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Settore Scientifico disciplinare: CHIM/06

Environmentally Sustainable Design of Innovative Chemical Processes and Synthetic Methods Focused on the Synthesis of Novel Molecular Libraries

Presentata da: **Nicola Armenise**

Coordinatore Dottorato **Relatore**

Prof. Aldo Roda **Prof. Emilio Tagliavini**

Esame finale anno 2016

L'Ordine del Giorno è il seguente:

…
2. Presentazioni delle tesi dei Dottorandi del 28° Ciclo e dei prorogati del 27° Ciclo
…

2. Presentazioni delle tesi dei dottorandi del 28° Ciclo e dei prorogati del 27° Ciclo

Il Coordinatore fa presente al Collegio dei docenti che i dottorandi, iscritti all'ultimo anno di corso, hanno presentato, nei termini previsti, le dissertazioni finali scritte.

Il Collegio è chiamato a redigere, per ciascuno di essi, la "presentazione" da allegare alla tesi finale.

Si invitano, a tal fine, i componenti del Collegio, che prevalentemente hanno guidato le attività di ricerca dei dottorandi, a voler illustrare i contenuti delle predette tesi ed i risultati conseguiti.

Dopo ampia discussione, sentiti anche i dottorandi in merito alle ricerche svolte, oggetto della dissertazione scritta, il Collegio dei Docenti decide unanime di approvare le "presentazioni" di seguito riportate le quali illustrano l'attività scientifico-formativa svolta durante il corso, mettendone in luce gli aspetti positivi o, eventualmente, negativi.

…

2) Dott. Nicola Armenise
Supervisore: Prof. Emilio Tagliavini
Cosupervisore: Prof. Paola Galletti
Curriculum: Scienze Chimiche
Indirizzo: Chimica Organica
Titolo della tesi: Environmentally sustainable design of innovative chemical processes and synthetic methods focused on the synthesis of novel molecular libraries

The activity carried out by Nicola Armenise during his PhD has been principally addressed to the development of eco-sustainable chemical processes and syntheses. The most relevant topics pursued by Dr. Armenise are: 1) design and synthesis of surfactants from renewable sources; 2) development of methods aimed to the synthesis of novel molecular libraries; 3) design and exploitation of innovative catalysts for the aerobic oxidation of alcohols. The first two topics have been carried out during the first and the second year of the PhD program in the Laboratory of Organic Chemistry of the supervisors in Ravenna. The first has been focused to the synthesis and the evaluation of the physicochemical properties of a family of surfactants, obtained from fatty amines of different chain length and itaconic acid, through conjugate addition followed by spontaneous cyclization The candidate has develop a variety of selective transformation of the resulting polar head-groups, obtaining a library of

surfactants that possess specific physicochemical properties; for example they can be exploited in micellar catalysis and in the field of soft matter. The second topic has been focused to the challenging multicomponent cascade synthesis of biaryl-based chalcones in pure water and in aqueous micellar system. The first step of the protocol is a simple Pd-catalyzed, ligand-free and aerobic Suzuki-Miyaura reaction. Subsequently, the biarilyc intermediates undergo in situ aldol condensation reaction, providing biaryl(hetero)chalcones in good to excellent yields. When the protocol is applied to highly lipophilic or less reactive reagents, micellar catalysis is required for achieving good performances. To this aim one of the novel surfactant described previously proved to be particularly effective, allowing also the repeated recycling of the catalytic system.

During the third year of the PhD project, the candidate has been awarded a Marco Polo fellowship and he spent a period of research (8 months) at the University of Groningen under the supervision of Prof. A. J. Minnaard. In this period, he has pursued the straightforward deuteration of the methyl substituents in neocuproine ligand, that has allowed the development of a new catalyst system that increases the turnover number in aerobic oxidation of alcohols, respect to the non-deuterated ligand. This improvement is due to the longer lifetime of new catalyst respect to the self-oxidation. The increase in turnover number has allowed the aerobic oxidation of glycosides with acceptable catalyst loadings.

During his PhD project the candidate has acquired excellent skills in research projecting and work self-organization. He has been proficient in collaboration with peer colleagues and supervisors. He also acquired very good abilities of manuscript writing and discussion of results. He has been the co-supervisor of one 2nd level degrees thesis in organic chemistry, proving a great ability in coordination of the activities of the student.

The main results achieved during his period of PhD are documented by 3 scientific full papers (2 of these as first author) published in important peer-reviewed international journals. In addition, other 3 manuscripts are in preparation. He has taken part actively in 3 international congresses and 2 national congresses with poster presentations.

My overall evaluation of the candidate is excellent.

The Board expresses a score of excellence on the activity carried out by the candidate during the whole cycle of doctorate and considers him worthy to attain the PhD in Chemistry.

…

Le deliberazioni assunte nella presente seduta sono state redatte, lette, approvate e sottoscritte seduta stante.

Il verbale della presente seduta del Collegio dei Docenti, dopo essere stato firmato e scansionato, sarà inserito, in formato .pdf, a cura del Coordinatore, nell'apposito applicativo reperibile al link: https://www.aric.unibo.it/DottoratoDiRicerca/verbalizzazioni/default.aspx ed accessibile mediante l'utilizzo delle credenziali istituzionali (l'art. 5, comma 10 del "Regolamento per l'istituzione e il funzionamento dei corsi di dottorato di ricerca" DR n. 524

Il Coordinatore
Prof. Aldo Roda

Il Segretario
Prof. Massimo Guardigli

del 26/06/2013 prevede che: *"Delle riunioni e deliberazioni assunte dal Collegio dei docenti deve essere redatto verbale da archiviare, debitamente sottoscritto, nell'apposito applicativo di Ateneo entro cinque giorni lavorativi dalla data della riunione del Collegio"*).

Esaurito l'Ordine del Giorno, il Collegio dei Docenti del Corso di Dottorato in Chimica termina la seduta alle ore 16.30.

Il Presidente **Prof. Aldo Roda**

Segretario **Prof. Massimo Guardigli**

university of groningen / faculty of mathematics and natural sciences / stratingh institute for chemistry

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To whom it may concern

Date
14 March 2016

Our reference
23AJM/2016

Subject
Thesis manuscript assessment Nicola Armenise, MSc

Dear sir,

Hereby I give a short overview and analysis of the PhD-thesis manuscript of Nicola Armenise, entitled “Environmentally Sustainable Design of Innovative Chemical Processes and Synthetic Methods Focused on the Synthesis of Novel Molecular Libraries”. Nicola Armenise joined my lab from February 1st 2015 to October 1st 2015.
Chapter 1 gives an overview of the field of green chemistry, discusses extensively the various aspects, also in terms of application in bulk chemicals, fine chemicals and pharmaceuticals, and explains the use of the terms E-factor, QE factor etc. In the final part of the chapter, an overview is given of the following chapters in the thesis.
Chapter 2 describes the synthesis of a set of surfactants based on itaconic acid and alkylamines. The resulting products have been extensively studied by physical organic chemistry methods in order to establish their critical micellar concentration, Krafft temperature etc. This is essential in order to establish their usefulness in applications. In addition, it has been established how the synthesis of these amphiphiles fits in the green chemistry field. In a quantitative and accurate manner.
Chapter 3 gives a thorough overview on micellar catalysis. All important aspects are covered and documented, the chapter functions in connection with chapter 4.
Chapter 4 gives an overview of the literature on transition metal-catalyzed cross coupling reactions in water or aqueous environment. In particular attention is given on the use of surfactants in these processes.
In chapter 5 an efficient synthetic protocol for multicomponent cascade Suzuki-Aldol reactions is presented aiming at the synthesis of biarylchalcone derivatives in water. In some cases, micellar catalysis provided better results, obtained employing a new surfactant described in chapter 2.
In chapter 6 an overview is given of the most important advances made recently in the field of the (aerobic) oxidations of alcohols, in particular catalyzed by palladium in the form of homogeneous, heterogeneous and nanoparticle catalysts. The current status of palladium-catalyzed alcohol oxidation is critically evaluated. Attention is paid to concurrent autoxidation of the ligand in homogeneous palladium-catalyzed oxidation reaction. In my opinion the most important papers have been cited and used for this chapter and the content functions as a versatile guide for researchers that want to inform themselves on palladium-catalyzed alcohol oxidation.
In chapter 7 it is described how (partial) deuteration of the ligand used in the palladium-catalyzed oxidation of carbohydrates leads to an enhanced catalyst performance. First the ligand neocuproine is deuterated by proton exchange with D_2O/NaOD at high temperature. This

deuterated ligand was characterized and used for the preparation of the (deuterated) catalyst. In a careful comparative study, those two catalysts were used in the oxidation of 2-heptanol and Me-glucoside. This is particularly challenging as for this oxidation reaction it is difficult to carry out the reactions in an identical way, and reaction analysis according to Blackmond is not possible as the amount of oxidant (oxygen) cannot reliably varied. Nevertheless, the results were obtained, and reproduced. It has been shown that the deuterated catalyst is roughly twice as stable as the non-deuterated catalyst. This was a genuine team effort as expertise in different disciplines was required (NMR spectroscopy, GC-analysis, deuteration protocols, etc.) and all relevant ligands and complexes had to be thoroughly characterized and shown to be pure by elemental analysis. The results have been described in a manuscript that was accepted for publication in Chem Comm, recently.
Overall, in my opinion Nicola Armenise is a dedicated researcher who quickly learned in catalytic oxidation, not the easiest field of research, and was able to apply his experience in physical organic chemistry gained earlier in his PhD research. This is underpinned by the fact that his efforts, together with his colleagues in our team, were rewarded by a publication in an international, peer reviewed journal.

Would more information be required, do not hesitate to contact me

Sincerely yours

Adriaan Minnaard

Professor Teresa F Fernandes
Head of Environment Department
School of Life Sciences
Heriot-Watt University
Riccarton
Edinburgh EH14 4AS
United Kingdom

Edinburgh, 7th April 2016

To whom it may concern

Subject: Thesis manuscript assessment Nicola Armenise, MSc

I hereby give an assessment of the PhD-thesis manuscript of Nicola Armenise. The research in the thesis entitled "Environmentally Sustainable Design of Innovative Chemical Processes and Synthetic Methods Focused on the Synthesis of Novel Molecular Libraries" focuses on the development of surfactants starting from renewable sources, development of multicomponent cascade reactions in water and improving ligand stability. A brief overview and my opinion of the thesis are given below.

Chapter 1 reviews the advances in the field of green and sustainable chemistry and is in my opinion of interest to a broad readership.

The research in Chapter 2 aims at developing novel surfactants based on renewable sources. Synthetic strategies that allow efficient coupling of itaconic acid to alkyl-amines are described. The critical micellar concentration and the ability to lower the surface tension have been established for the obtained surfactants. Moreover, the greenness of the synthetic methods has been studied in detail.

Chapters 3 and 4 give a detailed literature overview of organic synthesis in water. The chemistries detailed in these chapters form the starting point for the development of a multicomponent cascade Suzuki-Aldol reaction that efficiently yields biarylchalcone derivatives in water. The results of these studies are accurately described in Chapter 5.

The advances in the metal catalysed oxidation of hydroxyl groups using oxygen as the oxidant are critically evaluated in Chapter 6.

In Chapter 7 it is described how (partial) deuteration of the ligand used in the palladium-catalysed oxidation of carbohydrates leads to an enhanced catalyst performance.

The research described in Chapter 2 is part of a collaborative project between my Laboratory at Heriot Watt University and the Laboratory of the supervisor of the candidate. In this framework, I can vouch for the good performance of the candidate in the preparation of the surfactants that have later assessed in my Laboratory.

Overall, the quality of the thesis is of high level.

Please let me know if you require any further information.

Yours faithfully

Teresa F Fernandes

Teresa F Fernandes
Professor
Heriot-Watt University

Email: t.fernandes@hw.ac.uk

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Chapter 5 - Multicomponent Cascade Synthesis of Biaryl-Based Chalcones in Pure Water and in an Aqueous Micellar Environment

Chapter 6 - Recent Advances in the Palladium-Catalyzed Aerobic Oxidation of Alcohols

Aim and arrangement of the thesis

Following the establishment of the *12 Principles of Green Chemistry*, there has been a gradual and constructive growth in our understanding of what green chemistry means. Green chemistry is a relatively young science in its own respect. Interest in this subject, however, has grown rapidly and, although no concerted agreement has been reached as yet about the exact content and limits of this interdisciplinary field, there appears to be increasing interest in countless environmental topics, which are based on chemistry embodied in this subject. To the pleasant surprise of all, this increased understanding of the principles that are the backbone of green chemistry has spurred many outstanding efforts to implement chemical processes and innovative technologies, that are incrementally moving society toward more sustainable practices and products that embody and foster environmental management and environmental protection.
The proposal and risk of changing the way chemistry is done and applied, the development of new chemistries and chemical synthetic pathways, and the establishment of novel and benign chemical processes that are significantly more efficient using non-petrochemical and renewable feedstocks have been challenging notions for a world that has been surrounded by the products of petroleum for more than a century. Green chemistry has hence brought a relatively prompt and positive shift in the paradigm as it concerns the overall use and management of natural resources and raw materials for the development of society with a promise to cause far less pronounced harm to the environment at large. By adopting green chemistry principles and methodologies, researchers are devising new processes to help protect and ultimately save the environment from further damage.
This thesis is intended to be a work that encompasses some of the various relevant aspects linking the Green Chemistry practice to environmental sustainability. The thesis covers sustainable development through chapters that contribute to the design of novel environmentally benign chemical processes and green approaches to minimize and/or remediate environmental pollution.

In this context, my PhD project has faced three main topics:

1. Design, synthesis and characterization of new surfactant molecules employing renewable feedstocks, itaconic acid and fatty amines, as starting materials; *Chapter 2* describes this topic.
2. Development of a sustainable procedure aimed to the multicomponent cascade synthesis of biaryl-based chalcones in pure water or under micellar catalysis conditions; in the latter case, one of the surfactants previously synthesized has been widely employed. *Chapter 5* describes this topic. *Chapter 3* and *Chapter 4* describe the scientific context and the most important innovations that have paved the way to the results that I achieved during the 2nd year of Ph.D. course; the former is an overview on the use of water as solvent for organic reactions; the latter

is an overview on cross-coupling reactions and the exploitation in this context of micellar catalysis.

3. Design, synthesis and exploitation of deuterated phenanthroline-type ligands for the aerobic palladium-catalyzed oxidation of methyl glucoside, allowing a high performance improvement in this challenging reaction; *Chapter 7* collects the obtained results, while *Chapter 6* summarizes the most important advances obtained in the last years in the palladium-catalyzed aerobic oxidations of alcohols.

Thesis outline

Chapter 1 gives an overview of the field of Green Chemistry, discusses extensively the various aspects, also in terms of application in bulk chemicals, fine chemicals and pharmaceuticals, and explains the use of the terms E-factor, QE factor etc.

Chapter 2 describes the synthesis of a new family of surfactants having C12 and C18 alkyl chains obtained from itaconic acid and fatty amines, molecules industrially obtained from renewable resources.

Chapter 3 is an overview on the use of water as solvent, that features many benefits such as improving reactivities and selectivities, simplifying the workup procedures, enabling the recycling of the catalyst and allowing mild reaction conditions and protecting-group free synthesis in addition to being benign itself.

Chapter 4 is an overview on cross-coupling reactions in the form of micellar catalysis, wherein nanoparticles composed of surfactants enable the same cross-couplings, albeit in water.

Chapter 5 describes the challenging multicomponent cascade synthesis of biaryl-based chalcones. It has been carried out in pure water and in aqueous micellar system, overcoming existing drawbacks.

Chapter 6 is an overview on the most important advances made in the last years in the field of aerobic oxidations of alcohols, in particular catalyzed by Palladium in the form of homogeneous, heterogeneous and, more recently, nanoparticles catalysts.

Chapter 7 describes that deuteration of a phenanthroline-type ligand leads to a significant increase in turnover number in the aerobic palladium-catalyzed oxidation of methyl glucoside and allows this reaction to be carried out using oxygen as the sole terminal oxidant.

CHAPTER 1

Introduction to Green Chemistry

Serious environmental concerns are changing the way chemical research evolves, in particular new advances in the chemical synthesis and catalysis areas are strongly linked to "Green Chemistry". The latter is not only a recent sub-discipline of chemistry; all new research studies in synthesis and catalysis have to comply with this new standard. It is mandatory to pass on these concepts to new generations of chemists and to change the perception the public has about their work.

1.1 Introduction

It is generally acknowledged that there is an increasing need for more environmentally acceptable processes in the chemical industry. This tendency towards what has become known as “Green Chemistry” or “Sustainable Technology” necessitates a paradigm shift from traditional concepts of process efficiency, that focus largely on chemical yield, to one that assigns economic value to eliminating waste at source and to avoiding the use of toxic and hazardous substances.[1]

The term “Green Chemistry” was coined by Paul Anastas of the US Environmental Protection Agency (EPA).[1c] In 1993 the EPA officially adopted the name “US Green Chemistry Program” which has served as a focal point for activities within the United States, such as the *Presidential Green Chemistry Challenge Awards* and the annual *Green Chemistry and Engineering Conference*. This does not mean that research on green chemistry did not exist before the early 1990s, but the idea of pursuing the common goal of greenness and of sharing a common framework of principles aimed to safe and environmentally benign chemistry was not present in the scientific community. Since the early 1990s both Italy and the United Kingdom have launched major initiatives in green chemistry and, more recently, the *Green and Sustainable Chemistry Network* was initiated in Japan. The inaugural edition of the journal Green Chemistry, sponsored by the Royal Society of Chemistry, appeared in 1999. Hence, it is possible to conclude that Green Chemistry is here to stay.

A reasonable working definition of Green Chemistry can be formulated as follows: “*Green chemistry efficiently utilizes (preferably renewable) raw materials, eliminates waste and avoids the use of toxic and/or hazardous reagents and solvents in the manufacture and application of chemical products”*.[2]

As Paul Anastas has pointed out, the guiding principle is the “*design of environmentally benign products and processes (benign by design)”*.[1d] This concept is embodied in the *12 Principles of Green Chemistry* which can be paraphrased as:[1a,1d]

1. Waste prevention instead of remediation
2. Atom efficiency
3. Less hazardous/toxic chemicals
4. Safer products by design
5. Innocuous solvents and auxiliaries
6. Energy efficient by design
7. Preferably renewable raw materials
8. Shorter syntheses (avoid derivatization)
9. Catalytic processes rather than stoichiometric reagents
10. Design products for degradation
11. Analytical methodologies for pollution prevention
12. Inherently safer processes

Green Chemistry addresses the environmental impact of both chemical products and the processes by which they are produced. Green chemistry eliminates waste at source, i.e. it is primary pollution prevention rather than waste remediation (end-of-pipe solutions).

An alternative term, that is currently favoured by the chemical industry, is "Sustainable Technologies". Sustainable development has been defined as: "*Meeting the needs of the present generation without compromising the ability of future generations to meet their own needs"*.[3]

1.2 Green metrics

Two useful measures of the potential environmental acceptability of chemical processes are the "E factor",[4] defined as the mass ratio of waste to desired product and the "atom efficiency", calculated by dividing the molecular weight of the desired product by the sum of the molecular weights of all substances produced in the stoichiometric equation. The sheer magnitude of the waste problem in chemicals manufacture is readily apparent from a consideration of typical E factors in various segments of the chemical industry (Table 1.1).

Table 1.1. The "E factor".

Industry segment	Product tonnage[a]	kg waste[b]/kg product
Oil refining	10^6-10^8	< 0.1
Bulk chemicals	10^4-10^6	< 1-5
Fine chemicals	10^2-10^4	5 - >50
Pharmaceuticals	10-10^3	25 - >100

[a] Typically represents annual production volume of a product at one site (lower end of range) or world-wide (upper end of range). [b] Defined as everything produced except the desired product (including all inorganic salts, solvent losses, etc.).

The E factor is the actual amount of waste produced in the process, defined as everything that is not the desired product. It takes the chemical yield into account and includes reagents, solvents losses, all process aids and, in principle, even fuel as energy source (although this is often difficult to quantify). There is one exception: water is generally not included in the E factor. For example, when considering an aqueous waste stream only the inorganic salts and organic compounds contained in the water are counted; the water is excluded. Otherwise, this would lead to exceptionally high E factors which are not useful for comparing processes.

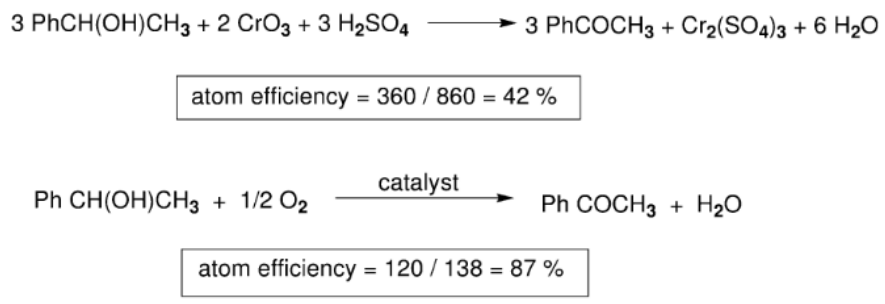
A higher E factor means more waste and, consequently, greater negative environmental impact. The ideal E factor is zero. Put quite simply, it is kilograms (of raw materials) in, minus kilograms of desired product, divided by kilograms of product out. It can be easily calculated from a knowledge of the number of tons of raw materials purchased and the number of tons of product sold, for a particular

product or a production site or even a whole company. It is perhaps surprising, therefore, that many companies are not aware of the E factors of their processes. However, this situation is rapidly changing and the E factor, or an equivalent thereof, is being widely adopted in the fine chemicals and pharmaceutical industries (where the need is greater). It is also possible to note that this method of calculation will automatically exclude water used in the process but not water formed.

Other metrics have also been proposed for measuring the environmental acceptability of processes. Hudlicky and co-workers,[5] for example, proposed the "effective mass yield" (EMY), which is defined as the percentage of product of all the materials used in its preparation. As proposed, it does not include so-called environmentally benign compounds, such as sodium chloride, acetic acid, etc. However, this is questionable as the environmental impact of such substances is very volume-dependent. Constable and co-workers of GlaxoSmithKline proposed the use of "mass intensity" (MI),[6] defined as the total mass used in a process divided by the mass of product, i.e. MI = E factor + 1, and the ideal MI is 1 compared with zero for the E factor. These authors also suggest the use of so-called "mass productivity" which is the reciprocal of the MI and, hence, is effectively the same as EMY. Nevertheless, none of these alternative metrics appears to offer any particular advantage over the E factor for giving a mental picture of how wasteful a process is.

As is clear from Table 1.1, enormous amounts of waste, comprising primarily inorganic salts, such as sodium chloride, sodium sulphate and ammonium sulphate, are formed in the reaction or in subsequent neutralization steps. The E factor increases dramatically on going downstream from bulk to fine chemicals and pharmaceuticals, partly because production of the latter involves multi-step syntheses but also owing to the use of stoichiometric reagents rather than catalysts.

The "atom utilization",[4b-4g] "atom efficiency" or "atom economy" concept, first introduced by Trost,[7,8] is an extremely useful tool for rapid evaluation of the amounts of waste that will be generated by alternative processes. It is calculated by dividing the molecular weight of the product by the sum total of the molecular weights of all substances formed in the stoichiometric equation for the reaction involved. For example, the atom efficiencies of stoichiometric (CrO_3) vs. catalytic (O_2) oxidation of a secondary alcohol to the corresponding ketone are compared in Scheme 1.1.



Scheme 1.1. Atom efficiency of stoichiometric vs. catalytic alcohol oxidation.

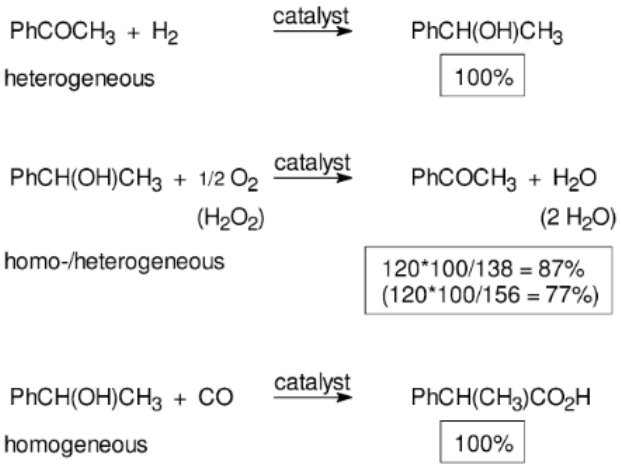
In contrast to the E factor, it is a theoretical number, i.e. it assumes a yield of 100% and exactly stoichiometric amounts and disregards substances which do not appear in the stoichiometric equation.

All of the metrics discussed above take only the mass of waste generated into account. However, what is important is the environmental impact of this waste, not just its amount, i.e. the nature of the waste must be considered. One kg of sodium chloride is obviously not equivalent to one kg of a chromium salt. Hence, the term “environmental quotient” (EQ), obtained by multiplying the E factor with an arbitrarily assigned unfriendliness quotient (Q), was introduced.[4d] For example, one could arbitrarily assign a Q value of 1 to NaCl and, say, 100-1000 to a heavy metal salt, such as chromium, depending on its toxicity, ease of recycling, etc. The magnitude of Q is obviously debatable and difficult to quantify but, importantly, “quantitative assessment” of the environmental impact of chemical processes is, in principle, possible. It is also worth noting that Q for a particular substance can be both volume-dependent and influenced by the location of the production facilities. For example, the generation of 100-1000 tons per annum of sodium chloride is unlikely to present a waste problem, and could be given a Q of zero. The generation of 10 000 tons per annum, on the other hand, may already present a disposal problem and would warrant assignation of a Q value greater than zero. But, when very large quantities of sodium chloride are generated the Q value could decrease again as recycling by electrolysis becomes a viable proposition, e.g. in propylene oxide manufacture via the chlorohydrin route. Thus, generally speaking the Q value of a particular waste will be determined by its ease of disposal or recycling. Hydrogen bromide, for example, could warrant a lower Q value than hydrogen chloride as recycling, via oxidation to bromine, is easier. In some cases, the waste product may even have economic value. For example, ammonium sulphate, produced as waste in the manufacture of caprolactam, can be sold as fertilizer. It is worth noting, however, that the market could change in the future, thus creating a waste problem for the manufacturer.

1.3 The role of catalysis

As noted above, the waste generated in the manufacture of organic compounds consists primarily of inorganic salts. This is a direct consequence of the use of stoichiometric inorganic reagents in organic synthesis. In particular, fine chemicals and pharmaceuticals manufacture is rampant with antiquated “stoichiometric” technologies. Examples, which readily come to mind, are stoichiometric reductions with metals (Na, Mg, Zn, Fe) and metal hydride reagents ($LiAlH_4$, $NaBH_4$), oxidations with permanganate, manganese dioxide and chromium(VI) reagents and a wide variety of reactions, e.g. sulfonations, nitrations, halogenations, diazotizations and Friedel-Crafts acylations, employing stoichiometric amounts of mineral acids (H_2SO_4, H_3PO_4) and Lewis acids ($AlCl_3$, $ZnCl_2$, BF_3). The solution is evident: substitution of classical stoichiometric methodologies with cleaner catalytic

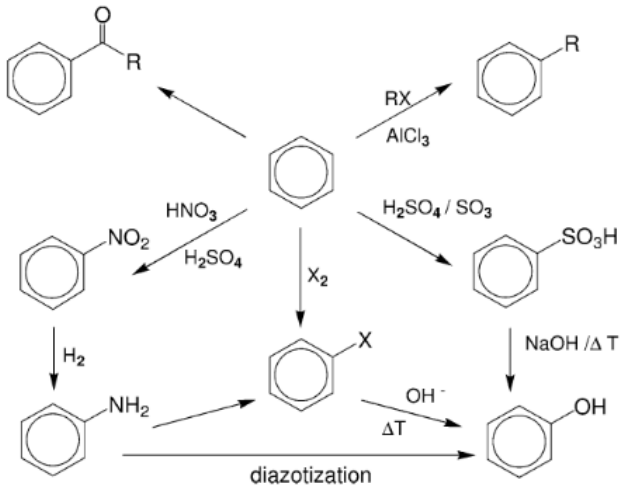
alternatives. Indeed, a major challenge in (fine) chemicals manufacture is to develop processes based on H_2, O_2, H_2O_2, CO, CO_2 and NH_3 as the direct source of H, O, C and N. Catalytic hydrogenation, oxidation and carbonylation (Scheme 1.2) are good examples of highly atom efficient, low-salt processes.



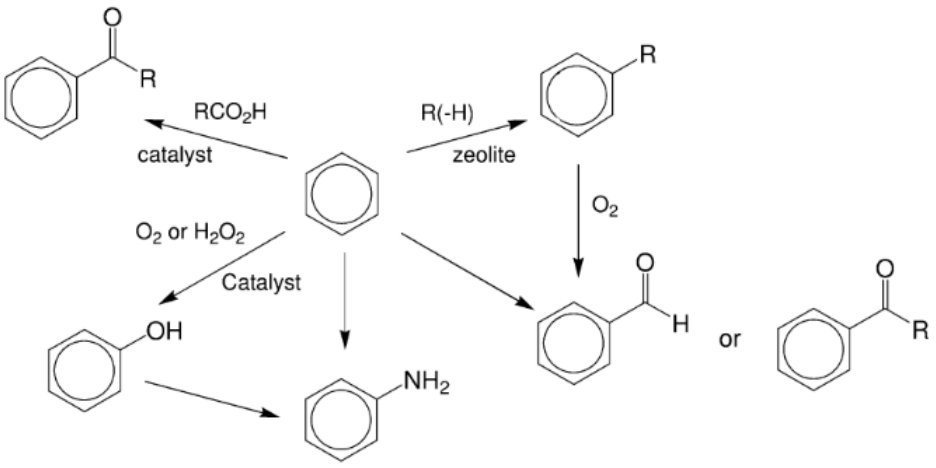
Scheme 1.2. Atom efficient catalytic processes.

The generation of copious amounts of inorganic salts can similarly be largely circumvented by replacing stoichiometric mineral acids (such as H_2SO_4), Lewis acids and stoichiometric bases (such as NaOH and KOH) with recyclable solid acids and bases, preferably in catalytic amounts.

For example, the technologies used for the production of many substituted aromatic compounds (Scheme 1.3) have not changed in more than a century and are, therefore, ripe for substitution by catalytic, low-salt alternatives (Scheme 1.4).



Scheme 1.3. Classical aromatic chemistry.



Scheme 1.4. Non-classical aromatic chemistry.

Catalysis has many advantages in the context of green chemistry, e.g. mild reaction conditions and often fewer steps than conventional chemical procedures because protection and deprotection of functional groups are often not required. Consequently, classical chemical procedures are increasingly being replaced by cleaner catalytic alternatives in the fine chemicals industry.

1.4 The development of organic synthesis

If the solution to the waste problem in the fine chemicals industry is so obvious (replacement of classical stoichiometric reagents with cleaner, catalytic alternatives) why was it not applied in the past? There are several reasons for this. First, because of the smaller quantities compared with bulk chemicals, the need for waste reduction in fine chemicals was not widely appreciated.

A second, underlying, reason is the more or less separate evolution of organic chemistry and catalysis; catalysis developed as a sub-discipline of physical chemistry. With the advent of the petrochemicals industry in the 1930s, catalysis was widely applied in oil refining and bulk chemicals manufacture. However, the scientists responsible for these developments, which largely involved heterogeneous catalysts in vapour phase reactions, were generally not organic chemists.

Organic synthesis followed a different line of evolution. Fine chemicals and pharmaceuticals have remained primarily the domain of synthetic organic chemists who, generally speaking, have clung to the use of classical “stoichiometric” methodologies and have been reluctant to apply catalytic alternatives.

A third reason, which partly explains the reluctance, is the pressure of time. Fine chemicals generally have a much shorter lifecycle than bulk chemicals and, especially in pharmaceuticals, “time to market” is crucial. An advantage of many time-honoured classical technologies is that they are well-tried and broadly applicable and, hence, can be implemented rather quickly. In contrast, the development of a cleaner, catalytic alternative could be more time consuming. Consequently,

environmentally (and economically) inferior technologies are often used to meet market deadlines. Moreover, in pharmaceuticals, subsequent process changes are difficult to realise owing to problems associated with FDA approval.

There is no doubt that, in the twentieth century, organic synthesis has achieved a high level of sophistication with almost no molecule beyond its capabilities, with regard to chemo-, regio- and stereoselectivity, for example. However, little attention was focused on atom selectivity and catalysis was only sporadically applied. Hence, now the paradigm is changing: under the increasing pressure of environmental legislation, organic synthesis and catalysis have come together to achieve waste minimisation.

1.5 The question of solvents: alternative reaction media

Green chemistry strongly influences chemical research, and there is an insistence on the use of "greener" reaction conditions.[9] It has been estimated by GSK workers[10] that volatile organic solvents amount to over 85% of mass utilization in a typical chemical manufacturing process, and because recovery efficiency is far from satisfactory they are major contributors to environmental pollution.[11] It is also worth noting that in the redesign of the sertraline manufacturing process,[12] for which Pfizer received a Presidential Green Chemistry Challenge Award in 2002, among other improvements a three-step sequence was streamlined by employing ethanol as the sole solvent. This eliminated the need to use, distil and recover four solvents (methylene chloride, tetrahydrofuran, toluene and hexane) employed in the original process.

The use of chlorinated hydrocarbon solvents, traditionally the solvent of choice for a wide variety of organic reactions, has been severely curtailed. Indeed, so many of the solvents that are favoured by organic chemists have been blacklisted that the whole question of solvent use requires rethinking and has become a primary focus, especially in the fine chemicals industry.[13]

In order to remove volatile organic solvents from the chemical process, an important aspect pertains to their replacement by non-flammable, non-volatile, non-toxic and inexpensive "green solvents".[14] In this regard, development of solvent-free alternative processes is the best solution, especially when either one of the substrates or the products is a liquid and can be used as the solvent of the reaction.[15] However, if solvents are crucial to a process, we should select solvents that will have no or limited impact on health and the environment.

Indeed, the use of unconventional green solvents in organic reactions has improved not only the aspect of the reactions from the viewpoint of green and sustainable properties, but also the synthetic efficiency by stabilizing the catalyst, changing the reaction selectivity or facilitating product isolation.[16]

Different non-classical reaction media have, in recent years, attracted increasing attention from the viewpoint of avoiding environmentally unattractive solvents and/or facilitating catalyst recovery and

recycling. Two examples, which readily come to mind, are supercritical carbon dioxide and room temperature ionic liquids. Catalytic hydrogenation in supercritical CO_2, for example, has been commercialised by Thomas Swan and co-workers.[17] Ionic liquids are similarly being touted as green reaction media for organic synthesis in general and catalytic reactions in particular.[18] They exhibit many properties which make them potentially attractive reaction media, e.g. they have essentially no vapour pressure and cannot, therefore, cause emissions to the atmosphere.

The best solvent is no solvent and if a solvent (diluent) is needed then water is preferred.[19] Water is non-toxic, non-flammable, abundantly available and inexpensive. Moreover, owing to its highly polar character one can expect novel reactivities and selectivities for organometallic catalysis in water. Furthermore, this provides an opportunity to overcome a serious shortcoming of homogeneous catalysts, namely the cumbersome recovery and recycling of the catalyst. Thus, performing the reaction in an aqueous biphasic system, whereby the catalyst resides in the water phase and the product is dissolved in the organic phase,[20] allows recovery and recycling of the catalyst by simple phase separation (for more detailed explanations of the effects of water on organic reactions, see the chapters 3, 4 and 5 of this thesis). An example of novel catalysis in an aqueous medium is the use of lanthanide triflates as water-tolerant Lewis acid catalysts for a variety of organic transformations in water.[21]

1.6 Multicomponent reactions

The conventional multistep preparation of a complex molecule generally involves a large number of synthetic operations, including extraction and purification processes in each individual step. This leads to not only synthetic inefficiency but also generates large amounts of waste. Multicomponent reactions (MCRs), defined as one-pot reactions in which at least three different substrates join through covalent bonds, have steadily gained importance in synthetic organic chemistry. MCRs allow the creation of several bonds in a single operation and offer remarkable advantages like convergence, operational simplicity, facile automation, reduction in the number of workup, extraction and purification processes, and hence minimize waste generation, rendering the transformations green.[22] One-pot MCRs often shorten reaction periods, giving higher overall chemical yields than multiple-step syntheses, and therefore can reduce the use of energy and manpower. MCRs are useful for the expedient creation of chemical libraries of drug-like compounds with high levels of molecular complexity and diversity, thereby facilitating identification/optimization in drug discovery programmes.[23] Therefore, the design of new MCRs with green procedure has attracted great attention, especially in the areas of drug discovery, organic synthesis, and material science.[24] Moreover, improving already known MCRs also is of substantial interest in current organic synthesis. Recently there has been increasing concern with regard to the tight legislation on the maintenance of “greenness” in synthetic pathways and processes.[25]

Particularly, unconventional solvents also showed a great ability for assisting development of MCRs. Many new one-pot MCRs have been successfully developed by means of using an innovative solvent instead of conventional organic solvents. Moreover, taking advantage of utilizing unconventional solvents as reaction media, various known MCRs have also been improved in terms of reaction yield, substrate generality, isolation of products and catalyst recycling. In view of the emerging importance of this area, a plethora of reviews have summarized the recent achievements in performing MCRs in unconventional solvents. Because water and ionic liquids are the main contenders in the area of green solvents, the majority of these reviews have covered MCRs in these two solvents. Polyethylene glycol polymers (PEGs) have also been considered as a new class of green solvents. Recent attempts at using PEGs as reaction media for MCRs also has been described. Benefiting from recent innovation in utilizing bio-based chemicals as green solvents,[26] some MCRs have also been developed in bio-based solvents.

Because performing MCRs in water combines the synthetic efficiency of multicomponent protocols with the environmental benefits of using water as the reaction medium, which would lead to processes close to the ideal synthetic reaction, this topic thus constitutes a very important challenge for green chemistry. Indeed, many unique MCRs that cannot be attained in conventional organic solvents have been developed.[27]

1.7 Renewable raw materials

The UN World Summit on Sustainable Development, held in Johannesburg in 2002, called for the promotion of a sustainable use of biomass.[28] It was recently shown that biomass can be produced in a volume sufficient for industrial utilization without compromising the food supply for the increasing global population.[29] Chemists have much to contribute to meet this challenge.[30,31]

Oils and fats of vegetable and animal origin are historically and currently the most important renewable feedstock of the chemical industry. Classical and well-established oleo-chemical transformations occur preferentially at the ester functionality of the native triglycerides,[32] such as hydrolysis to free fatty acids and glycerol[33] and trans-esterification to fatty acid methyl esters. Fatty acids are transformed by reactions at the carboxy group to soaps, esters, amides, or amines. Hydrogenation of both fatty acids and their methyl esters gives fatty alcohols, which are used for the production of surfactants.[34] Competitive petrochemical processes to produce fatty alcohols, such as the Ziegler-Alfol process and hydroformylation of alkenes, exist, but the share of fatty alcohols from renewable resources is steadily increasing, from about 50% in 2000 to just under 65% in 2010.[35] The basic oleochemicals (Figure 1.1) are fatty acids (~ 52%), the respective methyl esters (~ 11%), amines (~ 9%), and alcohols (~ 25%).[36] These are used for the production of important product groups, that is, surfactants,[37,38] lubricants,[39,40] and coatings.[41]

The production volume of fatty acid methyl esters strongly increased during the last ten years because of their large-scale utilization as biodiesel,[42,43,44] giving as side product about 10 w% of glycerol which has to be utilized. This fact stimulated research on glycerol as a platform chemical for the production of bulk chemicals, that is, 1,2- and 1,3-propanediol, acrylic acid, or epichlorohydrin.[45,46,47] The latter is an especially interesting development, since during the second half of the last century glycerol was petro-chemically produced based on propene via epichlorohydrin.

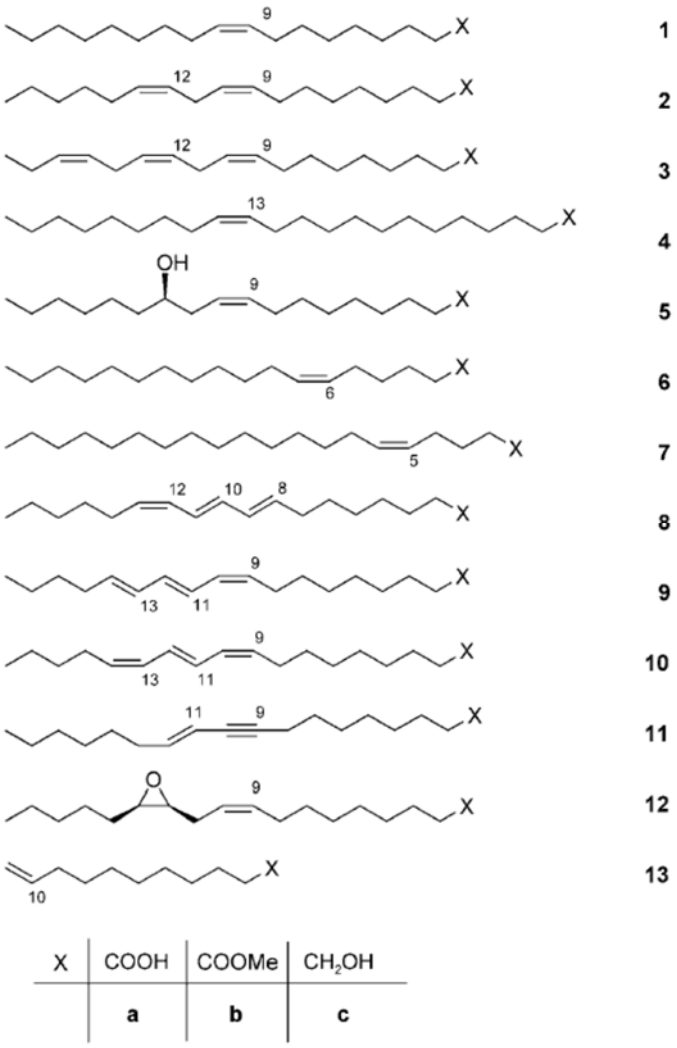


Figure 1.1. Fatty compounds as starting materials for synthesis: oleic acid (**1a**), linoleic acid (**2a**), linolenic acid (**3a**), erucic acid (**4a**), ricinoleic acid (**5a**), petroselinic acid (**6a**), 5-eicosenoic acid (**7a**), calendic acid (**8a**), α-eleostearic acid (**9a**), punicic acid (**10a**), santalbic acid (**11a**), vernolic acid (**12**), 10-undecenoic acid (**13a**), and the respective methyl esters (**1b–13b**) and alcohols (**1c–13c**).

Most of the native oils contain unsaturated fatty acids, such as oleic acid (**1a**), which is a *cis*-configured alkene and thus allows, in principle, the application of the well-known reactions of petrochemical alkenes. Remarkably, only very few reactions across the double bond of unsaturated fatty compounds are currently applied in the chemical industry (i.e., hydrogenation, ozone cleavage,

and epoxidation). Moreover, there are no industrial processes utilizing selective C-H functionalization of the alkyl chain of saturated and unsaturated long-chain fatty acids. Interesting exceptions are the production of C2-branched Guerbet alcohols from fatty alcohols and the microbial ω-oxidation of methyl oleate **1b** to cis-octadec-9-endioic acid dimethyl ester.[48] The latter is an example of the amazing opportunities offered by enzymatic and microbial reactions. Fatty acids of plant seed oils show a remarkable variety.[49,50,51] In contrast, the fatty acids of bulk oils currently used in oleochemistry are rather uniform. Saturated fatty acids with an even number of carbon atoms (C8–C18) and unsaturated C18 fatty acids, such as **1a** and linoleic acid (**2a**) as well as relatively small amounts of linolenic acid (**3a**), erucic acid (**4a**), and ricinoleic acid (**5a**) are industrially utilized. The most important oleochemical reactions performed with **5a** are the thermal cleavage to 10-undecenoic acid **13a**[52] and basic cleavage to sebacic acid (decanedioc acid).[53] Interestingly, the enantiomeric purity of **5a**, which makes it an interesting substrate for organic synthesis, has not yet been exploited appropriately.

Thus, it will be important to introduce and to cultivate more and new oil plants that provide fatty acids with new and interesting properties for chemical utilization. The cultivation of the respective plants for the production of these oils would increase the agricultural biodiversity, an important aspect of a sustainable utilization of renewable feedstocks. Moreover, classic breeding as well as genetic engineering will be necessary to improve the oil yield and the fatty acid composition for chemical utilization.[54,55,56,57] Here again, the processes used for the conversion of renewable feedstocks should produce minimal waste, i.e. they should preferably be catalytic. White biotechnology is currently the focus of considerable attention and is perceived as the key to developing a sustainable chemical industry.[58] Metabolic pathway engineering is used to optimise the production of the required product based on the amount of substrate (usually biomass-derived) consumed.[59] A so-called bio-based economy is envisaged in which commodity chemicals (including biofuels), specialty chemicals such as vitamins, flavours and fragrances and industrial monomers will be produced in bio-refineries.

1.8 Outlook on Green Chemistry: the road to sustainability

There is no doubt that Green Chemistry is here to stay. Chemical companies and, indeed, companies in general are placing increasing emphasis on sustainability and environmental goals in their corporate mission statements and annual reports.

The European Technology Platform on Sustainable Chemistry (*SusChem*) has recently published an Implementation Action Plan entitled “Putting Sustainable Chemistry into Action”.[60] The report defines three key technology areas: (i) industrial biotechnology, (ii) materials technology, and (iii) reaction and process design. The goal is “improving the eco-efficiency of products and processes to optimize the use of resources and minimize waste and environmental impact”.

Similarly, the US chemical industry produced a strategic plan (*Technology Vision 2020*) which defined a long-term technology roadmap for the future.[61] Important goals were to "improve efficiency in the use of raw materials, the reuse of recycled materials, and the generation and use of energy and to continue to play a leadership role in balancing environmental and economic considerations". Initially, many people confused Green Chemistry with what is generally known as environmental chemistry which is concerned with the effects of chemicals on the environment and remediation of waste and contaminated land and water. In contrast, Green Chemistry is concerned with redesigning chemical products and processes to avoid the generation and use of hazardous substances and the formation of waste, thus obviating the need for a lot of the environmental chemistry.

The twelve principles of Green Chemistry, as expounded by Anastas and Warner in 1998,[1] have played an important role in promoting its application. They inspired others to propose additional principles[62] and, more recently, Anastas and Zimmerman[63] proposed the twelve principles of green engineering which embody the same underlying features, conserve energy and resources and avoid waste and hazardous materials, as those of green chemistry, but from an engineering viewpoint.

Graedel has reduced the concept of green chemistry and sustainable development to four key areas: (i) sustainable use of chemical feedstocks, (ii) sustainable use of water, (iii) sustainable use of energy and (iv) environmental resilience.[64] These reflect the central tenets of sustainability, that is, "using natural resources at rates that do not unacceptably draw down supplies over the long term and generating and dissipating residues at rates no higher than can be assimilated readily by the natural environment".

1.8.1 Concluding Remarks

With sustainability as the driving force, the production and applications of chemicals are undergoing a paradigm change in the 21st century and Green Chemistry and catalysis are playing a pivotal role in this change. This revolutionary development manifests itself in the changing feedstocks for fuels and chemicals, from fossil resources to renewable feedstocks, and in the use of green catalytic processes for their conversion. In addition, there is a marked trend towards alternative, greener products that are less toxic and readily biodegradable. Ultimately this revolution will enable the production of materials of benefit for society while, at the same time, preserving the earth's precious resources and the quality of our environment for future generations.

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CORRIGENDA

List of additional references

Paragraph 1.1, pp. 2-3: “It is generally acknowledged that there is an increasing need for more environmentally acceptable processes in the chemical industry… Sustainable development has been defined as: “*Meeting the needs of the present generation without compromising the ability of future generations to meet their own needs”.*”[i]

Paragraph 1.2, pp. 3-5: “Two useful measures of the potential environmental acceptability of chemical processes are… It is worth noting, however, that the market could change in the future, thus creating a waste problem for the manufacturer.”[ii]

Paragraph 1.3, pp. 5-7: “As noted above, the waste generated in the manufacture of organic compounds consists primarily of inorganic salts… Consequently, classical chemical procedures are increasingly being replaced by cleaner catalytic alternatives in the fine chemicals industry.”[iii]

Paragraph 1.4, pp. 7-8: “If the solution to the waste problem in the fine chemicals industry is so obvious… Hence, now the paradigm is changing: under the increasing pressure of environmental legislation, organic synthesis and catalysis have come together to achieve waste minimisation.”[iv]

Paragraph 1.5, pp. 8-9: “Green chemistry strongly influences chemical research, and there is an insistence on the use of “greener” reaction conditions… An example of novel catalysis in an aqueous medium is the use of lanthanide triflates as water-tolerant Lewis acid catalysts for a variety of organic transformations in water.”[v]

Paragraph 1.6, pp. 9-10: “The conventional multistep preparation of a complex molecule generally involves a large number of synthetic operations… Indeed, many unique MCRs that cannot be attained in conventional organic solvents have been developed.”[vi]

Paragraph 1.7, pp. 10-12: “The UN World Summit on Sustainable Development, held in Johannesburg in 2002, called for the promotion of a sustainable use of biomass… Here again, the processes used for the conversion of renewable feedstocks should produce minimal waste, i.e. they should preferably be catalytic.”[vii]

Paragraph 1.8, pp. 12-13: “There is no doubt that Green Chemistry is here to stay… and generating and dissipating residues at rates no higher than can be assimilated readily by the natural environment.”[viii]

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[i] *Green Chemistry and Catalysis* (Eds: R. A. Sheldon, I. W. C. E. Arends, U. Hanefeld), Wiley-VCH Verlag GmbH & Co. KGaA, **2007**, pp. 1-2.

[ii] *Green Chemistry and Catalysis* (Eds: R. A. Sheldon, I. W. C. E. Arends, U. Hanefeld), Wiley-VCH Verlag GmbH & Co. KGaA, **2007**, pp. 2-5.

[iii] *Green Chemistry and Catalysis* (Eds: R. A. Sheldon, I. W. C. E. Arends, U. Hanefeld), Wiley-VCH Verlag GmbH & Co. KGaA, **2007**, pp. 5-7.

[iv] *Green Chemistry and Catalysis* (Eds: R. A. Sheldon, I. W. C. E. Arends, U. Hanefeld), Wiley-VCH Verlag GmbH & Co. KGaA, **2007**, pp. 8-9.

[v] *Green Chemistry and Catalysis* (Eds: R. A. Sheldon, I. W. C. E. Arends, U. Hanefeld), Wiley-VCH Verlag GmbH & Co. KGaA, **2007**, pp. 27-28.

[vi] Y. Gu, *Green Chem.* **2012**, 14, 2091-2128.

[vii] U. Biermann, U. Bornscheuer, M. A. R. Meier, J. O. Metzger, H. J. Schäfer, *Angew. Chem. Int. Ed.* **2011**, *50*, 3854-3871.

[viii] *Green Chemistry and Catalysis* (Eds: R. A. Sheldon, I. W. C. E. Arends, U. Hanefeld), Wiley-VCH Verlag GmbH & Co. KGaA, **2007**, pp. 409-410.

CHAPTER 2

Surfactants from Itaconic Acid: Physicochemical Properties and Assessment of the Synthetic Strategies

Surfactants are a large class of compounds used in a broad spectrum of applications. In this chapter, it is presented the synthesis of a new family of surfactants having C12 and C18 alkyl chains obtained from itaconic acid and fatty amines; these molecules are industrially obtained from renewable resources. Main physicochemical properties of synthesized surfactants have been measured and their rheological behaviours have been evaluated at the air−water interface using the pendant drop technique. Some of the synthesized surfactants are stimuli responsive compounds, switchable to a polar form in the presence of CO_2. The synthetic strategies have been optimized aiming at the sustainability of the process, employing a complete set of green metrics and the software EATOS.[i]

[i] This chapter is an adaptation of the original paper: Danilo Malferrari, Nicola Armenise, Stefano Decesari, Paola Galletti and Emilio Tagliavini, *ACS Sustainable Chem. Eng.* **2015**, *3 (7)*, 1579-1588.

2.1 Introduction

Since their introduction in the early 20th century, the use of synthetic surfactants has continually increased and, as a result, surfactants are currently among the highest volume synthetic chemicals produced globally. Nowadays, the overall market of surfactants is growing at a rate of 3−4% each year and synthetic surfactants cover the majority of the market share.[1] Surfactants, which are here not meant to include soaps, have historically been produced using either petrochemical or oleochemical feedstocks, favouring petrochemicals which account for roughly two thirds of the organic carbon embodied in the final products.[2]

In the last decades, however, the industrial and research interest in surfactants obtainable from renewable resources has considerably increased. This interest in renewable feedstocks is driven by awareness and concern for the environmental impact of various household products. Moreover, petroleum is a finite resource, the availability of fossil feedstocks in the next future will decrease and its use has adverse effects.[3] Several studies have shown that the use of renewable feedstocks can significantly reduce the CO_2 emissions associated with the production and use of surfactants. For example, Patel *et al.* estimate that oleochemicals may lead to greater CO_2 savings when used for surfactant production rather than in the production of biodiesel.[4] Patel *et al.* further estimated that, if renewable surfactants were to entirely replace petrochemical surfactants in the EU, total CO_2 emissions associated with surfactant production and use could be reduced by as much as 37%.

While the full replacement of petrochemical surfactants may be desirable from a CO_2 abatement standpoint, considerations such as cost and performance will ultimately determine the success of a surfactant technology, and the expansion in the use of renewable chemicals must be implemented with care in order to avoid adverse environmental impacts associated with land and water use. To this end, next generation renewable surfactant technologies must be derived from robust and sustainable feedstocks, must be produced efficiently, and must have physicochemical properties that are comparable or superior to petrochemical surfactants, all while maintaining a low production cost. Surfactant performance is evaluated by a multitude of criteria, including stability, foaming power, detergency, solubility, emulsifying properties, toxicity, skin irritability, and environmental performance.[5] Although surfactants continue to be used predominantly as detergents and cleaners, they find use in a variety of industrial, agricultural, and specialty uses as well, with each application requiring unique performance characteristics. The diversity of function that is required from surfactants in turn requires diverse chemical building blocks and synthetic strategies to accommodate a range of physicochemical properties.

Synthetic surfactants are generally produced through the coupling of a hydrophilic ‘‘head’’ group and a lipophilic ‘‘tail,’’ generating an amphiphilic molecule that can be further modified or used directly. The properties of the surfactants are largely determined by the charge of the head group, which can be positive, negative, zwitterionic, or neutral, and by the ratio of the hydrophilic portion of the

molecule to the hydrophobic portion, often expressed as the Hydrophilic–Lipophilic Balance, or HLB.[6] Surfactant design requires considerate selection of a hydrophilic and hydrophobic pair such that they can be readily synthesized with minimum purification and have optimum properties for a given application.

Amphiphiles synthesized from renewable resources represent a commercial alternative to building blocks derived from petrochemical feedstocks. Recent examples of hydrophilic building blocks for "renewable surfactants" are constituted by carbohydrates, amino acids and polycarboxylic acids. Hydrophobic building blocks mainly comprise fatty acids, terpenes, sterols and sterols derivatives.

Some non-ionic surfactants classes obtained from renewable raw materials are also well established, like alkylpolyglucosides (APGs) that are used as self-emulsifiers, as agrochemicals, in personal care products and in pharmaceutical formulations.[7] Despite their popularity, alkylpolyglucosides have encountered a variety of synthetic challenges that result in the products being obtained as relatively expensive technical mixtures.[7] Recently, C-glycosides surfactants have been synthesized from carbohydrates through a nonulose intermediate.[8]

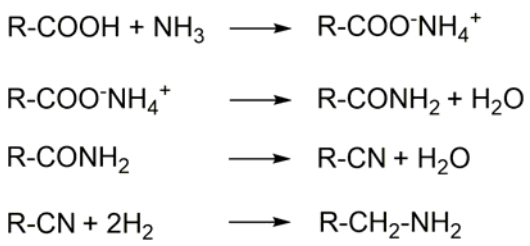
Compounds derived from waste carbohydrate biomass, such as 5-hydroxymethylfurfural,[9] furfural,[10] cellulose[11] and sorbitol,[12] have been proposed as starting materials for surfactants. Nevertheless, some of the compounds listed above come from edible feedstocks and it would be convenient to replace them with non-edible counterparts, such as lignocellulosic biomass.

Recently, the synthesis and biological properties of surfactants incorporating amino acids in the structure have been reported.[13,14] These molecules belong to the group of stimuli responsive amphiphiles: molecules that are responsive to a variety of triggers, including pH, light, magnetic field, CO_2 concentration and redox state.[15]

Another interesting group of surfactants presented in the recent years contains some examples derived from polycarboxylic acids like fumaric acid, itaconic acid (IA) and aconitic acid.[16] In this group, itaconic acid has not been fully exploited as building block in surfactants synthesis.[17]

2.2 Goal

Here is depicted a family of surfactants, obtained from fatty amines and itaconic acid, that present C12 and C18 alkyl chains. Specifically, fatty amines are industrially produced from fatty acids in three steps through the nitrile process (Scheme 2.1).[18] Itaconic acid is a naturally occurring compound, non-toxic and readily biodegradable;[19] itaconic acid is industrially obtained in high yields mainly through biotechnological processes based on fungi of the genus Aspergillus, grown on substrates like sucrose, glucose, starch hydrolysates and purified molasses.[20] It is mainly used by the polymer industry where it is employed as a co-monomer for the synthesis of polyesters,[21,22] but it finds applications also in other industrial compounds like additives, detergents, pharmaceuticals and in agriculture. Currently, the total market size involving itaconic acid is around 10.000−15.000 t/year.[23]



Scheme 2.1. Synthesis of fatty amines through the "Nitrile Process".

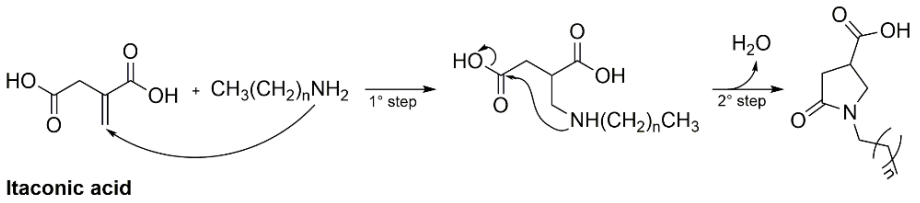
Herein we report the two step synthesis starting from itaconic acid that lead to a new group of surfactants, carrying different functionalities in the polar head-groups; these structural features permit us to design molecules that possess specific physicochemical properties and have the potential to be exploited in micellar organic catalysis and in the soft matter field. In surfactants design, the greenness of raw materials together with the choice of synthetic strategies are factors of paramount importance; thus, following this ultimate goal, a Green Metric assessment (exploiting the software EATOS[24] or a set of green metrics parameters) has been performed to evaluate the synthetic strategies.[25] The synthetic routes employed have been compared and evaluated looking at the sustainability of the process, solvents and by-products minimization.

2.3 Results and discussion

2.3.1 Optimization of synthetic pathways

Efficient synthetic routes used for the synthesis of compounds **1**−**8** are represented in Scheme 2.3. For the complete description of synthetic routes and reaction conditions, refer to Scheme 2.4 and to the Experimental Section.

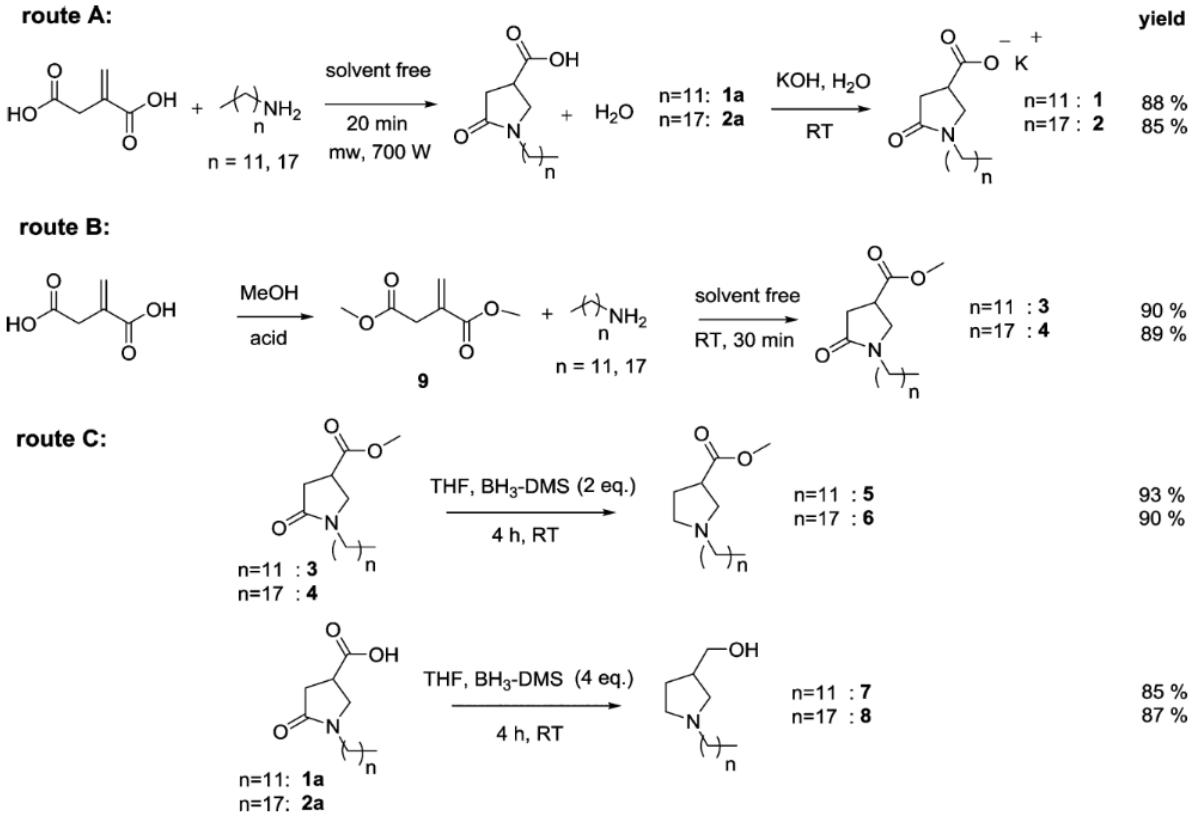
The compounds prepared are characterized by a 3-substituted pyrrolidine ring and can be divided into four main groups that belong to different classes of surfactants: anionic (**1**, **2**), non-ionic (**3**, **4**) and ionizable (**5**−**8**) in water solution. Compounds **1** and **2** bear a 2-pyrrolidone ring and a 3-carboxylic acid or 3-carboxylate functionality depending on pH, compounds **3** and **4** have a 2-pyrrolidone ring with a methyl ester group, compounds **5** and **6** have a pyrrolidine ring and a methyl ester group whereas compounds **7** and **8** have a pyrrolidine ring and a hydroxymethyl moiety in position three of the ring. The pyrrolidone scaffold was obtained by conjugate Michael addition of a primary alkyl amine to itaconic acid followed by intramolecular spontaneous lactamization between the carboxylic acid in *β*-position and the secondary amine (Scheme 2.2). In the literature, the conjugate Michael addition reactions of primary amines to the double bond of itaconic acid have been already explored in solvents like toluene and water.[26]



Scheme 2.2. Synthetic mechanism of the pyrrolidone scaffold.

Compounds **1a** (1-dodecyl-5-oxopyrrolidine-3-carboxylic acid) and **3** (1-dodecyl-5-oxopyrrolidine-3-carboxylic acid methyl ester) have been previously synthesized and tested as transdermal drug delivery agents[27,28] but their interfacial properties have not been reported yet, so a deeper knowledge of their physicochemical properties is desired.

The synthesis of **1a** and **2a** proceeded smoothly under microwave irradiation, but compounds **3** and **4** have been obtained from dimethylitaconate (**9**) and the corresponding primary amine in good yields simply by mixing the starting materials and crushing them at RT in a mortar. Compound **9** has been synthesized from itaconic acid and methanol both in the presence of Lewis and Brønsted acid catalysts. Compounds **5** and **6** have been obtained by reducing the lactam functionality of **3** and **4** with 2 eq. of borane dimethylsulfide (BH_3-DMS), whereas compounds **7** and **8** have been obtained by reducing both the lactam functionality and the carboxylic acid group of **1a** and **2a** with 4 eq. of BH_3-DMS**,** optimizing reaction time and product selectivity.



Scheme 2.3. General synthetic routes (A, B and C) to compounds **1**−**8**.

2.3.2 Physicochemical characterizations

Because of their amphipathic structure in solutions, surfactants tend to form micelles, namely thermodynamically stable molecular aggregates in water solutions. The micellar formation takes place above a certain surfactant concentration, the critical micellar concentration (CMC), below which surfactant molecules are present as monomers, above the CMC the free monomers coexist with micellar structures.

To determine the CMC of **1**−**8**, three different techniques have been used: two of them exploit the spectroscopic properties of a solubilized dye, the third one examines the behaviour of a bulk solution property (conductivity). We employed two different fluorescent probes: Pyrene (Py) and Nile Red (NR); the steady-state fluorescence emission spectra are presented in Figure 2.1.

Pyrene is a hydrophobic molecule and it has been recently proposed to be localized in the hydrophobic interior of the micelles or aggregates, under the hydrophilic heads of the molecules.[29,30] Nile Red is used to localize and quantitate lipids, particularly neutral lipid droplets within cells. Nile Red undergoes fluorescence enhancement and large absorption and emission blue shifts in nonpolar environments; on the contrary, in polar media Nile Red exhibits a red shift in the emission maximum, owing to its capability to establish H-bonds with protic solvents, together with fluorescence quenching (Figure 2.1).[31] The CMC values have been also measured by means of conductivity.[32]

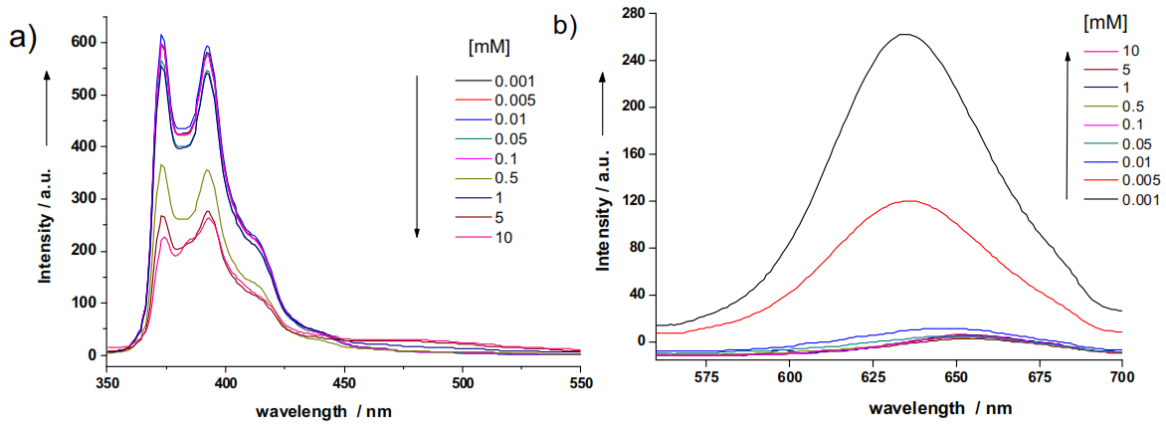


Figure 2.1. Steady-state fluorescence emission spectra of Py (Panel a) and NR (Panel b) at different concentrations (mM) of surfactant **1** in water solution.

Pyrene I_1/I_3 ratio measurements, maximum emission intensities for Nile Red and conductivity data are presented in Figure 2.2, Figure 2.3 and Figure 2.4, respectively; CMC results are summarized in Table 2.1. CMC values are in the concentration range between 0.1 and 5 mM, in line with values of common surfactants, to give few examples: sodium dodecyl sulphate (SDS, 7.4 mM, see Table 2.1), cetyltrimethylammonium bromide (CTAB, 0.92 mM) and Triton X-100 (0.2−0.9 mM).[33,34]

Compounds **7** and **8**, characterized by an alcohol functionality and a tertiary amine, present the low CMC values in the C12 series as well as in the C18; whereas CMC values of **5** and **6** are the highest of the C12 and C18 series, respectively. CMC values of compounds **3** and **4** (Table 2.1), which do

not present ionizable groups in the molecular structure, are not measurable by means of conductivity, thus the CMC is measured only by means of I_1/I_3 ratio and Nile Red.

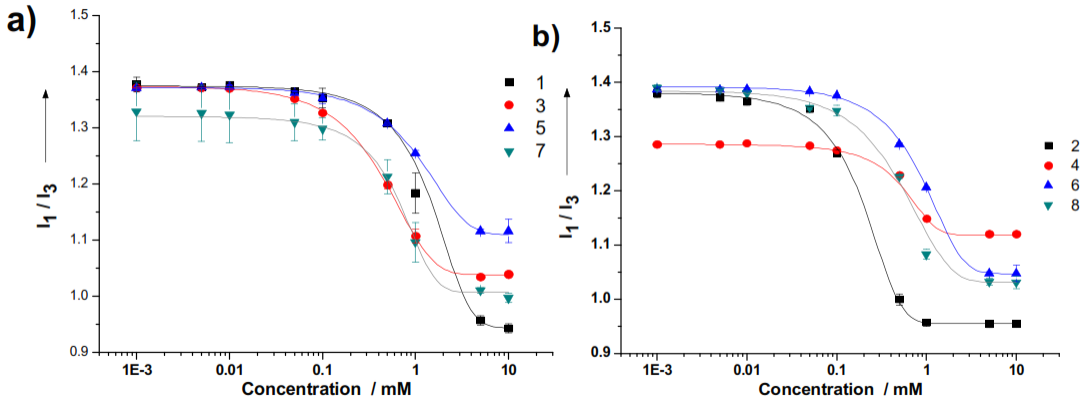


Figure 2.2. Vibronic ratio measurements (I_1/I_3) of Py for compounds **1**, **3**, **5** and **7** (Panel a) and **2**, **4**, **6** and **8** (Panel b).

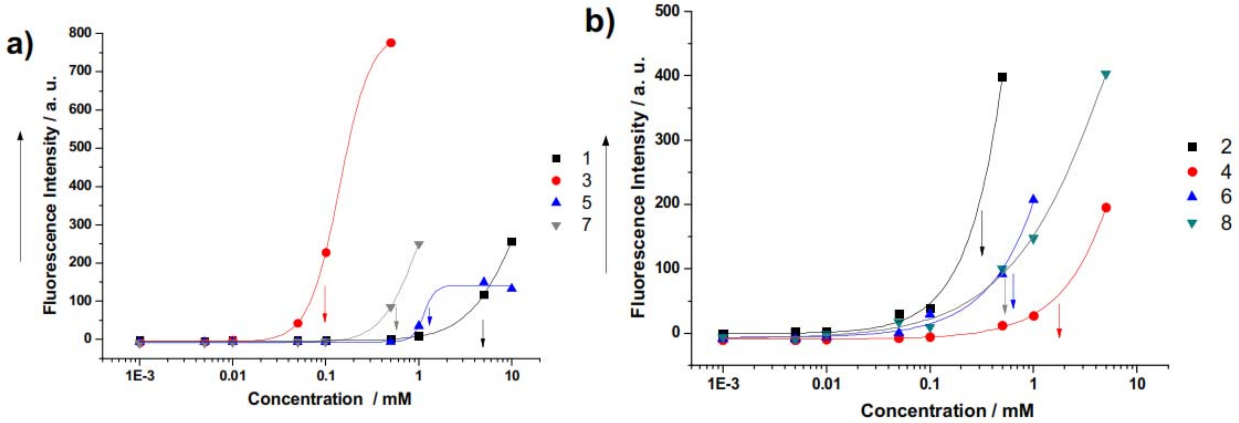


Figure 2.3. CMC of compounds **1**, **3**, **5** and **7** (Panel a) and **2**, **4**, **6** and **8** (Panel b) using the probe NR. CMC values are indicated by vertical arrows.

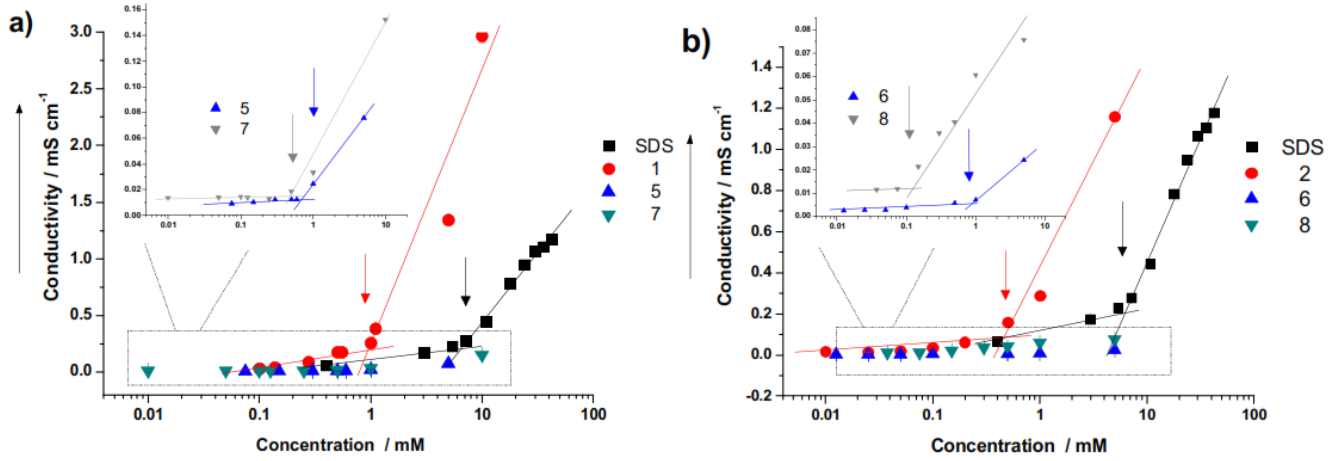


Figure 2.4. Conductivity vs. concentration of compounds **1**, **5**, **7** (Panel a) and **2**, **6**, **8** (Panel b). CMC values are indicated by vertical arrows.

Table 2.1. CMC values, mean aggregation numbers, logK_{ow}, log$D$ and pK_a values for compounds **1**−**8**.

Compound	CMC[a] [mM]	CMC[b] [mM]	CMC[c] [mM]	N^{agg}[d]	logK_{ow}[e]	log$D$[e]	pK_a[g]
SDS	7.4	8.1	7.2	63	/	/	/
1	1	5	1	54	4.8	2.0	4.5
2	0.3	0.3	0.3	64	7.0	5.2	4.5
3	0.2	0.1	n.d.	57	4.8 (4.7)[f]	5.3	n.d.
4	1.0	1.8	n.d.	68	7.5	8.4	n.d.
5	1.7	1.3	0.8	43	5.9 (5.8)[f]	4.4	9.2
6	0.8	0.7	0.4	52	8.6	7.5	9.3
7	0.7	0.6	0.8	57	5.5 (5.3)[f]	2.8	10.1
8	0.2	0.5	0.1	60	8.4	6.0	10.1

[a] From Py I_1/I_3 ratio. [b] From NR fluorescence. [c] From conductivity. [d] Value at 25 °C (RT).[35] [e] Predicted using ALOGPS software version 2.1; log$D$ values at pH 7.4.[36,37,38] [f] Measured with OECD method No. 117, 2004.[39] [g] Predicted using the EPISUITE software.[40]

In Table 2.1 are also recorded the mean aggregation numbers (N^{agg}) for compounds **1**−**8**, measured using cetylpyridinium chloride (CPC) as a quencher molecule and Pyrene as a fluorescent probe; SDS, a common anionic surfactant, was used to check the consistency of values.

In Table 2.1, the estimated logarithmic values of the octanol−water partition coefficient (logK_{ow}), the log$D$ values and pK_a values of **1**−**8** are reported. In the C12 and C18 series, it is visible that the reduction of the amide functionality in the pyrrolidone ring (in compounds **5**, **7** and **6**, **8**) is expected to determine a higher degree of lipophilicity, with respect to compounds characterized by the carboxylic (**1** and **2**) and methyl ester functionality (**3** and **4**).

The lower hydrophilicity and solubility in water of compound **4** with respect to **2** is reflected by the logK_{ow} (7.5) and by the log$D$ values. For non-ionizable compounds and for compounds characterized by logK_{ow} values lower than 7, corresponding values have also been measured using an OECD method (Figure 2.5) obtaining values comparable with those previously estimated.

Given the pK_a values of these compounds, the pH of the aqueous solutions of compound **1** is acidic, compound **5** and **7** are basic and compound **3** is neutral (Figure 2.6); titration curves are reported in Figure 2.7.

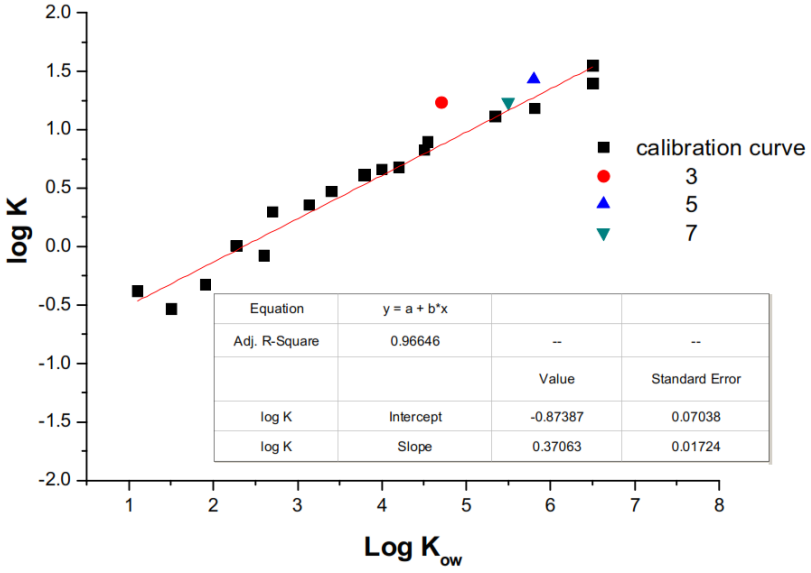


Figure 2.5. LogK_{ow} values for compounds **3**, **5** and **7** and the relative calibration curve.

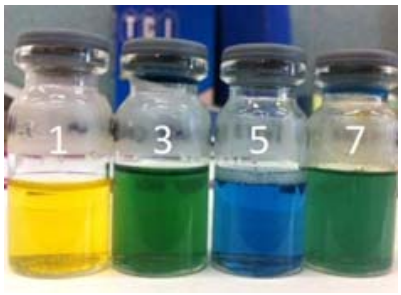


Figure 2.6. 5 mM water solutions of **1**, **3**, **5** and **7** in the presence of bromothymol blue.

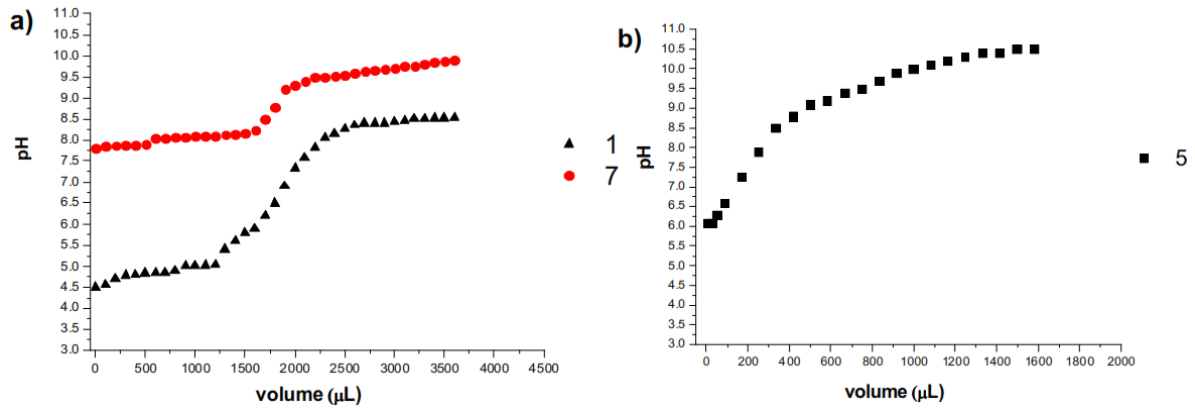


Figure 2.7. Titration curves of water solutions of compounds **1** (Panel a), **5** (Panel b) and **7** (Panel a).

The study of surface tension and other surface properties is another important parameter, motivated by the large number of industrial processes involving interfaces, such as coating, detergency, printing and foams. At the air−water or oil−water interface, above the CMC, the equilibrium surface tension (σ_{eq}) of a surfactant solution is not achieved instantaneously: surfactant molecules must first diffuse from the bulk solution to the interface and then adsorb.

For compounds **1**−**8**, this phenomenon is visible in the surface tension profiles plotted in Figure 2.8.

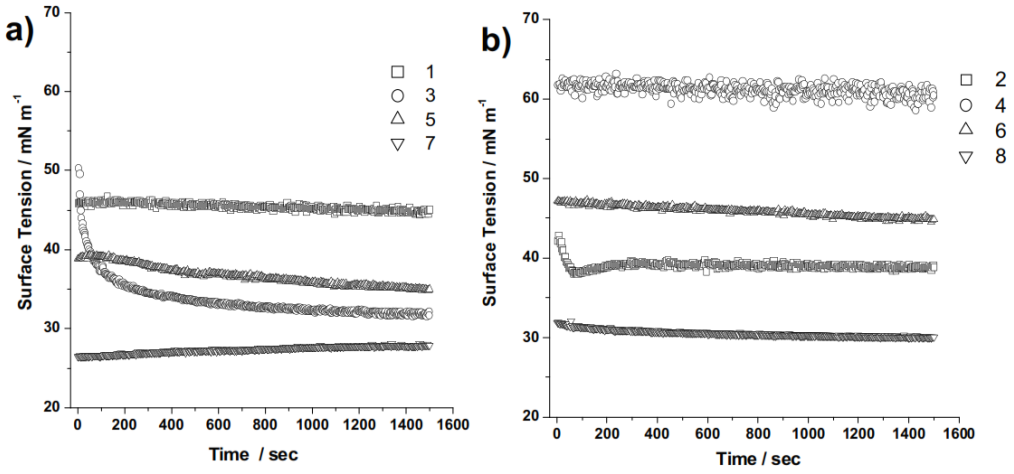


Figure 2.8. Surface tension profiles for compounds **1**, **3**, **5** and **7** (Panel a) **2**, **4**, **6**, and **8** (Panel b) (5 mM).

Compounds **1**−**8** have been solubilized at concentrations above the CMC values (5 mM). Each compound presents a different profile, indicating a specific tendency to go at the air−water interface associated with specific kinetics. It is interesting to notice the difference between σ_{eq} values of compounds **3** and **4**. Even if **3** and **4** have the same polar head-group, the difference in the length of the hydrophobic tail is fundamental to determine different kinetics of absorption; compound **4** presents a high lipophilicity, as suggested by high values of logK_{ow} and log$D$ and the lowest value of HLB of the series (according the Davies' method). Lower values of σ_{eq} are achieved with compounds **7** and **8**, which are characterized by quick kinetics of absorption. Compounds **3**, **5** and **6** are the ones characterized by slower kinetics to σ_{eq}.

Table 2.2 summarizes the σ_{eq} values, the elastic modulus (ε) and the effective dilation viscosity (η_d) values for compounds **1**−**8**. These data have been collected to characterize different types of rheological properties of the surfactant films formed at the air−water interface, because the macroscopic response of film properties to surface deformation is inherently linked to fundamental physicochemical properties of surfactants.

Several technological steps in the detergent industry, flotation and sewage disposal are based on the formation of foams of a definite lifetime. The stability or instability of foams and emulsions is to a great extent determined by the surface rheological properties of adsorption layers at the liquid interfaces; for these aspects, the knowledge of dilational elasticity, dilational viscosity and transport effects are important.

Dynamic surface tension was measured while variations of the surface area were induced using the "pending drop" technique. The σ_{eq} values reported in Table 2.2 are referred to the equilibrium state of the films.

Common surface dilatational parameters like ε and η_d were derived by increasing or reducing the volume of the drop, resulting in the expansion or compression of its surface.[41] The σ_{eq} values for compounds **7** and **8** are the lowest in the group of surfactants synthesized. Interestingly, the two compounds alter dramatically the surface tension at the air−water interface. Compound **4** is characterized by a low solubility in the water phase and consequently does not change the σ_{eq} to a great extent (61 mN m^{-1} at equilibrium). These data can be explained in terms of poor solubility of compound **4** and reflect its scarce tendency to distribute at the air−water interface. Compound **4** also presents a high CMC value and the minimum decrease in the σ_{eq} can be related to the higher number of molecules that participate to the formation of micellar aggregates. Moreover, the kinetic of absorption at the air−water interface (similarly to compound **3**, Figure 2.8) is linear for compound **4** and presents a value that is not far from that of pure water surface tension (72 mN m^{-1} at RT).

Table 2.2. σ_{eq}, ε, η_d, HLB and Kt of compounds **1**−**8** for 5 mM solutions.

Compound	σ_{eq}, surface tension [mN m^{-1}]	ε, elastic modulus [mN m^{-1}]	η_d, viscosity [mN m^{-1}]	HLB[a]	Kt [°C]
1	45	36	37	8.6 (27.8)	64
2	39	147	480	6.7 (24.9)	70
3	33	34	151	9.1 (9.1)	48
4	61	31	26	7.2 (6.2)	56
5	35	11	25	8.6 (11.2)	48
6	44	38	149	6.7 (8.4)	68
7	28	11	58	7.4 (10.2)	26
8	30	20	170	5.7 (7.4)	38

[a] Calculated using the Griffin's and Davies' (between brackets) methods.[42,43]

For three homologues of surfactants couples, **1**−**2**, **5**−**6** and **7**−**8**, it can be noted that the ε and η_d values increase moving from compounds that present C12 chains to the compounds having C18 chains. In these cases, the lengthening of the alkyl chain increases the viscoelastic behaviour of the water layer at the air−water interface. Increases in ε and η_d values are particularly evident for anionic compounds **1** and **2**, but are also relevant for non-ionic compounds **5**−**6** and for the couple **7**−**8**, where the difference in σ_{eq} values is not so relevant.

In Table 2.2 are also reported the hydrophile−lipophile balance (HLB) values calculated for compounds **1**−**8** using the Griffin's and Davies' methods. The HLB of a surfactant is an empirical correlation that measures the tendency to partition between oil and water phase and the value is directly proportional to the surfactants' solubility in water. The Griffin's method does not take into

account the contribution of highly hydrophilic substituents like carboxylate and sulfonate ones, whereas the Davies' method does. As it is predictable, big differences are registered in HLB values of compounds **1** and **2** when measured employing the two different methods. According to Griffin's HLB values, compounds **1**, **4**, **5** and **7** can be classified as wetting agents; compound **3**, which is non-ionic, can be classified as a wetting agent or an oil in water (o/w) emulsifier. Compounds **2**, **6** and **8** present the lower HLB values and are classified as water in oil (w/o) emulsifiers.

In Table 2.2, Krafft temperature (Kt) values for **1**−**8** are listed. Kt is the temperature at which the solubility of the surfactant monomer becomes equal to the CMC and is generally interpreted as the melting temperature of a hydrated solid surfactant. Kt usually coincides with the temperature of full clarification of the system and above the Kt, micelles begin to form provoking a rapid increase in the solubility of the surfactants (see also Figure 2.9).

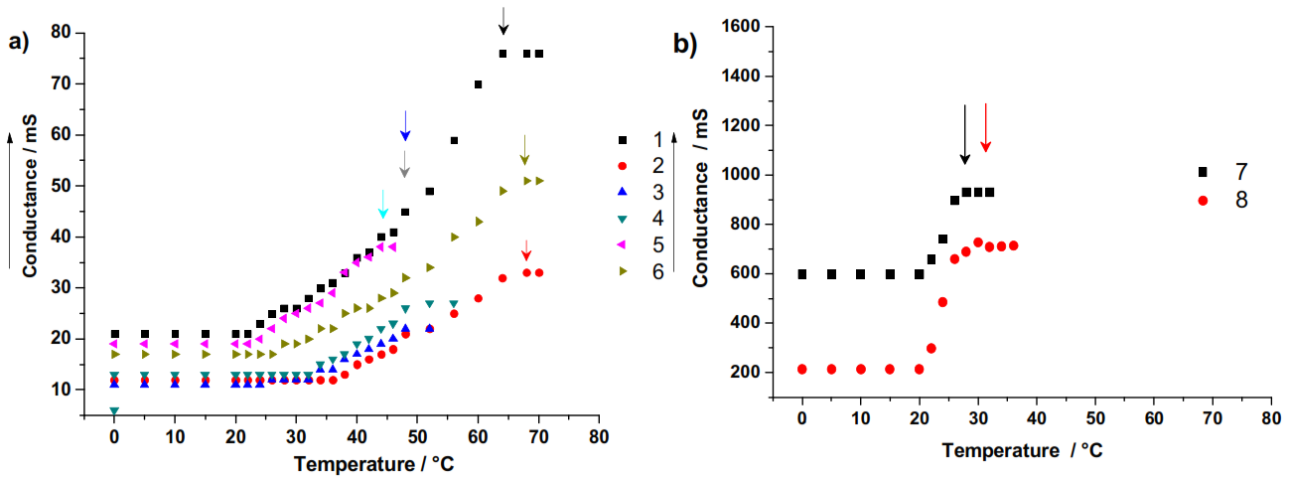


Figure 2.9. The Krafft temperatures (Kt) of compounds **1**-**6** (Panel a) and **7**-**8** (Panel b), indicated by arrows in figure, correspond to a complete clarification of the solutions.

Data clearly show that compounds **1**, **2**, **4** and **6** are characterized by the higher Kt values (around 70 °C). This property undoubtedly limits their applications in certain processes. Therefore, it is desirable to tailor the molecular structure of surfactants or adjust the aqueous environment by introducing inorganic salts to decrease their Kt for practical uses. Compounds **7** and **8** are the most interesting ones in terms of solubility at low temperatures, the Kt values are present at 26 °C and 38 °C, respectively.

Compounds **5**−**8** present in their structure two functionalities that allow them to be switched to a polar structure in water phase in the presence of water and CO_2. The tertiary amine can be converted into a quaternary ammonium group and the alcohol functionality converted into a carbonate moiety (Figure 2.10a). As straightforward example, solely the switching of surfactants **5** and **7** is presented in Figure 2.10b. To measure the property of switching polarity, solutions of **5** and **7** at 5 mM in DMSO have been prepared; we chose DMSO solutions thanks to the good solubility of both amphiphilic molecules and CO_2.

Figure 2.10b shows that the conductivity of DMSO solutions can increase during time in the presence of a CO_2 flux directly bubbled into the solution (for details, see the Experimental Section). The conductivity values, indicative of the presence of the charged form, can be reversibly decreased by removing CO_2 through heating and bubbling an inert gas like nitrogen (N_2) into the solution containing surfactant. It is interesting to note that the increase or decrease in conductivity from bubbling CO_2 or N_2 is not registered in pure DMSO, indicating that the "switching process" of compounds **5** and **7** (as well as for compounds **6** and **8**) needs water (150 µL of H_2O in 3 mL of DMSO), as outlined in Figure 2.10a. Interestingly, this property can be useful in applications where the increase in surfactant hydrophilicity can decrease its loss into an extracting organic phase.

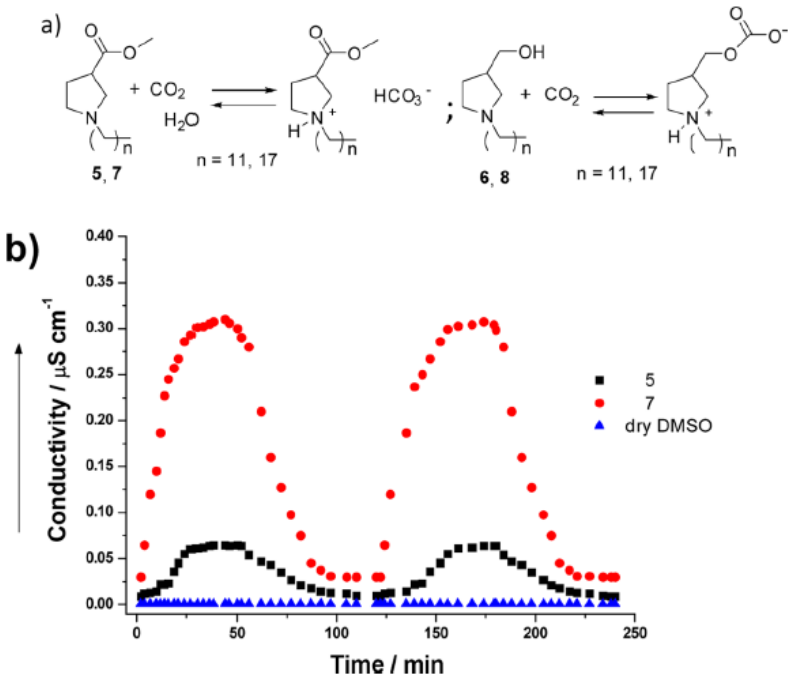
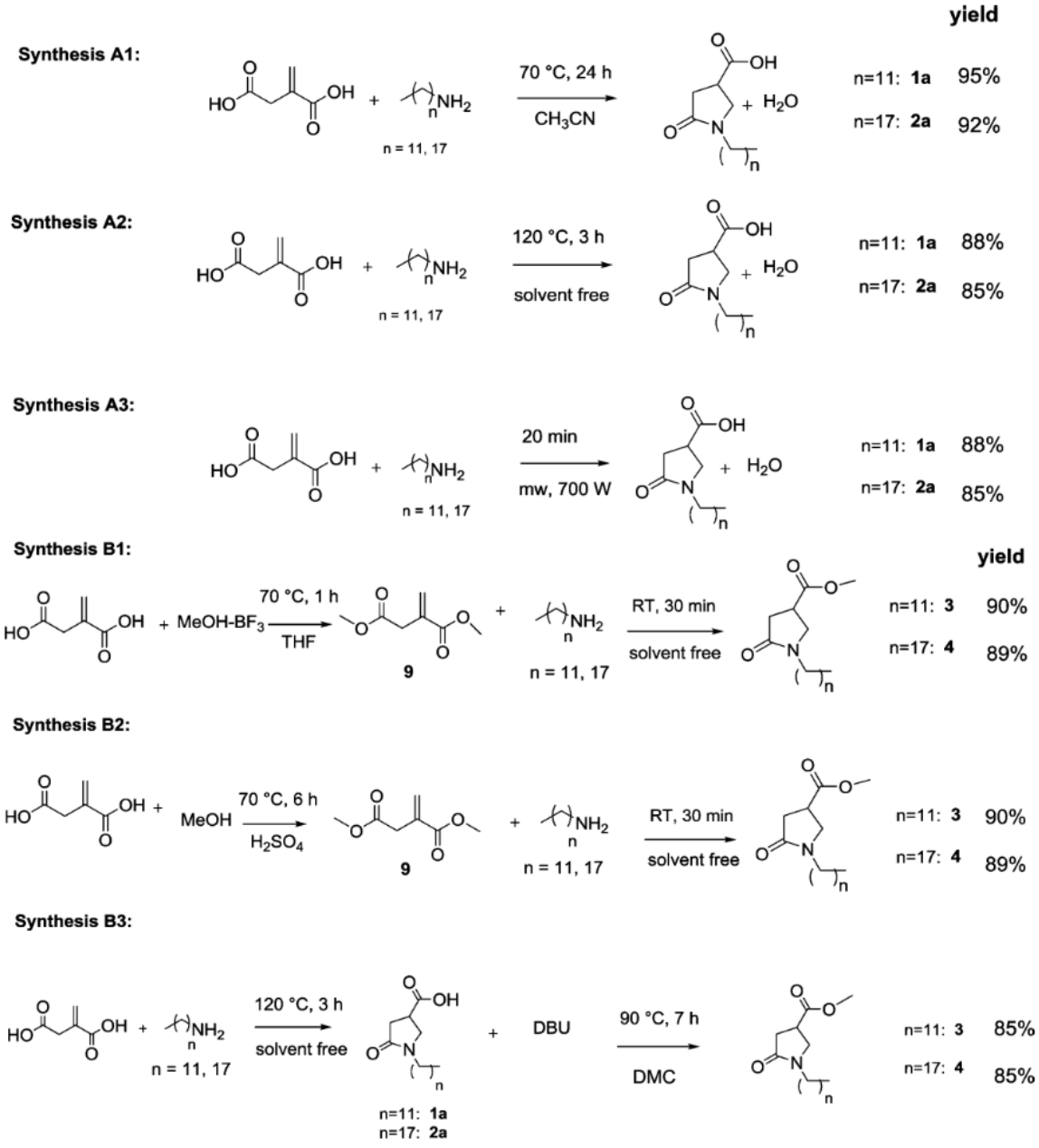


Figure 2.10. (a) Switching of **5**−**8** in the presence of H_2O and CO_2. (b) Conductivity of DMSO solutions of **5** and **7** as a function of time during two cycles of treatment with CO_2 followed by N_2.

2.3.3 Assessment of the synthetic strategies

Looking for the sustainability of the synthetic processes, we conducted the synthesis of **1**−**8** with three different pathways and we have analyzed the procedures using two complementary types of green metrics: we employed the software EATOS and the worksheet developed by Andraos.[25]

In the Experimental Section, these metrics and their definitions are specified. Interconnections between these parameters were demonstrated by Andraos.[44,45] The variables measured with EATOS are the quantity of substrate used (indicated as S^{-1}), the Environmental Index in input of the reaction (EI input), that measures the resources used and the risk connected with the chemical reaction and the Environmental Index in output (EI output) that measures the toxicity, the eutrophication potential, the ozone depletion and the greenhouse effect of products and by-products.



Scheme 2.4. Reaction schemes of the synthetic routes used for the synthesis of compounds **1**−**4**.

We have decided to limit the green metrics investigation to the synthesis of the lactam surfactants **1**−**4** through conjugate addition of primary fatty amines to itaconic acid and its methyl ester, corresponding to the synthetic routes depicted in Scheme 2.4. Besides the reaction conditions usually employed and shown in Scheme 2.3, here a comparison is performed with other synthetic conditions that also lead to compounds **1**−**4**. Evaluation of the further elaboration of the lactam moiety goes beyond the aim of the present study. Therefore, the synthetic procedures used for the synthesis of **5**−**8** will not be taken into account here. Comparison between the synthetic routes A1, A2 and A3 using EATOS is visible in Figure 2.11a; comparison between routes B1, B2 and B3 is depicted in Figure 2.11b.

The corresponding numerical values are summarized in Table 2.3, and summarize the greenness of the processes evaluated following this approach. Routes A1, A2 and A3 mainly differ in the presence/absence of solvent, in reaction duration, temperature and in the kind of energy input used: external heating with a silicon oil bath (for routes A1 and A2) or a microwave irradiation (for route A3). Interestingly, routes A2 and A3 provide exactly the same profile, when assessed with EATOS software. However, we should point out that the energy consumption in route A3 is lower than in route A2; indeed, microwaves energy supply to chemical reaction is much more efficient than heat transfer from external heating[46] but this aspect is not taken into account by the EATOS approach. For A routes, the major impact on S^{-1}, EI input and EI output is due to the solvent. The reactions conducted in solventless conditions (A2 and A3) proved to be more efficient in terms of energy and substrates consumption. We postulate that possible concerns that could arise when solvent free reactions are carried out on a larger scale, like heat release of strongly exothermic reactions, local temperature increase and inhomogeneity,[47] should be of minimal impact in our system, but further investigation will be required before moving to a pilot-plant or industrial scale. A1 and A2 proceed at high temperatures whereas in routes B1 and B2 dodecylamine and **9** reacted quickly at room temperature (mechanically crushing the reagents in a mortar) so a dramatic temperature increase is not expected. Clearly, in view of the scaling up of the solvent free reaction, a deeper understanding of the thermal characteristics is required. For the synthesis of compounds **3** and **4**, three synthetic procedures have been compared. Routes B1 and B2 exploit dimethylitaconate **9** that is obtained from itaconic acid using MeOH-BF_3 and H_2SO_4, respectively. Otherwise, the methylation of the carboxylic acid functionality of **1a** and **2a** in route B3 has been carried out with dimethyl carbonate (DMC) in the presence of the base 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU). DMC has been chosen because it is considered a green solvent with low toxicity values, it is not classified as a volatile organic compound (VOC)[48] and is a potential green methylating agent. DBU was used as a base because the less expensive and toxic K_2CO_3 or KOH gave rise to the formation of itaconic anhydride only.

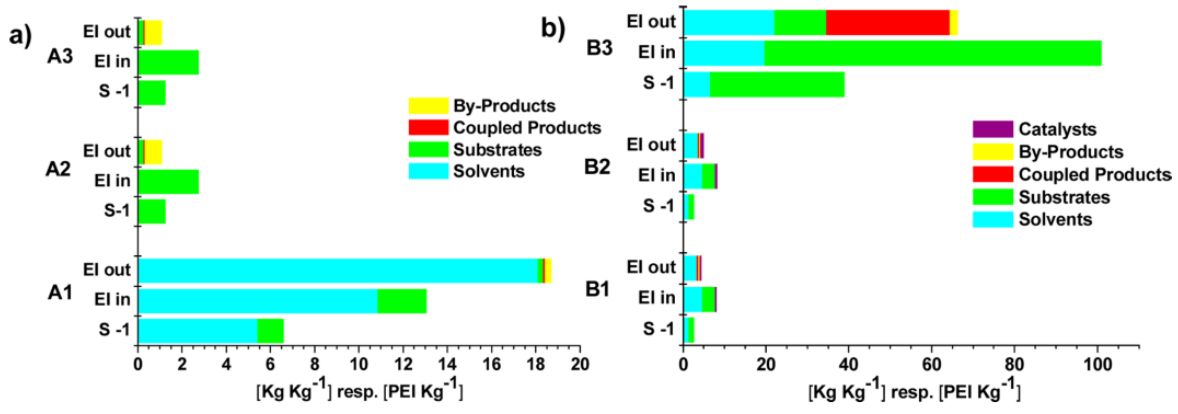


Figure 2.11. S^{-1}, EI input and EI output values for synthetic routes A1, A2, A3 (a) and B1, B2, B3 (b) investigated with EATOS software.

Figure 2.11b shows that route B3 is by far less convenient in terms of solvents consumption, substrates use and by-products production according to the EATOS evaluation. It is interesting to notice that the more efficient route is B1, involving the use of MeOH-BF_3 complex instead of H_2SO_4, acid that presents serious health and environmental drawbacks (Figure 2.11b and Table 2.3).

Table 2.3. S^{-1}, EI input and EI output values for synthetic routes A1, A2, A3, B1, B2 and B3 calculated with EATOS software.

Synthetic route	S^{-1} [Kg Kg^{-1}] resp. [PEI Kg^{-1}]	EI input [Kg Kg^{-1}] resp. [PEI Kg-1]	EI output [Kg Kg^{-1}] resp. [PEI Kg^{-1}]
A1	6.58	13.04	18.69
A2	1.24	2.73	1.08
A3	1.24	2.73	1.08
B1	2.66	8.03	4.31
B2	2.72	8.16	5.01
B3	38.95	100.85	66.28

Moving now to the Andraos approach, Figure 2.12 shows the pentagons that summarize the raw material footprints for the synthetic routes compared; corresponding numerical values are summarized in Table 2.4.

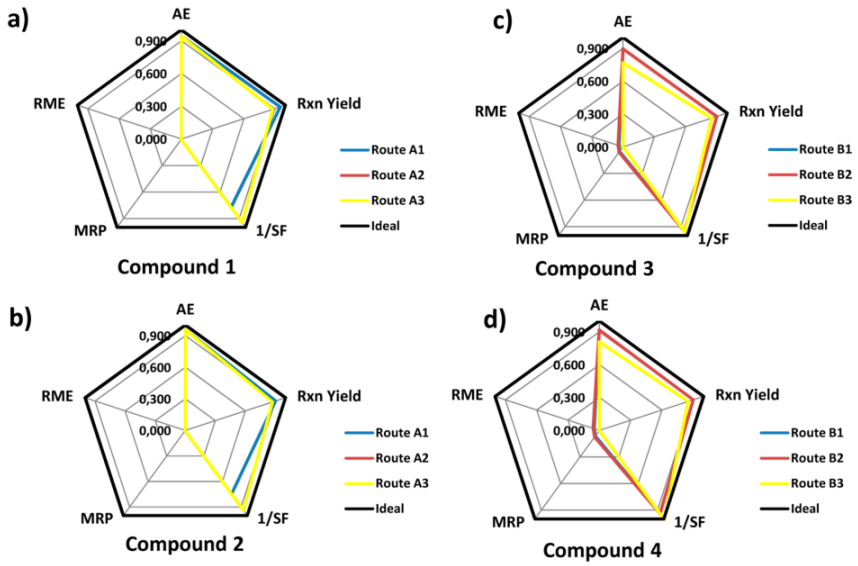


Figure 2.12. Comparison of the raw material footprints for synthetic routes A1, A2, A3 to compounds **1** (a) and **2** (b); for synthetic routes B1, B2, B3 to compounds **3** (c) and **4** (d), including the purification steps.

The synthetic routes A1−B2, with the exception of route B3, are characterized by high levels of reaction yield (Rxn Yield), atom economy (AE) and stoichiometric factor (SF). These data are in agreement with green chemistry principles,[49] which suggest to prefer addition reactions and solventless conditions. With respect to the other two parameters taken into account, Reaction Mass Parameter (RMP) and Process Mass Intensity (PMI), the assessment through Andraos method is not highly meaningful for processes carried out with typical laboratory methods. Interestingly, as underlined in the worksheets present in the Experimental Section, the values of RMP and PMI are low if solvents and materials used in the purification steps are taken into account, independently from the synthetic route considered. Otherwise, RMP and PMI values are high if measured considering exclusively the amount of solvent used in the synthetic steps (Figure 2.13).

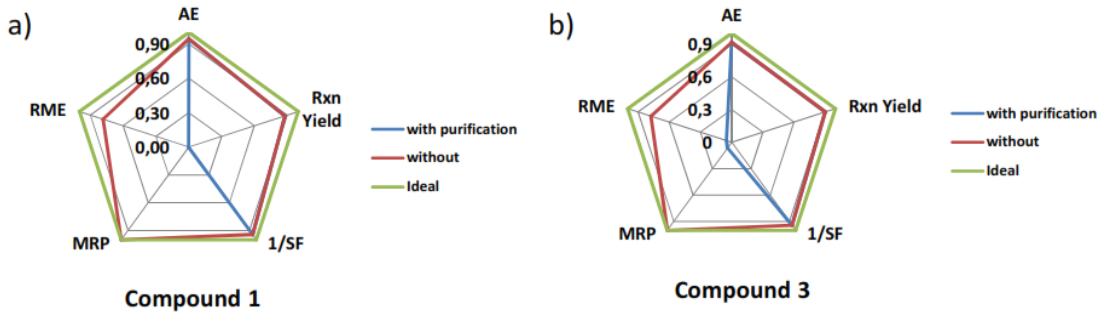


Figure 2.13. Comparison of the raw material footprints (considering or not the contribution of purification steps) for synthetic routes A3 to compound **1** (Panel a) and for synthetic routes B1 to compound **3** (Panel b).

Molar Efficiency (ME) values summarized in Table 2.4 highlight that solvents used during the reactions or in the purification steps have a heavy influence on this metric, rarely highlighted by other metrics.

Table 2.4. Comparison of raw material footprints for synthetic routes A1, A2, A3, B1, B2 and B3.

Routes	Rxn Yield [%]	AE [%]	SF [%]	RMP [%]	RME [%]	E-Factor	PMI	ME[a] [%]
A1	95	94	77	100	69	0.44	1.4	38 (24)
A2	88	94	94	100	78	0.28	1.28	42
A3	88	94	94	100	78	0.28	1.28	42
B1	90	90	95	100	77	0.3	1.3	29 (4)
B2	90	90	95	100	77	0.3	1.3	28 (4)
B3	85	77	1.28	100	84	0.2	1.9	21 (1)

[a] Values between brackets have been calculated taking into account the solvent presence.

In the synthesis of compounds **3** or **4** is recorded the higher difference in terms of ME, depending on the presence of the solvent. In conclusion, we point out that a complete toxicological characterization such as biodegradability and eco-toxicity of the surfactants has to be assessed to have a complete picture of the toxicological properties and environmental fate of the compounds.

2.4 Conclusions

We have reported the two step synthesis of a new class of surfactants derived from itaconic acid and fatty amines. The synthetic strategies have been designed for minimizing waste, by-products and energy consumption. The products obtained constitute an exploitable pool of surface active compounds that thanks to different structures present specific rheological behaviours. Moreover, the compounds synthesized can be exploited in reactions of micellar catalysis in water phase (see Chapter 5). When assessed through green metrics protocols, reactions conducted in solventless conditions and using microwave devices proved to be efficient and sustainable in terms of toxicity, substrate, solvent and energy consumption. Evaluation of biodegradability and eco-toxicity of the surfactants presented in the present chapter, as well as the design of similar surfactants still based on itaconic acid, is ongoing in our laboratory.

2.5 Experimental Section

2.5.1 Materials

All reactants were purchased from Sigma Aldrich and used without purifications. Aqueous solutions were prepared using Milli-Ro water (resistivity 18.2 MΩ cm at 25 °C; filtered through a 0.22 μm membrane). Flash chromatography was performed on silica gel (230−400 mesh).

2.5.2 General methods and techniques

NMR analyses

^{1}H and ^{13}C NMR spectra were recorded on a Varian Mercury 400 spectrometer.

GC−MS analyses

GC−MS analyses were performed using a 6850 Agilent HP gas chromatograph connected to a 5975 Agilent HP quadrupole mass spectrometer. The GC−MS analysis of compounds **1a**, **2a**, **1**, **2**, **7** and **8** was done by means of silylation.

LC-MS analyses

LC-MS analyses were performed on a 1200 series Agilent liquid chromatograph coupled with an electrospray ionization-mass spectrometer (LC-ESI-MS) Quattro Premier XE Waters, using H_2O/CH_3CN as solvents at RT (positive scan, 50−800 m/z).

Elemental analyses

The elemental composition of the compounds was determined by using an elemental analyzer (Thermo Scientific, Flash 2000, Organic Elemental Analyzer) by means of the flash combustion technique.

FT-IR analyses

Spectra were measured on a Bruker Alpha FT-IR spectrometer as neat films between NaCl plates and reported in cm^{-1}.

Microwave reactions

Microwave assisted reactions were performed in a Milestone Mycrosynth equipped with a dual magnetron system with pyramid-shaped diffuser, 1000 W maximum output power, temperature monitor and control via an optic fibre up to 250 °C in the vessel.

Conductivity measurements

Measurements for the determinations of CMC, Kt and switching properties of **5**−**8** were carried out with an AMEL 160 conductivity-meter.

Steady-state fluorescence measurements

Pyrene and Nile Red steady-state fluorescence emission spectra (Figure S21 in the Experimental Section) were acquired with a Jasco spectrofluoro-meter FP-6200 equipped with a thermostated cuvette holder and a magnetic stirring device.

2.5.3 Biophysical characterization techniques

Critical micellar concentration (CMC)

The CMC of **1**−**8** has been measured using three different techniques: a) Pyrene I_1/I_3 vibronic ratio measurement, b) Nile Red fluorescence (the CMC has been measured as stated in the literature),[50] c) conductivity method.

a) Pyrene I_1/I_3 vibronic ratio measurement

Water solutions (3 mL) of **1**-**8** were prepared at different concentrations (0.001, 0.005, 0.01, 0.05, 0.1, 0.5, 1, 5, 10 mM) and left to stabilize at RT before each measurement. A stock solution of Pyrene in ethanol (0.75 mM) was prepared daily and stored in the dark at 4 °C for one night before usage. For the preparation of water solutions containing Pyrene, an aliquot of ethanol solution containing Pyrene was used, the solvent was evaporated under vacuum and then an adequate volume of water was added to obtain the final concentration of 0.75 μM. Pyrene's final concentration in solution was low enough to avoid excimer formation. Before measurements, solutions containing Pyrene and surfactants have been sonicated. Solutions of **1**−**8** were placed into a thermostated bath where temperature was maintained constant within ±0.05 °C. A gentle flow of N_2 for 20 min was used to degas all solutions before measurements. The conductivitymeter was previously calibrated with a KCl standard solution of 0.01 M (1.29 mS cm^{-1}).

The steady-state fluorescence emission spectra excited at 334 nm were recorded in the 350 to 550 nm range (see Figure 2.1). Pyrene is a hydrophobic molecule and it has been recently proposed to be localized in the hydrophobic interior of the micelles or aggregates,[51] under the hydrophilic heads of the molecules. Typical features of the structured emission spectra of Pyrene are the maxima at 375 nm, 385 nm and 395 nm due to vibronic bands (see Figure 2.1), known to be environmentally sensitive[52] and this property has been effectively used for evaluating the polarity of microenvironments in which Pyrene is dissolved.[53] The ratio of the first (I_1, 375 nm) and third (I_3, 385 nm) vibronic peak intensities (I_1/I_3) in Pyrene emission spectra provides a measure of the apparent polarity of the environment: an increase in the I_1/I_3 ratio is indicative of an increased polarity, while a decrease is indicative of a reduction of polarity, for example the presence of an organized lipidic environment (Figures 2.2). It is fundamental to point out that the I_1/I_3 ratio considerably changes in different experimental settings depending on the optical configuration used for the measurements (front-face or right-angle geometry and slits bandwidth), Pyrene concentration, temperature and ionic strength of the solution.[54] The spectra of all solutions were acquired with the usual right angle configuration. The fluorescence intensities of the first (I_1 - 375 nm) and third (I_3 - 385 nm) emission peaks were measured. Excitation and emission slits had a nominal bandpass of 5 nm. The CMC has been measured as stated in the literature, using the Boltzman sigmoidal eq. (1) and the χ^2 (chi-square) coefficient:

$$y = \frac{A_1 - A_2}{1 + e^{\frac{x - x_0}{dx}}} + A_2 \qquad (1)$$

where the dependent variable (y) corresponds to the Pyrene I_1/I_3 ratio value, the independent variable (x) is the total concentration of the tested compound, A_1 and A_2 are the upper and lower limits of the sigmoid, respectively, x_0 is the centre of the sigmoid and the corresponding CMC value. Each measurement has been carried out in at least three replicates.

b) NR fluorescence

Water solutions (3 mL) of **1**-**8** have been prepared at different concentrations (0.001, 0.005, 0.01, 0.05, 0.1, 0.5, 1, 5, 10 mM). For the preparation of water solutions containing Nile Red a final concentration of 0.2 μM Nile Red was added to the surfactant dispersions by injection. The samples were sonicated with an ELMASonic S 70 system. Then the surfactant samples were left to stabilize at RT for at least 1 day prior to the measurements. Steady-state emission spectra of Nile Red were recorded at RT using 5 nm slit widths (nominal) at excitation of 550 nm using a Jasco spectrofluorometer FP-6200 equipped with a thermostated cuvette holder and a magnetic stirring device (PerkinElmer, MA, USA). The emission spectra were recorded at a scanning speed of 60 nm/min from 560 to 700 nm.

The given data are plotted as the Nile Red emission peak (λ max) in the surfactant system versus the logarithmic function of the surfactant concentration (mM): obtained data in CMC determination experiments were extrapolated by logistic fitting curve using the eq. (2) (software Origin 8, OriginLabTM Northampton, MA, US):

$$y = \frac{A_1 - A_2}{1 + (\frac{x}{x_0})^p} + A_2 \qquad (2)$$

where the dependent variable (y) corresponds to the fluorescence intensity value, the independent variable (x) is the total concentration of the compound tested, A_1 and A_2 are the lower and upper limits of the curve, respectively, x_0 is the centre of the curve and the corresponding CMC value, p is the exponent of the power law. Each measurement has been carried out in three replicates.

Mean aggregation number (N^{agg})

The steady-state fluorescence quenching method was used for the determination of N^{agg} at RT.[55] In all experiments, CPC was used as the quencher. Working solutions containing 0.75 μM Py and 5 mM of **1**−**8** or 10 mM for SDS (above the CMC) were prepared in milli-Ro water. Quencher concentration [CPC] in solution was maintained low enough (0.012 mM) to not perturb the surfactant micelle assembly. The nominal slit widths of excitation and emission were 5 nm, the scan speed was 250 nm min^{-1}. Fluorescence steady-state emission spectra were recorded between 350 and 500 nm using excitation at λ = 334 nm (Figure 2.1).

The micelle N^{agg} was obtained from eq. (3):[56]

$$\ln(I_0/I_Q) = (N^{agg} \times [CPC]) / ([surf] - CMC) \qquad (3)$$

where I_0 and I_Q are the fluorescence intensities of Pyrene in the absence and presence of the quencher CPC, respectively; [surf] is the total concentration of **1**−**8**, which was kept constant and [CPC] is the concentration of quencher, which was varied (0.00012, 0.0006, 0.0012, 0.006, 0.012 mM). The slope of the linear plots between $\ln(I_0/I_Q)$ versus [CPC] yielded the mean aggregation number (N^{agg}) of the micelles.

Hydrophile−Lipophile Balance methods (HLB)

HLB values have been measured using the Griffin's and Davies' methods.[41,42]

Krafft temperature measurements (Kt)

To determine Kt, aqueous solutions of **1**−**8** (10 mM) and SDS were prepared and placed in a refrigerator at ~4 °C for 24 h, where the precipitation of surfactants occurred. The temperature of the precipitated system was raised gradually under constant stirring using a thermostated bath (Heating

Immersion Circulator Julabo 13) and its conductance (G, mS) was measured. At each temperature, the conductance reading was checked every 2 min until it reached a steady value.[57]

logK_{ow}, log$D$, pK_a predictions

The software Alogps 2.1,[37,38] ECOSAR 1.11 and EPIWEB[39] were employed for the prediction of logK_{ow}, log$D$ and pK_a values of **1**−**8**. logK_{ow} values have been measured using the OECD method No. 117, 2004.[40]

Colorimetric changes

5 mM water solutions of **1**, **3**, **5** or **7** were prepared and 5 drops of bromothymol blue solution were added. The solutions were gently shaken and the colorimetric response observed.

Acid−base titrations

Titration curves were determined with a pH electrode at RT under a N_2 atmosphere and magnetic stirring. Aqueous surfactant solutions (1.5 mL) of 5 mM were titrated with aqueous NaOH solution of the same concentration. The experiment was twice repeated.

Surface tension measurements

Surface tension measurements were performed by a SINTECH PAT1 tensiometer. The σ_{eq} values of **1**−**8** were measured using solutions (5 mM) of deionized water above the CMC (cf. with data in Table 2.2). The σ_{eq} values were determined at RT using the pendant drop method (data are reported in Figure 2.3). Elastic module ε and viscosity values η_d (Table 2.2) for each compound have been calculated acquiring dynamic surface tension data.[46] Elastic module values $|\varepsilon|$ have been calculated using eq. (4):

$$|\varepsilon| = -d\sigma/d\ln A \qquad (4)$$

where A is the area of the drop surface and σ_{eq} is the equilibrium surface tension. Viscosity values η_d have been calculated using eq. (5):

$$\eta_d = \varepsilon_0 \omega^{-1} \sin\theta \qquad (5)$$

where ε_0 equals the dilatation elasticity modulus $|\varepsilon|$ only for an instantaneous deformation and ω is the angular frequency of the area variation.

Conductivity measurements of compounds **5−8**

The conductivity of **5**−**8** (10 mM) in wet DMSO (150 µL of H_2O in 3 mL of DMSO) was measured. CO_2 was bubbled through the solution for 30 min at RT (24 °C). After this step, N_2 was bubbled through the solution and in the meanwhile the temperature was raised to 60 °C for 30 min. The CO_2 and temperature increase cycles were repeated two times (60 and 60 minutes, respectively). In a control experiment, air was bubbled through the solution of **5** (10 mM) in undried DMSO (3 mL) for

15 min at RT. The conductivity did not rise. CO_2 was then bubbled through for 2 min, causing the conductivity to rise.

2.5.4 Green metrics

S^{-1} values, EI in and EI out values have been measured employing the software EATOS v 1.1[24] and a group of metrics described hereby.

The data required for EATOS were obtained from the MSDS downloadable from the Sigma-Aldrich website and from the database of the European Chemical Agency (ECHA).[19] They include: information dealing with risk (R phrases), human toxicity (LD50 oral or dermal, hazard symbols), chronic toxicity (suspect of carcinogen, teratogen, mutagen by International Agency for Research on Cancer - IARC), eco-toxicology (WGK, EC50 48h Daphnia magna), biodegradation and accumulation (BCF, log Pow). Prices were taken from the Aldrich catalogue (updated March 2015). For the calculation of stoichiometric factor (SF), reaction mass parameter (RMP) and the reaction mass efficiency (RME), the spreadsheet produced by J. Andraos[44,45] has been used.

The *E*-factor[58] was calculated as eq. (6):

$$E - \text{factor} = \frac{(\text{total waste [kg]})}{(\text{mass of product/s [kg]})} \qquad (6)$$

Process mass intensity (PMI) was calculated applying eq. (7):[59]

$$\text{PMI} = \frac{\text{total mass used in a process or in a step [kg]}}{\text{mass of product/s [kg]}} \qquad (7)$$

Molar efficiency (ME)[60] was calculated using eq. (8):

$$\text{ME} = \frac{\text{moles products}}{\sum(\text{moles starting materials} + \text{moles of additives} + \text{moles catalyst} + \text{moles solvent})} \times 100 \qquad (8)$$

2.5.5 General procedures for the synthesis of compounds 1-8

Synthesis of compounds **1a** and **2a**: Route A1

In a typical experiment itaconic acid (2-methylidenebutanedioic acid, 1 eq.) was added to a stirring solution of the alkylamine (dodecylamine for compound **1a**, octadecylamine for compound **2a**; 1.1 eq.) in CH_3CN at RT and then the solution stirred at 70 °C for 24 h; the course of the reaction was monitored by means of TLC and GC–MS. Evaporation of the solvent under reduced pressure left a solid, which was purified on a silica gel column chromatography (cyclohexane/ethyl acetate 9:1) to give a white solid (**1a** yield 95%; **2a** yield 92%).

Synthesis of compounds **1a** and **2a**: Route A2

Reaction was adapted from previously reported one.[61] Itaconic acid (1 eq.) was added to a stirring solution of the alkylamine (dodecylamine for compound **1a**, octadecylamine for compound **2a**; 1.3 eq.) in solventless conditions and the reaction mixture heated at 120 °C for 3 h. Purification procedure is the same as in route A1 (**1a** yield 88%; **2a** yield 85%).

Synthesis of compounds **1a** and **2a**: Route A3

The reactions were carried out in analogous conditions of Route A2 but in a microwave oven; the reaction mixture was heated at 120 °C at 700 Watt for 20 min (**1a** yield 88%; **2a** yield 85%).

Synthesis of compounds **1** and **2**

Compounds **1a** and **2a** have been added at RT in an equimolar ratio to a water stirring solution containing KOH, at the end of the procedure the neutral pH of the solution was checked with a pH-meter, water was evaporated under reduced pressure to give solids (quantitative yield).

Synthesis of compounds **3** and **4**: Route B1 – 1st step

Itaconic acid (1 eq.) was added to a stirring solution of MeOH-BF_3 (1.3 M in THF, 1 eq.) and the solution stirred for 1 h under reflux. The solvent was evaporated and the product (dimethyl itaconate, **9**) extracted in *n*-hexane (x2) from water. The organic layers were combined and dehydrated with anhydrous Na_2SO_4. After filtration the solvent was evaporated under reduced pressure to give a liquid (quantitative yield).

Synthesis of compounds **3** and **4**: Route B2 – 1st step

Reaction was adapted from previously reported one.[62] Itaconic acid (50 mmol, 1 eq.) has been added to a stirring solution of MeOH (25 mL) and H_2SO_4 (30 % moles) and the solution stirred for 6 h under reflux. The solvent was evaporated under reduced pressure and the crude product (dimethyl itaconate, **9**) extracted in ethyl acetate (x2) from water. The organic layers were combined, dried over sodium sulphate and concentrated under reduced pressure (quantitative yield).

Synthesis of compounds **3** and **4**: Routes B1 and B2 – 2nd step

For routes B1 and B2 dimethyl itaconate (**9**) was added to the corresponding alkylamine (dodecylamine for compound **3**, octadecylamine for compound **4**; 1.1 eq.) at RT and the solution stirred for 30 min; the course of the reaction was monitored by means of TLC and GC–MS (**3** yield 90%; **4** yield 89%).

Synthesis of compounds **3** and **4**: Route B3

Reaction was adapted from previously reported one.[63] Compound **1a** or **2a** were synthesized as stated in route A2. Dimethylcarbonate (DMC) (70 eq., 2 mL) was added to the crude product (0.34 mmol, 1 eq.) and then DBU was added (0.34 mmol, 1 eq.), the mixture was stirred at 90 °C for 7 h. DMC was evaporated under reduced pressure and the product extracted in H_2O / Ethyl acetate (x2). The organic layers were combined, dried over sodium sulphate and concentrated under reduced pressure, the crude product purified by means of column chromatography (cyclohexane : ethyl acetate gradient elution, 8 : 2); (**3** yield 85%; **4** yield 85%).

Synthesis of compounds **5** and **6**

Reaction was adapted from previously reported one.[64] To a solution of methyl 1-dodecyl-5-oxopyrrolidine-3-carboxylate (**3** - 500 mg, 1.68 mmol) or methyl 1-octadecyl-5-oxopyrrolidine-3-carboxylate (**4** - 641 mg, 1.68 mmol) in dry THF (4 mL), a THF solution of borane dimethyl sulphide (2 M, 1.7 mL, 3.36 mmol) was added dropwise stirring under inert atmosphere at 0 °C over 10 min. After the addition was completed, the temperature was left to rise to RT and the solution was stirred for a further 3 h at RT. Then 4N HCl in methanol was added (1.9 mL) and the solution refluxed for 1 h. The reaction mixture was concentrated, water was added and the pH was raised to 10 adding NaOH. The basic water phase was extracted with CH_3CN and the combined organic phases were dried over magnesium sulphate and concentrated under reduced pressure. Evaporation of the solvent left an oily residue, which was purified by means of column chromatography on silica gel (eluent: methanol) to give a liquid (**5** yield 93%; **6** yield 90%).

Synthesis of compounds **7** and **8**

To a solution of 1-dodecyl-5-oxopyrrolidine-3-carboxylic acid (**1a** - 500 mg, 1.68 mmol) or 1-octadecyl-5-oxopyrrolidine-3-carboxylic acid (**2a** - 641 mg, 1.68 mmol) in dry THF (4 mL), a THF solution of borane dimethyl sulphide (2 M, 3.4 mL, 6.72 mmol) was added dropwise stirring under inert atmosphere at 0 °C over 10 min. After the addition was completed, the temperature was left to rise to RT and the solution was stirred for a further 3 h at RT. Then 4N HCl in methanol was added (3.7 mL) and the solution refluxed for 1 h. The reaction mixture was concentrated, water was added and the pH was raised to 10 adding NaOH. The basic water phase was extracted with CH_3CN and the combined organic phases were dried over Na_2SO4 and concentrated under reduced pressure. Evaporation of the solvent left an oily residue, which was purified by column chromatography on silica gel (eluent: methanol) to give a white solid (**7** yield 85%; **8** yield 87%).

2.5.6 Characterization data of compounds 1-8

1-Dodecyl-5-oxopyrrolidine-3-carboxylic acid (**1a**); m.p. 39 °C; Retention factor (Rf = 0.34, AcOEt : cyclohexane = 7:3); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.68 (dd, J(H,H) = 10, 8 Hz, 1H), 3.60 (dd, J(H,H) = 12, 10 Hz, 1H), 3.32-3.21 (m, 3H), 2.80 (dd, J(H,H) = 16, 8 Hz, 1H), 2.74 (dd, J(H,H) = 16, 8 Hz, 1H), 1.53-1.49 (m, 2H), 1.29-1.25 (m, 18H), 0.87 (t, J(H,H) = 8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 175.81, 173.23, 49.11, 42.75, 35.86, 34.09, 31.83, 30.85, 29.54, 29.49, 29.43, 29.27, 29.18, 26.99, 26.70, 22.60, 14.04. IR (neat): 2922, 2852,1722, 1632, 1467, 1350, 1225, 676 cm^{-1}; ESI-MS positive scan (cone 30 V): m/z (%): 296.31 (100) [M^-]; GC-MS retention time (rt) 26.6 min; m/z (EI) 369.44 ((M-1) + $Si(CH_3)_3$), 354 ((M-1) + $Si(CH_3)_2$), 298 (M+1), 252 (M - COO), 239 (M - COOCH), 214 (M – $COOCH(CH_2)_2$), 185 (M – $COOCH(CH_2)_2CO$), 129 (M – $CH_3(CH_2)_{11}$); elemental analysis: calculated (%) for $C_{17}H_{31}NO_3$ (297.4): C 68.65, H 10.51, N 4.71; found: C 68.93, H 10.63, N 4.72.

1-Octadecyl-5-oxopyrrolidine-3-carboxylic acid (**2a**); m.p. 81-92 °C; Retention factor (Rf = 0.28, AcOEt : cyclohexane = 8:2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.65 (dd, J(H,H) = 10, 8 Hz, 1H), 3.58 (dd, J(H,H) = 12, 10 Hz, 1H), 3.30-3.20 (m, 3H), 2.77 (dd, J(H,H) = 16, 8 Hz, 1H), 2.71 (dd, J(H,H) = 16, 8 Hz, 1H), 1.52-1.48 (m, 2H), 1.31-1.23 (m, 30H), 0.86 (t, J(H,H) = 8 Hz, 3H);13C NMR (100 MHz, $CDCl_3$): δ = 176.28, 172,82, 48.97, 42.72, 35.85, 34.12, 31.90, 29.68, 29.63, 29.56, 29.50, 29.34, 29.25, 27.08, 26.88, 26.76, 22.67, 14.10; IR (neat): 2917, 2850, 1723, 1640, 1468, 1225 cm^{-1}; GC-MS rt 30.8 min; m/z (EI) 453.6 ((M-1) + $Si(CH_3)_3$), 438 ((M-1) + $Si(CH_3)_2$), 382 (M+1), 336 (M - COOH), 318 (M - COOHO), 214 (M – $COOCH(CH_2)_2$), 185 (M - $COOCH(CH_2)_2CO$), 129 (M – $CH_3(CH_2)_{11}$); elemental analysis: calculated (%) for $C_{23}H_{43}NO_3$ (381.6): C 72.39, H 11.36, N 3.67; found: C 72.51, H 11.68, N 3.96.

Potassium 1-dodecyl-5-oxopyrrolidine-3-carboxylate (**1**); ^{1}H NMR (400 MHz, CD_3OD): δ = 3.59 (d, J(H,H) = 4 Hz, 2H), 3.24 (t, J(H,H) = 8 Hz, 2H), 3.09-3.01 (m, 1H), 2.68 (dd, J(H,H) = 20, 8 Hz, 1H), 2.55 (dd, J(H,H) = 16, 8 Hz, 1H), 1.55-1.48 (m, 2H), 1.32-1.27 (m, 18H), 0.88 (t, J(H,H) = 8 Hz, 3H); ^{13}C NMR (100 MHz, CD_3OD): δ = 180.69, 174.99, 50.68, 42.07, 38.52, 35.23, 31.64, 29.34, 29.32, 29.29, 29.25, 29.04, 28.94, 26.66, 26.42, 22.30, 13.01; GC-MS rt 26.6 min; m/z (EI) 369.44 ((M-1) + $Si(CH_3)_3$), 354 ((M-1) + $Si(CH_3)_2$), 298 (M+1), 252 (M - COO), 239 (M - COOCH), 214 (M – $COOCH(CH_2)_2$), 185 (M – $COOCH(CH_2)_2CO$), 129 (M – $CH_3(CH_2)_{11}$); elemental analysis: calculated (%) for $C_{17}H_{30}NO_3K$ (335.5): C 60.85, H 9.01, N 14.01; found: C 61.05, H 10.05, N 14.25.

Potassium 1-octadecyl-5-oxopyrrolidine-3-carboxylate (**2**); ^{1}H NMR (400 MHz, CD_3OD): δ = 3.59 (d, J(H,H) = 8 Hz, 2H), 3.24 (t, J(H,H) = 8 Hz, 2H), 3.07-2.99 (m, 1H), 2.68 (dd, J(H,H) = 20, 8 Hz, 1H), 2.54 (dd, J(H,H) = 16, 8 Hz, 1H), 1.55-1.47 (m, 2H), 1.31-1.23 (m, 30H), 0.88 (t, J(H,H) = 8 Hz, 3H); ^{13}C NMR (100 MHz, CD_3OD): δ = 179.29, 175,06, 50.79, 42.08, 38.73, 35.32, 31.65, 29.36, 29.27, 29.05, 28.97, 26.68, 26.45, 22.32, 13.03; GC-MS rt 30.8 min; m/z (EI) 453.6 ((M-1) + $Si(CH_3)_3$), 438 ((M-1) + $Si(CH_3)_2$), 382 (M+1), 336 (M - COOH), 318 (M - COOHO), 214 (M – $COOCH(CH_2)_2$), 185 (M - $COOCH(CH_2)_2CO$), 129 (M – $CH_3(CH_2)_{11}$); elemental analysis: calculated (%) for $C_{23}H_{42}NO_3K$ (419.7): C 65.82, H 10.08, N 3.34; found: C 65.98, H 10.33, N 3.36.

1-Dodecyl-5-oxopyrrolidine-3-carboxylic acid methyl ester (**3**) m.p. 30-35 °C; Retention factor (Rf = 0.52, AcOEt : cyclohexane = 7:3); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.75 (s, 3H), 3.61 (dd, J(H,H) = 10, 8 Hz, 1H), 3.57 (dd, J(H,H) = 10, 8 Hz, 1H), 3.34-3.19 (m, 3H), 2.71 (dd, J(H,H) = 16, 7 Hz, 1H), 2.65 (dd, J(H,H) = 16, 10 Hz, 1H), 1.55-1.49 (m, 2H), 1.28-1.26 (m, 30H), 0.88 (t, J(H,H) = 8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.17, 172.00, 52.24, 48.78, 42.37, 35.88, 34.10, 31.78, 29.50, 29.49, 29.43, 29.39, 29.21, 29.15, 27.03, 26.64, 22.55, 13.98; IR (neat): 2925, 2854, 1740, 1695, 1437, 1267, 1199 cm–1; ESI-MS positive scan (cone 35 V): m/z (%): 312.25 (100) [M+]; GC-MS rt 25.2 min, m/z (EI) 312 (M +1), 294 (M – CH_3), 280 (M – OCH_3), 252 (M – $COOCH_3$), 156 (M – $CH_2NHCO(CH_2)_2CHCOOCH_3$), 127 (M – $CH_3(CH_2)_{11}N$); elemental analysis: calculated (%) for $C_{18}H_{33}NO_3$ (311.46): C 69.41, H 10.68, N 4.5; found: C 69.78, H 10.77, N 4.42.

1-Octadecyl-5-oxopyrrolidine-3-carboxylic acid methyl ester (**4**); m.p. 58-61 °C; Retention factor (Rf = 0.24, AcOEt : cyclohexane = 1:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.69 (s, 3H), 3.57 (dd, J(H,H) = 10, 8Hz, 1H), 3.52 (dd, J(H,H) = 12, 8 Hz, 1H), 3.29-3.14 (m, 3H), 2.67 (dd, J(H,H) = 16, 8 Hz, 1H), 2.60 (dd, J(H,H) = 16, 8 Hz, 1H), 1.49-1.44 (m, 2H), 1.23-1.20 (m, 30H), 0.83 (t, J(H,H) = 8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.2, 172.02, 52.32, 48.81, 42.43, 35.94, 34.15, 31.83, 29.57, 29.55, 29.43, 29.20, 27.07, 26.69, 22.59, 14.02; IR (neat): 2952, 2915, 2849, 1735, 1682 cm^{-1}; GC-MS rt 30.3 min, m/z (EI) 396 (M + 1), 378 (M – CH_3), 364 (M – OCH_3), 336 (M – $COOCH_3$), 156 (M – $CH_2NHCO(CH_2)_2CHCOOCH_3$), 144 (M - $NHCO(CH_2)_2CHCOOCH_3$), 127 (M – $CH_3(CH_2)_{11}N$); elemental analysis: calculated (%) for $C_{24}H_{45}NO_3$ (395.63): C 72.86, H 11.46 , N 3.54 , found: C 72.53, H 11.64, N 3.36.

Methyl 1-dodecylpyrrolidine-3-carboxylate (**5**); liquid at RT; Retention factor (Rf = 0.17, 100% AcOEt); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.66 (s, 3H), 3.02 (dd, J(H,H)=16, 8 Hz, 1H), 2.91 (dd, J(H,H) = 10, 8 Hz, 1H), 2.70 (dd, J(H,H) = 14, 8 Hz, 1H), 2.59 (dd, J(H,H) = 10, 8 Hz, 1H), 2.48-2.34 (m, 3H), 2.09-2.03 (m, 2H), 1.48-1.45 (m, 2H), 1.24-1.22 (m, 18H), 0.84 (t, 3J(H,H) = 8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.37, 56.66, 56.15, 53.84, 51.84, 41.79, 31.86, 29.60, 29.57, 29.55, 29.51, 29.50, 29.29, 28.65, 27.57, 27.54, 22.63, 14.06; GC-MS rt 23.7 min, m/z (EI) 298 (M +1), 282 (M – CH_3), 266 (M – OCH_3), 238 (M – $COOCH_3$), 212 (M – $CH_2CHCOOCH_3$), 142 (M - $NHCO(CH_2)_2CHCOOCH_3$); elemental analysis: calculated (%) for $C_{18}H_{35}NO_2$ (297.48): C 72.68, H 11.86, N 4.71, found: C 72.74, H 11.96, N 4.77.

Methyl 1-octadecylpyrrolidine-3-carboxylate (**6**); liquid at RT; Retention factor (Rf = 0.41, AcOEt : MeOH = 9:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.67 = (s, 3H), 3.04 (dd, J(H,H) = 16, 8 Hz, 1H), 2.94 (dd, J(H,H) = 10, 8 Hz, 1H), 2.74 (dd, J(H,H) = 16, 8 Hz, 1H), 2.63 (dd, J(H,H) = 16, 8 Hz, 1H), 2.50-2.37 (m, 3H), 2.12-2.06 (m, 2H), 1.50-1.47 (m, 2H), 1.25-1.23 (m, 30H), 0.86 (t, J(H,H) = 8 Hz, 3H);^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.36, 56.67, 56.19, 53.87, 51.90, 41.82, 31.90, 29.67, 29.64, 29.59, 29.54, 29.52, 29.34, 28.64, 27.59, 27.56, 22.67, 14.10; GC-MS rt 27.4 min, m/z (EI) 382 (M +1), 366 (M – CH_3), 350 (M – OCH_3), 338 (M – $COOCH_3$), 322 (M – CH_2COOCH_3), 198 (M – $(CH_2)_4NH(CH2)_3CHCH_2OH$), 142(M – $CH_3(CH_2)_{16}$); elemental analysis: calculated (%) for $C_{24}H_{47}NO_2$ (381.64): C 75.53, H 12.41, N 3.67, found: C 75.86, H 12.27, N 3.40.

(1-Dodecylpyrrolidin-3-yl)methanol (**7**); m.p. 45-47 °C; Retention factor (Rf = 0.22, AcOEt : MeOH = 8:2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.69 (dd, J(H,H) = 12, 4 Hz, 1H), 3.62 (dd, J(H,H) = 10, 4 Hz, 1H), 3.32-3.21 (m, 2H), 3.13-3.07 (m, 1H), 2.92-2.88 (m, 2H), 2.68-2.61 (m, 1H), 2.21-2.12 (m, 1H), 1.96-1.88 (m, 1H), 1.80-1.72 (m, 2H), 1.28-1.21 (m, 20), 0.85 (t, J(H,H)=8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 63.20, 56.19, 55.71, 53.69, 38.96, 31.83, 29.53, 29.44, 29.35, 29.26, 29.04, 26.84, 26.28, 26.00, 22.61, 14.05; ESI-MS positive scan (cone 30 V): m/z (%): 270.49 (100) [M+]; GC-MS rt 22.6 min, m/z (EI) 341 ((M-1) + $Si(CH_3)_3$), 326 ((M-1) + $Si(CH_3)_2$), 312 ((M-1) + $SiCH_3$), 270 (M+1), 186 (M -$CO(CH_2)_2CHCH_2OH$), 143 (M – $(CH_2)_2NH(CH_2)_3CHCH_2OH$); elemental analysis: calculated (%) for $C_{17}H_{35}NO$ (269.47): C 75.77 , H 13.09, N 5.2, found: C 76.10, H 13.33, N 5.2.

(1-Octadecylpyrrolidin-3-yl)methanol (**8**); m.p. 58-62 °C; Retention factor (Rf = 0.35, AcOEt : MeOH = 7:3); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.54 (dd, J(H,H) = 12, 8 Hz, 1H), 3.46 (dd, J(H,H) = 8, 4 Hz, 1H), 2.92-2.86 (m, 2H), 2.79-2.72 (m, 1H), 2.63-2.59 (m, 2H), 2.47-2.39 (m, 1H), 2.02-1.94 (m, 1H), 1.72-1.64 (m, 1H), 1.54-1.46 (m, 2H), 1.15-1.12 (m, 32H), 0.77 (t, J(H,H) = 8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 64.36, 56.67, 55.67, 53.58, 38.82, 31.67, 29.45, 29.40, 29.34, 29.28, 29.10, 26.99, 26.47, 26.18, 22.42, 13.85; GC-MS rt 27.4 min, m/z (EI) 426 (M + $Si(CH_3)_3$), 410 (M + $Si(CH_3)_2$), 396 ((M-1) + $SiCH_3$), 382 (M + Si), 354 (M+1), 323 (M - CHOH), 242 (M – $CH_2NH(CH_2)_3CHCH_2OH$),186 (M - $(CH_2)_6NH(CH_2)_3CHCH_2OH$), 143 (M - $(CH_2)_9NH(CH_2)_3CHCH_2OH$); elemental analysis: calculated (%) for $C_{23}H_{47}NO$ (353.63): C 78.12, H 13.4, N 3.96, found: C 78.2, H 13.77, N 4.35.

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CHAPTER 3

Green Chemistry Oriented Organic Synthesis in Water

The utilization of water as solvent presents many benefits such as improving reactivities and selectivities, simplifying the workup procedures, enabling the recycling of the catalyst and allowing mild reaction conditions and protecting-group free synthesis. In addition, exploring organic chemistry in water can lead to uncommon reactivities and selectivities supplementing the organic chemists' synthetic toolbox in organic solvents. Studying chemistry in water also allows insight to be gained into Nature's way of chemical synthesis.

3.1 Organic reactions in aqueous media

The utilization of water as solvent in organic chemistry was revisited in the 1980s by Breslow,[1] who showed that hydrophobic effects could strongly enhance the rate of several organic reactions. Previously, the limited solubility of the reactants in water was the main reason that restricted the use of aqueous media in chemical reactions. Notably, in the exploration of new ‘‘green’’ procedures, high temperature water (HTW) was found to be useful in synthetic organic conversions.[2] Under near-critical and supercritical conditions water behaves as a ‘‘pseudo-organic solvent’’[3] because its dielectric constant decreases substantially; the solvating power toward organic molecules becomes comparable with that of ethanol or acetone at room temperature, and acid or base-catalyzed reactions typically require less catalyst and often proceed rapidly.[4]

Considering the importance of environmentally friendly protocols in organic chemistry, the applications of aqueous chemistry protocols have attracted significant interest in synthetic processes.[5] Water is the solvent of choice not only from an environmental standpoint but also from an economic point of view since it is cheap, non-flammable, and abundantly available.[6] Compared with common organic solvents, the unique and unusual physical properties such as high specific heat, high surface tension, high dielectric constant, large cohesive energy density and chemical properties (ability to form hydrogen bonds and amphoteric nature) of water can in principle influence positively the reactivity and selectivity of chemical reactions (Figure 3.1).[7]

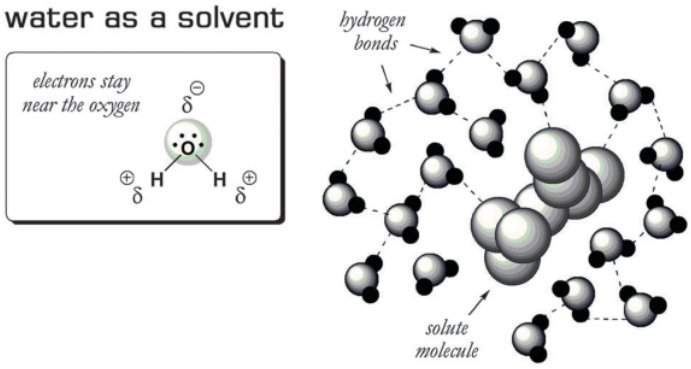

Figure 3.1. Chemical structure of water and its physical interactions with solute molecules.

The main advantages of using water are based on:

- Its flexibility to form strong hydrogen bonds that give it a significant surface tension (three times that of liquid ammonia) which could facilitate the aggregation of reactants.
- Its ability to form weak non-covalent bonds with other compounds.
- Its ability to engage in electron transport reactions as exemplified by many biological and synthetic reactions.[8]
- It provides an ideal environment for fast proton transfer processes.

In spite of the described interesting properties of water as solvent for chemical processes, water has several associated issues. Most importantly, the solubility of organic reactants is the main drawback in aqueous processes, which generally leads to immiscible and/or biphasic reaction mixtures. Several ways to solve this issue have been proposed by using surfactant combined phases, mixing with co-solvents, heating the reaction mixture, grinding the reactants or, finally, exploiting phase-transfer catalysis (PTC). Moreover, water is a readily reacting molecule. Some of reactants and products can decompose upon heating of the aqueous reaction mixture, while in other cases water sensitive reactants are simply not compatible or are unable to react in the presence of water. In the case of heterogeneously catalyzed protocols, aqueous phases require stable and water tolerant catalysts which need to be designed to work under these conditions.[9] Formation of unwanted side products is also a major drawback of the utilization of water in organic synthesis. However, some of these issues have been addressed and solved by designing protocols based on the use of microwaves, ultrasound or pressure reactors, and using other benign (co)solvents. Very recently, water-promoted reactions were classified by Butler and Coyne as *in-water* or *on-water* reactions, according to the associated experimental conditions.[10]

3.1.1 *On-water* organic reactions

Water is considered a green solvent for disparate chemical and biological reactions. It commonly agreed that reactants should be soluble in solvents for the successful performance of reactions. This concept completely changed with the earlier research work on Diels–Alder reactions, the first reports on the use of water as solvent.[1a] Subsequently, the advancements in studying the existence of hydrophobic effect in organic synthesis are mainly responsible for the emerging interest in water as a solvent.[11]

Recently, this concept was revisited by Sharpless and co-workers with some representative reactions where water insoluble reactants are converted to products in high yields; the reaction mixture is usually stirred vigorously in water for a short period.[12] The representative examples included cycloadditions, such as classic Diels–Alder reactions, as well as nucleophilic ring-opening of epoxides and aromatic Claisen rearrangements. Since the reactants were highly insoluble in water, the reactions were described as being *on-water*. Due to the aforementioned versatile and unique properties of water, rates and selectivities of pericyclic reactions under on-water conditions can be improved, as well as in a series of related organic transformations in the presence and/or absence of catalysts.[13]

Nowadays, *on-water* reactions refer to the remarkable phenomenon of substantial rate accelerations, when insoluble reactants are stirred in aqueous suspensions.[14] The water surface itself has been proposed as a catalyst in such reactions, but a clear rationalization for the *on-water* effect is still not available.

Jung and Marcus proposed a kinetic model[15] and compared the rate of the reaction for neat, surface and aqueous homogeneous reactions with experimental data. According to their theory, the free OH groups in the case of *on-water* catalysis are better promoters of organic reactions when compared to ‘‘*in-water* conditions’’, but additional validation of the reaction mechanisms with experimental data is required.

A summary of these molecular interpretations is depicted in Figure 3.2 and a range of selected examples of these acceleration effects will be highlighted in subsequent sections. According to the Jung and Marcus model, to apprehend the *on-water* chemistry it is essential to understand the singular pathway that occurs at the water-oil phase boundary where hydrogen-bonding interactions that utilize free OH groups of interfacial water molecules are facilitated.

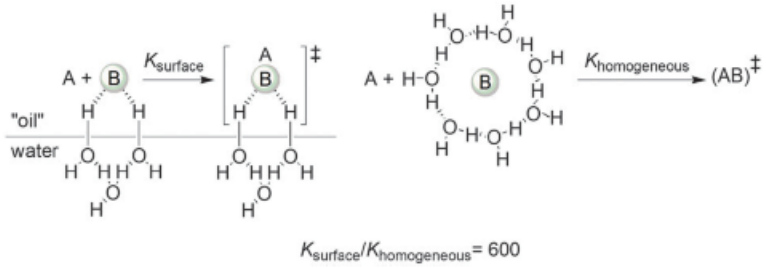

Figure 3.2. *On-water* catalysis in comparison with surface and aqueous homogeneous conditions.

3.1.2 *In-water* organic reactions

Water can be a better solvent to perform catalyst-free organic reactions. Currently, organic reactions that are carried out in water are classified as *on-water* or *in-water*, depending on the solubility of reactants. According to Breslow, *in-water*, the organic molecules are forced to form aggregates in order to decrease the exposed organic surface area.[1b] Due to these aggregates, holes are formed in the cluster structure of liquid water and the bulk water molecules surround or hydrate the aggregates.[10] In the final layer of the hydration shell, as the bulk water molecules approach the surface of small aggregates their H-bond links run laterally along the hydrophobic surface.[16] This effect is known as the ‘‘*Breslow hydrophobic effect*’’. With large hydrophobic surfaces some dangling hydrogen bond (OH-free) groups are orientated toward the barrier to maximize the packing density of the molecule.[17]

In the last few decades *in-water* reactions have been studied in detail,[18] the main characteristics being: (a) hydrophobicity, which speeds up reactions; (b) hydrogen bonding, with impact on reactants and transition states which may or may not favour the hydrophobic effect; and (c) water polarity, which may again increase or decrease the reaction rates.

3.2 Catalysis in micellar media

Concepts such as the hydrophobic effect and the donor–acceptor hydrogen bonding ability of water have allowed to rationalize the enhanced productivity as well as regio-, diastereo- and enantioselectivity in several catalytic reactions.[19] The above mentioned advantages are some of the motivations that prompt scientists to deeply explore the use of water as a solvent in organic synthesis. As far as catalysis is concerned, water as a solvent provides an additional advantage of possible catalyst recycling when products are extracted with a water immiscible organic solvent leaving the catalyst dissolved in water.

However, the need for product extraction from aqueous phases poses some critical issues about the green character of catalysis in water, such as (i) the volume of organic solvent used in the workup often exceeds the total volume of water used in the reaction by factors of up to 30-fold and this operation is of major concern for the overall green character of the system and (ii) the resulting water solution is essentially a water stream contaminated by organics that is subject to strict regulations and purified usually by stripping under vacuum or adsorption of activated carbon.[20] From this point of view the green character of aqueous media in replacing organic solvents while using an organic solvent to extract products from water is questionable, but as long as water provides extra performance in terms of activity and selectivity, the concerns about the use of limited amounts of traditional solvents at the end of the reaction are at least mitigated and in the cases of successful recycling, reduced to a minimum.

Once again, Nature provides inspiration with enzymes as highly active water soluble catalysts operating within cells. In these systems weak intermolecular interactions that are the toolbox of supramolecular chemistry play a pivotal role. The supramolecular viewpoint is helpful in rationalizing enzyme catalysis and this is testified by the emerging interest in supramolecular catalysis as the contact point between supramolecular chemistry and traditional homogeneous catalysis. Development of artificial enzyme models mimicking natural enzymes is a promising and active field that has been pursued by researchers for several decades.[21]

Enzymes are macromolecular catalysts while traditional homogeneous catalysts are orders of magnitude smaller and can at most mimic the behaviour of the enzyme active site without the extra properties induced by the surrounding protein. Therefore, the simplest approach to mimic some of the features of enzymes consists of exploiting self-assembling units that generate highly ordered structures capable of surrounding the catalyst. This ensures the formation of nano-metric environments that, similarly to enzymes, can accommodate substrates, accelerate the reaction and impart peculiar selectivities on both sides of the reaction, i.e. reagents and products.[22]

The marriage between supramolecular chemistry and homogeneous catalysis led to the proposal of a number of supramolecular artificial enzymes based on various unimolecular building blocks (like macrocycles, cyclodextrins, calixarenes, cyclophanes, crown ethers, cavitands, capsules, molecular

cages and others), and self-assembled nanometre sized objects (metal–ligand or hydrogen bonded capsules, micelles, vesicles, nanoparticles, nanotubes and nano-gels).[23] The ultimate goal of such systems consists of mimicking biosynthesis and catalysis even in total synthesis, emulating enzymatic cascade reactions.[24]

3.2.1 Micelles: structure and properties

Surfactants as amphiphilic molecules (Figure 3.3) in the presence of water and immiscible organic species tend to mediate between the two phases. If water is present in a large amount the hydrophobic effect drives the formation of spontaneous micellar aggregates in solution when the surfactant is present above a certain minimum concentration (CMC, critical micelle concentration). The nanoscale assemblies formed by aggregation of about 50–100 monomers are in thermodynamic equilibrium where monomers rapidly exchange among aggregates. For example, the typical lifetime of a surfactant micelle is on the order of 10^{-3}–10^{-2} seconds.[25]

The use of surfactants under micellar conditions represents one of the simplest methods to achieve catalysis in water since surfactants are in most cases very economical thanks to their extensive everyday use in detergency. As recently pointed out by Sorrenti,[26] micellar environments are not just a soapy version of homogeneous catalysis, but micelles behave much more as nano-reactors characterized by unique features.

Most of the commercially available surfactants are derived from petroleum feedstock. In recent years some classes of bio-surfactants have emerged where the amphiphilic molecule presents biological functionalities. Examples are known based on glycolipids, lipopeptides, phospholipids, fatty acids, and neutral lipids. In most cases they are anionic or neutral with the hydrophobic part of the molecule based on long-chain fatty acids, hydroxyl fatty acids or α-alkyl-β-hydroxy fatty acids and the hydrophilic portion based on carbohydrates, amino acids, cyclic peptides, phosphates, carboxylic acids or alcohols.[27] Bio-surfactants, thanks to their self-assembling properties,[28] found interesting application directly in the environment,[29] or heavy metal or organic contaminant removal such as oil removal from contaminated soil or for bioremediation enhancement. Their extension as reaction media for chemical transformations is still an un-investigated topic; the auspice is that in the near future their peculiar properties, in particular the presence of several enantiomerically pure bio-surfactants, will spur their employment for catalytic applications as alternative more environmentally friendly media. Similar to enzymes, micelles are characterized by a hydrophobic core, shielded from the contact with water, and a hydrophilic surface where the hydrophilic groups remain exposed to water ensuring solubility. Water molecules surround the polar external surface of the aggregate and their behaviour and properties are rather different from water molecules in the bulk.[30] The type of aggregate formed is a function of several variables: (i) the molecular structure of the amphiphile, (ii) the proportion between hydrophilic and hydrophobic parts, (iii) the geometry of the molecule and (iv) the experimental conditions in which they are used such as temperature, pH and ionic strength.[31]

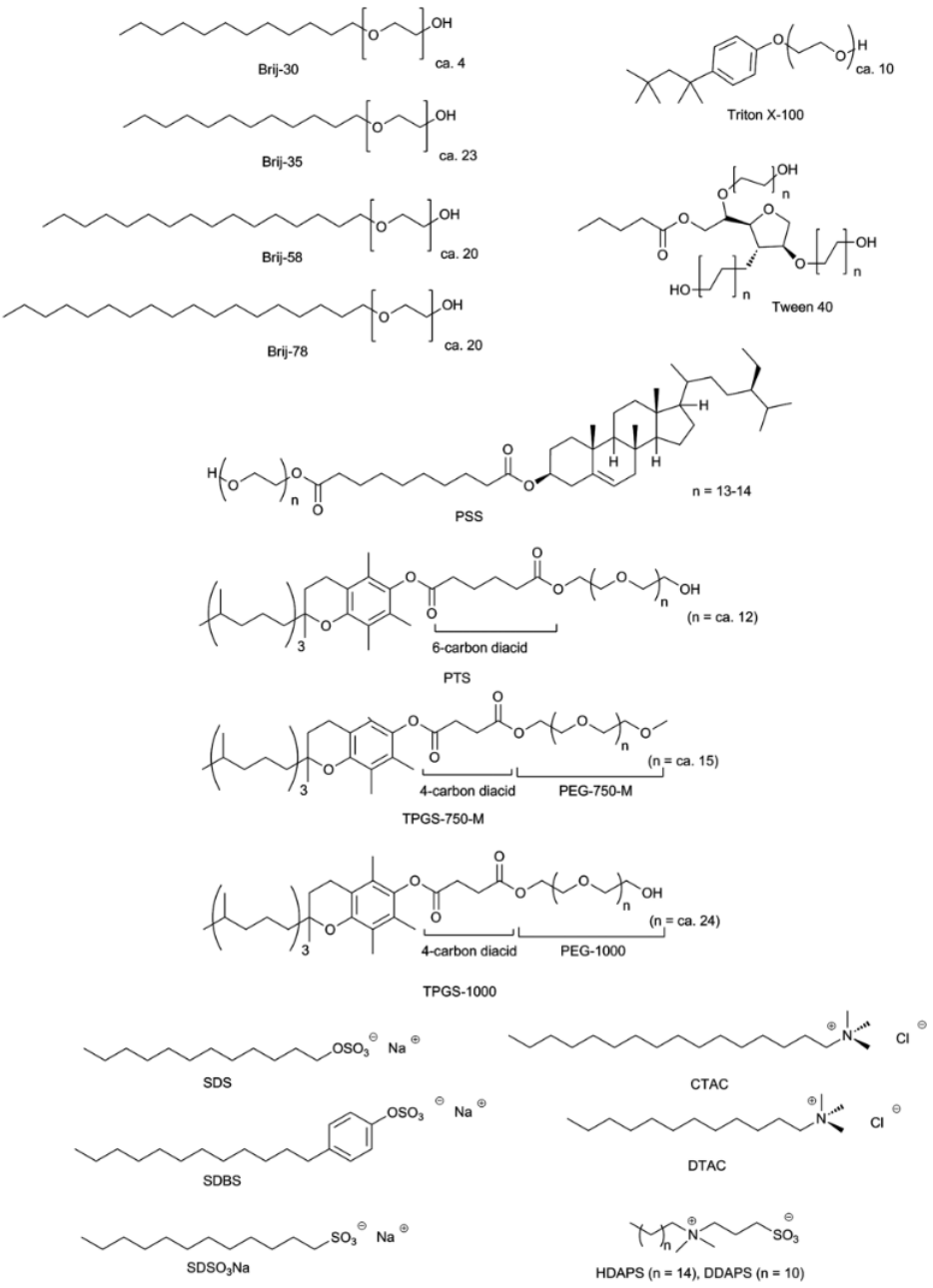

Figure 3.3. Structures of some commercially available surfactants.

The effect of concentration is extremely important since possible aggregates are initially typically spherical micelles, but as soon as the concentration increases also ellipsoidal micelles, rods, hexagonal liquid crystal phase (LC, hexagonal arrangement of long cylinders), lamellar LC phase and, eventually, reverse phases are possible. In the presence of large amounts of substrates, usually liquids, to favour their close contact with water and the surfactant, micro-emulsions are obtained and also under these conditions, enhancement of catalytic activity and selectivity has been observed.

3.2.2 Micellar effects

Early papers on the topic of micellar catalysis date back to the late 1970s describing catalysis directly performed by the supramolecular aggregates.[32] Since that time this area has witnessed a growing interest demonstrated by the periodical update provided on some specific aspects of the topic.[33] Depending on the surfactant employed, micelles can be either charged or neutral with size and polar properties encompassing a wide range.

From a certain point of view micelles behave like enzymes, isolating species from the bulk solvent, playing several roles at a time like improving solubilisation of organic reagents in water, favouring compartmentalization of reagents with enhancement of the local concentration and reactivity, imparting unique chemo-, regio- and stereoselectivities. A limitation of micellar catalysis is related to the amounts of substrates that can be loaded into the micelles, usually lower than in common organic solvents, although the higher selectivities often observed with micelles can partially compensate the disadvantage of working in diluted media. Since solubilisation of the organic reagents occurs predominantly within micelles and not in the entire volume of the liquid phase, the local concentration may be higher even if the overall concentration of substrates typical for catalysis in the entire micellar medium is usually smaller than that possible in traditional organic solvents and usually falls in the range 10^{-1}–10^{-3} M. It is also worth noting that often the concentrations of surfactant used are much higher than the CMC and micro-emulsion conditions are present. Under these conditions, the loading of substrates in the medium can be much higher than previously described.

Organic species added to micellar media are distributed between bulk water and micelles depending on their polarity, charge and dimension. Apolar substrates that are almost exclusively hosted within micelles experience a local concentration in the supramolecular aggregates some orders of magnitudes higher than that calculated considering the entire volume of solution. This is one of the main advantages of micelles, again a consequence of the hydrophobic effect. Moreover, charged micelles tend to concentrate species of opposite charge on their surface. Therefore, in cationic micelles the surface local pH is slightly more basic than in the bulk solution, and the opposite is observed for anionic micelles.[34]

Similarly, intrinsically water insoluble charged metal species can be concentrated and dissolved in micellar media thanks to ionic interactions with micelles of opposite charge. Like in metallo-enzymes non-covalent interactions in the second coordination sphere[35] play a significant role in determining the activity and selectivity. Thus micellar catalysis represents one of the simplest methods to combine easy metal catalyst dissolution in close contact with apolar or charged secondary interactions thus providing suitable model complexes with a functional second coordination sphere. The use of water as a solvent opens the way to biphasic extraction of products and recycle of the catalyst. This is possible if the catalyst remains confined in the micellar aggregates during product removal. In the best cases, the product is insoluble and can be filtered off from the reaction mixture, but more often it is extracted with the aid of an organic water immiscible solvent. A frequent problem

is emulsion formation that limits the number of successful examples in the area. Moreover, the chemical nature of the extraction solvent and its amount contribute heavily to the environmental impact of the entire process. When product extraction is accomplished by adding directly in the flask a limited amount of a single organic solvent followed by removal of the organic phase, then the environmental impact of the process is greatly reduced. This was recently pointed out by Bruce Lipshutz and co-workers that underlined the extremely positive effect of the use of specific surfactants and water, with respect to traditional organic solvents, on the *E* factor of a broad series of transition-metal-catalyzed carbon–carbon and carbon–heteroatom bond formation reactions broadly employed both in industry and in the academia.[36]

These authors observed that the *E* factor drops dramatically, becoming in some cases much lower than one tenth of the original value in organic solvents, thus reaching values typical of bulk rather than fine chemicals. Moreover, the possible recycling of the micellar medium containing the catalyst further reduces the dependence on organic solvents. Since industrial fine chemical synthesis is more and more moving from old processes to new environmentally friendly processes, one of the driving forces for the future implementation of micellar catalysis in industry could certainly be the reduction of waste which is also an economic cost.

Recycling is subject to catalyst robustness as well as proper solvent choice for efficient phase separation. This point is more critical with neutral surfactants that generally have similar affinity to both water and organic solvents. Conversely, charged anionic or cationic surfactants can usually be exploited for extraction with apolar solvents like alkanes or diethyl ether as they remain in the aqueous phase.

Catalyst and surfactant interactions open a different scenario. Under the best conditions it could be possible to simply extract efficiently the product leaving the catalyst and the surfactant in the micellar medium. This occurs when the metal catalyst and surfactant are oppositely charged and the organic reagents and reaction products are rather apolar and easily removable from the micellar medium. In other cases, product isolation is much more difficult because extraction with a solvent removes partially the surfactant and the catalyst from the aqueous phase. This often occurs when neutral surfactants, neutral metal complexes or organocatalysts are used. Nevertheless, even in these cases despite a less straightforward product isolation, the use of micellar media instead of organic solvents is justified when the activity and selectivity are higher and overcome the drawbacks.

3.3 Outlook on micellar catalysis

Green chemistry is a complicated challenge. Though complete greenness may be difficult to reach, it is a goal that chemists must aim at, through the improvement of several aspects and parameters of a given reaction, from the synthesis and availability of its reactants and reagents, to the separation and purification of the product. In this context, the use of water as solvent features many benefits:

not only because water itself is innocuous, but also it can potentially improve reactivities and selectivities, simplify the workup procedures, enable the recycling of the catalyst and allow mild reaction conditions and protecting group free synthesis. In addition, development of organic chemistry in water can lead to uncommon reactivities and reverse selectivities compared to organic solvents, thus complementing the organic chemists' synthetic toolbox. Moreover, the emergence of this field is also crucial for novel applications and developments in biology and bioorganic chemistry, leading to rich research opportunities. Studying chemistry in water is also an interesting way to gain insights into the biosynthesis of natural products and then to learn how Nature does chemistry and, ultimately, to which extent we can mimic it.

Like in Nature, the ideal micellar medium working well in all cases simply does not exist. Rather, the chemical nature of the surfactant, its concentration and molar ratio are all parameters with a profound influence on the outcome of the catalytic reaction and they deserve careful optimization. A critical balance between catalyst, substrate and surfactant properties must be analyzed in detail in order to ensure high yield, selectivity and recyclability. The wide availability of surfactants and their generally low cost are definite benefits that clearly speak for their potential towards practical synthetic methods and also the possible scale up of suitable industrial productions. Micellar catalysis offers the great advantage of using catalysts already developed for use in organic media, where the tuning of subtle electronic and steric effects associated with the use of ligands has been already optimized, without the need to perturb these properties modifying the ligands to make the catalyst compatible with water. What is still largely under-investigated is a deeper look into the positioning and the interactions between the catalyst employed and the surfactant aggregates. Only with a larger interdisciplinary approach it would be possible to shed light onto these aspects of micellar catalysis thus greatly helping in understanding the reasons for improved selectivities and activities.

The development of new surfactants, with the auspice to be made with renewable sources, is one of the next challenges for micellar catalysis, together with the development of chiral micelles from economic natural sources able to impart high levels of stereocontrol possibly acting as self-assembled organocatalysts themselves or in combination with achiral metal catalysts.

The self-assembly strategy that lies at the base of micellar catalysis recently suggested the preparation of hydrophobic core–hydrophilic shell-structured heterogeneous catalysts that showed good catalytic performance in pure water opening the way to metal-supported catalysts based on the same strategy for reactions in water.[37] Catalysis with dendrimers shares similar concepts. Once again, this clearly speaks for the versatility of micelles that have the great advantage of not requiring synthetic modification of the catalytic system because self-assembly of the structure is spontaneous.

A cross-contact is possible between micellar catalysis and heterogeneous catalysis especially for the stabilization of catalytically active metal nanoparticles. A recent report on Ag nanoparticles stabilized by traditional surfactants[38] suggests the employment of surfactants and micellar conditions for tailoring the shape and properties of metal nanoparticles to be exploited in catalysis.

Reversibility is another important feature in catalysis to implement control over catalytic activity and catalyst recovery. For instance, recent findings showed that by addition of carbon dioxide it is possible to reversibly modify the aggregation properties of surfactants, as also showed by our research group.[39] It is therefore advisable that in the near future recovery of the surfactant or separation of the catalytic system from the reaction mixture would be feasible using this approach.
In summary, micellar catalysis is nowadays a well-established green alternative to traditional homogeneous catalysis in organic media and will certainly benefit new features in the coming future that will favour its larger diffusion especially in fine chemical production. In this context it is possible to attribute the results recently published by our research group, depicted in this thesis (see chapter 5).

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CORRIGENDA

List of additional references

Abstract, p. 46: “The utilization of water as solvent presents many benefits such as… Studying chemistry in water also allows insight to be gained into Nature’s way of chemical synthesis.”[i]

Paragraph 3.1, pp. 47-48: “The utilization of water as solvent in organic chemistry was revisited in the 1980s by Breslow… Very recently, water-promoted reactions were classified by Butler and Coyne as *in-water* or *on-water* reactions, according to the associated experimental conditions.”[ii]

Subparagraph 3.1.1, pp. 48-49: “Water is considered a green solvent for disparate chemical and biological reactions… to apprehend the on-water chemistry it is essential to understand the singular pathway that occurs at the water-oil phase boundary where hydrogen-bonding interactions that utilize free OH groups of interfacial water molecules are facilitated.”[iii]

Subparagraph 3.1.2, p. 49: “Water can be a better solvent to perform catalyst-free organic reactions… which may again increase or decrease the reaction rates.”[iv]

Paragraph 3.2, pp. 50-51: “Concepts such as the hydrophobic effect and the donor–acceptor hydrogen bonding ability of water have allowed to rationalize… The ultimate goal of such systems consists of mimicking biosynthesis and catalysis even in total synthesis, emulating enzymatic cascade reactions.”[v]

Subparagraph 3.2.1, pp. 51-52: “Surfactants as amphiphilic molecules (Figure 3.3) in the presence of water and immiscible organic species tend to mediate between the two phases… to favour their close contact with water and the surfactant, micro-emulsions are obtained and also under these conditions, enhancement of catalytic activity and selectivity has been observed.”[vi]

Subparagraph 3.2.2, pp. 53-54: “Early papers on the topic of micellar catalysis date back to the late 1970s describing catalysis directly performed by the supramolecular aggregates… the use of micellar media instead of organic solvents is justified when the activity and selectivity are higher and overcome the drawbacks.”[vii]

Paragraph 3.3, pp. 54-56: “Green chemistry is a complicated challenge… and will certainly benefit new features in the coming future that will favour its larger diffusion especially in fine chemical production.”[viii,ix]

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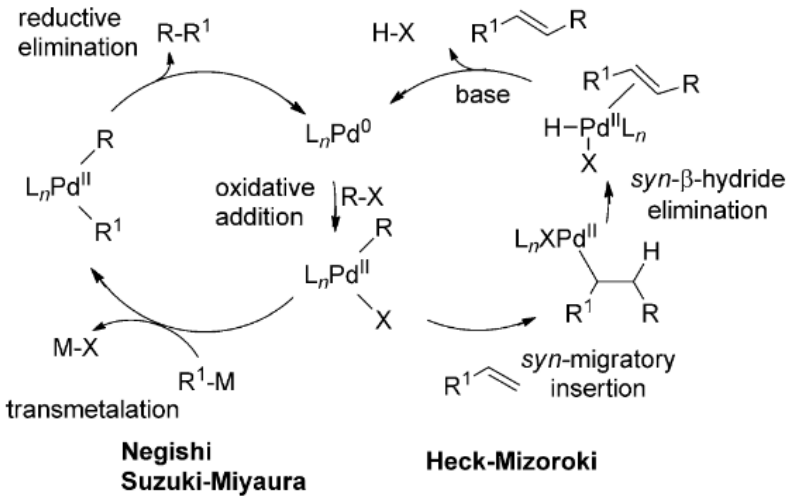
CHAPTER 4

On the Way Towards Greener Transition-Metal Catalyzed Processes

Transition-metal-catalyzed carbon–carbon bond formations are among the most massively used types of reactions in both academic and industrial contexts. As important as these reactions are to the synthetic community, such cross-couplings have a heavy price for our environment and sustainability. In particular, organic solvents are the main contributors to the waste created by the pharmaceutical and fine-chemical companies which utilize these reactions. An alternative to organic solvents in which cross-couplings are run can be found in the form of micellar catalysis, wherein nanoparticles composed of surfactants enable the same cross-couplings, albeit in water.

4.1 Pd-catalyzed cross-coupling reactions: a historical contextual perspective to the 2010 Nobel Prize

The award of the 2010 Nobel Prize in Chemistry to Richard Heck, Ei-ichi Negishi,[1] and Akira Suzuki[2] was a monumental event that was applauded by chemists worldwide, since their discoveries laid the foundations of the field of palladium-catalyzed cross-coupling reactions.
Their observations revolutionized the way chemists conceptualized and constructed molecules whilst simultaneously providing methods for previously impossible, yet highly significant, C-C bond forming processes. With time, these discoveries served to inspire chemists to develop a wide-range of additional cross-coupling reactions such as carbon–heteroatom coupling, α-arylation, direct arylation by C-H activation, and decarboxylative coupling. Researchers worldwide strove to extend, apply, and discover new variants of these powerful chemistries and, indeed, such efforts continue at an ever increasing rate today. Substantial growth in this area has taken place during the last decade in terms of publications and patents[3] with the Suzuki–Miyaura cross-coupling proving by far the most popular, followed by the Heck and Sonogashira coupling reactions. Nonetheless, all of the palladium-mediated transformations continue to enjoy attention from the academic and industrial communities. The generally accepted mechanisms for these palladium-catalyzed cross-coupling reactions are depicted in Scheme 4.1.[4]



Scheme 4.1. General catalytic cycles for Mizoroki–Heck, Negishi, and Suzuki–Miyaura reactions.

Common to both types of coupling reaction is the oxidative addition of the aryl halide (or pseudo-halide) to the catalytically active L_nPd^0 species which initiates the catalytic cycle. At this stage the processes diverge. In the Mizoroki–Heck coupling,[5] the reaction progresses by coordination of an alkene to the Pd^{II} species, followed by its *syn* migratory insertion. The regioselectivity of this insertion depends on the nature of the alkene, the catalyst, and the reaction conditions employed.

The newly generated organo-palladium species then undergoes *syn* β-hydride elimination to form the alkene product. Subsequently, base-assisted elimination of H-X from [$L_nPd(H)(X)$] occurs to regenerate the L_nPd^0 catalyst (n=2 typically).[6] Alternatively, in the Negishi and Suzuki–Miyaura reactions (and the related Corriu–Kumada, Stille, and Hiyama coupling processes), the oxidative addition is followed by trans-metalation of an organometallic species to generate a Pd^{II} intermediate bearing the two organic coupling partner fragments. Subsequent reductive elimination results in C-C bond formation with the regeneration of Pd^0 species to re-enter into the catalytic cycle.

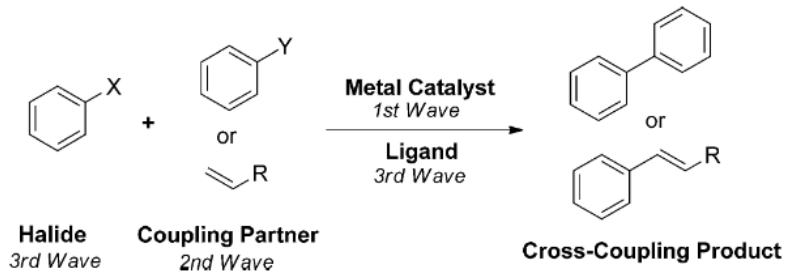
These cross-coupling processes have a rich and intriguing history, commencing in the 19th century. The 1970s was ripe with innovation in the field of transition-metal catalysis with important contributions from Corriu, Kumada, Sonogashira, Stille, Trost, Tsuji and Yamamoto. These contributions, among which stand the defining work by Heck, Negishi, and Suzuki, demonstrated that carbon atoms in all hybridization states (dominated by sp^2 carbon) undergo C-C bond forming reactions under palladium catalysis. This work ushered in a new era in organic chemistry, which stimulated dedicated research efforts worldwide towards broadening the scope of all of these reactions. As a consequence, coupling reactions under milder conditions with lower Pd loadings were developed, using more efficient catalytic systems by incorporating a plethora of ligands with different steric and electronic properties. These powerful ligands ultimately led to the discovery of new cross-coupling reactions generating other bonds (e.g. C-N, C-O, C-P, C-S, C-B).

In a broad sense, the development of coupling chemistry outlined above may be contemplated to occur over three periods or waves after the discovery of cross-coupling as a concept (Scheme 4.2):

1st wave: investigation of the metal catalysts capable of promoting these transformations in a selective fashion.

2nd wave: expansion of coupling partner scope.

3rd wave: the continuous improvement and extension of each reaction type through ligand variation, accommodating wider substrate scope, by reaction optimization and fine tuning.



Scheme 4.2. The three waves of coupling chemistry as defined by reaction component.

4.2 Pd-catalyzed cross-couplings to form C–C bonds in aqueous media

Water is an exceptionally attractive alternative solvent,[7] inasmuch it is a renewable, although limited, resource that is nontoxic, non-flammable, and relatively inexpensive. The unusual properties of water, such as its strong hydrogen bonding ability, can lead to unusual reactivity that is not seen in traditional organic solvents. Nevertheless, water is a poor solvent for most organic compounds. Although this can limit the use of water as a reaction medium, it also provides opportunities for alternative reactivity and simplified product isolation compared to organic solvents. Water is also highly reactive with many useful reagents, particularly many organometallic reagents. This can limit the types of reactions that can be performed in water. Late transition metal–carbon bonds as well as many of the common organometallic reagents used in cross-coupling reactions, such as organotin, organoboron, and organosilicon compounds, are tolerant of water, however. The primary motivations to carry out cross-coupling reactions in aqueous solvents have been economic and environmental. For the reasons described above, water is potentially safer than organic solvents. Although water is often considered an environmentally benign solvent, water contaminated with organic materials must still be treated as hazardous waste. Recycling of water and decreased solvent demand in purification may still make water a better choice economically and environmentally. Another motivation to use water is to allow for simple separation of the catalyst from the product stream. The simplified separation can significantly decrease cost and waste output for a given process. The palladium catalysts most commonly used in these reactions are expensive. The possibility to recover and reuse the palladium catalyst is critical for the application of these methodologies in large-scale production of fine chemicals. Because the catalysts are often homogeneous, separation of the metal from the product stream can also be quite challenging, particularly to the low levels required in pharmaceutical synthesis.[8] With respect to solubility in water, metal catalysts can be classified into four general types (Figure 4.1):

(a) intrinsically soluble catalysts;

(b) catalysts developed for organic media containing ligands modified with water soluble pony tails[9] that often turn out in tedious and time consuming synthetic efforts and that in some cases deeply alter the electronic and steric properties of the catalysts;

(c) organic soluble catalysts that are dissolved in water, maintaining their original integrity, thanks to the employment of supramolecular aggregates;

(d) metallo-surfactant molecules that self-assemble into micelles in solution.

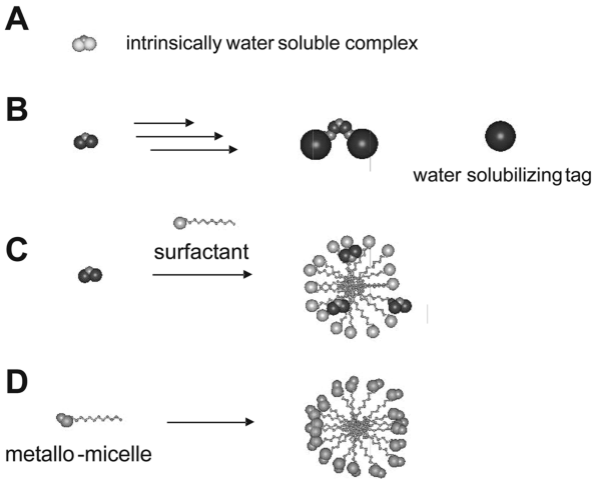


Figure 4.1. Approaches to metal catalysis in water: (A) intrinsically water soluble catalyst; (B) covalent modification of ligands with water solubilizing tags; (C) solubilization of catalysts in micelles or in hosts by means of the supramolecular hydrophobic effect. (D) Covalent metal–surfactant adduct forming metallo-micelles.

The use of a water-soluble catalyst in an aqueous–organic biphasic system helps in potentially constraining the catalyst to the aqueous phase, allowing for simple separation of the catalyst from the organic product stream.

A number of authors have shown that water can be used as the reaction medium even when using hydrophobic catalysts and substrates. In some cases, reactions carried out in this manner give superior results to traditional homogeneous organic-phase reactions. In recent years, ‘‘on-water’’ reactions of this sort have received significant attention, as it has been shown that water can have promoting effects on cross-coupling reactions of hydrophobic substrates.[10]

Even though the third approach reported in Figure 4.1C is the simplest one and provides the best advantages in terms of greening up existing processes developed to run in organic solvents, the first two approaches (Figures 4.1A and 4.1B) based on water-soluble catalysts can also benefit from the presence of micelles in aqueous media. In fact, interactions between apolar substrates dissolved within micelles and water-soluble charged catalysts are possible employing surfactants with complementary charge with respect to the catalyst, thus favouring the interaction between the two reaction partners in the double layer of the micelles (Figure 4.1C). The approach reported in Figure 4.1D was introduced some time ago[11] but, even if a complex synthetic effort is made, it provides excellent micellar catalysts especially for asymmetric reactions.

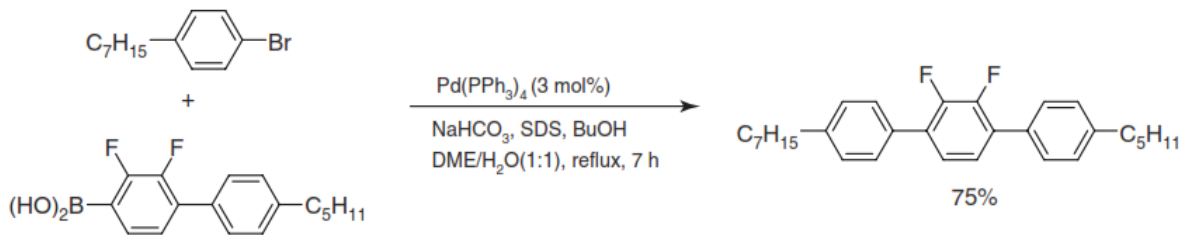
4.3 Surfactant-promoted cross-couplings

Owing to the poor solubility of typical organic substrates in water, reaction rates are often lowered when an organic co-solvent is not used. One approach to overcoming this limitation is through the use of surfactants or phase-transfer catalysts to enhance the solubility of water-insoluble reactants in the aqueous phase. A wide variety of surfactants and phase-transfer catalysts have been

employed, including tetraalkylammonium salts, anionic surfactants, and non-ionic surfactants. Surfactants and PTCs have been shown to promote cross-coupling reactions using water-soluble catalysts, hydrophobic catalysts, and heterogeneous catalysts.

The role of tetraalkylammonium salts in accelerating palladium-catalyzed cross-coupling reactions carried out in water was first demonstrated by Jeffery.[12] Low yields were obtained in the Heck coupling of phenyl iodide and methyl acrylate catalyzed by $Pd(PPh_3)_4$ in water at 50 °C. When 1 equivalent of tetrabutylammonium chloride (TBAC) was added, the yield increased from 5 to 98% under otherwise identical conditions. Nearly identical yields were obtained with the corresponding bromide (TBAB) and hydrogensulfate salts. In contrast, LiCl and KCl did not improve reaction yields significantly. Jeffery concluded that the tetrabutylammonium ion promoted the reaction by acting as a PTC. TBAB is the most commonly used PTC for promoting cross-coupling reactions in aqueous media.

Anionic surfactants such as SDS or SLS are inexpensive commodity chemicals that can be used to generate microemulsions from water organic biphasic media. The high interfacial surface area of the microemulsion promotes reactions taking place at the water/organic interface. In the synthesis of liquid crystalline compounds by $Pd(PPh_3)_4$-catalyzed Suzuki coupling, SDS was shown to significantly improve product yields (Scheme 4.3).[13] Water/toluene/*n*-BuOH (1 : 1 : 0.14) was used as the solvent system. Butanol was added as a co-surfactant in the reaction mixture. The anionic surfactant was chosen because of the basic conditions required by the Suzuki coupling.



Scheme 4.3. Synthesis of liquid crystalline compounds by $Pd(PPh_3)_4$-catalyzed Suzuki coupling.

PEG is a cheap, nontoxic surfactant that is commonly used to enhance solubility of hydrophobic compounds in water. When homogeneous catalysts are used in aqueous media, they often cannot be recycled because they cannot be easily separated from the organic product. The $Pd(DPPF)Cl_2$-catalyzed Suzuki coupling of aryl bromides could be carried out in water with good yield, but the catalyst could not be recycled.[14] Using a 20% PEG 2000 aqueous solution, the catalyst could be retained in the aqueous/PEG phase, while the biaryl product was extracted with pentane. The aqueous catalyst solution was used for three reaction cycles with the yield decreasing from 91% in the first cycle to 80% in the third. PEG-400 was used in the Pd/DABCO-catalyzed Suzuki, Stille, Sonogashira, and Heck coupling of aryl bromides and iodides.[15] In the Suzuki coupling of 4-bromoanisole, a quantitative yield was obtained with PEG-400 compared to 87% without a

surfactant. Other surfactants such as TBAB and 18-crown-6 did not significantly improve the yield compared to the reaction without surfactant.

4.3.1 Designer surfactants

In the last decade, thanks to the intuition of Lipshutz and co-workers, the nature of the surfactant started to become the subject of in depth investigations. This led to the design, synthesis, development and application of new surfactants in catalysis. In fact, while traditional surfactants have been developed focusing on the cheapness of the starting materials employed and looking at their properties as dispersing agents, recent tailored surfactants are specifically designed to exploit the nanoreactor properties of micelles. This is the case of polyoxyethanyl-α-tocopheryl sebacate (PTS, Figure 4.2) that is a non-ionic surfactant composed of racemic vitamin E as the apolar portion, sebacic acid, and PEG-600 as the hydrophilic portion. Neither PTS that actually is a pro-vitamin molecule, nor any of its three components is environmental concerning, clearly showing the green design of the molecule.[16] The PTS amphiphile is commercially available and forms nanoscale micelles in water that can accommodate hydrophobic compounds within the micelle interior.

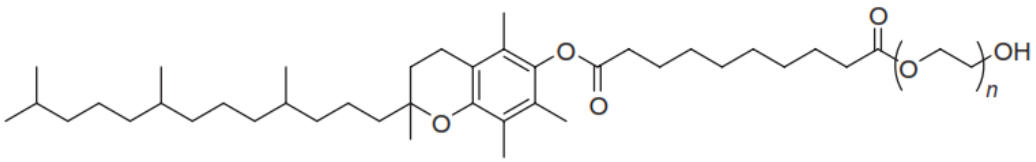
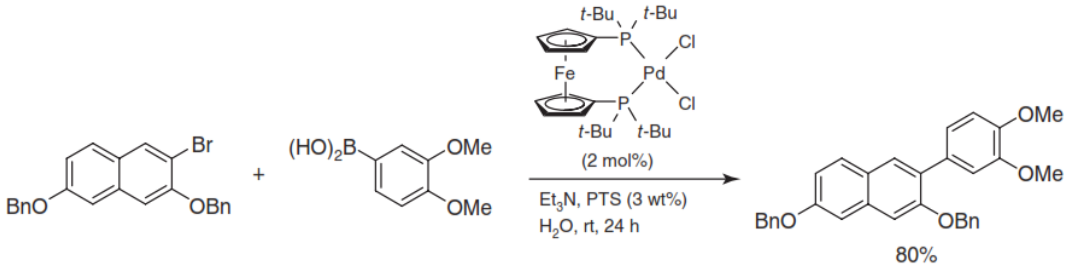


Figure 4.2. Polyoxyethanyl-α-tocopheryl sebacate (PTS).

The Lipshutz group has applied the PTS surfactant to a wide range of palladium-catalyzed cross-coupling reactions, including those that normally do not proceed in aqueous solvents. The catalysts used in these reactions are based on hydrophobic phosphines that have been successfully applied in organic-phase reactions. The hydrophobic catalyst is believed to partition into the hydrophobic core of the micelle. Hydrophobic substrates can also partition into the micelle allowing the reactions to occur at very high local concentration. The PTS/water solvent system allows Suzuki coupling of aryl and heteroaryl halides catalyzed by Pd(D*t*BPPF)Cl_2 to be carried out under mild conditions even with highly hydrophobic substrates (Scheme 4.4).[17]



Scheme 4.4. Suzuki coupling of aryl and heteroaryl halides catalyzed by Pd(D*t*BPPF)Cl_2.

An evolution of PTS is polyoxyethanyl-α-tocopheryl succinate (TPGS) that represents a second example of a designer green surfactant. It is composed of a lipophilic a-tocopherol moiety, a succinic spacer and a hydrophilic poly(ethyleneglycol) methyl ether chain (PEG-750-M) with the average molecular weight of 750 u.m.a. The proportion between lipophilic and hydrophilic portions has been tailored in order to allow a broader array of chemical reactions in water.

An example of straightforward reaction promoted by TPGS-750-M is the Miyaura borylation of aryl bromides catalyzed by $Pd(P(t\text{-}Bu)_3)_2$.

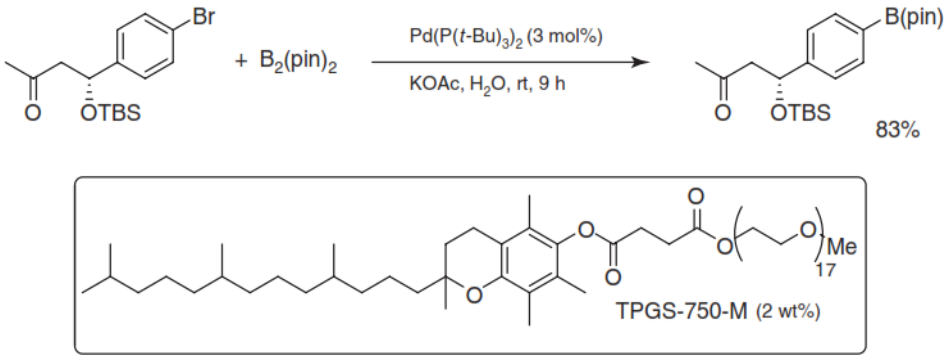


Figure 4.3. Miyaura borylation of aryl bromides catalyzed by $Pd(P(t\text{-}Bu)_3)_2$ in presence of TPGS-750-M.

These two surfactants, even if sharing similar lipophilic structures, lead to different outcomes in several catalyzed reactions. This is likely due to the different kinds and shapes of micellar aggregates formed. While PTS forms both 8–10 nm spheres and larger worm- or rod-like particles with the overall average size of 25 nm, TPGS in water provides very sharp 12–13 nm spherical micelles. In the following part contributions from the Lipshutz group concerning the application of these tailored surfactants are described.[18]

Very recently the same group developed the latest designer surfactant SPGS-550-M called “Nok” based on a β-sitosterol methoxypolyethyleneglycol succinate structure, prepared in two steps from β-sitosterol with succinic anhydride and PEG-550-M (Figure 4.4).[19]

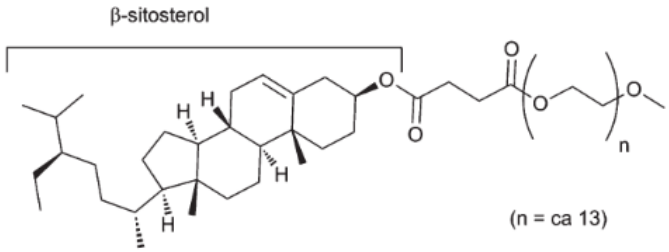


Figure 4.4. Structure of SPGS-550-M “Nok” as a new designer surfactant.

Third generation surfactants were tested in a wide series of reactions and compared with the performance observed with TPGS-750-M. In most of the cases, the new surfactant led to similar or better yields than those typically obtained with TPGS-750-M. The main advantage of SPGS-550-M consists of its much lower cost that will favour its use in micellar catalysis in the near future.
The peculiar application of these new surfactants covers several aspects of palladium-catalyzed cross-coupling reactions, such as Heck, Suzuki–Miyaura, Sonogashira and Buchwald–Hartwig aminations, specifically carried out under mild room temperature conditions in water.

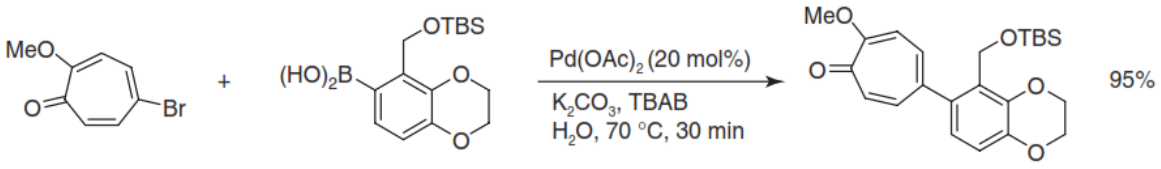
4.4 Heterogeneous catalysts in aqueous media: nanoparticle-catalyzed cross couplings

Palladium nanoparticles are readily formed under typical cross-coupling conditions, particularly in reactions performed at high temperatures. It is often unclear whether a particular Pd/ligand complex catalyzes a reaction as molecular species or through the formation of nanoparticles.[20] In some cases, the ligand may play a role in stabilizing the nanoparticles from agglomeration into larger catalytically inactive particles.

4.4.1 Unsupported Pd-nanoparticle catalysts

The use of phosphine or other strong ligands increases the cost of the catalyst system and can potentially complicate the product isolation. Early studies by Novak showed that triphenylphosphine can inhibit catalytic activity in the Suzuki coupling of highly activated aryl iodides in water/acetone.[21] Palladium acetate is an effective catalyst for the Suzuki coupling of water-soluble aryl iodides and bromides in water without supporting ligands or surfactants.[22] In the absence of ligands, the palladium nanoparticles aggregate into larger particles that precipitate from the solution as palladium black. To avoid precipitation, the substrate must react rapidly with the nanoparticles. Thus, these systems are often limited to highly reactive and water-soluble aryl iodides. Adding the base last to the reaction mixture resulted in improved catalyst performance with less reactive aryl iodides.[23] By adding the base last, nanoparticle formation occurs in the presence of the aryl iodide substrate and the catalytically active nanoparticle can enter the catalytic cycle before agglomeration occurs.
The ligand-free reactions in water show limited activity with hydrophobic substrates. Improved reaction rates can be achieved using water-miscible organic co-solvents or surfactants. Excellent yields were obtained with hydrophobic aryl bromides by using a water/acetone-mixed solvent system.[24] The anionic SDS surfactant has been used to promote palladium nanoparticle-catalyzed Suzuki,[25] Sonogashira,[26] and Heck,[27] couplings in water. The cationic CTAB surfactant was shown to give higher yields in Heck coupling of aryl iodides in water catalyzed by $Pd(OAc)_2$ than SDS, Brij 56, or TBAB.[28]

Tetraalkylammonium salts are commonly used in ligand-free systems to improve the catalyst activity and stability of the palladium nanoparticles. Badone showed that TBAB significantly increased the yield in ligand-free palladium-catalyzed Suzuki coupling of aryl bromides in water.[29] A 35% yield was obtained in water alone, whereas the yield was 95% with 1 equiv. of TBAB. An 80% yield was obtained under homogeneous conditions in DMF. This methodology was used in the synthesis of colchinoids to overcome isolation problems encountered with triphenylphosphine, which was used as a ligand.[30] Coupling of tropolone with boronic acid gave colchinoid precursor in 95% yield (Scheme 4.5).



Scheme 4.5. Coupling of tropolone with boronic acid to synthesize colchinoid precursor.

Using aryl trihydroxyborates rather than arylboronic acids allows $Pd(OAc)_2$-catalyzed Suzuki coupling of aryl bromides and iodides to be carried out at room temperature in water/TBAB.[31] Activated aryl chlorides could be coupled at 100 °C. Using microwave heating, coupling of aryl bromides could be accomplished in 5 min at 150 °C in water/TBAB.[32]

4.5 Outlook on cross-coupling reactions in aqueous media

The field of study concerning the aqueous-phase cross-coupling reactions has grown from an effort to an area receiving significant attention. The initial motivations of decreasing the cost and environmental impact of catalytic processes remain the driving forces behind current research. There is still strong interest in developing efficient and recoverable catalysts for use in pharmaceutical and other fine chemical synthetic processes. An interesting development in recent years is that water can promote cross-coupling reactions of hydrophobic substrates. Reactions carried out on water with hydrophobic substrates and catalysts can in many cases occur faster than traditional homogeneous phase reactions, while avoiding organic solvents. In this context it is possible to attribute the results recently published by our research group, depicted in this thesis (see chapter 5).

Challenges for future developments in this area will be to develop catalysts with scope and activity comparable to the best organic-phase catalytic systems. Good progress has been made in recent years in developing catalysts capable of activating aryl chlorides, but most systems remain limited to aryl iodides or bromides.

In addition, the majority of work on aqueous-phase catalysis has focused on the Suzuki and Hiyama couplings, which occur with a wide range of catalyst systems. Further development of efficient catalysts for Heck reactions, as well as carbon–heteroatom bond formation, is welcome.

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CORRIGENDA

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Abstract, p. 59: “Transition-metal-catalyzed carbon–carbon bond… wherein nanoparticles composed of surfactants enable the same cross-couplings, albeit in water.”[i]

Paragraph 4.1, pp. 60-61: “The award of the 2010 Nobel Prize in Chemistry to Richard Heck, … the continuous improvement and extension of each reaction type through ligand variation, accommodating wider substrate scope, by reaction optimization and fine tuning.”[ii]

Paragraph 4.2, pp. 62-63: “Water is an exceptionally attractive alternative solvent, inasmuch it is a renewable, although limited, resource that is nontoxic, non-flammable, and relatively inexpensive… even if a complex synthetic effort is made, it provides excellent micellar catalysts especially for asymmetric reactions.”[iii,iv]

Paragraph 4.3, pp. 63-65: “Owing to the poor solubility of typical organic substrates in water, reaction rates are often lowered when an organic co-solvent is not used… Other surfactants such as TBAB and 18-crown-6 did not significantly improve the yield compared to the reaction without surfactant.”[v]

Subparagraph 4.3.1, pp. 65-67: “In the last decade, thanks to the intuition of Lipshutz and co-workers, the nature of the surfactant started to become the subject of in depth investigations… such as Heck, Suzuki–Miyaura, Sonogashira and Buchwald–Hartwig aminations, specifically carried out under mild room temperature conditions in water.”[vi,vii]

Paragraph 4.4, pp. 67-68: “Palladium nanoparticles are readily formed under typical cross-coupling conditions, particularly in reactions performed at high temperatures… Activated aryl chlorides could be coupled at 100 °C. Using microwave heating, coupling of aryl bromides could be accomplished in 5 min at 150 °C in water/TBAB.”[viii]

Paragraph 4.5, pp. 68-69: “The field of study concerning the aqueous-phase cross-coupling reactions has grown from an effort to an area receiving significant attention… Further development of efficient catalysts for Heck reactions, as well as carbon–heteroatom bond formation, is welcome.”[ix]

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CHAPTER 5

Multicomponent Cascade Synthesis of Biaryl-Based Chalcones in Pure Water and in an Aqueous Micellar Environment

In this chapter, the challenging multicomponent cascade synthesis of biaryl-based chalcones is presented. It has been carried out in pure water and in an aqueous micellar system, overcoming existing drawbacks. The first step of the protocol is a simple Pd-catalyzed, ligand-free and aerobic Suzuki-Miyaura reaction in aqueous medium, which has proved to be extremely efficient for the coupling of aryl and heteroaryl bromides with different arylboronic acids. Consequently, the obtained intermediates undergo an in situ aldol condensation reaction, providing biaryl(hetero)chalcones in good to excellent yields. When the protocol has been applied to highly lipophilic or less reactive reagents, micellar catalysis has been required for achieving good performances. To this aim it has been successfully employed a new surfactant, obtained from renewable resources, that our research group have recently designed. Besides, thanks to this additive, the catalytic system can be repeatedly recycled without significant loss of activity.[i]

[i] This chapter is an adaptation of the original paper: Nicola Armenise,* Danilo Malferrari, Sara Ricciardulli, Paola Galletti and Emilio Tagliavini, *Eur. J. Org. Chem.* **2016**, doi: 10.1002/ejoc.201600095.

5.1 Introduction

From the environmental point of view, the large employment of solvents is highly concerning since it gives rise to toxicity, hazard and pollution issues. Moreover, solvents generally account for the major source of the wasted mass of a chemical process or a synthetic route.[1] Consequently, many efforts have been dedicated to the finding of sustainable reaction media.[2] In this context the employment of water as solvent has attracted much interest in recent years. In fact, water offers many advantages because it is a cheap, readily available, non-toxic and non-flammable solvent, thus being very attractive from both an economical and an environmental point of view.[3]

Among the organic reactions that can be conducted in water, cross-coupling[4] and aldol condensation reactions[5] play an outstanding role; moreover, these reactions can be coupled together with one-pot and sequential procedures.

The traditional multistep design of complex molecules generally involves several operations, including extraction and purification processes for each single synthetic step, leading to synthetic inefficiency and also generating large amounts of waste.

Multicomponent reactions (MCRs) allow to generate several chemical bonds in a single synthetic operation and offer notable advantages like convergence, operational simplicity, reduction in the number of workup and purification steps, minimizing therefore the generation of waste. Generally, one-pot MCRs decrease overall reaction time, affording higher chemical yields respect to usual multistep synthesis. MCRs are useful for the development of chemical libraries of potential drugs and lead compounds with high levels of molecular complexity and diversity. Therefore, the design of new MCRs in water[6] has attracted great attention, especially in the areas of drug discovery and material science.

In the literature there are a lot of examples involving Suzuki-Miyaura cross-coupling reaction followed by aldol or Knoevenagel condensation as the steps of larger synthetic strategies; these are aimed to the total synthesis of different classes of natural products, such as alkaloids, fungal metabolites and hetero-polycyclic compounds that exhibit manifold biological activities.[7]

In particular, the one-pot synthesis of biarylchalcones in aqueous medium, through the sequential Suzuki–Miyaura coupling and aldol condensation reactions, is a challenging but attractive synthetic route. Unfortunately, the poor solubility of many substrates in water, the incompatibility of some of these with different catalysts and the formation of β-arylated ketones as side product still limit the exploitation of this strategy (Figure 5.1).[8]

Chalcones are relevant natural products and they are pivotal intermediates in the synthesis of flavonoids and isoflavonoids. Because of their importance, numerous preparation procedures have been developed.[9] Chalcones exhibit a wide range of biological activities; some of them display anti-inflammatory, anti-microbial (antibacterial, antifungal), anti-malarial, anti-mitotic, antioxidant and anticancer properties.[10]

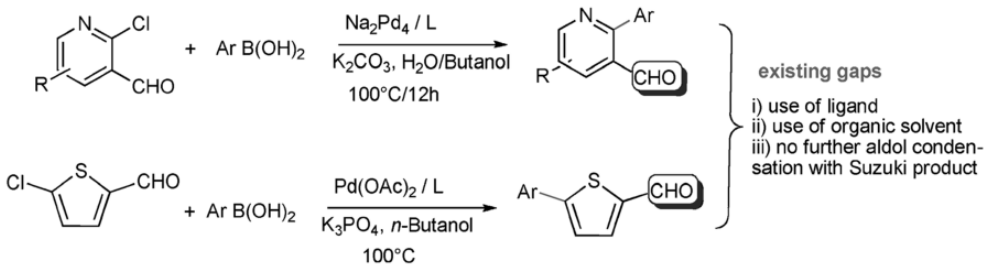


Figure 5.1. Drawbacks in the one-pot synthesis of biarylchalcones in aqueous medium.

Structurally, in chalcones two aryl groups are linked to a 2-propenone moiety and any alteration of this arrangement is known to result in loss of their biological activity, therefore the two aromatic rings have been extensively modified by appending different hydrophilic or hydrophobic substituents, obtaining a variety of biologically active chalcone-based compounds.[11] As a consequence, biarylchalcones and more complex chalcone derivatives have gained importance in the field of medicinal chemistry (Figure 5.2), although their syntheses still proceed through two distinct steps and in water/organic co-solvents mixtures as reaction media.[12]

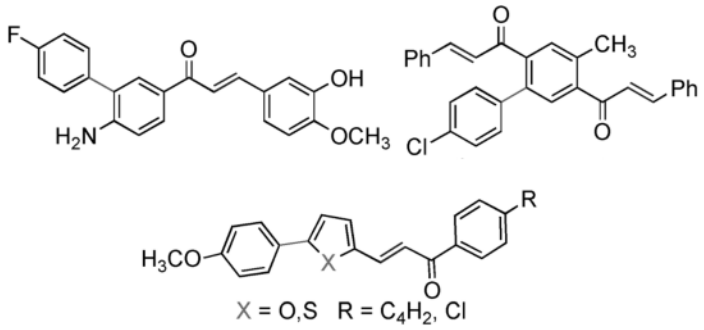


Figure 5.2. Examples of valuable biarylchalcone derivatives as anti-cancer agents.[12d]

5.2 Goal

Looking for the environmental sustainability of the synthetic processes, herein we report a highly efficient protocol aimed to perform the multicomponent cascade synthesis of biaryl(hetero)chalcones and of their functionalized derivatives, in pure water or in an aqueous micellar system, overcoming the existing drawbacks. The first step of our protocol is a simple Pd-catalyzed, ligand-free and aerobic Suzuki-Miyaura reaction in aqueous medium,[13] which has proved to be extremely efficient for the coupling of aryl and heteroaryl bromides, bearing a carbonyl moiety, with different arylboronic acids. The second step consists in the addition of the third substrate (the appropriate ketone or aldehyde) that undergoes an *in situ* aldol condensation reaction. A major limitation sometimes encountered in the just described protocol is the poor solubility of some substrates that prevented the achievement of good results.

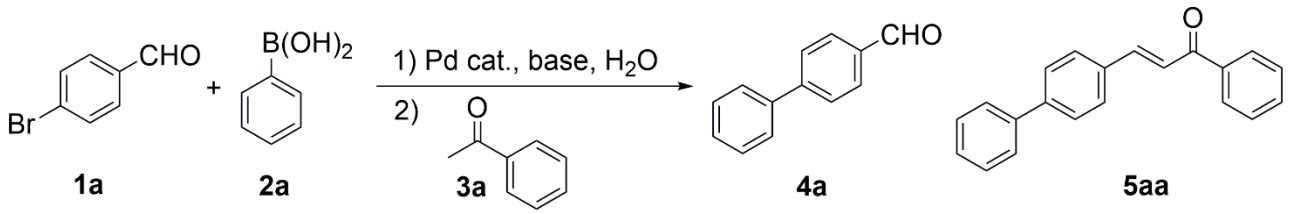
We have found an environmentally sustainable solution to this issue employing a new ionic surfactant recently developed by our group.[14] This amphiphilic compound allows the system to undergo micellar catalysis; furthermore, the catalytic system composed of Pd, base, water and surfactant has proved to be highly recyclable without significant loss of activity.

5.3 Results and discussion

5.3.1 Optimization of reaction conditions

The optimal reaction conditions were determined carrying out a set of experiments, adopting as model reaction the Suzuki cross-coupling of 4-bromobenzaldehyde (**1a**; 0.27 mmol) with phenylboronic acid (**2a**; 0.32 mmol) catalyzed by $Pd(OAc)_2$ (3 mol%) at 80 °C for 1 h in pure water (3 mL) in the presence of a base, to afford biphenyl-4-carboxaldehyde (**4a**), followed by the addition of acetophenone (**3a**; 0.30 mmol) to perform *in situ* the aldol condensation at 80 °C in 5 h, to give biarylchalcone **5aa** (see Table 5.1).

Table 5.1. Screening of bases and catalysts for the synthesis of biarylchalcone **5aa** in pure water.[a]



1a **2a** **3a** **4a** **5aa**

Entry	Catalyst	Base	Eq.	Conv. [%][b]	Yield [%][e]	
					4a	5aa
1	$Pd(OAc)_2$ (3 mol%)	Et_3N	3	100	100	0
2	$Pd(OAc)_2$ (3 mol%)	*n*-Pr_3N	3	100	100	0
3	$Pd(OAc)_2$ (3 mol%)	*n*-Bu_3N	3	100	100	0
4	$Pd(OAc)_2$ (3 mol%)	DMCHA	3	100	97	3
5	$Pd(OAc)_2$ (3 mol%)	DMCHA	6	98	98	0
6	$Pd(OAc)_2$ (3 mol%)	DMAP	3	59[c]	0	0

7	$Pd(OAc)_2$ (3 mol%)	DBU	3	100[d]	5	4
8	$Pd(OAc)_2$ (3 mol%)	Pyrrolidine	3	99	56	35
9	$Pd(OAc)_2$ (3 mol%)	K_2CO_3	3	85	82	0
10	$Pd(OAc)_2$ (3 mol%)	KOH	3	100	96	4
11	$Pd(OAc)_2$ (3 mol%)	KOH	6	100	4	88 (83)[f]
12	$Pd(OAc)_2$ (3 mol%)	KOH	9	100	2	81
13	$Pd(OAc)_2$ (1.5 mol%)	KOH	6	100	15	60
14	Pd/C (3 wt. %)	KOH	6	100	0	13
15	Pd/C (4 wt. %)	KOH	6	100	0	25

[a] Reaction conditions: 1) 4-bromobenzaldehyde (**1a**; 0.27 mmol), phenylboronic acid (**2a**; 0.32 mmol), Pd catalyst, base, H_2O (3 mL), 80 °C, 1 h; 2) acetophenone (**3a**; 0.30 mmol), 80 °C, 5 h. [b] Conversion determined by GC-MS (1,3,5-*tri*-*tert*-butylbenzene as the internal standard) is referred to **1a**. [c,d] For characterization of the crude reaction mixtures and the identification of obtained by-products, see Experimental Section. [e] Yield of product **5aa** determined by GC-MS. [f] Yield of isolated **5aa**.

Firstly, we screened different bases: tertiary amines such as Et_3N, *n*-Pr_3N, *n*-Bu_3N and N,N-dimethylcyclohexylamine (DMCHA) were very effective for promoting the Suzuki coupling reaction and we obtained the quantitative formation of the intermediate **4a**, but they were completely ineffective toward aldol condensation and we could not observe the formation of the desired product **5aa** (Table 5.1, entries 1-4), also when the amount of DMCHA was increased from 3 to 6 molar eq. (Table 5.1, entry 5). When we moved to 4-dimethylaminopyridine (DMAP) and diazabicycloundecene (DBU) only by-products formed (Table 5.1, entries 6 and 7),[15] while the secondary amine pyrrolidine performed better and the desired product **5aa** was obtained in 35% yield (Table 5.1, entry 8). We realized that strong bases were required at least for promoting the aldol condensation, thus we switched to screen some inorganic bases. K_2CO_3 (3 eq.) was completely ineffective to the aim of reaction (Table 5.1, entry 9) and using 3 eq. of KOH we obtained only 4% of **5aa** along with 96% of the intermediate **4a** (Table 5.1, entry 10). An increase in the amount of KOH to 6 eq. was however successful, affording 88% of **5aa** (Table 5.1, entry 11); further addition of KOH did not improve the yield (Table 5.1, entry 12). Although it is still not

completely clear why such excess of base is required for achieving good yield, we have consciousness that 2 eq. of KOH are consumed in the catalytic cycle of Suzuki cross-coupling reaction.[16]

Then we screened different quantities and types of Pd catalyst: the decrease in the amount of $Pd(OAc)_2$ from 3 mol% to 1.5 mol% afforded lower yield (Table 5.1, entry 13), as well as employing 3 wt. % and 4 wt. % of Pd/C (Table 5.1, entries 14 and 15). Thus we chose $Pd(OAc)_2$ (3 mol%) and KOH (6 eq.) as the optimal conditions of the synthetic protocol.

Later, we focused on improving the greenness of the work-up procedure. After extracting the crude reaction mixture with ethyl acetate, we isolated the pure product **5aa** in very good yield (83%) by means of simple recrystallization from methanol, avoiding purification by flash chromatography.

5.3.2 Screening of different aromatic ketones and additives

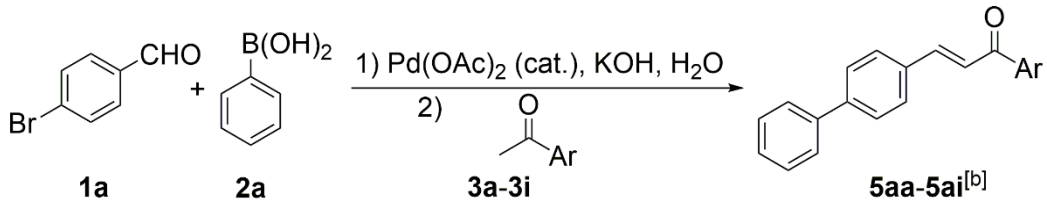
After optimization of the reaction conditions, we explored the scope and limitations of this protocol (Table 5.2). Therefore, 4-bromobenzaldehyde (**1a**) and phenylboronic acid (**2a**) were coupled in water and subsequently condensed with different aromatic ketones (**3a**-**3g**) to provide biarylchalcones **5aa**-**5ag** in various yields (65%-93%). Interestingly, several functional groups were tolerated in the substrates: 4'-hydroxy-3'-methoxyacetophenone (**3b**), 2-acetylfuran (**3f**) and 2-acetylthiophene (**3g**) successfully afforded the corresponding hetero-biarylchalcones **5ab**, **5af** and **5ag** respectively in good to excellent yields.

Sharpless *et al.* adopted the term *on-water* to describe the substantial rate acceleration that is observed when some insoluble organic reactants are stirred in aqueous suspension;[17] recently, McErlean *et al.* proposed a mechanism that explains the phenomenon of *on-water* catalysis.[18] Based on the concepts of *on-water* catalysis, we expected that in all the investigated cases the rate of aldol condensation of the intermediate **4a** with aromatic ketones could be accelerated by conducting the reaction as a heterogeneous suspension of organic droplets in water (the reaction conditions described by Sharpless *et al*. as *on-water*). On the other hand, two highly lipophilic ketones such as 2-acetonaphthone (**3h**) and *α*-tetralone (**3i**) were poorly reactive under the optimized reaction conditions and provided low yields of the expected products **5ah** and **5ai** (42% and 44%, respectively) only at higher concentration for longer reaction times. Therefore, we tested different additives to improve reaction performances of lipophilic ketones (Table 5.3). Addition of 0.5 eq. of each selected additive provided different results: we observed lower yields of **5ah**, along with larger amounts of by-products, in presence of *tetra*-*n*-butyl ammonium bromide (TBAB) and sodium dodecyl sulphate (SDS) (Table 5.3, entries 2 and 4). On the contrary, we obtained the desired **5ah** in 87% yield in presence of Triton X-100 (Table 5.3, entry 3).

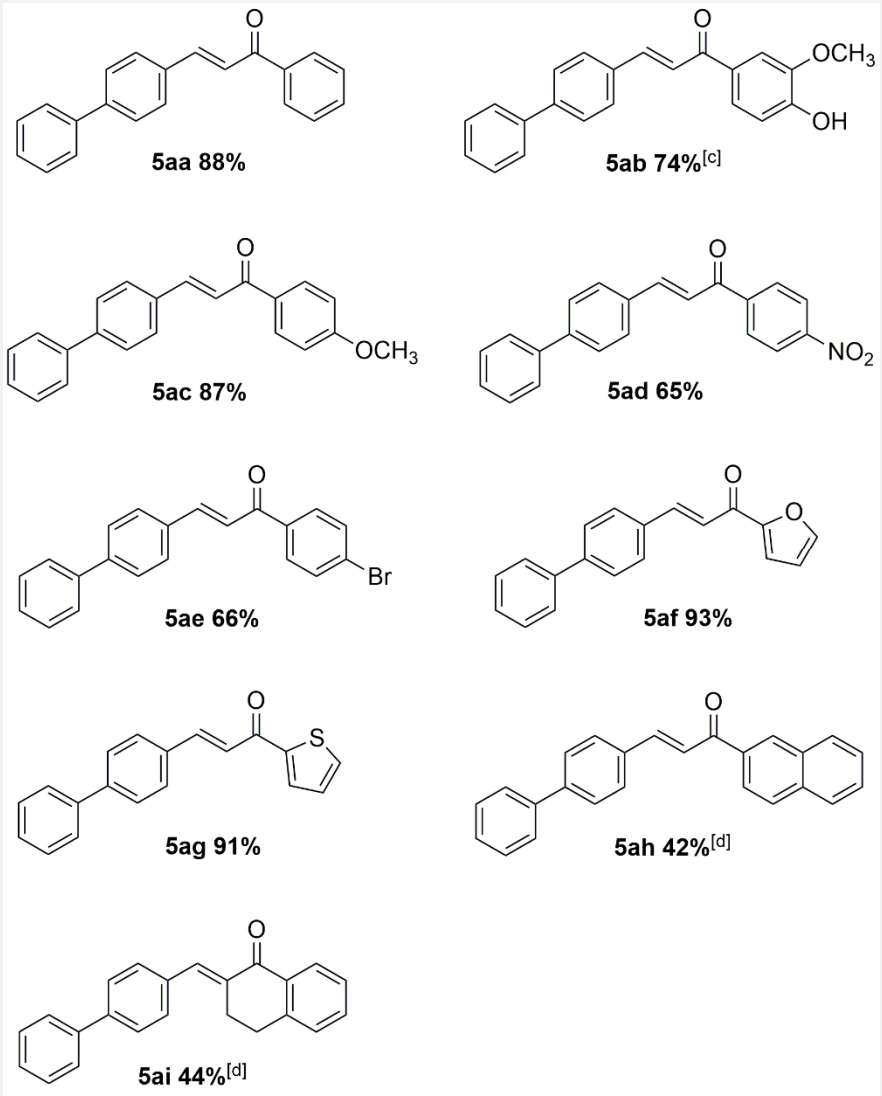
Thereafter we tested the new surfactant **C18-OPC** developed by our research group starting from itaconic acid (Scheme 5.1).[19] Given that the carboxylic acid moiety of this surfactant was

converted into carboxylate anion under basic reaction conditions, we slightly increased the amount of KOH and pleasingly we obtained **5ah** with a comparable high yield (89%) (Table 5.3, entry 5).

Table 5.2. Cascade Suzuki-aldol reaction of 4-bromobenzaldehyde and phenylboronic acid with different aromatic ketones in water.[a]

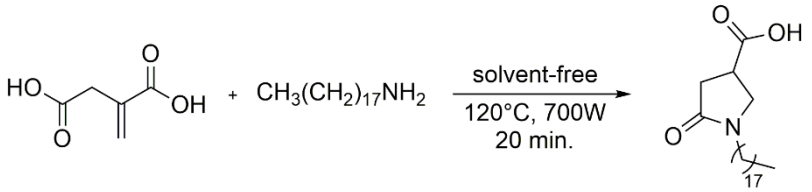


1a **2a** **3a-3i** **5aa-5ai**[b]



5aa 88% **5ab 74%**[c] **5ac 87%** **5ad 65%** **5ae 66%** **5af 93%** **5ag 91%** **5ah 42%**[d] **5ai 44%**[d]

[a] Reaction conditions: 1) 4-bromobenzaldehyde (**1a**; 0.27 mmol), phenylboronic acid (**2a**; 0.32 mmol), $Pd(OAc)_2$ (3 mol%), KOH (6 eq.), H_2O (3 mL), 80 °C, 1 h; 2) aromatic ketone (**3a-3i**; 0.30 mmol), 80 °C, 5 h. [b] Yield determined by GC-MS (internal standard). [c] KOH (7.1 eq.) was used. [d] 2 mL of H_2O were used, 15 h to perform the second step.

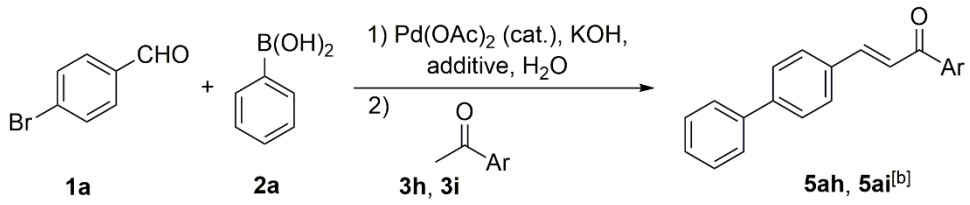


A **B** **C18-OPC**

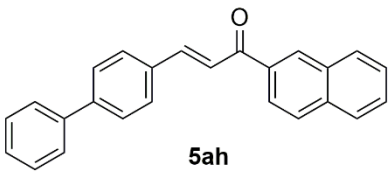
Scheme 5.1. Synthesis of surfactant **C18-OPC**.

Moreover, we studied the effect of adding **C18-OPC** only during the second synthetic step and we observed a comparable result, obtaining **5ah** in 86% yield (Table 5.3, entry 6). It means that, in the specific case of the Suzuki coupling reaction of **1a** with **2a**, the addition of **C18-OPC** exerted only a little beneficial effect on the cross-coupling step, in which smaller and less lipophilic molecules are involved. On the contrary, **C18-OPC** revealed itself to be crucial for providing a suitable reaction medium for the next aldol condensation with the bulky ketone **3h**.

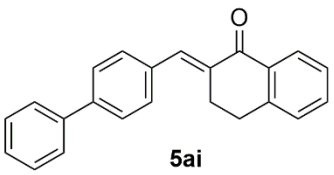
Table 5.3. Cascade Suzuki-aldol reaction of 4-bromobenzaldehyde and phenylboronic acid with lipophilic aromatic ketones in water, in presence of different additives.[a]



1a **2a** **3h**, **3i** **5ah**, **5ai**[b]



5ah



5ai

Entry	Additive	Yield [%][b]	
		5ah	**5ai**
1	/	42	44
2	TBAB	21	/
3	Triton X-100[c]	87	54
4	SDS	73	/
5	**C18-OPC**[c]	89	67
6	**C18-OPC**[c,d]	86	/

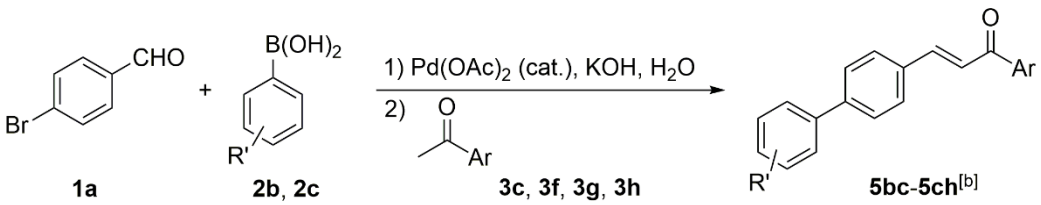
[a] Reaction conditions: 1) 4-bromobenzaldehyde (**1a**; 0.27 mmol), phenylboronic acid (**2a**; 0.32 mmol), $Pd(OAc)_2$ (3 mol%), KOH (6 eq.), additive (0.5 eq.), H_2O (3 mL), 80 °C, 1 h; 2) aromatic ketone (**3h**, **3i**; 0.30 mmol), 80 °C, 5 h. [b] Yield determined by GC-MS (internal standard). [c] KOH (6.5 eq.) was used. [d] **C18-OPC** (0.5 eq.) was added during the second step.

Encouraged by this result, we compared our surfactant with Triton X-100 also in presence of *α*-tetralone (**3i**); exploiting **C18-OPC** we obtained **5ai** in higher yield (67%) (Table 5.3, entry 5).
Subsequently, we tested the generality of the previously optimized work-up procedure. Pleasingly, after extracting the crude reaction mixtures with ethyl acetate, we were able to isolate pure products **5ab**-**5ai** without appreciable losses of yield by means of simple recrystallization from methanol, confirming the robustness of our work-up procedure.
To the best of our knowledge, no reports are available in which biaryl-based chalcone derivatives are isolated through a similar procedure, avoiding tedious and solvent consuming chromatographic purifications.

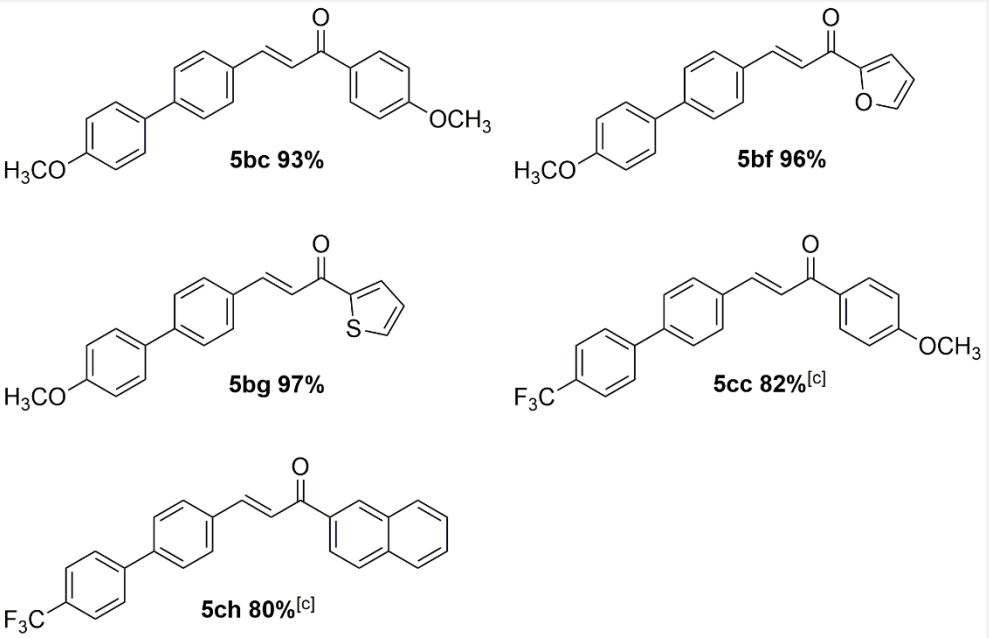
5.3.3 Screening of different arylboronic acids

Next, the influence of the electronic properties of arylboronic acid derivatives on the reaction with 4-bromobenzaldehyde was investigated carrying out the Suzuki coupling reaction of **1a** with different arylboronic acids (Table 5.4). 4-methoxyphenylboronic acid (**2b**), bearing a *para* electron-donating group, provided the desired products **5bc**-**5bg** in pure water in excellent yields.

Table 5.4. Cascade Suzuki-aldol reaction of 4-bromobenzaldehyde and arylboronic acids with different aromatic ketones in water.[a]



1a **2b**, **2c** **3c**, **3f**, **3g**, **3h** **5bc**-**5ch**[b]



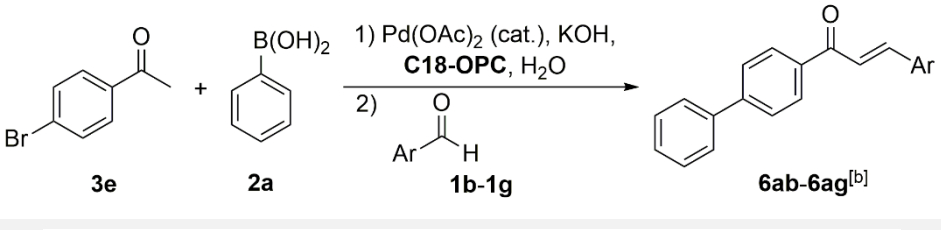
[a] Reaction conditions: 1) 4-bromobenzaldehyde (**1a**; 0.27 mmol), arylboronic acid (**2b**, **2c**; 0.32 mmol), $Pd(OAc)_2$ (3 mol%), KOH (6 eq.), H_2O (3 mL), 80 °C, 1 h; 2) aromatic ketone (**3c**, **3f**, **3g**, **3h**; 0.30 mmol), 80 °C, 5 h. [b] Yield determined by GC-MS (internal standard). [c] **C18-OPC** (0.5 eq.), KOH (6.5 eq.) were used, 2 h to perform the first step.

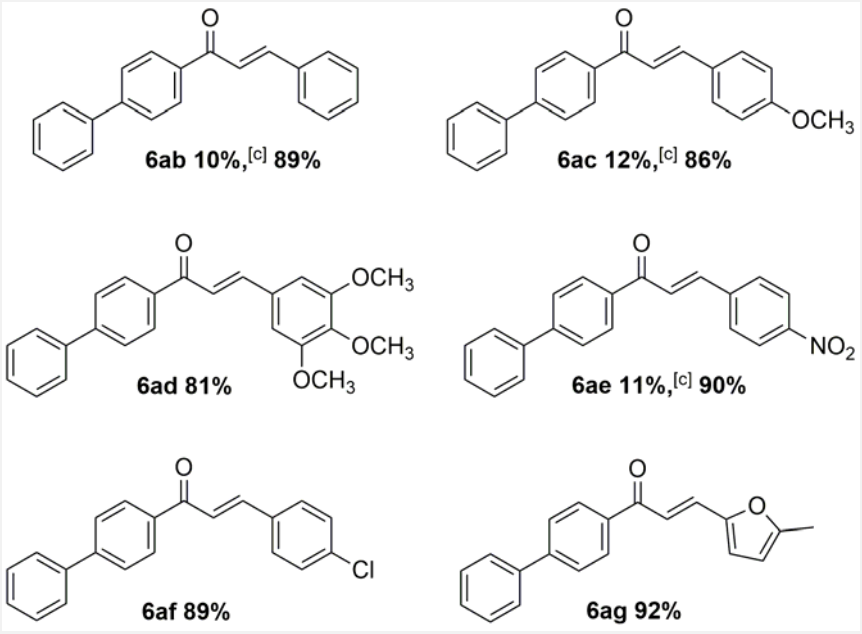
On the other hand, 4-(trifluoromethyl)phenylboronic acid (**2c**) showed a much lower reactivity in the Suzuki coupling reaction with **1a** in pure water, but we obtained the expected products **5cc** and **5ch** in high yields exploiting micellar catalysis conditions (**C18-OPC**; 0.5 eq.).

5.3.4 Suzuki coupling reaction on the ketone moiety followed by aldol condensation

To further extend the flexibility of our synthetic protocol and to synthesize new biaryl-based chalcones, we changed the halogenated partner of the Suzuki coupling reaction from 4-bromobenzaldehyde (**1a**) to 4-bromoacetophenone (**3e**) obtaining the 4-biphenyl methyl ketone able to subsequently react with various aromatic aldehydes (Table 5.5).

Table 5.5. Cascade Suzuki-aldol reaction of 4-bromoacetophenone and phenylboronic acid with different aromatic aldehydes in water.[a]





[a] Reaction conditions: 1) 4-bromoacetophenone (**3e**; 0.25 mmol), phenylboronic acid (**2a**; 0.30 mmol), $Pd(OAc)_2$ (3 mol%), KOH (6.5 eq.), **C18-OPC** (0.5 eq.), H_2O (3 mL), 80 °C, 1 h; 2) aromatic aldehyde (**1b-1g**; 0.28 mmol), 80 °C, 5 h. [b] Yield determined by GC-MS (internal standard). [c] KOH (6 eq.), pure water (3 mL) were used.

On the other hand, in this case pure water did not prove to be a suitable reaction medium both for the synthesis and for the further aldol condensation of such poorly polar intermediate ketone (final yields of **6ab**, **6ac** and **6ae** in pure water were about 10%). Therefore, micellar catalysis conditions were exploited by the addition of **C18-OPC** (0.5 eq.) providing the desired products **6ab**-**6ag** in very high to excellent yields.

To the best of our knowledge, no reports are available in which the micellar catalysis (mediated by an environmentally sustainable surfactant) is deeply investigated for synthesizing new biaryl-based chalcone derivatives and also obtaining these very promising results.

We observed that also when the micellar catalysis conditions were required we were able to take advantage of the previously optimized work-up technique, isolating pure products **6ab**-**6ag** without appreciable losses of yield.

5.3.5 Synthesis of thiophene-centered biarylchalcones

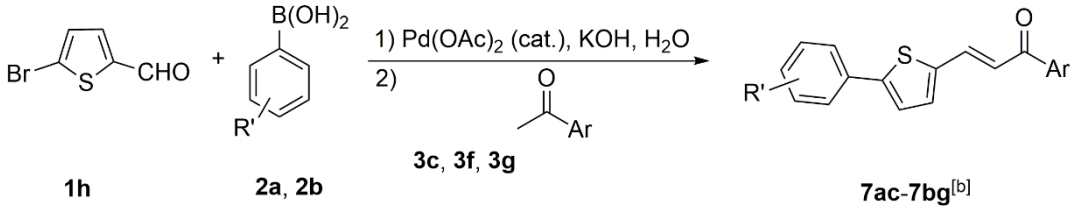
Thiophene-containing biarylchalcone is an intriguing scaffold in medicinal chemistry because thiophene nuclei are found in many natural products exhibiting promising anticancer, antibacterial and antifungal activities.[20,21] Peculiarly, a biarylchalcone containing a thiophene nucleus flanked by a phenyl ring on one side and a phenylpropenone on the other side is a scaffold that is found in specific classes of DNA-binding-anticancer drugs.[21b]

Many reports dealing with the synthesis of thiophene-containing biarylchalcones[22] through Suzuki-coupling–Wittig-olefination reactions,[22a] Vilsmeier-Haack chloroformylation–cyclization reaction,[22b] direct arylation of thiophene-containing alkenes,[22c] and Pd-catalyzed C-H olefination of (hetero)arenes with (hetero)aryl ethyl ketones[22e] are present in the literature. However, some of these methods exhibit relevant drawbacks, such as the requirement of harsh reaction conditions (phosphine reagents, hazardous organic solvents, high temperature, etc.) and very long reaction times. In particular (hetero)biaryl-carboxaldehydes,[23] the key intermediates for synthesizing (hetero)aryl-centered biarylchalcones, are commonly obtained through cross-coupling reactions that exploit various Pd catalysts containing expensive ligands, such as dialkyl(biphenyl-2-yl)phosphines[23a,b] or 1,1'-bis(diphenylphosphino)ferrocene.[23d]

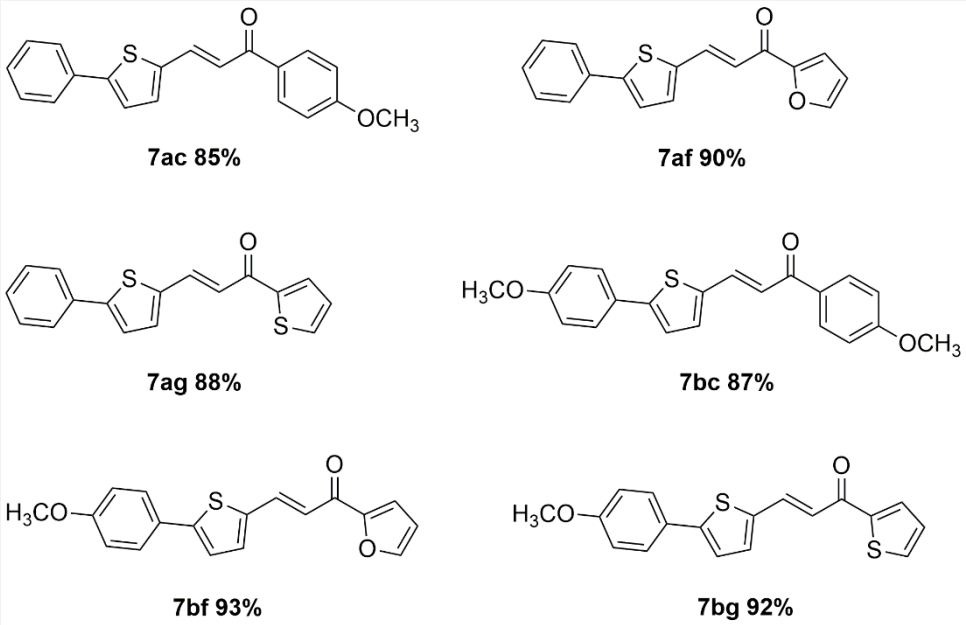
Aware of the importance of just discussed scaffolds, we tested our unprecedented synthetic protocol for achieving thiophene-centered biarylchalcones (Table 5.6). Firstly, 5-bromo-2-thiophene carboxaldehyde (**1h**) was successfully coupled with phenylboronic acid (**2a**) and subsequently condensed with selected aromatic ketones (**3c**, **3f** and **3g**), providing (hetero)biarylchalcones **7ac**-**7ag** in very high yields. Thereafter, we moved to 4-methoxyphenylboronic acid (**2b**) as the Suzuki coupling partner of **1h**, obtaining the corresponding (hetero)biarylcarboxaldehyde intermediate which condensed with selected aromatic ketones to afford the desired products **7bc**-**7bg** in very high to excellent yields.

To the best of our knowledge, no reports are available in which Suzuki coupling and aldol condensation reactions were carried out in a cascade manner, employing pure water as the only reaction medium, for the synthesis of these bisthiophene-substituted enone derivatives.

Table 5.6. Cascade Suzuki-aldol reaction of 5-bromo-2-thiophene carboxaldehyde and arylboronic acids with different aromatic ketones in water.[a]



1h **2a**, **2b** **3c**, **3f**, **3g** **7ac**-**7bg**[b]



7ac 85% **7af 90%** **7ag 88%** **7bc 87%** **7bf 93%** **7bg 92%**

[a] Reaction conditions: 1) 5-bromo-2-thiophene carboxaldehyde (**1h**; 0.26 mmol), arylboronic acid (**2a**, **2b**; 0.31 mmol), $Pd(OAc)_2$ (3 mol%), KOH (6 eq.), H_2O (3 mL), 80 °C, 1 h; 2) aromatic ketone (**3c**, **3f**, **3g**; 0.29 mmol,), 80 °C, 5 h. [b] Yield determined by GC-MS (internal standard).

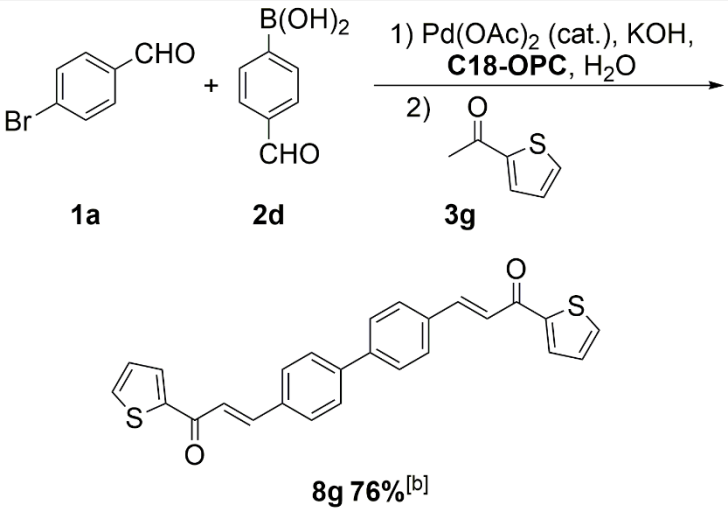
5.3.6 Synthesis of bischalcones and (bis)biarylated-chalcones

As final implementation of the synthetic strategy described above, we investigated aldol-Suzuki-aldol and Suzuki-aldol-Suzuki cascade reactions in water, in order to obtain more complex biaryl-based chalcone derivatives.

Bischalcones display a wide range of pharmacological properties,[24] including antibacterial activity,[24b,d] cytotoxic activity against a number of human cancer cell lines[24a,e,f] and anti-inflammatory activity by inhibiting NO production.[24c]

Thus, we synthesized bischalcone **8g** through a cascade aldol-Suzuki-aldol approach under micellar catalysis conditions realized by addition of **C18-OPC** (0.75 eq.). Firstly, we performed the Suzuki coupling reaction of 4-bromobenzaldehyde (**1a**) with 4-formylphenylboronic acid (**2d**) and then the double aldol condensation between the [1,1'-biphenyl]-4,4'-dicarbaldehyde intermediate and the aromatic ketone **3g** obtaining the bischalcone **8g** in good yield (Table 5.7).

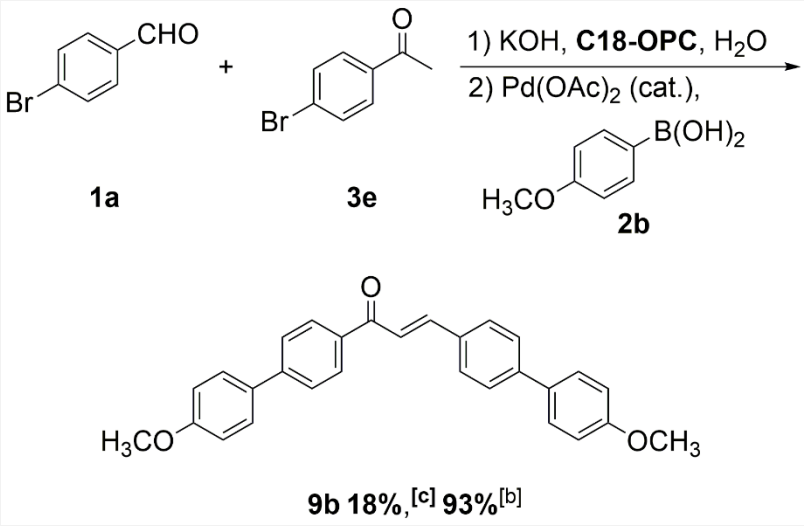
Table 5.7. Synthesis of bischalcone **8g** by cascade aldol-Suzuki-aldol reaction in water.[a]



[a] Reaction conditions: 1) 4-bromobenzaldehyde (**1a**; 0.27 mmol), 4-formylphenylboronic acid (**2d**; 0.32 mmol), $Pd(OAc)_2$ (3 mol%), KOH (10.75 eq.), **C18-OPC** (0.75 eq.), H_2O (4 mL), 80 °C, 2 h; 2) 2-acetylthiophene (**3g**; 0.59 mmol), 80 °C, 5 h. [b] Yield determined by GC-MS (internal standard).

Subsequently, we developed a synthetic strategy for accomplishing (bis)biarylated-chalcones.[25] These interesting scaffolds not only possess wide-ranging pharmacological properties, including anti-cancer, anti-microbial, analgesic and DPPH scavenging activities,[25a,c] but some of their derivatives are essential components for organic-based electroluminescent devices.[25b] However, the attempted one-pot Suzuki-aldol-Suzuki approach provided **9b** in only 18% yield (Table 5.8).

Table 5.8. Synthesis of (bis)biarylated chalcone **9b** by cascade Suzuki-aldol-Suzuki reaction in water.[a]



[a] Reaction conditions: 1) 4-bromobenzaldehyde (**1a**; 0.27 mmol), 4-bromoacetophenone (**3e**; 0.30 mmol), KOH (8.75 eq.), **C18-OPC** (0.75 eq.), H_2O (5mL), 80 °C, 2 h; 2) 4-methoxyphenylboronic acid (**2b**; 0.65 mmol), $Pd(OAc)_2$ (6 mol%), 80 °C, 2 h. [b] Yield determined by GC-MS (internal standard). [c] One-pot, 80 °C, 4 h.

On the contrary, performing first the aldol condensation between 4-bromobenzaldehyde (**1a**) and 4-bromoacetophenone (**3e**) and subsequently the double Suzuki coupling reaction on the intermediate 4,4'-dibromochalcone with 4-methoxyphenylboronic acid (**2b**) we obtained the expected product **9b** in 93% yield.

We were pleased to obtain the desired products **8g** and **9b** in good to excellent yields, respectively, confirming the robustness of our new surfactant **C18-OPC** to promote both Suzuki coupling and aldol condensation reactions aimed to the synthesis of highly functionalized biaryl-based chalcone derivatives.

5.3.7 Recycling tests of catalytic systems

Recycling of solvents, additives and catalysts is one of the main goal of sustainable chemistry. In fact, it not only reduces the overall cost of the synthetic process, but it also avoids the generation of waste and potentially polluting materials, and the requirement of new feedstocks.

To evaluate the lifetime and reusability of Pd catalyst, recycling experiments were carried out. First of all, we performed recycling tests choosing as model reaction the synthesis of **5aa** under the best conditions previously found. After the reaction was complete (starting material consumption), the product was extracted with ethyl acetate and the remaining aqueous phase was charged again with 4-bromobenzaldehyde (**1a**), phenylboronic acid (**2a**), KOH and acetophenone (**3a**). The yields of **5aa** for the first three cycles were 88%, 46% and 35%, respectively, clearly evidencing a worsening of catalyst performance. Thus, we passed to investigate if micellar catalysis conditions (water–**C18-OPC**) could provide better results in the synthesis of **6af**. After the first cycle, the catalytic system composed of Pd, **C18-OPC** and H_2O was subjected to the next run by charging with 4-bromoacetophenone (**3e**), phenylboronic acid (**2a**), KOH and 4-chlorobenzaldehyde (**1f**). Notably, we performed five cycles without significant loss in activity; the yield of each cycle is shown in Figure 5.3.

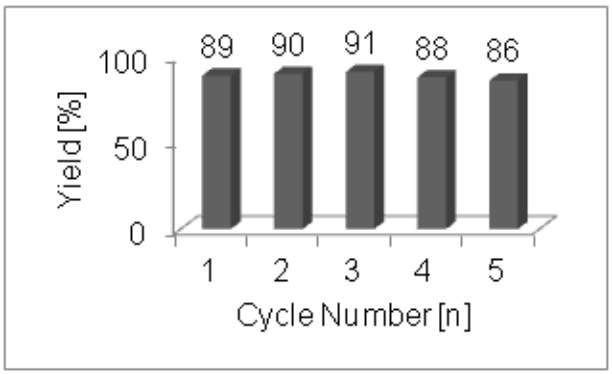


Figure 5.3. Recycle of the system Pd–**C18-OPC**–H_2O in the synthesis of biarylchalcone **6af**.

As extensively described in literature, $Pd(OAc)_2$ in aqueous phase acts as a catalyst precursor, in fact it is reduced *in situ* to catalytically active Pd(0) species both in molecular, colloidal and nanoparticles forms. Further aggregation of these species occurs in pure water to form larger and less reactive particles (Figure 5.4), eventually leading to the deposition of black Pd.[26] Addition of additives/stabilizers can prevent aggregation, significantly prolonging catalyst's lifespan and recycling.[27]

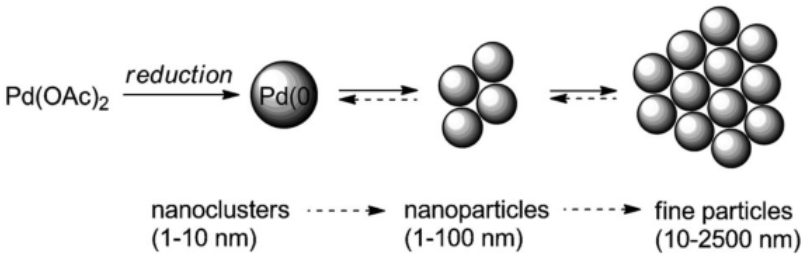


Figure 5.4. Aggregation of Pd(0) species.

Our new surfactant **C18-OPC** proved to be highly effective to this purpose, probably interacting with the *in situ* generated Pd nanoparticles through its carboxylic moiety. Careful analysis of the extraction medium allowed to exclude any appreciable loss of **C18-OPC** during the work-up of reaction; this allows to employ the whole micellar catalytic system for different cycles, as reported above (Figure 5.3).

The loss of Pd catalyst was determined by atomic absorption measurements (GFAAS) and it was found that, at the end of each synthetic cycle, the extraction solvent employed (15 mL) contained approximately 3-7 ppm of Pd (see Table 5.11 in the Experimental Section). This means that a significant amount of Pd catalyst remained into the aqueous micellar environment and it could be reused in the next cycle maintaining its high activity.

5.4 Conclusions

We have developed a highly efficient synthetic protocol for multicomponent cascade Suzuki-aldol reactions aimed to the synthesis of (hetero)biarylchalcones derivatives in water. In some cases, micellar catalysis, obtained employing the new surfactant **C18-OPC** developed by our research group upon manipulation of itaconic acid (see chapter 2 of this thesis), provided much better results. A wide range of functional groups were tolerated in the reactants and good to excellent yields were obtained under the optimized conditions. Further, this synthetic protocol was extended to the multiple construction of carbon-carbon bonds through aldol-Suzuki-aldol and Suzuki-aldol-Suzuki cascade reactions performed in micellar environment, in order to obtain more complex biarylchalcones derivatives, demonstrating the generality and robustness of the developed synthetic routes.

Besides the green reaction medium, our catalytic system showed other sustainable features such as the employment of a Pd catalyst free from phosphine ligands and the fact that no significant presence of metal or additive was found in the final product. The most important one is that the catalytic system $Pd(OAc)_2$-**C18-OPC**-H_2O could be recycled at least five times without significant loss in activity.

Finally, due to high yields and few by-products, the pure products could be isolated without a significant loss of yield by means of simple recrystallization from methanol, avoiding chromatographic separation.

We anticipate that the design of similar new catalytic systems and the development of multicomponent tandem/cascade cross-coupling reactions are in progress at our laboratory.

5.5 Experimental Section

5.5.1 General methods and techniques

NMR analyses

^{1}H, ^{13}C and ^{19}F NMR spectra were recorded with a Varian Mercury 400 spectrometer with a 5 mm probe. All chemical shifts have been quoted relative to deuterated solvent signals ($CDCl_3$), δ in ppm, J in Hz.

GC-MS analyses

GC-MS analyses were performed with a 6850 Agilent HP gas chromatograph connected to a 5975 Agilent HP quadrupole mass spectrometer. Measurement solutions were injected under splitless condition with injector temperature set at 280 °C. Analytes were separated by a HP-5 fused-silica capillary column (stationary phase poly[5% diphenyl / 95% dimethyl]siloxane, 30 m, 0.25 mm i.d., 0.25 mm film thickness), with helium as carrier gas (at constant pressure, 33 cm s^{-1} linear velocity at 200 °C).

Mass spectra were recorded under electron ionization (EI, 70eV) at a frequency of 1 scan s^{-1} within the 12-500 mz^{-1} range. The following thermal program was used: 50 °C for 5 min, then 10 °C min^{-1} up to 310 °C and hold for 10 min.

GC-MS analyses of compounds **C18-OPC** and **5ab** were done by means of silylation: 5 mg of compound were dissolved in acetonitrile (1 mL), then 0.1 mL of bis-trimethylsilyltrifluoroacetamide (BSTFA) containing 1% of trimethylchlorosilane (TMCS) and triethylamine (0.05 mL) were added. The sample was placed in an incubator at 60 °C for 20 min.

FT- IR spectra

FT-IR spectra were measured on a Bruker Alpha FT-IR spectrometer as neat films between NaCl plates and reported in cm^{-1}.

Elemental analyses

The elemental analyses of compounds were determined using an elemental analyzer (Thermo Scientific, Flash 2000, Organic Elemental Analyzer) by means of the flash combustion technique. The reported data are means of at least two replicates.

Melting point analyses

Melting point of compounds was determined by using a Büchi Melting Point B-540 analyzer.

Chromatographic techniques

Analytical thin-layer chromatography (TLC) was done using Merck 60 F_{254} silica gel plates and a UV lamp. Chromatographic purifications were done with 240-400 mesh silica gel.

Microwave assisted synthesis

Microwave assisted synthesis of **C18-OPC** was performed in a Milestone Mycrosynth oven equipped with a dual magnetron system with pyramid-shaped diffuser, 1000W maximum output power, temperature monitor and control via optical fiber up to 250 °C in the vessel.

Fluorescence emission experiments

Steady state fluorescence emission spectra of pyrene (for determination of critical micellar concentration of **C18-OPC**) were acquired with a Jasco spectrofluorometer FP-6200 equipped with a thermostated cuvette holder and a magnetic stirring device.

Conductivity measurements

Conductivity measurements for the determination of Krafft temperature of **C18-OPC** were carried out with an AMEL 160 conductivity meter.

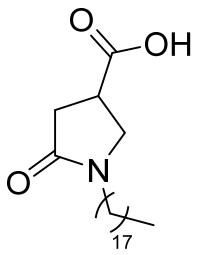
5.5.2 Materials

Unless otherwise specified, all reactions were carried out in a two-necks round-bottom flask equipped with a reflux condenser and a magnetic stirrer, in open air without nitrogen atmosphere. Reagents and solvents were purchased from commercial sources (Sigma Aldrich and Fluka) and were used as received without further purifications.

5.5.3 General procedure for the synthesis of surfactant C18-OPC

In a typical experiment itaconic acid (**A**; 3.84 mmol) and octadecylamine (**B**; 4.99 mmol) were added in a two-necks round-bottom flask equipped with a thermometer and a magnetic stirrer. The reaction mixture was heated at 120 °C and 700W for 20 min in a microwave oven under solvent-free conditions, in open air without nitrogen atmosphere. The progress of reaction was monitored by means of TLC and GC–MS. After the reaction was complete, the solid residue was purified by means of flash-chromatography on a silica gel column (cyclohexane/ethyl acetate 1:1) to give **C18-OPC** as a white solid (yield 88%).

5.5.4 Characterization data of surfactant C18-OPC



1-octadecyl-5-oxopyrrolidine-3-carboxylic acid (**C18-OPC**)

White solid; MW = 381.59; m.p. = 81-92 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ=3.65 (dd, *J*=10, 8 Hz, 1H), 3.58 (dd, *J*=12, 10 Hz, 1H), 3.30-3.20 (m, 3H), 2.77 (dd, *J* =16, 8 Hz, 1H), 2.71 (dd, *J*=16, 8 Hz, 1H), 1.52-1.48 (m, 2H), 1.31-1.23 (m, 30H), 0.86 (t, *J*=8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=176.28, 172,82, 48.97, 42.72, 35.85, 34.12, 31.90, 29.68, 29.63, 29.56, 29.50, 29.34, 29.25, 27.08, 26.88, 26.76, 22.67, 14.10; IR (neat): 2917, 2850, 1723, 1640, 1468, 1225 cm^{-1}; GC-MS: retention time = 30.8 min; GC-MS: *m/z* (EI) = 453 (MW + $Si(CH_3)_3$), 438 (MW + $Si(CH_3)_3$ – CH_3), 382 (MW), 336 (MW - COOH), 318 (MW - COOH - O), 281 (MW - COOH - CO - CH_2 - CH); elemental analysis: calculated (%) for $C_{23}H_{43}NO_3$ (381.59): C 72.39, H 11.36, N 3.67; found: C 72.31, H 11.48, N 3.96.

Table 5.9. Equilibrium surface tension (σ_{eq}), critical micellar concentration (CMC), hydrophilic-lipophilic balance (HLB) and Krafft temperature (Kt) of surfactant **C18-OPC**.

Surfactant	(σ_{eq}) [mN/m][a]	CMC [mM][b]	HLB[c]	Kt [°C][d]
C18-OPC	39	0.3	6.7	70

[a] Calculated by means of the pendant drop technique.[28] [b] Calculated by means of the ratio of pyrene vibronic peak intensities (I1/I3).[29] [c] Calculated by means of the Griffin's method.[30] [d] Calculated by means of conductance.[31]

5.5.5 General procedures for the synthesis of products 5aa-9b

Synthesis of products **5aa**-**5ag**

A mixture of 4-bromobenzaldehyde (**1a**; 0.27 mmol), phenylboronic acid (**2a**; 0.32 mmol), $Pd(OAc)_2$ (3 mol%) and KOH (6 eq.) was dissolved in H_2O (3 mL) and stirred at 80 °C for 1 h (until complete conversion of **1a**). Then aromatic ketone (**3a**-**3g**; 0.30 mmol) was added and the mixture was stirred at 80 °C for 5 h. The progress of reaction was monitored by means of TLC and GC-MS. After the reaction was complete, the mixture was allowed to cool to RT, diluted with water (2 mL) and extracted with ethyl acetate (3 x 5 mL).[32] The combined organic phases were washed with brine and dried over Na_2SO_4. After solvent removal under reduced pressure, the solid residue was purified by means of recrystallization from methanol to provide pure **5aa**-**5ag**.

Synthesis of products **5ah** and **5ai**

A mixture of 4-bromobenzaldehyde (**1a**; 0.27 mmol), phenylboronic acid (**2a**; 0.32 mmol), $Pd(OAc)_2$ (3 mol%), KOH (6.5 eq.) and **C18-OPC** (0.5 eq.) was dissolved in H_2O (3 mL) and stirred at 80 °C for 1 h (until complete conversion of **1a**). Then aromatic ketone (**3h**, **3i**; 0.30 mmol) was added and the mixture was stirred at 80 °C for 5 h. The progress of reaction was monitored by means of TLC and GC-MS. After the reaction was complete, the same work-up procedure reported before was adopted to provide pure **5ah** and **5ai**.

Synthesis of products **5bc**-**5bg**

A mixture of 4-bromobenzaldehyde (**1a**; 0.27 mmol), 4-methoxyphenylboronic acid (**2b**; 0.32 mmol), $Pd(OAc)_2$ (3 mol%) and KOH (6 eq.) was dissolved in H_2O (3 mL) and stirred at 80 °C for 1 h (until complete conversion of **1a**). Then aromatic ketone (**3c**, **3f**, **3g**; 0.30 mmol) was added and the mixture was stirred at 80 °C for 5 h. The progress of reaction was monitored by means of TLC and GC-MS. After the reaction was complete, the same work-up procedure reported before was adopted to provide pure **5bc**-**5bg**.

Synthesis of products **5cc** and **5ch**

A mixture of 4-bromobenzaldehyde (**1a**; 0.27 mmol), 4-(trifluoromethyl)phenylboronic acid (**2c**; 0.32 mmol), $Pd(OAc)_2$ (3 mol%), KOH (6.5 eq.) and **C18-OPC** (0.5 eq.) was dissolved in H_2O (3 mL) and stirred at 80 °C for 2 h (until complete conversion of **1a**). Then aromatic ketone (**3c**, **3h**; 0.30 mmol) was added and the mixture was stirred at 80 °C for 5 h. The progress of reaction was monitored by means of TLC and GC-MS. After the reaction was complete, the same work-up procedure reported before was adopted to provide pure **5cc** and **5ch**.

Synthesis of products **6ab**-**6ag**

A mixture of 4-bromoacetophenone (**3e**; 0.25 mmol), phenylboronic acid (**2a**; 0.30 mmol), $Pd(OAc)_2$ (3 mol%), KOH (6.5 eq.) and **C18-OPC** (0.5 eq.) was dissolved in H_2O (3 mL) and stirred at 80 °C for 1 h (until complete conversion of **3e**). Then aromatic aldehyde (**1b**-**1g**; 0.28 mmol) was added and the mixture was stirred at 80 °C for 5 h. The progress of reaction was monitored by means of TLC and GC-MS. After the reaction was complete, the same work-up procedure reported before was adopted to provide pure **6ab**-**6ag**.

Synthesis of compounds **7ac**-**7bg**

A mixture of 5-bromothiophene-2-carboxaldehyde (**1h**; 0.26 mmol), arylboronic acid (**2a**, **2b**; 0.31 mmol), $Pd(OAc)_2$ (3 mol%) and KOH (6 eq.) was dissolved in H_2O (3 mL) and stirred at 80 °C for 1 h (until complete conversion of **1h**). Then aromatic ketone (**3c**, **3f**, **3g**; 0.29 mmol) was added and the mixture was stirred at 80 °C for 5 h. The progress of reaction was monitored by means of TLC and GC-MS. After the reaction was complete, the same work-up procedure reported before was adopted to provide pure **7ac**-**7bg**.

Synthesis of compound **8g**

A mixture of 4-bromobenzaldehyde (**1a**; 0.27 mmol), 4-formylphenylboronic acid (**2d**; 0.32 mmol), $Pd(OAc)_2$ (3 mol%), KOH (10.75 eq.) and **C18-OPC** (0.75 eq.) was dissolved in H_2O (4 mL) and stirred at 80 °C for 2 h (until complete conversion of **1a**). Then 2-acetylthiophene (**3g**; 0.59 mmol) was added and the mixture was stirred at 80 °C for 5 h. The progress of reaction was monitored by

means of TLC and GC-MS. After the reaction was complete, the mixture was allowed to cool to RT, diluted with water (2 mL) and extracted with ethyl acetate (3 x 6 mL). The combined organic phases were washed with brine and dried over Na_2SO_4. After solvent removal under reduced pressure, the solid residue was purified by means of recrystallization from methanol to provide pure **8g**.

Synthesis of compound **9b**

A mixture of 4-bromobenzaldehyde (**1a**; 0.27 mmol), 4-bromoacetophenone (**3e**; 0.30 mmol), KOH (8.75 eq.) and **C18-OPC** (0.75 eq.) was dissolved in H_2O (5 mL) and stirred at 80 °C for 2 h (until complete conversion of **1a**). Then 4-methoxyphenylboronic acid (**2b**; 0.65 mmol) and $Pd(OAc)_2$ (6 mol%) were added and the mixture was stirred at 80 °C for 2 h. The progress of reaction was monitored by means of TLC and GC-MS. After the reaction was complete, the mixture was allowed to cool to RT, diluted with water (2 mL) and extracted with ethyl acetate (3 x 7 mL). The combined organic phases were washed with brine and dried over Na_2SO_4. After solvent removal under reduced pressure, the solid residue was purified by means of recrystallization from methanol to provide pure **9b**.

5.5.6 General procedure for recycling test of catalytic system Pd–H_2O

A mixture of 4-bromobenzaldehyde (**1a**; 0.27 mmol), phenylboronic acid (**2a**; 0.32 mmol), $Pd(OAc)_2$ (3 mol%) and KOH (6 eq.) was dissolved in H_2O (3 mL) and stirred at 80 °C for 1 h (until complete conversion of **1a**). Then acetophenone (**3a**; 0.30 mmol) was added and the mixture was stirred at 80 °C for 5 h. The progress of reaction was monitored by means of TLC and GC-MS. After the reaction was complete, the mixture was allowed to cool to RT, diluted with water (2 mL) and extracted with ethyl acetate (3 x 5 mL). The combined organic phases were washed with brine and dried over Na_2SO_4. After solvent removal under reduced pressure, the solid residue containing the product **5aa** was stored.

After the first cycle, the aqueous phase containing Pd catalyst and base was subjected to the next run by charging with 4-bromobenzaldehyde (**1a**; 0.27 mmol), phenylboronic acid (**2a**; 0.30 mmol), KOH (2 eq.) and acetophenone (**3a**; 0.30 mmol) under the same reaction conditions. At the end of each of the later runs, the same work-up procedure reported before was adopted. The solid residues obtained at the end of the three runs, each containing the product **5aa**, were separately stored for following determination of the Pd catalyst lost during the work-up procedure.

5.5.7 General procedure for recycling test of catalytic system Pd–C18-OPC–H_2O

A mixture of 4-bromoacetophenone (**3e**; 0.25 mmol), phenylboronic acid (**2a**; 0.30 mmol), $Pd(OAc)_2$ (3 mol%), KOH (6.5 eq.) and **C18-OPC** (0.5 eq.) was dissolved in H_2O (3 mL) and stirred at 80 °C for 1 h (until complete conversion of **3e**). Then 4-chlorobenzaldehyde (**1f**; 0.28 mmol) was

added and the mixture was stirred at 80 °C for 5 h. The progress of reaction was monitored by means of TLC and GC-MS. After the reaction was complete, the mixture was allowed to cool to RT, diluted with water (2 mL) and extracted with ethyl acetate (3 x 5 mL). The combined organic phases were washed with brine and dried over Na_2SO_4. After solvent removal under reduced pressure, the solid residue containing the product **6af** was stored. After the first cycle, the aqueous phase containing Pd catalyst, **C18-OPC** and base was subjected to the next run by charging with 4-bromoacetophenone (**3e**; 0.25 mmol), phenylboronic acid (**2a**; 0.30 mmol), KOH (2 eq.) and 4-chlorobenzaldehyde (**1f**; 0.28 mmol) under the same reaction conditions. At the end of each of the later runs, the same work-up procedure reported before was adopted. H_2O (0.5 mL) was added to the catalytic system in the third run. The solid residues obtained at the end of the five runs, each containing the product **6af**, were separately stored for following determination of the Pd catalyst lost during the work-up procedure.

5.5.8 Determination of Pd by graphite furnace atomic absorption spectrometry (GFAAS)

All atomic absorption measurements were carried out with Perkin Elmer Analyst 100 flame and graphite furnace (HGA 800) spectrometer equipped with a Zeeman effect background corrector, and an automatic data processor. A 20-µl volume sample solution was injected by an auto sampler. Single element hollow cathode lamp of Pd was used as radiation source.

Aqueous solutions of $Pd(OAc)_2$ and palladium samples were prepared using Milli-Ro water (resistivity 18.2 MΩ cm at 25 °C; filtered through a 0.22 µm membrane). Calibration curve for Pd quantification was done using known amounts of Pd (20, 40, 60, 80 and 100 ppb) prepared from $Pd(OAc)_2$. Samples of $Pd(OAc)_2$ were dissolved in 5 mL of Piranha solution (H_2SO_4 : H_2O_2 = 3 : 1, v/v) and stirred one night at RT before measurements. Mother solutions were diluted to appropriate amounts. Blank, calibration and samples solutions were prepared using Milli-Ro water with 2% (v/v) of HNO_3. Analytes solutions were prepared dissolving the crude material of the examined reaction in 5 mL of Piranha solution (H_2SO_4 : H_2O_2 = 3 : 1, v/v) and stirring them for one night at RT before measurements. Each measurement was carried out in at least three replicates. The reported data are mean values with the associated standard errors (SE) and they are expressed in part per million (ppm).

Table 5.10. Amount of Pd lost at the end of each synthetic cycle for the product **5aa**.

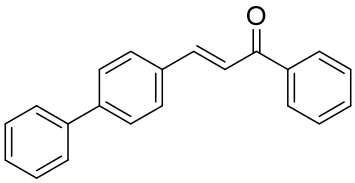
Cycle	Pd [ppm] (Mean ± SE)
1st	4.9 ± 0.1
2nd	10.1 ± 0.1
3rd	5.8 ± 0.1

Table 5.11. Amount of Pd lost at the end of each synthetic cycle for the product **6af**.

Cycle	Pd [ppm] (Mean ± SE)
1st	5.6 ± 0.2
2nd	6.9 ± 0.2
3rd	6.8 ± 0.2
4th	3.5 ± 0.2
5th	3.2 ± 0.2

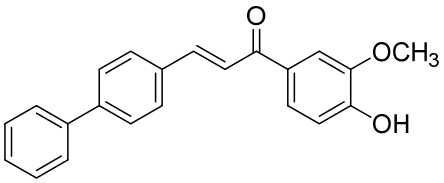
5.5.9 Characterization data of products 5aa-9b

(*E*)-3-([1,1'-biphenyl]-4-yl)-1-phenylprop-2-en-1-one **(5aa)**



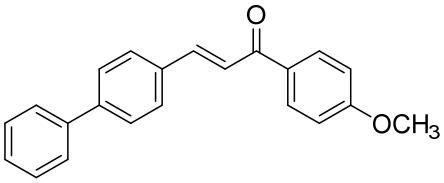
Pale yellow solid; 88% yield; m.p. 120-122 °C; ^{1}H NMR (400 MHz, $CDCl_3$): *δ*=8.03 (d, *J*=8 Hz, 2H, CH), 7.85 (d, *J*=16 Hz, 1H, CH), 7.72 (d, *J*=8 Hz, 2H, CH), 7.66-7.44 (m, 10H, CH), 7.38 (d, *J*=8 Hz, 1H, CH); ^{13}C NMR (100 MHz, $CDCl_3$): *δ*=190.36, 144.35, 143.24, 140.04, 138.23, 137.08, 133.82, 133.07, 132.77, 132.16, 130.22, 129.78, 128.98, 128.90, 128.50, 128.28, 127.61, 127.53, 127.31, 127.00, 121.82; GC-MS retention time (rt): 30.31 min; m/z (EI) (%): 285 (21%), 284 (100%), 207 (45%), 178 (79%), 152 (18%), 77 (50%); elemental analysis: calculated (%) for $C_{21}H_{16}O$ (284.35): C 88.70, H 5.67; found: C 88.48, H 5.83.

(*E*)-3-([1,1'-biphenyl]-4-yl)-1-(4-hydroxy-3-methoxyphenyl)prop-2-en-1-one **(5ab)**



Light yellow solid; 74% yield; m.p. 157-159 °C; ^{1}H NMR (400 MHz, $CDCl_3$): *δ*=8.07 (d, *J*=12 Hz, 1H, CH), 7.85 (d, *J*=16 Hz, 1H, CH), 7.71 (d, *J*=8 Hz, 2H, CH), 7.65-7.60 (m, 5H, CH), 7.57 (s, 1H, CH), 7.46 (t, *J*=8 Hz, 2H, CH), 7.39 (d, *J*=8 Hz, 1H, CH), 6.99 (d, *J*=12 Hz, 1H, CH), 6.24 (s, 1H, OH), 3.89 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): *δ*=190.19, 163.81, 156.09, 144.76, 142.92, 142.38, 141.62, 133.67, 131.19, 130.78, 130.15, 129.94, 129.03, 128.48, 127.42, 121.35, 119.33, 115.10, 114.55, 114.09, 113.89, 55.52; GC-MS (rt): 25.81 min (silylated compound); m/z (EI) (%): 359 (19%), 358 (63%), 344 (30%), 300 (10%), 299 (34%), 269 (31%), 73 (35%); elemental analysis: calculated (%) for $C_{22}H_{18}O_3$ (330.38): C 79.98, H 5.49; found: C 79.66, H 5.58.

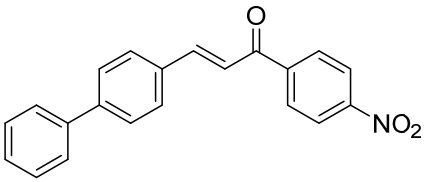
(*E*)-3-([1,1'-biphenyl]-4-yl)-1-(4-methoxyphenyl)prop-2-en-1-one **(5ac)**



Light brown solid; 87% yield; m.p. 143-146 °C; ^{1}H NMR (400 MHz, $CDCl_3$): *δ*=8.05 (d, *J*=12 Hz, 2H, CH), 7.83 (d, *J*=16 Hz,

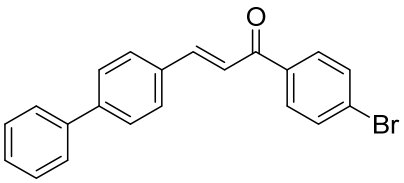
1H, CH), 7.70 (d, *J*=8 Hz, 2H, CH), 7.64-7.59 (m, 5H, CH), 7.45 (t, *J*=8 Hz, 2H, CH), 7.37 (d, *J*=8 Hz, 1H, CH), 6.98 (d, *J*=12 Hz, 2H, CH), 3.87 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): *δ*=188.61, 163.39, 143.49, 143.05, 140.13, 133.99, 133.12, 131.09, 130.80, 129.69, 128.88, 127.83, 127.53, 127.02, 121.63, 113.82, 55.48; GC-MS (rt): 32.61 min; m/z (EI) (%): 314 (100%), 237 (20%), 178 (39%), 152 (24%), 135 (25%), 92 (18%), 77 (30%); elemental analysis: calculated (%) for $C_{22}H_{18}O_2$ (314.38): C 84.05, H 5.77; found: C 83.81, H 5.96.

(*E*)-3-([1,1'-biphenyl]-4-yl)-1-(4-nitrophenyl)prop-2-en-1-one **(5ad)**



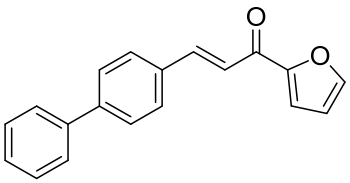
Brown solid; 65% yield; m.p. 206-209 °C; ^1H NMR (400 MHz, $CDCl_3$): *δ*=8.49 (d, *J*=8 Hz, 2H, CH), 8.10 (d, *J*=8 Hz, 2H, CH), 7.98 (d, *J*=16 Hz, 1H, CH), 7.73-7.64 (m, 6H, CH), 7.53-7.40 (m, 3H, CH), 7.27 (d, *J*=8 Hz, 1H, CH); ^{13}C NMR (100 MHz, $CDCl_3$): *δ*=192.66, 152.58, 147.08, 144.23, 143.30, 140.13, 130.11, 129.61, 129.45, 128.86, 128.80, 128.32, 127.91, 127.53, 127.36, 127.20, 127.03, 126.91, 124.52, 120.77; GC-MS (rt): 31.05 min; m/z (EI) (%): 299 (64%), 284 (100%), 254 (8%), 152 (11%), 77 (7%), 43 (14%); elemental analysis: calculated (%) for $C_{21}H_{15}NO_3$ (329.35): C 76.58, H 4.59, N 4.25; found: C 76.27, H 4.91, N 4.60.

(*E*)-3-([1,1'-biphenyl]-4-yl)-1-(4-bromophenyl)prop-2-en-1-one **(5ae)**



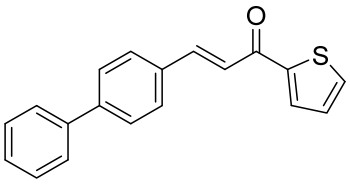
White solid; 66% yield; m.p. 202-205 °C; ^1H NMR (400 MHz, $CDCl_3$): *δ*=7.89 (d, *J*=8 Hz, 2H, CH), 7.85 (d, *J*=16 Hz, 1H, CH), 7.71 (d, *J*=8 Hz, 2H, CH), 7.66-7.61 (m, 7H, CH), 7.46 (t, *J*=8 Hz, 2H, CH), 7.38 (d, *J*=8 Hz, 1H, CH); ^{13}C NMR (100 MHz, $CDCl_3$): *δ*=189.30, 144.96, 143.51, 140.01, 136.93, 133.57, 131.92, 130.01, 129.04, 128.92, 127.95, 127.88, 127.62, 127.04, 124.49, 121.19; GC-MS (rt): 32.51 min; m/z (EI) (%): 364 (83%), 363 (98%), 362 (87%), 283 (68%), 178 (100%), 152 (52%); elemental analysis: calculated (%) for $C_{21}H_{15}BrO$ (363.25): C 69.44, H 4.16; found: C 69.19, H 4.40.

(*E*)-3-([1,1'-biphenyl]-4-yl)-1-(furan-2-yl)prop-2-en-1-one **(5af)**



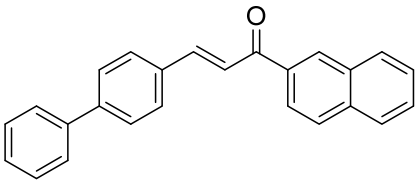
Pale yellow solid; 93% yield; m.p. 138-140 °C; ^1H NMR (400 MHz, $CDCl_3$): *δ*=7.91 (d, *J*=16 Hz, 1H, CH), 7.71 (d, *J*=8 Hz, 2H, CH), 7.65-7.60 (m, 5H, CH), 7.50 (d, *J*=4 Hz, 1H, CH), 7.47-7.43 (m, 3H, CH), 7.37 (d, *J*=8 Hz, 1H, CH), 7.34 (d, *J*=4 Hz, 1H, CH); ^{13}C NMR (100 MHz, $CDCl_3$): *δ*=177.96, 153.71, 146.51, 143.52, 143.35, 140.08, 133.64, 132.17, 129.85, 129.04, 128.89, 127.89, 127.56, 127.03, 120.92, 117.49, 112.56; GC-MS (rt): 29.23 min; m/z (EI) (%): 274 (95%), 273 (100%), 217 (21%), 197 (40%), 178 (48%), 152 (29%), 95 (33%), 39 (19%); elemental analysis: calculated (%) for $C_{19}H_{14}O_2$ (274.31): C 83.19, H 5.14; found: C 82.97, H 5.38.

(*E*)-3-([1,1'-biphenyl]-4-yl)-1-(thiophen-2-yl)prop-2-en-1-one **(5ag)**



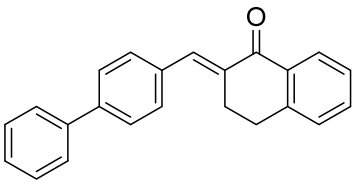
Off white solid; 91% yield; m.p. 136-138 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.90-7.86 (m, 2H, CH), 7.72-7.60 (m, 7H, CH), 7.47-7.43 (m, 3H, CH), 7.37 (t, *J*=8 Hz, 1H, CH), 7.18 (t, *J*=4 Hz, 1H, CH); ^{13}C NMR (100 MHz, $CDCl_3$): δ=181.95, 145.56, 143.61, 143.34, 140.07, 133.88, 133.61, 131.76, 128.99, 128.90, 128.24, 127.89, 127.58, 127.03, 121.37; GC-MS (rt): 30.82 min; m/z (EI) (%): 291 (24%), 290 (100%), 261 (14%), 213 (39%), 178 (52%), 152 (34%), 111 (46%); elemental analysis: calculated (%) for $C_{19}H_{14}OS$ (290.38): C 78.59, H 4.86, S 11.04; found: C 78.83, H 4.63, S 11.01.

(*E*)-3-([1,1'-biphenyl]-4-yl)-1-(naphthalen-2-yl)prop-2-en-1-one **(5ah)**



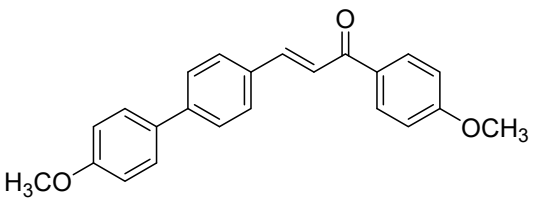
Yellow solid; 89% yield; m.p. 130-132 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.56 (s, 1H, CH), 8.11 (d, *J*=8 Hz, 1H, CH), 8.01-7.89 (m, 3H, CH), 7.77 (d, *J*=8 Hz, 3H, CH), 7.71-7.55 (m, 7H, CH), 7.46 (t, *J*=8 Hz, 2H, CH), 7.39 (t, *J*=8 Hz, 1H, CH); ^{13}C NMR (100 MHz, $CDCl_3$): δ=190.23, 144.34, 143.30, 140.13, 135.57, 135.44, 133.88, 132.54, 132.12, 129.93, 129.52, 129.02, 128.92, 128.59, 128.39, 127.90, 127.83, 127.61, 127.06, 126.79, 124.49, 121.85; GC-MS (rt): 35.08 min; m/z (EI) (%): 335 (25%), 334 (100%), 257 (22%), 178 (37%), 152 (25%), 127 (51%), 77 (14%); elemental analysis: calculated (%) for $C_{25}H_{18}O$ (334.41): C 89.79, H 5.43; found: C 90.06, H 5.18.

(*E*)-2-([1,1'-biphenyl]-4-ylmethylene)-3,4-dihydronaphthalen-1(2H)-one **(5ai)**



Dark red solid; 67% yield; m.p. 42-45 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.91 (s, 1H, CH), 7.64 (t, *J*=8 Hz, 4H, CH), 7.53-7.45 (m, 6H, CH), 7.36 (t, *J*=8 Hz, 3H, CH), 3.18 (t, *J*=8 Hz, 2H, CH_2), 2.96 (t, *J*=8 Hz, 2H, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$): δ=187.83, 143.19, 141.33, 140.31, 136.33, 135.42, 134.76, 133.45, 133.29, 131.65, 131.36, 130.49, 130.27, 129.88, 128.89, 128.21, 128.18, 127.68, 127.08, 127.04, 28.81, 27.32; GC-MS (rt): 32.59 min; m/z (EI) (%): 310 (68%), 309 (100%), 233 (38%), 191 (13%), 165 (12%), 90 (17%); elemental analysis: calculated (%) for $C_{23}H_{18}O$ (310.39): C 89.00, H 5.85; found: C 89.28, H 5.60.

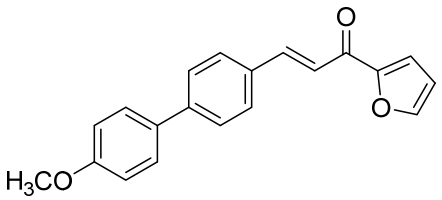
(*E*)-3-(4'-methoxy-[1,1'-biphenyl]-4-yl)-1-(4-methoxyphenyl)prop-2-en-1-one **(5bc)**



White solid; 93% yield; m.p. 148-150 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.05 (d, *J*=4 Hz, 2H, CH), 7.83 (d, *J*=16 Hz, 1H, CH), 7.68 (d, *J*=8 Hz, 2H, CH), 7.60-7.54 (m, 5H, CH), 6.98 (d, *J*=8 Hz, 4H, CH), 3.88 (s, 3H, CH_3), 3.85 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ=188.66, 163.37, 159.59, 143.62, 142.69, 133.37,

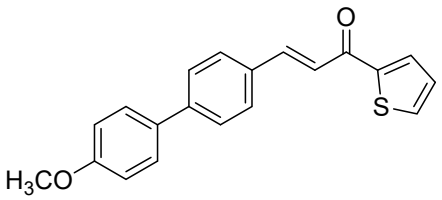
132.59, 131.17, 130.78, 128.88, 128.08, 126.99, 121.31, 114.33, 113.82, 55.35; GC-MS (rt): 34.73 min; m/z (EI) (%): 345 (24%), 344 (100%), 329 (12%), 237 (11%), 165 (24%), 135 (20%), 92 (11%), 77 (13%); elemental analysis: calculated (%) for $C_{23}H_{20}O_3$ (344.40): C 80.21, H 5.85; found: C 80.49, H 5.53.

(*E*)-1-(furan-2-yl)-3-(4'-methoxy-[1,1'-biphenyl]-4-yl)prop-2-en-1-one **(5bf)**



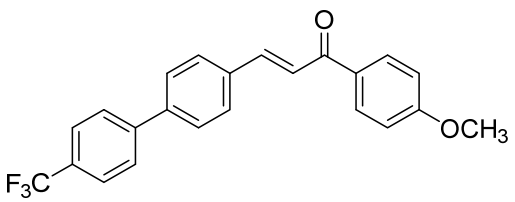
Yellow solid; 96% yield; m.p. 140-142 °C; ^{1}H NMR (400 MHz, $CDCl_3$): *δ*=7.93 (d, *J*=16 Hz, 1H, CH), 7.72 (d, *J*=8 Hz, 2H, CH), 7.67 (dd, *J*=8, 4 Hz, 1H, CH), 7.62 (d, *J*=8 Hz, 2H, CH), 7.59 (d, *J*=9 Hz, 2H, CH), 7.49 (d, *J*=16 Hz, 1H, CH), 7.36 (d, *J*=4 Hz, 1H, CH), 7.01 (d, *J*=8 Hz, 2H, CH), 6.62 (d, *J*=4 Hz, 1H, CH), 3.87 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): *δ*=177.99, 159.63, 153.76, 146.43, 143.66, 142.97, 133.01, 132.53, 129.06, 128.08, 126.98, 120.58, 117.39, 114.33, 112.51, 55.32; GC-MS (rt): 31.07 min; m/z (EI) (%): 305 (20%), 304 (100%), 275 (8%), 261 (12%), 197 (16%), 165 (28%), 139 (15%), 95 (17%); elemental analysis: calculated (%) for $C_{20}H_{16}O_3$ (304.34): C 78.93, H 5.30; found: C 78.57, H 5.33.

(*E*)-3-(4'-methoxy-[1,1'-biphenyl]-4-yl)-1-(thiophen-2-yl)prop-2-en-1-one **(5bg)**



Yellow solid; 97% yield; m.p. 138-140 °C; ^{1}H NMR (400 MHz, $CDCl_3$): *δ*=7.88-7.85 (m, 2H, CH), 7.69-7.66 (m, 3H, CH), 7.60 (d, *J*=8 Hz, 2H, CH), 7.55 (d, *J*=8 Hz, 2H, CH), 7.42 (d, *J*=16 Hz, 1H, CH), 7.17 (dd, *J*=8, 4 Hz, 1H, CH), 6.98 (d, *J*=8 Hz, 2H, CH), 3.84 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): *δ*=181.87, 159.61, 145.58, 143.61, 142.89, 133.72, 132.94, 132.43, 131.65, 128.96, 128.15, 128.01, 126.93, 120.99, 114.29, 55.24; GC-MS (rt): 32.95 min; m/z (EI) (%): 321 (25%), 320 (100%), 277 (10%), 213 (15%), 184 (17%), 165 (31%), 139 (17%), 111 (36%); elemental analysis: calculated (%) for $C_{20}H_{16}O_2S$ (320.40): C 74.97, H 5.03, S 10.01; found: C 75.16, H 5.32, S 9.72.

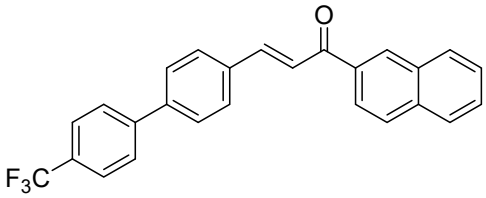
(*E*)-1-(4-methoxyphenyl)-3-(4'-(trifluoromethyl)-[1,1'-biphenyl]-4-yl)prop-2-en-1-one **(5cc)**



Grey solid; 82% yield; m.p. 109-112 °C; ^{1}H NMR (400 MHz, $CDCl_3$): *δ*=8.05 (d, *J*=8 Hz, 1H, CH), 7.79 (d, *J*=16 Hz, 1H, CH), 7.74-7.71 (m, 5H, CH), 7.68-7.63 (m, 3H, CH), 7.59 (d, *J*=16 Hz, 2H, CH), 7.15 (d, *J*=16 Hz, 1H, CH), 6.99 (d, *J*=8 Hz, 1H, CH), 3.89 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): *δ*=189.71, 163.49, 143.19, 143.08, 140.00, 133.98, 132.14, 131.10, 130.80, 129.89, 128.96, 127.93, 127.63, 127.12, 124.11, 121.73, 113.92, 55.58; ^{19}F NMR (376 MHz, $CDCl_3$): *δ*=-62.50 (s, 3F, CF_3); GC-MS (rt): 31.92 min; m/z (EI) (%): 383 (25%), 382 (100%), 354 (11%), 237 (11%), 178 (13%), 135 (28%),

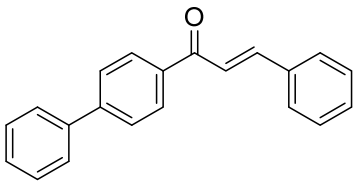
107 (8%) 92 (13%), 77 (14%); elemental analysis: calculated (%) for $C_{23}H_{17}F_3O_2$ (382.38): C 72.24, H 4.48; found: C 71.93, H 4.62.

(*E*)-1-(naphthalen-2-yl)-3-(4'-(trifluoromethyl)-[1,1'-biphenyl]-4-yl)prop-2-en-1-one **(5ch)**



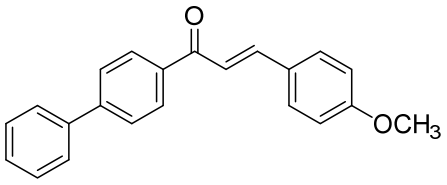
Black solid; 80% yield; m.p. 96-99 °C; ^{1}H NMR (400 MHz, $CDCl_3$): *δ*=8.59 (s, 1H, CH), 8.14 (d, *J*=8 Hz, 1H, CH), 8.03 (d, *J*=8 Hz, 1H, CH), 7.98 (d, *J*=9 Hz, 2H, CH), 7.93 (d, *J*=8 Hz, 2H, CH), 7.83-7.80 (m, 3H, CH), 7.77-7.75 (m, 3H, CH), 7.70 (d, *J*=8 Hz, 1H, CH), 7.66-7.58 (m, 3H, CH); ^{13}C NMR (100 MHz, $CDCl_3$): *δ*=190.06, 143.87, 141.63, 135.51, 135.45, 134.81, 132.54, 129.98, 129.52, 129.13, 128.64, 128.47, 127.84, 127.78, 127.34, 127.22, 126.84, 125.87, 125.83, 125.61, 124.44, 122.42; ^{19}F NMR (376 MHz, $CDCl_3$): *δ*=-62.47 (s, 3F, CF_3); GC-MS (rt): 34.33 min; m/z (EI) (%): 403 (24%), 402 (100%), 257 (16%), 178 (18%), 152 (22%), 127 (70%), 77 (12%); elemental analysis: calculated (%) for $C_{26}H_{17}F_3O$ (402.41): C 77.60, H 4.26; found: C 77.29, H 4.59.

(*E*)-1-([1,1'-biphenyl]-4-yl)-3-phenylprop-2-en-1-one **(6ab)**



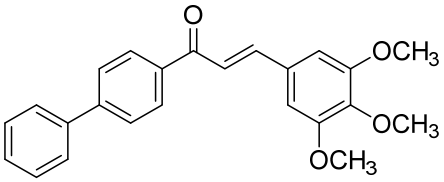
Off white solid; 89% yield; m.p. 145-148 °C; ^{1}H NMR (400 MHz, $CDCl_3$): *δ*=8.11 (d, *J*=8 Hz, 2H, CH), 7.85 (d, *J*=12 Hz, 1H, CH), 7.73 (d, *J*=8 Hz, 2H, CH), 7.65-7.56 (m, 5H, CH), 7.50-7.41 (m, 6H, CH); ^{13}C NMR (100 MHz, $CDCl_3$): *δ*=189.92, 145.51, 144.75, 139.90, 136.87, 134.90, 130.56, 129.12, 128.95, 128.47, 128.21, 127.28, 121.97; GC-MS (rt): 30.20 min; m/z (EI) (%): 285 (20%), 284 (100%), 181 (18%), 178 (15%), 152 (58%), 103 (24%), 77 (27%); elemental analysis: calculated (%) for $C_{21}H_{16}O$ (284.35): C 88.70, H 5.67; found: C 88.45, H 5.89.

(*E*)-1-([1,1'-biphenyl]-4-yl)-3-(4-methoxyphenyl)prop-2-en-1-one **(6ac)**



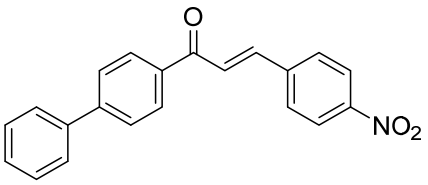
Orange solid; 86% yield; m.p. 125-127 °C; ^{1}H NMR (400 MHz, $CDCl_3$): *δ*=8.01 (d, *J*=8 Hz, 2H, CH), 7.73 (d, *J*=16 Hz, 1H, CH), 7.62 (d, *J*=8 Hz, 2H, CH), 7.54 (t, *J*=8 Hz, 4H, CH), 7.41 (s, 1H, CH), 7.37 (t, *J*=8 Hz, 2H, CH), 7.31 (d, *J*=4 Hz, 1H, CH), 6.85 (d, *J*=9 Hz, 2H, CH), 3.75 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): *δ*=189.64, 161.60, 145.14, 144.44, 139.84, 137.07, 130.16, 128.92, 128.82, 128.03, 127.13, 127.07, 119.47, 114.30, 55.23; GC-MS (rt): 32.60 min; m/z (EI) (%): 315 (23%), 314 (100%), 299 (19%), 206 (14%), 161 (16%), 152 (49%), 77 (15%); elemental analysis: calculated (%) for $C_{22}H_{18}O_2$ (314.38): C 84.05, H 5.77; found: C 83.84, H 5.97.

(*E*)-1-([1,1'-biphenyl]-4-yl)-3-(3,4,5-trimethoxyphenyl)prop-2-en-1-one **(6ad)**



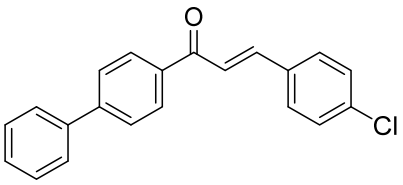
Yellow solid; 81% yield; m.p. 198-201 °C; ^{1}H NMR (400 MHz, $CDCl_3$): *δ*=8.00 (d, *J*=8 Hz, 2H, CH), 7.67-7.64 (m, 3H, CH), 7.56 (d, *J*=8 Hz, 2H, CH), 7.40-7.30 (m, 4H, CH), 6.81 (s, 2H, CH), 3.84-3.81 (m, 9H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): *δ*=190.52, 153.31, 145.58, 145.21, 139.70, 136.67, 130.32, 129.05, 128.87, 128.17, 127.19, 127.13, 121.28, 105.66, 60.87, 56.09; GC-MS (rt): 34.54 min; m/z (EI) (%): 375 (25%), 374 (100%), 359 (27%), 343 (48%), 331 (11%), 181 (13%), 152 (42%); elemental analysis: calculated (%) for $C_{24}H_{22}O_4$ (374.43): C 76.99, H 5.92; found: C 76.71, H 6.18.

(*E*)-1-([1,1'-biphenyl]-4-yl)-3-(4-nitrophenyl)prop-2-en-1-one **(6ae)**



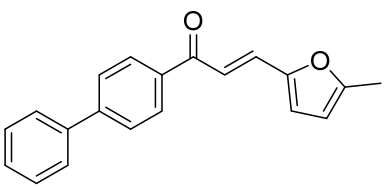
Yellow solid; 90% yield; m.p. 231-233 °C; ^{1}H NMR (400 MHz, $CDCl_3$): *δ*=8.27 (d, *J*=8 Hz, 2H, CH), 8.11 (d, *J*=8 Hz, 2H, CH), 7.80 (t, *J*=8 Hz, 3H, CH), 7.74 (d, *J*=8 Hz, 2H, CH), 7.70 (s, 1H, CH), 7.65 (d, *J*=9 Hz, 2H, CH); 7.48 (t, *J*=8 Hz, 2H, CH), 7.41 (t, *J*=8 Hz, 1H, CH); ^{13}C NMR (100 MHz, $CDCl_3$): *δ*=188.93, 148.47, 146.03, 141.34, 141.02, 139.61, 136.13, 130.20, 129.17, 128.94, 128.92, 128.33, 127.35, 127.21, 125.57, 124.14; GC-MS (rt): 33.94 min; m/z (EI) (%): 330 (23%), 329 (100%), 301 (26%), 282 (16%), 181 (35%), 152 (64%), 102 (23%), 77 (13%); elemental analysis: calculated (%) for $C_{21}H_{15}NO_3$ (329.35): C 76.58, H 4.59, N 4.25; found: C 76.31, H 4.84, N 4.57.

(*E*)-1-([1,1'-biphenyl]-4-yl)-3-(4-chlorophenyl)prop-2-en-1-one **(6af)**



Light yellow solid; 89% yield; m.p. 216-219 °C; ^{1}H NMR (400 MHz, $CDCl_3$): *δ*=8.09 (d, *J*=9 Hz, 2H, CH), 7.77 (d, *J*=16 Hz, 1H, CH), 7.71 (d, *J*=8 Hz, 2H, CH), 7.63 (d, *J*=8 Hz, 2H, CH), 7.57 (t, *J*=8 Hz, 3H, CH), 7.47 (t, *J*=8 Hz, 2H, CH), 7.39 (t, *J*=8 Hz, 3H, CH); ^{13}C NMR (100 MHz, $CDCl_3$): *δ*=189.57, 145.65, 143.19, 139.82, 136.66, 136.40, 133.38, 129.59, 129.23, 129.09, 128.95, 128.24, 127.30, 127.26, 122.33; GC-MS (rt): 31.60 min; m/z (EI) (%): 319 (36%), 318 (100%), 283 (28%), 152 (79%), 102 (30%); elemental analysis: calculated (%) for $C_{21}H_{15}ClO$ (318.80): C 79.12, H 4.74; found: C 78.86, H 4.92.

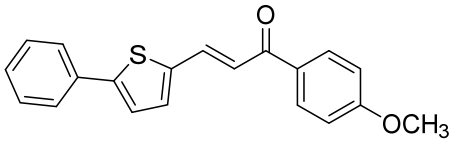
(*E*)-1-([1,1'-biphenyl]-4-yl)-3-(5-methylfuran-2-yl)prop-2-en-1-one (**6ag)**



Orange solid; 92% yield; m.p. 143-146 °C; ^{1}H NMR (400 MHz, $CDCl_3$): *δ*=8.02 (d, *J*=8 Hz, 2H, CH), 7.62 (d, *J*=8 Hz, 2H, CH), 7.55 (d, *J*=4 Hz, 2H, CH), 7.45 (s, 1H, CH), 7.38-7.24 (m, 4H, CH), 6.56 (d, *J*=4 Hz, 1H, CH), 6.05 (d, *J*=4 Hz, 1H, CH), 2.30 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): *δ*=189.02, 155.76, 150.26, 145.12, 139.89, 136.97, 130.58, 128.85,

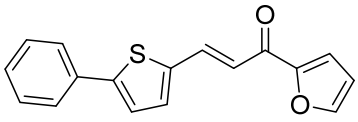
128.79, 127.99, 127.12, 127.06, 118.16, 117.29, 109.26, 14.01; GC-MS (rt): 29.52 min; m/z (EI) (%): 289 (21%), 288 (95%), 273 (100%), 217 (26%), 202 (15%), 152 (41%), 77 (18%); elemental analysis: calculated (%) for $C_{20}H_{16}O_2$ (288.34): C 83.31, H 5.59; found: C 83.07, H 5.85.

(*E*)-1-(4-methoxyphenyl)-3-(5-phenylthiophen-2-yl)prop-2-en-1-one **(7ac)**



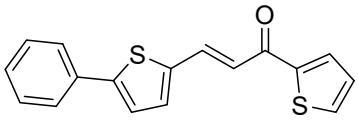
Yellow solid; 85% yield; m.p. 152-155 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.02 (d, *J*=8 Hz, 2H, CH), 7.89 (d, *J*=16 Hz, 1H, CH), 7.62 (d, *J*=8 Hz, 2H, CH), 7.42-7.28 (m, 6H, CH), 6.97 (d, *J*=8 Hz, 2H, CH), 3.87 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ=188.15, 163.25, 139.77, 136.44, 133.58, 133.21, 131.03, 130.66, 129.03, 128.41, 125.96, 125.77, 124.15, 124.04, 120.19, 113.81, 109.94, 55.44; GC-MS (rt): 32.52 min; m/z (EI) (%): 321 (24%), 320 (100%), 289 (18%), 277 (22%), 184 (25%), 160 (22%), 115 (18%), 92 (19%), 77 (27%); elemental analysis: calculated (%) for $C_{20}H_{16}O_2S$ (320.40): C 74.97, H 5.03, S 10.01; found: C 74.69, H 5.32, S 10.28.

(*E*)-1-(furan-2-yl)-3-(5-phenylthiophen-2-yl)prop-2-en-1-one **(7af)**



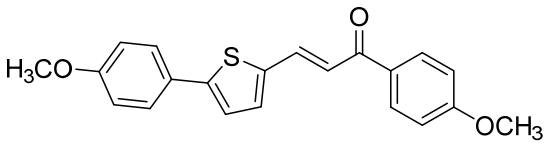
Orange solid; 90% yield; m.p. 108-111 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.88 (d, *J*=16 Hz, 1H, CH), 7.60-7.55 (m, 3H, CH), 7.35-7.31 (m, 2H, CH), 7.28-7.23 (m, 4H, CH), 7.15 (d, *J*=16 Hz, 1H, CH), 6.53 (d, *J*=8 Hz, 1H, CH); ^{13}C NMR (100 MHz, $CDCl_3$): δ=177.55, 153.69, 147.96, 146.42, 139.36, 136.42, 133.62, 133.46, 129.06, 128.52, 125.99, 124.25, 119.62, 117.26, 112.52; GC-MS (rt): 29.11 min; m/z (EI) (%): 281 (20%), 280 (100%), 252 (21%), 223 (53%), 184 (32%), 121 (19%), 115 (20%), 95 (26%), 39 (22%); elemental analysis: calculated (%) for $C_{17}H_{12}O_2S$ (280.34): C 72.83, H 4.31, S 11.44; found: C 72.56, H 4.54, S 11.46.

(*E*)-3-(5-phenylthiophen-2-yl)-1-(thiophen-2-yl)prop-2-en-1-one **(7ag)**



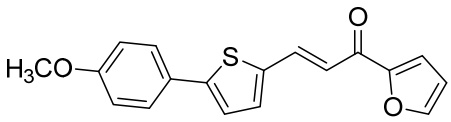
Yellow solid; 88% yield; m.p. 105-108 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.92 (d, *J*=16 Hz, 1H, CH), 7.84 (d, *J*=4 Hz, 1H, CH), 7.67-7.62 (m, 3H, CH), 7.42-7.38 (m, 2H, CH), 7.34-7.28 (m, 3H, CH), 7.21-7.16 (m, 2H, CH); ^{13}C NMR (100 MHz, $CDCl_3$): δ=181.45, 145.59, 139.28, 136.50, 133.74, 133.67, 131.54, 129.05, 128.53, 128.20, 125.99, 124.25, 119.94, 109.99; GC-MS (rt): 30.59 min; m/z (EI) (%): 297 (21%), 296 (100%), 267 (24%), 184 (32%), 160 (21%), 152 (20%), 111 (40%), 39 (23%); elemental analysis: calculated (%) for $C_{17}H_{12}OS_2$ (296.41): C 68.89, H 4.08, S 21.64; found: C 68.62, H 4.32, S 21.77.

(*E*)-1-(4-methoxyphenyl)-3-(5-(4-methoxyphenyl)thiophen-2-yl)prop-2-en-1-one **(7bc)**



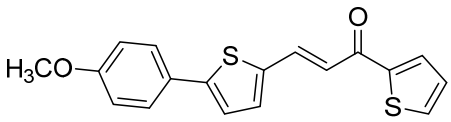
Orange solid; 87% yield; m.p. 175-178 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.02 (d, *J*=4 Hz, 2H, CH), 7.90 (d, *J*=16 Hz, 1H, CH), 7.55 (d, *J*=4 Hz, 2H, CH), 7.32-7.16 (m, 3H, CH), 6.97-6.91 (m, 4H, CH), 3.87 (s, 3H, CH_3), 3.83 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ=187.99, 163.31, 159.93, 142.85, 136.63, 133.49, 130.63, 130.59, 127.30, 123.11, 119.65, 114.43, 113.79, 55.47, 55.38; GC-MS (rt): 34.84 min; m/z (EI) (%): 351 (24%), 350 (100%), 335 (18%), 319 (15%), 307 (23%), 190 (15%), 171 (17%), 135 (15%), 92 (14%), 77 (17%); elemental analysis: calculated (%) for $C_{21}H_{18}O_3S$ (350.43): C 71.98, H 5.18, S 9.15; found: C 71.73, H 5.34, S 9.11.

(*E*)-1-(furan-2-yl)-3-(5-(4-methoxyphenyl)thiophen-2-yl)prop-2-en-1-one **(7bf)**



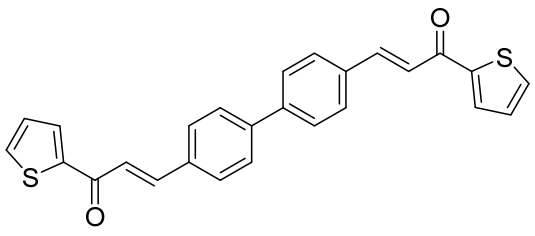
Orange solid; 93% yield; m.p.146-148 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.94 (d, *J*=16 Hz, 1H, CH), 7.63 (d, *J*=4 Hz, 1H, CH), 7.56 (d, *J*=8 Hz, 2H, CH), 7.30-7.28 (m, 2H, CH), 7.19 (d, *J*=8 Hz, 1H, CH), 7.16 (d, *J*=4 Hz, 1H, CH), 6.92 (d, *J*=8 Hz, 2H, CH), 6.57 (d, *J*=4 Hz, 1H, CH), 3.83 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ=177.54, 160.01, 153.76, 148.12, 146.28, 138.45, 136.54, 133.90, 127.32, 126.31, 123.16, 119.08, 117.05, 114.44, 112.45, 55.35; GC-MS (rt): 31.17 min; m/z (EI) (%): 311 (20%), 310 (100%), 267 (18%), 253 (19%), 239 (11%), 171 (20%), 151 (18%), 95 (23%), 39 (13 %); elemental analysis: calculated (%) for $C_{18}H_{14}O_3S$ (310.37): C 69.66, H 4.55, S 10.33; found: C 69.35, H 4.86, S 10.71.

(*E*)-3-(5-(4-methoxyphenyl)thiophen-2-yl)-1-(thiophen-2-yl)prop-2-en-1-one **(7bg)**



Yellow solid; 92% yield; m.p.142-144 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.91 (d, *J*=16 Hz, 1H, CH), 7.83 (d, *J*=4 Hz, 1H, CH), 7.65 (d, *J*=4 Hz, 1H, CH), 7.56 (d, *J*=9 Hz, 2H, CH), 7.30 (d, *J*=4 Hz, 1H, CH), 7.18-7.13 (m, 3H, CH), 6.92 (d, *J*=8 Hz, 2H, CH), 3.83 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ=181.41, 160.00, 148.03, 145.65, 138.28, 136.60, 133.88, 133.55, 131.40, 128.13, 127.33, 126.26, 123.14, 119.38, 114.42, 109.91, 55.73; GC-MS (rt): 32.68 min; m/z (EI) (%): 327 (24%), 326 (100%), 298 (12%), 283 (21%), 190 (18%), 171 (21%), 151 (13%), 111 (32%); elemental analysis: calculated (%) for $C_{18}H_{14}O_2S_2$ (326.43): C 66.23, H 4.32, S 19.65; found: C 65.96, H 4.57, S 19.81.

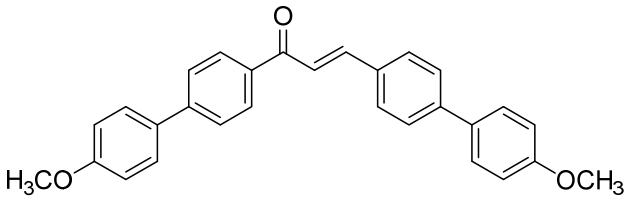
(2*E*,2'*E*)-3,3'-([1,1'-biphenyl]-4,4'-diyl)bis(1-(thiophen-2-yl)prop-2-en-1-one) **(8g)**



Yellow solid; 76% yield; m.p. 116-119 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.88-7.81 (m, 2H, CH), 7.72-7.61 (m, 5H, CH), 7.55 (d, *J*=4 Hz, 2H, CH), 7.45 (d, *J*=16 Hz,

1H, CH), 7.39-7.34 (m, 1H, CH), 7.27-7.22 (m, 3H, CH), 7.18-7.14 (m, 2H, CH), 7.08-7.05 (m, 2H, CH); ^{13}C NMR (100 MHz, $CDCl_3$): δ=181.85, 145.50, 144.21, 144.02, 143.26, 143.16, 142.04, 134.24, 134.01, 133.89, 133.71, 132.19, 132.14, 131.89, 131.66, 129.25, 129.11, 128.61, 128.29, 128.18, 128.12, 127.47, 127.40, 126.80, 121.74; GC-MS (rt): 32.46 min; m/z (EI) (%): 296 (7%), 295 (51%), 126 (16%), 113 (11%), 111 (100%), 83 (12%), 39 (12%); elemental analysis: calculated (%) for $C_{26}H_{18}O_2S_2$ (426.55): C 73.21, H 4.25, S 15.03; found: C 73.47, H 3.99, S 15.16.

(*E*)-1,3-bis(4'-methoxy-[1,1'-biphenyl]-4-yl)prop-2-en-1-one **(9b)**



Pale brown solid; 93% yield; m.p. 227-230 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.01 (d, *J*=8 Hz, 1H, CH), 7.62 (d, *J*=8 Hz, 2H, CH), 7.55 (d, *J*=8 Hz, 2H, CH), 7.48-7.45 (m, 2H, CH) 7.35 (d, *J*=8 Hz, 2H, CH), 7.01-6.77 (m, 9H, CH), 3.84 (s, 3H, CH_3), 3.82 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ=198.28, 159.86, 145.34, 134.95, 132.19, 130.87, 128.81, 128.34, 127.98, 127.84, 127.69, 127.00, 126.90, 126.61, 115.28, 114.36, 114.12, 114.10, 55.30; GC-MS (rt): 40.71 min; m/z (EI) (%): 421 (22%), 420 (100%), 358 (26%), 283 (28%), 178 (33%), 152 (50%), 77 (10%); elemental analysis: calculated (%) for $C_{29}H_{24}O_3$ (420.50): C 82.83, H 5.75, O 11.41; found: C 83.14, H 5.64.

5.5.10 Identification of the by-products obtained in the entries 6 and 7 of Table 5.1

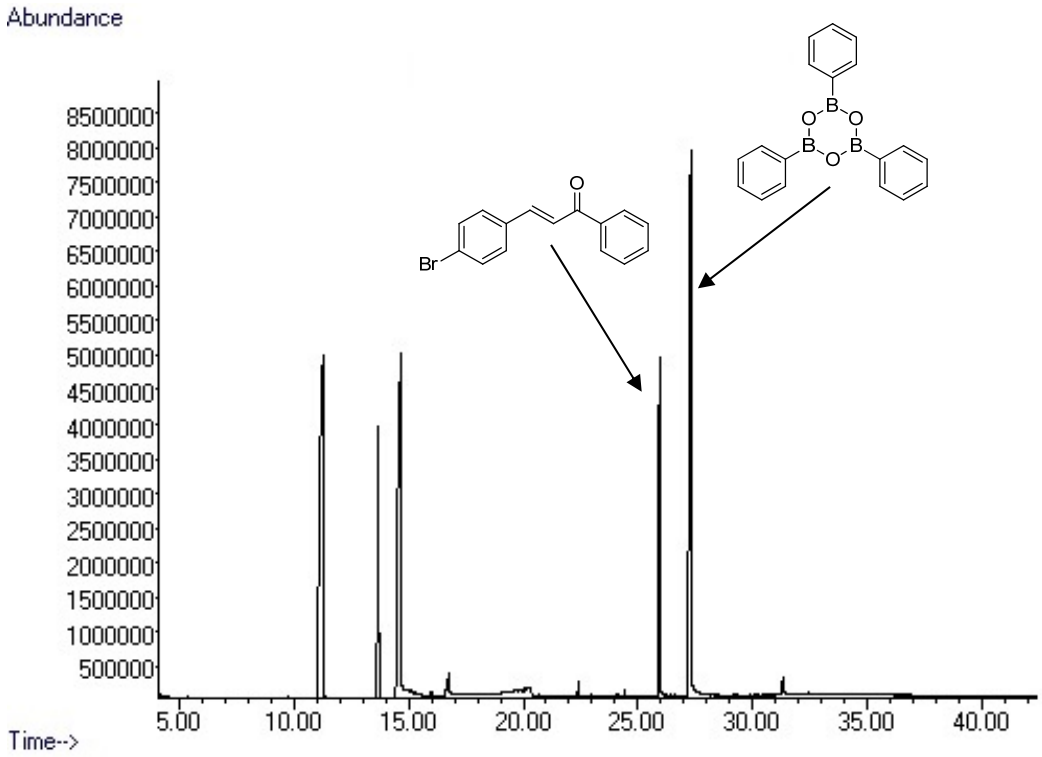


Figure 5.5. GC chromatogram of the crude reaction mixture (Table 5.1, entry 6).

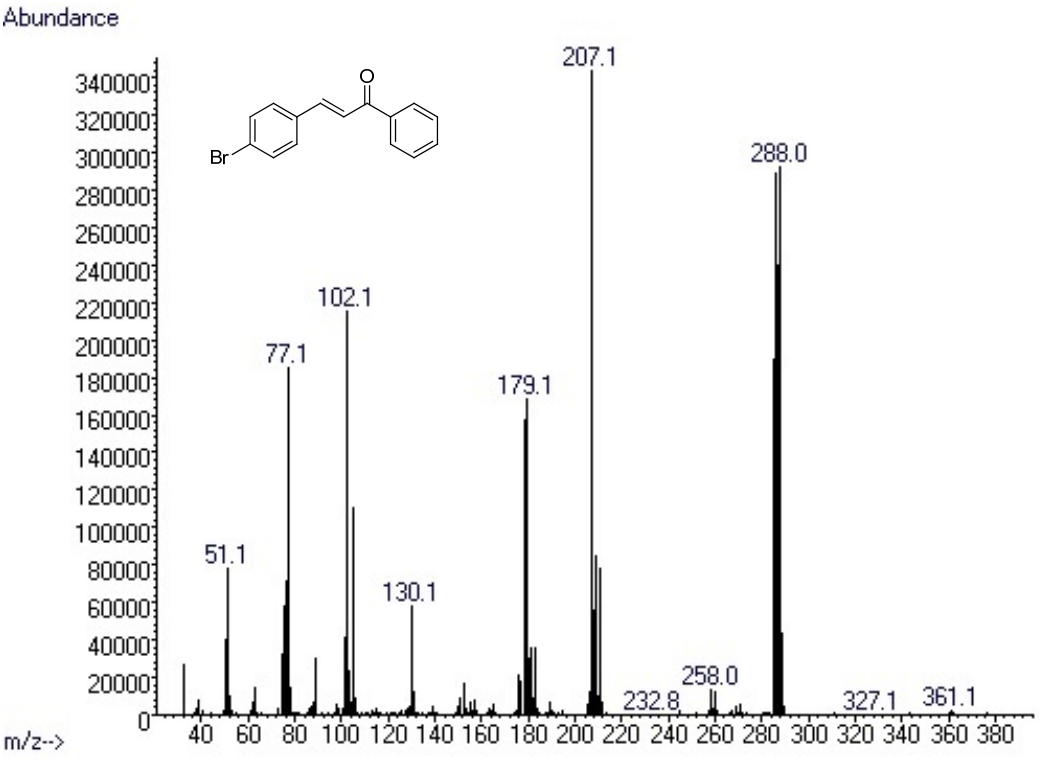


Figure 5.6. MS spectrum of the by-product (peak with retention time 25.96 min.).

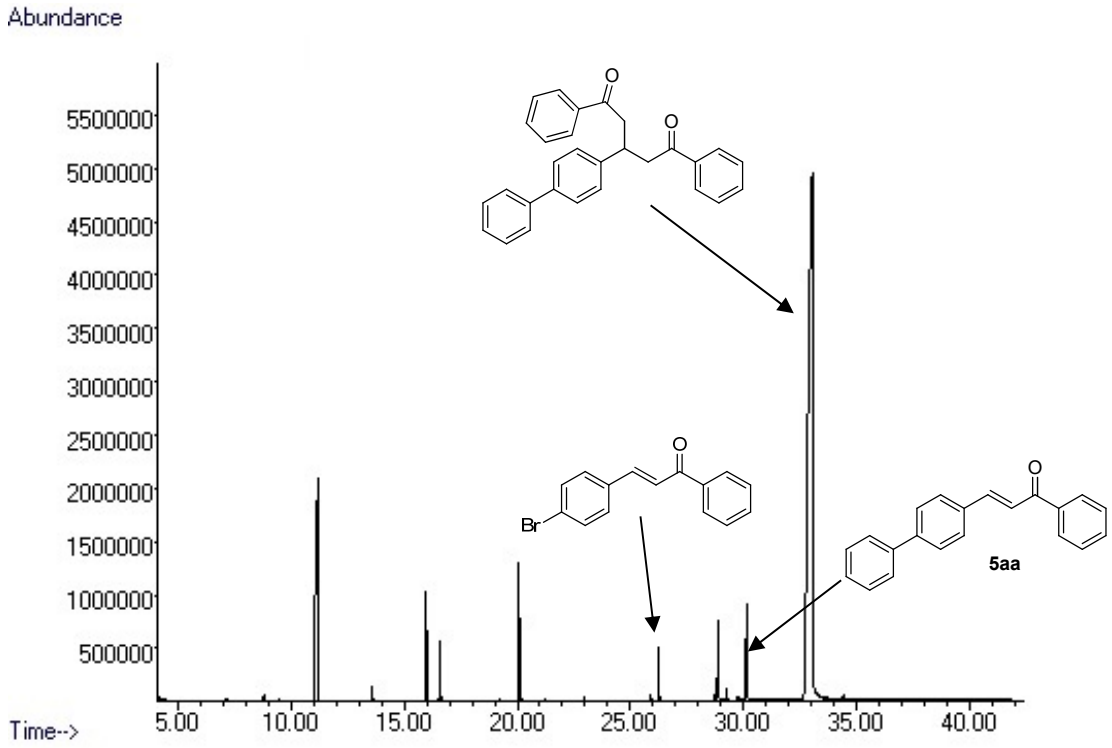


Figure 5.7. GC chromatogram of the crude reaction mixture (Table 5.1, entry 7).

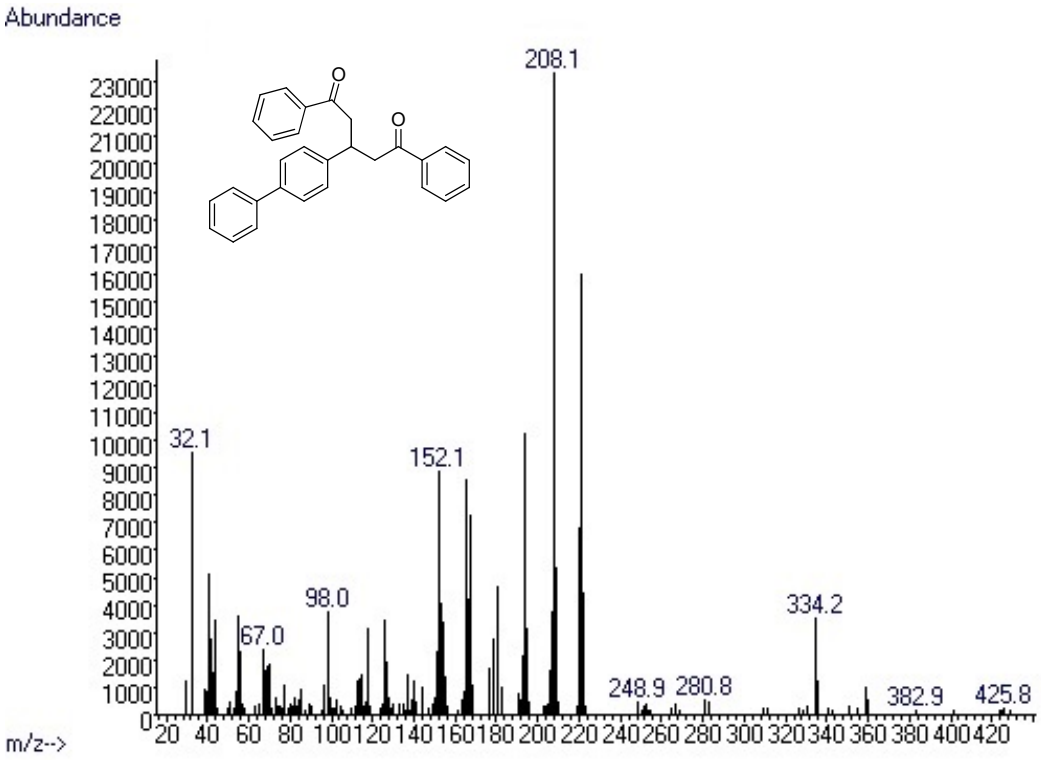


Figure 5.8. MS spectrum of the main by-product (peak with retention time 33.09 min).

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[32] For product **5ab**, the cold reaction mixture was slightly acidified with an aqueous hydrochloric acid solution and subsequently extracted with ethyl acetate (3 x 5 mL).

CHAPTER 6

Recent Advances in the Palladium-Catalyzed Aerobic Oxidation of Alcohols

The oxidation of alcohols to the equivalent carbonyl compounds is a crucial reaction in organic synthesis. Nevertheless, conventional oxidants are toxic and release copious amounts of by-products. As an alternative, oxygen (or even better air) is among the cheaper and less polluting stoichiometric oxidants, because it produces no waste or water as the unique by-product. The development of a transition metal-based catalyst in combination with oxygen represents an emerging alternative to the customary procedures. This chapter aims to give an overview on the most important advances made in the last years in the field of aerobic oxidations of alcohols, in particular catalyzed by Palladium in the form of homogeneous, heterogeneous and, more recently, nanoparticle catalysts.[1]

6.1 Introduction

Oxidation reactions are among the most helpful and applied reactions in industrial processes. Nevertheless, they are among the most hazardous and polluting processes, often occurring with a high E-factor[2] and producing considerable amounts of toxic waste, for example metal salts in oxidations employing stoichiometric Cr(VI) or Mn(VII) derivatives or nitrogen oxides in oxidations carried out with HNO_3.

Specifically, the oxidation of primary and secondary alcohols to the equivalent carbonyl compounds is of crucial importance in organic synthesis, due to the broad ranging utility of these products as relevant precursors and intermediates for many drugs.

From the environmental point of view, it is very important to develop methods which adopt cleaner oxidants and minimize the amount and toxicity of the released waste. Furthermore, the employment of catalysis, that allows processes to occur under mild conditions in order to save the overall implied energy, is convincingly encouraged.[3] In this respect, the recovery and reuse of the catalyst is an additional important target.

Oxygen (or even better air) is among the cheaper and less polluting stoichiometric oxidants, because it produces no waste or water as the unique by-product.[4] The development of a catalyst in combination with molecular oxygen represents an emerging alternative to the customary procedures. In the development of transition metal-catalyzed aerobic alcohol oxidations exist numerous challenges, as the necessity of low pressures of oxygen in particular in flammable organic solvents, mild reaction conditions, low catalyst loadings, and avoidance of expensive or toxic additives. Another important issue is the tolerance of functional groups and the chemo-selectivity of the alcohol transformation when other groups vulnerable to oxidation are present. An additional goal is the development of methods able to oxidize one class of alcohols in the presence of another.

Both homogeneous and heterogeneous catalytic systems have been developed,[5] and more recently, metals in the form of nanoparticles.[6] In fact, mainly in industrial chemistry, heterogeneous catalytic systems are preferred over homogeneous systems due to easier recyclability. On the other hand, they generally suffer from low catalytic activity relative to their homogeneous analogues. Much endeavour has been made to overcome the difficulties encountered with heterogeneous catalysis, because lowering of environmental loading due to easy separation and reuse of the catalyst could result. In addition, in view of a possible recycling of the catalyst, alternative solvents such as ionic liquids, fluorinated solvents and supercritical CO_2 have been considered.

6.2 Homogeneous, heterogeneous and nanoparticle catalysts

A homogeneous catalyst, that is usually a soluble metal complex, is in the same phase as the reactants, having the advantage to possess catalytic sites accessible to all reagents. Appropriate

modification of the ligands allows to tune the chemo-, regio- and enantioselectivity of homogeneous catalysts, that have numerous other advantages such as high efficiency, high selectivities, and yields. They are applied both in academia and in industry; on the other hand, their utilization in industrial applications (where metal contamination is heavily regulated) is limited by the difficulties found in the separation of catalyst from the final products. Removal of trace amounts of catalyst from the target product is of pivotal importance and still remains a key challenge that homogeneous catalysis has to address.

To overcome the separation problems found in homogeneous catalysis, heterogeneous catalysts have been introduced. Even if the first tests of heterogenization were made with polymeric materials as solid supports, the greatest part of the new heterogenized catalysts are based on silica supports, because silica has an excellent chemical and thermal stability, good accessibility and porosity. Furthermore, organic moieties can be strongly anchored to the surface to provide catalytic centres for metal-based catalysis. These hybrid organic/inorganic catalysts can anchor the catalytic metal owing to covalent binding or by simple adsorption. On the other hand, some issues still remain, as the accessibility of all active sites to reagents which renders heterogeneous catalysts often less efficient than homogeneous catalysts, and the leaching of metals from solid supports, which again requires separation of metal traces from the target product.

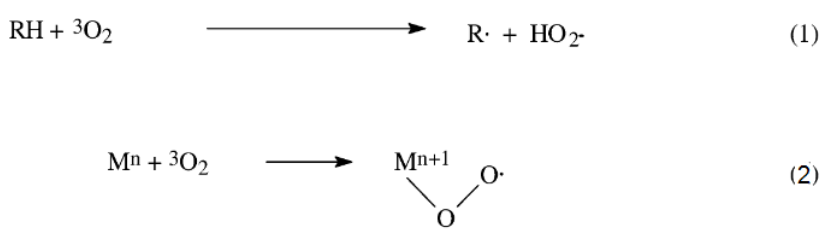
Nanoparticles are emerging as excellent sustainable alternatives to conventional solid supports, because they enhance the exposed surface area of the active component of the catalyst, thus increasing the contact among the reagents and the catalytic centre, as it happens in homogeneous catalysis. On the other hand, if nanoparticles are immobilized on a solid and insoluble support, they can be simply separated from the reaction mixture, which is the main advantage of heterogeneous catalysis. Therefore, nanocatalysis is generally considered as the “bridge” between homogeneous and heterogeneous catalysis, because it offers a new sustainable alternative to customary materials.[6]

6.3 Mechanisms of metal-catalyzed oxidations: general considerations

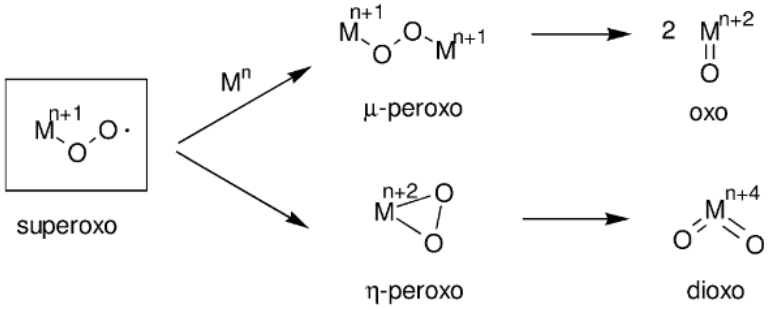
The ground state of dioxygen is a triplet containing two unpaired electrons with parallel spins. The direct reaction of $^3O_2$ with singlet organic molecules to give singlet products is a spin forbidden process with a very low rate. Fortunately, this precludes the spontaneous combustion of living matter, a thermodynamically very favourable process.

One way of circumventing this activation energy barrier involves a free radical pathway in which a singlet molecule reacts with $^3O_2$ to form two doublets (free radicals) in a spin-allowed process (Scheme 6.1, reaction (1)). However, this process is highly endothermic (up to 50 kcal mol^{-1}) and it is observed at moderate temperatures only with very reactive molecules that afford resonance stabilized radicals.

A second way to overcome this spin conservation obstacle is via reaction of $^3O_2$ with a paramagnetic (transition) metal ion, affording a superoxo-metal complex (Scheme 6.1, reaction (2)). Subsequent inter- or intramolecular electron-transfer processes can lead to the formation of a variety of metal-oxygen species (Scheme 6.2) which may play a role in the oxidation of organic substrates.



Scheme 6.1. Reactions of triplet oxygen.



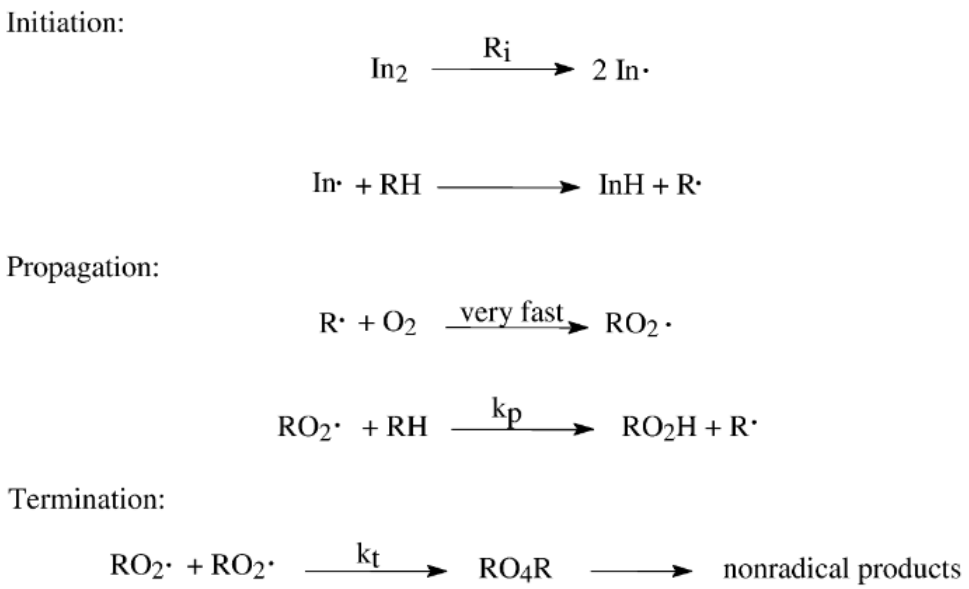
Scheme 6.2. Metal–oxygen species.

Basically, all (catalytic) oxidations, with dioxygen or peroxide reagents, either under homogeneous or heterogeneous conditions, can be divided into two types on the basis of their mechanism: homolytic and heterolytic. The former involves free radicals as reactive intermediates. Such reactions can occur with most organic substrates and dioxygen, in the presence or absence of metal catalysts. This ubiquity of free radical processes in dioxygen chemistry renders mechanistic interpretation more difficult than in the case of hydrogenations or carbonylation reactions, where there is no reaction in the absence of the catalyst. Heterolytic oxidations generally involve the (metal-mediated) oxidation of a substrate by an active oxygen compound, e.g. H_2O_2 or ROH. Alternatively, stoichiometric oxidation of a substrate by a metal ion or complex is coupled with the re-oxidation of the reduced metal species by the primary oxidant (e.g. O_2 or H_2O_2).

6.3.1 Homolytic mechanisms

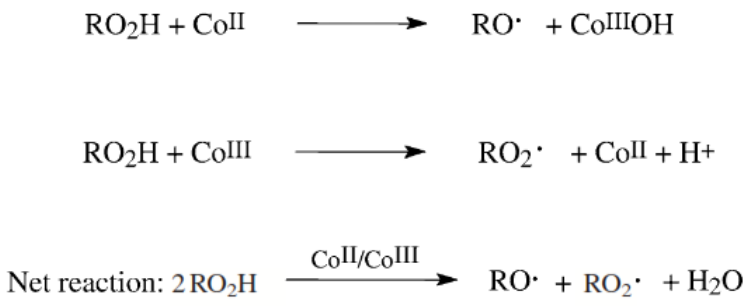
As noted above, dioxygen reacts with organic molecules, e.g. hydrocarbons, via a free radical pathway. The corresponding hydroperoxide is formed in a free radical chain process (Scheme 6.3). The reaction is autocatalytic, i.e. the alkyl hydroperoxide accelerates the reaction by undergoing homolysis to chain initiating radicals, and such processes are referred to as autoxidations.[7] The

susceptibility of any particular substrate to autoxidation is determined by the ratio $k_p/(2k_t)^{1/2}$, which is usually referred to as its oxidizability.[8]



Scheme 6.3. Mechanism of autoxidation.

The reaction can be started by adding an initiator which undergoes homolytic thermolysis at the reaction temperature to produce chain-initiating radicals. The initiator could be the alkyl hydroperoxide product although relatively high temperatures (> 100 °C) are required for thermolysis of hydroperoxides. Alternatively, chain-initiating radicals can be generated by the reaction of trace amounts of hydroperoxides with variable valence metals, e.g. cobalt, manganese, iron, etc. The corresponding alkoxy and alkylperoxy radicals are produced in one-electron transfer processes (Scheme 6.4).



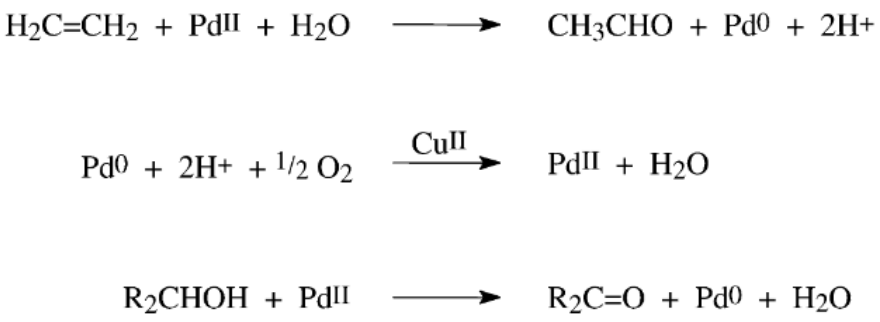
Scheme 6.4. Metal initiated and mediated autoxidation.

In such processes the metal ion acts (in combination with ROOH) as an initiator rather than a catalyst. It is important to note that homolytic decomposition of alkyl hydroperoxides via one-electron transfer processes is generally a competing process even with metal ions that catalyze heterolytic processes with hydroperoxides (see above).

Since dioxygen can be regenerated via subsequent chain decomposition of the alkyl hydroperoxide, this can lead to competing free radical autoxidation of the substrate. Generally speaking, this has not been recognized by many authors and can lead to a misinterpretation of results.

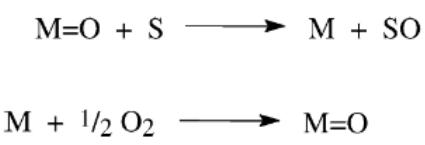
6.3.2 Heterolytic mechanisms

Catalytic oxidations with dioxygen can also proceed via heterolytic pathways which do not involve free radicals as intermediates. They generally involve a two-electron oxidation of a (coordinated) substrate by a metal ion. The oxidized form of the metal is subsequently regenerated by reaction of the reduced form with dioxygen. Typical examples are the Pd(II)-catalyzed oxidation of alkenes (Wacker process) and oxidative dehydrogenation of alcohols (Scheme 6.5).



Scheme 6.5. Wacker oxidation and oxidative dehydrogenation of alcohols.

In a variation on this theme, which pertains mainly to gas phase oxidations, an oxo-metal species oxidizes the substrate and the reduced form is subsequently re-oxidized by dioxygen (Scheme 6.6). This is generally referred to as the *Mars-van Krevelen mechanism*.[9]



Scheme 6.6. Mars-van Krevelen mechanism.

A wide variety of oxidations mediated by mono-oxygenase enzymes are similarly thought to involve oxygen transfer from a high-valent oxo-iron intermediate to the substrate (although the mechanistic details are still controversial).[10] However, in this case a stoichiometric cofactor is necessary to regenerate the reduced form of the enzyme.

Indeed, the holy grail in oxidation chemistry is to design a “suprabiotic” catalyst capable of mediating the transfer of both oxygen atoms of dioxygen to organic substrates, such as alkenes and alkanes.[11] This would obviate the need for a stoichiometric cofactor as a sacrificial reductant, i.e. it would amount to a Mars-van Krevelen mechanism in the liquid phase.

6.4 Ligand design in oxidation catalysis

In the majority of catalytic oxidations simple metal salts are used as the catalysts. In contrast, oxidations mediated by redox enzymes involve metal ions coordinated to complex ligands: amino acid residues in a protein or a prosthetic group, e.g. a porphyrin ligand in heme-dependent enzymes. Indeed, many of the major challenges in oxidation chemistry involve demanding oxidations, such as the selective oxidation of inactivated C–H bonds, which require powerful oxidants. This presents a dilemma: if an oxidant is powerful enough to oxidize an inactivated C–H bond then, by the same token, it will readily oxidize most ligands, which contain C–H bonds that are more active than the C–H bonds of the substrate. The low operational stability of, for example, heme-dependent enzymes is a direct consequence of the facile oxidative destruction of the porphyrin ring. Nature solves this problem *in vivo* by synthesizing fresh enzyme to replace that destroyed. *In vitro* this is not a viable option. In this context it is worth bearing in mind that many simple metal complexes that are used as catalysts in oxidation reactions contain ligands, e.g. acetylacetonate, that are rapidly destroyed under oxidizing conditions.

Collins has addressed the problem of ligand design in oxidation catalysis in some detail and developed guidelines for the rational design of oxidatively robust ligands.[12] Although progress has been achieved in understanding ligand sensitivity to oxidation, the ultimate goal of designing metal complexes that are both stable and exhibit the desired catalytic properties remains largely elusive. In this context, an additional requirement has to be fulfilled: the desired catalytic pathway should compete effectively with the ubiquitous free radical autoxidation pathways. In this context it is possible to attribute the results recently published by Minnaard research group, depicted in this thesis (see chapter 7).

6.5 Oxidation of alcohols

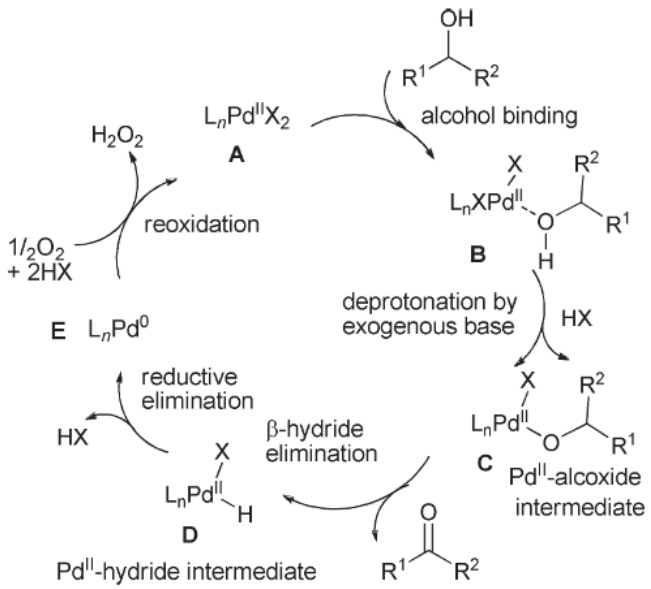
Traditional methods to perform the oxidation of primary and secondary alcohols generally involve the use of stoichiometric quantities of inorganic oxidants, notably Cr(VI) reagents.[13] However, from both an economic and environmental point of view, atom efficient, catalytic methods that employ clean oxidants such as O_2 and H_2O_2 are more desirable.

The catalytic oxidation of alcohols is a heavily studied field, where many metals can be applied. New developments in the 21st century can be discerned, such as the use of nanocatalysts (notably Pd and Au) which combine high stability with high activity. Furthermore, catalysis in water and the use of non-noble metals such as copper are important green developments. In addition, biocatalysis is on the rise. In combination with a mediator, the copper-dependent oxidase, laccase is very promising for alcohol oxidation.[14]

It should be noted that hydrogen peroxide is not really needed for alcohol conversion, compared to the use of oxygen it has little advantage. The focus in this section will therefore be on molecular oxygen.

6.5.1 Pd-based homogeneous catalysts

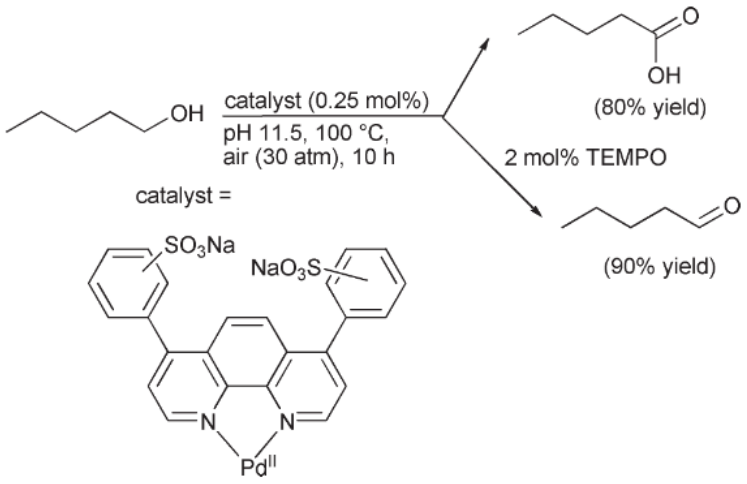
Generally, Pd(II) catalysis is one of the most evolved fields in the aerobic oxidation of alcohols. Much exertion has been dedicated to finding synthetically helpful methods.[15] A large number of mechanistic studies have been undertaken and a broadly accepted mechanism involves initial coordination of the alcohol to the Pd(II) catalyst A to give intermediate B (Scheme 6.7). An exogenous base helps deprotonation of the alcohol to yield the Pd(II)-alkoxide intermediate C. Next, β-hydride elimination affords the Pd(II) hydride intermediate D, that undergoes reductive elimination to give E.[16,17] The transient Pd(0) species E is metastable and prone to aggregation to bulk palladium metal (Pd black) with concomitant loss of catalytic activity. One approach to avoid this issue is to add coordinating ligands, that stabilize the transient Pd(0) species.



Scheme 6.7. The generally accepted mechanism of the aerobic Pd(II)-catalyzed oxidation of alcohols.

The first synthetically helpful system was reported in 1998 by Peterson and Larock, showing that simple $Pd(OAc)_2$, in combination with $NaHCO_3$ as a base in DMSO as solvent, catalyzed the aerobic oxidation of primary and secondary allylic and benzylic alcohols to the equivalent aldehydes and ketones, respectively.[18] Uemura reported an improved procedure using $Pd(OAc)_2$ (5 mol%) that allowed oxidation of primary and secondary aliphatic alcohols in addition to benzylic and allylic ones.[19] This approach could also be applied under fluorous biphasic conditions.[20]

A more active catalyst is represented by a water-soluble Pd(II) complex of sulphonated bathophenantroline developed by Sheldon.[21] This stable and recyclable catalyst (0.25 mol%) permitted oxidation in a two-phase aqueous–organic medium. No organic solvent was necessary (except for solid alcohols) and the carbonyl product was recovered simply by phase separation. Primary alcohols provided the corresponding carboxylic acids by further oxidation of the aldehyde intermediate; differently, in the presence of 1 mol% of TEMPO, the aldehyde was obtained in high yield (Scheme 6.8).

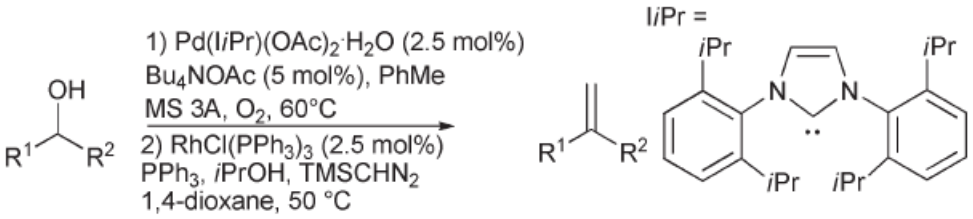


Scheme 6.8. Sheldon's Pd-catalyzed aerobic oxidation of alcohols.

Pd-neocuproine (in the presence of ethylene carbonate as co-solvent) was found to be even more active and exceptionally tolerant to many functional groups such as C=C bonds, triple bonds, halides, ethers, amines etc., thus demonstrating a large synthetic utility.[22] On the other hand, a deeply detailed recent investigation of this latter ligand confirmed that in this case formation of Pd nanoparticles, which are presumably the active catalytic species, occurs.[23]

One of the principal problems linked to homogeneous Pd(II)-catalysts is frequently represented by Pd black formation. Tsuji used substituted pyridines as ligands to prevent formation of Pd black, allowing oxidations to be conducted under air and employing low catalyst loading.[24] Sigman also developed three novel Pd(II)-catalysts,[25] and in a comparison study it has been evaluated the substrate scope and the reaction conditions of each of them, concluding that the $Pd(OAc)_2$/triethylamine system represents the most convenient among the three developed.[26]

Another interesting example of Pd oxidation catalysis in tandem reactions was shown by Lebel and Paquet, applying the catalyst developed by Sigman to the one-pot synthesis of alkenes through a tandem oxidation/olefination process (Scheme 6.9).[27]



Scheme 6.9. One-pot Pd-catalyzed oxidation and Rh-catalyzed methylenation reaction.

Nevertheless, all the Pd(II)-catalysts reported to date are not broadly used on a larger industrial scale. Catalysts with improved stability and activity need to be developed and the research is still very active in this field. A recent study investigated the use of N,O-ligated Pd(II) complexes, which compared well with the previously reported N,N-ligands in the aerobic oxidation of 2-octanol on the gram scale.[28] In this context it is possible to attribute the results recently published by Minnaard research group, depicted in the next chapter of this thesis.

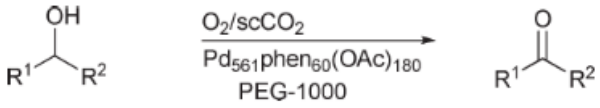
6.5.2 Pd-based heterogeneous catalysts

Beyond the aerobic oxidation of alcohols, palladium catalyzes various oxidative transformations including epoxidation of alkenes, oxidation of terminal alkenes to ketones and other Wacker-type reactions, oxidation of alkanes, hydroxylation of benzenes, and oxidative coupling reactions.[29] Among the transition metals, palladium exhibits very promising catalytic properties in the form of heterogeneous metal catalysts or nanoparticles. For example, Uemura heterogenized $Pd(OAc)_2$ on hydrotalcite (a naturally produced basic clay mineral) and applied it to the oxidation of allylic alcohols such as geraniol and nerol.[30]

The general routes to nanoclusters/nanoparticles synthesis are based on the chemical reduction of transition metal salts with the suitable reducing agent in the presence of a stabilizer for the metal. The resulting stabilized metal nanoclusters dispersed in solution can be applied as catalysts as such or consequently heterogenized on solid supports through different methods, such as surface adsorption, covalent anchoring or embedding by sol–gel techniques.

Several examples of palladium-based heterogeneous catalysts obtained by dispersion of the metal on an inorganic support have been recently reported, such as Pd/MgO[31] or Pd/Al_2O_3.[32] It should be noted that the preparation method of such catalysts is important for the catalytic performance.[33] A specific mechanistic study in the aerobic oxidation of benzyl alcohol by $PdOx/Al_2O_3$ in $scCO_2$ as solvent was undertaken by Grunwaldt and co-workers, that helped to explain the structure–activity relationships at the solid/fluid interphase.[34]

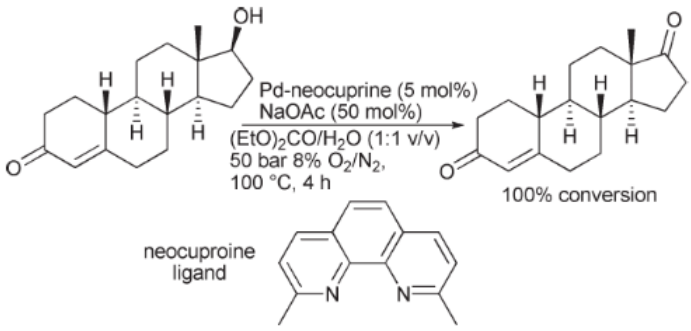
Supercritical CO_2 was also studied by Leitner, who developed a quite different approach. He found that the giant palladium cluster, $[Pd_{561}Phen_{60}(OAc)_{180}]$, dispersed in poly(ethylene glycol) (PEG), efficiently catalyzes the aerobic oxidation of alcohols in $scCO_2$ (Scheme 6.10).[35]



Scheme 6.10. Aerobic oxidation of alcohols catalyzed by PEG-stabilized Pd-nanoparticles in $scCO_2$.

In this biphasic system, the PEG matrix contains the catalyst (helping in preventing aggregation and deactivation of the catalytically active nanoparticles) while the $scCO_2$ phase dissolves the substrate and the product (therefore providing a safe environment for the use of O_2 under essential solvent-free conditions and allowing continuous operation, even with substrates of low volatility). The author postulates that the high activity and long term stability of the novel catalytic system is due to the high dispersion of Pd-nanoparticles in the PEG phase during the reaction. A variety of alcohols were oxidized under these conditions. Both the catalyst matrix and the mobile phase utilized in this approach are toxicologically innocuous and environmentally benign materials, therefore making this approach particularly interesting for “green” nanoparticle catalysis.

As previously mentioned, Sheldon recently demonstrated that, oppositely to the catalytic system based on the bathophenanthroline disulphonate ligand (Scheme 6.8),[21] his previously described homogeneous catalytic system based on Pd(II) acetate in combination with the more hindered neocuproine ligand actually involves palladium nanoparticles.[22] The substrate alcohol acts as the reducing agent and in situ generates Pd-nanoparticles which are the effective catalysts. The catalytic system based on neocuproine-stabilized palladium nanoparticles was applied to the oxidation of nandrolone (Scheme 6.11).[23]



Scheme 6.11. Aerobic oxidation of nandrolone with Pd nanoparticles in aqueous media.

In conclusion, much effort has to be done yet in order to study in detail the mechanisms involved when nanoparticles are formed in the reaction. Certainly, it is difficult to attribute the actual catalytic activity uniquely to the ligand bound palladium or to the palladium nanoparticles.

6.6 Outlook on Pd-catalyzed aerobic alcohol oxidations

During the last years there has been a noteworthy increase of interest in the area of metal-catalyzed aerobic alcohol oxidations. In the area of homogeneous alcohol oxidations, the Sheldon's Pd-(sulphonated bathophenantroline) and the Sigman's $Pd(OAc)_2$/trimethylamine systems are the most ripe.

Also, a notable effort has been made to supplant common organic solvents with alternative solvents such as ionic liquids, fluorinated solvents or supercritical CO_2 or to conduct the oxidation reactions in water or without the use of any solvent at all.

Moreover, the discovery that Pd nanoparticles are effective catalysts for the oxidation of alcohol moieties has expanded this research area in the search for new heterogeneous systems, that can allow recovery and reuse of the metal catalyst and the accomplishment of pure products. From a mechanistic point of view, not much work has been done to explain the fine details for many of the metal-catalyzed aerobic alcohol oxidations, except for Pd-catalyzed ones. Particularly for the new heterogeneous procedures involving nanoparticles, the exact nature of the active catalyst has still to be understood. While there has been an enormous amount of effort applied to the development of metal-catalyzed aerobic alcohol oxidations, many improvements can be still envisioned. To cite an instance, in order to apply these methods in target synthesis, the scope of the individual catalytic systems must be broadened to include more complex alcohols that are synthetically relevant, such as carbohydrates. Moreover, each method should be tested on a larger scale to explore its potential utility in the industrial processes. In this context it is possible to attribute the results recently published by Minnaard research group, depicted in this thesis (see chapter 7).[36]

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[36] a) M. Jager, M. Hartmann, J. G. de Vries, A. J. Minnaard, *Angew. Chem. Int. Ed.*, **2013**, *52*, 7809-7812; b) N. Armenise, N. Tahiri, N. N. H. M. Eisink, M. Denis, M. Jäger, J. G. De Vries, M. D. Witte, A. J. Minnaard, *Chem.Commun.* **2016**, *52*, 2189-2191.

CORRIGENDA

List of additional references

Paragraph 6.1, p. 107: “Oxidation reactions are among the most helpful and applied reactions in industrial processes… In addition, in view of a possible recycling of the catalyst, alternative solvents such as ionic liquids, fluorinated solvents and supercritical CO_2 have been considered.”[i]

Paragraph 6.2, pp. 107-108: “A homogeneous catalyst, that is usually a soluble metal complex, is in the same phase as the reactants, having the advantage to possess catalytic sites accessible to all reagents… Therefore, nanocatalysis is generally considered as the “bridge” between homogeneous and heterogeneous catalysis, because it offers a new sustainable alternative to customary materials.”[ii]

Paragraph 6.3, pp. 108-111: “The ground state of dioxygen is a triplet containing two unpaired electrons with parallel spins… This would obviate the need for a stoichiometric cofactor as a sacrificial reductant, i.e. it would amount to a Mars-van Krevelen mechanism in the liquid phase.”[iii]

Paragraph 6.4, p. 112: “In the majority of catalytic oxidations simple metal salts are used as the catalysts… the desired catalytic pathway should compete effectively with the ubiquitous free radical autoxidation pathways.”[iv]

Paragraph 6.5, p. 112: “Traditional methods to perform the oxidation of primary and secondary alcohols generally involve the use of stoichiometric quantities of inorganic oxidants… The focus in this section will therefore be on molecular oxygen.”[v]

Subparagraph 6.5.1, pp. 113-115: “Generally, Pd(II) catalysis is one of the most evolved fields in the aerobic oxidation of alcohols. Much exertion has been dedicated to finding synthetically helpful methods… A recent study investigated the use of N,O-ligated Pd(II) complexes, which compared well with the previously reported N,N-ligands in the aerobic oxidation of 2-octanol on the gram scale.”[vi]

Subparagraph 6.5.2, pp. 115-116: “Beyond the aerobic oxidation of alcohols, palladium catalyzes various oxidative transformations including… Certainly, it is difficult to attribute the actual catalytic activity uniquely to the ligand bound palladium or to the palladium nanoparticles.”[vii]

Paragraph 6.6, p. 117: “During the last years there has been a noteworthy increase of interest in the area of metal-catalyzed aerobic alcohol oxidations… Moreover, each method should be tested on a larger scale to explore its potential utility in the industrial processes.”[viii]

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[i] C. Parmeggiani, F. Cardona, *Green Chem*. **2012**, *14*, 547-564.

[ii] C. Parmeggiani, F. Cardona, *Green Chem*. **2012**, *14*, 547-564.

[iii] *Green Chemistry and Catalysis* (Eds: R. A. Sheldon, I. W. C. E. Arends, U. Hanefeld), Wiley-VCH Verlag GmbH & Co. KGaA, **2007**, pp. 134-136.

[iv] *Green Chemistry and Catalysis* (Eds: R. A. Sheldon, I. W. C. E. Arends, U. Hanefeld), Wiley-VCH Verlag GmbH & Co. KGaA, **2007**, pp. 136-137.

[v] *Green Chemistry and Catalysis* (Eds: R. A. Sheldon, I. W. C. E. Arends, U. Hanefeld), Wiley-VCH Verlag GmbH & Co. KGaA, **2007**, pp. 138-139.

[vi] C. Parmeggiani, F. Cardona, *Green Chem*. **2012**, *14*, 547-564.

[vii] C. Parmeggiani, F. Cardona, *Green Chem*. **2012**, *14*, 547-564.

[viii] C. Parmeggiani, F. Cardona, *Green Chem*. **2012**, *14*, 547-564.

CHAPTER 7

Deuteration Enhances Catalyst Lifetime in Palladium-Catalysed Alcohol Oxidation

Aerobic oxidation of secondary alcohols catalyzed by the complex [(neocuproine)Pd(μ-OAc)]$_2$-(OTf)$_2$ (neocuproine = 2,9-dimethyl-1,10-phenanthroline) proceeds under mild conditions, but competitive ligand oxidation leads to catalyst inactivation. In an effort to mitigate the oxidative degradation of the catalyst, an innovative deuterated neocuproine-ligated palladium complex is prepared. The catalyst palladium/2,9-CD$_3$-phenanthroline has a 1.8 times higher turnover number than its non-deuterated counterpart in the aerobic alcohol oxidation of methyl glucoside and allows the regioselective oxidation with dioxygen as the terminal oxidant.[i]

[i] This chapter is an adaptation of the original paper: Nicola Armenise, Nabil Tahiri, Niek N. H. M. Eisink, Mathieu Denis, Manuel Jäger, Johannes G. De Vries, Martin D. Witte and Adriaan J. Minnaard, *Chem. Commun*. **2016**, 52, 2189-2191.

7.1 Introduction

The oxidation of alcohols to carbonyl compounds (aldehydes, ketones and carboxylic acids) is one of the most widely used synthetic transformations.[1] In an incessant search for more sustainable technologies, selective catalytic oxidations are environmentally attractive alternatives to those utilizing stoichiometric heavy-metal oxidants.[2] In this regard, palladium-catalyzed oxidations have turned out to be attractive due to the mild conditions and the high chemo-[3] and stereoselectivities.[4] Moreover, the use of air or oxygen as the terminal oxidant contributes to a more atom efficient process, producing water as the only by-product.

Waymouth *et al.* recently reported that cationic palladium complexes[5] ligated by neocuproine ligands[6] catalyze the chemoselective oxidation of vicinal diols to α-hydroxy ketones at room temperature; α-hydroxy ketones are versatile synthetic intermediates and common functional groups in biologically active natural products.[7]

In particular, Waymouth showed that $[(\text{neocuproine})\text{Pd}(\text{OAc})]_2[\text{OTf}]_2$ selectively oxidizes the secondary hydroxyl group of glycerol and 1,2-propanediol with excellent selectivity and yield.[8]

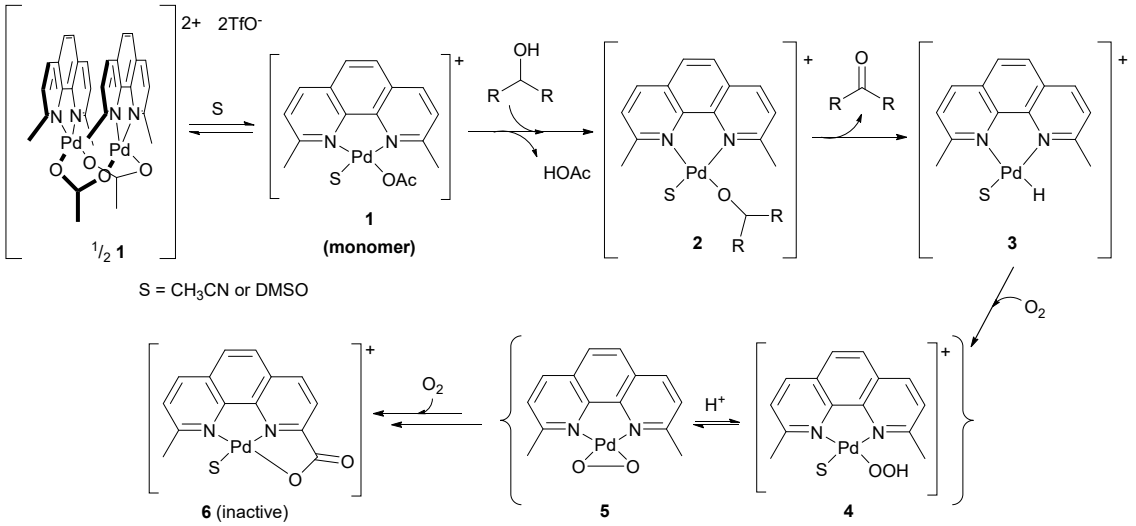
Still on the issue of synthetically suitable natural feedstock, carbohydrate chemistry has always been an intriguing field of research. Especially, the selective oxidation of unprotected carbohydrates, of which pyranosides are the most important representatives, is a longstanding challenge in organic chemistry. The selective oxidation of the primary hydroxyl group in pyranosides has been well-described.[9] In contrast, the selective oxidation of the secondary hydroxyl groups is extremely difficult and marginally known.[10] Since we wondered whether the approach of Waymouth would also be able to discriminate between multiple secondary hydroxyl groups, extending this work, we showed that the catalyst system is also able to discriminate between different secondary hydroxyl groups in the first catalytic, regioselective oxidation of unprotected pyranosyl glycosides to the corresponding ketosaccharides.[11]

Although designed, and effective, for aerobic oxidation, the reactions using air or dioxygen require high Pd loadings up to 10 mol%.[5a,5c,8] This is caused by concomitant autoxidation of the ligand (Scheme 7.1). Oxidation of a methyl substituent via C-H insertion of Pd(II) hydroperoxide (**4**), followed by subsequent further oxidation, forms an inactive palladium complex (**6**).

When employing other terminal oxidants, such as benzoquinone, oxidation of the ligand is much slower and the turnover number of the catalyst therefore considerably enhanced. However, the use of oxygen or air is highly desirable, in particular also for carbohydrate oxidation, as it strongly simplifies the isolation of the products.

The presence of substituents at the 2 and 9 position of the phenanthroline ligand is critical. In this way, the dimeric pre-catalyst is in equilibrium with the active monomeric catalyst in solution. Palladium complexes ligated by unsubstituted phenanthrolines are inactive at room temperature.

Therefore, efforts were made to develop oxidation resistant 2,9-phenanthroline ligands, but with limited success. Also, Waymouth *et al.* reported a mono-trifluoromethyl substituted phenanthroline ligand and studied it in the palladium-catalyzed oxidation of 2-heptanol.[5c] The turnover number of this catalyst doubled, and no ligand oxidation was observed, however at the cost of a 3.7 times lower initial rate compared to **1**. Furthermore, the ligand is difficult to access.



Scheme 7.1. Ligand oxidation in palladium-catalyzed aerobic alcohol oxidation.

Considering the requirement of substituents and their desired resistance against C-H activation, we realized that deuteration of the methyl groups in neocuproine could enhance the stability of palladium catalyst against autoxidation to such an extent that the aerobic alcohol oxidation, in particular of carbohydrates, would become feasible.

The lower zero point energy of the deuterium-carbon bond compared to the hydrogen-carbon bond (around 5 kJ/mol) results in a higher activation energy for C-H bond cleavage manifested as a *kinetic* isotope effect.[12] In addition, as the deuterium-carbon bond is slightly shorter than the hydrogen-carbon bond, also a *steric* isotope effect might be present.[13] Consequently, the deuterated catalyst should be more stable without changing its properties in catalysis.

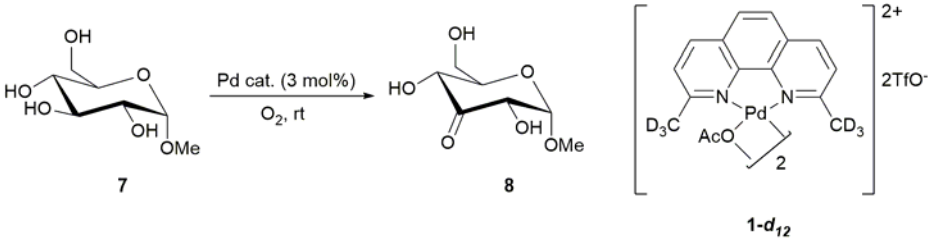
Hydrogen–deuterium (H–D) exchange reactions at carbon witnessed increasing attention since isotopically labelled compounds were recognized as having cumulative significance in NMR spectroscopy and mass spectrometry.[14] For example, deuterated compounds are widely used as efficient tools for mechanistic investigations of chemical reactions,[15] for mapping metabolic pathways[16] and for the structural elucidations of biological macromolecules.[17]

The approach is reminiscent to deuteration strategies in drug development, that are used to enhance the stability of a drug in oxidative metabolism.[18] In synthesis, deuteration has been applied in specific cases to alter reaction selectivity.[19] The strategy of ligands deuteration for tuning their physicochemical properties is reported,[20] to the contrary there are a few papers on the use of deuterium as protecting or steering group to mitigate competitive ligands oxidation pathways.[21]

Besides, efficient deuterium labelling approaches are of high importance to prepare deuterated ligands. Browne *et al*. have described a practical perdeuteration of bipyridine and phenanthroline ligands with $NaOD/D_2O$ at high temperature.[22] More recently, Neranon and Ramström extended this method applying microwave heating.[23]

7.2 Goal

Herein we report that deuteration of neocuproine leads to a significant increase in turnover number in the aerobic Pd-catalyzed oxidation of methyl glucoside (**7**) and allows this reaction to be carried out using oxygen as the sole terminal oxidant (Scheme 7.2).



Scheme 7.2. Regioselective aerobic oxidation of methyl α-D-glucopyranoside at room temperature.

7.3 Results and Discussion

7.3.1 Preparation of deuterated catalyst

Deuteration of the methyl groups of neocuproine was carried out according to the procedure reported for a similar substrate, 6,6'-dimethyl-2,2'-bipyridine.[23] Treatment of **9** with aqueous sodium deuteroxide at 190 °C for 180 min in a microwave provided **9-*d*$_6$** in 99% isotopic purity and 92% isolated yield. The degree of deuteration was determined by NMR using the residual solvent peak as internal standard.

In their early work,[5a] Waymouth *et al.* found that comproportionation of (neocuproine)$Pd(OAc)_2$[6a] and the ditriflate analogue (neocuproine)$Pd(MeCN)_2(OTf)_2$[24] in acetonitrile afforded the dimeric acetate-bridged complex $[(neocuproine)Pd(\mu\text{-}OAc)]_2[OTf]_2$ **1**, which could be isolated and used in aerobic alcohol oxidations. Later, it was shown that dimer formation can be carried out *in situ* preceding the catalysis, and we followed the latter method for the preparation of the deuterated catalyst.[5c] The new deuterated neocuproine palladium precursor complexes **10-*d*$_6$** and **11-*d*$_6$** were prepared similar to their non-deuterated analogues. Complexation of ligand **9-*d*$_6$** with palladium acetate gave **10-*d*$_6$** in 87% yield (pure according to NMR and elemental analysis), and subsequent treatment of **10-*d*$_6$** with triflic acid furnished **11-*d*$_6$** in 93% yield (pure according to NMR, see Experimental Section).

7.3.2 Aerobic oxidation of 2-heptanol

In order to accurately determine the difference in activity between the deuterated and the non-deuterated catalyst, first, the oxidation of 2-heptanol under an oxygen atmosphere at room temperature was studied as a model reaction. This reaction is readily monitored by GC-MS, contrary to the oxidation of methyl α-D-glucopyranoside.

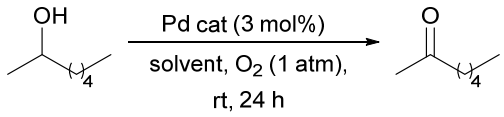
As the goal was aerobic oxidation of carbohydrates, which is carried out in DMSO, we chose this solvent also for the oxidation of 2-heptanol (**12**, 1 mmol, 0.5 M). Deuterated catalyst **1-*d*$_{12}$** (3 mol% of the Pd dimer) prepared *in situ* from the deuterated complexes **10-*d*$_6$** and **11-*d*$_6$** (3 mol% each) exhibited a turnover frequency (TOF) of 13 h^{-1}. The conversion was 81% after 24 h (TON = 13.5, entry 1, Table 7.1). Waymouth and co-workers reported that the addition of water has an accelerating effect on the rate of diol oxidation but not on the rate of mono-alcohol oxidation, and that water (produced by oxygen reduction) does not inhibit the catalyst. In fact, the addition of molecular sieves even leads to a lower initial rate and conversion.[5a]

Therefore, the oxidation of **12** (0.5 M) in DMSO in the presence of 1 mol% of water (with respect to DMSO) was evaluated. Under these conditions, **1-*d*$_{12}$** showed a higher TOF (19 h^{-1}) compared to the reaction in pure DMSO, and full conversion of **12** was reached in 14 h (entry 2, Table 7.1). Although an explanation for this improvement is currently lacking, we attribute it to this solvent system (Figure 7.1).

Subsequently, the maximum turnover number for the deuterated catalyst was determined by doubling the amount of substrate to prevent complete conversion. The oxidation of **12** (1 M) catalyzed by **1-*d*$_{12}$** (1.5 mol%) resulted in 68% conversion of 2-heptanol after 24 h (TON = 23).

Compared to the activity of **1-*d*$_{12}$**, complex **1** shows a similar TOF (20 h^{-1}) but during the course of the reaction the rate decreases to afford 84% conversion after 24 h (entry 4, Table 7.1). Since the oxidation of **12** with catalyst **1** did not result in full conversion, the maximum turnover number of **1** could be directly determined (TON = 14).

Table 7.1. Deuterated vs. non-deuterated neocuproine in the palladium-catalyzed aerobic oxidation of 2-heptanol (**12**).[a]



12 **13**

Entry	Solvent	Pd cat.	Conv. [%][b]	TON	TOF [h^{-1}][e]
1	DMSO	**1-*d*$_{12}$**	81	13.5	13
2	DMSO/H_2O	**1-*d*$_{12}$**	100[c]	17	19
3	DMSO/H_2O	**1-*d*$_{12}$**	68[d]	Max (23)	-
4	DMSO/H_2O	**1**	84	Max (14)	20

[a] Reaction conditions: **12** (1 mmol, 0.5 M), O_2 (1 atm), Pd cat. (3 mol%), solvent, rt, 24 h. [b] Conversion determined by GC-MS (ratiometric method, see Experimental Section). [c] After 14 h. [d] Reaction conditions: **1**2 (2 mmol, 1 M), O_2 (1 atm), Pd cat. (1.5 mol%), DMSO/H_2O (1 mol% with respect to DMSO), rt, 24 h. After 30 h the conversion had not changed. [e] TOF determined by interpolation of reaction progress curves, see Experimental Section.

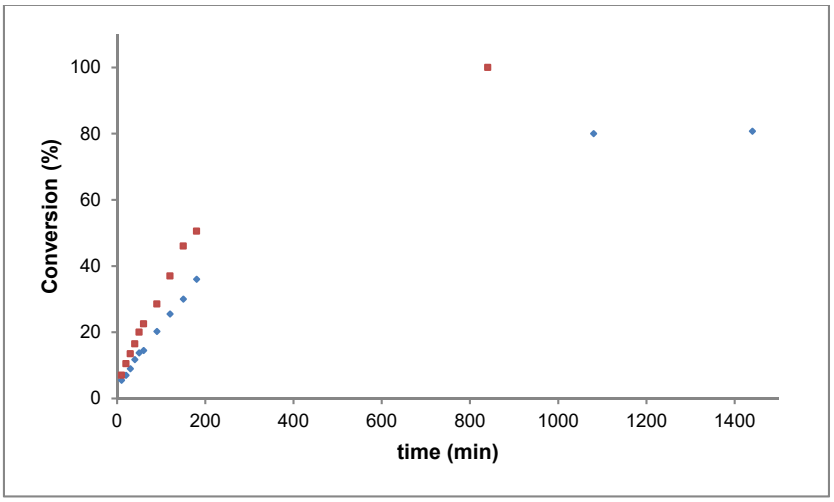


Figure 7.1. Reaction progress curves for the aerobic oxidation of 2-heptanol (**12**) with catalyst **1-*d*$_{12}$** in DMSO (♦) and in DMSO/H_2O (■) at room temperature. The reaction was carried out in *quadruplo* and the mean values were plotted.

The comparison of the reaction curves highlights the improved stability of the new deuterated neocuproine palladium complex **1-*d*$_{12}$** in the oxidation of mono-alcohols, against non-deuterated **1** (Figure 7.2) and the increase in maximum turnover number for **1-*d*$_{12}$** over **1** underlines this further.

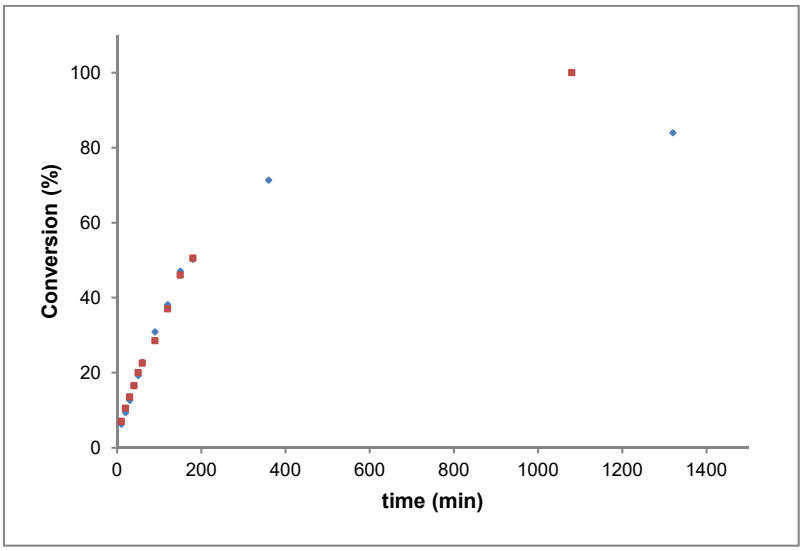


Figure 7.2. Reaction progress curves for the aerobic oxidation of 2-heptanol (**12**) with catalysts **1-*d*$_{12}$** (■) and **1** (♦) in DMSO/H_2O at room temperature. Reactions were carried out in *duplo* with the mean conversion being plotted.

7.3.3 Aerobic oxidation of methyl α-D-glucopyranoside

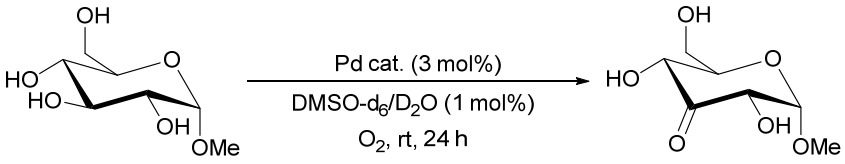
With these results in hand, we focussed on the oxidation of methyl α-D-glucopyranoside (**7**) under the same conditions. As we reported,[11] **7** is selectively oxidized at the C3 position and this permits accurate determination of the conversion by ^{1}H-NMR.

The oxidation of **7** (0.5 M) in DMSO-d_6/D_2O with **1-*d*$_{12}$** (3 mol% Pd cat.) gave a TOF of 8 h^{-1} and full conversion to the sole product **8** within 14 h (entry 1, Table 7.2). Non-deuterated catalyst **1** under the same reaction conditions gave a slightly lower rate (TOF = 7 h^{-1}) and a considerably lower

conversion (58% after 24 h, TON = 10, Figure 7.3). These results demonstrate the increased stability of **1-*d*$_{12}$** in the oxidation of glucopyranosides as well. The TON for **1-*d*$_{12}$** was determined by doubling the amount of glucopyranoside. The oxidation of **7** (1 M) catalyzed by **1-*d*$_{12}$** (1.5 mol%) resulted in 53% conversion of α-D-glucopyranoside after 24 h (TON = 18).

For both substrates **7** and **12**, turnover numbers of the deuterated catalyst are increased by a factor of at least 1.6 compared to the non-deuterated catalyst.

Table 7.2. Catalyst efficiency in the selective oxidation of glucopyranoside (**7**).[a]



7 **8**

Entry	Pd cat.	Conv. [%][b]	TON	TOF [h^{-1}][e]
1	**1-*d*$_{12}$**	100[c]	17	8
2	**1**	58	Max (10)	7
3	**1-*d*$_{12}$**	53[d]	Max (18)	-

[a] Reaction conditions: **7** (1.25 mmol, 0.5 M), O_2 (1 atm), Pd cat. (3 mol%), DMSO-d_6/D_2O, rt, 24 h. [b] Conversion determined by ^{1}H-NMR (ratiometric method, see Experimental Section). [c] After 18 h. [d] Reaction conditions: **7** (2.5 mmol, 1 M), O_2 (1 atm), Pd cat. (1.5 mol%), DMSO-d_6/D_2O, rt, 24 h. After 30 h the conversion had not changed. [e] TOF determined by interpolation of reaction progress curves, see Experimental Section.

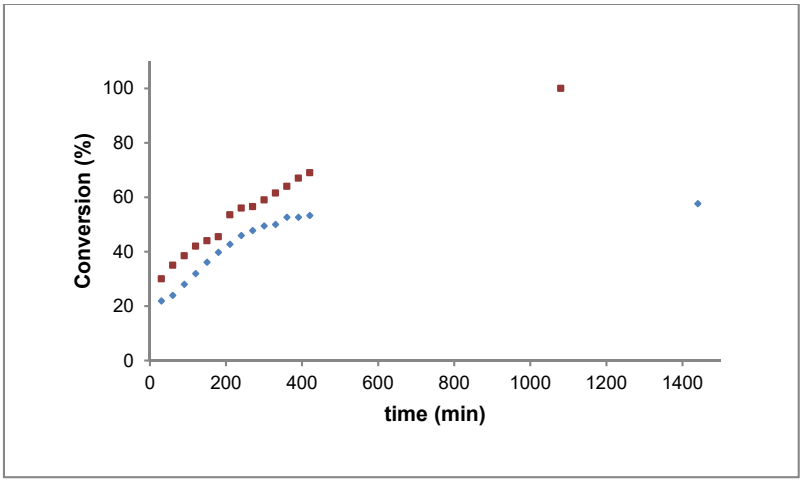


Figure 7.3. Reaction progress curves for the oxidation of glucopyranoside (**7**) with catalyst **1-*d*$_{12}$** (■) and **1** (♦) in DMSO-d_6/D_2O (1 mol%) at room temperature. Reactions were carried out in *duplo* with the mean conversion being plotted.

7.4 Conclusions

Concluding, the straightforward deuteration of the methyl substituents in neocuproine allowed the development of a catalyst system (**1-*d*$_{12}$**) that increased the turnover number in aerobic alcohol oxidation with at least 1.6 times and for methyl glucoside with 1.8 times.

The turnover frequency of the catalyst is similar, as expected, but as inactivation of the catalyst by intramolecular C–H activation is retarded due to the kinetic isotope effect, the catalyst **1-*d*$_{12}$** has a longer lifetime. The increase in turnover number allows the aerobic oxidation of glycosides with acceptable catalyst loadings and this is a major practical advantage compared to the use of benzoquinone, as purification of the oxidation products is considerably simplified.

Deuteration of neocuproine and other pyridine and phenanthroline-type ligands is so straightforward and inexpensive that neocuproine-d_6 (**9-*d*$_6$**) should find application in related catalytic oxidation reactions as well. Although the problem of ligand oxidation is not solved in this way, it is significantly relaxed.

7.5 Experimental Section

7.5.1 General methods and techniques

All solvents used for syntheses, extractions and filtrations were of commercial grade, and used without further purification. Reagents were purchased from Sigma-Aldrich, TCI and Merck, and used without further purification.

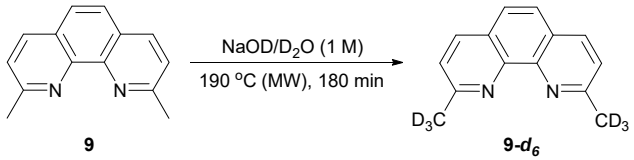
Microwave assisted syntheses were conducted in a CEM Discover Explorer Hybrid microwave.

^{1}H-, ^{13}C- and ^{19}F-NMR spectra were recorded on a Varian AMX400 (400 MHz, 101 MHz and 376 MHz respectively) using $CDCl_3$, CD_3CN or DMSO-*d*$_6$ as solvent. Chemical shift values are reported in ppm with the solvent resonance as the internal standard ($CDCl_3$: δ 7.26 for ^{1}H, δ 77.3 for ^{13}C; CD_3CN: δ 1.94 for ^{1}H, δ 118.3 for ^{13}C; DMSO-*d*$_6$: δ 2.50 for ^{1}H, δ 39.5 for ^{13}C). Data are reported as follows: chemical shifts (δ), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), coupling constants J (Hz), and integration.

GC-MS measurements were performed with an HP 6890 series gas chromatography system equipped with a HP 5973 mass sensitive detector. GC measurements were made using a Shimadzu GC 2014 gas chromatograph system bearing a AT5 column (Grace Alltech) and FID detection.

High Resolution Mass Spectrometry (HR-MS) measurements were performed with a Thermo Scientific LTQ OribitrapXL spectrometer.

7.5.2 General procedure for synthesis of ligand 2,9-bis(methyl-*d*$_3$)-1,10-phenanthroline (9-*d*$_6$)



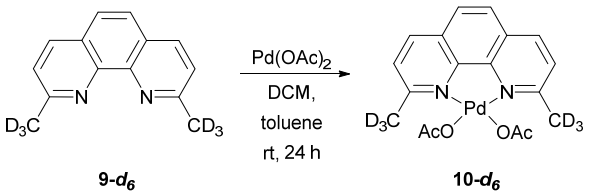
9 **9-*d*$_6$**

Neocuproine (**9**, 2.4 mmol, 500 mg) and 1 M NaOD/D_2O (15 mL) were placed in a 40 mL pressure-resistant glass ampoule. The ampoule was sealed with a silicone cap and placed into a microwave reactor and subjected to continuous irradiation with stirring at 190 °C for 180 min.

The reaction mixture was then allowed to cool to room temperature, followed by filtration of the produced white precipitation by vacuum filtration. The separated product **9-*d*$_6$** was washed with water several times and dried under vacuum. Yield: 470 mg (2.19 mmol, 92%). The degree of deuteration was 99%; determined by ^{1}H-NMR using the residual solvent peak ($CDCl_3$) as internal standard.

7.5.3 General procedures for synthesis of complexes 1, 10-*d*$_6$ and 11-*d*$_6$

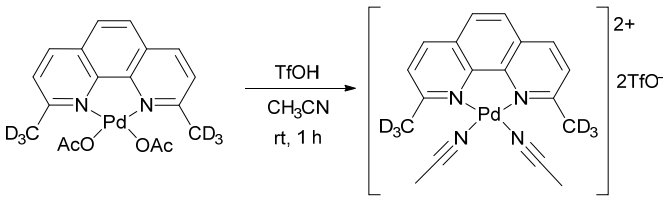
Synthesis of (2,9-bis(methyl-*d*$_3$)-1,10-phenanthroline)Pd(OAc)$_2$ **(10-*d*$_6$)**



9-*d*$_6$ **10-*d*$_6$**

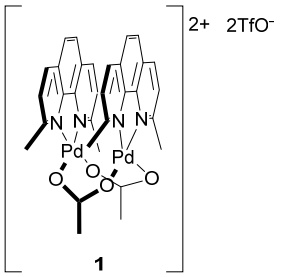
A solution of 2,9-bis(methyl-*d*$_3$)-1,10-phenanthroline (**9-*d*$_6$**) (1.89 mmol, 400 mg) in anhydrous CH_2Cl_2 (7 mL) was added to a solution of $Pd(OAc)_2$ (1.72 mmol, 385 mg) in anhydrous toluene (35 mL) at room temperature under nitrogen. The mixture was stirred overnight and pentane was added to precipitate the complex. Solids were filtered off, washed with acetone and dried under vacuum to give **10-*d*$_6$** as a dark yellow solid (660 mg, 1.5 mmol, 87% yield).

Synthesis of (2,9-bis(methyl-*d*$_3$)-1,10-phenanthroline)Pd(MeCN)$_2$(OTf)$_2$ (**11-*d*$_6$**)



10-*d*$_6$ **11-*d*$_6$**

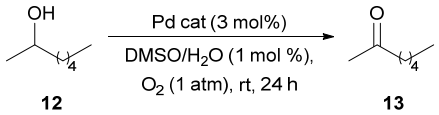
To a slurry of **10-*d*$_6$** (2.5 mmol, 1.1 g) in anhydrous acetonitrile (5 mL) was added a solution of triflic acid (6.2 mmol, 550 µL) in anhydrous acetonitrile (0.33 M, 19 mL) at room temperature under nitrogen. The mixture was stirred for 1 h and diethyl ether was added to precipitate the complex. Solids were filtered off and dried under vacuum to give **11-*d*$_6$** as a light yellow solid (1.62 g, 2.31 mmol, 93% yield).



1

The complex [(neocuproine)Pd(OAc)]$_2$[OTf]$_2$ (**1**) was prepared and crystallized according to the literature procedure.[5a]

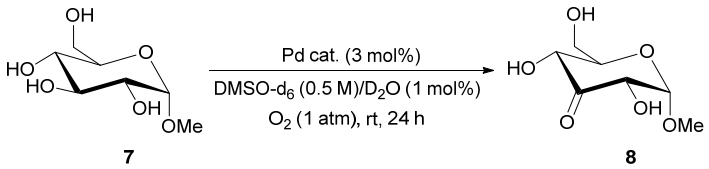
7.5.4 General protocol for aerobic oxidation of 2-heptanol (12)



To a 20 mL vial with magnetic stirrer were added **10-*d*$_6$** (26.32 mg, 0.06 mmol), **11-*d*$_6$** (42.06 mg, 0.06 mmol), DMSO (0.5 M, 4 mL) and H_2O (1 mol%, 10 µL). The mixture was vigorously stirred at room temperature until the Pd complexes had dissolved completely.

To two different 20 mL vials, equipped with magnetic stirrers, were added in each one Pd catalyst solution (2 mL, 3 mol%) and 2-heptanol (**12**) (142 µL, 1 mmol). The reaction mixtures were vigorously stirred at room temperature under a balloon of oxygen. During the reactions, aliquots were taken, quenched by dilution into ethyl acetate, and subjected to GC analysis to determine the conversion of **12**.

7.5.5 General protocol for aerobic oxidation of methyl-α-D-glucopyranoside (7)



To a 20 mL vial with magnetic stirrer were added **10-*d*$_6$** (32.91 mg, 0.075 mmol), **11-*d*$_6$** (52.58 mg, 0.075 mmol), DMSO-d_6 (0.5 M, 5 mL) and D_2O (1 mol%, 12 µL). The mixture was vigorously stirred at room temperature until the Pd complexes had dissolved completely.

To two different 20 mL vials, equipped with magnetic stirrers, were added in each one methyl-α-D-glucopyranoside (**7**) (243 mg, 1.25 mmol) and Pd catalyst solution (2.5 mL, 3 mol%). The reaction mixtures were vigorously stirred at room temperature under a balloon of oxygen. During the reactions, aliquots were taken, quenched by dilution into DMSO-d_6, and subjected to ^{1}H-NMR analysis to determine the conversion of **7**.

7.5.6 Determination of reaction progress

The reaction progress in the aerobic oxidation of both the substrates, 2-heptanol (**12**) and methyl-α-D-glucopyranoside (**7**), was determined using a ratiometric method, shown by the following equation:

$$\% \text{ conversion} = [area_{substrate} / (area_{product} + area_{substrate})] \times 100$$

This equation is valid because:

1) 2-heptanol (and methyl-α-D-glucopyranoside) is converted selectively to 2-heptanone (or methyl-α-D-ribo-hexapyranoside-3-ulose);

2) equimolar amounts of 2-heptanol and 2-heptanone produce the same FID response in GC-MS. In cases where the secondary alcohol and its corresponding ketone produce different detector responses, it is necessary to account for this using a response factor.

7.5.7 Reaction progress curves with indicated standard deviations

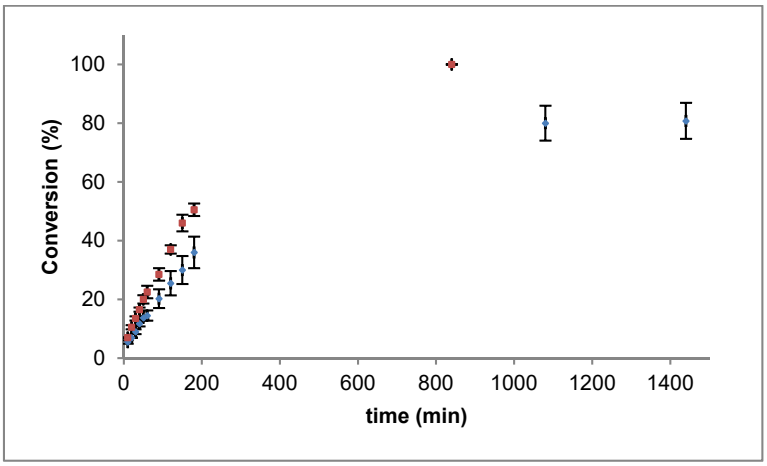


Figure 7.4. Reaction progress curves for the aerobic oxidation of 2-heptanol (**12**) with catalyst **1-*d*$_{12}$** in DMSO (♦) and in DMSO/H_2O (1 mol% with respect to DMSO) (■) at room temperature. Reactions were carried out in quadruplo and the mean conversion and the standard deviation are plotted.

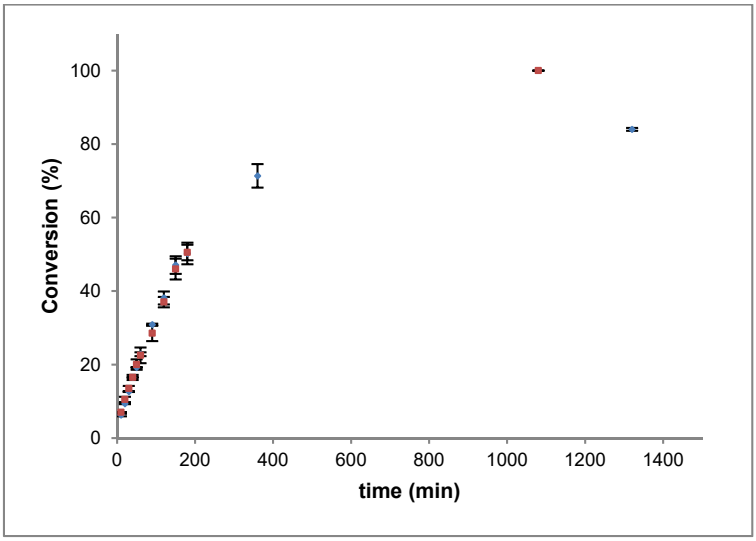


Figure 7.5. Reaction progress curves for the aerobic oxidation of 2-heptanol (**12**) with catalysts **1-*d*$_{12}$** (■) and **1** (♦) in DMSO/H_2O (1 mol% with respect to DMSO) at room temperature. Reactions were carried out in duplo and the mean conversion and the standard deviation are plotted.

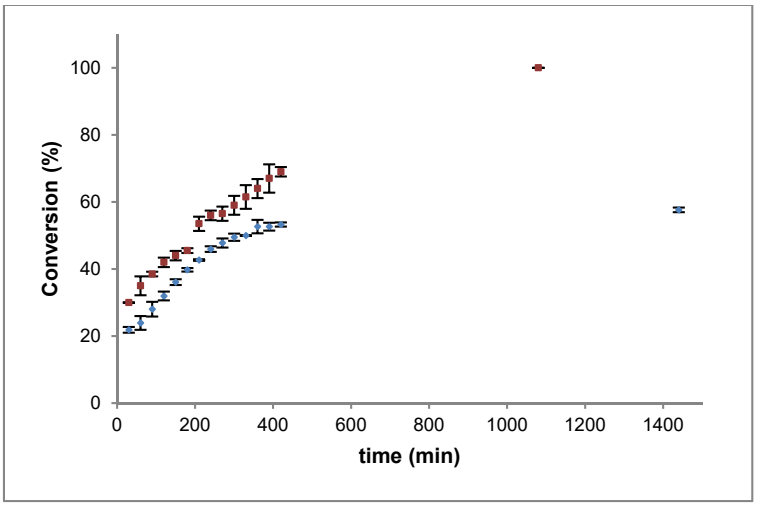


Figure 7.6. Reaction progress curves for the oxidation of glucopyranoside (**7**) with catalyst **1-*d*$_{12}$** (■) and **1** (♦) in DMSO-d_6/D_2O (1 mol% with respect to DMSO) at room temperature. Reactions have been carried out in duplo and the mean conversion is plotted.

7.5.8 Interpolation of reaction progress curves for determination of initial TOF

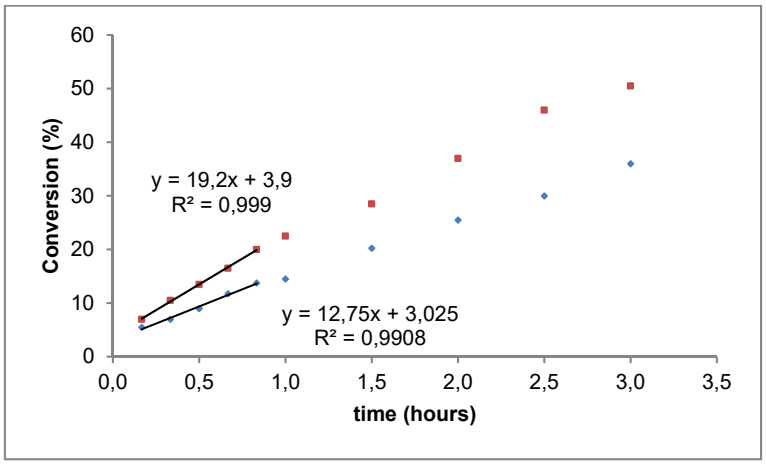


Figure 7.7. Interpolation of reaction progress curves for the aerobic oxidation of 2-heptanol (**12**) with catalyst **1-*d*$_{12}$** in DMSO (♦) and in DMSO/H_2O (1 mol%) (■) at room temperature.

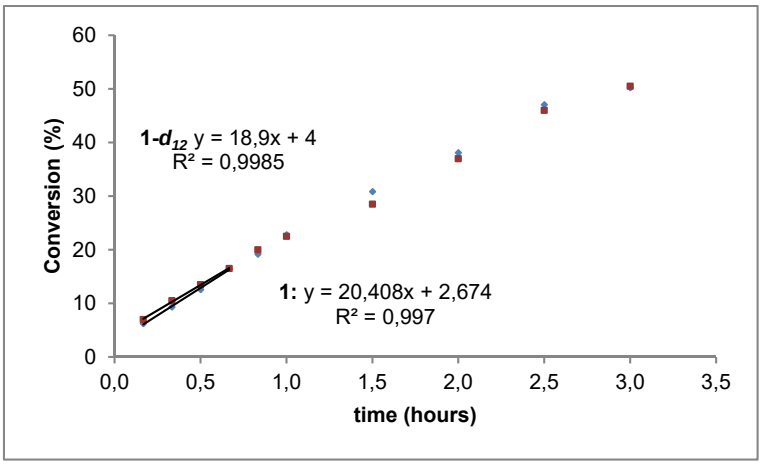


Figure 7.8. Interpolation of reaction progress curves for the aerobic oxidation of 2-heptanol (**12**) with catalysts **1-*d*$_{12}$** (■) and **1** (♦) in DMSO/H_2O (1 mol%) at room temperature.

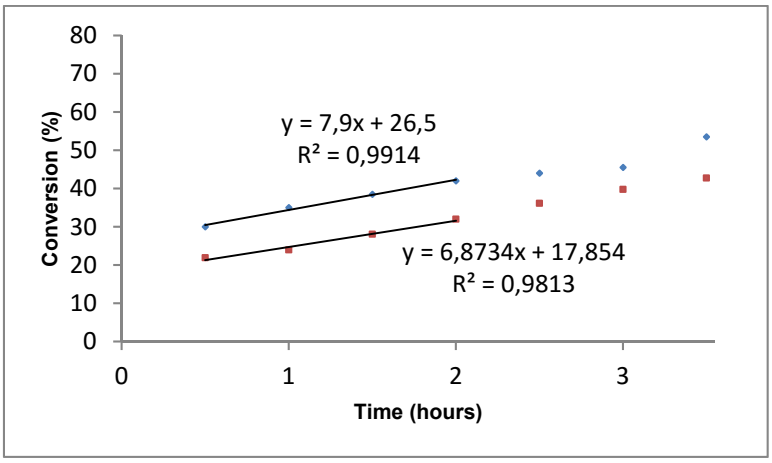
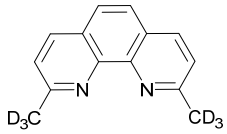


Figure 7.9. Interpolation of the reaction progress curves for the oxidation of glucopyranoside (**7**) with catalyst **1-*d*$_{12}$** (■) and **1** (♦) in DMSO-d_6/D_2O (1 mol%) at room temperature.

7.5.9 Characterization data of ligand (9-*d*$_6$)

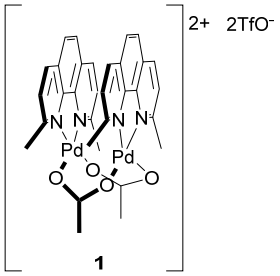
2,9-bis(methyl-*d*$_3$)-1,10-phenanthroline



Off-white solid; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.11 (d, *J* = 8.2 Hz, 2H), 7.69 (s, 2H), 7.48 (d, *J* = 8.2 Hz, 2H); ^{13}C NMR (101 MHz, Chloroform-*d*) δ 159.1, 145.2, 136.1, 126.7, 125.3, 123.3, 25.0; HRMS (ESI+) Calcd. for $C_{14}H_6D_6N_2$ ([M + H]$^+$): 215.145, found: 215.145 (100%); elemental analysis calculated (%) for $C_{14}H_6D_6N_2$ (214.30): C 78.47, H (corrected for deuterium) 2.82, N 13.07; found: C 78.58, H 2.81, N 13.31.

7.5.10 Characterization data of complexes 1, 10-*d*$_6$ and 11-*d*$_6$

[(2,9-Dimethyl-1,10-phenanthroline)Pd(*μ*-OAc)]$_2$(OTf)$_2$ (**1**)

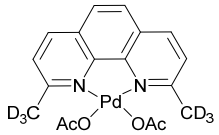


1

Characterization matches literature. Purity confirmed by element analysis.[5a]

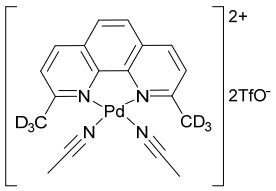
Elemental analysis calculated (%) for $C_{34}H_{30}F_6N_4O_{10}Pd_2S_2$ (1045.582): C 39.06, H 2.89, N 5.36, found: C 38.97, H 2.87, N 5.57.

(2,9-bis(methyl-d_3)-1,10-phenanthroline)Pd(OAc)$_2$ (**10-d_6**)



Pale brown solid; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.37 (d, *J* = 8.4 Hz, 2H), 7.86 (s, 2H), 7.41 (d, *J* = 8.4 Hz, 2H), 2.05 (s, 6H, 2CH_3COO$^-$); ^{13}C NMR (101 MHz, Chloroform-*d*) δ 178.56, 165.21, 147.26, 138.56, 127.98, 126.81, 126.48, 23.09; HRMS (ESI+) Calcd. for $C_{18}H_{12}D_6N_2O_4Pd$ ([M + H]$^+$): 439.075, found ([M - CH_3COO^- + H]$^+$): 379.054 (100%), ([M - 2CH_3COO^- + H]$^+$): 320.041 (28%); elemental analysis calculated (%) for $C_{18}H_{12}D_6N_2O_4Pd$ (438.81): C 49.27, H (corrected for deuterium) 2.76, N 6.48, found: C 49.57, H 3.08, N 6.89.

(2,9-bis(methyl-d_3)-1,10-phenanthroline)Pd(CH_3CN)$_2$(OTf)$_2$ (**11-d_6**)



Pale yellow solid; ^{1}H NMR (400 MHz, Acetonitrile-d_3) δ 8.69 (d, *J* = 8.4 Hz, 2H), 8.08 (s, 2H), 7.78 (d, *J* = 8.4 Hz, 2H); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.87 (d, *J* = 8.3 Hz, 1H), 8.79 (d, *J* = 8.4 Hz, 1H), 8.28 (s, 1H), 8.16 (s, 1H), 7.96 (d, *J* = 8.3 Hz, 1H), 7.89 (d, *J* = 8.3 Hz, 1H), 2.06 (s, 6H, 2CH_3CN); **^{13}C** NMR (101 MHz, DMSO-d_6) δ 164.75, 163.18, 144.95, 140.15, 128.88, 128.54, 127.47, 127.22, 127.07, 126.72, 125.54, 122.34, 119.13, 118.13, 115.93, 1.19; ^{19}F NMR (376 MHz, Acetonitrile-d_3): δ -79.30 (s); HRMS (ESI+) Calcd. for $C_{20}H_{12}D_6F_6N_4O_6Pd^{2+}S_2$ ([M + H]$^+$): 701.006, found ([M - 2CH_3CN - 2$CF_3SO_3^-$ + H]$^+$): 321.048 (100%), ([M - $CF_3SO_3^-$ - 2CH_3CN]): 468.992 (34%); As acetonitrile slowly evaporated from the complex even at low temperature, a correct elemental analysis could not be obtained. This has been noted before, see ref 5a.

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