C NMR (CDCl$_3$, 25°C, 100 MHz): δ (ppm): 144.0 (1C), 138.7 (1C), 128.3 (2C), 125.8 (2C), 31.6 (3C), 30.5(d, J(P,C) = 15Hz, 3C), 28.9 (3C), 28.8 (3C), 22.5 (3C), 21.6 (d, J(P,C) = 5Hz, 3C), 21.1 (1C), 19.9 (d, J(P,C) = 48Hz, 3C, P-CH$_2$), 13.9 (3C), 4.1 (d, J(P,H) = 52Hz, 1C; P-CH$_3$).

PIL9 [(*i*-Bu)$_3$MeP][Br]: white hygroscopic solid.

^{1}H NMR (CDCl$_3$, 25°C, 400 MHz): δ (ppm): 2.17 (dd, J(P,H) = 13Hz, J(H,H) = 7Hz, 6H; P-CH_2), 1.88 (d, J(P,H) = 13Hz, 3H; P-CH_3), 1.92-1.82 (m, 3H; P-CH$_2$-CH(CH$_3$)$_2$), 0.84 (d, J(H,H) = 7Hz, 18H; P-CH$_2$-CH(CH_3)$_2$).

^{13}C NMR ($CDCl_3$, 25°C, 100 MHz): δ (ppm): 29.9 (d, J(P,C) = 46Hz, 3C), 23.9 (d, J(P,C) = 9Hz, 6C), 23.0 (d, J(P,C) = 5Hz, 3C), 7.5 (d, J(P,C) = 50Hz, 1C).

PIL10 [(*n*-Bu)$_3$MeP][Br]: viscous clear colourless liquid.

^{1}H NMR ($CDCl_3$, 25°C, 400 MHz): δ (ppm): 2.03-1.96 (m, 6H; P-CH_2), 1.62 (d, J(P,H) = 13, 3H, P-CH_3), 1.14-1.03 (m, 12H), 0.50 (brt, 9H).

^{13}C NMR ($CDCl_3$, 25°C, 100 MHz): δ (ppm): 22.6 (d, J(P,C) = 16Hz, 3C), 22.5 (d, J(P,H) = 4Hz, 3C), 19.3 (d, J(P,H) = 49, 3C), 12.3 (3C), 4.1 (d, J(P,H) = 52Hz, 1C).

PIL11 [(*n*-Hex)$_3$MeP][Br]: viscous pale yellow liquid.

^{1}H NMR ($CDCl_3$, 25°C, 400 MHz): δ (ppm): 2.29-2.23 (m, 6H; P-CH_2), 1.91 (d, J(P,H) = 13, 3H, P-CH_3), 1.42-1.28 (m, 12H), 1.15-1.12 (m, 12H), 0.71 (brt, 9H).

^{13}C NMR ($CDCl_3$, 25°C, 100 MHz): δ = 30.6 (3C), 29.9 (d, J(P,C) = 15Hz, 3C), 21.9 (3C), 21.3 (d, J(P,C) = 4Hz, 3C), 20.3 (d, J(P,C) = 49Hz, 3C), 13.5 (3C), 4.9 (d, J(P,H) = 53Hz, 1C).

PIL12 [(*n*-Oct)$_3$MeP][Br]: white hygroscopic solid.

^{1}H NMR ($CDCl_3$, 25°C, 400 MHz): δ (ppm): 2.42-2.36 (m, 6H; P-CH_2), 2.06 (d, J(P,H) = 13, 3H, P-CH_3), 1.52-1.38 (m, 12H), 1.26-1.20 (m, 24H), 0.82 (brt, 9H).

^{13}C NMR ($CDCl_3$, 25°C, 100 MHz): δ (ppm): 31.4 (3C), 30.4 (d, J(P,C) = 15Hz, 3C), 28.9 (3C), 28.8 (3C), 22.5 (3C), 21.6 (d, J(P,C) = 5Hz, 3C), 21.1 (1C), 19.9 (d, J(P,C) = 48Hz, 3C), 13.9 (3C), 4.1 (d, J(P,H) = 52Hz, 1C; P-CH_3).

PIL13 [(*n*-Oct)$_3$MeP][I]: viscous yellow liquid.

^{1}H NMR ($CDCl_3$, 25°C, 400 MHz): δ (ppm): 2.45-2.38 (m, 6H; P-CH_2), 2.09 (d, J(P,H) = 13, 3H, P-CH_3), 1.56-1.41 (m, 12H), 1.30-1.1.23 (m, 24H), 0.84 (brt, 9H).

^{13}C NMR ($CDCl_3$, 25°C, 100 MHz): δ (ppm): 31.5 (3C), 30.4 (d, J(P,C) = 15Hz, 3C), 28.7 (3C), 28.8 (3C), 22.4 (3C), 21.6 (d, J(P,C) = 5Hz, 3C), 20.7 (d, J(P,C) = 48Hz, 3C, P-CH_2), 13.8 (3C), 5.6 (d, J(P,H) = 52Hz, 1C).

Bis-*N*-(2-hydroxy)ethyl aniline, **17a:**[15] dark yellow oil. GC/MS (relative intensity, 70 eV) m/z: 181 ($[M]^+$, 12%), 151 (10), 150 ($[M\text{-}CH_2OH]^+$, 100), 107 (10), 106 ($[M\text{-}(CH_2OH)\text{-}(CH_2CH_2O)]^+$, 86), 104 (11), 91 ($[M\text{-}(CH_2CH_2OH)_2]^+$, 14), 79 (16), 77 (38), 51 (19), 45 (28), 31 ($[CH_2OH]^+$, 10).

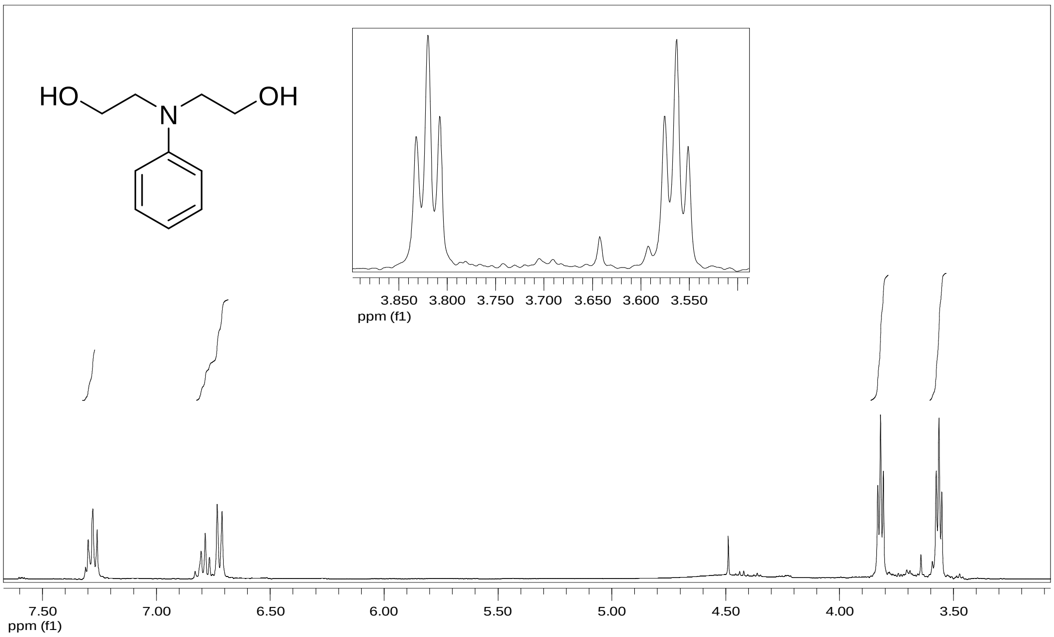


Figure A.46. ^{1}H NMR of bis-*N*-(2-hydroxy)ethyl aniline

^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.27-7.20 (m, 2H), 6.81-6.60 (m, 3H), 3.84 (t, J = 4.9 Hz, 4H), 3.57 (t, J = 4.9 Hz, 4H).

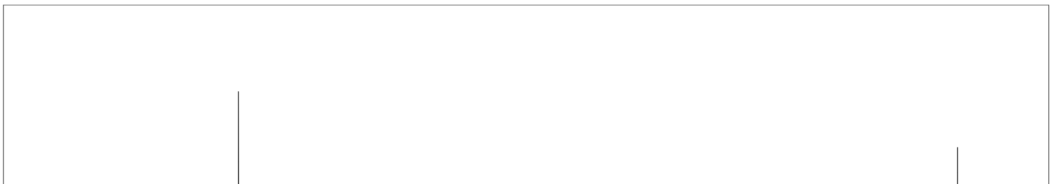


Figure A.47. ^{13}C NMR of bis-*N*-(2-hydroxy)ethyl aniline

^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 147.7 (1C), 129.1 (2C), 116.7 (1C), 112.4 (2C), 60.5 (2C), 55.1 (2C).

Bis-*N*-(2-hydroxy)ethyl *p*-anisidine, **17c:** [15a,16] brown solid. GC/MS (relative intensity, 70 eV) m/z: 211 ([M]$^+$, 13%), 181 (12), 180 ([M-CH_2OH]$^+$, 100), 136 ([M-CH_2OH-$CHCH_2OH$]$^+$, 55), 121 ([M-$(CH_2CH_2OH)_2$]$^+$, 17), 120 (18), 108 (15), 77 (12), 65 (11), 45 (28), 31 ([CH_2OH]$^+$, 10).

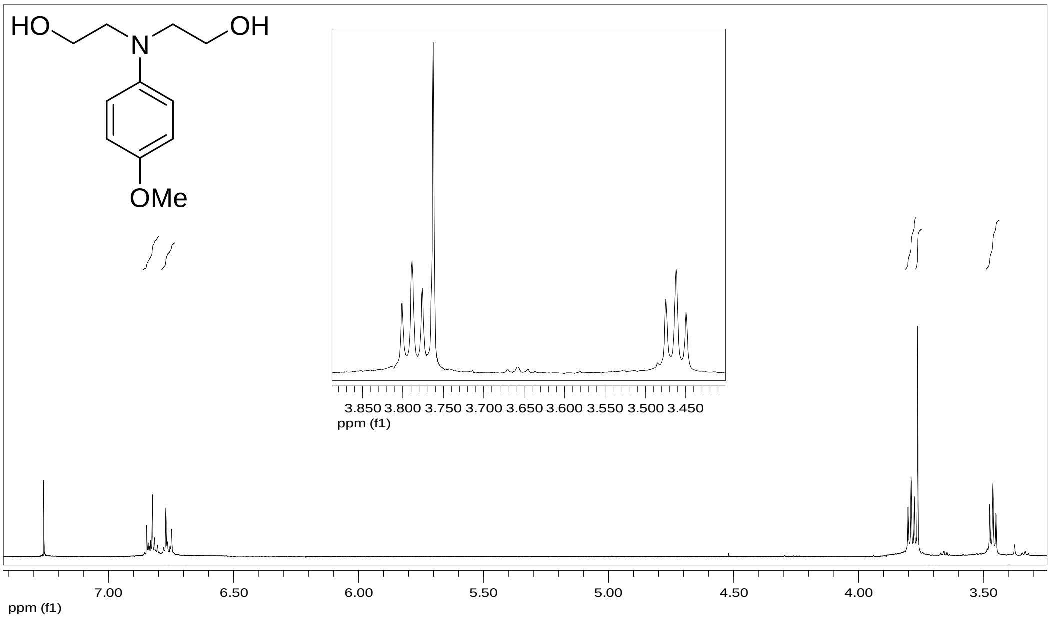


Figure A.48. ^{1}H NMR of bis-*N*-(2-hydroxy)ethyl *p*-anisidine

^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 6.83 (d, J = 9.2 Hz, 2H), 6.76 (d, J = 9.2 Hz, 2H), 3.79 (t, J = 5.0 Hz, 4H), 3.76 (s, 3H), 3.46 (t, J = 5.0 Hz, 4H).

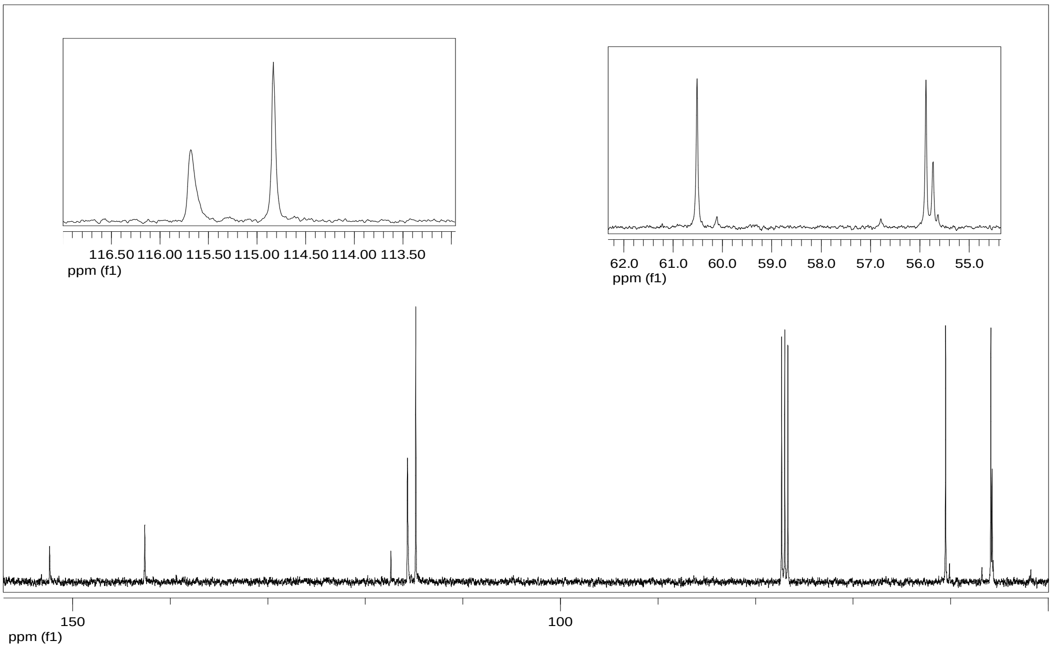


Figure A.49. ^{13}C NMR of bis-*N*-(2-hydroxy)ethyl *p*-anisidine

^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 152.4 (1C), 142.6 (1C), 115.7 (2C), 114.8 (2C), 60.5 (2C), 55.9 (2C), 55.7 (1C).

Bis-*N*-(2-hydroxy)ethyl *p*-toluidine, **17e:**[16] dark brown solid. GC/MS (relative intensity, 70 eV) m/z: 195 ([M]$^+$, 12%), 165 (11), 164 ([M-CH_2OH]$^+$, 100), 121 (10), 120 ([M-CH_2OH-$CHCH_2OH$)]$^+$, 71), 118 (12), 105 ([M-(CH_2CH_2OH)$_2$]$^+$, 10), 91 (33), 65 (18), 45 (28), 31 ([CH_2OH]$^+$, 10).

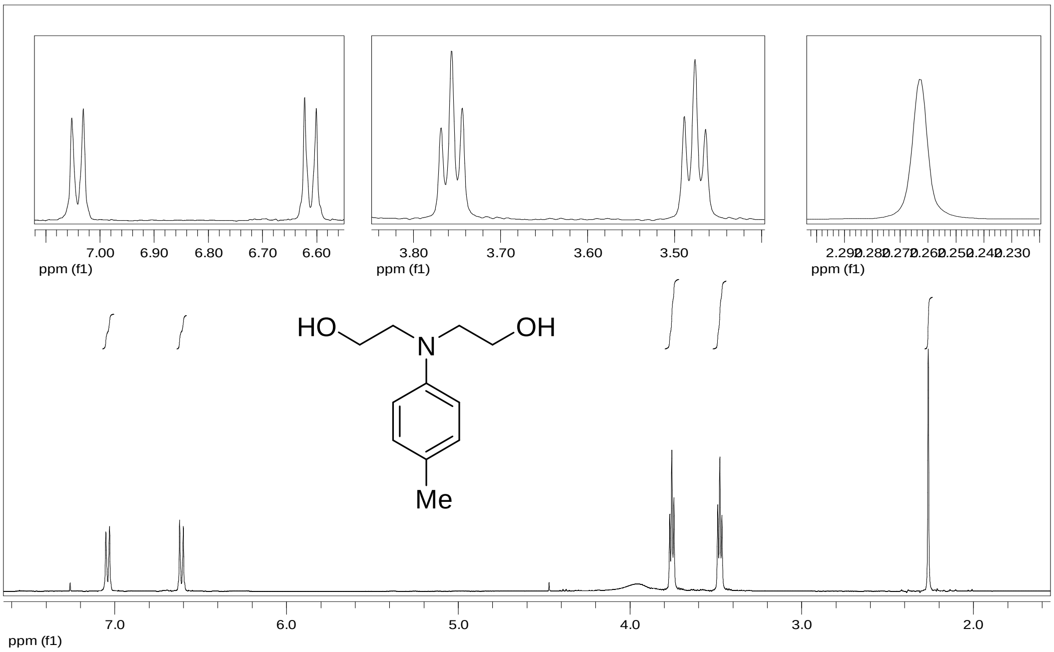


Figure A.50. ^{1}H NMR of bis-*N*-(2-hydroxy)ethyl *p*-toluidine

^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.04 (d, J = 8,7 Hz, 2H), 6.63 (d, J = 8,7 Hz, 2H), 3.81 (t, J = 4.9 Hz, 4H), 3.52 (t, J = 4.9 Hz, 4H), 2.25 (s, 3H).

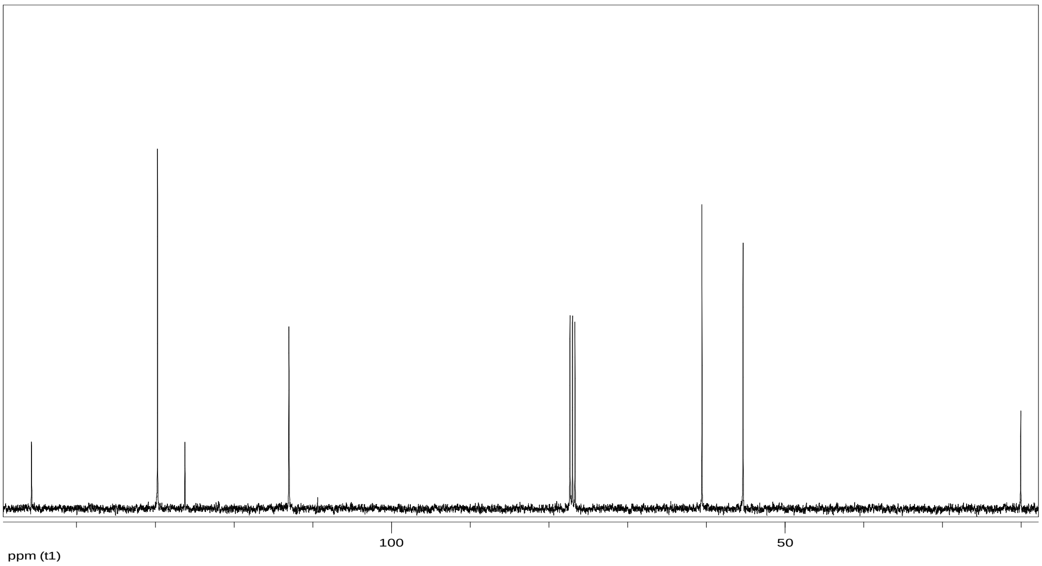


Figure A.51. ^{13}C NMR of bis-*N*-(2-hydroxy)ethyl *p*-toluidine

^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 145.7 (1C), 129.7 (2C), 126.2 (1C), 113.0 (2C), 60.5 (2C), 55.3 (2C), 20.0 (1C).

Bis-*N*-(2-hydroxy)ethyl *p*-chloroaniline, **17b:**[16] pale brown solid. GC/MS (relative intensity, 70 eV) m/z: 215 ($[M]^+$, 14%), 186 (35), 185 (13), 184 ($[M\text{-}CH_2OH]^+$, 100), 142 (24), 141 (12), 140 ($[M\text{-}CH_2OH\text{-}CHCH_2OH]^+$, 76), 138 (13), 125 ($[M\text{-}(CH_2CH_2OH)_2]^+$, 10), 111 (20), 105 (10), 77 (19), 75 (19), 51 (11), 45 (28), 31 ($[CH_2OH]^+$, 10).

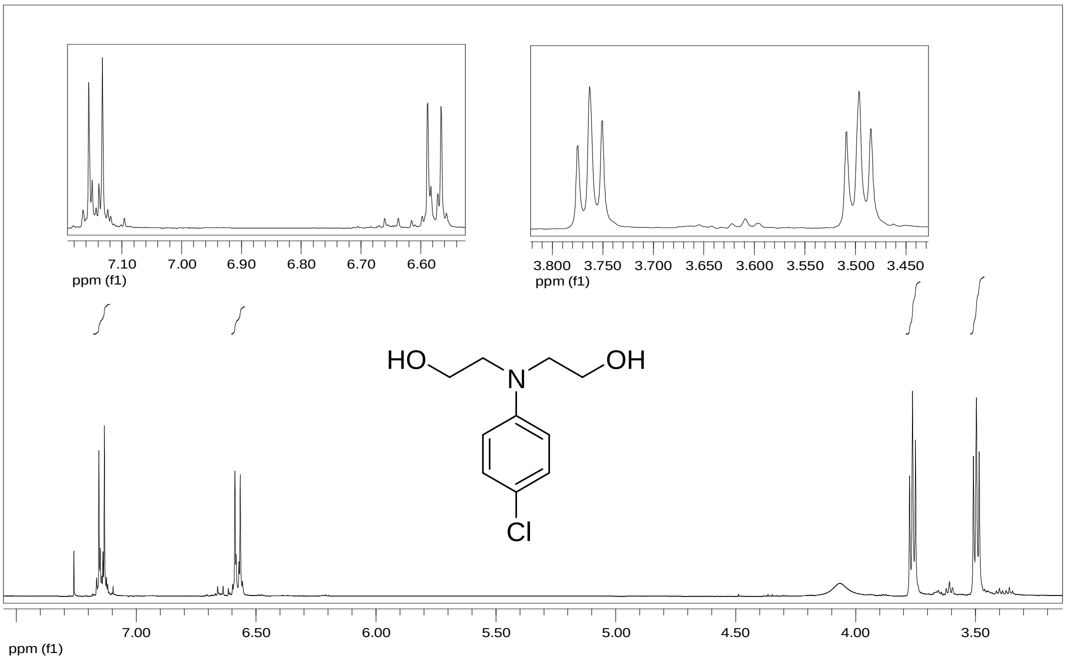


Figure A.52. ^{1}H NMR of bis-*N*-(2-hydroxy)ethyl *p*-chloroaniline

^{1}H NMR (CD_3OD, 400 MHz) δ (ppm): 7.05 (d, J = 9,2 Hz, 2H), 6.64 (d, J = 9.2 Hz, 2H), 3.64 (t, J = 6.0 Hz, 4H), 3.45 (t, J = 6.0 Hz, 4H).

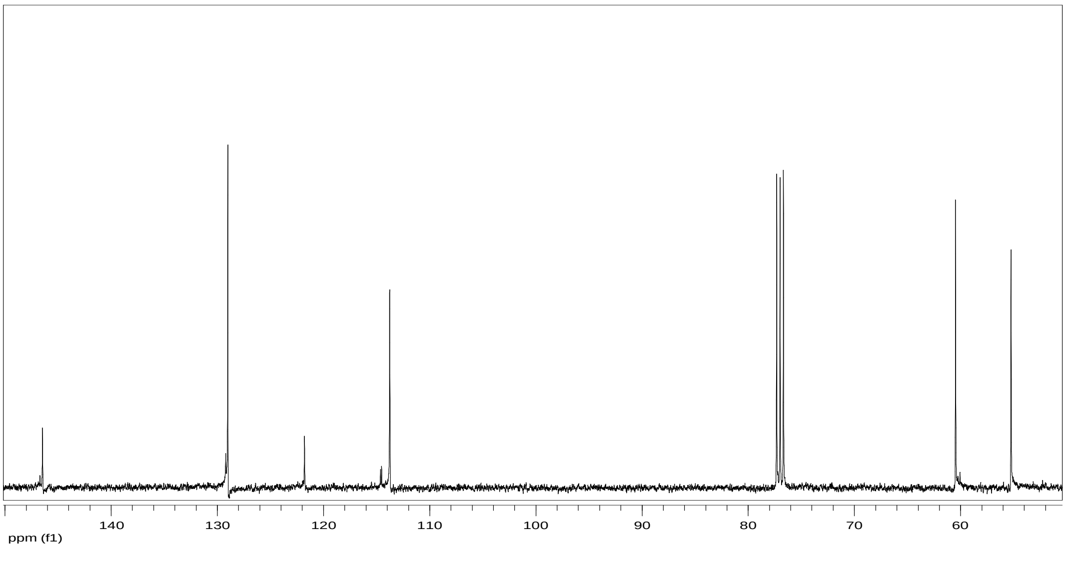


Figure A.53. ^{13}C NMR of bis-*N*-(2-hydroxy)ethyl *p*-chloroaniline

^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 146.5 (1C), 129.0 (2C), 121.8 (1C), 113.8 (2C), 60.5 (2C), 55.2 (2C).

Bis-*N*-(2-hydroxy)propyl aniline, 20a: (sum of diastereoisomers) pale yellow oil. GC/MS (relative intensity, 70 eV) m/z: 209 ([M]$^+$, 11%), 165 (11), 164 ([M-CH(CH$_3$)OH]$^+$, 100), 107 (13), 106 ([M-CH(CH$_3$)OH-CH$_2$CH(CH$_3$)O]$^+$, 84) 104 (10), 91 (10) 77 (25), 59 ([CH$_2$CH(CH$_3$)OH]$^+$, 28), 31 ([CH$_2$OH]$^+$, 12).

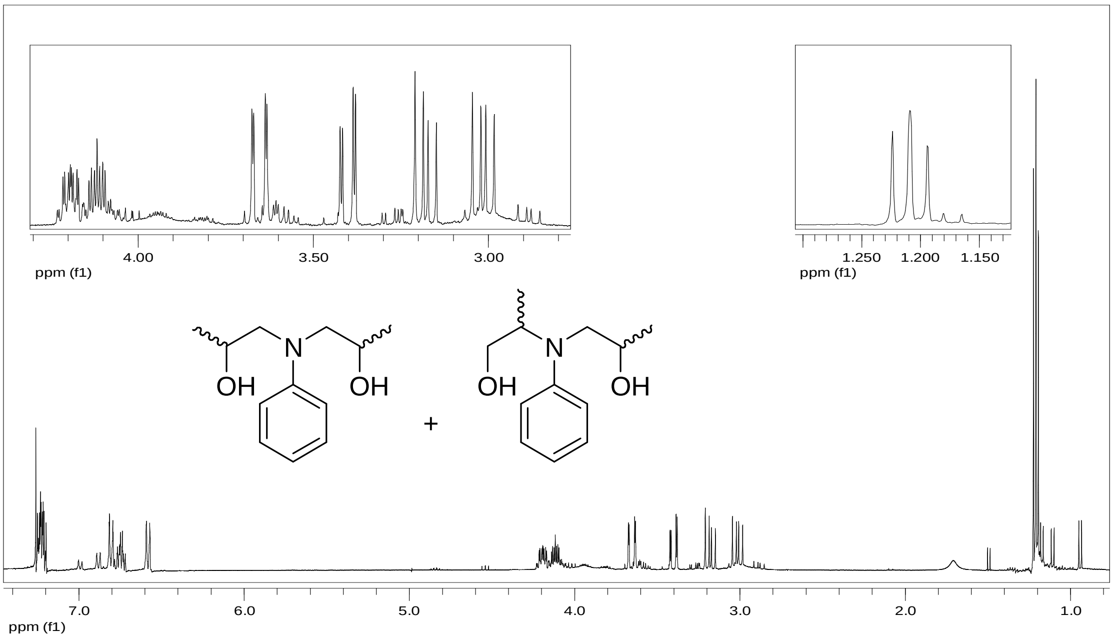


Figure A.54. ^{1}H NMR of bis-*N*-(2-hydroxy)propyl aniline

^{1}H NMR (CDCl$_3$, 400 MHz) δ (ppm): 7.26-7.20 (m, 4H), 6.82-6.78 (m, 2H), 6.78 6.71 (m, 2H), 6.59-6.57 (m, 2H), 4.24-4.16 (m, 2H), 4.16-4.08 (m, 2H), 3.65 (dd, J_1 = 15Hz, J_2 = 2Hz, 2H), 3.40 (dd, J_1 = 15Hz, J_2 = 3Hz, 2H), 3.18 (dd, J_1 = 15Hz, J_2=9Hz, 2H), 3.02 (dd, J_1 = 15Hz, J_2 = 10Hz, 2H), 1.22 (d, J = 6Hz, 6H), 1.20 (d, J = 6Hz, 6H).

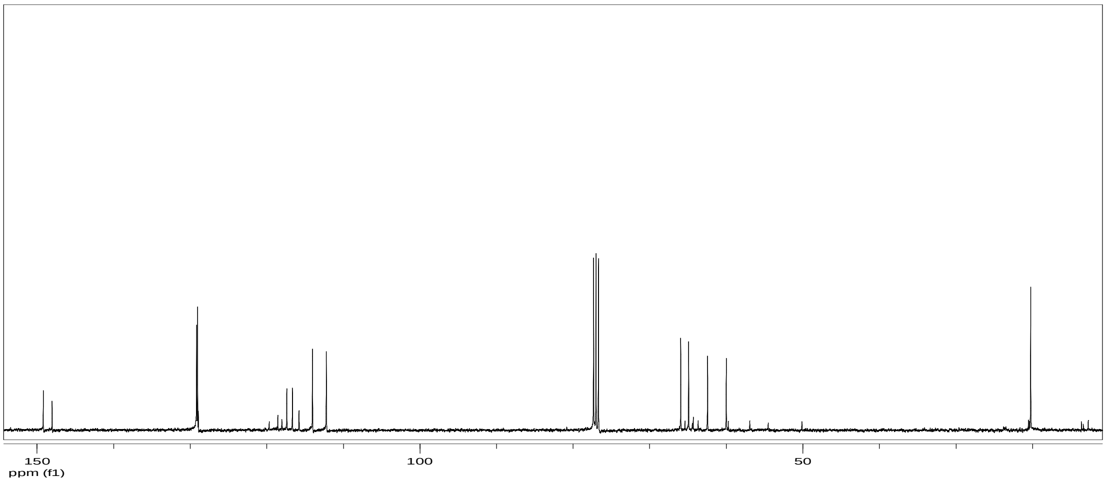


Figure A.55. ^{13}C NMR of bis-*N*-(2-hydroxy)propyl aniline

^{13}C NMR (CDCl$_3$, 25°C, 100 MHz): δ (ppm): 149.2 (1C), 148.0 (1C), 129.2 (2C), 129.0 (2C), 117.4 (1C), 116.6 (1C), 114.0 (2C), 112.2 (2C), 65.9 (2C), 64.9 (2C), 62.4 (2C), 60.0 (2C), 20.2 (4C).

Bis-*N*-(2-hydroxy)propyl *p*-anisidine, 20c:[17] (sum of diastereoisomers) brown oil. GC/MS (relative intensity, 70 eV) m/z: 239 ($[M]^+$, 11%), 195 (12), 194 ($[M\text{-}CH(CH_3)OH]^+$, 100), 137 (17), 136 ($[M\text{-}(CH(CH_3)OH)\text{-}(CH_2CH(CH_3)O)]^+$, 76), 121 ($[M\text{-}(CH_2CH(CH_3)OH)_2]^+$, 15), 120 (13), 77 (10), 59 ($[CH_2CH(CH_3)OH]^+$, 14), 31 ($[CH_2OH]^+$, 14).

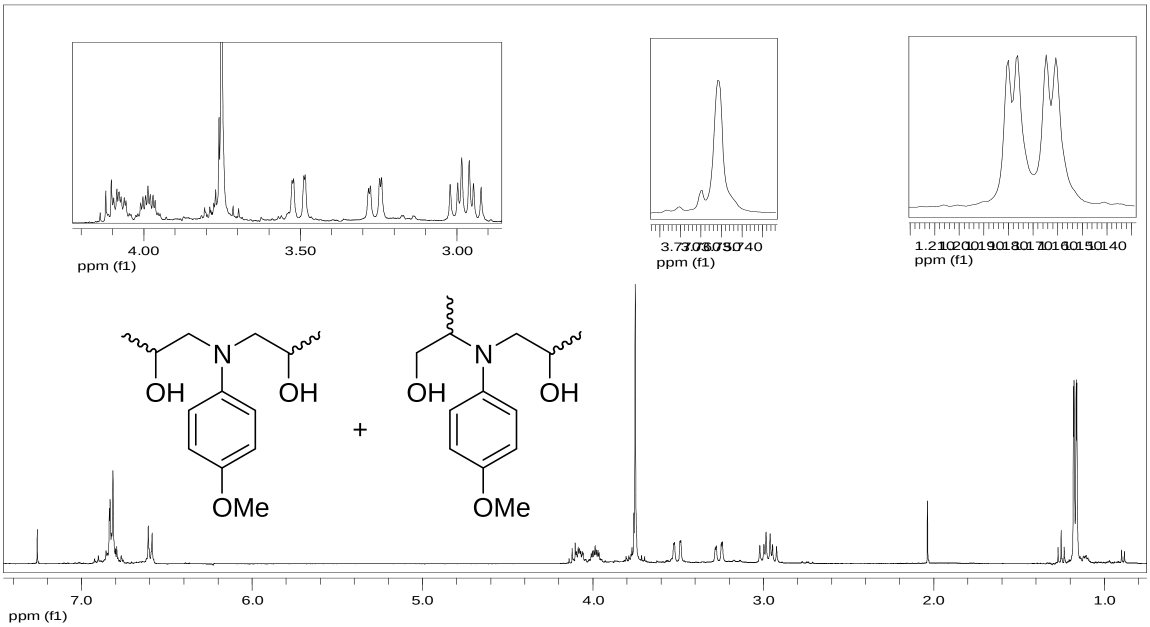


Figure A.56. ^{1}H NMR of bis-*N*-(2-hydroxy)propyl *p*-anisidine

^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 6.86-6.78 (m, 6H), 6.61-6.58 (d, J = 9Hz, 2H), 4.12-4.03 (m, 2H), 4.03-3.94 (m, 2H), 3.75 (s, 6H), 3.51 (dd, J_1 = 15Hz, J_2 = 2Hz, 2H) , 3.26 (dd, J_1 = 14Hz, J_2 = 2Hz, 2H), 3.02-2.92 (m, 4H), 1.17 (d, J = 6Hz, 6H), 1.16 (d, J = 6Hz, 6H).

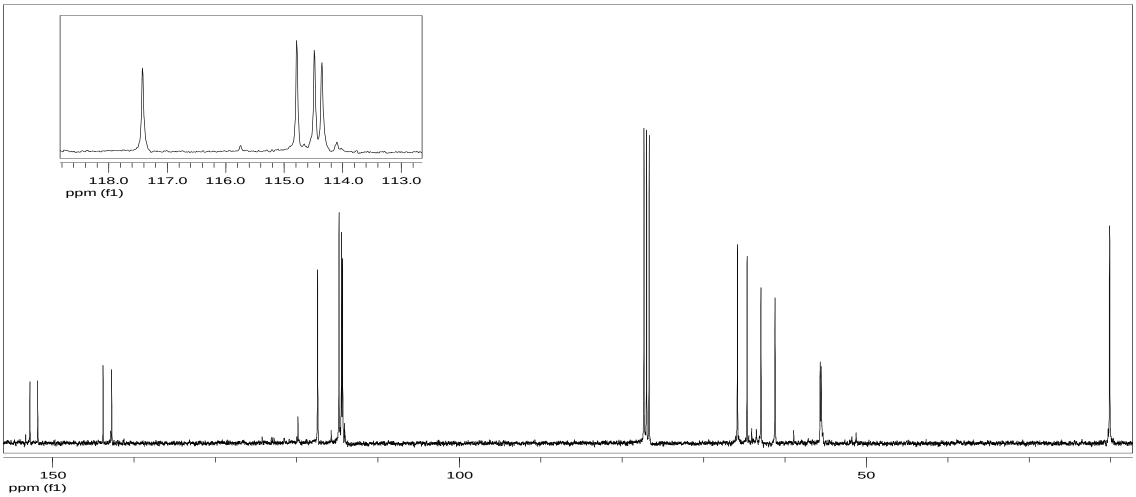


Figure A.57. ^{13}C NMR of bis-*N*-(2-hydroxy)propyl *p*-anisidine

^{13}C NMR ($CDCl_3$, 25°C, 100 MHz): δ (ppm): 152.8 (1C), 151.8 (1C), 143.8 (1C), 142.7 (1C), 117.4 (2C), 114.8 (2C), 114.5 (2C), 114.4 (2C), 65.8 (2C), 64.7 (2C), 63.0 (2C), 61.2 (2C), 55.7 (1C), 55.5 (1C), 20.1 (4C).

Table A.3. Synopsis of MS spectra of non isolated products

Compound	**GC/MS (EI, 70 eV)**
13a	m/z: 137 ([M]$^+$, 18%), 106 [M-CH$_2$OH]$^+$, 100), 79 (16), 77 (34), 54 (18), 32 (16)
16a	m/z: 163 ([M]$^+$, 38%), 106 (13), 105 ([C$_6$H$_5$N=CH$_2$]$^{+\cdot}$, 100), 104 (53), 77 (40), 51 (23), 32 (26)
18a	m/z: 163 ([M]$^+$, 50%), 118 ([M-CO$_2$-H]$^+$, 16), 104 [M-CO$_2$-H-CH$_2$]$^+$, 81), 91 (16), 77 (100), 52 (15), 51 (27), 50 (10), 29 (10)
13c	m/z: 167 ([M]$^+$, 20%), 136 ([M-CH$_2$OH]$^+$, 100), 121 (13), 108 (13), 32 (14)
16c	m/z: 193 ([M]$^+$, 61%), 178 (23), 136 (10), 135 ([M-CH$_2$OH]$^+$, 100), 121 (10), 120 (66), 92 (13), 77 (15), 65 (17), 64 (10), 39 (11)
18c	m/z: 193 ([M]$^+$, 60%), 148 ([M-CO$_2$-H]$^+$, 10), 135 (11), 134 ([M-CO$_2$-H-CH$_2$]$^+$, 100), 121 (17), 107 (15), 91 (12), 80 (10), 79 (10), 78 (11), 77 (25), 65 (11), 64 (16), 63 (13), 52 (13), 51 (12), 39 (12), 32 (12)
13e	m/z: 151 ([M]$^+$, 18%), 121 (10), 120 ([M-CH$_2$OH]$^+$, 100), 91 (27), 77 (11), 65 (16)
16e	m/z: 177 ([M]$^+$, 36%), 120 (18), 119 ([M-CH$_2$OH]$^+$, 100), 118 (31), 91 (45), 65 (22), 39 (12), 32 (36)
18e	m/z: 177 ([M]$^+$, 54%), 132 ([M-CO$_2$-H]$^+$, 18), 118 ([M-CO$_2$-H-CH$_2$]$^+$, 79), 105 (20), 91 (100), 89 (10), 77 (13), 65 (36), 63 (13), 52 (10), 51 (17), 39 (21), 32 (10)
13b	m/z: 171 ([M]$^+$, 15%), 142 (33), 141 (10), 140 ([M-CH$_2$OH]$^+$, 100), 111 (11), 105 (12), 77 (19), 75 (16)
16b	m/z: 197 ([M]$^+$, 42%), 141 (33), 140 (22), 139 ([M-CH$_2$OH]$^+$, 100), 138 (40), 111 (20), 75 (16)
18b	m/z: 197 ([M]$^+$, 44%), 152 ([M-CO$_2$-H]$^+$, 15), 140 (33), 139 (12), 138 ([M-CO$_2$-H-CH$_2$]$^+$, 100), 125 (13), 113 (26), 111 (79), 90 (10), 76 (16), 75 (36), 74 (10), 69 (14), 63 (19), 51 (14), 50 (19), 39 (10), 38 (10), 32 (93)
19a	m/z: 151 ([M]$^+$, 11%), 106 ([M-CH(CH$_3$)OH]$^+$, 100), 79 (11), 77 (23), 51 (12)
21a	m/z: 191 ([M]$^+$, 24%), 106 (10), 105 ([C$_6$H$_5$N=CH$_2$]$^{+\cdot}$, 100), 104 (29), 77 (21)
22a	m/z: 177 ([M]$^+$, 24%), 163 (10), 162 ([M-CH$_3$]$^+$, 100), 134 ([M-CH$_3$-CO]$^+$, 36), 118 ([M-CH$_3$-CO$_2$]$^+$, 32], 117 (11), 105 ([M-CO$_2$CHCH$_3$]$^+$, 15), 104 (23), 91 (22), 77 (69), 51 (28), 43 (14)
19c	m/z: 181 ([M]$^+$, 14%), 136 ([M-CH(CH$_3$)OH]$^+$, 100), 121 (11), 108 (11), 77 (6)
21c	m/z: 221 ([M]$^+$, 39%), 136 (17), 135 ([CH$_3$OC$_6$H$_4$N=CH$_2$]$^{+\cdot}$, 100), 134 (11), 120 (39), 92 (9), 77 87)
22c	m/z: 207 ([M]$^+$, 44%), 193 (13), 192 ([M-CH$_3$]$^+$, 100], 164 ([M-CH$_3$-CO]$^+$, 48), 162 (12), 150 (10), 148 ([M-CO$_2$-CH$_3$]$^+$, 26), 136 (11), 135 ([M-CO$_2$CHCH$_3$]$^+$, 14), 134 (76), 122 (14), 121 (35), 120 (11), 109 (11), 108 (14), 107 (20), 92 (18), 79 (10), 77 (17), 65 (13), 64 (11), 63 (13), 51 (10), 43 (13), 41 (23)

A.6 Decarboxylation of Dialkyl Carbonates to Dialkyl Ethers over Alkali Metal-exchanged Faujasites [Ch. 4, par. 1]

Dipropyl carbonate, DPrC: GC/MS (relative intensity, 70 eV) m/z: 146 ($[M]^+$, <1%), 63 (42), 59 (27), 43 (100), 42 (16), 41 (28).

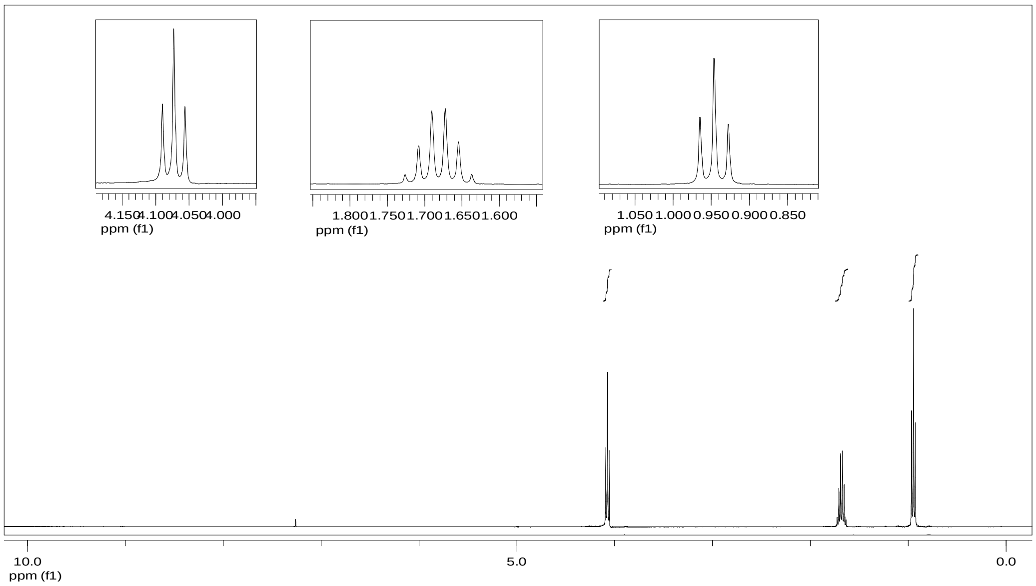


Figure A.58. ^{1}H NMR of dipropyl carbonate

^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 4.07 (t, 4H, J=6.7Hz), 1.68 (m, 4H), 0.95 (t, 6H, J=7.4Hz). Spectroscopic properties were in agreement with those of an authentic commercial sample of DPrC.

Dioctyl carbonate, DOC: GC/MS (relative intensity, 70 eV) m/z: 286 ($[M]^+$, <1%), 113 (32), 84 (22), 83 (26), 71 (100), 70 (33), 69 (37), 57 (74), 56 (35), 55 (46), 43 (49), 42 (24), 41 (64).

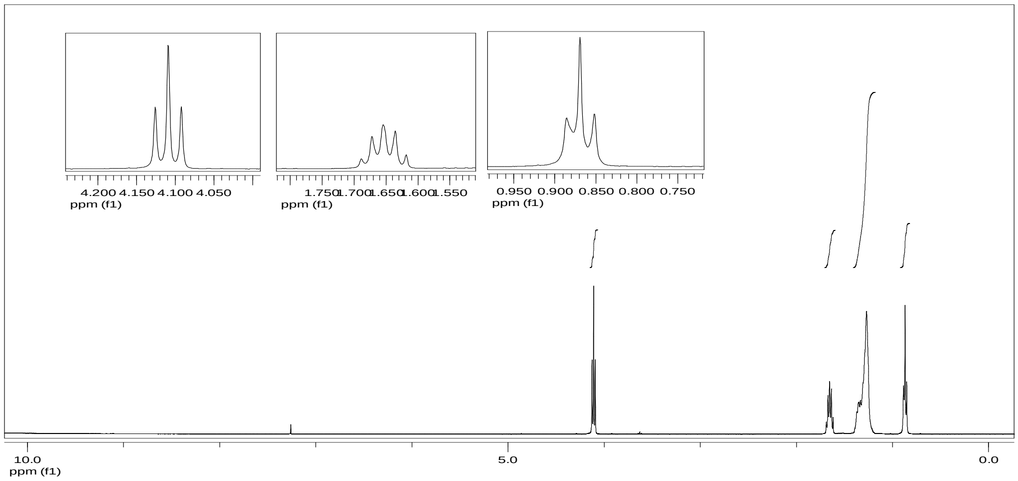


Figure A.59. ^{1}H NMR of dioctyl carbonate

^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 4.11 (t, 4H, J=6.7Hz), 1.65 (m, 4H), 1.33 (m, 20H), 0.87 (t, 6H, J=6.8Hz). Spectroscopic properties were in agreement with those reported in the literature.[18]

Table A.4. Synopsis of MS signals for major gaseous and liquid products, including DME, CO_2, propylene, diethyl ether, diproyl ether, dioctyl ether, isomeric octenes, and glycidol

Compound	**GC/MS (EI, 70 eV)**	**Match Qality (%) (Ref. Wiley)**
DME	m/z: 46 ($[M]^+$, 42%), 45 (90), 29 (100), 17 (17), 15 ($[CH_3]^+$, 64), 14 (15)	91 (265)
CO_2	m/z: 44 ($[M]^+$, 100%), 28 ($[M\text{-}O]^+$, 59), 16 (10)	9 (178)
Propylene	m/z: 42 ($[M]^+$, 45%), 41 ($[M\text{-}H]^+$, 100), 40 ($[M\text{-}(H)_2]^+$, 23), 39 ($[M\text{-}(H)_3]^+$, 55), 38 ($[M\text{-}(H)_4]^+$, 14), 37 ($[M\text{-}(H)_5]^+$, 9), 16 (11), 14 (10)	45 (156)
Diethyl ether	m/z: 74 ($[M]^+$, 65%), 59 ($[M\text{-}CH_3]^+$, 100), 45 ($[M\text{-}CH_2CH_3]^+$, 94), 43 (29), 41 (27)	90 (1853)
Dipropyl ether	m/z: 102 ([M]+, 8%), 73 ($[M\text{-}CH_2CH_3]^+$, 19), 59 ($[M\text{-}CH_2CH_2CH_3]^+$,11), 55 (6), 43 ($[CH_2CH_2CH_3]^+$, 100), 41 (26)	80 (7877)
Dioctyl ether	m/z: 242 ($[M]^+$, 0%), 131.10 (2), 113 (11), 112 (12), 111 (7), 84 (28), 83 (23), 71 (84), 70 (25), 69 (31), 68 (12), 57 (100), 56 (29), 55 (30), 43 (59), 42 (20), 41 (43)	91 (128177)
1-octene	m/z: 112 ($[M]^+$, 11%), 84 ($[M\text{-}(CH_2)_2]^+$, 23), 83 (39), 71 (12), 70 ($[M\text{-}(CH_2)_3]^+$, 88), 69 (50), 57 (16), 56 ($[M\text{-}(CH_2)_4]^+$, 86), 55 (100), 54 (11), 53 (10)	91 *(116372)*
2-octene	m/z: 112 ($[M]^+$, 40%), 84 ($[M\text{-}(CH_2)_2]^+$, 10), 83 (21), 70 ($[M\text{-}(CH_2)_3]^+$, 53), 69 (29), 57 (18), 56 ($[M\text{-}(CH_2)_4]^+$, 53), 55 (100), 54 (10)	91 *(3597)*
Glycidol	m/z: 57 (2%), 53 (1), 55 (2), 45 (9), 44 (85), 43 (100), 42 (16), 31 (65)	78 (1716)

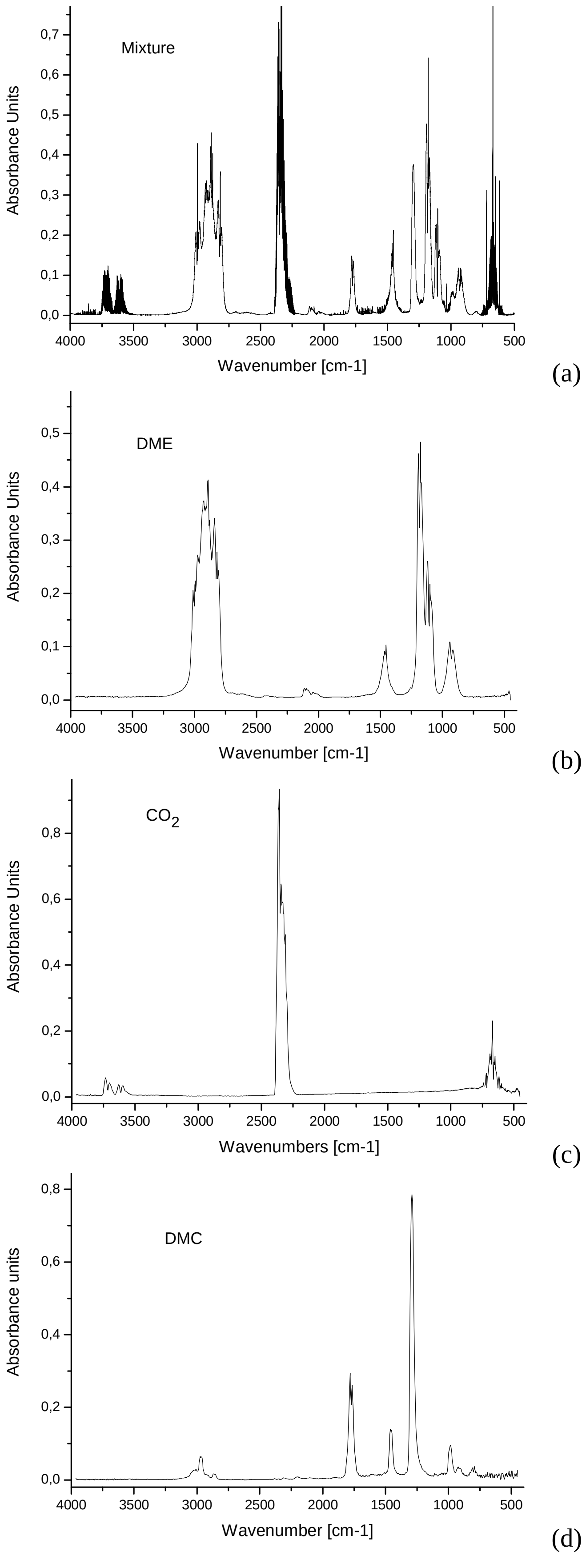


Figure A.60. Comparison of IR spectra for the confirmation of DME structure: reaction mixture (a) standard DME (b), CO_2 (c) and DMC (d)

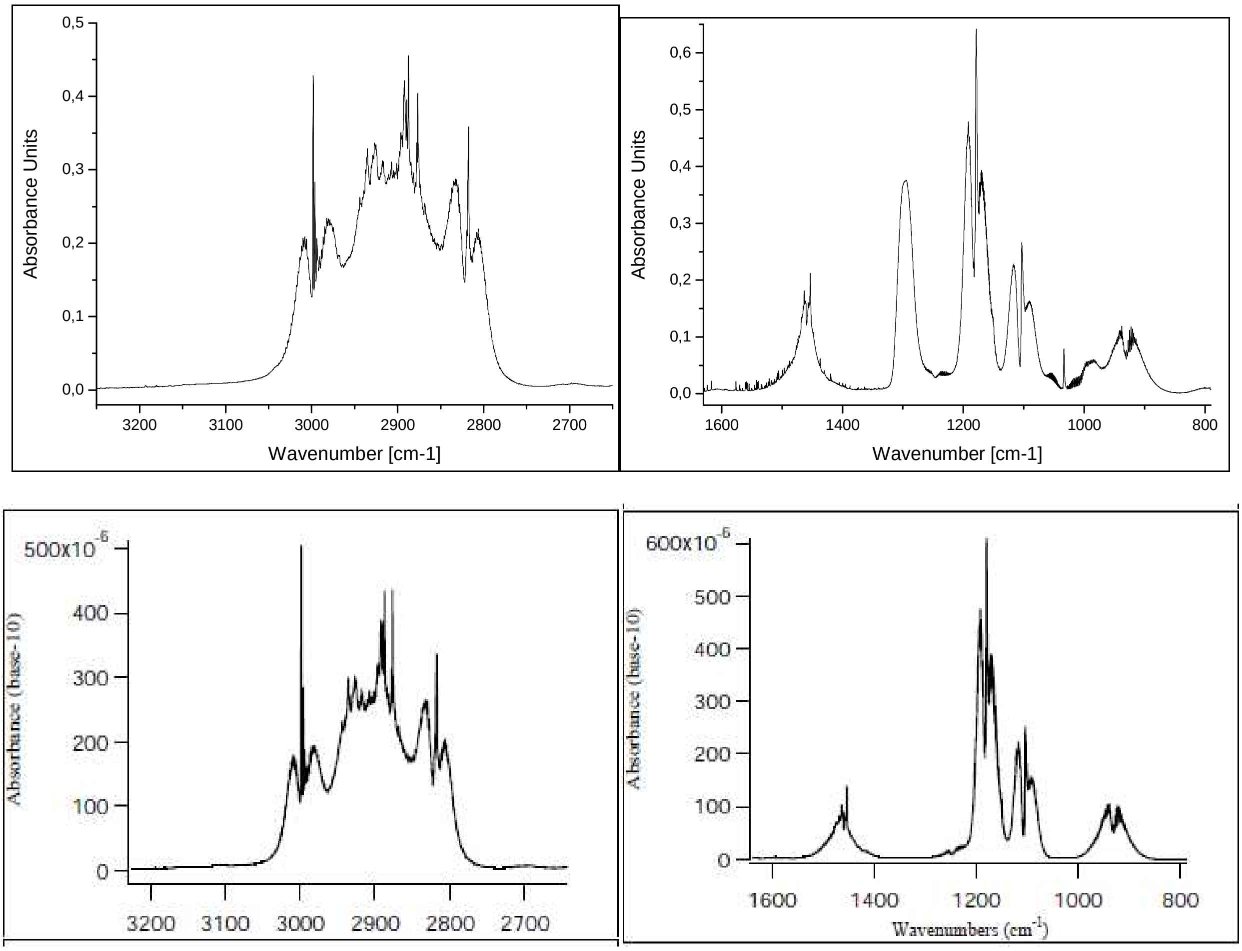
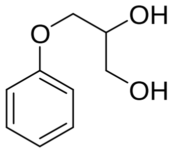
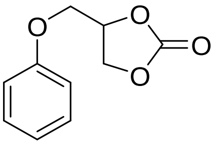
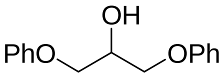


Figure A.61. Expansion of DME IR absorbance bands. Comparison between reaction mixture (top) and reference (bottom)

A.7 Q The Reaction of Glycerol Carbonate with Phenol in the Presence of NaY Zeolites [Ch. 4, par. 2]

Table A.5. Synopsis of MS spectra of non isolated products

Copound	**GC/MS (EI, 70 eV)**	**Match Qality (%) (Ref. Wiley)**
O-(2,3-dihydroxy)propyl phenol  **24**	m/z: 168 ([M]$^+$, 29%), 137 (M$^+$-CH$_2$OH, 3), 119 ([PhOCH=CH]$^+$, 16), 108 (11), 107 (M$^+$-CH(CH$_2$OH)OH, 10), 65 (28), 94 (100), 90 (11), 79 (10), 78 (15), 77 (41), 66 (20), 65 (22), 51 (22)	64 (52783)
4-(phenoxymethyl)-1,3-dioxolan-2-one  **25**	m/z: 194 ([M]$^+$, 61%), 107 ([PhO=CH$_2$]$^+$, 100), 95 (11), 94 (83), 79 (36), 78 (11), 77 (97), 66 (23), 65 (30), 57 (11), 51 (36)	
1,3-diphenoxypropan-2-ol  **26**	m/z: 244 ([M]$^+$, 28%), 151 (M$^+$-OPh, 8), 150 (M$^+$-OPh-H, 24), 133 (M$^+$-OPh-H-OH, 19), 108 (24), 107 ([PhO=CH$_2$]$^+$, 74), 105 (13), 95 (15), 94 ([PhOH]$^+$, 82) 91 (11), 79 (26), 78 (14), 77 (100), 66 (13), 65 (26), 51 (36)	

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Student: Massimo Fabris matriculation number: 955502
PhD: PhD in Chemical Sciences, PhD School in Sciences and Technologies
Cycle: XXIII°
Title of the thesis: Innovative Green Methodologies for C-C, C-N and C-O Bond Forming Reactions

Abstract: In this PhD thesis it is presented the use of some Green Chemistry Tools (supercritical carbon dioxide, ionic liquids and dialkylcarbonates) for the set up of new green methodologies for C-C, C-N and C-O bond forming reactions. The following reactions have been investigated: the self-metathesis of 1-octene catalysed by supported Re oxide systems, carried out using dense CO_2 as solvent; the Michael addition of nitroalkanes and β-diketones to α,β-unsaturated ketons catalyzed by task specific phosphonium based ionic liquids; the selective mono-hydroxyalkylation of anilines with glycerol carbonate catalysed by alkali metal exchanged faujasites; the selective bis-*N*-methylation of anilines carried by dimethylcarbonate prepared *in situ* via the transesterification of alkylene carbonate with methanol catalysed by alkali metal exchanged faujasites; the alkylation of primary aromatic amines with alkylene carbonates, catalysed by phosphonium based ionic liquids; the decarboxylation reaction of dialkyl carbonates catalyzed by different heterogeneous systems; the reaction of glycerol carbonate with phenol, in the presence of faujasites as catalysts.

Signature of the student

Studente: Massimo Fabris matricola: 955502
Dottorato: Dottorato di ricerca in Scienze Chimiche, Scuola di dottorato in Scienze e Tecnologie
Ciclo: XXIII°
Titolo della tesi: Innovative Green Methodologies for C-C, C-N and C-O Bond Forming Reactions

Estratto: In questo lavoro di tesi è riportato l'impiego di alcuni strumenti della Green Chemistry (come la CO_2, i liquidi ionici e i dialchilcarbonati) per la messa a punto di metodologie innovative a ridotto impatto ambientale per la formazione di legami C-C, C-N e C-O. Sono state investigate le seguenti reazioni: la metatesi dell'1-ottene catalizzata da sistemi a base di Re ossido, in presenza di CO_2 densa come solvente; l'addizione di Michael di nitroalcani e β-dichetoni a chetoni α,β-insaturi catalizzata da liquidi ionici; la selettiva mono-idrossialchilazione di aniline con la glicerina carbonato, catalizzata da faujasiti; la selettiva bis-*N*-alchilazione di aniline da parte del dimetilcarbonato prodotto *in situ* via transesterificazione di carbonati ciclici con metanolo, catalizzata da faujasiti; l'alchilazione di aniline con carbonati ciclici catalizzata da liquidi ionici; la reazione di decarbossilazione dei dialchilcarbonati in presenza di diversi catalizzatori eterogenei; la reazione tra fenolo e glicerina carbonato catalizzata da faujasiti.

Firma dello studente