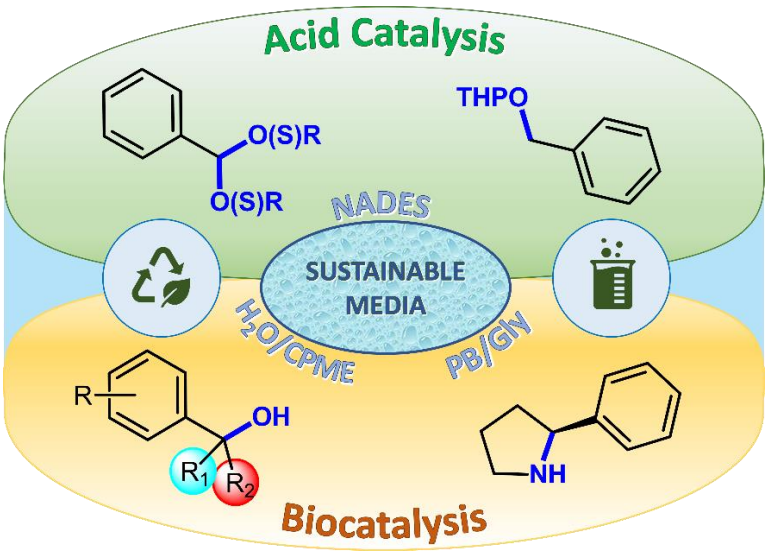
Università degli Studi di Torino

Doctoral School of the University of Turin
PhD Programme in Chemical and Materials Sciences XXXV Cycle

Unconventional sustainable media as efficient promoters in organic synthesis: from reaction development to telescoped approaches



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What I cannot create I do not understand.
Know how to solve every problem that has been solved.

Richard Feynman

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Foreword

My PhD grant was supported by the Italian Ministry of University and Research (MUR) and I worked in the Organic Synthesis research group of the Department of Chemistry in the University of Turin under the supervision of Prof. Salvatore Baldino and Prof. Marco Blangetti. The aim of my PhD project was to revise common synthetic procedures applied in organic synthesis in terms of Green Chemistry perspectives and in the long term of the sustainable development goals.

The focus of my PhD project consisted in addressing the environmental impact of the use of solvents in organic synthesis and in evaluating their substitution with more sustainable options. Solvents are of great environmental concern in a chemical process mainly because they are used in vast quantities; it has been estimated that they represent more than 70% of the waste associated with active pharmaceutical ingredients (APIs) production. Common volatile organic compounds (VOCs), which are the conventional solvents used in most industrial processes, as well as in academic research, possess many drawbacks from an environmental point of view, as they show accumulation in the atmosphere, flammability, high toxicity, and non-biodegradability. However, a "solvent-shift" strategy may also change how functional groups react. The use of non-conventional solvents implies that, at a basic research level, there is a need to investigate novel and often not predictable reactivity, but also unexpected chemo- and regioselectivities. Application of new *greener* conditions to synthetic methodologies, with a focus on strategies to overcome the use of VOCs, was the crucial aim of the investigated chemical processes in my research.

The first two chapters of this thesis give an overview of the nature, origin, and uses of organic solvents (Chapter 1), followed by a deep analysis of their sustainable alternatives (Chapter 2). Chapters 3-6 are dedicated to the scientific development of the PhD project in the background of novel synthetic methodologies in non-conventional sustainable reaction media. A detailed abstract dedicated to these projects' background is given on page 45.

List of abbreviations and acronyms

API	active pharmaceutical ingredient
AZADO	2-azaadamantane *N*-oxyl radical
ChCl	choline chloride
CPME	cyclopentyl methyl ether
DCM	dichloromethane
DES	deep eutectic solvents
DHP	3,4-dihydro-2*H*-pyran
DME	dimethoxyethane
DMF	*N*,*N*-dimethylformamide
ee	enantiomeric excess
EI	electron ionization
ESI-TOF	electrospray ionization - time of flight
FAD	flavin adenine dinucleotide
FID	flame ionization detector
FMN	riboflavin-5'-phosphate
GC-MS	gas chromatography - mass spectrometry
GDH	glucose dehydrogenase
Gly	glycerol
HBA	hydrogen bond acceptor
HBD	hydrogen bond donor
HPLC	high-performance liquid chromatography
HRMS	high-resolution mass spectrometry
IL	ionic liquid
IRED	imino reductase
KRED	ketone reductase
LCA	life cycle assessment
LD_{50}	lethal dose 50
2-MeTHF	2-methyltetrahydrofuran
4-MeTHP	4-methyltetrahydropyran
MMC	methyl(2,2-dimethyl-1,3-dioxolan-4-yl)methyl carbonate
MSDS	material safety data sheet
MT	metric tonn
NADES	natural deep eutectic solvent
NADP	nicotinamide adenine dinucleotide phosphate
NMR	nuclear magnetic resonance spectroscopy
PB	potassium phosphate buffer
PDE	permitted daily exposure
PE	petroleum ether
PMI	process mass intensity
ppm	parts per million
PQQ	pyrroloquinoline quinone

qNMR	quantitative nuclear magnetic resonance spectroscopy
RDES	reactive deep eutectic solvent
R_f	retention factor
SDG	sustainable development goals
scCO2	supercritical carbon dioxide
SCF	supercritical fluid
TAME	*tert*-amyl methyl ether
TBEE	*tert*-butyl ethyl ether
TBME	*tert*-butyl methyl ether
TEMPO	(2,2,6,6-tetramethylpiperidin-1-yl)oxyl radical
THF	tetrahydrofuran
THP	tetrahydropyranyl
TLC	thin-layer chromatography
TMEDA	*N,N,N',N'*-tetramethylethane-1,2-diamine
TMS	trimethylsilyl
TMTHF	2,2,5,5-tetramethyltetrahydrofuran
UV	ultra violet
VOC	volatile organic compound

CHAPTER 1. Organic solvents and Green Chemistry

1.1 Organic solvents: uses and drawbacks

For hundreds of years solvents, and dissolution phenomena in general, have played fundamental roles in numerous industrial processes. The etymology for the word "solvent" comes from Latin, in which the verb "*solvo*" means "to weaken" or "to untie". This meaning corresponds in fact to one of the key properties of solvents, namely the ability to loosen intermolecular interactions between the molecules of the solute separating them from each other through the solvation phenomenon. As early as the 15th century, alchemists began to look for suitable solvents to achieve the dissolution of chemical substances.[1] Throughout the past centuries, solvents have gained increasing attention, and nowadays they surround our everyday life. Ranging from the production of life-saving drugs to the polymer manufacturing processes, solvents play key roles in modern society's needs, product manufacturing, and market demands. In particular, solvents are one of the main actors in industrial chemical processes, and most of the manufacturing methods require various typologies of solvents.

Nowadays, organic solvents are widely used in various industrial sectors including pharmaceutical, paint, oil refineries, agriculture, and food industry (Figure 1.1). The largest demand for organic solvents arises from paint and coating manufacturing (accounting for about 2 million tons per year). For instance, the most common solvents in paints are aromatic (benzene, toluene, ethylbenzene, mixtures of xylenes) and aliphatic hydrocarbons (hexanes, heptane, and light naphtha).[2]

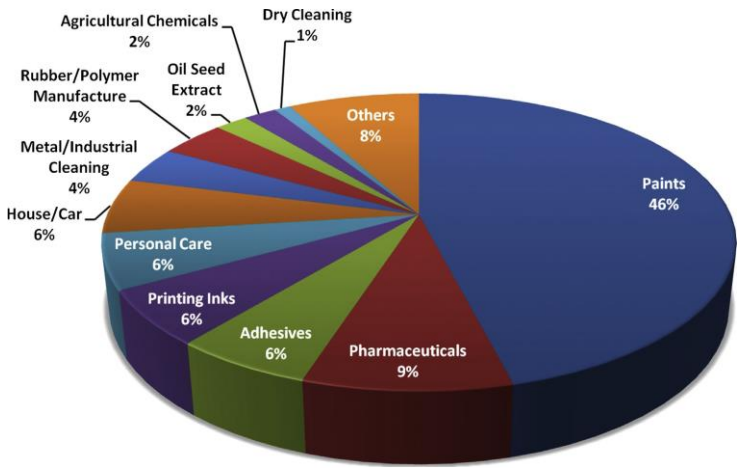

Figure 1.1. Organic solvents consumption in industrial processes. Image adapted from ref. [2]

The pharmaceutical industry, however, counts as the second main use for organic solvents in this classification, being around 10% of the total (Figure 1.1). A growing market with increasing demand for obtaining high-purity drugs via downstream processing. In general, fine chemical industries use large amounts of solvents per mass of final products as reaction media, for purification requirements as well as for chemical plants cleaning. The breakdown of solvent usage by class reveals that the major contributors are alcohols (30%), followed by aromatic hydrocarbons (20%) and diethyl ether (13%).[3] Considering these high volumes of production and usage, it is imperative for solvents to have minimal impact on human health and the environment.[4] Other main common uses of organic solvents (Figure 1.1) are related to the fabrication of personal care products, printing inks, and adhesive-based materials.

Solvents define a significant portion of the environmental response of a chemical process but also affect its efficiency, energy consumption, yield, kinetics, safety, cost, toxicity, and health implications (Figure 1.2).[5]

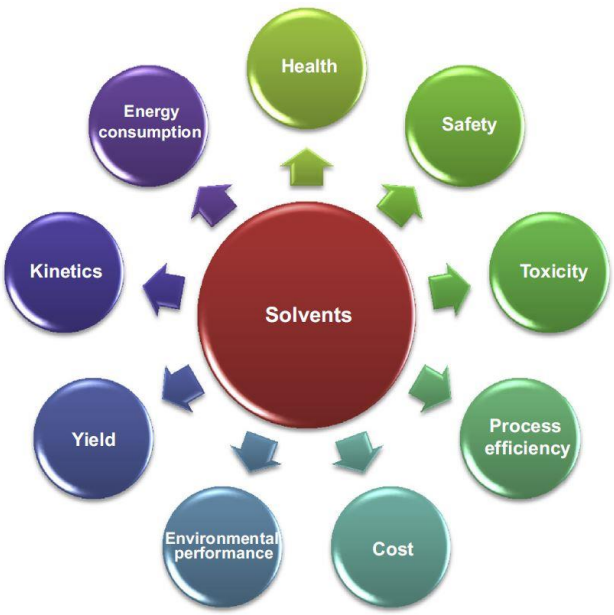

Figure 1.2. Major factors of an industrial process affected by solvent usage. Image adapted from ref. [2]

The pharmaceutical and fine chemical industries produce the majority of their drugs/intermediates in batch processes, which often require multiple reactions and purification procedures. Although in most cases solvents are not present in the final product, they play important roles in most processes, which needs to be considered during process design. The appropriate selection of solvents depends to

a large extent on the application, more specifically on what reagent/product combination needs to be dissolved and under which conditions. Solvents may be used as a reaction media to bring reactants together, or as carriers to deliver chemical compounds in solutions to their point of use in the required amounts. Most APIs are produced using organic reactions in homogeneous solutions, which often utilize large quantities of organic solvents either to perform reactions and/or to ensure the stability of chemical intermediates and final products. Solvents are also used in the pharmaceutical industry for cleaning process equipment and in a wide variety of analytical instruments employed for process control and quality techniques monitoring, for instance, high-pressure liquid chromatography. Solvent use can account for as much as 90% (of which 30% water and 60% organic solvents, estimated) of the total mass in a typical pharmaceutical batch process (Figure 1.3).[6]

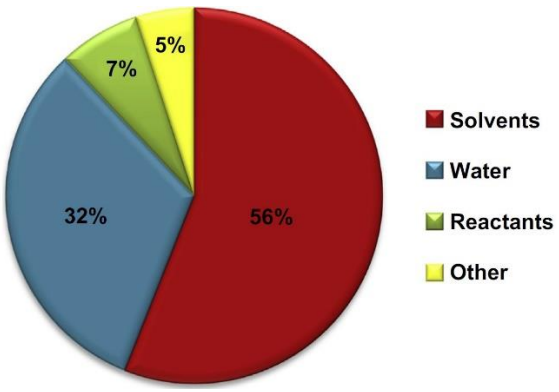

Figure 1.3. Composition by mass % of chemicals used in API production. Image adapted from ref. [2]

Consequently, organic solvents are also a major contributor to the overall toxicity potential associated with these industrial processes,[7] and to the waste generation of chemical industries. Therefore, process development through solvent elimination (neat reactions), minimization, and recycling is of fundamental importance in the 21st century. Some alternative chemical procedures have been proposed to help in reducing the amount of harmful organic solvents.

Mechanochemistry can be used to avoid the usage of solvents altogether;[8] however, these processes are limited by slow reaction rates, high capital costs, and low energy efficiencies. Replacing harmful organic solvents with less toxic alternatives (e.g., chloroform with ethanol) can offer simpler solutions; however, such substitutions can be synthetically restricting and may be economically unfeasible.[9]

In addition, more than half of the chemical production-related waste still does not undergo recycling and reuse, and this trend has not changed in the last decades. Historically, the generation of solvent waste has usually been due to poor solvent selection and process inefficiencies.[2] The waste generated by pharmaceutical companies has increased concerns about human and environmental safety. Direct or accidental release of untreated wastes and toxic chemicals into the environment, along with hazardous work conditions have led to the implementation of numerous new laws and regulations.

These governmental regulations have created a widespread interest in Green Chemistry and sustainable technologies in general.[6, 10] As a result of this growing interest new peer-reviewed journals have been established and the number of published articles including "Green Chemistry", "sustainability" and "recycling" in their keywords has grown quickly in the last two decades.

1.2 Sustainability demand

Despite numerous precautions and regulations, the use of solvents from industrial applications to everyday life tasks inevitably contaminates our environment, including air, soil, and water, because they are inherently difficult to contain and recycle. Consequently, serious threats to humans, animals, and plants arise. Also, other intrinsic major risks have to be considered when dealing with organic solvents like their stability, volatility, and flammability. Both industrial and academic researchers have therefore focused their attention on minimizing solvent consumption through the development of solvent-free processes and more efficient solvent recovery and recycling methodologies. As a matter of fact, the need for a contamination preventive approach and the search for environmentally benign so-called *green* solvents are highly desirable. However, these approaches have their drawbacks and limitations. Opportunities for the practical implementation of such solvents in sustainable chemistry have been reviewed.[1]

A definition of sustainable chemistry should be established and applied for the assessment of each chemical reaction or process. In general, sustainable chemistry should be based on resources, including energy, at a rate at which they can be replaced naturally, and the generation of waste cannot be faster than the rate of their remediation.[11] It should be noted that not all sustainable chemicals, reactions, or processes could be *green*. Therefore, the selection of chemicals, reactions, and processes which are sustainable and *green* at the same time should be preferred.

Some of the greatest challenges of sustainability are energy storage,[12] carbon dioxide,[13] biomass conversion to chemicals,[14] non-toxic and bio-derived

solvents[9] (including water),[15] biocatalysis,[16] renewable and biodegradable polymers.[17] Sustainable chemistry is a concept of increasing interest in the scientific and manufacturing community. Major pharmaceutical companies such as GSK or Pfizer are making increasing efforts to minimize their environmental impact and diminish the risk for the people in their workplace.

To share the same vision of more sustainable and *green* syntheses of APIs, several companies joined working groups, such as the ACS GCI Pharmaceutical Roundtable, formed in 2005. Their mission is to facilitate the implementation of the principles of Green Chemistry and sustainable engineering in the global pharmaceutical industry.[2] Later in 2015, the UN outlined a new sustainability-focused development plan under the title "*Transforming Our World: The 2030 Agenda for Sustainable Development*".[18] The plan is composed of 17 sustainable development goals (SDGs) that address a wide range of issues, many of which recognize the need for *green* and sustainable chemistry and engineering. This ambitious project highlights the role of sustainable imperatives as drivers in chemical research, which provide new challenges, opportunities, and most importantly, a new direction.

1.3 Green Chemistry and *green* solvents

1.3.1 Green Chemistry and the twelve principles

Green Chemistry is defined as the design of chemical products synthesis and processes to reduce or eliminate the use and generation of hazardous substances while reducing energy consumption and moving toward renewable resources.[9] This definition and the concept of Green Chemistry were introduced at the beginning of the 1990s nearly 30 years ago.[19] The most important feature of Green Chemistry is the concept of design. Design is a statement of human intention, and one cannot do design by accident. It includes novelty, planning, and systematic conception. The Twelve Principles of Green Chemistry can be interpreted as "design rules" to help chemists to achieve the intentional goals of sustainability.[20] Green Chemistry is characterized by fine planning of chemical syntheses and molecular design approaches to reduce adverse consequences. Through proper design, one can achieve synergies, not merely trade-offs. Because of this goal, it is not surprising it has been applied to all industry sectors. The concept of Green Chemistry has gained a large impact owing to that it goes beyond the research laboratory and has touched industry, education, environment, and the general public.[20] The Twelve Principles of Green Chemistry were introduced in 1998 by Paul Anastas and John Warner:[21]

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

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

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

IV. **Designing Safer Chemicals**. Chemical products should be designed to preserve the efficacy of function while reducing toxicity.

V. **Safer Solvents and Auxiliaries**. The use of auxiliary substances (solvents, separation agents, etc.) should be made unnecessary whenever possible and, when used, innocuous.

VI. **Design for Energy Efficiency**. Energy requirements should be recognized for their environmental and economic impacts and should be minimized. Synthetic methods should be conducted at ambient temperature and pressure.

VII. **Use of renewable feedstock**. A raw material or feedstock should be renewable rather than depleting whenever technically and economically practical.

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

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

X. **Design for Degradation**. Chemical products would be designed so that at the end of their function they do not persist in the environment and instead break down into innocuous degradation products.

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

XII. **Inherently Safer Chemistry fo Accident Prevention**. Substances and the form of a substance used in a chemical process should be chosen in order to minimize the potential for chemical accidents, including releases, explosions, and fires.

These principles can be applied to all aspects of the process life-cycle from the raw materials used to the efficiency and safety of the transformation, the toxicity, and biodegradability of products and reagents used. They were more

recently summarized by Prof. Martyn Poliakoff *et al*. into the more memorable and convenient acronym, PRODUCTIVELY:[22]

P. Prevent wastes
R. Renewable materials
O. Omit derivatization steps
D. Degradable chemical products
U. Use safe synthetic methods
C. Catalytic reagents
T. Temperature, Pressure ambient
I. In-Process monitoring
V. Very few auxiliary substances
E. E-factor, maximize feed in product
L. Low toxicity of chemical products
Y. Yes, it is safe

These principles constitute an overtop construct for the design of safer chemicals and synthetic transformations. Chemistry has been long perceived by the public as a "dangerous" science and has often been associated with the word "toxic". Designing safer sustainable chemicals and processes requires striving to reduce the intrinsic hazards to a minimum and therefore limiting the risk of accident and damage.[20] The aim of Green Chemistry is in general to reduce hazards across all the life-cycle stages and has been shown to be economically profitable. Hazard is defined as the ability to cause adverse consequences to humans or the environment. Intrinsic hazards of chemical substances or processes can be designed to be minimized at every level, whether their toxicity, physical hazards (e.g., explosion, flammability), or global hazards such as stratospheric ozone depletion. Risks based on these hazards may rise from the nature of the feedstock and raw materials that are used in the chemical transformations as well as the final products that are made. Careful process design, based on the integration of the twelve principles as one cohesive set, will reduce or eliminate intrinsic hazards.[20]

1.3.2 Green Chemistry metrics

During the 1990s a series of metrics have been introduced for the evaluation, in terms of sustainability, of chemical processes and synthesis.[23] Green Chemistry metrics serve to quantify the efficiency or environmental performance of chemical processes and allow changes in performance to be measured. The goal of using those metrics is based on the idea that quantifying technical and environmental

improvements can make benefits of new technologies more tangible, perceptible, and understandable. This, in turn, is likely to aid the communication of research and potentially facilitate the wider adoption of Green Chemistry technologies in the industry. Atom economy, E-factor (Equation 1.1), and process mass intensity are some of the most common mass-based metrics, as they compare the mass of desired product to the mass of waste in chemical processes.[24]

$$\boldsymbol{E-factor} = \frac{Waste\ [g]}{Product\ [g]}$$

Equation 1.1 E-factor calculation for a general chemical process.

The E(nvironmental)-factor is defined as the mass ratio of waste to the desired product. The now well-known table of E-factors for the various segments of the chemical industry was published in 1992.[25] The publication of Table 1.1 provided an important challenge to the industry, particularly for the fine chemical and pharmaceutical sectors, to reduce the amount of waste formed in their manufacturing processes. What was needed was not end-of-pipe remediation of waste but waste prevention at the source by developing cleaner processes. Since the ideal goal was zero-waste manufacturing plants, a new paradigm was clearly needed to achieve efficiency in organic synthesis.[26]

Table 1.1. E-factor parameters range for different industrial segments.

Industry segment	Product tonnage	E-factor
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 (API)	10-10^3	25-100

In addition, impact-based metrics such as those used in life-cycle assessment (LCA) evaluations take into account the environmental impact as well as mass, making them more suitable in the selection of the "*greenest*" option or synthetic pathway.[27]

Today, Green Chemistry is considered a tool for introducing sustainable concepts at the fundamental level and therefore aimed toward inventing new products, routes, and processes, rather than improving the existing ones.[28] Many published articles claim to provide *green* alternatives to existing processes,[29] often by stating how their research complies with one or more of the *green* principles. This viewpoint is in accordance with sustainable chemistry, which takes a more

holistic approach to the development of chemical technologies. A multidisciplinary approach is therefore an integral part of Green and sustainable chemistry at the development stage, due to the inherent interconnections with sustainability.[9]

1.3.3 Green solvents: general features

Solvents are conceivably the most active area of Green Chemistry research.[1, 30] They represent a crucial challenge because they often account for the vast majority of mass wasted in syntheses and processes.[31] Recovery and reuse, when possible, are often associated with energy-intensive distillations and sometimes cross contaminations.

To address all these limitations, chemists began a search for safer solutions in accordance with the twelve principles of Green Chemistry. Solventless systems,[32] water,[33] supercritical fluids (SCFs)[34] and in particular supercritical carbon dioxide ($scCO_2$),[35] ionic liquids[36] polyethylene glycol,[37] and perfluorinated solvents[38] appeared as the most promising investigated approaches for current solvent innovation in the last decades. Although fascinating results have been reported, the use of these solvents is still subjected to strict limitations, i.e. high-cost equipment for $scCO_2$.[39] Whenever possible, the ideal situation from a *green* point-of-view would completely avoid the use of solvents, as the introduction of an auxiliary implies efforts and energy to remove it from a designated system. Efforts have therefore been spent in developing solventless systems.[32] Depending on the physical properties of the reagents used or the desired outcome of the transformation, this approach often requires a new or redesigned chemistry to allow the reaction to proceed without the original solvent and is not appliable in a vast majority of cases in organic synthesis performed in homogeneous conditions (e.g. fine chemical synthesis in the pharmaceutical industry).

During the last decades, the possibility of using biorenewable fuels emerged as a valuable *greener* alternative. Plant biomass is currently considered the primary source of renewable chemicals for the chemical industry.[9] Crops such as sugar cane and corn, agricultural residues, and agroforestry byproducts including timber are considered valuable feedstocks for the generation of renewable fuels and bioderived solvents. The sustainability of biomass production is a complex concept and highly depends on the implementation of sustainable land-management.[40] However, an increase in the cultivation of trees and crops for biomass production could also have secondary benefits such as increased tree cover areas, leading to better air quality, higher soil carbon sequestration, and increased farmers' incomes. The biomass-based economy can offer a potential win–win environment for

addressing the climate change issue and the agricultural economy if implemented in the correct way.

First-generation biofuels such as bioethanol are obtained via sugar or starch fermentation from crops such as corn or sugar cane. In 2010, the world production of bioethanol exceeded 22 billion gallons/year. Bioethanol is mainly used as an additive in gasoline, but could quickly provide a route to renewable ethanol, a highly demanded industrial solvent with low toxicity and useful properties (e.g., polarity and low boiling point). However, the dilemma regarding the risk of diverting farmland or crops for first-generation biofuels production to the detriment of the food supply (food versus fuel debate) does have negative consequences. The biofuel and food price/supply debate involves wide-ranging views, is long-standing and controversial.[41]

Second-generation biofuel production using agricultural residues, grasses, and agroforestry byproducts (lignocellulosic biomass), provides a renewable feedstock without competing directly with the food price or supply, but processing of lignocellulosic biomass is more expensive (in terms of energy and costs). From an industrial perspective, the biorefinery concept faces many challenges. These include feedstock diversity (species-to-species composition differences, geographical locations, and environmental factors), biomass supplies and transport, issues with land usage, and most importantly, economic feasibility.[42] The integrated biorefinery concept is an attempt to recognize the need for flexibility and economic potential in the circular economy emerging landscape of sustainable opportunities.

Taking advantage of highly investigated and gradually more efficient chemical transformations, these "bioprivileged" precursors also offer distinct advantages over current common or *green* solvents, these could provide bioderived solvents with a competitive edge.[42] Some examples of renewable second-generation bioderived solvents, their chemical intermediates, and feedstock precursors are shown in Figure 1.4.

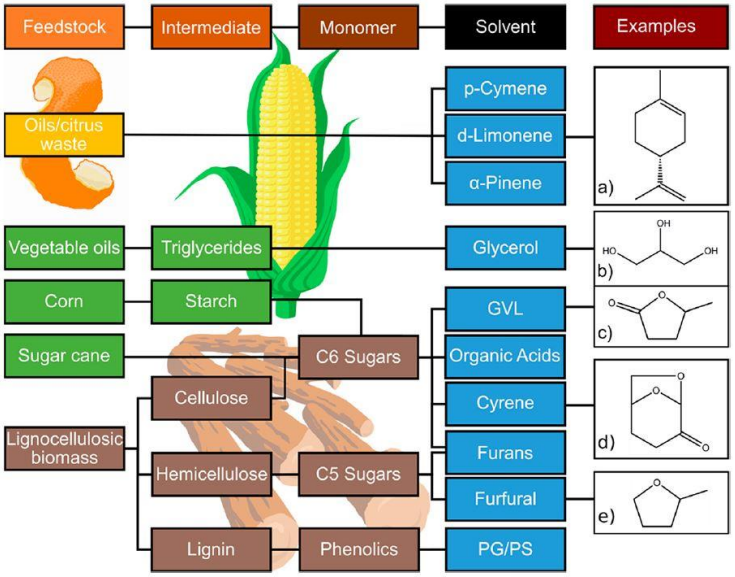

Figure 1.4. Sustainable solvents derived from plant biomass: (a) D-limonene, (b) glycerol, (c) γ-valerolactone, (d) cyrene, (e) 2-MeTHF. Image adapted from ref. [9]

It is worth pointing out that, when a product or chemical is bioderived, it does not mean that it is automatically sustainable with a low health or environmental impact. For example, the aprotic bioderived solvent methyl(2,2-dimethyl-1,3-dioxolan-4-yl)methyl carbonate (MMC) is cleanly synthesized from glycerol in two steps, and it represents a promising replacement for solvents such as dichloromethane, acetone, and ethyl acetate.[43] However, MMC was found to be a mutagen and possible carcinogen, and consequently, MMC was not developed further as a *green* solvent alternative.

Bioderived solvents must be conform to the same regulations as fossil-fuel-derived common organic solvents.[9] Data about toxicity and environmental compatibility have to be collected before the utilization of a *green* solvent on a large scale.

D-Limonene (Figure 1.4-a) derived from citrus peel waste is a potential solvent alternative to toluene in the cleaning sector.[44] The worldwide citrus peel waste was estimated at 65 million metric tonnes (MT) per year, a figure significantly lower than the global toluene consumption at 14.8 million MT. It is theoretically possible for large citrus-producing countries (e.g., Brazil and U.S.) to completely replace fossil fuel-derived toluene in their industrial cleaning sectors with D-limonene derived from citrus peels waste. Unfortunately, terpenes such as *β*-pinene, *α*-pinene, *p*-cymene, and D-limonene have been recently identified as high-risk solvents for environmental emissions.[45] Their moderate inhalation toxicities and high photochemical ozone creation potentials are made worse by their environmental partitioning into the air.[45]

In this context, glycerol emerges with clear advantages compared to other organic solvents. Indeed, glycerol is non-toxic ($LD_{50(oral,\ rat)}$ = 12600 mg/Kg), biodegradable, and non-flammable, and no special handling or storage precautions are required.[46] In particular, the low toxicity of glycerol also allows its use as a solvent in the synthesis of APIs, in which the toxicity and residue of solvents have to be carefully controlled. Also, glycerol is one of the most common components in Deep Eutectic Solvents (DESs) formulations (see Chapter 2, section 2.1.1). Further characteristics and features of glycerol as a valuable sustainable and alternative to common solvents are highlighted in Chapter 2, section 2.2.

Another interesting and valuable second-generation derivative is 2-MeTHF (Figure 1.4-e), a chemical that can be produced from renewable resources using furfural or levulinic acid as substrates.[47] 2-MeTHF can be abiotically degraded by sunlight and air, presumably *via* oxidation and ring-opening concurrent reactions. Hence, 2-MeTHF possesses a promising environmental footprint (biobased and easy to degrade).[48] 2-MeTHF was originally intended as a biofuel; however, it is now considered a renewable alternative to tetrahydrofuran (THF).[48] The production of 2-MeTHF from biomass-derived precursors (agricultural waste) has been calculated to reduce solvent emissions by 97% relative to non-renewable THF production (Figure 1.5).[49]

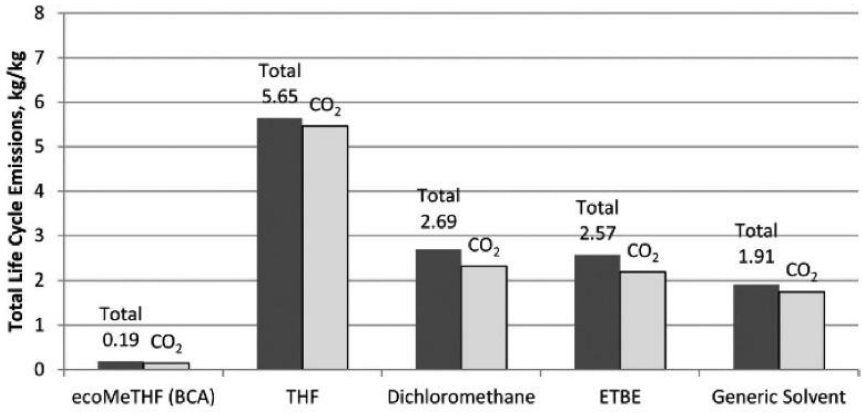

Figure 1.5. Total and CO_2 life cycle emissions for 2-MeTHF (ecoMeTHF), THF, DCM, ethyl tert-butyl ether (ETBE), and a generic solvent (common organic solvent). Image adapted from ref. [9]

From this perspective, the investigation on novel chemical processes in the future will largely depend on lower energy demands, waste prevention, reduced emissions, and the use of renewable materials. As a matter of fact, the employment of alternative non-toxic solvents with a broad range of suitable physicochemical properties will play a central role in achieving these goals. A great deal of efforts to

produce new biobased compounds from renewable sources is providing researchers with a remarkable variety of solvents, some of them with novel structures and unique features and chemistry. Therefore, it is likely and highly desirable that the next generation of sustainable solvents will originate from a wider range of renewable resources, making them more attractive as replacements for non-renewable solvents.

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CHAPTER 2. Bioinspired sustainable reaction media: *green* ethers, glycerol and Deep Eutectic Solvents

2.1 Cyclopentyl methyl ether (CPME) and 2-methyltetrahydrofuran (2-MeTHF) as *green* ethers

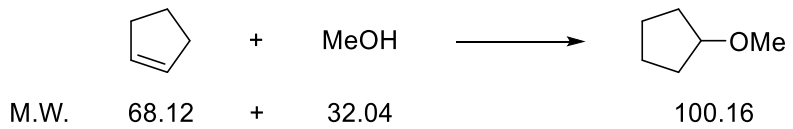
As mentioned, the proper selection of a reaction solvent is crucial in a myriad of synthetic processes to obtain chemicals and pharmaceutical products. From an industrial point of view, safety, health, and environmental aspects are seriously taken into account in addition to the general requirements of solubility, stability, removability (volatility), and compatibility of reactants.[1] Traditional ethereal solvents, such as diethyl ether (Et_2O), tetrahydrofuran (THF), 1,4-dioxane, and 1,2-dimethoxyethane (DME) are widely used in synthesis in many laboratory experiments and in industry today. However, it is highly recommended to replace those with safer and *greener* solvents in pilot-scale synthesis to avoid the associated risks of flammability, explosion from peroxide build-up formation and toxic exposure. Also, partial solubility in water often leads to an inefficient ethereal solvent recovery. The research for new sustainable ethers represents an important perspective as they feature physicochemical properties similar to VOCs but with a reduced overall toxicological and environmental impact.[2]

In this regard, less risky and easy-to-recycle ethereal solvents such as 2-methyltetrahydrofuran (2-MeTHF),[3] cyclopentyl methyl ether (CPME)[4] and 4-methyltetrahydropyran (4-MeTHP)[5] have been developed as alternatives to conventional ethers, which are nowadays widely used in process chemistry.[6] *Tert*-butyl methyl ether (TBME), developed as an antiknock agent for gasoline, is also used occasionally as alternative solvent. However, its flammable nature, low flash point and VOC emissions are matters of concern. In addition, TBME has some limitations such as low solubility of organic compounds in it, and instability under acidic conditions.[7] Other related ethers such as *tert*-butyl ethyl ether (TBEE) and *tert*-amyl methyl ether (TAME), the possible replacements for TBME, are still less common and more expensive, and their use in organic synthesis has yet to be explored.[7a] More recently, 2,2,5,5-tetramethyltetrahydrofuran (TMTHF) has been reported as a non-polar, non-peroxide forming ether, and the solvent properties were found to be similar to those of toluene rather than traditional ethers.[8] The versatility of these solvents has been turned into advantages in several fields, for which their use in the setup of syntheses was investigated. At the same time, significant contributions to more sustainable laboratory waste management could derive from their broader use as substitutes for chlorinated solvents and also in the

chromatographic purifications of reaction crudes.[9] In the following sections CPME and 2-MeTHF will be discussed more in detail as they were used as alternative solvents in my research for this PhD thesis work.

2.1.1 CPME

Cyclopentyl methyl ether (CPME) has proven to be a promising alternative to common VOCs as reaction medium in organic synthesis applications since it does not suffer from some associated drawbacks of other classical ethereal solvents.[4a] The current industrial production of CPME developed by Zeon Corporation is based on the 100% atom economical electrophilic addition of MeOH (reagent and solvent) to the readily available cyclopentene (Scheme 2.1).[4b] A drawback in terms of sustainability is that the primary source for CPME synthesis (cyclopentene) comes from petrochemicals, however, several biomass-based synthetic routes have been investigated for the generation of chemical precursors that may be used for CPME production, such as cyclopentanone or cyclopentanol.[4c] Both these precursors can be synthesized from one of the most important biomass-derived chemicals, furfural, thus creating a potential biogenic pathway for CPME that could be implemented in biorefinery plants in the upcoming future.[10]



Scheme 2.1. Zeon Corporation process for the production of CPME.

CPME has a wide temperature range in its liquid form owing to a high boiling point and a low melting point, an appreciable feature that enlarges its range of suitability for a variety of synthetic approaches. It has also low heat of vaporization and it does form a positive azeotrope with H_2O (azeotrope b.p. = 83 °C, Table 2.1). Additionally, it is highly hydrophobic, which allows for its use as an extraction solvent to reduce the quantities of drying agents during work-up procedures and for its easier recovery by simple distillation. These properties are considered appealing in terms of potential industrial-scale applications.

Table 2.1. Physical proprieties of CPME.[4a, 4b]

Boiling point (°C)	106
Melting point (°C)	<-140
Density (20 ° C, g/mL)	0.86
Solubility in H_2O (23 °C, g/100g)	1.1
Azeotropic boiling point with H_2O (°C)	83
Azeotropic composition (w/w%, CPME: H_2O)	83.7:16.3
Dielectric constant (25 °C)	4.76
Explosion range (vol%, lower limit, upper limit)	1.84-9.9
Latent heat of vaporization (kcal/kg, at the bp)	69.2
Ignition point (°C)	180
Flash point (°C)	-1

Furthermore, the possibility to prepare anhydrous CPME by simpler and more efficient drying with molecular sieves, compared to the well-known anhydrous THF, makes it particularly attractive for organometallic chemistry (Figure 2.1).

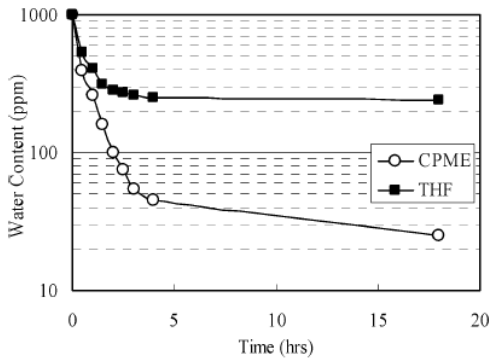


Figure 2.1. CPME drying profile in time with 4Å-MS (compared to THF). Image adapted from ref. [4a]

Additionally, CPME is highly stable under strongly basic conditions.[4a] This parameter, together with its hydrophobicity, is crucial in the design and development of novel procedures and reactions in the presence of *s*-block polar organometallic species.[4b] As a matter of fact, half-lives of *n*-BuLi in various ethereal solvents (THF, DEE, CPME) were compared to assess the relative stabilities in strongly basic conditions. *n*-BuLi is not compatible with THF at "high" temperatures because of the undesired metalation followed by ring opening resulting in

acetaldehyde lithium enolate formation.[11] On the contrary, *n*-BuLi in CPME has an adequate half-life even at 40 °C (Figure 2.2) comparable to diethyl ether solutions.

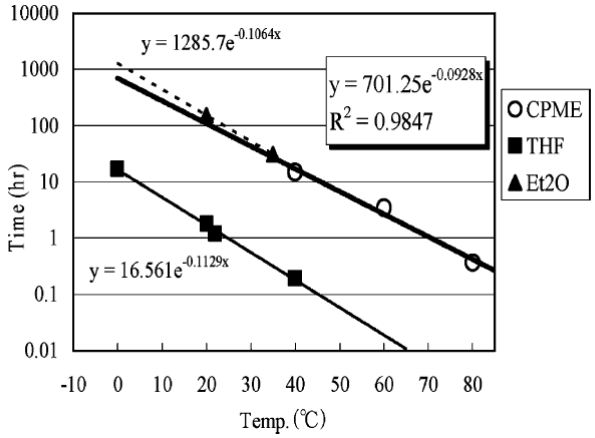


Figure 2.2. *n*-BuLi half-life in ethereal solvents. Image adapted from ref. [4a]

Safety concerns for ethers are closely related to their explosive hazards which arises upon the formation of peroxides (POs). CPME however, shows a particularly high resistance to POs generation compared with other ethereal solvents. This is due to the high bond dissociation energy of the secondary *α*-CH bond (Figure 2.3). For additional safety, CPME is indeed commercially supplied with about 50 ppm of butylated hydroxytoluene (BHT) as a peroxide inhibitor additive, while the commercially available THF contains 250 ppm of BHT in comparison. For the abovementioned features, in addition to its narrow explosion range, CPME can be considered a particularly safe ethereal solvent to be stored and handled.

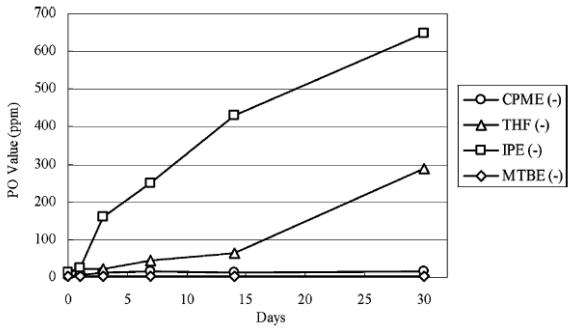


Figure 2.3. Peroxide formation for common ethereal solvents. Image adapted from ref. [4a]

Moreover, several ethers are fairly reactive under acidic conditions. MTBE for example is sensible and tends to cleave into the corresponding alcohols. THF is

also prone to ring-opening process, followed by polymerization. On the other hand, CPME is relatively stable towards Brønsted and Lewis acids, in both homogeneous and heterogeneous conditions.[11] Watanabe *et al.*[4a] reported the relative stability of CPME towards commonly employed Brønsted acids in catalysis or during quenching steps of base-mediated transformations, such as H_2SO_4, HCl, and camphorsulfonic acid. In all cases, CPME showed impressive stability under strongly acidic conditions, also at high temperatures. Recently, Azzena *et al.*[12] reported successful use of CPME and 2-MeTHF as alternative *green* solvents in the synthesis of a variety of acetals and (hemi)aminals carried out under Dean-Stark conditions in the presence of various heterogeneous acidic catalysts. Under these conditions, ammonium salts, either as such or supported over SiO_2, performed better or equally well than widely employed homogeneous and heterogeneous acidic catalysts such as *p*-toluenesulfonic acid. CPME was also successfully employed in a variety of other chemical protocols: transition metal catalysis, organocatalysis, biocatalysis, biphasic systems, oxidations, and radical mediated reactions as well as chromatography in the purification of synthetic intermediates and products.[4b]

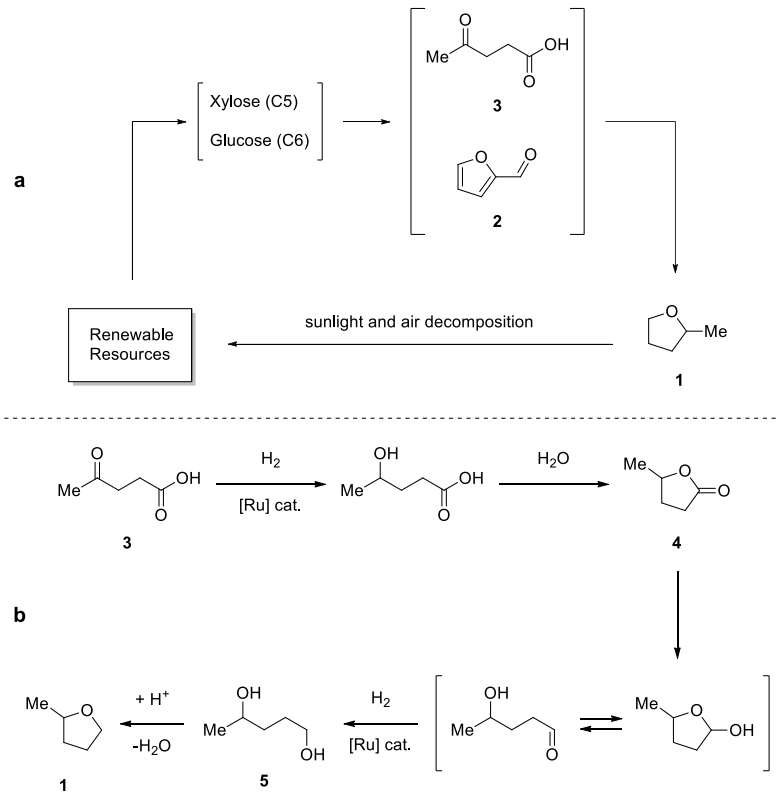
Finally, CPME was reported to have low acute or subchronic toxicity, negative genotoxicity and mutagenicity, and negative skin sensitization (Local Lymph Node Assay). Calculated Permitted Daily Exposure (PDE) values for CPME obtained by 28-day oral toxicity test is 1.5 mg/day, and CPME is thus assumed to be a class 2 equivalent solvent in the ICH (International Conference on Harmonization) Harmonized Tripartite Guideline Q3C (R5). Wide synthetic utility and a detailed toxicity study suggest CPME as a *green* and sustainable solvent of choice for modern chemical transformations.[13]

2.1.2 2-MeTHF

2-MeTHF is emerging in recent years as a promising sustainable alternative to common aprotic ethereal solvents like THF and diethyl ether above all for organometallic-promoted polar reactions.[3b, 3c] Its applications as a reaction medium have significantly increased in accordance with the growing demand for synthetic protocols in line with the sustainability principles of Green Chemistry.[14]

One of the most relevant features of 2-MeTHF **1**, in comparison for example with CPME, is its accessibility from renewable resources as a second-generation derivative. It can be easily synthesized from two routes (Scheme 2.2): (a) by a two-steps hydrogenation of biomass-derived furfural **2**[15] via the formation of 2-methylfuran as intermediate; (b) from levulinic acid **3** via a dehydration-reduction sequence, in which other interesting biomass-derived chemicals are produced, such

as *γ*-valerolactone **4** and 1,4-pentanediol **5**.[16] Moreover, 2-MeTHF can be abiotically degraded in the presence of air and sunlight (Scheme 2.2-a).



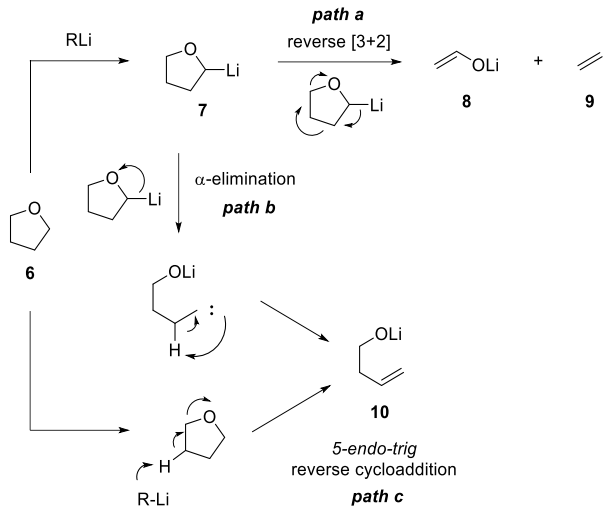
Scheme 2.2. 2-MeTHF synthetic routes. (a) from biomass-derived furfural **2**. (b) from levulinic acid **3**.

Considering the physical properties of 2-MeTHF compared to THF one crucial difference is the water miscibility. THF is miscible with water and this is an issue during common work-up procedures. In general, THF removal *in vacuo* and the employment of other VOCs in a second step for the liquid-liquid extraction process is required. However, 2-MeTHF is highly hydrophobic and it allows for easy work-up procedures avoiding additional organic extractions of the aqueous phases. Similarly to diethyl ether, 2-MeTHF is a water-immiscible ether, however with significantly lower volatility and higher boiling point (see Table 2.2). These properties, along with its polarity and intrinsic Lewis basicity make it suitable for pilot plant-scale applications. Unfortunately, in analogy with THF, the formation of peroxides cannot be avoided, but the use of stabilizers as mentioned previously can positively inhibit this hazardous potential drawback.[3a]

Table 2.2. Physical proprieties of 2-MeTHF compared to THF.[3a]

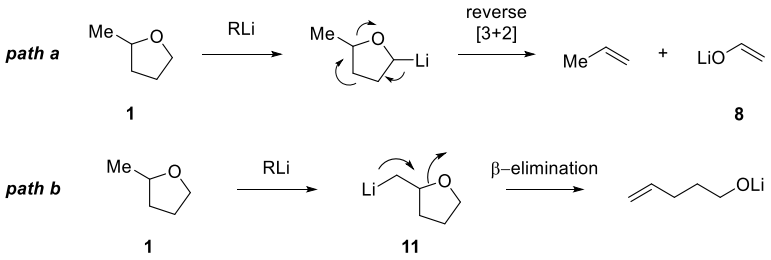
Proprieties	**2-MeTHF**	**THF**
Boiling point (°C)	80	66
Melting point (°C)	-136	-108
Density (20 ° C, g/mL)	0.85	0.89
Viscosity (20 °C, cP)	0.60	0.55
Solubility in H_2O (23 °C, g/100g)	14	miscible
Azeotropic boiling point with H_2O (°C)	71	64
Azeotrope composition (% water)	10.6	-
Dielectric constant (25 °C)	6.97	7.58
Latent heat of vaporization (kcal/kg, at the bp)	87.1	98.1
Flash point (°C)	-11	-14.5

The use of ethereal solvents in polar *s*-block organometallic synthetic chemistry is based on one of their main properties: their capability to disaggregate oligomeric species (e.g. organolithiums in hydrocarbons commercial solutions) resulting in increased reactivity.[17] Furthermore, common ethers have the drawback to be reactive toward organolithiums (see paragraph 2.1.1). It was observed that *n*-BuLi half-life in 2-MeTHF at 35 °C is almost 13 times higher than in THF solutions.[11] The main THF (**6**) decomposition pathway by alkyllithiums, called *α*-cleavage (Scheme 2.3), involves the initial *α*-lithiation to oxygen, followed by a reverse [3+2] cycloaddition of anion **7** to afford ethylene **9** and lithium enolate of acetaldehyde **8**. Then, in the presence of highly basic organolithium-disaggregating agents additives mixtures, such as *t*-BuLi/HMPA 6/1 (HMPA: hexamethylphosphoramide), an alternative pathway is possible, leading to the formation of but-3-en-1-oxide **10**, via a different *α*-elimination (Scheme 2.3, path b) or reverse 5-endo-trig cyclization (Scheme 2.3, path c).[18] These degradation paths mechanisms were proved by trapping the lithiated THF intermediate species.[19]



Scheme 2.3. THF decomposition pathways.

For 2-MeTHF (**1**) however, the presence of an *α*-methyl group decreases its polarity, and the *α*-cleavage is highly suppressed (Scheme 2.4, path a). The decomposition pathway via *β*-elimination is likely reduced since the abstraction of a *β*-proton from the exocyclic methyl group (**1**) could proceed via the formation of a very unstable primary carbanion **11** (Scheme 2.4, path b).[11]

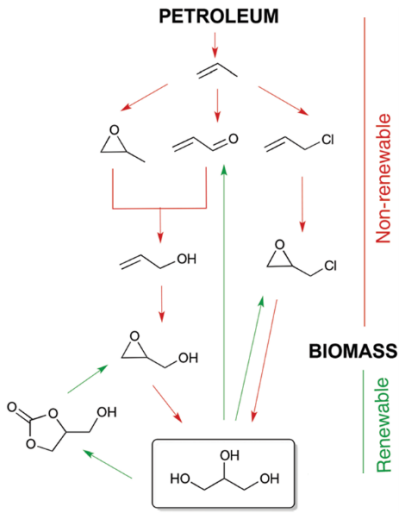


Scheme 2.4. 2-MeTHF **1** degradation pathways.

Finally, water-miscible cyclic ethers, such as THF, are not stable under acidic aqueous conditions being decomposed via ring opening and subsequent polymerization.[20] The use of 2-MeTHF as a sustainable alternative to THF is advantageous due to the lower miscibility in water of 2-MeTHF. The resulting biphasic system preserves the solvent bulk from the hydrolytic acidic conditions. As a result, in 2 N HCl at 60 °C, THF degrades 9 times faster than its *α*-methylated analog.[3a] For the abovementioned features, 2-MeTHF has already reached wide adoption in organometallic chemistry, with clear advantages in both reaction efficiency and sustainability.[3b, 3c]

2.2 Glycerol

Glycerol (also known as glycerin or 1,2,3-propanetriol) is a triol, naturally occurring in the chemical backbone of triglycerides, which are fatty acid esters derivatives of this alcohol. There is currently a huge number of applications of this substance (>2000) in different fields such as cosmetic, pharmaceutical, or food industry, where it is mainly employed as an additive in various formulations as humectant, thickener, lubricant, sweetener or anti-freezer, among other uses.[21] Because of the high industrial demand for this substance, synthetic chemical routes from propene (a petroleum derivative) were developed in the past century to obtain glycerol, mainly through two oxirane intermediates: glycidol and epichlorohydrin (Scheme 2.5).[22] Its production from soap manufacturing or fatty acid production was quantitatively less important.



Scheme 2.5. Synthetic pathways for the industrial supplies of glycerol.

However, the exponential growth of biodiesel production in the last few years has dramatically changed the situation. In the production of biodiesel, glycerol appears as a byproduct, representing around 10 % in weight of the process total output. In the last few years, global glycerol production has surpassed 2 million MT per year. This surplus in the production of glycerol resulted in a decreasing trend in the price of crude glycerol, given the fact that the traditional industrial uses of this substance were not able to absorb the oversupply. To be viable, a *green* solvent has to be cheap and available on a large scale. Glycerol indeed meets these criteria since its cost is around 0.50 €/Kg for pharmaceutical grade purity (99.9%) and 0.15 €/Kg for the technical grade (80%), being sometimes even cheaper than water.

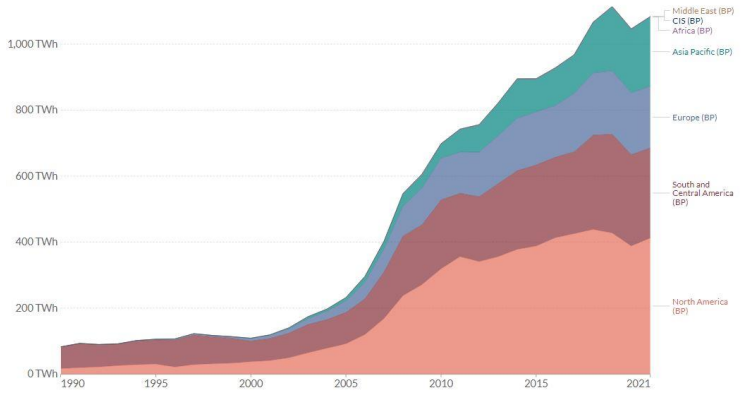


Figure 2.4. World glycerol production divided by region (measured in TW per hour).

As a consequence, in the last few years, an increasing interest has been directed by researchers toward new possible uses of glycerol, which could be advantageous given its high availability. From the mid-2000s several articles and critical reviews have been published on this topic.[23] One of the most common approaches is based on the transformation of glycerol into other small platform molecules which are value-added commodity chemicals (e.g., glycidol, epichlorohydrin, acrolein, propylene glycol).[24] This represents the sustainable "pathway back" within the routes illustrated in Scheme 2.5, in which the non-renewable petroleum sources as starting materials have been substituted by a renewable biomass-derived substrate. Also, the conversion of glycerol into olefins, such as propene or ethylene, has been recently reviewed.[25] One of the possible new uses of glycerol and its derivatives, such as glycerol carbonate[26] and glycerol ethers[27] is as alternative solvents. Even if this topic does not aim to consume glycerol as a reactant, it is noteworthy that its direct use as a solvent offers an economically and environmentally viable application for this natural polyol.

In its pure form, glycerol is a sweet-tasting, clear, colorless, odorless, and viscous polar protic solvent. It can dissolve many organic and inorganic compounds, including transition-metal complexes. Its immiscibility with some common organic solvents, such as hydrocarbons, ethers, and esters, allows easy separation of reaction products, and in the best cases, the possibility of reusing the glycerol phase in further reactions (being completely soluble in water). Glycerol is nonvolatile at atmospheric pressure and has a high boiling point (290 °C, Table 2.3), thus making distillation of the reaction products a feasible separation technique. Moreover, taking advantage of its high boiling point, reactions in glycerol can be carried out at high temperatures, thus allowing acceleration of the reaction, or making possible reactions that do not proceed in solvents with a low boiling point.

Table 2.3. Physical proprieties of glycerol.[22]

Boiling point (°C)	290
Melting point (°C)	17.8
Density (20 °C, g/mL)	1.261
Solubility in H_2O	miscible
Vapor pressure (mmHg at 50°C)	0.003
Dipole moment (D)	2.7
Dielectric constant (25 °C)	44.4
Flash point (°C)	160

In comparison with most common organic solvents, glycerol is non-toxic ($LD_{50(oral,rat)}$ = 12600 mg/Kg), biodegradable, and non-flammable hence, no special handling precautions or storage are required. In particular, the low toxicity of glycerol also allows its use as a solvent in the synthesis of pharmaceutically active ingredients, in which the toxicity and residue of solvents have to be carefully controlled. Despite these advantages, the possible use of glycerol as a solvent also requires chemists to overcome a few obstacles such as:

1. The **high viscosity** of glycerol can induce important mass transfer issues. Fortunately, the viscosity drawback is usually overcome by heating above 60 °C or by using co-solvents, but also by using high-intensity ultrasound or microwave activation in a standalone or combined manner.

2. The **chemical reactivity** of hydroxyl groups can lead to the formation of side products. In particular, the three hydroxyl groups of glycerol are more reactive in highly acidic or basic conditions. Therefore, glycerol has to be used as a solvent in a mild reaction environment to remain stable and avoid decomposition.

3. The **coordinating properties** of glycerol may induce some problems in the use of transition metal complex catalysts. In particular, deactivation of organometallic complexes might occur.[28]

Therefore, innovative solutions should be explored in order to maximize the potential of glycerol. Although it seems difficult, after a few years of investigation researchers have developed some successful examples that not only have

demonstrated the feasibility and the necessity of using glycerol as a solvent but have also contributed to the emergence of efficient methods especially in the fields of organic synthesis, catalysis, separations, and materials chemistry. Glycerol has been used, for these and other miscellaneous applications, both as a single solvent and as a co-solvent, being part of a eutectic mixture, or playing the dual role of solvent and a reagent.

Several examples of the use of glycerol in organic synthesis were reported by numerous research groups. Michael reactions,[29] epoxide ring opening,[29b] synthesis of di(indolyl)arylmethanes,[30] heterocycles synthesis,[31] multicomponent reactions,[32] Pd-catalysed cross couplings,[33] ring-closing metathesis[34] and chemoselective additions of ArLi reagents to nitriles[35] were investigated.

Because of its unique properties such as low toxicity and high affinity for hydrophilic compounds, glycerol has also been proposed as a solvent for bio-catalysis. It has been reported that Baker's yeast catalysed reduction of prochiral ketones can be conveniently performed in glycerol.[36] More recently, a clear improvement in the bioreduction of 2-chloroacetophenones by *Aspergillus terreus* using glycerol as a co-solvent was reported.[37] Comparing these results with those obtained in aqueous or other aqueous-organic media, the use of glycerol as a co-solvent increased the reaction yield while maintaining high enantioselectivities. Yields of chiral benzyl alcohols have been also successfully achieved at preparative scale, thus showing the potential of glycerol for biocatalysis. Despite these promising results, clear explanations of the beneficial impact of glycerol on reaction selectivity are still missing at this stage. Therefore, further efforts are needed in order to shed light on its role in biocatalytic transformations.

The use of glycerol as a sustainable solvent clearly offers new tools in the search for innovative solutions and for the progressive replacement of volatile organic solvents by *greener* alternatives. In general, this new topic largely contributes to widening the portfolio of available *green* solvents. In this context, glycerol has all the features to become a central *green* solvent not only in catalysis or organic chemistry but also in biology and materials chemistry.

2.3 Deep Eutectic Solvents (DESs)

A novel class of solvents has emerged in 2003 and coined as "the solvents of the 21st century" has become well-known as Deep Eutectic Solvents (DESs). Their physicochemical properties and their potential in terms of *green* features, as well as their active role in the course of various organic reactions, prompted the interest of

several research groups in their applications, especially (but not exclusively) in organic chemistry. DESs are nowadays a widespread field of investigation in the academic world. In the present section, a general overview of the characteristics of DESs and their applications in organic synthesis will be discussed.

2.3.1 Composition

DESs can be defined in general as mixtures of two or more components, with a melting point of the corresponding mixture significantly lower than those of the components alone, and are usually liquid at room temperature (i.e. components A and B in Figure 2.5).[38]

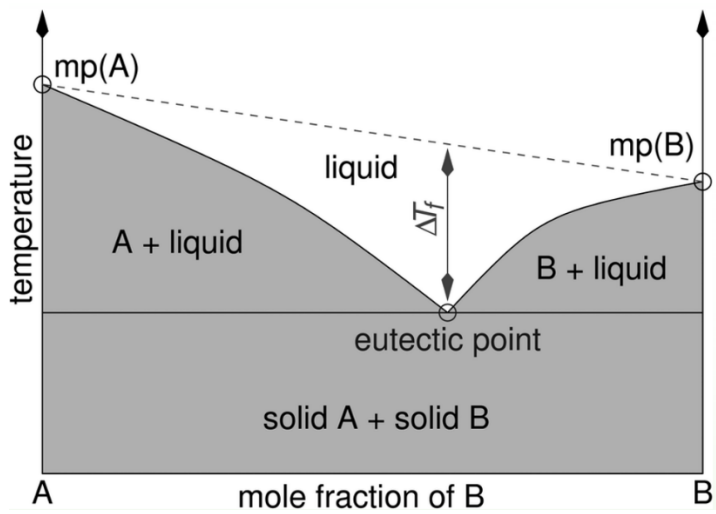


Figure 2.5. General two component (A and B) eutectic diagram.

DESs were considered at the beginning as a new class of ionic liquids (ILs), and in fact they share with ILs some features, such as very low vapor pressure, high viscosities, and the possibility of tuning their properties by an appropriate design. However, this analogy has been overcome, and nowadays DESs and ILs should be regarded as two separate classes of solvents. While an IL is an organic salt composed of one anion and one cation, a DES is always a mixture of two or more compounds (one of them often charge neutral).[39] Paiva *et al.* have reviewed the history and development of DESs and emphasized their potential as "the next generation solvents".[40]

The components constituting a DES are usually small organic molecules able to interact through hydrogen bonding. In most cases, the mixture is composed by a Brønsted or Lewis acid acting as hydrogen bond donor (HBD) and a Brønsted or Lewis base acting as hydrogen bond acceptor (HBA). The role of HBA is often played

by a halide counterion of a quaternary ammonium salt, among which choline chloride (ChCl) stands out (Figure 2.6). In his seminal work in 2003,[41] Abbott *et al.* reported that mixing ChCl (mp = 303 °C) with urea as HBD (mp = 134 °C) in 1:2 molar ratio resulted in the formation of a liquid with a mp of 12 °C. Other commonly employed HBDs are short-chain polyols, such as glycerol, sugars, carboxylic acids, and even water. Metal halides, such as $ZnCl_2$, $FeCl_3$, $CrCl_3$, and others, can also form DESs with organic molecules.[42]

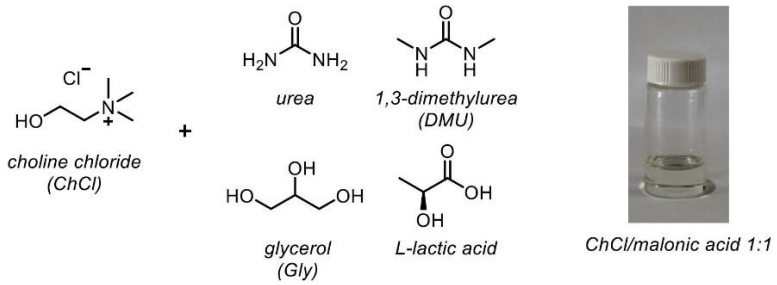


Figure 2.6. Common DESs and a picture of the ChCl (m.p. = 303 °C) and malonic acid (m.p. = 136 °C) based DES in 1:1 molar ratio.

Hydrogen bonding functional groups or species in DES composition gives the mixture a Lewis or Brønsted acidic character, and eutectic mixtures can be classified into five different types (Table 2.4). In types I, II, and IV DESs, the presence of a metal salt such as $ZnCl_2$ gives a Lewis acidic character to the eutectic mixture. On the other hand, in Type III DES the use of tri-carboxylic acids provides the mixture a Brønsted acidic character. The recently proposed type V hydrophobic DESs are solely made of non-ionic precursors.[43] As such, they typically display lower viscosities than their ionic counterparts,[44] negligible vapor pressures,[45] and are chloride-free.

Table 2.4. Different types of DESs.

Type	Composition	Example
I	Organic salt + Metal salt	ChCl + $ZnCl_2$
II	Organic salt + Metal salt hydrate	ChCl + $CrCl_3 \cdot 6H_2O$
III	Organic salt + HBD	ChCl + malonic acid, ChCl + urea, ChCl + glycerol (Gly)
IV	Metal salt + HBD	$ZnCl_2$ + urea, $ZnCl_2$ + Gly
V	HBA + HBD	thymol + (D)-menthol

Hydrogen bonding interactions highly characterize the nature and properties of DESs. The significant lowering in the melting point of the mixture, compared to its single components, has been attributed indeed to the formation of a network of hydrogen bonds between the components of the mixture.[46]

2.3.2 Natural Deep Eutectic Solvents (NADESs)

Recently, the concept of Natural Deep Eutectic Solvent (NADES) has been proposed. In their seminal report of 2011, Verpoorte *et al.* observed that a small number of primary metabolites, such as cholinium, sugars, carboxylic acids, and some amino acids are found in unexpected high amounts in a wide number of living organisms.[47] The hypothesis was that these compounds could be employed by the organism to form eutectic mixtures that would serve as reaction media for the biosynthesis of non-water-soluble organic molecules. It has been also proposed that NADESs may be involved in the self-protection of some organisms towards low-temperature environments.[48] Taking inspiration from this interesting natural phenomenon, several eutectic mixtures have been prepared from bio-derived compounds, and investigated in many different applications.[49] Among those, also hydrophobic DESs based on terpenes or long-chain fatty acids have been reported and studied.[50] The term NADES is thus generally intended to designate deep eutectic solvents composed only by naturally occurring compounds (Figure 2.7).

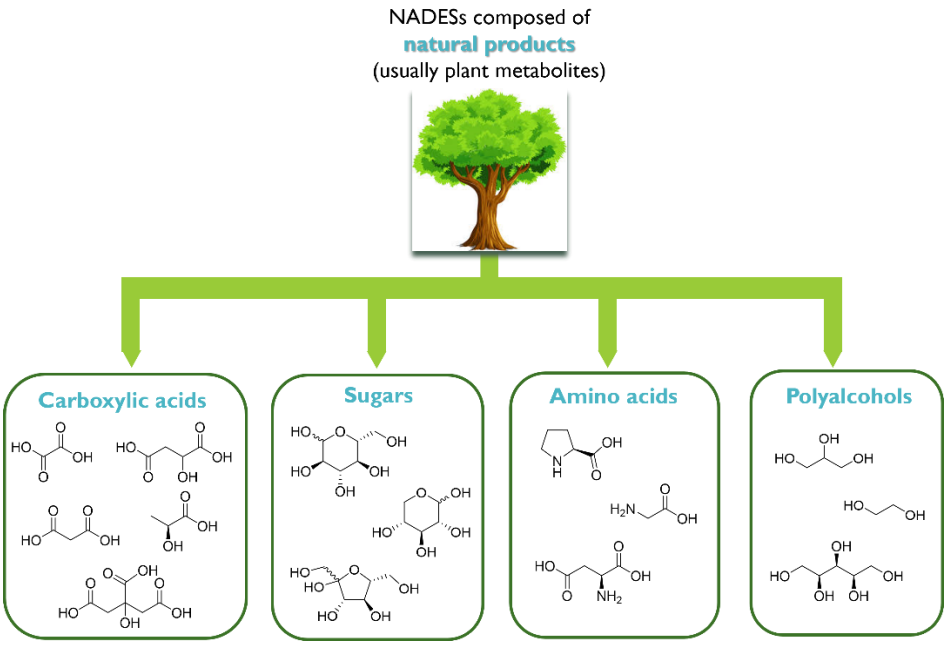


Figure 2.7. Common NADESs components.

The wide range of bioderived components found in DESs and the popularization of NADESs have vastly improved the reputation of deep eutectic mixtures as environmentally friendly solvents. Furthermore, the biocompatibility of NADESs has enabled the development of many biotechnology and bioengineering applications[51] as well as being alternative and sustainable solvents in organic synthesis.[52]

2.3.3 Green credentials

(NA)DESs have emerged as a possible alternative to conventional solvents disclosing a general improvement in terms of sustainability, especially compared to ionic liquids. The first crucial difference between DESs and ILs is that the latter are synthesized via chemical reactions, e.g. alkylation of imidazoles in the case of imidazolium-based ones. The often numerous synthetic steps (considering also their precursors) imply the use of solvents and reagents for reactions, extractions, purification steps, and disposal of waste materials, which are often non-biodegradable.[53] By comparison, the preparation of DESs is much simpler and cleaner: the components are mixed and stirred under heating (often 60–100 °C) until a clear, homogeneous liquid is formed (Figure 2.8), without further purification steps generally required, entailing a procedure that is by definition 100% atom-economic.[54]

Figure 2.8. DESs components mixing stages which affords the liquid and homogenous eutectic.

Among the reasons why DESs are widely considered as *green* solvents is their supposed low toxicity.[14] DESs display negligible vapor pressure, resulting in a low risk for atmospheric pollution and very low flammability. On the other hand, a substantial difference is found in the intrinsic safety of many DESs components, which are often biocompatible. It should be noted that this does not necessarily imply a low toxicity of their combination in a DES. A study by Hayyan *et al*. revealed

a higher toxicity of the considered DESs towards brine shrimp *Artemia salina*, compared to solutions of their single components.[55] On the other hand, opposite outcomes were observed by Yang *et al*. on another aquatic organism, the *Hydra sinensis*.[56] Up to now, evaluations of DES toxicity have been performed on microorganisms, human cell lines, mice, and plants, and the results suggest that the initial assumption of DESs as "biocompatible solvents" still needs deeper and further investigations.[57] Nevertheless, the gathered data suggest DESs be safer than conventional solvents and ILs, in particular when their components are essential ingredients of cellular metabolism.[58] Furthermore, applications of DESs for drug solubilization and administration have already been investigated.[59]

In the sustainability evaluation process for DESs, their whole lifecycle should be considered. NADESs certainly constitute an attractive option since their components are obtained from potentially renewable resources and are often biodegradable. Studies employing the closed bottle test,[60] a standard method in which the substrate is added to an aerobic aqueous medium inoculated with wastewater microorganisms, indicated that several DESs are "readily biodegradable".[57a] Biodegradability is a crucial feature, as it reduces not only the impact on human health and the environment but also the often high costs related to waste disposal.

2.3.4 (NA)DESs in organic synthesis

Along with the widespread investigation of their fundamental physicochemical properties, applications of DESs have been studied in several fields, including metals[38] and metal oxides[61] processing, fuel industry,[62] extractions of bioactive molecules,[63] analytical applications,[64] biomass treatment,[65] DNA and RNA preservation,[66] and solubilization of gases[67] including CO_2.[68] They have also recently gained increasing attention in the research fields of solar energy,[69] photosynthesis,[70] and electrochemistry.[70]

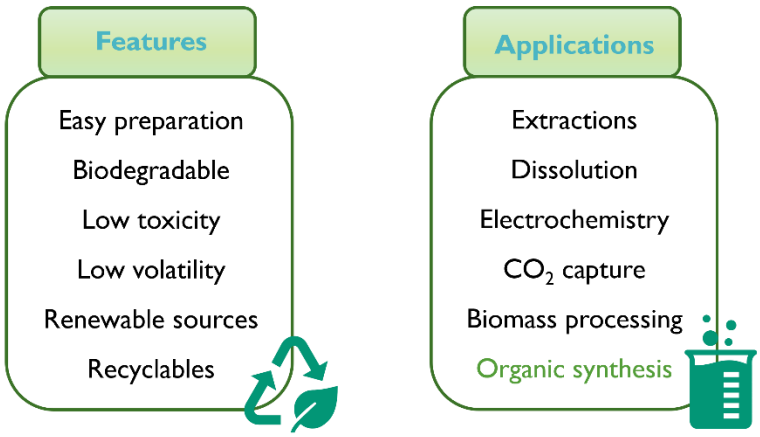


Figure 2.9. DESs notable features and fields of application.

Interestingly, the introduction of DESs in organic synthesis as new possible reaction media has not only directed the research towards the revisitation of a large number of organic reactions under more sustainable conditions but has also disclosed novel and unpredicted reactivities opening new synthetic possibilities.[52]

Numerous examples of metal-mediated organic transformations have been reported in DES.[71] Ru-,[72] Fe-[73] and Au-catalysed[74] isomerizations, Cu-catalysed click chemistry approaches,[75] C–C bond formation such as Pd-catalysed cross-coupling[75-76] and Tsuji–Trost reaction,[77] as well as Rh-catalysed hydrogenation[76b] and alkene hydroformylation[77] processes are some examples of widely investigated topics in transition metal catalysis chemistry.

Also *s*-block organometallics, strongly basic and nucleophilic species such as organolithiums and Grignard reagents, have been used in the DESs strongly protic environment, in some cases under heterogeneous conditions in the presence of an additive. Addition of RMgX and RLi compounds to ketones,[78] regioselective *ortho*-[79] and lateral[80] lithiation of aryltetrahydrofurans were reported.

In particular, the interest of our research group in polar organometallic chemistry has led to some contributions on this topic: regioselective *ortho*-[81] and lateral[82] lithiation of carboxamide derivatives, along with chemo- and regioselective anionic Fries rearrangements promoted by lithium amides under aerobic conditions[83] have been investigated under sustainable conditions using DESs as reaction media.

As testified by the numerous articles and reviews published over the last years,[84] isolated enzymes (e.g., lipases, dehydrogenases, laccases, peroxidases, and lyases) and whole-cell microorganisms are reactive in eutectic media. These biocatalysts are able to convert cheap and simple starting materials into high value-

added products in particular of pharmaceutical interest, working under very mild conditions of pH, temperature, and pressure together with high environmental and economic advantages. Thus, DESs can act as possible alternative reaction media to water in biochemical processes via mimicking metabolites and lipids of the cellular environment, and at the same time preserving proteins' active conformations[70, 85] paving the way in cofactors recycling procedures.[86] Typical features of biocatalytic processes performed in DESs are (a) higher reaction rates (even for poorly water-soluble substrates and products), (b) catalysts selectivity and stability enhancement,[87] (c) higher performances towards competitive side reactions such as hydrolysis, esterifications and amidations[88] and (d) the possibility of performing cascade processes by interfacing metal catalysis with biocatalysis in the same reaction medium for new C-C bond forming reactions and/or functional group interconversions.[89]

During the last year of my PhD, owing to the rising interest among researchers (including our research group) on the topic of biocatalysis performed in non-conventional media, we gave our contribution to collecting the latest trends and developments in the field by recently publishing a review.[90] This review entitled "Combination of Enzymes and Deep Eutectic Solvents as Powerful Toolbox for Organic Synthesis" aims to show the newly reported protocols in the field, subdivided by reaction class as a 'toolbox' guide for organic synthesis.

In general terms, it has been widely demonstrated that DESs can play active roles in promoting organic transformations, thus going beyond the traditional application of reaction medium or solvent. During the last decade, several examples of organic reactions performed in DESs have been reported in the literature, higher yields, and milder conditions are often reported and, in some cases, the elimination of catalysts and additives is easily achieved.[91] In fact, this "non-innocent" effect is an emerging property of eutectic mixtures which has been largely attributed to the supramolecular hydrogen bond network that characterizes DES structures and properties.[46] The case is similar to the definition of organocatalysis (catalysis by small organic molecules). In DESs the hydrogen bond network acts likewise in non-covalent substrates activation mechanisms.

The key roles of both solvents and catalysts/promoters of DESs particularly emerge with acid- and base-mediated reactions. Moreover, the use of DES bearing reactive components to the substrates of interest has been reported in the so-called reactive DESs (RDESs).[92] The choice/design of the right components/molar ratios of the eutectic mixture, especially the HBD, is often crucial for the reaction outcome, as it allows to tune the acid-base character of the DES (Figure 2.10).

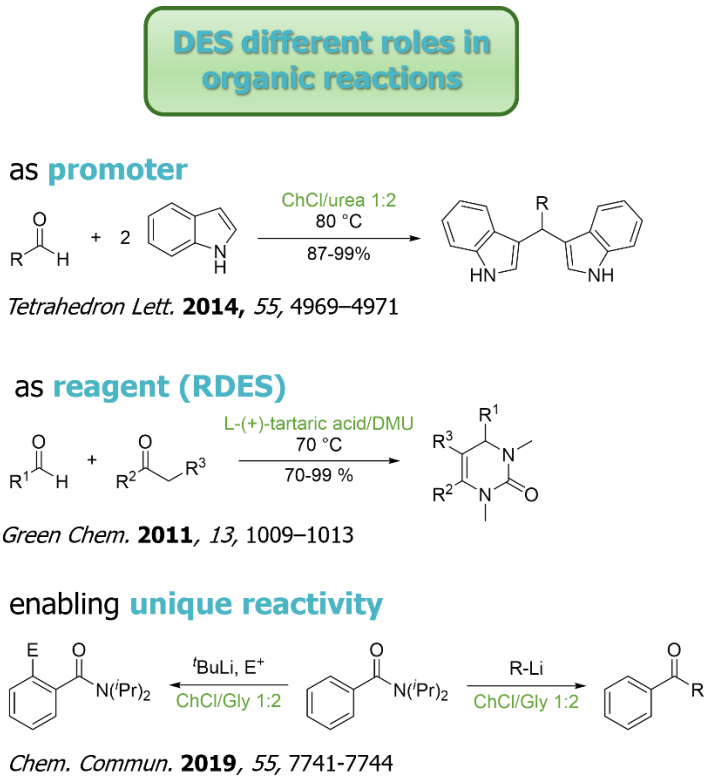


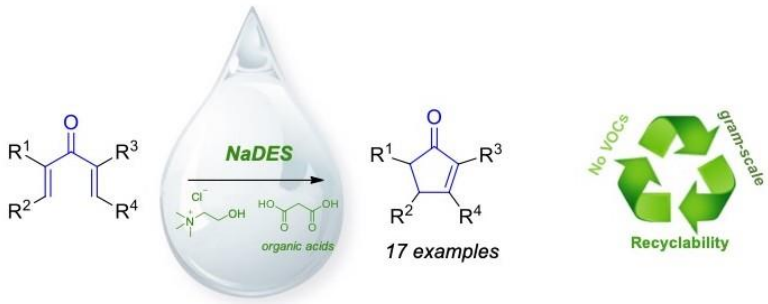
Figure 2.10. DESs active roles in promoting organic reactions.

Accordingly, acidic DESs have been successfully employed in a broad range of acid-catalysed reactions. The catalytic effect can be interpreted mostly by hydrogen bonding between the reactants and DES components. Also, the acidic character is prone to facilitate the breakage of the required bonds in the reaction mechanism.[93]

The use of DESs as acid catalyst has several potential features such as utilization in stoichiometric amount, non-toxicity, possibility of recovery, similar or higher catalytic effect than the sole acidic component, recyclability and reusability without a significant loss of activity. Among Lewis acid catalyzed reactions with type I, II, and IV DESs, chemoselective ring opening of epoxides,[94] amide synthesis from aldehydes and nitriles,[95] Friedel-Crafts alkylations[96] and acylations,[97] cationic polymerizations,[98] *N*-formylations[99] and multi-component reactions[100] were reported. For type III Brønsted acidic DESs D-fructose conversion into valuable 5-hydroxymethylfurfural (5-HMF),[101] Claisen–Schmidt condensations,[102] chemoselective synthesis of tetraketone and xanthene derivatives via tandem Knoevenagel condensation/Michael addition,[103] multicomponent type reactions[104] including Biginelli reactions,[103] functionalized pyrroles synthesis,[105] Paal-Knorr

reactions,[106] and biodiesel production[107] via esterification approach[108] were investigated.

Recently, the interest of our research group was also focused on the use of Brønsted acid-based NADESs for organic transformations. In the present case, we reported the use of sustainable and non-innocent media for the synthesis of cyclopentenones via the Nazarov electrocyclization reaction (Scheme 2.6).[109] The reaction conditions were optimized and the scope was investigated on *C*-, *O*- and *N*-derived compounds. To assess the full sustainability of the proposed approach, the recyclability and scalability of the process were investigated, thus proving that multi-gram preparations are possible with complete recycling of the medium. This work represents a conceptually new, flexible, versatile, and high-yielding methodology, in which the reaction medium plays a dual role both as a solvent and as a promoter of the cyclization. This work can be considered as a proof of concept for the developed projects described in Chapters 3 and 4 of this PhD thesis.



Scheme 2.6. Natural deep eutectic solvents as an efficient and reusable active system for the Nazarov cyclization.[109]

2.3.5 Practical and operational aspects

The physico-chemical properties and the chemical behaviour of DESs influence the laboratory practices and scale-up procedure designs that need to be implemented for the use of these reaction media.

The first crucial propriety for chemical synthesis is viscosity. In analogy with ILs, DESs often present high viscosities (Table 2.5). The typical values are in the range of 101-103 cP [mP·s]. By comparison, toluene (0.59 cP), dichloromethane (0.45 cP at 20 °C), ethyl acetate (0.46 cP), and other organic solvents are much less viscous.

Table 2.5. Viscosity of some DESs determined by NMR diffusion at 25 °C.[110]

DES components		Ratio	Viscosity (cP)[a]
ChCl	glycerol	1:2	259
ChCl	ethylene glycol	1:2	37
ChCl	urea	1:2	750
ChCl	malonic acid	1:1	1124

[a] $cP = mP \cdot s = g \cdot s^{-1} \cdot cm^{-1}$

The viscosity of DESs can be attributed to the hydrogen bond network that characterizes the mixtures. The nature of the components is also fundamental since their relative volume determines the formation of holes in the structure of the fluid, which allow suitable molecular motion.[38, 111] This parameter is of paramount importance for the application of DESs as media in organic synthesis, as it dramatically changes the ability to ensure proper mechanical stirring and homogeneity of the reaction mixtures. The stirring is crucial for reactions outcome since substrates are often not completely soluble in the polar DES media. However, it should be noted that the viscosity of DESs may also be influenced both by water content and additives that can be employed to obtain lower viscosities.[112]

Another crucial aspect to consider to work with deep eutectic solvents is represented by the work-up procedures after the reaction has occurred. From this point of view, this class of solvents appears to be particularly appealing, because DES components are usually water-soluble. The addition of water disrupts the structure of the eutectic mixture, and the components are dissolved into the aqueous layer, where the organic product of the reaction is frequently insoluble. Thus, under optimal conditions, a solid organic product can precipitate and collected by simple vacuum filtration, while in the case of an oil a separate layer could form. This procedure not only avoids sometimes the use of extraction solvents but also triggers the possibility of DESs recycling. Water removal regenerates the eutectic mixture, which can be used again for further reaction cycles, usually up to 5 consecutive runs (depending on the reaction). Other recycling procedures are also feasible: the product can be directly separated from the reaction mixture by extraction using organic solvents (e.g., CPME or EtOAc), which are able to dissolve the organic product but not the more polar DES or its components. Alternatively, a classic aqueous phase/organic solvent liquid-liquid extraction is also possible, followed by vacuum distillation of the aqueous layer to restore the DES.

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Abstract

One of the most crucial challenges of modern synthetic chemistry is the development of new and efficient chemical processes under sustainable conditions. During my PhD project I was involved in such aim by investigating new synthetic strategies based on catalysis and reactivity in unconventional and *green* solvents.

Catalytic transformations represent an incredibly large and diversified area of organic chemistry. New synthetic approaches based on catalytic systems are continuously reported. The efforts in the development of new methodologies are generally oriented towards three main aims, all in pursuit of improving the efficiency and robustness of catalytic procedures as a key aspect of chemical processes:

1) The discovery of novel reactions or the application of known reactivities to new classes of substrates.
2) Improving a known reaction in terms of yield and selectivity.
3) Enhancing the sustainability of a process by reducing both its environmental and economic impact.

The latter aspect has experienced growing attention from the scientific community since the formulation of the 12 principles of Green Chemistry in 1998. Among the main topics, the replacement of hazardous reagents and solvents with safer materials is of the utmost importance. In this direction, alternative, sustainable and unconventional reaction media (discussed in detail in Chapter 2) are of particular interest, because of their promising sustainable features and their effectiveness in promoting several organic reactions without the need for additional additives or catalysts.

In this framework, in the first part of this project acid catalysed processes were investigated. Natural deep eutectic solvents bearing an acidic component were employed as key non-innocent reaction media for the organic transformation investigated. In Chapter 3 the acetalization of carbonyl compounds under feasible conditions was explored. This novel methodology allows for mild reaction conditions (temperature, atmosphere, short time, stoichiometric amounts of reagents) with a large variety of applicability in its scope and for media recycling and reuse, even in multi-gram scale. As an extension of this process, the tetrahydropyranylation of alcohols was investigated and illustrated in Chapter 4. The newly developed procedures offered the possibility to extend the applicability, beyond the reaction scope, on the design of telescoped approaches for one-pot tandem protocols in multi-step synthesis in the same reaction environment, exploiting the chemistry of protecting groups under sustainable conditions.

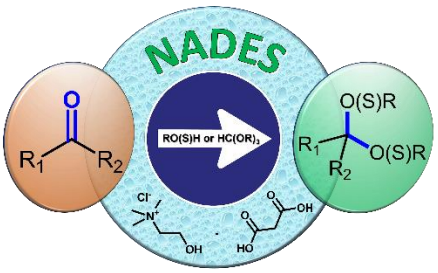
Afterwards, the possibility to perform biocatalysed processes in *green* unconventional solvents has been considered. Following a collaboration with Prof. Ernesto G. Occhiato at the University of Florence, where I spent one month in learning the skills required for working with imino reductase (IRED) biocatalysts, in the last year of my PhD project I focused my efforts on the development of a biocatalysed methodology to achieve the asymmetric reduction of cyclic imine substrates using phosphate buffer/glycerol mixtures as reaction media. The crucial improvements of the methodology, including the sustainability aspects with the use of glycerol as solvent, were also based on the properties of this solvent which gave us the possibility to perform the reaction at preparative scale concentrations and in short reaction times. Details are highlighted in Chapter 5.

Moreover, the chemistry of highly polar *s*-block organometallic compounds has proven to be exquisitely compatible with environmentally friendly operating conditions: the feasibility of running organometallic-mediated transformations under air, at room temperature using new protic '*green*' reaction media and even in water, has broken the traditional paradigm which imposes the handling of both organolithiums and Grignard reagents under strictly anhydrous conditions, using dangerous and toxic dry ethereal solvents at extremely low temperatures to better control their reactivity. In this context, we investigated the possibility to combine enzymatic-mediated organic transformation with the chemistry of RLi/RMgX organometallic compounds, working in aqueous media and under bench-type reactions conditions which are typically employed in biocatalytic chemistry but forbidden for polar organometallic reagents. The new "hybrid" one-pot tandem protocol links the simple experimental connection between a biocatalytic deoximation procedure and the chemoselective and fast addition of RLi/RMgX reagents on transiently formed ketones, giving rise to the desired and highly-substituted tertiary alcohols without the need of any intermediate step (*i.e.*, tedious and time/energy consuming purifications/isolations steps). This last part of the project, discussed in Chapter 6, was carried out during my period as PhD visiting scholar in the group of Prof. Joaquín Garcia-Alvarez at the University of Oviedo, Spain.

CHAPTER 3: Natural Deep Eutectic Solvents as biorenewable systems for efficient and low impact acetalization reactions

Part of the results presented in this chapter are published in *Chem. Eur. J.* **2023**, e202300820 (DOI: 10.1002/chem.202300820).

The synthesis of acetals in acidic Natural Deep Eutectic Solvents (NADES) in which the solvent itself participates in the catalytic promotion of the reaction is herein discussed. The reaction is performed under feasible conditions, open air, without the need for external additives, co-catalysts or water-removing techniques and it is wide in scope. The products are easily recovered, and the reaction medium is fully recycled and reused without weakening of its catalytic activity after 10 times. Remarkably, the entire process has been realized on gram scale.



- *Wide Scope (48 examples)*
- *High Yields*
- *Mild Conditions*
- *Short Reaction Times*
- *Easy scale up/NADES Recycling*
- *Cascade Process*

3.1 Introduction

Among organic compounds, acetals are basilar and widely represented functional groups. Besides being the key functional group in carbohydrates, they are well represented in many other natural compounds, flavouring additives and aroma enhancers in cosmetic and food products,[1] and anti-freezing additives in biodiesel fuels.[2] Acetals are formed from aldehydes or ketones and have the same oxidation state at the central carbon, with substantially different chemical stability and reactivity compared to the analogous carbonyl compounds. Carbonyl moieties, such as aldehydes, have a crucial synthetic interests and are classified among the most widely used functional groups in organic synthesis.[3] In some cases, their high reactivity towards nucleophilic, metal-hydride, alkyl- and aryl- reagents, constitutes an inhibiting factor that needs to be confronted, in order to achieve the desired synthetic transformations. As a matter of fact, the protection of carbonyl functional groups into acetals with alcohols or diols is a widely employed method in pharmaceutical industry, i.e. in drug design, and other fields.[4] The importance of

acetals as carbonyl protecting groups relies in their stability under neutral and strongly basic conditions, which allows a wide spectrum of reactions to occur in their presence. Acetals, apart from their role as protecting groups, can also be exploited as excellent intermediates in many synthetic transformations.[5]

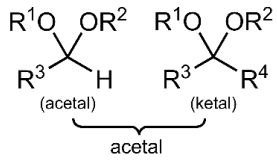
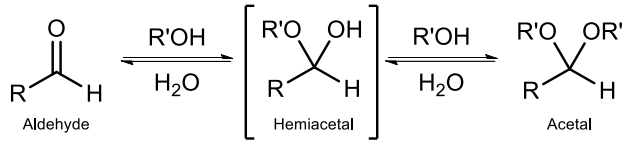


Figure 3.1. Generic structure of acetals.

The term ketal (Figure 3.1) is sometimes used to identify structures associated with ketones (both R- groups organic fragments) rather than aldehydes and, historically, the term acetal was used specifically for the aldehyde-related cases (having at least one hydrogen in place of an R- on the central carbon). However, in contrast to the historical usage, ketals are now a subset of acetals, a term that now encompasses both aldehyde- and ketone-derived structures.[6] Acetals are stable compared to their parent hemiacetals intermediates (Scheme 3.1), but their formation is a reversible equilibrium.



Scheme 3.1. Acetal formation from aldehydes.

The formation of acetals reduces the total number of molecules in the system (carbonyl + 2 R'OH → acetal + water) and therefore is generally not favoured with regards to entropy, whereas the use of a single diol molecule (carbonyl + diol → acetal + water) does not cause significant entropic variations. Another way to avoid the entropic cost is to perform a transacetalization using a pre-existing acetal-type reagent as the OR'-group donor rather than simple addition of alcohols themselves. One type of reagent used for this method is an orthoester (Figure 3.2).[7] In this case water removal is achieved by hydrolysis with excess orthoester to form the corresponding alcohol.

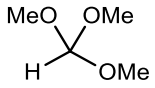


Figure 3.2. Trimethylorthoformate, an orthoester.

Traditionally, acetals are generated starting from aldehydes or ketones and alcohols in the presence of typical strong acid catalysts (trifluoroacetic acid, *p*-

toluenesulfonic acid, dry HCl or H_2SO_4 among others) which are often used in stoichiometric amount and are corrosive.[8] In addition, acidic conditions are often incompatible with many functional groups of the substrate such as alkenes, alkynes, silyl-protected alcohols and *N*-Boc-protected amines among others.[9]

In addition, acetals often suffer of high hydrolytic instability because of the reversibility of the reaction equilibrium (Scheme 3.1), making water removal essential to avoid the backshift of the equilibrium to hemiacetals and eventually to carbonyl starting materials. Dehydrating agents or azeotropic removal (water/toluene mixtures often employed) are common solutions for such purpose. Dean-Stark distillation[10] is the most common technique for azeotropic water removal (Figure 3.3), however it requires refluxing the reaction mixtures at high temperatures, with consequent long reaction times, resulting in too harsh conditions for sensitive functionalities.

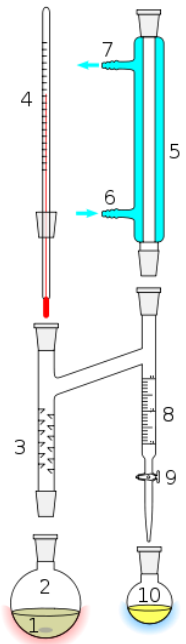
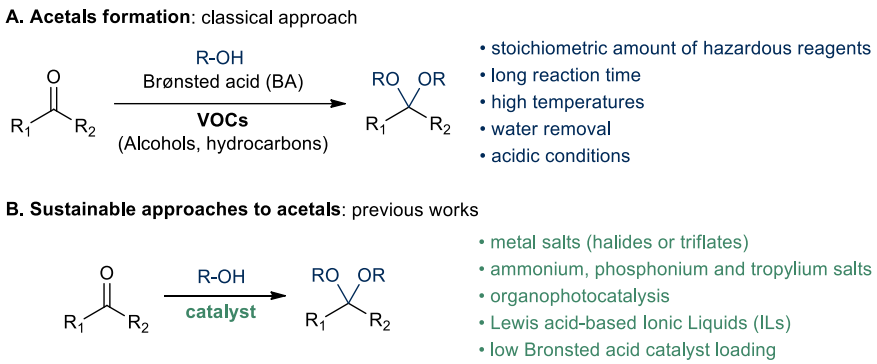


Figure 3.3. Dean-Stark apparatus for azeotropic separations (setup for an azeotrope with a solvent whose density is lower than water): 1. Stirrer bar/anti-bumping granules; 2. Still pot; 3. Fractionating column; 4. Thermometer; 5. Condenser; 6. Cooling water in; 7. Cooling water out; 8. Burette; 9. Tap; 10. Collection flask for water.

These main drawbacks have been addressed in the last two decades by several *greener* approaches (Scheme 3.2-B). $Fe(HSO_4)_3$,[11] InF_3,[12] $In(OTf)_3$,[13] $Bi(OTf)_3$,[14] as well as metal free conditions in the presence of catalytic organic acids as ammonium,[15] phosphonium,[16] tropylium salts,[17] Schreiner's thiourea[18] and arylazo sulfones[19] under photocatalytic conditions have been proposed.

Heterogenous catalysis also accounts for successful acetalization conversions at room temperature.[20] Very mild conditions with 0.1 mol% acid catalyst and no need of water removal have also been proposed.[21] Both ILs based on benzimidazolium[22] and Lewis acid-based ILs[23] have been reported as recyclable catalysts to promote acetalizations. Among more recent approaches which rely on the use of unconventional solvents, Azzena *et al*. developed acetalization processes of aliphatic and aromatic carbonyls with diols employing ammonium salts as acidic catalysts, either under homogeneous[24] or heterogeneous catalysis.[25] Lastly, deep eutectic solvent ChCl/MA (choline chloride/malic acid) was used to convert monosaccharides and methyl glycosides in mono- and di-*O*-isopropylidene derivatives.[26] However, most of the several reports found in the literature suffer from several drawbacks such as poor chemoselectivity and atom economy, the need of drying agents, high reaction temperatures, stoichiometric amounts of acids and limited scope of substrates, thus limiting the application of acetalization in chemical synthesis. Moreover, the preparation of acetals is commonly achieved in solvents such as acetonitrile, THF, benzene, toluene and DMF leading to complex recovery procedures and isolation (Scheme 3.2). Therefore, the need for *greener*, safer and more environmentally friendly technologies is highly desirable.



Scheme 3.2. State-of-the-art of the acetalization reaction.

In this context, we became recently interested in the use of DESs either as reaction media[27] or non-innocent solvents in organic synthesis.[28] The supramolecular structure of these mixtures, characterized by an extensive hydrogen bonding pattern,[29] impacts on the reactivity of common reagents and often provides an unexpected reactivity compared to traditional synthetic transformations.[27a, 27b]

Natural deep eutectic solvents, being much more than a sustainable alternative to traditional solvents, can have an active role in promoting organic reactions by improving the reaction rate, the yield and allow for milder conditions.[30]

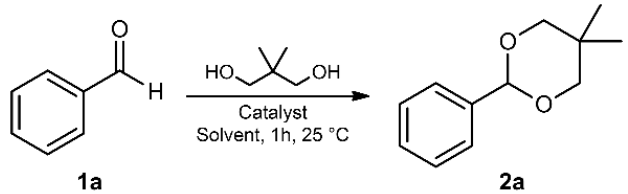
As an extension of our experience with unconventional solvents,[28a] in this work the feasibility of the use of acidic NADESs as non-innocent solvents to perform the acetalization reaction was investigated, with a special focus on the scalability and recyclability of the process.

3.2 Optimization of the reaction conditions

Bearing in mind the crucial role played by the (NA)DES medium in promoting the acetalization reaction, we started our investigation by the evaluation of the reaction conditions on benzaldehyde **1a** and neopentyl glycol as model substrates (Table 3.1). A first set of ChCl/carboxylic acid-based NADESs was tested (Table 3.1, entries 1-5) with 1.2 equiv of neopentyl glycol at room temperature, (1 mmol of **1a** for 400 mg of NADES) and 1 h reaction time. Very good yields were obtained using the NADES containing malonic (entry 1), oxalic (entry 2), L-(-)-malic (entry 3) and L-(+)-lactic acid (entry 5), acceptable yields with glutaric acid (entry 4), very low yields are instead obtained with glycerol and urea-based NADESs (entries 6 and 7). Assuming that in general the acidity of the NADES employed is governed by the acidity of the HBD (Hydrogen Bond Donor) component, we then tried to rationalize these results, taking into consideration the pK_a of the acidic component of the eutectic mixture. NADESs containing L-(-)-malic acid (pK_a = 3.40) and L-(+)-lactic acid (3.86), were as effective as those containing oxalic (1.23)[31] and malonic (2.83) acid,[32] with glutaric acid (4.34) (see entry 4, Table 3.1) there is a drop in the yield to 50%, while glycerol (14.4)[33] and urea (26.9)[34] were ineffective in promoting the reaction. The data gathered indicate that there is a coherence between the performance of the acetalization reaction and the pK_a of the acidic component of the NADES. We then decided to proceed our study with ChCl/malonic acid 1:1 mol/mol and optimize the equivalents of diol used. With 1.0 equiv of diol the yield decreases to 72% (entry 8), while using 2.0 equiv there is no significant gain in the yield (entry 9). Based on these results we decided to proceed in our investigation using 1.2 eq. of diol as the best compromise between yield and amount of reagent used. We then tried to elucidate the role of the acidic component of the NADES. To this purpose, we performed the acetalization reaction in various organic solvents by addition of the NADES single components either in stoichiometric or in catalytic amount with respect to the substrate. The results obtained show that the use of 1.6 eq. (entries 10-13) affords moderate to good yields, even though not as high as those obtained in NADES, thus confirming an active role of the DES as non-innocent reaction solvent. We then performed the reaction in acetonitrile with 1.6 eq. of ChCl (entry 14) or alternatively in the absence of catalyst (entry 15). In both cases, we recovered the starting material thus proving that the acidic component is essential

in promoting the reaction and no other mechanisms or alternative pathways come into play in this case. Finally, 0.2 equivalents of malonic acid in catalytic amount (entries 16-19) appeared to be rather ineffective in promoting the reaction.

Table 3.1. Acetalization reaction of benzaldehyde **1a** under different conditions.[a]



1a **2a**

Entry	Solvent	Catalyst (eq.)	Diol (eq.)	2a yield (%)[b]
1	ChCl/Malonic Acid	—	1.2	89
2	ChCl/Oxalic Acid	—	1.2	81
3	ChCl/L-(-)-Malic Acid	—	1.2	86
4	ChCl/Glutaric Acid	—	1.2	50
5	ChCl/L-(+)-Lactic Acid	—	1.2	78
6	ChCl/Glycerol	—	1.2	8
7	ChCl/Urea	—	1.2	0
8	ChCl/Malonic Acid	—	1.0	72
9	ChCl/Malonic Acid	—	2.0	87
10	Toluene	Malonic Acid (1.6)	1.2	73
11	CPME	Malonic Acid (1.6)	1.2	74
12	DCM	Malonic Acid (1.6)	1.2	84
13	MeCN	Malonic Acid (1.6)	1.2	83
14	MeCN	ChCl (1.2)	1.2	0
15	MeCN	/	1.2	0
16	Toluene	Malonic Acid (0.2)	1.2	28
17	CPME	Malonic Acid (0.2)	1.2	0
18	DCM	Malonic Acid (0.2)	1.2	23
19	MeCN	Malonic Acid (0.2)	1.2	55

[a] Reaction conditions: 1 hour, 25 °C; Neopentyl glycol (eq.), 400 mg NADES *or* 500 µL organic solvent per 1.0 mmol of **1a**; NADES: (ChCl)/malonic acid (1:1 mol/mol); ChCl/oxalic acid dihydrate (1:1 mol/mol); ChCl/L-(-)-malic acid (1:1 mol/mol); ChCl/glutaric acid (1:1 mol/mol); ChCl/ L-(+)-lactic acid (1:1 mol/mol) ChCl/urea (1:2 mol/mol); ChCl/glycerol (Gly) (1:2 mol/mol). [b] Determined by quantitative GC-FID analysis with external standard method using calibration curve of **2a**; 10 µL from the organic phase diluted with 490 µL CPME, injection: 1 µL, attenuation: 2^{10}, initial temperature: 70 °C, initial time: 3 min, ramp: 30 °C/min, final temperature: 250 °C.

We also investigated the kinetic of the reaction at two different temperatures, 25 °C and 0 °C respectively (Figure 3.4). The obtained results indicate that the process is very fast, and high conversions are reached within less than 5 minutes at room temperature. The highest conversion is reached in 10 minutes and remains unchanged even after 3 h. This supports the hypothesis that the NADES itself retains the water formed during the acetalization reaction thus preventing the backshift of the equilibrium to the starting reagents. Indeed, most DES have already been demonstrated to show hygroscopic behaviour. Water can be absorbed both at the surface and in the bulk.[35] At 0 °C the reaction resulted as expected slower, and the highest conversion is reached in only 30 min.

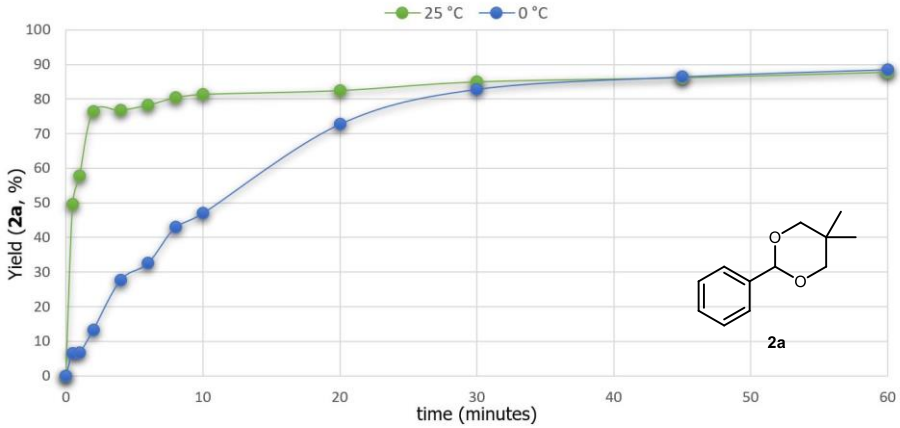
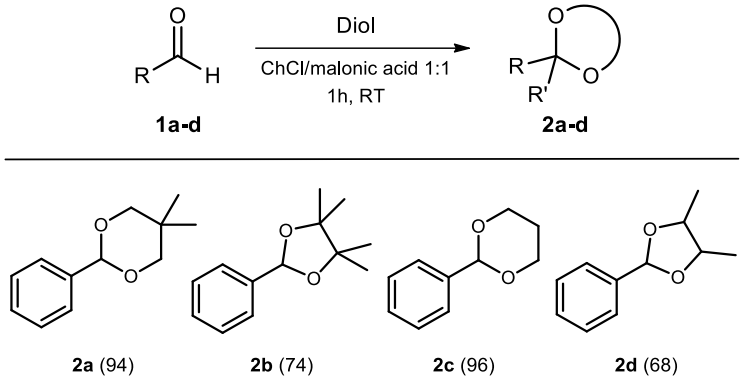


Figure 3.4. Kinetic analysis of **2a** formation in ChCl/malonic acid (1:1 mol/mol).

3.3 Substrate scope and chemoselectivity

We then explored the scope of the reaction on various substrates. Different diols have been used with benzaldehyde **1a** giving acetals **2a**-**2d** in good yields (Scheme 3.3), with 1,3-propanediol achieving the highest yield (**2c**, 96%), being the six-membered ring acetals the most thermodynamically stable compounds.[36] Unfortunately, under these conditions ethylene glycol acetals cannot be obtained.

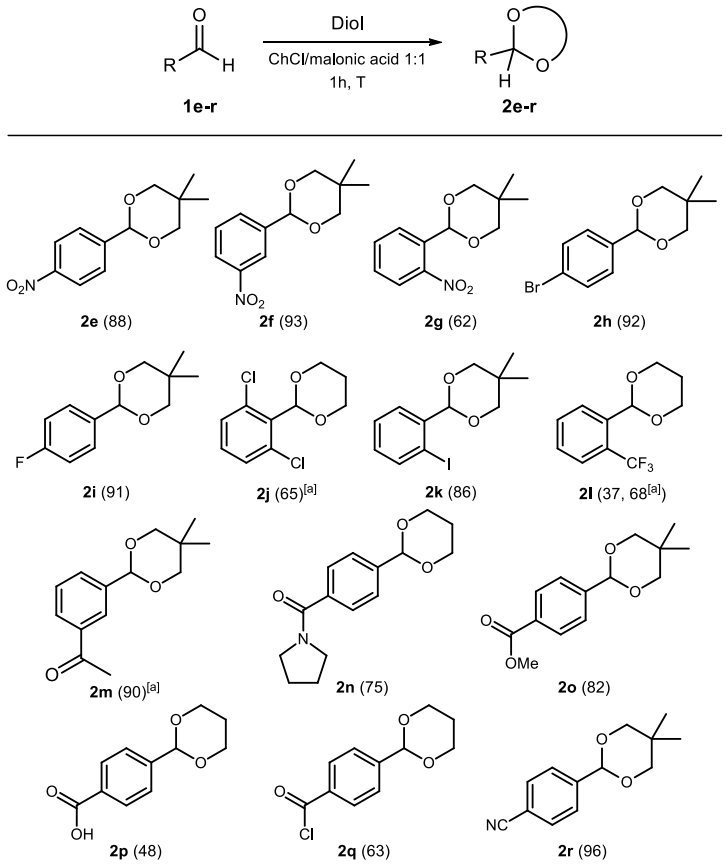
Neopentyl glycol and 1,3-propanediol were indeed used as diols of choice for the scope expansion on various carbonyl compounds.



Scheme 3.3. Acetalization reaction in ChCl/malonic acid 1:1 mol/mol with different diols.

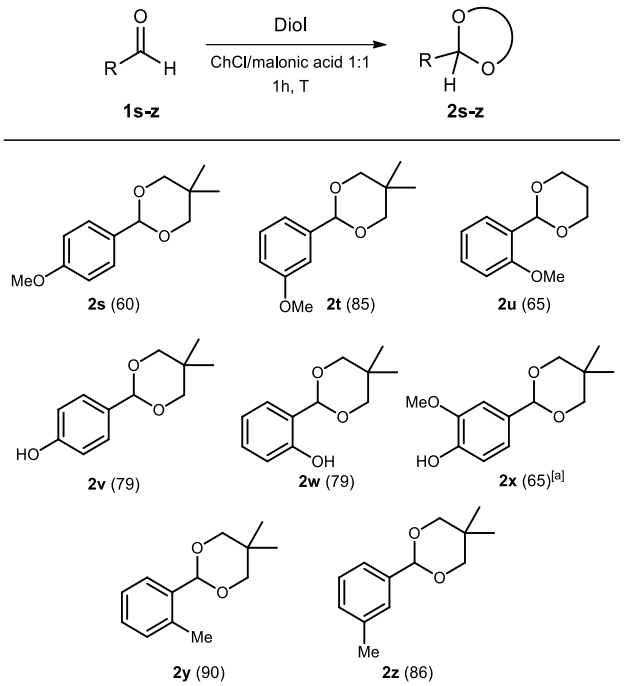
The scope on the carbonyl substrates was then explored starting with electron-poor benzaldehydes (Scheme 3.4). This class of substrates presents a more electrophilic carbonyl group, hence nucleophilic attack by the diol is favored. All regioisomers of nitrobenzaldehyde show very good reactivity and the corresponding acetals **2e**-**2g** have been obtained with good yields (62-93%). Halides in *para*-position (**2h**, **2i**), *ortho*- (**2k**), *ortho*-trifluoromethyl (**2l**) or *di-ortho*- (**2j**) are well tolerated and afforded the corresponding acetals in good yields.

Interestingly, the reaction proceeded with excellent chemoselectivity when a *m*-acetyl group was present, achieving dioxane **2m** with no appreciable acetalization of the ketone moiety. This outcome indicates that ketone substrates are not reactive under these reaction conditions. Furthermore, amide (**2n**), ester (**2o**), carboxylic acid (**2p**) and nitrile (**2r**) groups did not exhibit appreciable hydrolysis or alcoholysis side products, hinting that most acid labile functionalities are well-tolerated with this procedure under mild conditions. On the other hand, acyl chloride **1q** was transformed into its corresponding acetal **2q** in moderate yield (63%) with no recovery of ester compounds, suggesting that partial hydrolysis of the acyl group occurred.



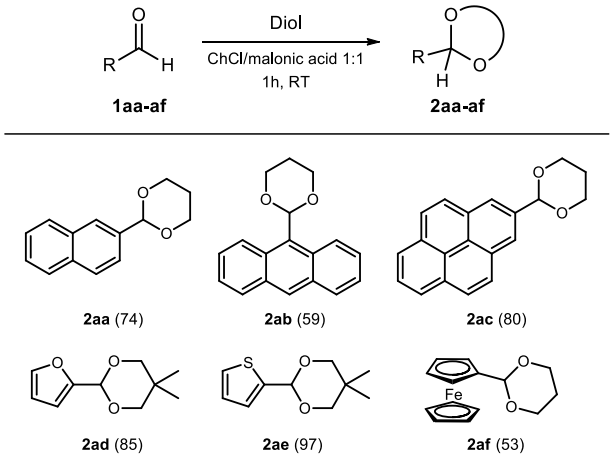
Scheme 3.4. Acetalization reaction in ChCl/malonic acid 1:1 mol/mol on electron poor benzaldehydes. [a] Reaction was performed at 50 °C.

Good yields have been also obtained with electron-donating substituted benzaldehydes (Scheme 3.5). Not surprisingly, among methoxy-substituted aldehydes the best yields are obtained with the *meta-* isomer (**2t**). Also phenol aldehydes **1v** and **1w** were transformed into their corresponding acetals **2v** and **2w** with high yields (both 79%), revealing that phenol compounds are feasible substrates under these reaction conditions. Notably, highly deactivated vanillin **1x** required gentle heating at 50 °C to achieve acetal **2x** in 65% yield, whereas, with the less deactivating *ortho-* (**2y**) and *meta-* (**2z**) methyl groups higher yields are obtained.



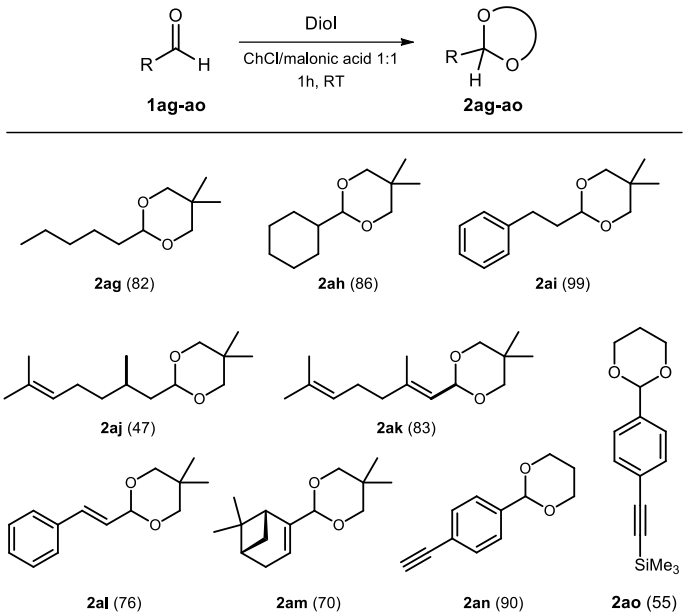
Scheme 3.5. Acetalization reaction in ChCl/malonic acid 1:1 mol/mol on electron rich benzaldehydes. [a] Reaction was performed at 50 °C.

Polyaromatic and heterocyclic substrates were also tested under the usual reaction conditions (Scheme 3.6), affording napthyl- (**2aa**), anthranyl- (**2ab**), pyrenyl- (**2ac**), furyl- (**2ad**), thienyl- (**2ae**) and ferrocenyl- (**2af**) acetals with moderate to high yields.



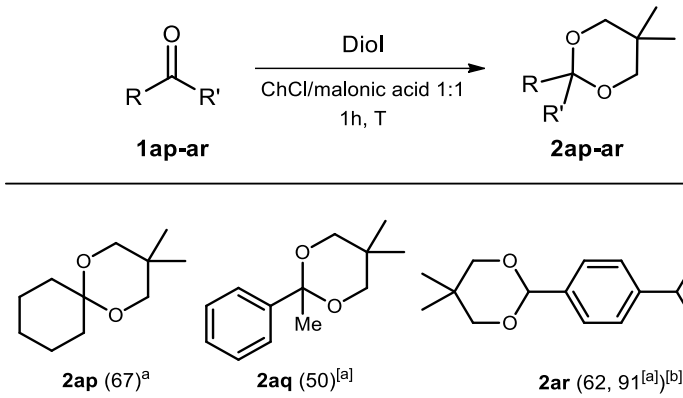
Scheme 3.6. Acetalization reaction in ChCl/malonic acid 1:1 mol/mol on poly(hetero)aromatic aldehydes.

The scope of the reaction was also extended to aliphatic and conjugated aldehydes. The corresponding alkyl- (**2ag**, **2ai, 2aj**), cycloalkyl- (**2ah**), and alkenyl- (**2ak**-**2am**) acetal compounds were obtained with very high yields without any self-condensation, isomerization or hydration/electrophilic addition side products (Scheme 3.7). An excellent yield was also obtained for the alkynyl substrate **2an**, while its TMS derivative gave a significantly lower yield of **2ao**, although no loss of the TMS group was detected (recovery of the unreacted starting material was attained).



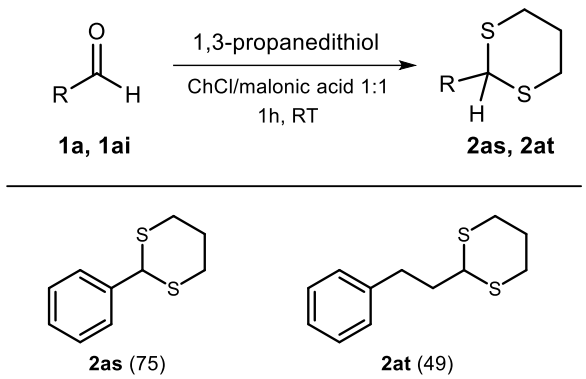
Scheme 3.7. Acetalization reaction in ChCl/malonic acid 1:1 mol/mol on alkyl-, alkenyl- and alkynyl-subtrates.

Furthermore, less reactive ketone substrates **1ap** and **1aq** were mixed with neopentylglycol at 50 °C for 1 h, showing a lower reactivity under these acetalization conditions. As a matter of fact, cyclohexanone acetal **2ap** was obtained in 67% yield, while in the case of acetophenone the yield was even lower (50%, **2aq**). Intriguingly, product **2ar** was obtained from terephthalaldehyde with 2.4 equivalents of neopentyl glycol (Scheme 3.8). Unfortunately, the reaction is not selective towards mono- or bis- acetalization depending on the equivalents of diol used. Indeed, with 1.2 eq. of diol a mixture of starting material and double adduct **2ar** was obtained.



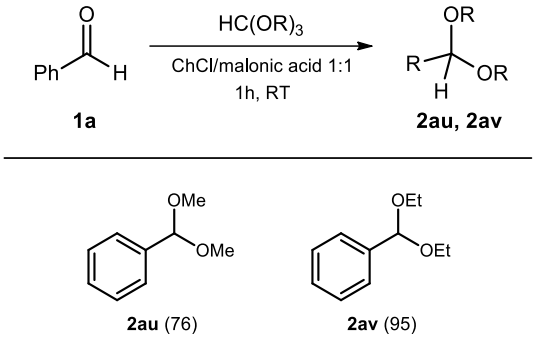
Scheme 3.8. Acetalization reaction in ChCl/malonic acid 1:1 mol/mol on ketones **1ap**, **1aq** and terephthalaldehyde **1ar**. [a] Reaction was performed at 50 °C. [b] 2.4 eq. of neopentylglycol were used.

Notably, the methodology can be also extended to the formation of 1,3-dithiane derivatives (Scheme 3.9), which are intermediates of high utility in organic synthesis.[37] With 1.2 equivalents of 1,3-propanedithiol aryl- **2as** and alkyl- **2at** dithioacetals were obtained.



Scheme 3.9. Thioacetalization reaction in ChCl/malonic acid 1:1 mol/mol.

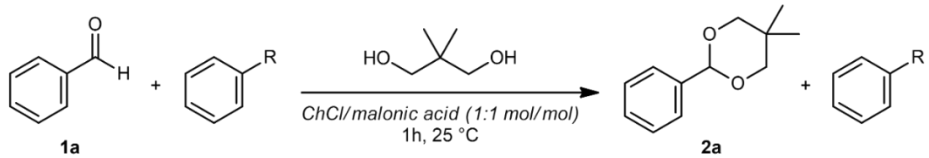
Remarkably, this procedure can be also applied to the synthesis of open-chain acetals. In this case, the replacement of diol with 1.5 equivalents of trimethylorthoformate or triethylorthoformate afforded the dimethyl **2au** and diethyl **2av** acetals of benzaldehyde in good yields at room temperature (Scheme 3.10). Unexpectedly, when benzaldehyde was reacted with 1.2 eq. of MeOH or EtOH, no conversion was observed.



Scheme 3.10. Open-chain acetals formation in ChCl/malonic acid 1:1 mol/mol.

Competitive reactivity of diverse functional groups towards the NADES environment have also been carried out. As shown in Table 3.2, high chemoselectivities were obtained when the acetalization reaction of benzaldehyde **1a** was performed in the presence of acetophenone (entry 1), benzonitrile (entry 2) and benzoyl chloride (entry 3). 5,5-Dimethyl-2-phenyl-1,3-dioxane **2a** was obtained in high yield and the competitive carbonyl compounds were recovered almost unchanged except for benzoyl chloride for which partial hydrolysis to benzoic acid is expected (cf. Scheme 3.4, prod. **2q**).

Table 3.2. Competition experiments.[a]



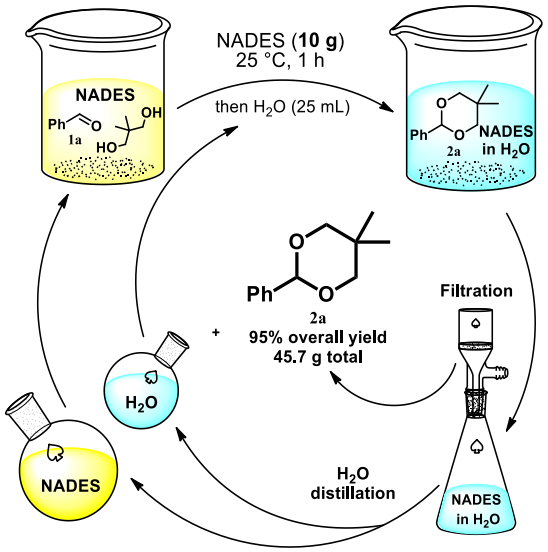
Entry	Competitive substrate	2a yield (%)[b]	Unreacted comp. sub. (%)[b]
1	R = $COCH_3$ (Acetophenone, **1aq**)	78	91
2	R = CN (Benzonitrile, **5**)	94	75
3	R = COCl (Benzoyl Chloride, **6**)	87	56[c]

[a] Reaction conditions: 1 hour, 25 °C; Neopentyl glycol (1.2 eq.), 400 mg NADES, 0.5 mmol of **1a** + 0.5 mmol competitive substrate; NADES: (ChCl)/malonic acid (1:1 mol/mol). [b] Determined by ^1H NMR using CH_3NO_2 as the internal standard. [c] Possible hydrolysis to benzoic acid.

3.4 Gram-scale reaction and NADES recycling

We then investigated the recyclability of the active solvent system. To this purpose, the reactions were performed on a 25 mmol scale starting from 2.65 g of benzaldehyde **1a**, 3.12 g (30 mmol, 1.2 equiv) of neopentyl glycol and 10 g of ChCl/malonic acid 1:1 mol/mol as NADES. The mixture was stirred at RT for 1 h and

20 mL of water were then added to dilute the NADES. Product **2a** precipitates as white crystals and was filtrated off. The NADES was then regenerated after removal of water by *in vacuo* distillation. After every cycle we carefully checked the structure of the NADES by ^{1}H-NMR and evaluated the content of residual water by Karl-Fischer titration (Table 3.3). The NADES was then reused again for the reaction together with the water recovered by distillation and used for the dilution (Scheme 3.11).



Scheme 3.11. NADES recycle procedure.

Impressively, ten reaction cycles were successfully performed without any decrease in the yield, which remains always above 88% (Figure 3.5) with a total of 45.7 g of product obtained with the same recycled NADES.

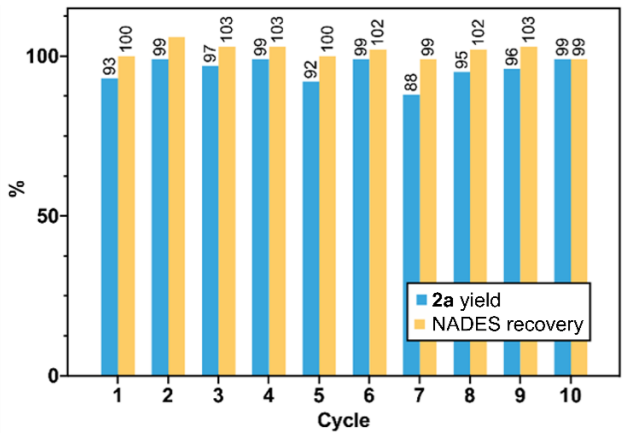


Figure 3.5. Acetal product **2a** yields (%) + ChCl/malonic acid (1:1 mol/mol) recovery (% w.) for each reaction cycle.

Table 3.3. Karl-Fischer titration for water content performed on ChCl/malonic acid (1:1 mol/mol) which was prepared or recycled with different procedures.

Entry	ChCl/malonic acid (1:1 mol/mol)	Density [g/mL][b]	Water content (% w./w.)[c]
1	Literature preparation[a]	1.296	0.7
2	Literature preparation[a] with ChCl stored in a dessicator	1.374	0.4
3	Recycled by removing water *in vacuo* (rotavap for 30', 7.5 Torr, 40 °C bath)	1.350	17.1
4	Recycled by removing water *in vacuo* (rotavap for 30', 20 mbar, 40 °C bath then vacuum line for 1 h, 1 mTorr, stirring at 40 °C)	1.385	1.4
5	Literature preparation[a] with ChCl stored in a desiccator + 1.0% water added via syringe	1.378	1.5
6	Recycled by removing water *in vacuo* (rotavap for 30', 20 mbar, 40 °C bath then vacuum line for 4h, 1 mTorr, stirring at 40 °C)	1.375	0.6

[a] Mixing the two solid components at room temperature for 10 minutes with a stir rod then at 40 °C until the mixture becomes homogeneous (around 30 minutes). [b] Density of ChCl/malonic acid (1:1 mol/mol) was determined at room temperature. Using a syringe, the mass of 500 µL was determined. This process was repeated three times in total and the average mass used to determine density. [c] Karl Fischer titration was repeated three times for each sample.

What emerges from the evaluation of the water content in different eutectic media (Table 3.3) was the best set up and procedure for NADES recovery (entry 6) to obtain a comparable water content with respect to the starting NADES (entry 2).

Moreover, after each reaction cycle, a capillary tube was filled with a small quantity of the recovered eutectic mixture (Table 3.3, entry 6) and analyzed with ^{1}H NMR spectroscopy (Figure 3.6). In entry 1 is reported the freshly prepared ChCl/malonic acid 1:1 eutectic mixture ^{1}H NMR spectra. It can be noticed that going from entry 2 to entry 11 (spectra of the last recovered NADES) at around 1.0 ppm there is an increase in the intensity of the signal related to the methyl groups in neopentylglycol. So, this demonstrates that the slight excess of diol for each reaction is retained in the NADES going through the recycling procedure. To confirm this, in entry 12 is reported the ^{1}H NMR spectra of the freshly prepared NADES to which it was added neopentyl glycol, the signals perfectly match the other stacked analyses.

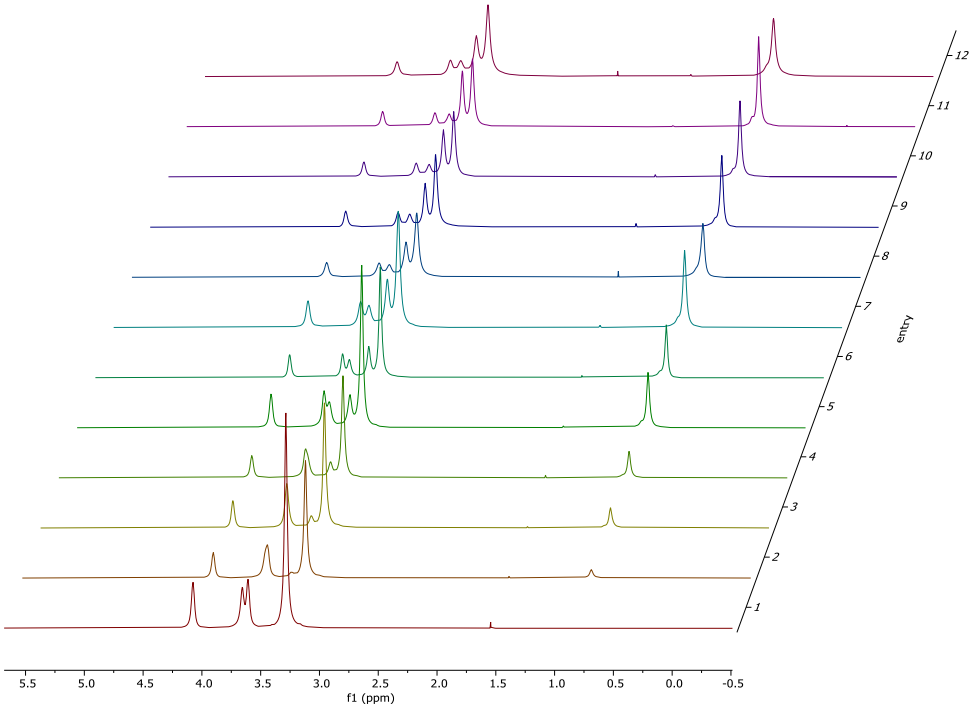
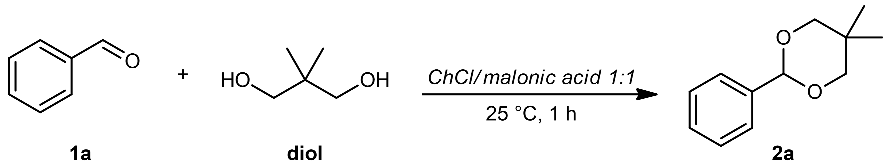


Figure 3.6. Recovered NADES used for each reaction cycle ^{1}H NMR analysis ($CDCl_3$ used to calibrate the scale outside the capillary in the NMR tube).

Key mass-based Green Chemistry metrics like E-factor and process mass intensity (PMI) were also evaluated for the gram-scale acetalization reaction of **1a** in ChCl/malonic acid (1:1 mol/mol). From the results shown in Scheme 3.12 a comparison between the single-run reaction and the ten-cycle process from NADES recycling highlights clear advantages in terms of sustainability (for detailed calculations see section 3.7.7).



	1a	diol		2a
Single run:				
	2.65 g	3.12 g (1.2 eq., 0.52 g excess)	10.0 g NADES 25.0 g H_2O	4.47 g (93%)

PMI = (2.65 + 3.12 + 10.0 + 25.0) g / 4.47 g = **9.1**

E-factor = (0.52 + 10.0 + 25.0) g / 4.47 g = **7.9**

10-cycles run:			
26.5 g	31.2 g (1.2 eq.,5.2 g excess)	10.0 g NADES 25.0 g H_2O (5.0 g loss/cycle)	45.7 g (95%)

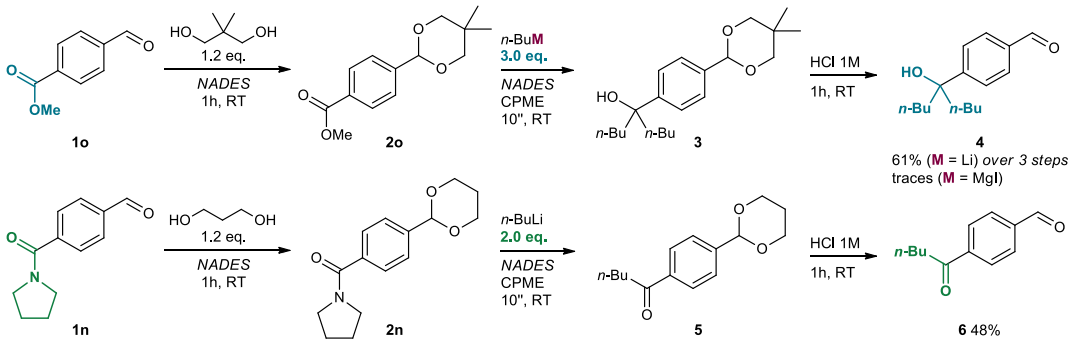
PMI = (26.5 + 31.2 + 10.0 + 70.0) g / 45.7 g = **3.0**

E-factor = (5.2 + 10.0 + 70.0) g / 45.7 g = **1.9**

Scheme 3.12. E-factor and Process Mass Intensity (PMI) for the gram-scale acetalization reaction of **1a** in ChCl/malonic acid 1:1 mol/mol.

3.5 Cascade process

We then explored the feasibility of implementing this methodology in cascade processes (Scheme 3.13). *p*-Formyl methyl benzoate **1o**, possessing both an aldehyde and an ester as functional groups, was chosen as substrate to realize the synthesis of target compound **4** (Scheme 3.13, top) by addition of the proper organolithium reagent to the ester group. This strategy implies the protection of the more electrophilic aldehyde. Therefore, the overall transformation should be performed exploiting the use of an acetal as protecting group for the aldehyde. We then applied our protocol starting from 0.5 mmol of *p*-formyl methyl benzoate **1o** to form acetal **2o**, which was not isolated and directly used in the following step. In this case, CPME (cyclopentyl methyl ether) is then added as co-solvent[27a, 27c] to form a heterogeneous mixture and thus facilitating the vigorous stirring, then 3.0 equiv of *n*-BuLi were rapidly spread over the heterogeneous mixture under air. The reaction was quenched after 10 seconds with water to finalize the formation of the tertiary alcohol **3**. Final product **4** was then obtained by simple acidic work-up with diluted HCl in 61% yield over three steps.



Scheme 3.13. One-pot cascade process (NADES: ChCl/malonic acid 1:1 mol/mol).

It has already been demonstrated that organolithium reagents can be used in protic medium,[27a, 27c] however it is noteworthy to emphasize that in this case the reaction successfully proceeds even in an acidic medium, implying that the kinetic of addition to the electrophile is faster than the protonolysis within the NADES system. On the other hand, the use of the corresponding Grignard reagent (*n*-BuMgI) to perform the same cascade transformation was unsuccessful (Scheme 3.13, top). Indeed, previous studies reported the complete protonation of Grignard reagents in competition with nucleophilic additions in protic environments.[38]

To further highlight the utility and the robustness of our methodology, we designed a cascade process for an efficient preparation of 4-pentanoylbenzaldehyde **6**. One pot acetalization of aldehyde **1n**, followed by an *in situ* nucleophilic acyl substitution reaction promoted by *n*-BuLi (2.0 equiv.) on *N*-acylpyrrolidine **2n** intermediate, afforded **6** in 48% overall yield (Scheme 3.13, bottom).[27b, 27c] Taken together, these cascade, one-pot protection/nucleophilic addition sequences contribute to enlarge the portfolio of organolithium-mediated transformations in protic eutectic mixtures under aerobic conditions.[27a, 27c, 39]

3.6 Conclusion

Deep eutectic solvents nowadays find a huge number of applications in organic synthesis. We have demonstrated that the NADES in which one of the components is an organic acid not only acts as a *green* and renewable solvent but plays an active role as promoter of the acetalization reaction. The procedure is easily performed at room temperature, in open air and in short reaction times. There is no need for water removal techniques to shift the reaction equilibrium towards the products as the NADES itself retains the water byproduct. The scope of the reaction is wide and applicable to almost every aldehyde, with high functional group tolerance including acid labile ones. Reactivity towards ketones is instead limited thus opening the way to chemoselective transformations. A very simple procedure

allows the recyclability of the solvents without decrease in the yield. After 10 reuses the yield of both the product and the solvent recovery remain close to quantitative. All these aspects, combined with the easy of scalability and the highly favorable *green* metrics obtained (E-factor, PMI) indicate that this procedure possesses several suitable features to be a promising candidate for future industrial applications.

3.7 Experimental section

3.7.1 Experimental details

Materials and methods. Flasks and all equipment used for the generation and reaction of moisture-sensitive compounds were dried by electric heat gun under nitrogen. Unless specified, all commercially available reagents were used as received without further purifications. Compounds **1a**, **1y**, **1z**, **1ad**, **1ag**, **1ai**, **1al** and **1am** were distilled under vacuum prior to use. Reactions were monitored by GC-MS analysis or by thin-layer chromatography (TLC) carried out on 0.25 mm silica gel coated aluminum plates (60 Merck F254) with UV light (254 nm) as visualizing agent. R_f values refer to TLC carried out on silica gel plates. Chromatographic separations were carried out under pressure on silica gel (40-63 μm, 230-400 mesh) using flash-column techniques. The exact concentration of *n*-BuLi in hexanes solution was determined by titration with *N*-benzylbenzamide in anhydrous THF prior to use.[40] Aldehydes **1an**,[41] **1ao**,[42] **1q**[43] and **1n**[44] were synthesized according to the procedures reported in the literature. Deep Eutectic Solvents [choline chloride (ChCl)/malonic acid (1:1 mol/mol); ChCl/oxalic acid dihydrate (1:1 mol/mol); ChCl/L-(**-**)-malic acid (1:1 mol/mol); ChCl/glutaric acid (1:1 mol/mol); ChCl/L-(+)-lactic acid (1:1 mol/mol) ChCl/urea (1:2 mol/mol); ChCl/glycerol (Gly) (1:2 mol/mol)] were prepared by heating under stirring at 50−80 °C for 15−30 min the corresponding individual components until a clear solution was obtained.[27a, 28a] Full characterization data have been reported for both the newly synthesized compounds and the known compounds.

Safety note. Organolithiums were handled under an inert atmosphere (Schlenk techniques) until the point at which they were mixed with a solution of the substrate in CPME/NADES, under an air atmosphere and with vigorous magnetic stirring, whereupon they react quickly. No particular problems were experienced during the addition. Organolithiums, however, are notoriously prone to ignition in air, and caution should be exercised in adopting the recommended procedure, especially on a larger scale.

Instrumentation. ^{1}H NMR (600 MHz), ^{13}C{^{1}H} NMR (150 MHz) and ^{19}F{^{1}H} NMR (564 MHz) spectra were recorded on a Jeol ECZR600 spectrometer at room temperature using residual solvent peak as an internal reference. NMR spectra of ChCl/malonic acid (1:1 mol/mol) were recorded in a capillary tube, using external $CHCl_3$ as locking solvent. Chemical shifts (δ) are given in parts per million (ppm) and coupling constants (J) in Hertz (Hz). Multiplicities are reported as follows: s (singlet), d (doublet), t (triplet), q (quartet), quint (quintet), m (multiplet), br (broad). Low-resolution mass spectra were recorded at an ionizing voltage of 70 eV on a HP 5989B mass selective detector connected to an HP 5890 GC with a methyl silicone capillary column (EI). High-resolution Mass spectra were obtained on a Bruker maXis 4G instrument (ESI-TOF, HRMS). Quantitative GC-FID analyses with external standard method were performed on a HP 5890 Series II chromatographic system (HP 3395 integrator) equipped with a methyl silicone capillary column. Water content in ChCl/malonic acid (1:1 mol/mol) was measured with a Metrohm Karl Fischer Titrator E-551. Melting points were determined on a Stuart Scientific SMP3 melting point apparatus.

Nitromethane was used as internal standard for quantitative NMR analyses on crude reaction mixtures. For each ^{1}H NMR the amount of product was determined by applying the following equation:

$$yield\ (\%) = \frac{x\ (product) \cdot n\ (CH_3NO_2)}{n(starting\ material)} \cdot f \cdot 100$$

where:

- x is the value of integral/number of protons;
- n is the amount of starting material or CH_3NO_2 in mmol;
- f the diluting factor used for the preparation of the sample.

*3.7.2 Acetalization reaction of benzaldehyde **1a** under different reaction conditions*

General procedure. All reactions were performed under air at room temperature. In an open screw cap vial, benzaldehyde **1a** (106 mg, 1.0 mmol, 1.0 eq.) and neopentyl glycol (selected equivalents) were dissolved in the selected solvent (with or without catalyst) and the resulting mixture was stirred for 1 hour. The reaction was then quenched with 2 M NaOH (2 mL) and extracted with CPME (1 x 2 mL). Yields of **2a** (Table 3.1) were determined by quantitative GC-FID analysis (external standard method, calibration curve for product **2a** reported in Figure 3.6). A sample of **2a** was synthesized according to the procedure reported in the literature[45] and used as reference for quantitative GC-FID analyses.

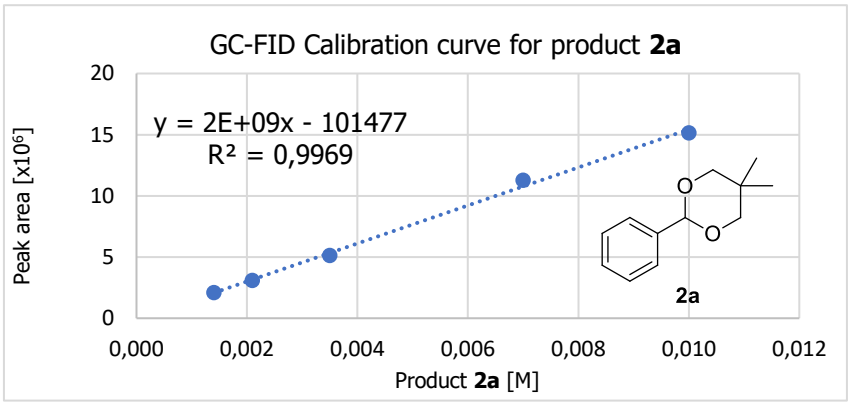


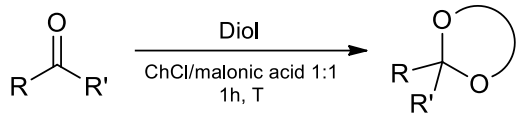
Figure 3.6. GC-FID calibration curve for 5,5-dimethyl-2-phenyl-1,3-dioxane **2a**.

*3.7.3 Kinetic analysis of **2a** formation in ChCl/malonic acid (1:1 mol/mol)*

General procedure. All reactions were performed under air. In an open screw cap vial, benzaldehyde **1a** (106 mg, 1.0 mmol, 1.0 eq.) and neopentyl glycol (125 mg, 1.2 mmol, 1.2 eq.) were dissolved in ChCl/malonic acid (1:1 mol/mol, 400 mg) and the resulting mixture was stirred for the selected time at 25 °C or 0 °C. The mixture was then quenched with 2 M NaOH (2 mL) and extracted with CPME (1 x 2 mL). Yields of **2a** (Figure 3.4) were determined by quantitative GC analysis (external standard method, calibration curve for product **2a** reported in Figure 3.6) of the crude reaction mixtures.

*3.7.4 Synthesis and analysis of compounds **2a**-**2av**.*

General procedure for the preparation of cyclic acetals. Reactions were performed under air at room temperature unless otherwise specified. In an open screw cap vial, substrates **1a-1ar** (1.0 mmol, 1.0 eq.), diols (1.2 mmol, 1.2 eq.) and ChCl/malonic acid (1:1 mol/mol, 400 mg) were added. The resulting mixture was stirred for 1 hour. The mixture was then diluted with water (10 mL) and extracted with the selected solvent (3 x 5 mL). The combined organic extracts were washed with sat. $NaHCO_3$ (1 x 5 mL), $NaHSO_3$ (1 x 5 mL) and brine (1 x 5 mL) then dried over Na_2SO_4 and the solvent removed under reduced pressure. When required, the crude product was purified by flash column chromatography or by recrystallization.



1a-1ar **2a-2ar**

5,5-Dimethyl-2-phenyl-1,3-dioxane (2a): general procedure starting from **1a** and 2,2-dimethylpropane-1,3-diol. Extraction with CPME gave pure **2a** as a white solid (181 mg, 94%, R_f = 0.75 pentane/Et_2O 95/5 v/v), mp 32.5−33.6 °C (pentane). **^{1}H NMR** (600 MHz, DMSO-d_6): δ 7.45-7.40 (m, 2H), 7.39-7.33 (m, 3H), 5.41 (s, 1H), 3.67 (d, J = 11.0 Hz, 2H), 3.63 (d, J = 10.7 Hz, 2H), 1.19 (s, 3H), 0.75 (s, 3H). **^{13}C{^{1}H} NMR** (150 MHz, DMSO-d_6): δ 138.7, 128.6, 128.0, 126.2, 100.8, 76.5, 29.8, 22.7, 21.4. **EI-MS** *m/z* (%): 192 (M^+, 51), 191 (100), 107 (74), 105 (57), 77 (24), 56 (29).[45]

4,4,5,5-Tetramethyl-2-phenyl-1,3-dioxolane (2b): general procedure starting from **1a** and 2,3-dimethylbutane-2,3-diol. Extraction with CPME gave pure **2b** as a colorless oil (153 mg, 74%, R_f = 0.65 pentane/Et_2O 95/5 v/v). **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.52-7.48 (m, 2H), 7.39-7.35 (m, 2H), 7.34-7.31 (m, 1H), 5.99 (s, 1H), 1.34 (s, 6H), 1.28 (s, 6H). **^{13}C{^{1}H} NMR** (150 MHz, $CDCl_3$): δ 139.8, 128.7, 128.3, 126.4, 100.0, 82.7, 24.4, 22.3. **EI-MS** *m/z* (%): 206 (M^+, 33), 205 (100), 147 (23), 105 (73), 90 (27), 83 (25).[46]

2-Phenyl-1,3-dioxane (2c): general procedure starting from **1a** and 1,3-propanediol. Extraction with CPME gave pure **2c** as a colorless oil (158 mg, 96%, R_f = 0.42 pentane/Et_2O 95/5 v/v). **^{1}H NMR** (600 MHz, DMSO-d_6): δ 7.42-7.38 (m, 2H), 7.37-7.31 (m, 3H), 5.50 (s, 1H), 4.16-4.11 (m, 2H), 3.96-3.89 (m, 2H), 1.99 (dtt, J = 13.3, 12.4, 5.0 Hz, 1H), 1.43 (dtt, J = 13.4, 2.7, 1.4 Hz, 1H). **^{13}C{^{1}H} NMR** (150 MHz, DMSO-d_6): δ 139.0, 128.5, 127.9, 126.0, 100.7, 66.6, 25.4. **EI-MS** *m/z* (%): 164 (M^+, 39), 163 (100), 106 (25), 105 (90), 77 (39).[13]

4,5-Dimethyl-2-phenyl-1,3-dioxolane (2d): general procedure starting from **1a** and 2,3-butanediol. Extraction with CPME gave **2d** as a colorless oil (121 mg, 68%, R_f = 0.55, 0.57, 0.60 pentane/Et_2O 95/5 v/v) as a mixture of three inseparable diastereomers (1.0: 1.45: 2.55 ratio). **^{1}H NMR** (600 MHz, DMSO-d_6, mixture of diastereoisomers): δ 7.46-7.34 (m, 15H), 6.01 (s, 1H), 5.87 (s, 1H), 5.68 (s, 1H), 4.34-4.29 (m, 2H), 4.28-4.23 (m, 2H), 3.79-3.70 (m, 2H), 1.29 (d, *J* = 5.9 Hz, 3H), 1.24 (d, *J* = 5.9 Hz, 3H), 1.17-1.12 (m, 12H). **^{13}C{^{1}H} NMR** (150 MHz, DMSO-d_6): δ 140.0, 138.8, 138.0, 129.1, 128.9, 128.6, 128.1, 126.8, 126.5, 126.1, 101.8, 101.7, 100.6, 79.6, 78.0, 74.3, 74.0, 17.0, 16.7, 15.3, 14.3. **EI-MS** (major diastereomer) *m/z* (%): 178 (M^+, 30), 177 (100), 133 (21), 105 (77), 90 (28), 77 (27).[47]

5,5-Dimethyl-2-(4-nitrophenyl)-1,3-dioxane (2e): general procedure starting from **1e** and 2,2-dimethylpropane-1,3-diol. Extraction with CPME gave pure **2e** as a slightly yellow solid (209 mg, 88%, R_f = 0.25 pentane/Et_2O 95/5 v/v), mp 83.3–84.2 °C (pentane). **^{1}H NMR** (600 MHz, $CDCl_3$): δ 8.23 (d, *J* = 8.6 Hz, 2H), 7.69 (d, *J* = 8.7 Hz, 2H), 5.46 (s, 1H), 3.80 (d, *J* = 11.3 Hz, 2H), 3.68 (d, *J* = 11.0 Hz, 2H), 1.28 (s, 3H), 0.82 (s, 3H). **^{13}C{^{1}H} NMR** (150 MHz, $CDCl_3$): δ 148.3, 145.1, 127.4, 123.6, 100.2, 77.8, 30.4, 23.1, 22.0. **EI-MS** *m/z* (%): 237 (M^+, 18), 236 (34), 150 (26), 107 (37), 56 (100), 41 (25).[48]

5,5-Dimethyl-2-(3-nitrophenyl)-1,3-dioxane (2f): general procedure starting from **1f** and 2,2-dimethylpropane-1,3-diol. Extraction with CPME gave pure **2f** as a white solid (220 mg, 93%, R_f = 0.25 pentane/Et_2O 95/5 v/v), mp 49.8–50.2 °C (pentane). **^{1}H NMR** (600 MHz, $CDCl_3$): δ 8.39 (t, *J* = 2.0 Hz, 1H), 8.22-8.18 (m, 1H), 7.84 (d, *J* = 8.2 Hz, 1H), 7.55 (t, *J* = 8.1 Hz, 1H), 5.47 (s, 1H), 3.80 (d, *J* = 11.5 Hz, 2H), 3.68 (d, *J* = 11.0 Hz, 2H), 1.28 (s, 3H), 0.82 (s, 3H). **^{13}C{^{1}H} NMR** (150 MHz, $CDCl_3$): δ 148.3, 140.6, 132.5, 129.4, 123.8, 121.7, 100.0, 77.8, 30.4, 23.1, 22.0. **EI-MS** *m/z* (%): 237 (M^+, 13), 236 (45), 150 (33), 107 (37), 56 (100).[49]

5,5-Dimethyl-2-(2-nitrophenyl)-1,3-dioxane (2g): general procedure starting from **1g** and 2,2-dimethylpropane-1,3-diol. Extraction with CPME gave pure **2g** as a yellow solid (147 mg, 62%, R_f = 0.48 PE/EtOAc 95/5 v/v), mp 75.8–77.0 °C (pentane). **^{1}H NMR** (600 MHz, DMSO-d_6): δ 7.90 (dd, *J* = 7.9, 1.3 Hz, 1H), 7.81 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.74 (td, *J* = 7.6, 1.3 Hz, 1H), 7.63 (td, *J* = 7.7, 1.5 Hz, 1H), 5.87 (s, 1H), 3.68 (d, *J* = 10.5 Hz, 2H), 3.65 (d, *J* = 10.8 Hz, 2H), 1.13 (s, 3H), 0.74 (s, 3H). **^{13}C{^{1}H} NMR** (150 MHz, DMSO-d_6): δ 148.2, 132.9, 131.4, 130.1, 127.3, 123.9, 96.4, 76.8, 29.9, 22.8, 21.2. **EI-MS** *m/z* (%): 237 (M^+, 1), 220 (72), 152 (58), 135 (84), 134 (62), 104 (49), 77 (26), 56 (100), 41 (41).[50]

2-(4-Bromophenyl)-5,5-dimethyl-1,3-dioxane (2h): general procedure starting from **1h** and 2,2-dimethylpropane-1,3-diol. Extraction with CPME gave pure **2h** as a white solid (250 mg, 92%, R_f = 0.40 pentane/Et_2O 95/5 v/v), mp 66.5–67.5 °C (pentane). **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.52-7.48 (m, 2H), 7.40-7.36 (m, 2H), 5.35 (s, 1H), 3.76 (d, *J* = 11.3 Hz, 2H), 3.64 (d, *J* = 11.3 Hz, 2H), 1.28 (s, 3H), 0.80 (s, 3H). **^{13}C{^{1}H} NMR** (150 MHz, $CDCl_3$): δ 137.7, 131.5, 128.1, 123.0, 101.1, 77.8, 30.4, 23.1, 22.0. **EI-MS** *m/z* (%): 272 (M^+, 47), 271 (70), 270 (M^+, 47), 269 (67), 187 (52), 185 (100), 183 (47), 69 (23), 56 (48).[51]

2-(4-Fluorophenyl)-5,5-dimethyl-1,3-dioxane (2i): general procedure starting from **1i** and 2,2-dimethylpropane-1,3-diol. Extraction with CPME gave pure **2i** as a white solid (191 mg, 91%, R_f = 0.32 PE/EtOAc 98/2 v/v), mp 58.3−59.6 °C (pentane). **^{1}H NMR** (600 MHz, DMSO-d_6): δ 7.50-7.43 (m, 2H), 7.22-7.14 (m, 2H), 5.41 (s, 1H), 3.67 (d, *J* = 11.0 Hz, 2H), 3.62 (d, *J* = 10.8 Hz, 2H), 1.18 (s, 3H), 0.75 (s, 3H). **^{13}C{^{1}H} NMR** (150 MHz, DMSO-d_6): δ 162.1 (d, *J* = 244.2 Hz, 1C), 135.1, 128.3 (d, *J* = 8.6 Hz, 1C), 114.8 (d, *J* = 21.6 Hz, 1C), 100.0, 76.5, 29.8, 22.7, 21.4. **^{19}F{^{1}H} NMR** (564 MHz, $CDCl_3$): δ -113.03 (s). **EI-MS** *m/z* (%): 210 (M^+, 51), 209 (90), 125 (100), 123 (75), 95 (27), 56 (58), 41 (24). **ESI-HRMS** $[M+Na]^+$: *m/z* 233.0960, $C_{12}H_{15}FNaO_2^+$ requires 233.0948.

2-(2,6-Dichlorophenyl)-1,3-dioxane (2j): general procedure starting from **1j** and 1,3-propanediol. Reaction was performed at 50 °C. Extraction with CPME followed by flash column chromatography (PE/Et_2O 99/1 v/v) gave **2j** as a white solid (151 mg, 65%, R_f = 0.33 PE/Et_2O 99/1 v/v), mp 70.0−71.3 °C (benzene). **^{1}H NMR** (600 MHz, DMSO-d_6): δ 7.46 (d, *J* = 8.2 Hz, 2H), 7.40-7.36 (m, 1H), 6.12 (s, 1H), 4.18-4.11 (m, 2H), 3.90 (td, *J* = 12.3, 2.2 Hz, 2H), 2.12-2.02 (m, 1H), 1.42 (d, *J* = 13.5 Hz, 1H). **^{13}C{^{1}H} NMR** (150 MHz, DMSO-d_6): δ 134.1, 132.3, 131.3, 129.6, 98.6, 67.0, 25.1. **EI-MS** *m/z* (%): 231 (57), 233 (40), 235 (8) $[M-H]^+$, 173 (100), 175 (74), 177 (17), 87 (72), 75 (26). **ESI-HRMS** $[M+Na]^+$: *m/z* 254.9952, $C_{10}H_{10}Cl_2NaO_2^+$ requires 254.9950.

2-(2-Iodophenyl)-1,3-dioxane (2k): general procedure starting from **1k** and 1,3-propanediol. Extraction with CPME gave pure **2k** as a colorless oil (250 mg, 86%, R_f = 0.43 PE/Et_2O 98/2 v/v). **^{1}H NMR** (600 MHz, DMSO-d_6): δ 7.84 (dd, *J* = 7.9, 1.2 Hz, 1H), 7.52 (dd, *J* = 7.6, 1.7 Hz, 1H), 7.40 (td, *J* = 7.6, 1.3 Hz, 1H), 7.12 (td, *J* = 7.6, 1.7 Hz, 1H), 5.48 (s, 1H), 4.19-4.12 (m, 2H), 3.95 (td, *J* = 12.2, 2.4 Hz, 2H), 2.07-1.96 (m, 1H), 1.44 (dtt, *J* = 13.4, 2.7, 1.4 Hz, 1H). **^{13}C{^{1}H} NMR** (150 MHz, DMSO-d_6): δ 140.2, 138.9, 130.8, 128.1, 127.7, 104.0, 97.7, 66.9, 25.2. **EI-MS** *m/z* (%): 290 (M^+, 46), 289 (100), 232 (26), 231 (43), 104 (32), 87 (25). **ESI-HRMS** $[M+H]^+$: *m/z* 290.9886, $C_{10}H_{12}IO_2^+$ requires 290.9877.

2-(2-(Trifluoromethyl)phenyl)-1,3-dioxane (2l): general procedure starting from **1l** and 1,3-propanediol. Reaction was performed at 50 °C. Extraction with CPME gave pure **2l** as a colorless oil (158 mg, 68%, R_f = 0.33 PE/EtOAc 9/1 v/v). **^{1}H NMR** (600 MHz, DMSO-d_6): δ 7.85 (d, J = 7.8 Hz, 1H), 7.73-7.68 (m, 2H), 7.58 (t, J = 7.6 Hz, 1H), 5.74 (s, 1H), 4.17-4.12 (m, 2H), 3.94 (td, J = 12.3, 2.4 Hz, 2H), 2.08-1.99 (m, 1H), 1.47-1.42 (m, 1H). **^{13}C{^{1}H} NMR** (150 MHz, DMSO-d_6): δ 136.8, 132.6, 129.4, 128.2, 125.9 (q, J = 30.4 Hz, 1C), 125.4 (q, J = 5.7 Hz, 1C), 124.1 (q, J = 274.4 Hz, 1C), 97.3, 67.0, 25.2. **^{19}F{^{1}H} NMR** (564 MHz, $CDCl_3$): δ -58.05 (s). **EI-MS** *m/z* (%): 232 (M^+, 21), 231 (39), 174 (22), 173 (100), 155 (25), 145 (28), 87 (39). **ESI-HRMS** $[M+Na]^+$: *m/z* 255.0614, $C_{11}H_{11}F_3NaO_2^+$ requires 255.0603.

1-(3-(5,5-Dimethyl-1,3-dioxan-2-yl)phenyl)ethanone (2m): general procedure starting from **1m** and 2,2-dimethylpropane-1,3-diol. Reaction was performed at 50 °C. Extraction with CPME gave pure **2m** as a colorless oil (210 mg, 90%, R_f = 0.18 PE/Et_2O 8/2 v/v). **^{1}H NMR** (600 MHz, DMSO-d_6): δ 7.99 (s, 1H), 7.96 (dt, J = 7.7, 1.5 Hz, 1H), 7.69 (d, J = 7.9 Hz, 1H), 7.53 (t, J = 7.7 Hz, 1H), 5.50 (s, 1H), 3.70 (d, J = 11.0 Hz, 2H), 3.65 (d, J = 10.9 Hz, 2H), 2.59 (s, 3H), 1.19 (s, 3H), 0.76 (s, 3H). **^{13}C{^{1}H} NMR** (150 MHz, DMSO-d_6): δ 197.6, 139.2, 136.7, 130.9, 128.6, 125.6, 100.1, 76.5, 40.1, 29.8, 26.7, 22.7, 21.4. **EI-MS** *m/z* (%): 234 (M^+, 16), 233 (39), 149 (100), 147 (86), 133 (30), 77 (17), 69 (23), 56 (50). **ESI-HRMS** $[M+Na]^+$: *m/z* 257.1131, $C_{14}H_{18}NaO_3^+$ requires 257.1148.

(4-(1,3-Dioxan-2-yl)phenyl)(pyrrolidin-1-yl)methanone (2n): general procedure starting from **1n** and 1,3-propanediol. Extraction with CPME followed by flash column chromatography (PE/acetone 8/2 v/v) gave **2n** as a white solid (196 mg, 75%, R_f = 0.21 PE/acetone 8/2 v/v), mp 163.2−164.8 °C (benzene). **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.51 (s, 4H), 5.52 (s, 1H), 4.27 (dd, J = 10.4, 5.1 Hz, 2H), 4.00 (td, J = 12.2, 2.5 Hz, 2H), 3.63 (t, J = 7.0 Hz, 2H), 3.37 (t, J = 6.7 Hz, 2H), 2.23 (dddd, J = 18.8, 12.7, 10.0, 5.0 Hz, 1H), 1.94 (quint, J = 6.9 Hz, 2H), 1.84 (quint, J = 6.7 Hz, 2H), 1.46 (d, J = 13.5 Hz, 1H). **^{13}C{^{1}H} NMR** (150 MHz, $CDCl_3$): δ 169.6, 140.3, 137.8, 127.2, 126.1, 101.1, 67.5, 49.7, 46.3, 26.5, 25.9, 24.6. **EI-MS** *m/z* (%): 261 (M^+, 90), 260 (72), 203 (13), 202 (24), 191 (48), 174 (11), 158 (19), 133 (38), 105 (100), 104 (12), 87 (26), 77 (27), 32 (22), 28 (93). **ESI-HRMS** $[M+H]^+$: *m/z* 262.1433, $C_{15}H_{20}NO_3^+$ requires 262.1438.

Methyl 4-(5,5-dimethyl-1,3-dioxan-2-yl)benzoate (2o): general procedure starting from **1o** and 2,2-dimethylpropane-1,3-diol. Extraction with EtOAc gave pure **2o** as a white solid (205 mg, 82%, R_f = 0.60 PE/EtOAc 9/1 v/v), mp 106.8−107.5 °C (petroleum ether). **^{1}H NMR** (600 MHz, DMSO-d_6): δ 7.97 (d, J = 8.0 Hz, 2H), 7.57 (d, J = 8.1 Hz, 2H), 5.49 (s, 1H), 3.85 (s, 3H), 3.69 (d, J = 11.0 Hz, 2H), 3.65 (d, J = 10.7 Hz, 2H), 1.18 (s, 3H), 0.76 (s, 3H). **^{13}C{^{1}H} NMR** (150 MHz, DMSO-d_6): δ 166.0, 143.4, 129.8, 129.0, 126.6, 99.9, 76.5, 52.2, 29.9, 22.7, 21.4. **EI-MS** *m/z* (%): 250 (M^+, 44), 249 (70), 165 (100), 163 (73), 149 (27), 133 (35), 105 (48), 77 (29), 56 (62).[52]

4-(1,3-Dioxan-2-yl)benzoic acid (2p): general procedure starting from **1p** and 1,3-propanediol. Extraction with EtOAc followed by crystallization (pentane) gave **2p** as a white solid (100 mg, 48%, R_f = 0.22 PE/EtOAc 7/3 v/v), mp 212.8−214.0 °C (pentane). **^{1}H NMR** (600 MHz, DMSO-d_6): δ 13.01 (br s, 1H), 7.93 (d, J = 8.3 Hz, 2H), 7.51 (d, J = 8.3 Hz, 2H), 5.58 (s, 1H), 4.19-4.11 (m, 2H), 3.95 (td, J =12.3, 2.5 Hz, 2H), 2.05-1.94 (m, 1H), 1.46 (dtt, J = 13.4, 2.6, 1.4 Hz, 1H). **^{13}C{^{1}H} NMR** (150 MHz, DMSO-d_6): δ 167.1, 143.3, 130.9, 129.1, 126.3, 99.9, 66.7, 25.3. **ESI-HRMS** $[M+H]^+$: *m/z* 209.0816, $C_{11}H_{13}O_4^+$ requires 209.0808.

4-(1,3-Dioxan-2-yl)benzoyl chloride (2q): general procedure starting from **1q** and 1,3-propanediol. Extraction with CPME followed by crystallization (pentane) gave **2q** as a white solid (143 mg, 63%, R_f = 0.27 PE/Et_2O 9/1 v/v), mp 90.3−92.8 °C (pentane). **^{1}H NMR** (600 MHz, C_6D_6): δ 7.86 (d, J = 8.4 Hz, 2H), 7.44 (d, J = 8.5 Hz, 2H), 5.10 (s, 1H), 3.84-3.78 (m, 2H), 3.36 (td, J = 12.3, 2.4 Hz, 2H), 1.83-1.73 (m, 1H), 0.64-0.59 (m, 1H). **^{13}C{^{1}H} NMR** (150 MHz, C_6D_6): δ 146.3, 133.6, 131.4, 128.4, 127.0, 100.2, 67.1, 25.8. **ESI-HRMS** (through derivatization as methyl ester in MeOH solution) $[M+H]^+$: *m/z* 223.0963, $C_{12}H_{15}O_4^+$ requires 223.0965.

4-(5,5-Dimethyl-1,3-dioxan-2-yl)benzonitrile (2r): general procedure starting from **1r** and 2,2-dimethylpropane-1,3-diol. Extraction with CPME gave pure **2r** as a white solid (209 mg, 96%, R_f = 0.57 PE/EtOAc 9/1 v/v), mp 110.1−111.7 °C (petroleum ether). **^{1}H NMR** (600 MHz, DMSO-d_6): δ 7.85 (d, J = 8.3 Hz, 2H), 7.62 (d, J = 8.3 Hz, 2H), 5.51 (s, 1H), 3.70 (d, J = 10.8 Hz, 2H), 3.65 (d, J = 10.8 Hz, 2H), 1.17 (s, 3H), 0.76 (s, 3H). **^{13}C{^{1}H} NMR** (150 MHz, DMSO-d_6): δ 143.4, 132.3, 127.2, 118.7, 111.5, 99.5, 76.5, 29.9, 22.7, 21.3. **EI-MS** *m/z* (%): 217 (M^+, 38), 216 (32), 132 (25), 130 (41), 56 (100), 41 (34).[50]

2-(4-Methoxyphenyl)-5,5-dimethyl-1,3-dioxane (2s): general procedure starting from **1s** and 2,2-dimethylpropane-1,3-diol. Extraction with CPME gave pure **2s** as a white solid (133 mg, 60%, R_f = 0.38 PE/EtOAc 95/5 v/v), mp 80.8–82.6 °C (pentane). **^{1}H NMR** (600 MHz, DMSO-d_6): δ 7.36-7.31 (m, 2H), 6.92-6.88 (m, 2H), 5.34 (s, 1H), 3.75 (s, 3H), 3.64 (d, J = 10.8 Hz, 2H), 3.59 (d, J = 10.7 Hz, 2H), 1.18 (s, 3H), 0.74 (s, 3H). **^{13}C{^{1}H} NMR** (150 MHz, DMSO-d_6): δ 159.4, 131.2, 127.5, 113.3, 100.7, 76.5, 55.1, 29.8, 22.7, 21.4. **EI-MS** *m/z* (%): 222 (M^+, 38), 221 (70), 136 (76), 135 (100).[50]

2-(3-Methoxyphenyl)-5,5-dimethyl-1,3-dioxane (2t): general procedure starting from **1t** and 2,2-dimethylpropane-1,3-diol. Extraction with CPME gave pure **2t** as a colorless oil (189 mg, 85%, R_f = 0.40 PE/EtOAc 95/5 v/v). **^{1}H NMR** (600 MHz, DMSO-d_6): δ 7.28 (t, J = 7.9 Hz, 1H), 7.01 (d, J = 7.6 Hz, 1H), 6.97 (s, 1H), 6.91 (dd, J = 8.2, 2.7 Hz, 1H), 5.37 (s, 1H), 3.75 (s, 3H), 3.67 (d, J = 11.0 Hz, 2H), 3.61 (d, J = 10.9 Hz, 2H), 1.18 (s, 3H), 0.75 (s, 3H). **^{13}C{^{1}H} NMR** (150 MHz, DMSO-d_6): δ 159.0, 140.3, 129.1, 118.4, 114.2, 111.5, 100.6, 76.5, 55.0, 29.8, 22.7, 21.4. **EI-MS** *m/z* (%): 222 (M^+, 55), 221 (73), 136 (100), 135 (84), 77 (17), 69 (20).[53]

2-(2-Methoxyphenyl)-1,3-dioxane (2u): general procedure starting from **1u** and 1,3-propanediol. Extraction with CPME gave pure **2u** as a white solid (126 mg, 65%, R_f = 0.40 PE/EtOAc 9/1 v/v), mp 77.8–78.6 °C (pentane). **^{1}H NMR** (600 MHz, DMSO-d_6): δ 7.44 (dd, J = 7.6, 1.9 Hz, 1H), 7.33-7.29 (m, 1H), 6.99 (d, J = 7.3 Hz, 1H), 6.93 (td, J = 7.5, 1.1 Hz, 1H), 5.74 (s, 1H), 4.12-4.07 (m, 2H), 3.92-3.86 (m, 2H), 3.78 (s, 3H), 1.99 (dtt, J = 13.6, 12.4, 5.1 Hz, 1H), 1.41 (dtt, J = 13.4, 2.7, 1.4 Hz, 1H). **^{13}C{^{1}H} NMR** (150 MHz, DMSO-d_6): δ 156.0, 129.9, 127.0, 126.9, 120.0, 110.9, 96.0, 66.8, 55.4, 25.5. **EI-MS** *m/z* (%): 194 (M^+, 66), 193 (94), 136 (51), 135 (100), 119 (28), 87 (30), 77 (34).[54]

4-(5,5-Dimethyl-1,3-dioxan-2-yl)phenol (2v): general procedure starting from **1v** and 2,2-dimethylpropane-1,3-diol. Extraction with EtOAc followed by crystallization (petroleum ether) gave **2v** as a white solid (164 mg, 79%, R_f = 0.30 PE/EtOAc 8/2 v/v), mp 138.2–139.4 °C (petroleum ether). **^{1}H NMR** (600 MHz, DMSO-d_6): δ 9.46 (s, 1H), 7.21 (d, J = 8.5 Hz, 2H), 6.72 (d, J = 8.6 Hz, 2H), 5.28 (s, 1H), 3.63 (d, J = 11.0 Hz, 2H), 3.57 (d, J = 10.7 Hz, 2H), 1.17 (s, 3H), 0.73 (s, 3H). **^{13}C{^{1}H} NMR** (150 MHz, DMSO-d_6): δ 157.6, 129.6, 127.5, 114.6, 101.0, 76.5, 29.7, 22.7, 21.4. **EI-MS** *m/z* (%): 208 (M^+, 42), 207 (83), 123 (55), 122 (50), 121 (100).[55]

2-(5,5-Dimethyl-1,3-dioxan-2-yl)phenol (2w): general procedure starting from **1w** and 2,2-dimethylpropane-1,3-diol. Extraction with EtOAc gave pure **2w** as a white solid (164 mg, 79%, R_f = 0.69 PE/EtOAc 7/3 v/v), mp 60.3–61.0 °C (pentane). **^{1}H NMR** (600 MHz, DMSO-d_6): δ 9.48 (s, 1H), 7.40 (dd, J = 7.5, 1.8 Hz, 1H), 7.16-7.11 (m, 1H), 6.82-6.76 (m, 2H), 5.65 (s, 1H), 3.63 (d, J = 10.8 Hz, 2H), 3.58 (d, J = 10.8 Hz, 2H), 1.21 (s, 3H), 0.74 (s, 3H). **^{13}C{^{1}H} NMR** (150 MHz, DMSO-d_6): δ 154.3, 129.5, 127.2, 125.0, 118.6, 115.3, 96.5, 76.7, 29.8, 22.8, 21.4. **EI-MS** *m/z* (%): 208 (M^+, 38), 123 (22), 122 (100), 121 (66).[56]

4-(5,5-Dimethyl-1,3-dioxan-2-yl)-2-methoxyphenol (2x): general procedure starting from **1x** and 2,2-dimethylpropane-1,3-diol. Reaction was performed at 50 °C. Extraction with EtOAc followed by flash column chromatography (PE/Et_2O 6/4 v/v) gave **2x** as a white solid (155 mg, 65%, R_f = 0.45 PE/Et_2O 6/4 v/v), mp 81.5–82.6 °C (pentane). **^{1}H NMR** (600 MHz, DMSO-d_6): δ 9.04 (s, 1H), 6.93 (d, J = 1.9 Hz, 1H), 6.82 (dd, J = 8.1, 1.9 Hz, 1H), 6.73 (d, J = 8.0 Hz, 1H), 5.28 (s, 1H), 3.75 (s, 3H), 3.64 (d, J = 11.1 Hz, 2H), 3.58 (d, J = 10.8 Hz, 2H), 1.18 (s, 3H), 0.74 (s, 3H). **^{13}C{^{1}H} NMR** (150 MHz, DMSO-d_6): δ 147.1, 146.7, 130.0, 118.8, 114.8, 110.1, 101.0, 76.5, 55.5, 29.8, 22.8, 21.4. **EI-MS** *m/z* (%): 238 (M^+, 52), 237 (47), 152 (100), 151 (82), 69 (17).[57]

5,5-Dimethyl-2-(o-tolyl)-1,3-dioxane (2y): general procedure starting from **1y** and 2,2-dimethylpropane-1,3-diol. Extraction with CPME gave pure **2y** as a colorless oil (186 mg, 90%, R_f = 0.90 PE/EtOAc 8/2 v/v). **^{1}H NMR** (600 MHz, DMSO-d_6): δ 7.49 (d, J = 7.6 Hz, 1H), 7.24 (t, J = 7.4 Hz, 1H), 7.20-7.14 (m, 2H) 5.51 (s, 1H), 3.68 (d, J = 10.3 Hz, 2H), 3.65 (d, J = 11.0 Hz, 2H), 2.34 (s, 3H), 1.21 (s, 3H), 0.75 (s, 3H). **^{13}C{^{1}H} NMR** (150 MHz, DMSO-d_6): δ 136.6, 135.5, 130.1, 128.4, 126.0, 125.4, 99.5, 76.7, 29.8, 22.9, 21.4, 18.4. **EI-MS** *m/z* (%): 206 (M^+,60), 205 (57), 191 (37), 121 (79), 120 (39), 119 (100), 91 (53), 69 (25). **ESI-HRMS** $[M+Na]^+$: *m/z* 229.1206, $C_{13}H_{18}NaO_2^+$ requires 229.1199.

5,5-Dimethyl-2-(m-tolyl)-1,3-dioxane (2z): general procedure starting from **1z** and 2,2-dimethylpropane-1,3-diol. Extraction with CPME gave pure **2z** as a colorless oil (177 mg, 86%, R_f = 0.89 PE/EtOAc 8/2 v/v). **^{1}H NMR** (600 MHz, DMSO-d_6): δ 7.26-7.19 (m, 3H), 7.17-7.13 (m, 1H), 5.36 (s, 1H), 3.66 (d, J = 11.1 Hz, 2H), 3.61 (d, J = 10.9 Hz, 2H), 2.31 (s, 3H), 1.19 (s, 3H), 0.75 (s, 3H). **^{13}C{^{1}H} NMR** (150 MHz, DMSO-d_6): δ 138.7, 137.1, 129.1, 127.9, 126.7, 123.3, 100.8, 76.5, 29.8, 22.7, 21.4, 21.0. **EI-MS** *m/z* (%): 206 (M^+, 54), 205 (87), 191 (42), 121 (69), 119 (100), 91 (48). **ESI-HRMS** $[M+Na]^+$: *m/z* 229.1209, $C_{13}H_{18}NaO_2^+$ requires 229.1199.

2-(Naphthalen-2-yl)-1,3-dioxane (2aa): general procedure starting from **1aa** and 1,3-propanediol. Extraction with CPME followed by flash column chromatography (PE/Et_2O 98/2 v/v) gave **2aa** as a white solid (158 mg, 74%, R_f = 0.42 PE/Et_2O 98/2 v/v), mp 74.9−76.5 °C (petroleum ether). **^{1}H NMR** (600 MHz, DMSO-d_6): δ 8.02-7.85 (m, 4H), 7.60-7.46 (m, 3H), 5.67 (s, 1H), 4.24-4.12 (m, 2H), 3.99 (td, J = 12.2, 2.4 Hz 2H), 2.11-1.96 (m, 1H), 1.52-1.42 (m, 1H). **^{13}C{^{1}H} NMR** (150 MHz, DMSO-d_6): δ 136.5, 133.0, 132.4, 128.2, 127.6, 127.5, 126.3, 126.2, 125.0, 124.1, 100.7, 66.7, 25.4. **EI-MS** *m/z* (%): 214 (M^+, 100), 213 (74), 156 (56), 155 (94), 128 (78), 127 (77), 87 (14).[58]

2-(Anthracen-9-yl)-1,3-dioxane (2ab): general procedure starting from **1ab** and 1,3-propanediol. Extraction with CPME followed by flash column chromatography (PE/Et_2O 9/1 v/v) gave **2ab** as a light yellow solid (156 mg, 59%, R_f = 0.21 PE/Et_2O 9/1 v/v), mp 154.5−155.6 °C (petroleum ether). **^{1}H NMR** (600 MHz, $CDCl_3$): δ 8.80 (d, J = 9.0 Hz, 2H), 8.48 (s, 1H), 8.00 (dd, J = 8.4, 1.2 Hz, 2H), 7.57-7.50 (m, 2H), 7.49-7.42 (m, 2H), 6.93 (s, 1H), 4.52-4.43 (m, 2H), 4.22 (td, J = 12.4 Hz, 2.4 Hz, 2H), 2.68-2.55 (m, 1H), 1.67-1.58 (m, 1H). **^{13}C{^{1}H} NMR** (150 MHz, $CDCl_3$): δ 131.7, 129.7, 129.7, 129.1, 128.4, 126.1, 125.2, 124.9, 100.7, 68.6, 26.3. **EI-MS** *m/z* (%): 206 (100), 205 (59), 178 (89), 177 (45), 176 (58).[59]

2-(Pyren-2-yl)-1,3-dioxane (2ac): general procedure starting from **1ac** and 1,3-propanediol. Extraction with EtOAc followed by crystallization (Et_2O) gave **2ac** as a yellow solid (231 mg, 80%, R_f = 0.32 PE/EtOAc 9/1 v/v), mp 154.5–155.6 °C (Et_2O). **^{1}H NMR** (600 MHz, DMSO-d_6): δ 8.54 (d, J = 9.3 Hz, 1H), 8.32 (dd, J = 7.6, 3.0 Hz, 2H), 8.28 (d, J = 7.9 Hz, 1H), 8.25-8.22 (m, 2H), 8.21-8.16 (m, 2H), 8.09 (t, J = 7.6 Hz, 1H), 6.40 (s, 1H), 4.32-4.26 (m, 2H), 4.24-4.17 (m, 2H), 2.25-2.14 (m, 1H), 1.58 (ddt, J = 13.6, 2.6, 1.2 Hz, 1H). **^{13}C{^{1}H} NMR** (150 MHz, DMSO-d_6): δ 132.0, 131.0, 130.7, 130.1, 127.7, 127.7, 127.4, 127.3, 126.3, 125.5, 125.4, 124.5, 124.2, 124.0, 123.9, 123.8, 99.9, 67.0, 25.6. **EI-MS** *m/z* (%): 288 (M^+, 57), 230 (38), 229 (35), 202 (100), 201 (49), 200 (31). **ESI-HRMS** $[M+H]^+$: *m/z* 289.1204, $C_{20}H_{17}O_2^+$ requires 289.1223.

2-(Furan-2-yl)-5,5-dimethyl-1,3-dioxane (2ad): general procedure starting from **1ad** and 2,2-dimethylpropane-1,3-diol. Extraction with CPME gave pure **2ad** as a colorless oil (155 mg, 85%, R_f = 0.55 pentane/Et_2O 95/5 v/v). **^{1}H NMR** (600 MHz, DMSO-d_6): δ 7.64-7.61 (m, 1H), 6.46-6.41 (m, 2H), 5.48 (s, 1H), 3.63 (d, J = 11.0 Hz, 2H), 3.59 (d, J = 10.9 Hz, 2H), 1.15 (s, 3H), 0.73 (s, 3H). **^{13}C{^{1}H} NMR** (150 MHz, DMSO-d_6): δ 151.1, 142.6, 110.2, 107.3, 95.2, 76.2, 29.9, 22.6, 21.3. **EI-MS** *m/z* (%): 182 (M^+, 32), 128 (32), 97 (100), 95 (51), 69 (23), 56 (31), 41 (31).[60]

5,5-Dimethyl-2-(thiophen-2-yl)-1,3-dioxane (2ae): general procedure starting from **1ae** and 2,2-dimethylpropane-1,3-diol. Extraction with CPME gave pure **2ae** as a white solid (192 mg, 97%, R_f = 0.50 pentane/Et_2O 95/5 v/v), mp 73.5–74.6 °C (pentane). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.30 (dd, J = 5.0, 1.5 Hz, 1H), 7.15-7.13 (m, 1H), 6.99 (dd, J = 4.9, 3.5 Hz, 1H), 5.65 (s, 1H), 3.76 (d, J = 11.4 Hz, 2H), 3.64 (d, J = 10.9 Hz, 2H), 1.29 (s, 3H), 0.80 (s, 3H). ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$): δ 141.5, 126.6, 125.8, 125.2, 98.5, 77.7, 30.4, 23.1, 22.0. EI-MS *m/z* (%): 198 (M^+, 100), 197 (42), 113 (86), 112 (23), 111 (67), 56 (19).[51]

2-Ferrocenyl-1,3-dioxane (2af): general procedure starting from **1af** and 1,3-propanediol. Extraction with EtOAc followed by flash column chromatography (PE/EtOAc 98/2 v/v) gave **2af** as an orange solid (144 mg, 53%, R_f = 0.36 PE/EtOAc 98/2 v/v), mp 115.6–117.1 °C (petroleum ether). **^{1}H NMR** (600 MHz, $CDCl_3$): δ 5.34 (s, 1H), 4.33 (s, 2H), 4.23-4.16 (m, 7H), 4.14 (s, 2H), 3.91 (t, J = 11.0 Hz, 2H), 2.20-2.08 (m, 1H), 1.38 (d, J = 13.5 Hz, 1H). **^{13}C{^{1}H} NMR** (150 MHz, $CDCl_3$): δ 100.7, 86.4, 69.1, 68.2, 67.4, 66.7, 26.0. **EI-MS** *m/z* (%): 272 (M^+, 100), 214 (19), 186 (38), 164 (18), 121 (38). **ESI-HRMS** $[M+Na]^+$: *m/z* 295.0393, $C_{14}H_{16}FeNaO_2^+$ requires 295.0392.

5,5-Dimethyl-2-pentyl-1,3-dioxane (2ag): general procedure starting from **1ag** and 2,2-dimethylpropane-1,3-diol. Extraction with CPME gave pure **2ag** as a colorless oil (153 mg, 82%, R_f = 0.48 PE/EtOAc 95/5 v/v). **^{1}H NMR** (600 MHz, DMSO-d_6): δ 4.38 (t, J = 5.0 Hz, 1H), 3.50 (d, J = 11.3 Hz, 2H), 3.36 (d, J = 10.7 Hz, 2H), 1.54-1.45 (m, 2H), 1.36-1.29 (m, 2H), 1.28-1.19 (m, 4H), 1.07 (s, 3H), 0.85 (t, J = 6.9 Hz, 3H), 0.66 (s, 3H). **^{13}C{^{1}H} NMR** (150 MHz, DMSO-d_6): δ 101.3, 76.1, 34.3, 31.2, 29.7, 23.1, 22.7, 22.1, 21.4, 13.9. **EI-MS** *m/z* (%): 186 (M^+, 2), 185 (12), 115 (100), 99 (19), 69 (41), 56 (51), 41 (23).[22]

2-Cyclohexyl-5,5-dimethyl-1,3-dioxane (2ah): general procedure starting from **1ah** and 2,2-dimethylpropane-1,3-diol. Extraction with Et_2O gave pure **2ah** as a colorless oil (170 mg, 86%, R_f = 0.81 PE/Et_2O 9/1 v/v). **^{1}H NMR** (600 MHz, DMSO-d_6): δ 4.15 (d, J = 4.8 Hz, 1H), 3.51 (d, J = 11.3 Hz, 2H), 3.34 (d, J = 10.7 Hz, 2H), 1.74-1.63 (m, 4H), 1.62-1.56 (m, 1H), 1.47-1.39 (m, 1H), 1.20-0.99 (m, 5H) superimposed to 1.06 (s, 3H), 0.66 (s, 3H). **^{13}C{^{1}H} NMR** (150 MHz, DMSO-d_6): δ 103.9, 76.1, 41.7, 29.8, 26.8, 26.1, 25.4, 22.6, 21.3. **EI-MS** *m/z* (%): 198 (M^+, 1), 197 (6), 115 (100), 95 (12), 83 (16), 69 (34), 56 (16), 41 (17).[12]

5,5-Dimethyl-2-phenethyl-1,3-dioxane (2ai): general procedure starting from **1ai** and 2,2-dimethylpropane-1,3-diol. Extraction with CPME gave pure **2ai** as a colorless oil (218 mg, 99%, R_f = 0.50 PE/Et_2O 9/1 v/v). **^{1}H NMR** (600 MHz, DMSO-d_6): δ 7.27 (t, J = 7.6 Hz, 2H), 7.20-7.14 (m, 3H), 4.41 (t, J = 5.0 Hz, 1H), 3.54 (d, J = 11.1 Hz, 2H), 3.36 (d, J = 10.9 Hz, 2H), 2.68-2.62 (m, 2H), 1.84-1.77 (m, 2H), 1.10 (s, 3H), 0.67 (s, 3H). **^{13}C{^{1}H} NMR** (150 MHz, DMSO-d_6): δ 141.6, 128.3, 128.2, 125.7, 100.5, 76.1, 36.1, 29.7, 29.5, 22.8, 21.4. **EI-MS** *m/z* (%): 220 (M^+,16), 219 (21), 142 (65), 115 (100), 105 (29), 92 (58), 91 (61), 69 (81), 41 (25). **ESI-HRMS** $[M+Na]^+$: *m/z* 243.1360, $C_{14}H_{20}NaO_2^+$ requires 243.1356.

(±)-2-(2,6-Dimethylhept-5-en-1-yl)-5,5-dimethyl-1,3-dioxane (2aj): general procedure starting from **1aj** and 2,2-dimethylpropane-1,3-diol. Extraction with CPME gave pure **2aj** as a colorless oil (113 mg, 47%, R_f = 0.69 PE/Et_2O 95/5 v/v). **^{1}H NMR** (600 MHz, DMSO-d_6): δ 5.10-5.02 (m, 1H), 4.46 (dd, J = 5.9, 4.5 Hz, 1H), 3.52-3.46 (m, 2H), 3.40-3.35 (m, 2H), 1.99-1.84 (m, 2H), 1.63 (s, 3H), 1.60-1.48 (m, 2H) superimposed to 1.56 (s, 3H), 1.34-1.26 (m, 2H), 1.14-1.08 (m, 1H), 1.07 (s, 3H), 0.86 (d, J = 6.6 Hz, 3H), 0.66 (s, 3H). **^{13}C{^{1}H} NMR** (150 MHz, DMSO-d_6): δ 130.5, 124.6, 100.4, 76.1, 41.5, 36.9, 29.7, 27.7, 25.5, 24.9, 22.8, 21.4, 19.6, 17.5. **EI-MS** *m/z* (%): 240 (M^+, 3), 155 (30), 136 (35), 121 (100), 115 (29), 95 (34), 81 (23), 69 (97), 56 (24), 41 (56).[61]

2-(2,6-Dimethylhepta-1,5-dien-1-yl)-5,5-dimethyl-1,3-dioxane (2ak): general procedure starting from **1ak** and 2,2-dimethylpropane-1,3-diol. Extraction with CPME followed by flash column chromatography (PE/Et_2O 98/2 v/v) gave **2ak** as a colorless oil (198 mg, 83%, R_f = 0.30 PE/Et_2O 98/2 v/v). *E* and *Z* stereoisomers (*E*/*Z* = 1/0.6) were not separated by chromatography. **^{1}H NMR** (600 MHz, DMSO-d_6, mixture of stereoisomers): δ 5.18-5.14 (m, 1H, *E* + 1H, *Z*), 5.12-5.08 (m, 1H, *Z*), 5.08-5.05 (m, 1H, *E*), 5.04 (d, *J* = 6.3 Hz, 1H, *E*), 5.02 (d, *J* = 6.4 Hz, 1H, *E*), 3.52-3.42 (m, 4H, *E* + 4H, *Z*), 2.08-1.92 (m, 4H, *E* + 4H, *Z*), 1.68 (d, *J* = 1.5 Hz, 3H, *Z*), 1.65-1.62 (m, 6H, *E* + 3H, *Z*), 1.58-1.55 (m, 3H, *E* + 3H, *Z*), 1.09 (s, 3H, *E* + 3H, *Z*), 0.68 (s, 3H, *E*) superimposed to 0.67 (s, 3H, *Z*). **^{13}C{^{1}H} NMR** (150 MHz, DMSO-d_6, mixture of stereoisomers): δ 140.8, 140.6, 131.2, 131.0, 123.8, 123.7, 123.6, 122.6, 98.3, 98.1, 76.1, 76.1, 38.6, 32.4, 29.5, 26.2, 25.7, 25.5, 25.5, 22.8, 22.8, 21.5, 21.5, 17.5, 17.4, 16.8. **EI-MS** (***E* stereoisomer**) *m/z* (%): 238 (M^+, 4), 169 (19), 115 (27), 84 (25), 69 (100), 55 (31), 41 (44). **EI-MS** (***Z* stereoisomer**) *m/z* (%): 238 (M^+, 6), 109 (31), 95 (27), 84 (27), 80 (35), 69 (100), 55 (34), 41 (65).[62]

(*E*)-5,5-Dimethyl-2-styryl-1,3-dioxane (2al): general procedure starting from **1al** and 2,2-dimethylpropane-1,3-diol. Extraction with CPME gave pure **2al** as a white solid (166 mg, 76%, R_f = 0.26 pentane/Et_2O 95/5 v/v), mp 55.6–56.3 °C (pentane). **^{1}H NMR** (600 MHz, DMSO-d_6): δ 7.50-7.46 (m, 2H), 7.36-7.32 (m, 2H), 7.30-7.26 (m, 1H), 6.72 (d, *J* = 16.2 Hz, 1H), 6.24 (dd, *J* = 16.3, 4.6 Hz, 1H), 5.04 (dd, *J* = 4.8, 1.3 Hz, 1H), 3.60 (d, *J* = 11.1 Hz, 2H), 3.52 (d, *J* = 10.8 Hz, 2H), 1.13 (s, 3H), 0.72 (s, 3H). **^{13}C{^{1}H} NMR** (150 MHz, DMSO-d_6): δ 135.7, 132.2, 128.6, 128.1, 126.7, 126.2, 100.1, 76.1, 29.8, 22.7, 21.4. **EI-MS** *m/z* (%): 218 (M^+, 96), 133 (35), 132 (28), 131 (89), 104 (100), 103 (30), 77 (20), 55 (19).[14]

2-((1*R*,5*S*)-6,6-Dimethylbicyclo[3.1.1]hept-2-en-2-yl)-5,5-dimethyl-1,3-dioxane (2am): general procedure starting from **1am** and 2,2-dimethylpropane-1,3-diol. Extraction with CPME followed by flash column chromatography (PE/Et_2O 95/5 v/v) gave **2am** as a white solid (165 mg, 70%, R_f = 0.22 PE/Et_2O 95/5 v/v), mp 50.6−51.8 °C. **^{1}H NMR** (600 MHz, DMSO-d_6): δ 5.59 (s, 1H), 4.71 (s, 1H), 3.52 (d, *J* = 11.0 Hz, 2H), 3.41 (d, *J* = 11.0 Hz, 2H), 2.39-2.32 (m, 2H), 2.26 (dt, *J* = 18.1, 3.1 Hz, 1H), 2.19 (dt, *J* = 18.1, 2.9 Hz, 1H), 2.07-2.03 (m, 1H), 1.26 (s, 3H), 1.08 (s, 3H), 1.05 (d, *J* = 8.3 Hz, 1H), 0.77 (s, 3H), 0.67 (s, 3H). **^{13}C{^{1}H} NMR** (150 MHz, DMSO-d_6): δ 145.4, 120.7, 101.7, 75.9, 40.9, 40.3, 37.2, 31.2, 30.6, 29.7, 26.0, 22.7, 21.4, 21.1. **EI-MS** *m/z* (%): 236 (M^+, 16), 191 (47), 115 (100), 107 (69), 79 (38), 69 (96), 41 (36). **ESI-HRMS** $[M+H]^+$: *m/z* 237.1852, $C_{15}H_{25}O_2^+$ requires 237.1849.

2-(4-Ethynylphenyl)-1,3-dioxane (2an): general procedure starting from **1an** and 1,3-propanediol. Extraction with CPME gave pure **2an** as a yellow solid (169 mg, 90%, R_f = 0.67 PE/EtOAc 8/2 v/v), mp 88.3–89.5 °C (pentane). **^{1}H NMR** (600 MHz, DMSO-d_6): δ 7.46 (d, J = 8.3 Hz, 2H), 7.40 (d, J = 8.3 Hz, 2H), 5.52 (s, 1H), 4.21 (s, 1H), 4.13 (dd, J = 10.5, 5.0 Hz, 2H), 3.93 (td, J = 12.3, 2.5 Hz, 2H), 2.03-1.93 (m, 1H), 1.47-1.40 (m, 1H). **^{13}C{^{1}H} NMR** (150 MHz, DMSO-d_6): δ 139.5, 131.4, 126.4, 121.9, 100.0, 83.2, 81.1, 66.6, 25.3. **EI-MS** *m/z* (%): 188 (M^+, 69), 187 (100), 130 (35), 129 (96), 102 (33), 101 (36).[63]

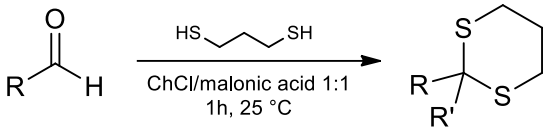
((4-(1,3-Dioxan-2-yl)phenyl)ethynyl)trimethylsilane (2ao): general procedure starting from **1ao** and 1,3-propanediol. Extraction with CPME followed by flash column chromatography (PE/DCM 1/1 v/v) gave **2ao** as a white solid (143 mg, 55%, R_f = 0.41 PE/DCM 1/1 v/v), mp 110.1−111.4 °C (petroleum ether). **^{1}H NMR** (600 MHz, DMSO-d_6): δ 7.44 (d, J = 8.3 Hz, 2H), 7.39 (d, J = 8.2 Hz, 2H), 5.52 (s, 1H), 4.15-4.10 (m, 2H), 3.95-3.89 (m, 2H), 2.03-1.93 (m, 1H), 1.47-1.41 (m, 1H), 0.23 (s, 9H). **^{13}C{^{1}H} NMR** (150 MHz, DMSO-d_6): δ 139.5, 131.3, 126.4, 122.3, 104.9, 100.0, 94.5, 66.6, 25.3, -0.1. **EI-MS** *m/z* (%): 260 (M^+, 76), 259 (100), 245 (68), 201 (29), 187 (81), 159 (46). **ESI-HRMS** $[M+Na]^+$: *m/z* 283.1130, $C_{15}H_{20}NaO_2Si^+$ requires 283.1125.

3,3-Dimethyl-1,5-dioxaspiro[5.5]undecane (2ap): general procedure starting from **1ap** and 2,2-dimethylpropane-1,3-diol. Reaction was performed at 50 °C. Extraction with Et_2O followed by flash column chromatography (pentane/Et_2O 95/5 v/v) gave **2ap** as a colorless oil (123 mg, 67%, R_f = 0.37 pentane/Et_2O 95/5 v/v). **^{1}H NMR** (600 MHz, DMSO-d_6): δ 3.41 (s, 4H), 1.69-1.60 (m, 4H), 1.42 (q, J = 5.9 Hz, 4H), 1.37-1.31 (m, 2H), 0.88 (s, 6H). **^{13}C{^{1}H} NMR** (150 MHz, DMSO-d_6): δ 96.9, 68.7, 32.2, 29.7, 25.2, 22.4, 22.1. **EI-MS** *m/z* (%): 184 (M^+, 20), 141 (100), 99 (21), 69 (32), 55 (31).[64]

2,5,5-Trimethyl-2-phenyl-1,3-dioxane (2aq): general procedure starting from **1aq** and 2,2-dimethylpropane-1,3-diol. Reaction was performed at 50 °C. Extraction with Et_2O followed by flash column chromatography (PE/EtOAc 9/1 v/v) gave **2aq** as a colorless oil (102 mg, 50%, R_f = 0.35 PE/EtOAc 9/1 v/v). **^{1}H NMR** (600 MHz, DMSO-d_6): δ 7.44-7.38 (m, 2H), 7.37-7.28 (m, 3H), 3.36 (d, J = 11.9 Hz, 2H), 3.27 (d, J = 11.0 Hz, 2H), 1.40 (s, 3H), 1.16 (s, 3H), 0.54 (s, 3H). **^{13}C{^{1}H} NMR** (150 MHz, DMSO-d_6): δ 140.8, 128.7, 127.7, 126.3, 99.5, 70.7, 31.8, 29.5, 22.6, 21.6. **EI-MS** *m/z* (%): 191 (100), 129 (80), 121 (54), 105 (84), 77 (36), 69 (39), 43 (48).[13]

1,4-Bis(5,5-dimethyl-1,3-dioxan-2-yl)benzene (2ar): general procedure starting from **1ar** and 2,2-dimethylpropane-1,3-diol (2.4 eq). Reaction was performed at 50 °C. Extraction with EtOAc gave pure **2ar** as a white solid (279 mg, 91%, R_f = 0.28 PE/Et_2O 8/2 v/v), mp 198.2−199.4 °C (petroleum ether). **^{1}H NMR** (600 MHz, DMSO-d_6): δ 7.42 (s, 4H), 5.41 (s, 2H), 3.67 (d, J = 10.7 Hz, 4H), 3.62 (d, J = 10.8 Hz, 4H), 1.18 (s, 6H), 0.75 (s, 6H). **^{13}C{^{1}H} NMR** (150 MHz, DMSO-d_6): δ 139.6, 126.4, 101.0, 77.1, 30.4, 23.3, 21.9. **EI-MS** *m/z* (%): 306 (M^+, 36), 305 (100), 221 (94), 219 (40), 191 (45), 176 (42), 133 (29), 105 (36), 69 (55), 56 (59), 41 (39).[65]

General procedure for the preparation of cyclic thioacetals. Reactions were performed under air at room temperature. In an open screw cap vial, substrates **1a**, **1ai** (1.0 mmol, 1.0 eq.), 1,3-propanedithiol (1.2 mmol, 1.2 eq.) and ChCl/malonic acid (1:1 mol/mol, 400 mg) were added. The resulting mixture was stirred for 1 hour. The mixture was then diluted with water (10 mL) and extracted with CPME (3 x 5 mL). The combined organic extracts were washed with sat. $NaHCO_3$ (1 x 5 mL), $NaHSO_3$ (1 x 5 mL) and brine (1 x 5 mL) then dried over Na_2SO_4 and the solvent removed under reduced pressure. The crude product was purified by flash column chromatography or by recrystallization.

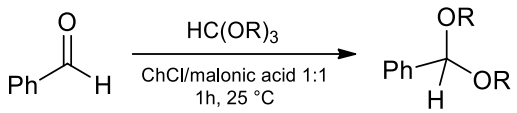


1a, 1ai **2as, 2at**

2-Phenyl-1,3-dithiane (2as): general procedure starting from **1a** and 1,3-propanedithiol. Extraction with CPME followed by crystallization (pentane) gave **2as** as a white solid (147 mg, 75%, R_f = 0.62 PE/EtOAc 95/5 v/v), mp 72.2–72.8 °C (pentane). **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.49-7.45 (m, 2H), 7.36-7.32 (m, 2H), 7.31-7.27 (m, 1H), 5.17 (s, 1H), 3.07 (ddd, *J* = 14.9, 12.5, 2.5 Hz, 2H), 2.92 (ddd, *J* = 14.5, 4.3, 2.9 Hz, 2H), 2.18 (dtt, *J* = 14.0, 4.7, 2.4 Hz, 1H), 1.94 (dtt, *J* = 14.2, 12.5, 3.0 Hz, 1H). **^{13}C{^{1}H} NMR** (150 MHz, $CDCl_3$): δ 139.2, 128.9, 128.6, 127.9, 51.6, 32.3, 25.2. **EI-MS** *m/z* (%): 196 (M^+, 100), 131 (30), 122 (74), 121 (89), 105 (19), 77 (19).[66]

2-Phenethyl-1,3-dithiane (2at): general procedure starting from **1ai** and 1,3-propanedithiol. Extraction with CPME followed by flash column chromatography (PE/EtOAc 95/5 v/v) gave **2at** as a colorless oil (110 mg, 49%, R_f = 0.52 PE/EtOAc 95/5 v/v). **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.29 (t, *J* = 7.6 Hz, 2H), 7.23-7.16 (m, 3H), 4.05 (t, *J* = 7.0 Hz, 1H), 2.85-2.80 (m, 4H), 2.76-2.71 (m, 2H), 2.06-2.00 (m, 1H), 1.95 (dt, *J* = 9.6, 7.0 Hz, 2H), 1.73-1.65 (m, 1H). **^{13}C{^{1}H} NMR** (150 MHz, $CDCl_3$): δ 140.8, 128.4, 128.3, 126.0, 45.5, 36.8, 32.0, 29.0, 25.7. **EI-MS** *m/z* (%): 224 (M^+, 99), 133 (35), 119 (100), 117 (55), 115 (26), 91 (80), 65 (20).[67]

General procedure for the preparation of dialkyl acetals. Reactions were performed under air at room temperature. In an open screw cap vial, substrate **1a** (1.0 mmol, 1.0 eq.), corresponding dialkylorthoformate (1.5 mmol, 1.5 eq.) and ChCl/malonic acid (1:1 mol/mol, 400 mg) were added. The resulting mixture was stirred for 1 hour. The mixture was then diluted with water (10 mL) and extracted with CPME (3 x 5 mL). The combined organic extracts were washed with sat. $NaHCO_3$ (1 x 5 mL), $NaHSO_3$ (1 x 5 mL) and brine (1 x 5 mL) then dried over Na_2SO_4 and the solvent removed under reduced pressure. When required, the crude product was purified by flash column chromatography.



1a **2au, 2av**

(Dimethoxymethyl)benzene (2au): general procedure starting from **1a** and trimethyl orthoformate. Extraction with CPME gave pure **2au** as a colorless oil (116 mg, 76%, R_f = 0.35 PE/Et_2O 98/2 v/v). **^{1}H NMR** (600 MHz, DMSO-d_6): δ 7.42-7.30 (m, 5H), 5.38 (s, 1H), 3.24 (s, 6H). **^{13}C{^{1}H} NMR** (150 MHz, DMSO-d_6): δ 138.2, 128.3, 128.1, 126.5, 102.6, 52.5. **EI-MS** *m/z* (%): 152 (M^+, 3), 122 (9), 121 (100), 105 (12), 91 (16), 77 (27).[68]

(Diethoxymethyl)benzene (2av): general procedure starting from **1a** and triethyl orthoformate. Extraction with CPME followed by flash column chromatography (PE/Et_2O 98/2 v/v) gave **2av** as a colorless oil (171 mg, 95%, R_f = 0.35 PE/Et_2O 98/2 v/v). **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.50-7.46 (m, 2H), 7.38-7.34 (m, 2H), 7.33-7.29 (m, 1H), 5.51 (s, 1H), 3.63 (dq, *J* = 9.5, 7.1 Hz, 2H), 3.54 (dq, *J* = 9.5, 7.1 Hz, 2H), 1.25 (t, *J* = 7.1 Hz, 6H). **^{13}C{^{1}H} NMR** (150 MHz, $CDCl_3$): δ 139.2, 128.4, 128.3, 126.8, 101.7, 61.1, 15.3. **EI-MS** *m/z* (%): 136 (11), 135 (100), 107 (58), 105 (15), 79 (36), 77 (24).[69]

3.7.5 Chemoselectivity analysis

General procedure. All reactions were performed under air at room temperature. In an open screw cap vial, benzaldehyde **1a** (53 mg, 0.5 mmol, 1.0 eq.), competitive substrate (0.5 mmol, 1.0 eq.) and neopentyl glycol (62 mg, 0.6 mmol, 1.2 eq.) were dissolved in ChCl/malonic acid (1:1 mol/mol, 400 mg) and the resulting mixture was stirred for 1 hour. The mixture was then diluted with water (10 mL) and extracted with Et_2O (3 x 5 mL). The combined organic extracts were washed with sat. $NaHCO_3$ (1 x 5 mL) and brine (1 x 5 mL) then dried over Na_2SO_4 and the solvent removed under reduced pressure. Yields of **2a** (Table 3.2) were determined by quantitative ^1H NMR analysis of the crude reaction mixtures using nitromethane (0.0925 mmol, 5 µL) as internal standard and a diluting factor of 2 for the preparation of the sample. A sample of product **2a** was synthesized according to the procedure reported in the literature[45] and used as reference for qNMR analyses.

3.7.6 NADES recycling and characterization

Procedure for NADES recycling. A 100 mL round bottom flask was charged with benzaldehyde **1a** (2.65 g, 25 mmol, 1.0 eq.), neopentyl glycol (3.12 g, 30 mmol, 1.2 eq.) and ChCl/malonic acid (1:1 mol/mol, 10 g, 0.4 g per mmol of substrate. The mixture was then stirred at room temperature for 1 hour. Deionized water (15 mL) was added, causing the precipitation of the product as white crystals. Product **2a** was recovered by vacuum filtration and washed with water (2 x 5 mL). Water (25 mL total) was then evaporated and recovered by distillation under reduced pressure to afford the eutectic mixture (Figure 3.5 and Table 3.3) which was used for the next reaction cycle. No further purification of **2a** was necessary as confirmed by GC-FID and ^1H NMR analysis of the reaction crudes for each step. The water recovered by distillation was used again in the following reaction cycles.

3.7.7 Green metrics calculation

E-factor. The E-factor for the ten-cycles, gram-scale reaction of **1a** in ChCl/malonic acid (1:1 mol/mol) was calculated as follows:[70]

$$\boldsymbol{E-factor} = \frac{Mass\ of\ waste\ [g]}{Mass\ of\ product\ \ [g]} = \frac{g\ diol + g\ NADES + g\ H_2O}{g\ \mathbf{2a}}$$

$$= \frac{5.2\ g + 10.0\ g + 70.0\ g}{45.7\ g} = \mathbf{1.9}$$

Mass of waste [g]:

- ***g diol***: 1.2 eq (30.0 mmol) of diol were used over ten reaction cycles, resulting in 0.2 eq. (5.0 mmol, 0.52 g) of reagent excess per cycle. **5.2 g** total of waste diol.
- ***g NADES***: **10.0 g** of ChCl/malonic acid (1:1 mol/mol) used as solvent and promoter over ten reaction cycles.
- ***g H_2O***: 15.0 g of H_2O were employed for dissolving the NADES at the end of the reaction and 2 x 5 mL for washing the filtered product **2a** (25 g of H_2O used per cycle). 20.0 g out 25.0 g of H_2O were recovered from the evaporation and used for the same purpose in the following cycles (5.0 grams loss per cycle). So, 5.0 g loss x 10 cycles = 50.0 g of unrecovered H_2O, plus 20.0 g of leftover H_2O from the last cycle, **70.0 g** total of waste H_2O.

Mass of product [g]:

- ***g 2a***: **45.7 g** of product **2a** obtained over the ten reaction cycles.

The E-factor for the single run, gram-scale reaction of **1a** in ChCl/malonic acid (1:1 mol/mol) was calculated as follows:[70]

$$\boldsymbol{E-factor} = \frac{Mass\ of\ waste\ [g]}{Mass\ of\ product\ \ [g]} = \frac{g\ diol + g\ NADES + g\ H_2O}{g\ \mathbf{2a}}$$

$$= \frac{0.52\ g + 10.0\ g + 25.0\ g}{4.47\ g} = \mathbf{7.9}$$

Mass of waste [g]:

- ***g diol***: 1.2 equiv. (30.0 mmol) of diol were used for the reaction, resulting in 0.2 equiv. (5.0 mmol, **0.52 g**) of reagent excess.
- ***g NADES***: **10.0 g** of ChCl/malonic acid (1:1 mol/mol) were used as solvent and promoter for the reaction.
- ***g H_2O***: 15.0 g of H_2O were employed for dissolving the NADES at the end of the reaction and 2 x 5 mL for washing the filtered product **2a** (**25** g of H_2O used).

Mass of product [g]:

- ***g 2a***: **4.47 g** of product **2a** obtained.

Process mass intensity (PMI). The PMI for the ten-cycles, gram-scale reaction of **1a** in ChCl/malonic acid (1:1 mol/mol) was calculated as follows:[70]

$$\boldsymbol{PMI} = \frac{Total\ mass\ in\ process\ [g]}{Mass\ of\ product\ [g]} = \frac{g\ \mathbf{1a} + g\ diol + g\ NADES + g\ H_2O}{g\ \mathbf{2a}}$$
$$= \frac{26.5 + 31.2\ g + 10.0\ g + 70.0\ g}{45.7\ g} = \mathbf{3.0}$$

Total mass in process [g]:

- ***g 1a***: **26.5 g** of benzaldehyde **1a** used over ten reaction cycles (25.0 mmol, 2.65 g per cycle).
- ***g diol***: **31.2 g** of diol used over the ten reaction cycles (30.0 mmol, 3.12 g per cycle).
- ***g NADES***: **10.0 g** of ChCl/malonic acid (1:1 mol/mol) used as solvent and promoter over the ten reaction cycles.
- ***g H_2O***: 15.0 g of H_2O were employed for dissolving the NADES at the end of the reaction and 2 x 5 mL for washing the filtered product **2a** (25 g of H_2O used per cycle). 20.0 g out 25.0 g of H_2O were recovered from the evaporation and used for the same purpose in the following cycles (5.0 grams loss per cycle). So, 5.0 g loss x 10 cycles = 50.0 g of unrecovered H_2O, plus 20.0 g of leftover H_2O from the last cycle, **70.0 g** total of used H_2O.

Mass of product [g]:

- ***g 2a***: **45.7 g** of product **2a** obtained over the ten reaction cycles.

The PMI for the single run, gram-scale reaction of **1a** in ChCl/malonic acid (1:1 mol/mol) was calculated as follows:[70]

$$\boldsymbol{PMI} = \frac{Total\ mass\ in\ process\ [g]}{Product\ [g]} = \frac{g\ \mathbf{1a} + g\ diol + g\ NADES + g\ H_2O}{g\ \mathbf{2a}}$$
$$= \frac{2.65 + 3.12\ g + 10.0\ g + 25.0\ g}{4.47\ g} = \mathbf{9.1}$$

Total mass in process [g]:

- ***g 1a***: **2.65 g** of benzaldehyde **1a** used over the ten reaction cycles (25.0 mmol, 2.65 g per cycle).
- ***g diol***: **3.12 g** of diol used over the ten reaction cycles (30.0 mmol, 3.12 g per cycle).
- ***g NADES***: **10.0 g** of ChCl/malonic acid (1:1 mol/mol) were used as solvent and promoter for the reaction.
- ***g H_2O***: 15.0 g of H_2O were employed for dissolving the NADES at the end of the reaction and 2 x 5 mL for washing the filtered product **2a** (**25** g of H_2O used).

Mass of product [g]:

- ***g 2a***: **4.47 g** of product **2a** obtained.

*3.7.8 Cascade synthesis procedures of compounds **4** and **6***

5-(4-(5,5-Dimethyl-1,3-dioxan-2-yl)phenyl)nonan-5-ol (3): general procedure for cyclic acetals starting from **1o** (0.5 mmol, 1.0 eq) and 2,2-dimethylpropane-1,3-diol (0.6 mmol, 1.2 eq). After 1h, CPME (200 µL) was added and then *n*-BuLi (1.5 mmol, 3.0 eq, 2.5 M in hexanes) was rapidly spread over the mixture. Then after 10 seconds water (10 mL) was added and the mixture extracted with CPME (3 x 5 mL). The organic phase was washed with sat. $NaHCO_3$ (1 x 5 mL), dried over Na_2SO_4, filtered and the solvent removed *in vacuo*. Purification by flash column chromatography (PE/Et_2O 8/2 v/v) gave **3** as a colorless oil (110 mg, 66%, R_f = 0.19 PE/Et_2O 8/2 v/v). **^{1}H NMR** (600 MHz, DMSO-d_6): δ 7.37-7.29 (m, 4H), 5.37 (s, 1H), 4.55 (br s, 1H), 3.66 (d, *J* = 10.7 Hz, 2H), 3.61 (d, *J* = 10.7 Hz, 2H), 1.75-1.67 (m, 2H), 1.66-1.59 (m, 2H), 1.27-1.11 (m, 6H) superimposed to 1.18 (s, 3H), 0.86-0.72 (m, 3H) superimposed to 0.76 (t, *J* = 7.3 Hz, 6H) superimposed to 0.75 (s, 3H). **^{13}C{^{1}H} NMR** (150 MHz, DMSO-d_6): δ 147.9, 135.9, 125.4, 125.0, 100.9, 76.6, 75.2, 42.7, 29.8, 25.4, 22.8, 22.7, 21.4, 14.1. **EI-MS** *m/z* (%): 333 (1), 278 (19), 277 (100), 191 (11), 69 (13). **ESI-HRMS** $[M+H]^+$: *m/z* 335.2586, $C_{21}H_{35}O_3^+$ requires 335.2581.

4-(5-Hydroxynonan-5-yl)benzaldehyde (4): general procedure for cyclic acetals starting from **1o** (0.5 mmol, 1.0 eq) and 2,2-dimethylpropane-1,3-diol (0.6 mmol, 1.2 eq). After 1h, CPME (200 µL) was added and then *n*-BuLi (1.5 mmol, 3.0 eq, 2.5 M in hexanes) was rapidly spread over the mixture. After 10 seconds water (2 mL) then HCl 1M (8 mL) and CPME (5 mL) were added and the mixture stirred vigorously for 1 hour at room temperature. Then the aqueous phase was further extracted with CPME (2 x 5 mL). The combined organic phases were washed with sat. $NaHCO_3$ (1 x 5 mL), dried over Na_2SO_4, filtered and the solvent removed *in vacuo*. Purification by flash column chromatography (PE/EtOAc 9/1 v/v) gave **4** as a colorless oil (76 mg, 61%, R_f = 0.31 PE/EtOAc 9/1 v/v). **^{1}H NMR** (600 MHz, $CDCl_3$): δ 10.00 (s, 1H), 7.85 (d, *J* = 8.3 Hz, 2H), 7.55 (d, *J* = 8.3 Hz, 2H), 1.89-1.70 (m, 5H), 1.30-1.19 (m, 6H), 0.98-0.90 (m, 2H), 0.82 (t, *J* = 7.2 Hz, 6H). **^{13}C{^{1}H} NMR** (150 MHz, $CDCl_3$): δ 192.3, 153.9, 134.8, 129.8, 126.2, 43.0, 25.6, 23.1, 14.1. **EI-MS** *m/z* (%): 230 (1), 192 (14), 191 (100), 135 (7), 91 (6), 28 (4).[71]

4-Pentanoylbenzaldehyde (6): general procedure for cyclic acetals starting from **1n** (0.5 mmol, 1.0 eq) and 1,3-propanediol (0.6 mmol, 1.2 eq). After 1h, CPME (200 µL) was added and then *n*-BuLi (1.0 mmol, 2.0 eq, 2.5 M in hexanes) was rapidly spread over the mixture. After 10 seconds water (2 mL) then HCl 1M (8 mL) and CPME (5 mL) were added and the mixture was stirred vigorously for 1 hour at room temperature. Then the aqueous phase was further extracted with CPME (2 x 5 mL). The combined organic phases were washed with sat. $NaHCO_3$ (1 x 5 mL), dried over Na_2SO_4, filtered and the solvent removed *in vacuo*. Purification by flash column chromatography (PE/Et_2O 8/2 v/v) gave **6** as a white solid (46 mg, 48%, R_f = 0.36 PE/Et_2O 8/2 v/v), mp 132.5–133.8 °C (pentane). **^{1}H NMR** (600 MHz, $CDCl_3$): δ 10.10 (s, 1H), 8.09 (d, *J* = 8.3 Hz, 2H), 7.97 (d, *J* = 8.4 Hz, 2H), 3.00 (t, *J* = 7.4 Hz, 2H), 1.73 (quint, *J* = 7.5 Hz, 2H), 1.42 (m, 2H), 0.96 (t, *J* = 7.4 Hz, 3H). **^{13}C{^{1}H} NMR** (150 MHz, $CDCl_3$): δ 200.0, 191.8, 141.4, 139.0, 130.0, 128.7, 38.9, 26.3, 22.5, 14.0. **EI-MS** *m/z* (%): 190 (M^+, 18), 148 (59), 133 (100), 105 (25), 77 (20), 51 (11).[72]

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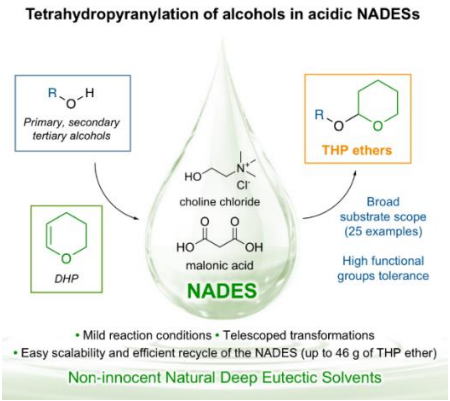
CHAPTER 4: A mild, efficient and sustainable tetrahydropyranylation of alcohols promoted by acidic Natural Deep Eutectic Solvents

Part of the results presented in this chapter are published in *ChemSusChem* **2023**, *16*, e202202066 (DOI:10.1002/cssc.202202066).

A straightforward protocol to promote the tetrahydropyranylation of alcohols, using for the first time bioinspired acidic Natural Deep Eutectic Solvents as non-innocent reaction media under mild reaction conditions, is herein presented. This approach enables the preparation of several tetrahydropyranyl (THP) ethers starting from primary, secondary and tertiary alcohols in short reaction times and with high levels of chemoselectivity, working under air and without the need of additional catalysts. The sustainability of the methodology has been further highlighted by its scalability and the easy recyclability of the NADES, allowing multigram preparations of THP ethers without any loss of the catalytic activity of the reaction media up to ten recycling steps. Telescoped, one-pot tetrahydropyranylation/nucleophilic acyl substitution transformations using the same eutectic mixture have also been demonstrated.

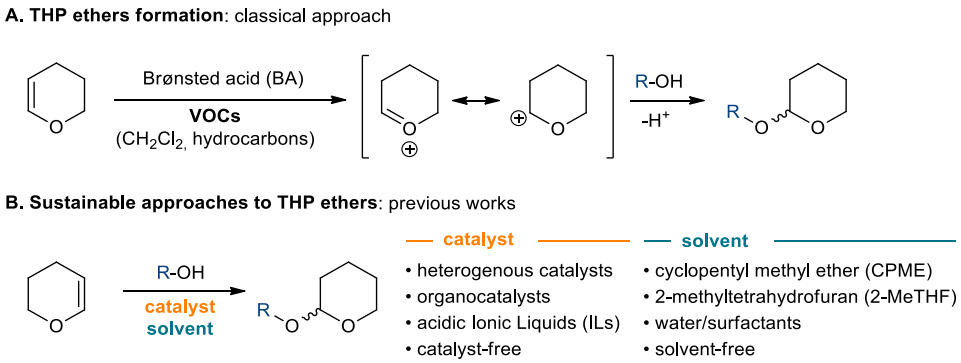


4.1 Introduction

Although the implementation of protecting-group free strategies in synthesis offers some undeniable advantages both from an economic and an environmental standpoint,[1] the development of novel methodologies for the introduction/removal of protecting groups which ideally fulfil the sustainability requirements (quantitative yields, use of environmentally responsible solvents, low E-factors and high atom economy) is of great significance and represents nowadays an urgent challenge of industrial research. In this context, the protection of hydroxy groups is of

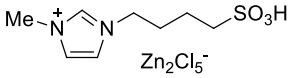
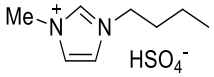
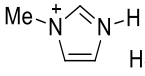
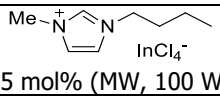
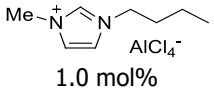
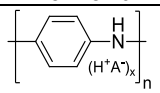
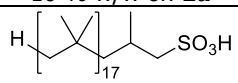
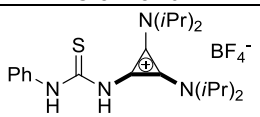
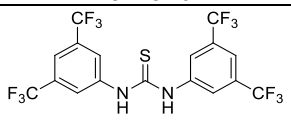
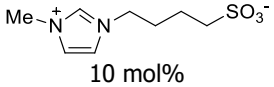
fundamental importance in almost every multi-step synthetic approach to complex molecular architectures of industrial interest, such as (glyco)peptides,[2] oligosaccharides,[3] nucleotides[4] and/or active pharmaceutical ingredients (APIs).[5] As a matter of fact, the introduction of a -OH protecting group is often essential to avoid undesired reaction pathways induced by the acidic and nucleophilic character of the hydroxy functionality. Among the myriad of hydroxy-protecting groups described so far, the tetrahydropyranyl moiety (THP) has attracted considerable attention owing to the high stability of THP ethers under strongly basic reaction conditions, as well as in the presence of highly nucleophilic (i.e. organometallics), oxidizing (metal oxides, peroxides) or reducing (molecular hydrogen, hydrides) agents.[6] The introduction of the THP protecting group (tetrahydropyranylation reaction) usually entails the addition of alcohols, thiols or phenols to the inexpensive and commercially available 3,4-dihydro-2*H*-pyran (DHP) at room temperature under Brønsted or Lewis acid catalysis (Scheme 4.1-A). To this purpose, several greatly diversified methods have been developed over the last three decades,[7] however these approaches often require the use of aprotic volatile organic solvents (VOCs), toxic and expensive reagents, broad excesses of chemicals, long reaction times and/or high temperatures.

Methods for the introduction of the tetrahydropyranyl moiety in a more sustainable fashion have been deeply investigated (Scheme 4.1-B, Table 4.1). These approaches mainly rely on the use of acidic ILs,[8] heterogenous catalytic systems[9] and organocatalysts[10] as promoters, or on the use of catalyst-free conditions.[11] Solvent-related issues have been addressed indeed by replacing the common VOCs with more environmentally friendly alternatives such as cyclopentyl methyl ether (CPME) and 2-methyltetrahydrofuran (2-MeTHF),[12] water[13] or working under solvent-free conditions.[14]



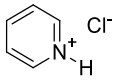
Scheme 4.1. State-of-the-art of the tetrahydropyranylation of alcohols.

Table 4.1. Selected comparative methods for the sustainable tetrahydropyranylation of benzyl alcohol **1a**.

Entry	Catalyst	DHP (eq.)	Solvent	time (h)	T (°C)	2a (%)	Ref.
1	 0.5 mol%	1.0	-	0.7	25	97	[8a]
2	 20 mol%	1.2	-	0.25	20	94	[8b]
3	 25 mol%	1.2	-	0.03	25	98	[8c]
4	 25 mol% (MW, 100 W)	1.1	-	0.08	60	79	[8d]
5	 1.0 mol%	1.1	-	0.25	25	98	[8e]
6	$H_{14}[NaP_5W_{30}O_{110}]$ 0.1 mol%	1.1	CH_2Cl_2	2	40	90	[9a]
7	$Fe_2(SO_4)_3 \cdot xH_2O$ 1.0 mol%	1.2	-	1	25	95	[9b]
8	 20 % w/w on DHP	1.2	-	8	50	59	[9c]
9	Sulfonic acid functionalized polycyclic aromatic carbon catalyst, 10 % w/w on **1a**	1.0	CH_2Cl_2	2	25	96	[9d]
10	 5.0 mol%	1.2	poly(α-olefin) PAO_{432}	1	25	91	[9e]
11	 1.0 mol%	2.0	CH_2Cl_2	1.5	25	95	[10a]
12	 1.0 mol%	2.0	-	13	25	98	[10b]
13	 10 mol%	1.2	-	10	60	90	[10c]

(continued)

Table 4.1. *Continued*

Entry	Catalyst	DHP (eq.)	Solvent	time (h)	T (°C)	2a (%)	Ref.
14	*p*-TsOH 10 mol%	1.2	Tween 20/H_2O (2% w/w)	0.25	25	44	[13a]
15	$Zn(BF_4)_2$ (40 % aq. sol.) 33 mol%	1.2	CH_2Cl_2	0.4	25	95	[13b]
16	$AlCl_3 \cdot 6H_2O$ 1.0 mol%	1.1	-	0.5	30	>99	[14a]
17	 20 mol% (grinding)	1.2	-	0.05	25	80	[14b]

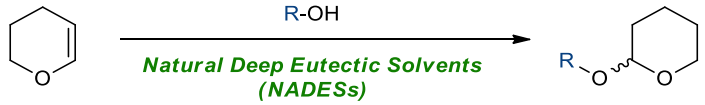
Since the seminal report by Abbott and co-workers,[15] many efforts have been devoted in the last decade to the development of DESs as new media for a wide range of uses. Owing to their peculiar physical properties, such as low volatility, flammability, and vapor pressure, increased chemical and thermal stability, DESs have been exploited as a superior class of improved solvents with impressive performances, both in terms of sustainability and reactivity, in a plethora of applications.[16] Among the impressive number of reports on the application of NADESs in organic synthesis,[17] those involving the strong participation of one (or more) component of the NADES into the transformation, i.e. by reacting with other molecules present in the environment or by actively promoting the process, appear as the most appealing.

Recently, acidic NADESs have been significantly employed as non-innocent reaction media in several transformations,[18] including the preparation of functionalized materials[19] and biomass valorization,[20] owing to their excellent physico-chemical properties, which can be easily tailored according to specific purposes. In this context, we recently reported the first application of carboxylic acid-based NADESs as environmentally benign reaction media to perform a versatile and high-yielding Nazarov cyclization of divinyl ketones, operating under simple aerobic reaction conditions and avoiding the use of strong Brønsted or Lewis acids.[21]

Despite the potential of acidic NADESs as active reaction media in acid-catalysed transformations, their use as solvents and promoters in protecting group chemistry remains hitherto unexplored and, to the best of our knowledge, the overall employment of NADESs as sustainable reaction media in functional group protection reactions is currently limited to few examples.[22]

On the basis of these considerations and motivated by our ongoing interest in the development of new sustainable synthetic methodologies,[23] we herein report a systematic study on the usefulness of acidic NADESs as non-innocent reaction media to promote the tetrahydropyranylation of alcohols, working under air and under mild reaction conditions (Scheme 4.2). Notable features of our report includes: a) the unprecedented use of bioinspired acidic deep eutectic systems as active reaction media for the introduction of a hydroxy-protecting group in a simple synthetic operation, b) the possibility to telescope tetrahydropyranylation/S_NAc transformations in a one-pot procedure using the same eutectic mixture and c) the easy scale-up of the methodology and the efficient recycling of the NADES, which are of great value in terms of efficiency and environmental sustainability.

This work: use of non-innocent acidic Natural Deep Eutectic Solvents (NADES)



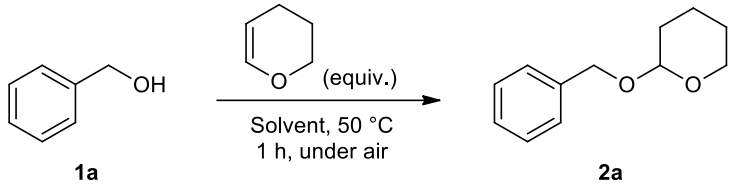
Scheme 4.2. Aim of the work.

4.2 Optimization of the reaction conditions

We started our preliminary investigations using phenylmethanol **1a** as a model substrate. Based on our previous results on the acetalization procedure (illustrated in Chapter 3) a homogenous solution of **1a** (1 mmol) and 3,4-dihydro-2*H*-pyran (DHP, 1.5 eq.) in a prototypical ChCl/malonic acid (1:1 mol/mol) eutectic mixture (400 mg) was vigorously stirred at 50 °C and under air for 1 h (Table 4.2, entry 1). After a simple workup procedure using the environmentally responsible CPME[24] as extraction solvent (see Experimental section for details), the tetrahydropyranyl ether product **2a** was recovered in quantitative yield, disclosing the unique mild catalytic activity of the acidic NADES as non-innocent reaction medium.

Less satisfactory results were obtained lowering the temperature (entry 2) or the amount of DHP (entry 3), while other ChCl/carboxylic acid based NADESs containing oxalic (entry 4), L-(-)-malic (entry 5), glutaric (entry 6) or L-(+)-lactic (entry 7) acid as HBDs were less effective to promote the tetrahydropyranylation reaction, although ether **2a** was produced in slightly lower but reasonable yields (86-96%).

Table 4.2. Tetrahydropyranylation of benzyl alcohol **1a** under different conditions.[a]



1a **2a**

Entry	Solvent	DHP (eq.)[b]	2a yield (%)[c]
1	ChCl/malonic acid 1:1	1.5	99
2	ChCl/malonic acid 1:1	1.5	59[d]
3	ChCl/malonic acid 1:1	1.0	88
4	ChCl/oxalic acid 1:1	1.5	88
5	ChCl/L-(-)-malic acid 1:1	1.5	91
6	ChCl/glutaric acid 1:1	1.5	96
7	ChCl/L-(+)-lactic acid 1:1	1.5	86
8	ChCl/Gly 1:2	1.5	-
9	ChCl/H_2O 1:2	1.5	-
10	ChCl/urea 1:2	1.5	-
11	H_2O[e]	1.5	91
12	CPME[e]	1.5	65
13	CPME[f]	1.5	75
14	2-MeTHF[e]	1.5	97
15	2-MeTHF[g]	1.5	-
16	4-MeTHP[e]	1.5	95
17	CH_2Cl_2[e]	1.5	87

[a] Reaction conditions: **1a** (1.0 mmol), NADES (mol/mol ratio, 400 mg) *or* solvent (0.500 mL), 1 h, 50 °C, under vigorous stirring. [b] DHP = 3,4-dihydro-2*H*-pyran. [c] Determined by quantitative GC-FID analyses using calibration curves of **2a** (see Experimental section) [d] T = 25 °C. [e] 1.6 eq. of malonic acid were added as promoter. [f] ChCl/malonic acid 1:1 mol/mol (10 % w/w) was added as catalyst. [g] 1.6 eq. of ChCl was added.

As expected, less acidic NADESs based on glycerol (entry 8), water (entry 9) and urea (entry 10) as HBDs were ineffective in promoting the reaction.

To further investigate the role of the components of the eutectic mixture, a series of tetrahydropyranylation reactions of **1a** were run using other nonacidic environmentally friendly reaction media, such as water (entry 11), 2-MeTHF (entry 14) and 4-methyltetrahydropyran (4-MeTHP, entry 16) in the presence of a stoichiometric amount of malonic acid (1.6 eq.) as promoter. Under these conditions

the THP ether **2a** was recovered with satisfactory yields (91-97%) while performing the reaction in the presence of the sole HBA component of the NADES (ChCl, 1.6 eq., entry 15) led to quantitative recovery of the starting material **1a** after workup. These results clearly indicate that the presence of an acidic component in the composition of the NADES is required to promote the tetrahydropyranylation reaction.

Noteworthy, the use of a classical VOC as dichloromethane (entry 17) was less effective than the above-mentioned sustainable media to promote the tetrahydropyranylation of **1a** under these conditions.

With CPME as solvent (entry 12) a moderate yield of **2a** (65%) was obtained, which is likely due to the low solubility of malonic acid in this highly hydrophobic reaction medium. However, the use of a catalytic amount (10% w/w) of ChCl/malonic acid (1:1 mol/mol) as promoter in CPME under the same reaction conditions led to an increase of **2a** yield up to 75% (entry 13).

Of value, this result discloses the possibility to employ catalytic amounts of acidic NADESs as promoter, overcoming potential solubility issues arising from the use of acid catalysts in highly hydrophobic solvents and common viscosity issues related to the employment of other acidic NADESs as reaction media.[18]

4.3 Reaction substrate scope

With satisfactory conditions in place, the scope and limitations of this transformation were evaluated for a series of functionalized primary, secondary and tertiary alcohols **1** exploiting the mild catalytic activity of the ChCl/malonic acid 1:1 (mol/mol) deep eutectic mixture as privileged reaction medium (Scheme 4.3).

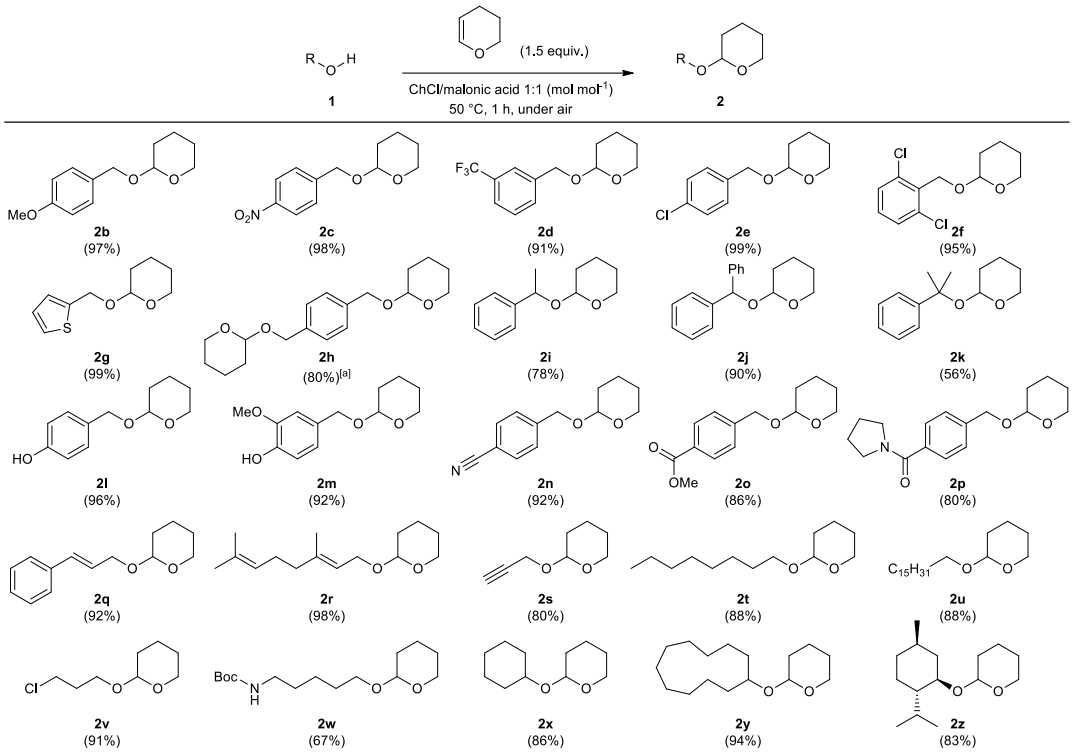
Pleasingly, the reaction proceeded smoothly *en route* to a variety of substituted (hetero)benzyl THP ethers **2b**-**g** bearing electron-donating (**2b**) and electron-withdrawing (**2c**-**f**) groups on the aromatic ring in excellent yields after workup (91-99%).

Secondary alcohols were also efficiently converted into the corresponding tetrahydropyranylated products **2i**-**j**, whereas the sterically hindered ether **2k** was recovered only in moderate yield (56%) upon treatment of the parent tertiary alcohol **1k** under these conditions.

The simultaneous protection of two hydroxyl groups was easily achieved by increasing the amount of DHP, providing the bis-THP ether **2h** in good overall yield (80%) in a single synthetic operation.

Remarkably, the use of the ChCl/malonic acid 1:1 (mol/mol) eutectic system as catalyst/solvent allowed the chemoselective introduction of the THP moiety a) on primary alcohol in the presence of a competitive phenolic group (**2l**-**m**), and b) in the presence of several acid-sensitive functional groups such as nitriles (**2n**), carboxylic acid derivatives (**2o**-**p**) and multiple C-C bonds (**2q**-**s**) without competitive pathways.

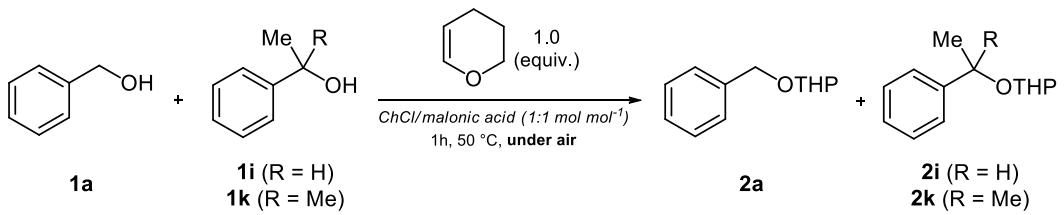
Also, assorted (cyclo)alkyl derivatives served as competent reaction partners as well, thereby delivering the desired THP ethers **2t**-**z** in 67–96% yield.



Scheme 4.3. Tetrahydropyranylation of alcohols **1** in ChCl/malonic acid (1:1 mol/mol) deep eutectic mixture. Reaction conditions: **1** (1 mmol), 3,4-dihydro-2*H*-pyran (1.5 mmol), NADES (400 mg), 50 °C, 1 h. Yields of **2** refer to isolated products after flash column chromatography. [a] 3.0 eq. of 3,4-dihydro-2*H*-pyran were used.

Intermolecular competition experiments revealed that the reaction is highly chemoselective towards primary alcohols in the presence of a competitive tertiary alcohol (**1k**), whereas no selectivity was observed when the tetrahydropyranylation was performed on an equimolar mixture of phenylmethanol **1a** and its *α*-methyl analogue **1i** (Table 4.3).

Table 4.3. Competition experiments.[a]



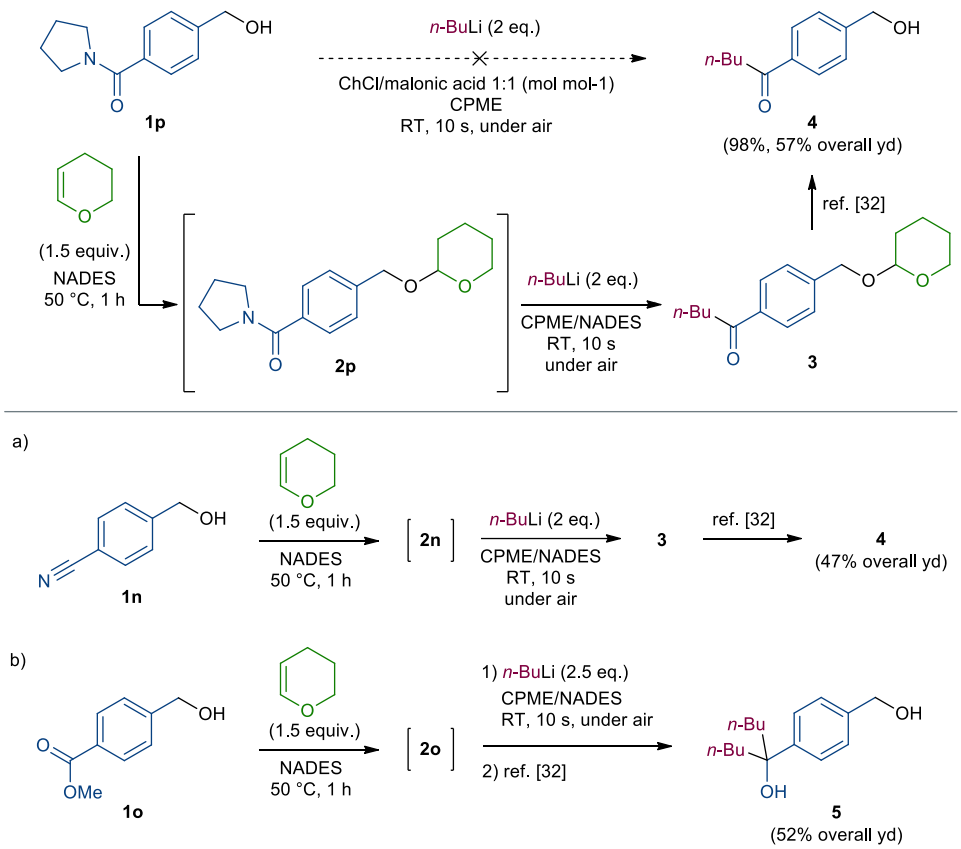
1a | **1i** (R = H), **1k** (R = Me) | **2a** | **2i** (R = H), **2k** (R = Me)

Entry	Competitive substrate	2a (%)[b]	Competitive product (%)[b]
1	**1i** (R = H)	19	**2i**, 23
2	**1k** (R = Me)	53	**2k**, trace

[a] Reaction conditions: 1 hour, 50 °C; DHP (1.0 eq.), ChCl/malonic acid 1:1 mol/mol (400 mg), 1.0 mmol of **1a** + 1.0 mmol competitive substrate. [b] Yield determined by quantitative ^{1}H NMR using CH_3NO_2 as the internal standard.

4.4 Design of telescoped one-pot processes

An attractive strategy to improve the efficiency of a chemical reaction in terms of efficiency and environmental sustainability is the design of telescoped, one-pot processes involving multiple sequential synthetic operations.[25] To further highlight the utility and the robustness of our methodology, we designed a telescoped approach for the preparation of the hydroxymethylated valerophenone **4** based on a preliminary tetrahydropyranylation of benzyl alcohol **1p**, followed by an *in situ* nucleophilic acyl substitution reaction promoted by *n*-BuLi (2 eq.) on *N*-acylpyrrolidine **2p** in a heterogeneous CPME/NADES mixture (Scheme 4.4, top),[23d, 23e] using environmentally benign reaction media under bench-type reaction conditions. Whereas the direct treatment of **1p** with *n*-BuLi was unsuccessful due to the predominant lithium alkoxide formation, the introduction of the THP moiety as protecting group easily allowed the preparation of ketone **3**, which was finally subjected to classical deprotection conditions[26] (see Experimental section) to release the target hydroxylated valerophenone **4** in 57% yield over three steps. Analogously, the conversion of nitrile **1n** into the corresponding hydroxymethylated valerophenone **4** has been efficiently achieved in 47% yield over three steps upon preliminary protection of the hydroxyl moiety (Scheme 4.4-a). The synthetic usefulness of this telescoped approach has been further illustrated with the preparation of tertiary alcohol **5** by performing a tandem protection/S_NAc sequence from ester **1o** (Scheme 2-b). Overall, this telescoped, one-pot methodology contributes to enlarge the portfolio of organolithium-mediated transformations in protic eutectic mixtures under aerobic conditions.[27]

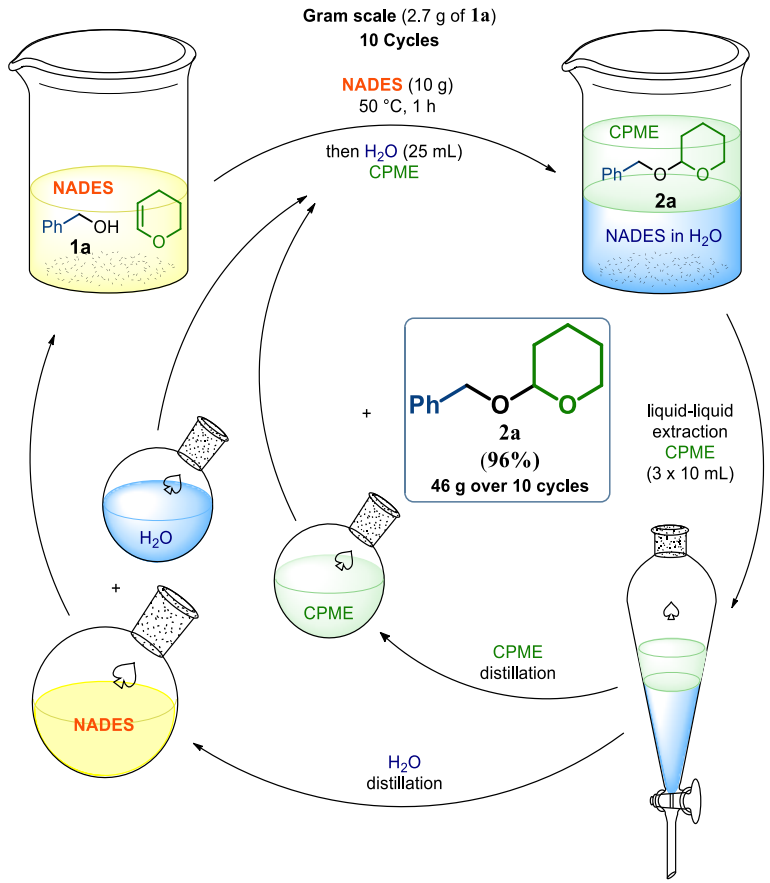


Scheme 4.4. Telescoped tetrahydropyranylation-S_NAc sequences promoted by highly polar organolithium reagents in protic deep eutectic mixtures. NADES: ChCl/malonic acid (1:1 mol/mol).

4.5 Scalability and recycle

With the aim to assess the sustainability of this new synthetic protocol, we finally investigated the scalability of the process and the recyclability/reusability of the solvent (Scheme 4.5). To this end, we set up a gram scale synthesis of **2a** starting from 2.7 g of **1a** and 10 g of ChCl/malonic acid (i.e. 2.5 mmol of substrate per g of NADES) under the optimized reaction conditions. The tetrahydropyranylation proceeded smoothly in 1 h at 50 °C and, upon completion of the reaction, water (25 mL) was added to dilute the eutectic mixture. Liquid-liquid extraction using CPME (3 x 10 mL) allowed the isolation of **2a** from the reaction mixture. Removal of CPME by distillation from the organic layer allowed the recovery of **2a** in 88% yield (4.22 g), while water was removed under reduced pressure from the aqueous layer to restore the ChCl/malonic acid (1:1 mol/mol) eutectic mixture. Remarkably, the NADES was recovered and reused in subsequent recycling steps without further purification. ^{1}H and ^{13}C NMR analyses of the NADES

performed after each recycling step shown no significant changes in the structure of the reaction media (unlike the example reported in Chapter 3, Figure 3.6). Both water (20 g out of 25 g) and CPME (28 mL out of 30 mL) were also recycled to increase the sustainability of the whole process. As shown in Figure 4.1, the catalytic activity of the ChCl/malonic acid (1:1 mol/mol) eutectic mixture remains essentially unchanged up to ten cycles, leading to nearly quantitative yields of **2a** for each recycling step. Overall, this recycling procedure allowed the preparation of 46.1 g of desired product, with an overall yield of 96% over 10 cycles (see Experimental section for full details).



Scheme 4.5. Gram-scale reaction and recycling procedure.

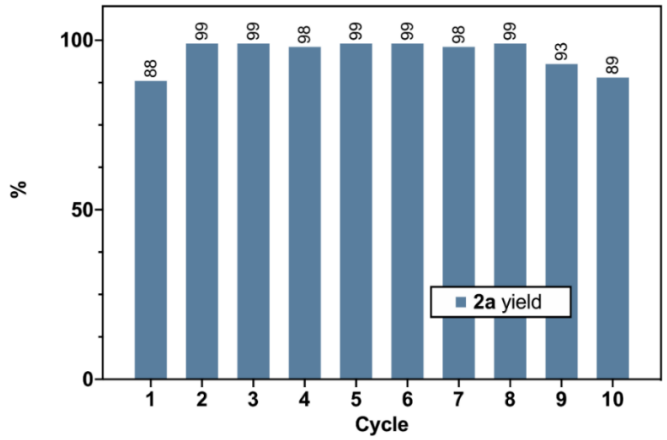
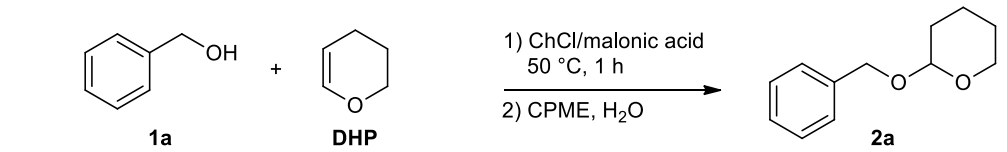


Figure 4.1. Recyclability of the ChCl/malonic acid 1:1 mol/mol deep eutectic mixture. Yields refer to isolated product **2a**.

The sustainability of the procedure has been evaluated by the calculation of *green* metrics such as the environmental factor (E-factor) and the process mass intensity (PMI).[28] The overall low impact of the NADES-based tetrahydropyranylation reaction herein described is clearly illustrated by the excellent atom economy of the reaction (100%) combined with the results shown in Scheme 4.6, with optimal calculated E-factors of 14.7 for a single run and 2.9 for the overall 10-steps recycling sequence.[29]



single run:

2.70 g	3.15 g (1.5 eq.,1.05 g excess)	10 g NADES 25 g H_2O 25.89 g CPME	4.22 g (88%)

PMI = (2.70 + 3.15 + 10 + 25 + 25.89) g / 4.22 g = **15.8**

E-factor = (1.05 + 10 + 25 + 25.89) g / 4.22 g = **14.7**

10-cycles run:

27.0 g	31.5 g (1.5 eq.,10.5 g excess)	10 g NADES 25 g H_2O (5.0 g loss/cycle) 25.89 g CPME (1.73 g loss/cycle)	46.1 g (96%)

PMI = (27.0 + 31.5 + 10 + 70 + 41.46) g / 46.1 g = **3.9**

E-factor = (10.5 + 10 + 70 + 41.46) g / 46.1 g = **2.9**

Scheme 4.6. *Green* metrics calculated for the tetrahydropyranylation of **1a** in NADES.

4.6 Conclusion

The efficiency of this NADES-based approach is pleasingly comparable with other previously reported synthetic methods for the tetrahydropyranylation of alcohols under sustainable reaction conditions (Table 4.1), such as imidazolium based acidic ILs catalytic systems.[8] Of note, the employment of acidic NADESs as promoters avoids the use of transition metal catalysts[8a, 8d, 8e, 14a] or hazardous VOCs,[9d, 10a, 13b] and provides comparable results in shorter reaction times with respect to some organocatalytic approaches.[10b, 10c] The high catalytic activity under mild reaction conditions, the low cost/easy preparation of the NADES and its high recyclability represent key advantages of this methodology coherently with Green Chemistry principles, paving the way to further applications of acidic eutectic mixtures as *green*, efficient and reusable catalysts in the development of protecting group techniques.

In summary, our report discloses that acidic Natural Deep Eutectic Solvents can be efficiently employed as effective reaction media to catalyze the tetrahydropyranylation of alcohols under mild reaction conditions. This methodology allows the preparation of several THP-ethers starting from primary, secondary and tertiary alcohols in short reaction times, and the products can be isolated resorting to a simple workup procedure using the environmentally responsible CPME as the extraction solvent. Remarkably, the reaction proceeds with excellent chemoselectivity in the presence of competitive hydroxy groups such as phenols, and well tolerates the presence of acid-labile functional moieties such as nitriles, esters or multiple C-C bonds. The utility and versatility of this new synthetic protocol have been further highlighted by its scalability and the easy recyclability/reusability of the NADES, CPME and water, which are of great value in terms of efficiency and environmental sustainability. This allows multigram preparations of THP-protected alcohols using simple synthetic operations without any loss of the catalytic activity of the reaction media up to ten recycling steps, lowering the overall environmental impact of the whole process. Overall, our new methodology represents one of the few examples of the use of bioinspired deep eutectic solvents as sustainable reaction media in functional group protection and constitutes the first application of bioinspired acidic DESs as catalytic systems in protecting group chemistry.

4.7 Experimental section

4.7.1 Experimental details

Materials and methods. Flasks and all equipment used for the generation and reaction of moisture-sensitive compounds were dried by electric heat gun under nitrogen. Unless specified, all reagents were used as received without further purifications. Benzyl alcohol (**1a**) was distilled under vacuum prior to use. Reactions were monitored by GC-MS analysis or by thin-layer chromatography (TLC) carried out on 0.25 mm silica gel coated aluminum plates (60 Merck F254) with UV light (254 nm) as visualizing agent. R_f values refer to TLC carried out on silica gel plates. Chromatographic separations were carried out under pressure on silica gel (40-63 μm, 230-400 mesh) using flash-column techniques. The exact concentration of *n*-BuLi in hexanes solution (Sigma-Aldrich) was determined by titration with *N*-benzylbenzamide in anhydrous THF prior to use.[30] Aldehyde **6** (precursor of alcohol **1p**) was synthesized according to the procedure reported in the literature.[31] *Deep Eutectic Solvents* [choline chloride (ChCl)/malonic acid (1:1 mol/mol); ChCl/oxalic acid dihydrate (1:1 mol/mol); ChCl/L-(-)-malic acid (1:1 mol/mol); ChCl/glutaric acid (1:1 mol/mol); ChCl/L-(+)-lactic acid (1:1 mol/mol) ChCl/urea (1:2 mol/mol); ChCl/glycerol (Gly) (1:2 mol/mol)] were prepared by heating under stirring at 50−80 °C for 15−30 min the corresponding individual components until a clear solution was obtained.[21, 23a] Full characterization data have been reported for both the newly synthesized compounds and the known compounds.

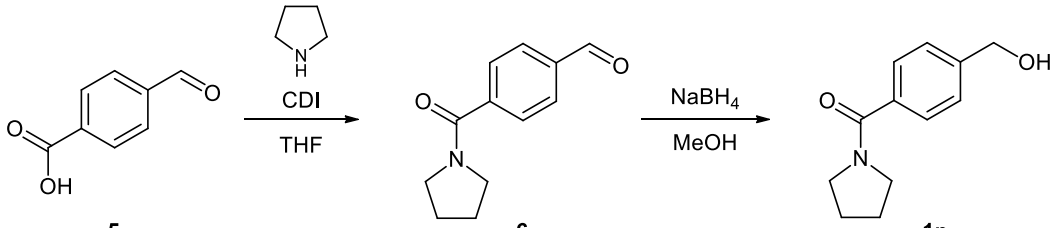
Instrumentation. ^{1}H NMR (600 MHz), ^{13}C{^{1}H} (150 MHz) and ^{19}F NMR (564 MHz) NMR spectra were recorded on a Jeol ECZR600 spectrometer at room temperature using residual solvent peak as an internal reference. NMR spectra of neat ChCl/malonic acid (1:1 mol/mol) were recorded in a capillary tube, using external $CDCl_3$ as locking solvent. Chemical shifts (δ) are given in parts per million (ppm) and coupling constants (J) in Hertz (Hz). Multiplicities are reported as follows: s (singlet), d (doublet), t (triplet), q (quartet), quint (quintet), sext (sextet), m (multiplet), br (broad). Low-resolution mass spectra were recorded at an ionizing voltage of 70 eV on a HP 5989B mass selective detector connected to an HP 5890 GC with a methyl silicone capillary column (EI). Quantitative GC-FID analyses with external standard method were performed on a HP 5890 Series II chromatographic system (HP 3395 integrator) equipped with a methyl silicone capillary column. High resolution mass flow-injection analyses were run on a high resolving power hybrid mass spectrometer (HRMS) Orbitrap Fusion (Thermo Scientific, Rodano, Italy), equipped with an ESI ion source. Samples were analyzed in methanol solution using a syringe pump at a flow rate of 5 μL/min. Tuning parameters adopted for the ESI source: source voltage 5.0 kV. The heated capillary temperature was maintained at 275 °C. The mass accuracy of the recorded ions (vs. the calculated ones) was ± 2.5 mmu (milli-mass units). Analyses were run using both full MS (150-2000 m/z range) and MS/MS acquisition, at 500000 resolutions (200 m/z). Melting points were determined on a Stuart Scientific SMP3 melting point apparatus. Nitromethane was used as internal standard for quantitative ^{1}H NMR analyses on crude reaction mixtures. For each ^{1}H NMR the amount of product was determined by applying the following equation:

$$yield\ (\%) = \frac{x\ (product) \cdot n\ (CH_3NO_2)}{n(starting\ material)}\ \cdot\ f\ \cdot\ 100$$

where:

- x is the value of integral/number of protons;
- n is the amount of starting material or CH_3NO_2 in mmol;
- f the diluting factor used for the preparation of the sample.

*4.7.2 Synthesis and analysis of compound **1p***



(4-(Hydroxymethyl)phenyl)(pyrrolidin-1-yl)methanone (1p): To a solution of terephthalaldehydic acid (**5**, 2.33 g, 15.5 mmol, 1 eq.) in THF (20 mL) was added 1,1'-carbonyldiimidazole (2.60 g, 16.5 mmol, 1.05 eq.) in small portions and the mixture stirred at room temperature for 1h. Then pyrrolidine (1.30 g, 18.6 mmol, 1.2 eq.) was added and left to react overnight (16h). The reaction was monitored by TLC analysis (PE/EtOAc 6/4) and then heated to reflux for one hour allowing complete consumption of the substrate. Then 10 mL of water were added and the THF removed under reduced pressure. The aqueous phase was extracted with DCM (3 x 10 mL). The combined organic extracts were washed with 1M HCl (1 x 10 mL), water (1 x 10 mL), brine (1 x 10 mL) and dried over Na_2SO_4 and the solvent removed *in vacuo* to afford crude **6** as a yellow oil (1.7 g, 54%) which was used without further purification in the second step.[31] Crude **6** (1.7 g, 8.3 mmol, 1 eq.) was dissolved in methanol (20 mL) then at 0 °C sodium borohydride (1.6 g, 41.5 mmol, 5 eq.) was added in small portions and the reaction mixture was then allowed to stir at room temperature. After 1h the mixture was poured in 30 mL of water then extracted with EtOAc (3 x 10 mL). The combined organic extracts were washed with sat. $NaHCO_3$ (1 x 10 mL), sat. $NaHSO_3$ (1 x 5 mL), brine (1 x 10 mL), dried over Na_2SO_4 and the solvent removed under reduced pressure to afford crude **1p**. Purification by flash column chromatography (acetone/PE 8/2 v/v) gave pure **1p** as a white solid (1.1 g, 65%, R_f = 0.42 acetone/PE 8/2 v/v), mp 79.5−80.8 °C (benzene). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.47-7.42 (m, 2H), 7.33 (d, J = 8.1 Hz, 2H), 4.68 (d, J = 5.4 Hz, 2H), 3.62 (t, J = 7.0 Hz, 2H), 3.40 (t, J = 6.7 Hz, 2H), 2.65 (t, J = 5.9 Hz, 1H), 1.95 (quint, J = 6.8 Hz, 2H), 1.86 (quint, J = 6.8 Hz, 2H). ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$): δ 169.8, 143.1, 136.2, 127.4, 126.6, 64.7, 49.8, 46.4, 26.5, 24.6. EI-MS *m/z* (%): 205 (M^+, 20), 204 (14), 146 (11), 135 (43), 32 (25), 28 (100). ESI-HRMS $[M+H]^+$: *m/z* 206.1176, $C_{12}H_{16}NO_2^+$ requires 206.1166.

*4.7.3 Tetrahydropyranylation reaction of benzyl alcohol **1a** under different reaction conditions*

General Procedure. All reactions were performed under air. In an open screw cap vial, benzyl alcohol **1a** (108 mg, 1.0 mmol, 1.0 eq.) and 3,4-dihydro-2*H*-pyran (DHP, eq.) were dissolved in the selected solvent (with or without catalyst) and the resulting mixture was stirred for 1h at different temperatures. The mixture was then quenched with 2M NaOH (2 mL) and extracted with CPME (1 x 2 mL). Yields of **2a** (Table 4.2) were determined by quantitative GC analysis (external standard method, calibration curve for product **2a** reported in Figure 4.2) of the crude reaction mixtures. A sample of **2a** was synthesized according to the procedure reported in the literature[32] and used as reference for quantitative GC analyses.

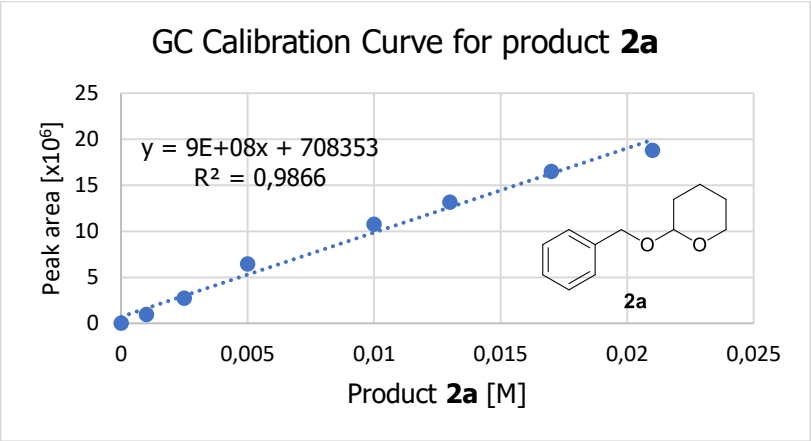
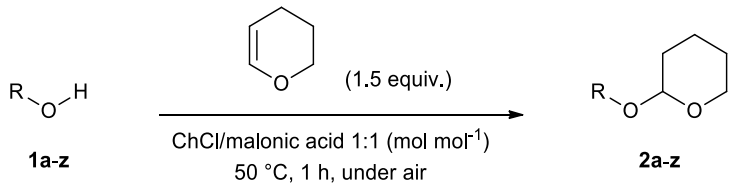


Figure 4.2. GC-FID calibration curve for 2-(benzyloxy)tetrahydro-2*H*-pyran **2a**.

*4.7.4 Synthesis and analysis of compounds **2a-z***

General procedure. Reactions were performed under air. In an open screw cap vial, substrates **1a**-**1z** (1.0 mmol, 1.0 eq.), 3,4-dihydro-2*H*-pyran (DHP, 126 mg, 1.5 mmol, 1.5 eq.) and ChCl/malonic acid (1:1 mol/mol, 400 mg) were added. The resulting mixture was stirred for 1 hour at 50 °C (unless otherwise specified). The mixture was then diluted with water (10 mL) and extracted with the selected solvent (3 x 5 mL). The combined organic extracts were washed with sat. $NaHCO_3$ (1 x 5 mL), brine (1 x 5 mL) then dried over Na_2SO_4 and the solvent removed under reduced pressure. The crude products were purified by flash column chromatography on silica gel.



2-(Benzyloxy)tetrahydro-2*H*-pyran (2a): general procedure starting from **1a**. Extraction with CPME followed by flash column chromatography (PE/Et_2O 95/5 v/v) gave **2a** as a colorless oil (192 mg, 100%, R_f = 0.35 PE/Et_2O 95/5 v/v). **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.41-7.33 (m, 4H), 7.31-7.24 (m, 1H), 4.80 (d, *J* = 12.0 Hz, 1H), 4.72 (t, *J* = 3.6 Hz, 1H), 4.51 (d, *J* = 12.0 Hz, 1H), 3.93 (ddd, *J* = 11.6, 8.7, 3.0 Hz, 1H), 3.61-3.50 (m, 1H), 1.93-1.82 (m, 1H), 1.79-1.71 (m, 1H), 1.70-1.50 (m, 4H). **^{13}C{^{1}H} NMR** (150 MHz, $CDCl_3$): δ 138.4, 128.5, 127.9, 127.6, 97.9, 68.9, 62.2, 30.7, 25.6, 19.5. **EI-MS** *m/z* (%): 146 (6), 117 (6), 108 (14), 101 (13), 92 (14), 91 (100), 85 (16), 65 (9).[32]

2-((4-Methoxybenzyl)oxy)tetrahydro-2*H*-pyran (2b): general procedure starting from **1b**. Extraction with EtOAc followed by flash column chromatography (PE/Et_2O 9/1 v/v) gave **2b** as a colorless oil (216 mg, 97%, R_f = 0.26 PE/Et_2O 9/1 v/v). **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.32-7.27 (m, 2H), 6.90-6.86 (m, 2H), 4.72 (d, *J* = 11.6 Hz, 1H), 4.70-4.67 (m, 1H), 4.44 (d, *J* = 11.6 Hz, 1H), 3.93 (ddd, *J* = 11.6, 8.7, 3.1 Hz, 1H), 3.80 (s, 3H), 3.58-3.50 (m, 1H), 1.90-1.81 (m, 1H), 1.79-1.68 (m, 1H), 1.67-1.48 (m, 4H). **^{13}C{^{1}H} NMR** (150 MHz, $CDCl_3$): δ 159.3, 130.5, 129.6, 113.9, 97.6, 68.6, 62.3, 55.4, 30.7, 25.6, 19.5. **EI-MS** *m/z* (%): 222 (M^+, 11), 122 (24), 121 (100), 85 (10).[33]

2-((4-Nitrobenzyl)oxy)tetrahydro-2*H*-pyran (2c): general procedure starting from **1c**. Extraction with EtOAc followed by flash column chromatography (PE/EtOAc 7/3 v/v) gave **2c** as a colorless oil (235 mg, 98%, R_f = 0.25 PE/EtOAc 7/3 v/v). **^{1}H NMR** (600 MHz, $CDCl_3$): δ 8.22-8.17 (m, 2H), 7.52 (d, *J* = 8.9 Hz, 2H), 4.88 (d, *J* = 13.4 Hz, 1H), 4.73 (dd, *J* = 4.0, 3.1 Hz, 1H), 4.60 (d, *J* = 13.5 Hz, 1H), 3.87 (ddd, *J* = 11.6, 8.8, 3.1 Hz, 1H), 3.59-3.50 (m, 1H), 1.92-1.82 (m, 1H), 1.81-1.73 (m, 1H), 1.72-1.50 (m, 4H). **^{13}C{^{1}H} NMR** (150 MHz, $CDCl_3$): δ 147.4, 146.2, 127.9, 123.7, 98.4, 67.7, 62.4, 30.6, 25.5, 19.4. **EI-MS** *m/z* (%): 237 (M^+, 4), 149 (13), 137 (42), 136 (61), 107 (18), 106 (24), 101 (18), 90 (25), 89 (36), 85 (100), 78 (28), 77 (13), 67 (11), 57 (11), 55 (25), 41 (14).[34]

2-((3-(Trifluoromethyl)benzyl)oxy)tetrahydro-2*H*-pyran (2d): general procedure starting from **1d**. Extraction with CPME followed by flash column chromatography (PE/Et_2O 95/5 v/v) gave **2d** as a colorless oil (237 mg, 91%, R_f = 0.30 PE/Et_2O 95/5 v/v). **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.64 (s, 1H), 7.54 (t, *J* = 7.3 Hz, 2H), 7.46 (t, *J* = 7.7 Hz, 1H), 4.84 (d, *J* = 12.4 Hz, 1H), 4.72 (t, *J* = 3.6 Hz, 1H), 4.55 (d, *J* = 12.4 Hz, 1H), 3.91 (ddd, *J* = 11.4, 8.6, 3.0 Hz, 1H), 3.60-3.52 (m, 1H), 1.91-1.83 (m, 1H), 1.80-1.73 (m, 1H), 1.71-1.51 (m, 4H). **^{13}C{^{1}H} NMR** (150 MHz, $CDCl_3$): δ 139.5, 131.0, 130.8 (q, *J* = 32.2 Hz, 1C), 128.9, 124.4 (q, *J* = 4.1 Hz, 1C), 124.3 (q, *J* = 272.4 Hz, 1C), 98.2, 68.2, 62.3, 30.6, 25.5, 19.4. **^{19}F{^{1}H} NMR** (564 MHz, $CDCl_3$): δ -62.49 (s, 3F). **EI-MS** *m/z* (%): 259 (1), 172 (22), 160 (13), 159 (100), 109 (11), 101 (13), 85 (28). **ESI-HRMS** $[M+H]^+$: *m/z* 261.1098, $C_{13}H_{16}F_3O_2^+$ requires 261.1097.

2-((4-Chlorobenzyl)oxy)tetrahydro-2*H*-pyran (2e): general procedure starting from **1e**. Extraction with EtOAc followed by flash column chromatography (PE/Et_2O 95/5 v/v) gave **2e** as a colorless oil (224 mg, 99%, R_f = 0.34 PE/Et_2O 95/5 v/v). **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.34-7.27 (m, 4H), 4.75 (d, *J* = 12.2 Hz, 1H), 4.69 (t, *J* = 3.6 Hz, 1H), 4.47 (d, *J* = 12.2 Hz, 1H), 3.90 (ddd, *J* = 11.5, 8.5, 2.9 Hz, 1H), 3.58-3.50 (m, 1H), 1.91-1.80 (m, 1H), 1.78-1.50 (m, 5H). **^{13}C{^{1}H} NMR** (150 MHz, $CDCl_3$): δ 137.0, 133.3, 129.2, 128.6, 97.9, 68.1, 62.3, 30.6, 25.5, 19.4. **EI-MS** *m/z* (%): 226 (M^+, 1), 180 (6), 145 (15), 127 (33), 126 (10), 125 (100), 101 (9), 89 (13), 85 (22).[35]

2-((2,6-Dichlorobenzyl)oxy)tetrahydro-2*H*-pyran (2f): general procedure starting from **1f**. Extraction with EtOAc followed by flash column chromatography (PE/Et_2O 95/5 v/v) gave **2f** as a colorless oil (248 mg, 95%, R_f = 0.36 PE/Et_2O 95/5 v/v). **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.31 (d, *J* = 8.0 Hz, 2H), 7.17 (dd, *J* = 8.4, 7.6 Hz, 1H), 5.06 (d, *J* = 10.7 Hz, 1H), 4.83 (t, *J* = 3.4 Hz, 1H), 4.69 (d, *J* = 10.7 Hz, 1H), 4.00 (ddd, *J* = 11.3, 9.6, 3.0 Hz, 1H), 3.62-3.54 (m, 1H), 1.89-1.78 (m, 1H), 1.76-1.47 (m, 5H). **^{13}C{^{1}H} NMR** (150 MHz, $CDCl_3$): δ 137.1, 133.8, 129.9, 128.1, 99.0, 64.5, 62.0, 30.5, 25.6, 19.2. **EI-MS** *m/z* (%): 261 (M^+, 1), 225 (8), 179 (17), 172 (14), 163 (11), 161 (65), 159 (100), 123 (10), 114 (13), 85 (22), 55 (12).[36]

2-(Thiophen-2-ylmethoxy)tetrahydro-2*H*-pyran (2g): general procedure starting from **1g**. Extraction with CPME followed by flash column chromatography (PE/Et_2O 95/5 v/v) gave **2g** as a colorless oil (196 mg, 99%, R_f = 0.45 PE/Et_2O 95/5 v/v). **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.28 (dd, *J* = 5.0, 1.2 Hz, 1H), 7.02 (dd, *J* = 3.4, 1.1 Hz, 1H), 6.97 (dd, *J* = 5.1, 3.4 Hz, 1H), 4.89 (dd, *J* = 12.6, 0.9 Hz, 1H), 4.74 (t, *J* = 3.7 Hz, 1H) superimposed to 4.72 (d, *J* = 12.5 Hz, 1H), 3.96-3.88 (m, 1H), 3.60-3.51 (m, 1H), 1.90-1.81 (m, 1H), 1.76-1.68 (m, 1H), 1.66-1.49 (m, 4H). **^{13}C{^{1}H} NMR** (150 MHz, $CDCl_3$): δ 141.0, 126.8, 126.6, 125.8, 97.1, 63.2, 62.2, 30.5, 25.5, 19.3. **EI-MS** *m/z* (%): 198 (M^+, 1), 114 (18), 98 (20), 97 (100), 85 (24).[37]

1,4-Bis(((tetrahydro-2*H*-pyran-2-yl)oxy)methyl)benzene (2h): general procedure starting from **1h** (3.0 eq. DHP). Extraction with CPME followed by flash column chromatography (PE/EtOAc 9/1 v/v) gave **2h** as a colorless oil (245 mg, 80%, R_f = 0.38 PE/EtOAc 9/1 v/v). **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.35 (s, 4H), 4.78 (d, *J* = 11.8 Hz, 2H), 4.70 (dd, *J* = 4.1, 3.0 Hz, 2H), 4.50 (d, *J* = 12.0 Hz, 2H), 3.92 (ddd, *J* = 11.6, 8.8, 3.0 Hz, 2H), 3.58-3.51 (m, 2H), 1.91-1.82 (m, 2H), 1.78-1.69 (m, 2H), 1.67-1.49 (m, 8H). **^{13}C{^{1}H} NMR** (150 MHz, $CDCl_3$): δ 137.6, 128.0, 97.7, 68.6, 62.2, 30.6, 25.6, 19.4. **EI-MS** *m/z* (%): 205 (18), 138 (12), 121 (70), 107 (19), 105 (10), 104 (30), 93 (11), 91 (28), 85 (100), 84 (19), 79 (15), 77 (19), 57 (10), 55 (28), 41 (13), 28 (16). **ESI-HRMS** $[M+Na]^+$: *m/z* 329.1711, $C_{18}H_{26}NaO_4^+$ requires 329.1723.

2-(1-Phenylethoxy)tetrahydro-2*H*-pyran (2i): general procedure starting from **1i**. Extraction with CPME followed by flash column chromatography (PE/Et_2O 95/5 v/v) gave **2i** as a colorless oil (161 mg, 78%, R_f = 0.45 PE/Et_2O 95/5 v/v). Minor and major diastereoisomers (d_r = 1:0.6) were not separated by chromatography. **^{1}H NMR** (600 MHz, $CDCl_3$, mixture of diastereoisomers): δ 7.42-7.39 (m, 1H, major), 7.37-7.31 (m, 3H, major + 4H, minor), 7.29-7.23 (m, 1H, major + 1H, minor), 4.91-4.89 (m, 1H, minor) superimposed to 4.89 (q, *J* = 6.6 Hz, 1H, major), 4.83 (q, *J* = 6.4 Hz, 1H, minor), 4.40 (dd, *J* = 5.0, 3.0 Hz, 1H, major), 3.96 (dt, *J* = 11.2, 5.7 Hz, 1H, major), 3.70 (ddd, *J* =11.7, 9.1, 3.3 Hz, 1H, minor), 3.49 (dt, *J* = 10.3, 4.9 Hz, 1H, major), 3.42-3.36 (m, 1H, minor), 1.92-1.82 (m, 1H, major + 1H, minor), 1.79-1.73 (m, 1H, minor), 1.72-1.62 (m, 1H, major + 1H, minor), 1.61-1.42 (m, 4H, major + 3H, minor) superimposed to 1.49 (d, *J* = 6.6 Hz, 3H, major) superimposed to 1.45 (d, *J* = 6.4 Hz, 3H, minor). **^{13}C{^{1}H} NMR** (150 MHz, $CDCl_3$, mixture of diastereoisomers): δ 144.6 (minor), 143.8 (major), 128.5 (major), 128.3 (minor), 127.5 (major), 127.1 (minor), 126.5 (major), 126.1 (minor), 96.3 (minor), 96.2 (major), 73.3 (major), 73.2 (minor), 62.8 (major), 62.1 (minor), 31.0 (minor), 30.9 (major), 25.6 (major), 25.6 (minor), 24.5 (major), 22.1 (minor), 19.9 (major), 19.4 (minor). **EI-MS** *m/z* (%): 106 (12), 105 (100), 85 (22), 79 (10), 77 (12).[10a]

2-(Benzhydryloxy)tetrahydro-2*H*-pyran (2j): general procedure starting from **1j**. Extraction with CPME followed by flash column chromatography (PE/Et_2O 98/2 v/v) gave **2j** as a white solid (241 mg, 90%, R_f = 0.32 PE/Et_2O 98/2 v/v), mp 60.6−61.7 °C (pentane). **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.40-7.25 (m, 9H), 7.24-7.20 (m, 1H), 5.82 (s, 1H), 4.68 (t, *J* = 3.4 Hz, 1H), 3.90 (ddd, *J* = 11.3, 9.2, 2.9 Hz, 1H), 3.54-3.49 (m, 1H), 1.99-1.89 (m, 1H), 1.74-1.63 (m, 2H), 1.64-1.51 (m, 3H). **^{13}C{^{1}H} NMR** (150 MHz, $CDCl_3$): δ 143.0, 141.9, 128.6, 128.3, 127.8, 127.7, 127.2, 127.0, 95.5, 78.2, 62.1, 30.7, 25.7, 19.3. **EI-MS** *m/z* (%): 184 (14), 168 (19), 167 (100), 166 (12), 165 (25), 152 (11), 85 (13).[38]

2-((2-Phenylpropan-2-yl)oxy)tetrahydro-2*H*-pyran (2k): general procedure starting from **1k** (2h, 3.0 eq. DHP). Extraction with CPME followed by flash column chromatography (PE/Et_2O 95/5 v/v) gave **2k** as a colorless oil (123 mg, 56%, R_f = 0.40 PE/Et_2O 95/5 v/v). **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.48-7.44 (m, 2H), 7.36-7.31 (m, 2H), 7.28-7.23 (m, 1H), 4.44 (dd, *J* = 6.1, 2.8 Hz, 1H), 3.97 (dddd, *J* = 11.3, 6.2, 3.9, 1.2 Hz, 1H), 3.39 (ddd, *J* = 11.3, 7.6, 3.7 Hz, 1H), 1.89-1.81 (m, 1H), 1.69 (s, 3H), 1.66-1.60 (m, 1H), 1.58-1.39 (m, 4H) superimposed to 1.53 (s, 3H). **^{13}C{^{1}H} NMR** (150 MHz, $CDCl_3$): δ 147.2, 128.2, 127.0, 125.9, 95.6, 78.0, 63.5, 32.3, 32.2, 26.7, 25.5, 20.8. **EI-MS** *m/z* (%): 220 (M^+, 1), 121 (11), 120 (13), 119 (100), 91 (28), 85 (27), 43 (10).[39]

4-(((Tetrahydro-2*H*-pyran-2-yl)oxy)methyl)phenol (2l): general procedure starting from **1l**. Extraction with EtOAc followed by flash column chromatography (PE/EtOAc 8/2 v/v) gave **2l** as a colorless oil (200 mg, 96%, R_f = 0.36 PE/EtOAc 8/2 v/v). **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.22 (d, *J* = 8.5 Hz, 2H), 6.82-6.74 (m, 2H), 5.63 (s, 1H), 4.73-4.70 (m, 1H) superimposed to 4.71 (d, *J* = 11.5 Hz, 1H), 4.43 (d, *J* = 11.5 Hz, 1H), 3.94 (ddd, *J* = 11.6, 8.8, 3.1 Hz, 1H), 3.61-3.53 (m, 1H), 1.89-1.81 (m, 1H), 1.77-1.70 (m, 1H), 1.67-1.49 (m, 4H). **^{13}C{^{1}H} NMR** (150 MHz, $CDCl_3$): δ 155.5, 130.1, 129.9, 115.4, 97.7, 68.8, 62.4, 30.7, 25.6, 19.5. **EI-MS** *m/z* (%): 208 (M^+, 3), 162 (1), 123 (3), 108 (7), 107 (43), 32 (25), 28 (100).[13a]

2-Methoxy-4-(((tetrahydro-2H-pyran-2-yl)oxy)methyl)phenol (2m): general procedure starting from **1m**. Extraction with EtOAc followed by flash column chromatography (PE/EtOAc 8/2 v/v) gave **2m** as a colorless oil (219 mg, 92%, R_f = 0.32 PE/EtOAc 8/2 v/v). **^{1}H NMR** (600 MHz, $CDCl_3$): δ 6.91-6.83 (m, 3H), 5.73-5.69 (m, 1H), 4.70 (d, *J* = 11.7 Hz, 1H) superimposed to 4.70-4.67 (m, 1H), 4.43 (d, *J* = 11.6 Hz, 1H), 3.93 (ddd, *J* = 11.6, 8.4, 3.1 Hz, 1H), 3.88 (s, 3H), 3.58-3.51 (m, 1H), 1.90-1.81 (m, 1H), 1.76-1.69 (m, 1H), 1.66-1.49 (m, 4H). **^{13}C{^{1}H} NMR** (150 MHz, $CDCl_3$): δ 146.6, 145.3, 130.1, 121.5, 114.3, 111.0, 97.6, 69.0, 62.4, 56.0, 30.7, 25.6, 19.6. **EI-MS** *m/z* (%): 238 (M^+, 13), 154 (12), 138 (37), 137 (100), 122 (10), 85 (13). **ESI-HRMS** $[M-H]^+$: *m/z* 237.1124, $C_{13}H_{17}O_4^+$ requires 237.1127.

4-(((Tetrahydro-2*H*-pyran-2-yl)oxy)methyl)benzonitrile (2n): general procedure starting from **1n**. Extraction with CPME followed by flash column chromatography (PE/EtOAc 85/25 v/v) gave **2n** as a colorless oil (200 mg, 92%, R_f = 0.36 PE/EtOAc 85/25 v/v). **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.63 (d, *J* = 8.1 Hz, 2H), 7.47 (d, *J* = 8.0 Hz, 2H), 4.83 (d, *J* = 13.2 Hz, 1H), 4.71 (t, *J* = 3.6 Hz, 1H), 4.55 (d, *J* = 13.3 Hz, 1H), 3.87 (ddd, *J* = 11.5, 8.8, 3.0 Hz, 1H), 3.58-3.50 (m, 1H), 1.91-1.82 (m, 1H), 1.80-1.72 (m, 1H), 1.71-1.50 (m, 4H). **^{13}C{^{1}H} NMR** (150 MHz, $CDCl_3$): δ 144.1, 132.3, 127.9, 119.0, 111.2, 98.3, 68.0, 62.3, 30.5, 25.4, 19.3. **EI-MS** *m/z* (%): 217 (M^+, 6), 133 (10), 132 (10), 129 (21), 117 (44), 116 (100), 104 (20), 101 (12), 89 (21), 85 (53), 55 (23), 41 (10). **ESI-HRMS** $[M+Na]^+$: *m/z* 240.1020, $C_{13}H_{15}NNaO_2^+$ requires 240.0995.

Methyl 4-(((tetrahydro-2*H*-pyran-2-yl)oxy)methyl)benzoate (2o): general procedure starting from **1o**. Extraction with CPME followed by flash column chromatography (PE/Et_2O 8/2 v/v) gave **2o** as a colorless oil (215 mg, 86%, R_f = 0.41 PE/Et_2O 8/2 v/v**). ^{1}H NMR** (600 MHz, $CDCl_3$): δ 8.01 (d, *J* = 8.3 Hz, 2H), 7.42 (d, *J* = 8.7 Hz, 2H), 4.83 (d, *J* = 12.9 Hz, 1H), 4.71 (t, *J* = 3.6 Hz, 1H), 4.55 (d, *J* = 12.9 Hz, 1H), 3.92-3.86 (m, 1H) superimposed to 3.90 (s, 3H), 3.56-3.51 (m, 1H), 1.91-1.82 (m, 1H), 1.78-1.71 (m, 1H), 1.70-1.50 (m, 4H). **^{13}C{^{1}H} NMR** (150 MHz, $CDCl_3$): δ 167.1, 143.8, 129.8, 129.3, 127.4, 98.1, 68.3, 62.3, 52.2, 30.6, 25.5, 19.4. **EI-MS** *m/z* (%): 250 (M^+, 1), 218 (19), 166 (22), 150 (25), 149 (100), 137 (11), 135 (24), 121 (16), 107 (21), 90 (13), 89 (18), 85 (28), 77 (15), 55 (13).[40]

Pyrrolidin-1-yl(4-(((tetrahydro-2*H*-pyran-2-yl)oxy)methyl)phenyl)methanone (2p): general procedure starting from **1p**. Extraction with CPME followed by flash column chromatography (PE/acetone 75/25 v/v) gave **2p** as a colorless oil (231 mg, 80%, R_f = 0.32 PE/acetone 75/25 v/v).), mp 49.5–50.6 °C (benzene). **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.50 (d, *J* = 8.1 Hz, 2H), 7.39 (d, *J* = 7.9 Hz, 2H), 4.80 (d, *J* = 12.4 Hz, 1H), 4.70 (t, *J* = 3.6 Hz, 1H), 4.53 (d, *J* = 12.4 Hz, 1H), 3.91 (ddd, *J* = 11.4, 8.4, 2.9 Hz, 1H), 3.64 (t, *J* = 7.0 Hz, 2H), 3.55 (dt, *J* = 10.6, 4.8 Hz, 1H), 3.43 (t, *J* = 6.7 Hz, 2H), 1.96 (quint, *J* = 6.8 Hz, 2H), 1.90-1.82 (m, 3H), 1.79-1.71 (m, 1H), 1.69-1.50 (m, 4H). **^{13}C{^{1}H} NMR** (150 MHz, $CDCl_3$): δ 169.7, 140.3, 136.5, 127.6, 127.4, 98.0, 68.5, 62.4, 49.8, 46.3, 30.7, 26.6, 25.6, 24.6, 19.5. **EI-MS** *m/z* (%): 289 (M^+, 21), 288 (12), 219 (16), 205 (56), 204 (50), 189 (33), 188 (97), 160 (14), 146 (25), 135 (100), 118 (18), 107 (12), 105 (10), 91 (15), 90 (19), 89 (30), 85 (20), 84 (11), 77 (20), 55 (19), 41 (10), 28 (16). **ESI-HRMS** $[M+H]^+$: *m/z* 290.1746, $C_{17}H_{24}NO_3^+$ requires 290.1751.

2-(Cinnamyloxy)tetrahydro-2*H*-pyran (2q): general procedure starting from **1q**. Extraction with CPME followed by flash column chromatography (PE/Et_2O 95/5 v/v) gave **2q** as a colorless oil (201 mg, 92%, R_f = 0.31 PE/Et_2O 95/5 v/v). **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.43-7.38 (m, 2H), 7.34-7.29 (m, 2H), 7.26-7.22 (m, 1H), 6.64 (d, *J* = 15.9 Hz, 1H), 6.33 (ddd, *J* = 15.9, 6.6, 5.6 Hz, 1H), 4.73 (dd, *J* = 4.3, 3.0 Hz, 1H), 4.42 (ddd, *J* = 12.9, 5.6, 1.6 Hz, 1H), 4.18 (ddd, *J* = 12.9, 6.6, 1.4 Hz, 1H), 3.93 (ddd, *J* = 11.2, 8.2, 3.1 Hz, 1H), 3.59-3.51 (m, 1H), 1.93-1.83 (m, 1H), 1.81-1.73 (m, 1H), 1.70-1.51 (m, 4H). **^{13}C{^{1}H} NMR** (150 MHz, $CDCl_3$): δ 136.9, 132.3, 128.6, 127.6, 126.5, 126.1, 97.9, 67.7, 62.2, 30.7, 25.5, 19.5. **EI-MS** *m/z* (%): 218 (M^+, 2), 118 (29), 117 (87), 116 (12), 115 (42), 91 (18), 85 (100), 67 (13), 57 (13), 41 (10).[41]

(*E*)-2-((3,7-Dimethylocta-2,6-dien-1-yl)oxy)tetrahydro-2*H*-pyran (2r): general procedure starting from **1r**. Extraction with CPME followed by flash column chromatography (PE/Et_2O 95/5 v/v) gave **2r** as a slightly green oil (234 mg, 98%, R_f = 0.40 PE/Et_2O 95/5 v/v). **^{1}H NMR** (600 MHz, $CDCl_3$): δ 5.35 (ddq, *J* = 7.6, 6.3, 1.3 Hz, 1H), 5.12-5.03 (m, 1H), 4.61 (dd, *J* = 4.5, 3.0 Hz, 1H), 4.22 (dd, *J* = 11.9, 6.4 Hz, 1H), 4.02 (dd, *J* = 11.9, 7.4 Hz, 1H), 3.88 (ddd, *J* = 11.2, 7.8, 3.1 Hz, 1H), 3.54-3.43 (m, 1H), 2.14-2.07 (m, 2H), 2.05-1.99 (m, 2H), 1.87-1.78 (m, 1H), 1.74-1.63 (m, 4H) superimposed to 1.67 (s, 3H), 1.62-1.46 (m, 4H) superimposed to 1.59 (s, 3H). **^{13}C{^{1}H} NMR** (150 MHz, $CDCl_3$): δ 140.3, 131.7, 124.2, 120.7, 97.9, 63.7, 62.4, 39.7, 30.8, 26.5, 25.8, 25.6, 19.8, 17.8, 16.5. **EI-MS** *m/z* (%): 154 (5), 137 (5), 136 (9), 121 (10), 93 (13), 85 (100), 84 (10), 81 (16), 69 (60), 68 (14), 67 (22), 57 (11), 55 (12), 41 (35).[42]

2-(Prop-2-yn-1-yloxy)tetrahydro-2*H*-pyran (2s): general procedure starting from **1s**. Extraction with CPME followed by flash column chromatography (PE/Et_2O 95/5 v/v) gave **2s** as a colorless oil (112 mg, 80%, R_f = 0.41 PE/Et_2O 95/5 v/v). **^{1}H NMR** (600 MHz, $CDCl_3$): δ 4.80 (t, *J* = 3.5 Hz, 1H), 4.27 (dd, *J* = 15.7, 2.4 Hz, 1H), 4.21 (dd, *J* = 15.7, 2.4 Hz, 1H), 3.82 (ddd, *J* = 11.4, 9.3, 3.0 Hz, 1H), 3.55-3.49 (m, 1H), 2.40 (t, *J* = 2.4 Hz, 1H), 1.86-1.77 (m, 1H), 1.76-1.69 (m, 1H), 1.65-1.48 (m, 4H). **^{13}C{^{1}H} NMR** (150 MHz, $CDCl_3$): δ 96.9, 79.9, 74.1, 62.1, 54.1, 30.3, 25.4, 19.1. **EI-MS** *m/z* (%): 140 (M^+, 1), 139 (12), 85 (100), 83 (10), 82 (13), 67 (10), 57 (25), 56 (42), 55 (30), 53 (12), 41 (34), 39 (38), 29 (16).[43]

2-(Octyloxy)tetrahydro-2*H*-pyran (2t): general procedure starting from **1t**. Extraction with CPME followed by flash column chromatography (PE/Et_2O 98/2 v/v) gave **2t** as a colorless oil (189 mg, 88%, R_f = 0.41 PE/Et_2O 98/2 v/v). **^{1}H NMR** (600 MHz, $CDCl_3$): δ 4.56 (dd, *J* = 4.5, 3.0 Hz, 1H), 3.86 (ddd, *J* = 11.0, 7.6, 3.0 Hz, 1H), 3.71 (dt, *J* = 9.6, 6.9 Hz, 1H), 3.52-3.45 (m, 1H), 3.36 (dt, *J* = 9.6, 6.7 Hz, 1H), 1.86-1.77 (m, 1H), 1.74-1.65 (m, 1H), 1.62-1.46 (m, 6H), 1.40-1.17 (m, 10H), 0.86 (t, *J* = 7.0 Hz, 3H). **^{13}C{^{1}H} NMR** (150 MHz, $CDCl_3$): δ 99.0, 67.8, 62.4, 32.0, 30.9, 29.9, 29.6, 29.4, 26.4, 25.6, 22.8, 19.8, 14.2. **EI-MS** *m/z* (%): 213 (2), 101 (10), 85 (100), 84 (15), 71 (15), 57 (25), 56 (29), 55 (16), 43 (17), 41 (19).[33]

2-(Hexadecyloxy)tetrahydro-2*H*-pyran (2u): general procedure starting from **1u**. Extraction with CPME followed by flash column chromatography (PE/Et_2O 98/2 v/v) gave **2u** as a colorless oil (287 mg, 88%, R_f = 0.51 PE/Et_2O 98/2 v/v). **^{1}H NMR** (600 MHz, $CDCl_3$): δ 4.57 (dd, *J* = 4.6, 2.9 Hz, 1H), 3.86 (ddd, *J* = 11.0, 7.7, 3.0 Hz, 1H), 3.72 (dt, *J* = 9.5, 6.9 Hz, 1H), 3.53-3.45 (m, 1H), 3.37 (dt, *J* = 9.6, 6.7 Hz, 1H), 1.88-1.77 (m, 1H), 1.74-1.66 (m, 1H), 1.63-1.46 (m, 6H), 1.38-1.15 (m, 26H), 0.87 (t, *J* = 6.9 Hz, 3H). **^{13}C{^{1}H} NMR** (150 MHz, $CDCl_3$): δ 99.0, 67.8, 62.4, 32.1, 30.9, 29.9, 29.8, 29.8, 29.8, 29.7, 29.6, 29.5, 26.4, 25.7, 22.8, 19.8, 14.2. **EI-MS** *m/z* (%): 326 (M^+, 1), 111 (10), 101 (8), 97 (19), 85 (100), 84 (25), 83 (26), 82 (10), 71 (15), 70 (12), 69 (23), 57 (30), 56 (25), 55 (36), 43 (26), 41 (23).[44]

2-(3-Chloropropoxy)tetrahydro-2*H*-pyran (2v): general procedure starting from **1v**. Extraction with CPME followed by flash column chromatography (PE/Et_2O 95/5 v/v) gave **2v** as a colorless oil (163 mg, 91%, R_f = 0.32 PE/Et_2O 95/5 v/v). **^{1}H NMR** (600 MHz, $CDCl_3$): δ 4.59 (dd, *J* = 4.3, 2.8 Hz, 1H), 3.91-3.81 (m, 2H), 3.66 (td, *J* = 6.5, 1.2 Hz, 2H), 3.52 (dt, *J* = 10.0, 5.9 Hz, 2H), 2.04 (p, *J* = 6.2 Hz, 2H), 1.84-1.75 (m, 1H), 1.74-1.66 (m, 1H), 1.62-1.46 (m, 4H). **^{13}C{^{1}H} NMR** (150 MHz, $CDCl_3$): δ 99.0, 64.0, 62.4, 42.1, 32.9, 30.7, 25.5, 19.6. **EI-MS** *m/z* (%): 179 (M^+, 5), 177 (M^+, 15), 123 (15), 85 (100), 67 (8), 57 (14), 58 (30), 55 (13), 47 (12), 41 (36).[45]

***tert*-Butyl (5-((tetrahydro-2*H*-pyran-2-yl)oxy)pentyl)carbamate (2w)**: general procedure starting from **1w**. Extraction with CPME followed by flash column chromatography (PE/Et_2O 8/2 v/v) gave **2w** as a colorless oil (193 mg, 67%, R_f = 0.30 PE/Et_2O 8/2 v/v). **^{1}H NMR** (600 MHz, $CDCl_3$): δ 4.59-4.51 (m, 2H), 3.87-3.81 (m, 1H), 3.75-3.68 (m, 1H), 3.52-3.45 (m, 1H), 3.37 (ddd, *J* = 9.7, 7.1, 5.8 Hz, 1H), 3.15-3.05 (m, 2H), 1.85-1.35 (m, 12H) superimposed to 1.42 (s, 9H). **^{13}C{^{1}H} NMR** (150 MHz, $CDCl_3$): δ 156.1, 99.0, 79.1, 67.5, 62.5, 40.6, 30.9, 30.0, 29.5, 28.5, 25.6, 23.7, 19.8. **EI-MS** *m/z* (%): 147 (10), 146 (50), 130 (38), 102 (14), 101 (14), 86 (18), 85 (100), 84 (13), 74 (21), 69 (14), 59 (12), 57 (67), 56 (17), 55 (12), 41 (30), 30 (11), 29 (10). **ESI-HRMS** $[M+H]^+$: *m/z* 288.2166, $C_{15}H_{30}NO_4^+$ requires 288.2169.

2-(Cyclohexyloxy)tetrahydro-2*H*-pyran (2x): general procedure starting from **1x**. Extraction with Et_2O followed by flash column chromatography (PE/Et_2O 95/5 v/v) gave **2x** as a colorless oil (158 mg, 86%, R_f = 0.30 PE/Et_2O 95/5 v/v). **^{1}H NMR** (600 MHz, $CDCl_3$): δ 4.69 (dd, *J* = 5.0, 2.7 Hz, 1H), 3.90 (ddd, J = 11.2, 6.7, 3.5 Hz, 1H), 3.57 (tt, *J* = 9.7, 4.0 Hz, 1H), 3.49-3.41 (m, 1H), 1.95-1.77 (m, 3H), 1.76-1.63 (m, 3H), 1.56-1.45 (m, 5H), 1.41-1.32 (m, 1H), 1.31-1.11 (m, 4H). **^{13}C{^{1}H} NMR** (150 MHz, $CDCl_3$): δ 96.7, 74.5, 62.8, 33.8, 31.9, 31.4, 25.8, 25.6, 24.5, 24.3, 20.1. **EI-MS** *m/z* (%): 184 (M^+, 6), 101 (35), 85 (100), 83 (21), 82 (10), 67 (19), 57 (16), 56 (36), 55 (33), 41 (21).[45]

2-(Cyclododecanyloxy)tetrahydro-2*H*-pyran (2y): general procedure starting from **1y**. Extraction with CPME followed by flash column chromatography (PE/Et_2O 98/2 v/v) gave **2y** as a colorless oil (252 mg, 94%, R_f = 0.30 PE/Et_2O 98/2 v/v). **^{1}H NMR** (600 MHz, $CDCl_3$): δ 4.67 (t, *J* = 3.8 Hz, 1H), 3.91 (ddd, *J* = 11.1, 7.1, 3.4 Hz, 1H), 3.79 (tt, *J* = 7.7, 4.0 Hz, 1H), 3.48 (dt, *J* = 10.8, 5.1 Hz, 1H), 1.87-1.76 (m, 1H), 1.73-1.65 (m, 2H), 1.62-1.24 (m, 25H). **^{13}C{^{1}H} NMR** (150 MHz, $CDCl_3$): δ 96.9, 73.9, 62.7, 31.4, 30.2, 28.5, 25.7, 24.9 (2C), 24.5, 23.5, 23.4, 23.0, 22.9, 21.2, 20.4, 20.0. **EI-MS** *m/z* (%): 268 (M^+, 2), 101 (10), 97 (8), 85 (100), 84 (12), 83 (10), 67 (12), 57 (12), 56 (11), 55 (20), 41 (15).[46]

2-(((1*R*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyl)oxy)tetrahydro-2*H*-pyran (2z): general procedure starting from **1z**. Extraction with CPME followed by flash column chromatography (PE/Et_2O 98/2 v/v) gave **2z** as a colorless oil (199 mg, 83%, R_f = 0.33 PE/Et_2O 98/2 v/v). Mixture of two diastereoisomers (d_r = 1:1) not separated by chromatography. **^{1}H NMR** (600 MHz, $CDCl_3$, mixture of diastereoisomers): δ 4.79 (t, *J* = 3.6 Hz, 1H), 4.58 (dd, *J* = 5.3, 2.9 Hz, 1H), 4.00-3.91 (m, 1H), 3.88 (ddd, *J* = 11.1, 7.6, 3.7 Hz, 1H), 3.52-3.42 (m, 3H), 3.30 (td, *J* = 10.6, 4.4 Hz, 1H), 2.35 (quintd, *J* = 7.0, 2.6 Hz, 1H), 2.14 (dddd, *J* = 12.4, 4.4, 3.4, 2.0 Hz, 1H), 2.11-2.03 (m, 2H), 1.86-1.76 (m, 2H), 1.74-1.46 (m, 14H), 1.43-1.30 (m, 2H), 1.27-1.18 (m, 2H), 1.08-0.77 (m, 18H), 0.79 (d, *J* = 6.9 Hz, 3H), 0.76 (d, *J* = 7.0 Hz, 3H). **^{13}C{1H} NMR** (150 MHz, $CDCl_3$, mixture of diastereoisomers): δ 101.4, 94.5, 80.1, 74.2, 63.2, 62.5, 49.0, 48.3, 43.7, 40.3, 34.7, 34.5, 31.9, 31.6, 31.5, 31.3, 25.7, 25.7, 25.6, 25.3, 23.4, 23.2, 22.5, 22.4, 21.4, 21.3, 20.4, 19.9, 16.4, 15.7. **EI-MS** *m/z* (%): 139 (32), 138 (13), 97 (8), 85 (100), 84 (15), 83 (48), 81 (13), 69 (14), 57 (18), 55 (20), 41 (15).[47]

4.7.5 Competition experiments

General procedure. All reactions were performed under air. In an open screw cap vial, benzyl alcohol **1a** (108 mg, 1.0 mmol, 1.0 eq.), competitive substrate (1.0 mmol, 1.0 eq.) and 3,4-dihydro-2*H*-pyran (DHP, 84 mg, 1.0 mmol, 1.0 eq.) were dissolved in ChCl/malonic acid (1:1 mol/mol, 400 mg) and the resulting mixture was stirred for 1 hour at 50 °C. The mixture was then diluted with water (10 mL) and extracted with CPME (3 x 5 mL). The combined organic extracts were washed with sat. $NaHCO_3$ (1 x 5 mL), brine (1 x 5 mL) then dried over Na_2SO_4 and the solvent removed under reduced pressure. Yields (Table 4.3) were determined by quantitative ^1H NMR analysis of the crude reaction mixtures using nitromethane (0.0925 mmol, 5 µL) as internal standard and a diluting factor of 2 for the preparation of the sample.

*4.7.6 Telescoped tetrahydropyranylation-S_NAc sequences for the synthesis of compounds **4** and **5***

1-(4-(((Tetrahydro-2*H*-pyran-2-yl)oxy)methyl)phenyl)pentan-1-one (3): in an open screw cap vial, substrate **1p** (103 mg, 0.5 mmol, 1.0 eq.), 3,4-dihydro-2*H*-pyran (DHP, 63 mg, 0.75 mmol, 1.5 eq.) and ChCl/malonic acid (1:1 mol/mol, 200 mg) were added. The resulting mixture was stirred for 1 hour at 50 °C, then allowed to cool to room temperature. After, CPME (200 µL) was added and then *n*-BuLi (1.0 mmol, 2.0 eq, 1.85 M in hexanes) was rapidly spread over the mixture. After 20 seconds the mixture was quenched with 5 mL of sat. NH_4Cl_{aq} and then extracted with CPME (3 x 5 mL). The combined organic extracts were washed with sat. $NaHCO_3$ (1 x 5 mL), brine (1 x 5 mL) then dried over Na_2SO_4 and the solvent removed *in vacuo*. Purification by flash column chromatography on silica gel (PE/acetone 75/25 v/v) gave pure **3** as a colorless oil (231 mg, 60%, R_f = 0.32 PE/acetone 75/25 v/v). **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.94 (d, *J* = 8.3 Hz, 2H), 7.45 (d, *J* = 8.6 Hz, 2H), 4.84 (d, *J* = 12.8 Hz, 1H), 4.72 (t, *J* = 3.6 Hz, 1H), 4.56 (d, *J* = 12.8 Hz, 1H), 3.90 (ddd, *J* = 11.4, 8.6, 2.9 Hz, 1H), 3.58-3.51 (m, 1H), 2.95 (t, *J* = 7.3 Hz, 2H), 1.92-1.83 (m, 1H), 1.79-1.51 (m, 5H) superimposed to 1.71 (quint, *J* = 7.7 Hz, 2H), 1.40 (sext, *J* = 7.7 Hz, 2H), 0.95 (t, *J* = 7.4 Hz, 3H). **^{13}C{^{1}H} NMR** (150 MHz, $CDCl_3$): δ 200.5, 143.8, 136.4, 128.4, 127.6, 98.1, 68.3, 62.3, 38.5, 30.6, 26.7, 25.5, 22.6, 19.4, 14.1. **EI-MS** *m/z* (%): 276 (M^+, 1), 234 (23), 219 (58), 176 (29), 175 (100), 174 (53), 161 (15), 150 (20), 147 (34), 135 (46), 133 (33), 118 (13), 105 (10), 91 (18), 90 (23), 89 (22), 85 (54), 77 (11), 57 (10), 55 (10), 41 (12). **ESI-HRMS** $[M+H]^+$: *m/z* 277.1791, $C_{17}H_{25}O_3^+$ requires 277.1798.

1-(4-(Hydroxymethyl)phenyl)pentan-1-one (4): in an open screw cap vial, substrate **1p** (103 mg, 0.5 mmol, 1.0 eq.) or **1n** (67 mg, 0.5 mmol, 1.0 eq.), 3,4-dihydro-2*H*-pyran (DHP, 63 mg, 0.75 mmol, 1.5 eq.) and ChCl/malonic acid (1:1 mol/mol, 200 mg) were added. The resulting mixture was stirred for 1 hour at 50 °C, then allowed to cool to room temperature. After, CPME (200 µL) was added and then *n*-BuLi (1.0 mmol, 2.0 eq, 1.85 M in hexanes) was rapidly spread over the mixture. After 20 seconds the mixture was quenched with 5 mL of sat. NH_4Cl_{aq} and extracted in the vial with CPME (5 mL) by vigorous stirring the heterogeneous mixture for 2 minutes. The aqueous phase was allowed to separate and then removed with a Pasteur pipette. Then methanol (5 mL) and Amberlist 15® (100 mg) were added and the mixture heated at 60 °C for 1h. The reaction mixture was allowed to cool back to room temperature, then Amberlist 15® was filtered over cotton followed by addition of water (10 mL). Solvents were removed under reduced pressure and the aqueous phase extracted with CPME (3 x 5 mL). The organic phase was washed with sat. $NaHCO_3$ (1 x 5 mL), brine (1 x 5 mL), dried over Na_2SO_4, filtered and the solvent removed *in vacuo* to afford crude **4**.[26] Purification by flash column chromatography (PE/EtOAc 8/2 v/v) gave pure **4** as a colorless oil (55 mg, 57% starting from **1p**, 45 mg, 47% starting from **1n**, R_f = 0.21 PE/EtOAc 8/2 v/v). **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.95 (d, *J* = 8.3 Hz, 2H), 7.45 (d, *J* = 8.7 Hz, 2H), 4.77 (s, 2H), 2.95 (t, *J* = 7.4 Hz, 2H), 1.97 (br s, 1H), 1.71 (quint, *J* = 7.5 Hz, 2H), 1.44-1.36 (m, 2H), 0.95 (t, *J* = 7.4 Hz, 3H). **^{13}C{^{1}H} NMR** (150 MHz, $CDCl_3$): δ 200.5, 146.0, 136.4, 128.5, 126.8, 64.8, 38.5, 26.6, 22.6, 14.1. **EI-MS** *m/z* (%): 161 (21), 150 (44), 135 (100), 107 (14), 89 (17), 77 (15).[48]

5-(4-(Hydroxymethyl)phenyl)nonan-5-ol (5): in an open screw cap vial, substrate **1o** (83 mg, 0.5 mmol, 1.0 eq.), 3,4-dihydro-2*H*-pyran (DHP, 63 mg, 0.75 mmol, 1.5 eq.) and ChCl/malonic acid (1:1 mol/mol, 200 mg) were added. The resulting mixture was stirred for 1 hour at 50 °C, then allowed to cool to room temperature. After, CPME (200 µL) was added and then *n*-BuLi (1.25 mmol, 2.5 eq, 1.85 M in hexanes) was rapidly spread over the mixture. After 20 seconds the mixture was quenched with 5 mL of sat. NH_4Cl_{aq} and extracted in the vial with CPME (5 mL) by vigorous stirring the heterogeneous mixture for 2 minutes. The aqueous phase was allowed to separate and then removed with a Pasteur pipette. Then methanol (5 mL) and Amberlist 15® (100 mg) were added and the mixture heated at 60 °C for 1h. The reaction mixture was allowed to cool back to room temperature, then Amberlist 15® was filtered over cotton followed by addition of water (10 mL). Solvents were removed under reduced pressure and the aqueous phase extracted with CPME (3 x 5 mL). The organic phase was washed with sat. $NaHCO_3$ (1 x 5 mL), brine (1 x 5 mL), dried over Na_2SO_4, filtered and the solvent removed *in vacuo* to afford crude **5**. Purification by flash column chromatography (PE/acetone 9/1 v/v) gave pure **5** as a colorless oil (65 mg, 52 %, R_f = 0.17 PE/acetone 85/15 v/v). **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.36 (d, *J* = 8.3 Hz, 2H), 7.33 (d, *J* = 8.3 Hz, 2H), 4.69 (s, 2H), 1.87-1.72 (m, 4H) superimposed to 1.69 (br s, 2H), 1.30-1.18 (m, 6H), 1.05-0.96 (m, 2H), 0.83 (t, *J* = 7.1 Hz, 6H). **^{13}C{^{1}H} NMR** (150 MHz, $CDCl_3$): δ 146.2, 138.8, 126.9, 125.7, 77.1, 65.3, 42.9, 25.7, 23.2, 14.2.

4.7.7 Gram-scale reaction and recycling procedure

General procedure. A 100 mL round bottom flask was charged with benzyl alcohol **1a** (2.7 g, 25.0 mmol, 1.0 eq.), 3,4-dihydro-2*H*-pyran (DHP, 3.15 g, 37.5 mmol, 1.5 eq.) and ChCl/malonic acid (1:1 mol/mol, 10 g) (0.4 g per mmol of substrate) and the mixture was stirred at 50 °C for 1 hour. Deionized water (25 mL) was added, causing the separation of the product as a colorless oil. Product **2a** was recovered by extraction with CPME (3 x 10 mL). The combined organic extracts were washed with sat. $NaHCO_3$ (1 x 10 mL), brine (1 x 10 mL), dried over Na_2SO_4 and CPME was removed under reduced pressure. No further purification of **2a** (Figure 4.1) was necessary as confirmed by GC-FID and ^1H NMR analysis of the reaction crudes for each step. ChCl/malonic acid (1:1 mol/mol) was recovered by removing water under reduced pressure to afford the eutectic mixture and then used for the next reaction cycle. The water and CPME, recovered by distillations under reduced pressure, were used again in the following reaction cycles (Scheme 4.5).

4.7.8 Green metrics calculation

E-factor. The E-factor for the ten-cycles, gram-scale reaction of **1a** in ChCl/malonic acid (1:1 mol/mol) was calculated as follows:[29]

$$\boldsymbol{E-factor} = \frac{Mass\ of\ waste\ [g]}{Mass\ of\ product\ \ [g]} = \frac{g\ DHP + g\ NADES + g\ H_2O + g\ CPME}{g\ \mathbf{2a}}$$

$$= \frac{10.5\ g + 10.0\ g + 70.0\ g + \ 41.5\ g}{46.1\ g} = \mathbf{2.9}$$

Mass of waste [g]:

- ***g DHP***: 1.5 eq. (37.5 mmol) of DHP were used over ten reaction cycles, resulting in 0.5 eq. (12.5 mmol, 1.05 g) of reagent excess per cycle. **10.5 g** total of waste DHP.
- ***g NADES***: **10.0 g** of ChCl/malonic acid (1:1 mol/mol) used as solvent and promoter over ten reaction cycles.
- ***g H_2O***: 25.0 g of H_2O were employed for dissolving the NADES at the end of the reaction. 20.0 g out 25.0 g of H_2O were recovered from the evaporation and used for the same purpose in the following cycles (5.0 grams loss per cycle). So, 5.0 g loss x 10 cycles = 50.0 g of unrecovered H_2O, plus 20.0 g of leftover H_2O from the last cycle, **70.0 g** total of waste H_2O.
- ***g CPME***: 3 x 10 mL of CPME (d: 0.863 g/mL) were employed for the liquid-liquid extraction at the end of the reaction. 28 mL out 30 mL of CPME were recovered from the distillation and used for the same purpose in the following cycles (1.73 grams loss per cycle). So, 1.73 g loss x 10 cycles = 17.3 g of unrecovered CPME, plus 24.16 g of leftover CPME from the last cycle, **41.5 g** total of waste CPME.

Mass of product [g]:

- ***g 2a***: **46.1 g** of product **2a** obtained over the ten reaction cycles.

The E-factor for the single run, gram-scale reaction of **1a** in ChCl/malonic acid (1:1 mol/mol) was calculated as follows:[29]

$$\boldsymbol{E-factor} = \frac{Mass\ of\ waste\ [g]}{Mass\ of\ product\ \ [g]} = \frac{g\ DHP + g\ NADES + g\ H_2O + g\ CPME}{g\ \mathbf{2a}}$$

$$= \frac{1.05\ g + 10.0\ g + 25.0\ g + \ 25.9\ g}{4.2\ g} = \mathbf{14.7}$$

Mass of waste [g]:

- ***g DHP***: 1.5 eq (37.5 mmol) of DHP were used for the reaction, resulting in 0.5 eq. (12.5 mmol, **1.05 g**) of reagent excess.
- ***g NADES***: **10.0 g** of ChCl/malonic acid (1:1 mol/mol) were used as solvent and promoter for the reaction.
- ***g H_2O***: **25.0 g** of H_2O were employed for dissolving the NADES at the end of the reaction.
- ***g CPME***: 3 x 10 mL of CPME (d: 0.863 g/mL) were employed for the liquid-liquid extraction at the end of the reaction. 30 mL of CPME corresponds to **25.9 g**.

Mass of product [g]:

- ***g 2a***: **4.2 g** of product **2a** obtained.

Process mass intensity (PMI). The PMI for the ten-cycles, gram-scale reaction of **1a** in ChCl/malonic acid (1:1 mol/mol) was calculated as follows:[29]

$$\boldsymbol{PMI} = \frac{Total\ mass\ in\ process\ [g]}{Mass\ of\ product\ [g]} = \frac{g\ \mathbf{1a} + g\ DHP + g\ NADES + g\ H_2O + g\ CPME}{g\ \mathbf{2a}}$$

$$= \frac{27.0 + 31.5\ g + 10.0\ g + 70.0\ g + \ 41.5\ g}{46.1\ g} = \mathbf{3.9}$$

Total mass in process [g]:

- ***g 1a***: **27.0 g** of benzyl alcohol **1a** used over ten reaction cycles (25.0 mmol, 2.7 g per cycle).
- ***g DHP***: **31.5 g** of DHP used over the ten reaction cycles (37.5 mmol, 3.15 g per cycle).
- ***g NADES***: **10.0 g** of ChCl/malonic acid (1:1 mol/mol) used as solvent and promoter over the ten reaction cycles.
- ***g H_2O***: 25.0 g of H_2O were employed for dissolving the NADES at the end of the reaction. 20.0 g out 25.0 g of H_2O were recovered from the evaporation and used for the same purpose in the following cycles (5.0 grams loss per cycle). So, 5.0 g loss x 10 cycles = 50.0 g of unrecovered H_2O, plus 20.0 g of leftover H_2O from the last cycle, **70.0 g** total of used H_2O.
- ***g CPME***: 3 x 10 mL of CPME (d: 0.863 g/mL) were employed for the liquid-liquid extraction at the end of the reaction. 28 mL out 30 mL of CPME were recovered from the distillation and used for the same purpose in the following cycles (1.73 grams loss per cycle). So, 1.73 g loss x 10 cycles = 17.3 g of unrecovered CPME, plus 24.16 g of leftover CPME from the last cycle, **41.5 g** total of used CPME.

Mass of product [g]:

- ***g 2a***: **46.1 g** of product **2a** obtained over the ten reaction cycles.

The PMI for the single run, gram-scale reaction of **1a** in ChCl/malonic acid (1:1 mol/mol) was calculated as follows:[29]

$$\boldsymbol{PMI} = \frac{Total\ mass\ in\ process\ [g]}{Product\ [g]} = \frac{g\ \mathbf{1a} + g\ DHP + g\ NADES + g\ H_2O + g\ CPME}{g\ \mathbf{2a}}$$

$$= \frac{2.70 + 3.15\ g + 10.0\ g + 25.0\ g + \ 25.9\ g}{4.2\ g} = \mathbf{15.8}$$

Total mass in process [g]:

- ***g 1a***: **2.70 g** of benzyl alcohol **1a** used over the ten reaction cycles (25.0 mmol, 2.7 g per cycle).
- ***g DHP***: **3.15 g** of DHP used over the ten reaction cycles (37.5 mmol, 3.15 g per cycle).
- ***g NADES***: **10.0 g** of ChCl/malonic acid (1:1 mol/mol) were used as solvent and promoter for the reaction.
- ***g H_2O***: **25.0 g** of H_2O were employed for dissolving the NADES at the end of the reaction.
- ***g CPME***: 3 x 10 mL of CPME (d: 0.863 g/mL) were employed for the liquid-liquid extraction at the end of the reaction. 30 mL of CPME corresponds to **25.9 g**.

Mass of product [g]:

- ***g 2a***: **4.2 g** of product **2a** obtained.

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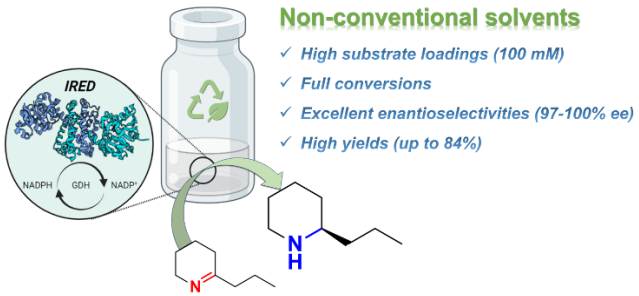
CHAPTER 5: Asymmetric synthesis of chiral cyclic amines from cyclic imines by enantioselective imine reductase (IRED) in non-conventional solvents

Part of the results presented in this chapter have been submitted for publication in a peer-reviewed journal.

The first enantioselective reduction of a number of 2-substituted cyclic imines to the corresponding amines (pyrrolidines, piperidines, and azepines) by imine reductases (IREDs) in non-conventional solvents is discussed. The best results were obtained in a glycerol/phosphate buffer 1:1 mixture, in which heterocyclic amines were produced with full conversions, moderate to high yields (22-84%) and excellent (*S*)-enantioselectivities (97-99 % *ee*). Remarkably, the process can be performed at a 100 mM substrate loading which, for the model compound, means a concentration of 14.5 g/L. This aspect strongly contributes to make the process potentially attractive for large-scale applications in terms of economic and environmental sustainability to a discrete number of substrates to produce enantiopure heterocyclic amines of high pharmaceutical interest.



5.1 Introduction

Biocatalysis is nowadays considered as a *green* and sustainable technology for transformation processes.[1] Water and phosphate buffers have been employed for years as solvents for biocatalysed reactions, however drawbacks related to the low solubility of organic compounds in such media, deeply limit the applications of biocatalysts in organic synthesis. In addition, low substrate (and product) concentrations in biocatalysis largely consume the benefits of water as unproblematic solvent, the increase of the reagent concentration thus represents a major current challenge of biocatalysis to fulfil its *green* promise and to make it an attractive alternative in preparative scale organic synthesis procedures.[2]

An ideal solvent for biotransformation should be non-toxic, biocompatible, biodegradable and sustainable, in addition it needs to support high enzyme activity and stability. Enzymes have also been demonstrated to be active and stable in non-aqueous media.[3] Various methodologies reporting the use of non-conventional media (*i.e.*, ILs, SCFs, organic solvents) for biocatalysed processes have been extensively reviewed.[4] In this research framework, the design of novel and more sustainable protocols is highly desirable and states the emerging interest of the scientific community in this direction.

Since the seminal report by Verpoorte,[5] NADES are well placed to overcome some of the main limitations encountered in the use of "non-natural" solvents. When the compounds that constitute the eutectic mixture are primary metabolites, namely amino acids, organic acids, sugars, or cholinium derivatives, they can provide a cytoplasm-like natural environment, meaning that enzymes can transform unnatural substrates in a natural environment.[5]

Moreover, a notable feature of enzymatic catalysis is represented by the high enantioselectivity outcome of such processes. The induction of chirality from the enzyme to the product of the reaction occurs owing to the spatial arrangement of the functional groups in the active site, which is strictly related to the conformation adopted by the protein. Since such conformations are affected by the interaction with the solvent, it is quite likely that the enantiomeric excess of a biocatalytic reaction could be altered, either in a positive or negative way, by changing the environment from "classic" conditions, such as aqueous medium (phosphate buffer), to a more structured DES-like system. The use of NADESs for an enzyme-catalysed reaction could be then considered as a chance to perform the reaction in an environment similar to intra- or extracellular physiological conditions.

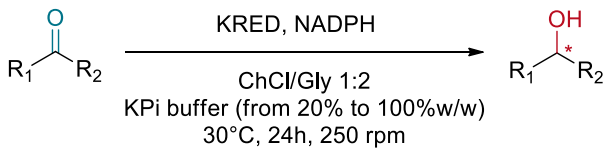
Due to the growing interest in biocatalytic reactions run in DES, exhaustive reviews covering this topic have recently emerged in the literature.[4, 6]

The first report on the use of DES in the presence of an enzyme was the work of Kazlauskas and co-workers in 2008.[7] Since then, several protocols have been developed for biotrasformations catalysed by both isolated enzymes and whole cells in DESs and DES-buffer mixtures.[6a, 6d, 6e], 7 Many enzymes have been used in DESs, such as lypases,[8] proteases,[9] epoxide hydrolases,[10] lyases,[11] oxidoreductases.[6b]

Redox reactions are performed by three main categories of enzymes: oxygenases, oxidases and reductases (*i.e.*, dehydrogenases). Among them, carbonyl reductases (alcohol dehydrogenases) have been widely used for the reduction of carbonyl groups (aldehydes and ketones).[4] In general, redox enzymes

require co-factors that are essentially co-substrates: they donate or accept the chemical equivalents for reduction/oxidation emerging from the enzymatic reaction in an altered form. In enzyme-catalysed synthesis and due to their high cost, co-factors must either be used in stoichiometric amounts or, preferably, be regenerated *in situ* by a separate reaction.[12] The most common cofactors are usually nicotinamide adenine dinucleotide (phosphate) [NAD(P)H] and, less frequently, riboflavin-5′-phosphate (FMN), flavin adenine dinucleotide (FAD) and pyrroloquinoline quinone (PQQ).[13] Instead, in whole cells catalysis, the regeneration of redox cofactors is governed by cellular metabolism. For this reason, biocatalysis by means of whole-cells is rapidly growing and widespread for redox reactions. Unfortunately, whole-cell systems have some drawbacks, for example, product toxicity towards the cells, byproducts formation, poor substrate uptake rates and troublesome products isolation.[14]

To the best of our knowledge, the use of DESs in bioreduction processes with isolated enzymes has been limited to ketoreductases (KREDs).[15] Capriati *et al*. reported in 2018 the first application of purified ketoreductases (KREDs) in the asymmetric bioreduction of ketones to secondary alcohols using DESs (Scheme 5.1).[16] In DES-buffer mixtures, the performance of the biocatalyst was enhanced as the increase in DES concentration led to higher enantiomeric excesses of the resulting secondary alcohols. The best results in terms of conversion (>99%) and *ee* (>99%) were obtained using ChCl/Gly 1:2 or ChCl/sorbitol 1:1 and phosphate buffer (DES content ranging from 50% to 20% w/w). Finally, the authors propose the combination of a metal-catalysed isomerization reaction of allylic alcohols with the previously described enantioselective bioreduction in aqueous buffer eutectic mixtures both in a sequential and in a concurrent strategy, thus describing the first example of a one-pot chemoenzymatic cascade.



R_1, R_2 = Ph, Et; *p*-Tol, Et; *p*-Anisole, Et; *p*-BrPh, Et; -EtPh, Me; 1-Nap, Et.

Scheme 5.1. KREDs asymmetric bioreduction of ketones using DESs aqueous buffer mixtures.[16]

Building on our interest in both biocatalysis[17] and use of DESs,[18] we decided to test DESs as solvents and cosolvents for biotransformations catalysed by an emergent class of NADPH-dependent enzymes, i.e. imine reductases (IREDs).[19]

This family of oxidoreductases was discovered in 2010 by Mitsukura and co-workers,[20] and has attracted growing attention because provides a promising biocatalytic approach to obtain primary, secondary and tertiary chiral amines, which are key intermediates in the synthesis of several biologically active compounds (Figure 5.1).[21]

Despite asymmetric reduction of imines represents a significant challenge for enzymatic reductions due to the aqueous lability of C=N bond, IREDs have shown great potential for the biocatalytic asymmetric reduction of cyclic and linear imines as well as reductive amination reactions.[22] The development of the optimal conditions for using this class of enzymes in non-conventional solvents at elevate substrate concentration up to 100 mM, in particular using cyclic imines as substrates is herein presented as the first successful asymmetric bioreduction of such imines by commercial isolated imine reductases (IREDs) in non-conventional media.

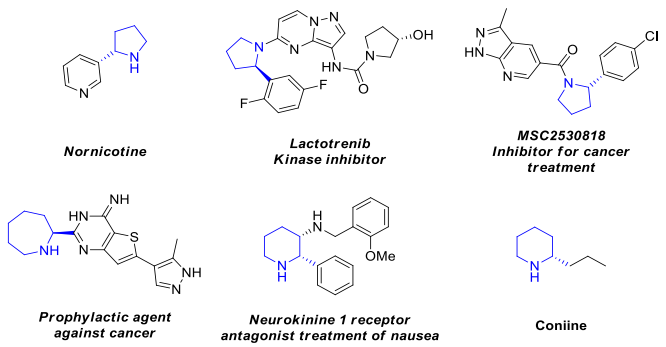


Figure 5.1. Natural and synthetic compounds showing chiral pyrrolidine and piperidine structural cores.

5.2 Optimization of the reaction conditions

We began our investigation by selecting 5-phenyl-3,4-dihydro-2*H*-pyrrole **1a** (Figure 5.2) as model imine substrate, which is increasingly used as key chiral intermediate for the synthesis of potential drugs,[23] such as selective KV1.5 blocker BMS394136[24] and *k*-opioid receptor antagonist LY2456302.[25] It is therefore not surprising that some efforts have already been devoted to the development of procedures employing IREDs for the reduction of these imines.[26]Turner and co-workers widely reported on the asymmetric reduction of cyclic imines with IREDs,[26b, 27] including a chemoenzymatic alkylation of tetrahydroquinolines.[28]

Using the procedure developed by Turner and co-workers,[29] we first carried out an initial screening of the commercial Johnson&Matthey IRED collection for the reduction of imine **1a** in potassium phosphate buffer. The mechanism of the IRED-catalyzed reduction implies the combined use of glucose dehydrogenase from

Bacillus subtilis (GDH) and α-D-glucose as a cofactor recycling system, as NADPH is consumed with the formation of $NADP^+$ in the IRED-catalyzed step; subsequent GDH-regeneration of NADPH leads to the formation of D-gluconolactone. In order to identify the most appropriate enzymes to be subsequently used in the optimization of the reaction conditions, we first evaluated the activity of the commercial IREDs in terms of consumption of NADPH in the reduction of the model substrate **1a** in phosphate buffer (PB, Figure 5.2).

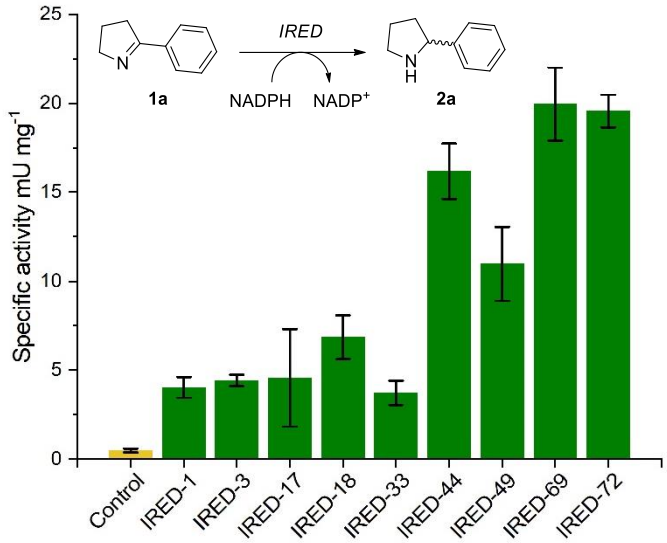
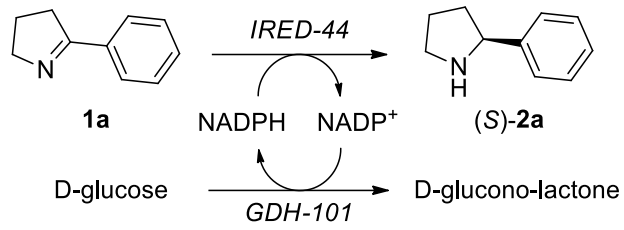


Figure 5.2. Johnson-Matthey IREDs specific activity (mU mg^{-1}) with substrate **1a**. Reaction conditions: 30 °C, substrate **1a** (0.5 mM) and NADPH (0.1 mM) in PB (100 mM, pH 8). "Control" performed without enzyme. Data calculated on three replicates per analysis.

As reported in Figure 5.2, enzymes IRED-44, -69 and -72 catalysed the reduction of imine **1a** to corresponding amine (*S*)-**2a**[27] with significant activity. These enzymes were thus selected for further investigation to explore the viability of non-conventional media as solvents in the IRED-catalysed bioreduction of prochiral imines.

We started with a eutectic mixture (DES) composed of choline chloride and glycerol, in a 1:2 stoichiometric ratio, and IRED-44 as enzyme. In fact, ChCl/Gly 1:2 mixture has a lower viscosity than other DESs and this allows to work at lower temperatures and with moderate stirring, thus avoiding the inactivation or degradation of the enzyme under harsher conditions. Of further importance is the well-known role of glycerol in the stabilization of proteins.[30]

Table 5.1. Initial study for the asymmetric reduction in non-conventional media.[a]



Entry	[1a] (mM)	Solvent	Recov. 1a (%)[b]	2a Yield (%)[b]	*ee* (%,*R*/*S*)[c,d]
1	5	PB	0	68	>99, *S*
2	100	PB	64	0	/
3	5	ChCl/Gly 1:2	74	0	/
4	100	ChCl/Gly 1:2	48	0	/
5	5	50% PB + 50% DES	77	0	/
6	100	50% PB + 50% DES	0	62	>99, *S*

[a] Reaction conditions: α-D-glucose (100 mg), NADP (6.4 mg), GDH-101(6 mg), IRED-44 (12 mg), **1a** (0.14 mmol, 20.3 mg, 1/85 mmol of substrate/mg of enzyme) added in DMF (30 µL), stirred (700 rpm) at 30 °C in the selected solvent system [phosphate buffer (PB): potassium phosphate buffer (100 mM, pH 8), 28 mL at 5 mM, 1.4 mL at 100 mM] for 16 h. [b] Determined by quantitative ^{1}H NMR analysis. [c] % *ee* values determined by Chiral-HPLC (see Experimental section). [d] Absolute configuration determined by α_D values measurements at 25 °C.

We first evaluated the behaviour of IRED-44 in phosphate buffer at 5 and 100 mM concentrations of **1a**, respectively (entries 1 and 2, Table 5.1). As shown in Table 5.1, at 5 mM IRED-44 led to the reduced amine **2a** in 68% yield, while at 100 mM the reaction was ineffective, and we recovered only starting material **1a**.

In further experiments (entries 3-4) we investigated the effect of pure DES as reaction medium. Imine **1a** was incubated with IRED-44 in DES ChCl/Gly 1:2 at 30 °C either at 5 mM or 100 mM concentration, and in both cases, we were not able to recover the reduced amine **2a**.

We therefore decided to use a DES percentage of 50% (v/v in PB), which corresponds also to the best relative amount of DESs to perform the KRED-catalysed reduction in DES.[16] Remarkably, the reaction did not take place at a 5 mM concentration of substrate (entry 5), but we were pleased to observe instead that at 100 mM of imine concentration, product **2a** was obtained in 62% yield and with >99% *ee* (entry 6).

From these studies it emerges that the best conditions to perform IRED-catalysed bioreductions of prochiral imines in a ChCl/Gly 1:2 DES (50%) + PB (50%) mixture is to work at a final imine concentration equal to 100 mM.

Comparing these results with those obtained in PB only, the most remarkable outcome consists in the possibility of working at higher concentrations, with consequent reduction of solvent volumes.

Gratified for the results obtained, we continued our investigation by carrying out the optimization of the IRED-catalysed bioreduction in DES-buffer mixture using IRED-44 to see if it was possible to improve these results by properly tuning the reaction conditions [Table 5.2, reference reaction conditions obtained by initial screening (Table 5.1) are reported in entry 1].

In the optimization study, we evaluated several parameters:

i. the role of the solvent components (Table 5.2, entries 2-5);
ii. the amount of enzyme (entries 6-7);
iii. the reaction time (entry 8);
iv. the role of cofactors (entries 9-11);
v. other DESs and organic solvents (entries 12-18).

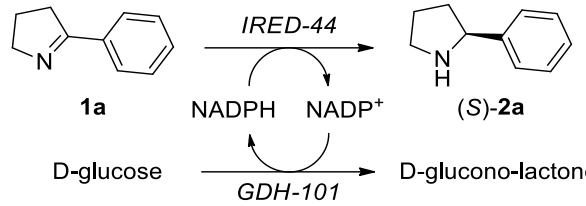
The first step was to evaluate the role of each single component of DES. To this end, we performed the reaction in PB and choline chloride only (entry 2), in PB and glycerol (entry 3), and in PB plus choline chloride and glycerol added independently one after the other (entry 4). As shown in Table 5.2, the PB and ChCl (entry 2) mixture was ineffective while using PB and glycerol (entry 3) we obtained slightly better results in terms of conversion and % *ee* than with DES (entry 1), and for this reason we decided to continue our investigation in PB/glycerol 50/50.[31]

We then evaluated the optimal amount of enzyme. Using a 1/40 $mmol_{substrate}/mg_{enzyme}$ ratio (entry 6), we observed a drop of the yield to 15%, while with a 1/20 ratio no conversion of the substrate was detected (entry 7). From these studies it emerges that the best conditions to perform IRED-catalysed bioreductions of prochiral imines is to use a $mmol_{substrate}/mg_{enzyme}$ ratio equal to 1/85.

We then optimized the reaction time. By monitoring the reaction, we found that after 4 hours (entry 8) a higher yield (70%) was reached. We thus decided to proceed with the optimization study keeping 4 h as the standard reaction time.

To complete this optimization study, the role of the redox system components was also examined. As expected, the absence of either the IRED enzyme itself (entry 9), $NADP^+$ (entry 10), or GDH (entry 11) prevented the reduction to occur.

Table 5.2. Enzymatic reduction of **1a** under different reaction conditions.[a]



Entry	Solvent (% v/v)[b]	*IRED* (mg)	NADP (mg)	GDH (mg)	α-D-glucose (mg)	1a (mmol)/ *IRED* (mg)	t [h]	1a (%)[c]	2a Yield (%)[c]	*% ee* (*R*/*S*)[d,e]
1	PB/(ChCl/Gly 1:2) 50/50	12.0	6.4	6.0	100	1/85	16	0	62	>99, *S*
				DES components						
2	PB/ChCl 50/50	12.0	6.4	6.0	100	1/85	16	67	6	-
3	PB/Gly 50/50	12.0	6.4	6.0	100	1/85	16	0	68	>99, *S*
4	PB/(ChCl + Gly 1/2) 50/50	12.0	6.4	6.0	100	1/85	16	0	61	>99, *S*
5	Gly	12.0	6.4	6.0	100	1/85	16	0	0	-
				1a (mmol)/IRED (mg)						
6	PB/Gly 50/50	5.6	2.9	2.8	46.7	1/40	16	43	15	-
7	PB/Gly 50/50	2.8	1.5	1.4	23.2	1/20	16	78	0	-
				Time						
8	PB/Gly 50/50	12.0	6.4	6.0	100	1/85	4	0	70	>99, *S*
				Control						
9	PB/Gly 50/50	-	6.4	6.0	100	1/85	4	70	0	-
10	PB/Gly 50/50	12.0	-	6.0	100	1/85	4	75	10	-
11	PB/Gly 50/50	12.0	6.4	-	100	1/85	4	81	0	-
				Solvents						
12	PB/(ChCl/urea 1:2) 50/50	12.0	6.4	6.0	100	1/85	16	33	38	>99, *S*
13	PB/(ChCl/H_2O 1:2) 50/50	12.0	6.4	6.0	100	1/85	16	0	44	>99, *S*
14	PB/(ChCl/D-glucose 2:1) 50/50	12.0	6.4	6.0	0	1/85	16	0	57	>99, *S*
15	PB/(TBABr/Gly 1:2) 50/50	12.0	6.4	6.0	100	1/85	16	75	0	-
16	PB/(ChCl/D-fructose 2:1) 50/50	12.0	6.4	6.0	100	1/85	16	2	18	-
17	PB/CPME 50/50	12.0	6.4	6.0	100	1/85	16	57	9	-
18	CPME	12.0	6.4	6.0	100	1/85	16	74	0	-

[a] Reaction conditions: α-D-glucose, $NADP^+$, GDH-101 and IRED-44 (selected amounts), **1a** (0.14 mmol, 20.3 mg) added in DMF (30 µL), stirred (700 rpm) at 30 °C in the selected solvent system (PB: potassium phosphate buffer 100 mM, pH 8) for the selected time. [b] 1.4 mL total. [c] Determined by quantitative ^1H NMR analysis. [d] % *ee* values determined by Chiral-HPLC (see Experimental Section). [e] Absolute configuration determined by α_D values measurements at 25 °C.

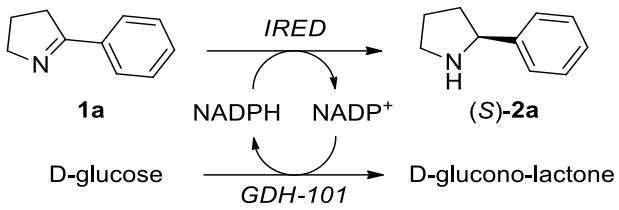
Other PB/DES 1:1 mixtures (entries 12-16) provided lower yields of amine **2a**, although when ChCl/D-glucose 2:1 was used as DES (entry 14), the addition of α-D-glucose as ingredient of the redox cycle can be avoided (57% yield, >99% *ee*). The *green* ethereal solvent CPME[32] is unsuitable to realize the bioreduction either in combination with PB (entry 17) and as pure solvent (entry 18). This is probably due to enzyme denaturation or inhibition in such hydrophobic media through unfavorable conformational changes in the protein secondary structure.

Additionally, a dedicated protocol was optimized in terms of work-up procedures. As illustrated in detail in the Experimental section, the optimized work-up allowed for an efficient recovery of product **2a** avoiding gelification issues which occurred after the basic quench of the enzymatic system.

5.3 IRED screening

In light of the new optimized reaction conditions (Table 5.2, entry 8) we re-evaluated the performance of the commercial IREDs (on substrate **1a**) with the optimized media and parameters (Table 5.3). As shown in Table 5.3, IRED-17, -69 and -72 gave good results in terms of yield, while IRED-44 (entry 6) confirmed its excellent performance with the highest yield (70%) and >99% *ee* (*S*-enantioselectivity).

Table 5.3. IRED screening for enzymatic reduction of **1a** in PB/Gly 50/50 v/v.[a]

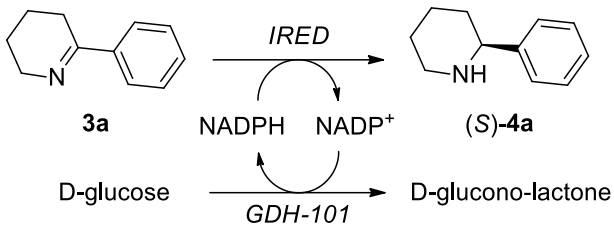


Entry	*IRED*	Recov. 1a (%)[b]	2a (Yield, %)[b]	*ee* (%, *R*/*S*)[c,d]
1	IRED-1	64	0	-
2	IRED-3	64	0	-
3	IRED-17	0	52	>99, *S*
4	IRED-18	53	0	-
5	IRED-33	64	16	-
6	IRED-44	0	70	>99, *S*
7	IRED-49	30	0	-
8	IRED-69	0	53	>99, *S*
9	IRED-72	0	57	>99, *S*

[a] Reaction conditions: α-D-glucose (100 mg), NADP (6.4 mg), GDH-101 (6.0 mg) and selected IRED (12.0 mg), **1a** (0.14 mmol, 20.3 mg) added in DMF (30 µL), stirred (700 rpm) at 30 °C in PB/Gly 50/50 1.4 mL (PB: potassium phosphate buffer 100 mM, pH 8), 4h. [b] Determined by quantitative ^{1}H NMR analysis. [c] % *ee* values determined by Chiral-HPLC analysis (See Experimental section). [d] Absolute configuration determined by α_D values measurements at 25 °C.

To demonstrate the scope of imine reduction by IRED in phosphate buffer/glycerol solvent, the IRED-catalysed reduction was applied to the reduction of a panel of cyclic imines, including six- and seven-membered ring substrates.[33] To this purpose, we firstly carried out a screening of the IRED collection for the reduction of 6-phenyl-2,3,4,5-tetrahydropyridine **3a** as a model compound for six-membered rings. As reported in Table 5.4, IRED-1, -17, -18, -33, -44, -49, -69 and -72 promoted the reduction of imine **3a** with satisfactory conversion and enantioselectivity. Among the IREDs active on substrate **3a**, we decided to continue our investigation on the scope selecting IRED-72 which gave the best results in terms of % *ee* (Table 5.4, entry 9).

Table 5.4. IRED screening for enzymatic reduction of **3a** in PB/Gly 50/50 v/v.[a]

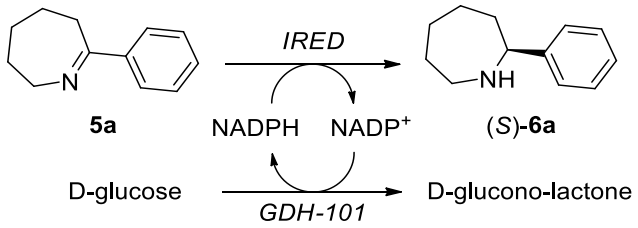


Entry	*IRED*	Recov. 3a (%)[b]	4a (Yield, %)[b]	*ee* (%, *R*/*S*)[c,d]
1	IRED-1	52	15	-
2	IRED-3	61	0	-
3	IRED-17	0	67	89, *S*
4	IRED-18	22	22	-
5	IRED-33	36	13	-
6	IRED-44	2	43	90, *S*
7	IRED-49	0	27	-
8	IRED-69	0	55	94, *S*
9	IRED-72	0	53	97, *S*

[a] Reaction conditions: α-D-glucose (100 mg), NADP (6.4 mg), GDH-101 (6.0 mg) and selected IRED (12.0 mg), **3a** (0.14 mmol, 22.2 mg) added in DMF (30 µL), stirred (700 rpm) at 30 °C in PB/Gly 50/50 1.4 mL (PB: potassium phosphate buffer 100 mM, pH 8), 4h. [b] Determined by quantitative ^{1}H NMR analysis. [c] % *ee* values determined by Chiral-HPLC analysis (See Experimental section). [d] Absolute configuration determined by α_D values measurements at 25 °C.

The same investigation was carried out for seven-membered imine 7-phenyl-3,4,5,6-tetrahydro-2*H*-azepine **5a,** as reported in Table 5.5. In this case, only IRED-44, -69 and 72 afforded good conversion (and excellent enantioselectivity) into expected amine **6a**.

Table 5.5. IRED screening for enzymatic reduction of **5a** in PB/Gly 50/50 v/v.[a]



Entry	*IRED*	Recov. 5a (%)[b]	6a (Yield, %)[b]	*ee* (%, *R*/*S*)[c,d]
1	IRED-1	41	18	-
2	IRED-3	38	0	-
3	IRED-17	39	0	-
4	IRED-18	35	0	-
5	IRED-33	46	6	-
6	IRED-44	10	50	>99, *S*
7	IRED-49	42	0	-
8	IRED-69	5	60	>99, *S*
9	IRED-72	10	74	>99, *S*

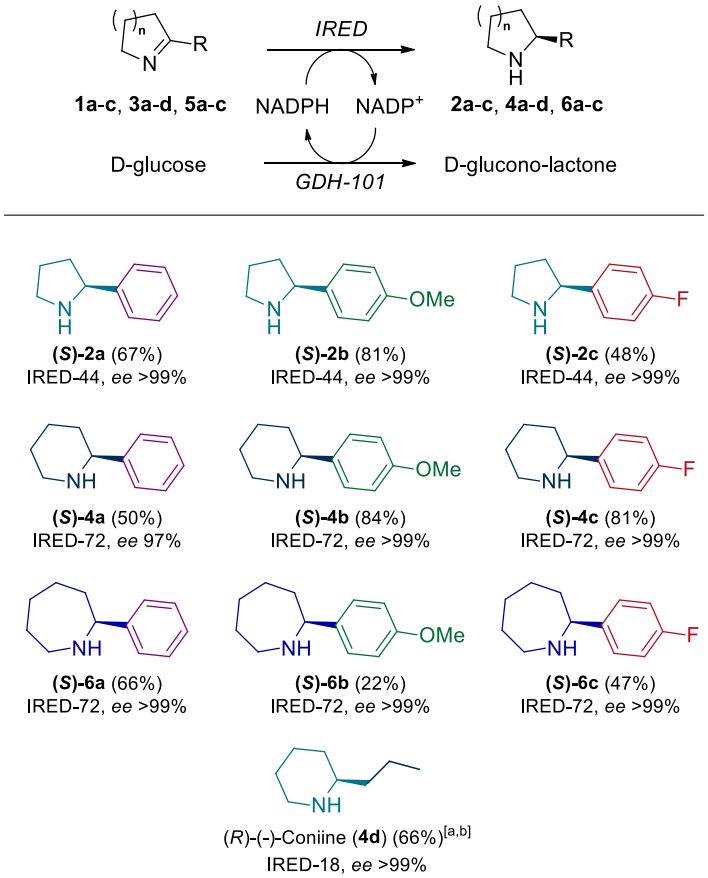
[a] Reaction conditions: α-D-glucose (100 mg), NADP (6.4 mg), GDH-101 (6.0 mg) and selected IRED (12.0 mg), **5a** (0.14 mmol, 24.7 mg) added in DMF (30 μL), stirred (700 rpm) at 30 °C in PB/Gly 50/50 1.4 mL (PB: potassium phosphate buffer 100 mM, pH 8), 4h. [b] Determined by quantitative ^{1}H NMR analysis. [c] % *ee* values determined by Chiral-HPLC analysis (See Experimental section). [d] Absolute configuration determined by α_D values measurements at 25 °C.

5.4 Scope of the reaction

We finally evaluated the scope of the reaction on different imines (Scheme 5.2). Based on the results obtained with imine **1a** reported above, we selected IRED-44 to catalyse the asymmetric reduction of 2-aryl-substituted-pyrrolines (**1a-c**, Scheme 5.2). To promote the asymmetric reduction of 2-aryl-substituted-pyridines **3a-d**, based on the results we obtained on imine **3a** (entry 9, Table 5.4), we selected IRED-72 which gave the (*S*)-amine with excellent enantiomeric excess. IRED-72 was also selected (entry 9, Table 5.5) to reduce seven-membered imines **5a-c**. Good yields and excellent enantioselectivities were obtained for azepines **6a** and **6c**, while **6b** was recovered only in moderate yield.

Remarkably, the methodology worked finely also with 2-alkyl pyrrolidines. The procedure was indeed successfully applied to 6-propyl-2,3,4,5-

tetrahydropyridine **3d** for the enantioselective synthesis of the piperidine alkaloid (*R*)-(-)-Coniine. In this case, upon a quick screening, IRED-18 turned out to be the most effective biocatalyst. This is in line with the results reported by Turner on the reduction of 2-alkylpiperidines with (*R*)-IRED[34] which shares a 70.9% sequence similarity to the IRED-18.[22b] Indeed, the reduction conducted with IRED-18 in glycerol successfully led to (*R*)-(-)-Coniine (**4d**, Scheme 5.2) in 66% yield and complete (*R*)-enantioselectivity. Remarkably, a study on the relative potencies of the two enantiomers of coniine on cells expressing human fetal nicotinic neuromuscular receptors demonstrated a higher activity for the same enantiomer (*R*)-(-)-Coniine.[35]



Scheme 5.2. Reaction scope. Yields refer to the isolated product. Conditions: α-D-glucose (100 mg), NADP (6.4 mg), GDH-101 (6.0 mg) and selected IRED (12.0 mg), substrate (0.14 mmol) added in DMF (30 µL), stirred (700 rpm) at 30 °C in PB/Gly 50/50 1.4 mL, 4 h. % *ee* values determined by Chiral-HPLC analysis. Absolute configuration determined by α_D values measurements at 25 °C. [a] Reaction was performed over 16 h. [b] Chiral-HPLC analyses were performed after derivatization with TsCl.

5.5 Conclusions

We have successfully developed the first enantioselective conversion of a number of 2-substituted cyclic imines to the corresponding amines (pyrrolidines, piperidines, and azepines) through reduction promoted by IREDs in glycerol/phosphate buffer mixture. Glycerol belongs to biomass-derived solvents, which are emerging as *greener* alternatives to volatile organic compounds (VOCs) in organic synthesis. Obtained as a major by-product of the biodiesel industry, glycerol is a particularly appealing *green* solvent, with low cost and renewable feedstock. The methodology herein proposed, allows to access heterocyclic amines with full conversions, good yields and excellent enantioselectivities. It is worth to remark that the process can be performed at 100 mM substrate loading which, specifically for **1a**, means a concentration of 14.5 g/L. This aspect strongly contributes to make the process potentially attractive for large scale applications in the framework of economic and environmental sustainability to a discrete number of substrates which allows for the obtaining of enantiopure heterocyclic amines of high pharmaceutical interest.

5.6 Experimental Section

5.6.1 Experimantal details

Materials and methods. Flasks and all equipment used for the generation and reaction of moisture-sensitive compounds were dried by an electric heat gun under nitrogen. Unless specified, all reagents were used as received without further purifications. IRED biocatalysts, $NADP^+$ co-factor and GDH-101 were purchased from Johnson-Matthey (Chiral amines kit EZK004). Reactions were monitored by GC-MS analysis or by thin-layer chromatography (TLC) carried out on 0.25 mm silica gel-coated aluminum plates (60 Merck F254) with UV light (254 nm) as visualizing agent. R_f values refer to TLC carried out on silica gel plates. Chromatographic separations were carried out under pressure on silica gel (40-63 μm, 230-400 mesh) using flash-column techniques. Substrates **1a-c**, **3a-d**, **5a-c**, were synthesized according to the procedures reported in the literature.[36] *Deep Eutectic Solvents* [choline chloride (ChCl)/urea (1:2 mol/mol); ChCl/glycerol (Gly) (1:2 mol/mol); ChCl/H_2O (1:2 mol/mol); ChCl/D-fructose (2:1 mol/mol); ChCl/α-D-glucose (2:1 mol/mol); tetrabutylammonium bromide (TBABr)/Gly (1:2 mol/mol)] were prepared by heating under stirring at 50−80 °C for 15−30 min the corresponding individual components until a clear solution was obtained.[37] Full characterization data, including copies of ^{1}H NMR, $^{13}C\{^1H\}$ NMR spectra and Chiral-HPLC analyses have been reported for the synthesized compounds. Nitromethane was used as internal standard for quantitative NMR analyses on crude reaction mixtures. For each ^{1}H NMR the amount of product was determined by applying Equation 1:

Equation 1) $$yield\ (\%) = \frac{x\ (product) \cdot n\ (CH_3NO_2)}{n(starting\ material)}\ \cdot\ f\ \cdot\ 100$$

where:

- x is the value of integral/number of protons;
- n is the amount of starting material or CH_3NO_2 in mmol;
- f is the diluting factor used for the preparation of the sample.

Instrumentation. ^{1}H NMR (600 MHz) and $^{13}C\{^1H\}$ (150 MHz) spectra were recorded on a Jeol ECZR600 spectrometer at room temperature using residual solvent peak as an internal reference. Chemical shifts (δ) are given in parts per million (ppm) and coupling constants (J) in Hertz (Hz). Multiplicities are reported as follows: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br (broad). UV spectra to determine IREDs activity in PB were recorded on a SPECTROstar Nano (BMG Labtech) UV-Vis spectrophotometer at 340 nm. Chiral-HPLC analyses were performed on a Waters 1500 chromatographic system (Waters, Milford, MA, USA) equipped with a manual injector (Rheodyne, Cotati, CA, USA), a binary pump (model 1525), a diode-array detector (DAD, model 2998) integrated into the Waters system. The injection volume was 20 μL. Analyses were performed on a Daicel CHIRALPAK® IC column (250 x 4.6 mm ID, 5 μM) using heptane/IPA mobile phase mixtures buffered with Et_2NH, 1 mL/min flow rate. The column effluent was monitored at 265 nm, referenced against a 700 nm wavelength. The data were processed using a Breeze software package (Waters). Melting points were determined on a Stuart Scientific SMP3 melting point

apparatus. Polarimetric analysis were performed on a Jasco P-2000 polarimeter to determine α_D values at 25 °C.

5.6.2 Spectrophotometric activity assay for IRED activity in phosphate buffer

General procedure. IREDs enzymatic activity (Figure S1) was assessed via spectrophotometric assay in 96-wells plates (200 µL). Phosphate buffer 100 mM, pH 8 (PB). The reactions were carried out at 30 ºC. For each well, 180 µL of **1a** solution (**1a** 0.5 mM in PB + 1.0 % EtOH as co-solvent), NADPH solution (0.1 mM in PB) and 20 µL of IRED solution (6 mg/mL in PB) were added in this order. Then the consumption of NADPH was monitored via UV-Vis. The absorbance values at 340 (ε_{NADPH} = 0.63 mL µmol^{-1} mm^{-1}) nm in the 300 s time window were used to determine activity values according to Equation 2.[38] Activity values were then converted into specific activity (mU mg^{-1}), according to Equation 3.[38] One unit (U) of IRED enzyme activity is defined as the amount of enzyme able to consume 1.0 µmol of NADPH per minute.

Equation 2) $$Activity\ (U\ mL^{-1}) = \frac{\Delta Abs}{\Delta t} \times \frac{V_T}{\varepsilon \times V_E \times d} \times f$$

where:

- *ΔAbs*: difference in absorbance values
- *Δt*: time difference (300 s)
- V_T: total volume of the well (200 µL)
- ε: ε_{NADPH} [NADPH extinction coefficient (0.63 mL µmol^{-1} mm^{-1})]
- V_E: volume of IRED solution (20 µL)
- *d*: optical path (6.62 mm)
- *f*: dilution factor

Equation 3) $$Specific\ activity\ (U\ mg^{-1}) = \frac{Activity\ (U\ mL^{-1})}{Total\ protein\ concentration\ \ (mg\ mL^{-1})}$$

*5.6.3 Enzymatic reduction of **1a** under different reaction conditions*

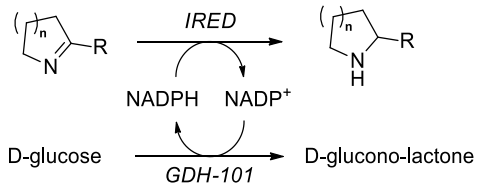
General procedure. All reactions were performed under air. In an open screw cap 7 mL vial α-D-glucose, NADP, GDH-101 and IRED-44 were added consecutively in this order to the selected solvent system. The mixture was allowed to homogenize for 5 minutes at 30 °C. A solution of substrate **1a** (0.14 mmol, 20.3 mg) in 30 µL of DMF was then added to the mixture. The reaction was stirred (700 rpm) at 30 °C for the selected time. 1.5 mL of 1 M NaOH was then added and the mixture shaken vigorously. The mixture was transferred in a 10 mL Erlenmeyer flask and 2 mL of Et_2O added. The heterogeneous mixture was stirred for 5 minutes to let the enzymes to denaturate and gelify. The mixture was then filtered over cotton *in vacuo*. The clear heterogeneous mixture was then transferred to a separating funnel and the acqueous phase extracted two more times with Et_2O (2 mL). The combined organic phases were washed with 1M NaOH (5 mL), dried with Na_2SO_4 and the solvent removed under reduced pressure. Yields of product **2a** and recovered starting material **1a** (Table 5.1 and 5.2) were determined by quantitative ^{1}H NMR analysis of the crude reaction mixtures using nitromethane (0.056 mmol, 3 µL) as internal standard and a diluting factor f = 1 for the preparation of the sample. Samples of **1a** and **2a** were synthesized according to the procedure reported in the literature[27] and used as references for qNMR analyses. If the reaction showed appropriate conversion and yield, crude **2a** was purified by flash column chromatography (Et_2O/Et_3N 98/2 v/v, R_f = 0.25) and enantiomeric excesses (% *ee*) were determined by Chiral-HPLC analysis. Racemic **2a** (for identification of *R* and *S* enantiomers retention times) was prepared according to the procedures reported in the literature.[27] Polarimetric analysis was performed to determine α_D values at 25 °C.

*5.6.4 IRED screening for enzymatic reduction of **1a**, **3a** and **5a** in PB/Gly 50/50 v/v*

General procedure. All reactions were performed under air. In an open screw cap 7 mL vial α-D-glucose (100 mg), NADP (6.4 mg), GDH-101 (6.0 mg) and the selected IRED (12.0 mg) were added consecutively in this order to PB/Gly 50/50 v/v (1.4 mL). The mixture was allowed to homogenize for 5 minutes at 30 °C. A solution of substrate **1a**, **3a** or **5a** (0.14 mmol) in 30 µL of DMF was then added to the mixture. The reaction was stirred (700 rpm) at 30 °C for 4 hours. 1.5 mL of 1 M NaOH was then added and the mixture shaken vigorously. The mixture was transferred in a 10 mL Erlenmeyer flask and 2 mL of Et_2O added. The heterogeneous mixture is stirred for 5 minutes to let the enzymes to denaturate and gelify. The mixture was then filtered over cotton *in vacuo*. The clear heterogeneous mixture was then transferred to a separating funnel and the acqueous phase extracted two more times with Et_2O (2 mL). The combined organic phases were washed with 1M NaOH (5 mL), dried with Na_2SO_4 and the solvent removed under reduced pressure. Yields of products **2a** (Table 5.3), **4a** (Table 5.4) or **6a** (Table 5.5) and recovered starting material **1a**, **3a** or **5a** were determined by quantitative ^1H NMR analysis of the crude reaction mixtures using nitromethane (0.056 mmol, 3 µL) as internal standard and a diluting factor $f = 1$ for the preparation of the sample. Samples of **1a**, **3a**, **5a** and **2a**, **4a**, **6a** were synthesized according to the procedure reported in the literature[27] and used as references for qNMR analyses. If the reaction showed appropriate conversion and yield, crude **2a**, **4a** or **6a** were purified by flash column chromatography and enantiomeric excesses (% *ee*) were determined by Chiral-HPLC analysis. Racemic **2a**, **4a** and **6a** (for identification of *R* and *S* enantiomers retention times) were prepared according to the procedures reported in the literature.[27] Polarimetric analyses were performed to determine α_D values at 25 °C.

*5.6.5 Synthesis and analysis of compounds **2a-c, 4a-d, 6a-c***

General procedure. All reactions were performed under air. In an open screw cap 7 mL vial α-D-glucose (100 mg), NADP (6.4 mg), GDH-101 (6.0 mg) and the selected IRED (12.0 mg) were added consecutively in this order to PB/Gly 50/50 v/v (1.4 mL). The mixture was allowed to homogenize for 5 minutes at 30 °C. A solution of substrate (0.14 mmol, see Scheme 5.2) in 30 µL of DMF was then added to the mixture. The reaction was stirred (700 rpm) at 30 °C for 4 hours. 1.5 mL of 1 M NaOH was then added and the mixture shaken vigorously. The mixture was transferred in a 10 mL Erlenmeyer flask and 2 mL of Et_2O added. The heterogeneous mixture is stirred for 5 minutes to let the enzymes to denaturate and gelify. The mixture was then filtered over cotton *in vacuo*. The clear heterogeneous mixture was then transferred to a separating funnel and the acqueous phase extracted two more times with Et_2O (2 mL). The combined organic phases were washed with 1M NaOH (5 mL), dried with Na_2SO_4 and the solvent removed under reduced pressure. Crude products were purified by flash column chromatography, characterised by NMR spectroscopy and enantiomeric excesses (% *ee*) were determined by Chiral-HPLC analysis. Yields refer to isolated products (Scheme 5.2). Racemic **2a**-**c**, **4a**-**c**, **6a**-**c** (for identification of *R* and *S* enantiomers retention times) were prepared according to the procedures reported in the literature.[27] Racemic and purified **4d** (Scheme 5.2), were derivatized with TsCl according to the procedures reported in the literature,[39] which were then analysed *via* Chiral-HPLC. Polarimetric analyses were performed to determine α_D values at 25 °C.



(*S*)-2-Phenylpyrrolidine (2a): general procedure with IRED-44 starting from **1a**. Purification by flash column chromatography (PE/Et_3N 98/2 v/v) gave **2a** as a colorless oil (13.8 mg, 67%, R_f = 0.16 PE/Et_3N 98/2 v/v). % *ee*: >99. $[\alpha]_{25}^{D}$: - 35.3 (c = 0.4, $CHCl_3$). **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.38-7.34 (m, 2H), 7.33-7.29 (m, 2H), 7.25-7.21 (m, 1H), 4.12 (t, *J* = 8.0 Hz, 1H), 3.21 (ddd, *J* = 10.2, 7.8, 5.3 Hz, 1H), 3.02 (ddd, *J* = 10.2, 8.4, 6.6 Hz, 1H), 2.24-2.16 (m, 1H) superimposed to 2.16 (br s, 1H), 1.98-1.81 (m, 2H), 1.73-1.64 (m, 1H). **^{13}C{^{1}H} NMR** (150 MHz, $CDCl_3$): δ 144.7, 128.5, 127.0, 126.7, 62.8, 47.1, 34.4, 25.7.[1]

(*S*)-2-(4-Methoxyphenyl)pyrrolidine (2b): general procedure with IRED-44 starting from **1b**. Purification by flash column chromatography (EtOAc/MeOH 9/1 v/v + 1.0 % Et_3N) gave **2b** as a yellow oil (20.1 mg, 81%, R_f = 0.1 EtOAc/MeOH 9/1 v/v + 1% Et_3N). % *ee*: >99. $[\alpha]_{25}^{D}$: - 12.8 (c = 0.5, CH_2Cl_2). **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.29 (d, *J* = 8.6 Hz, 2H), 6.86 (d, *J* = 8.7 Hz, 2H), 4.07 (t, *J* = 7.8 Hz, 1H), 3.79 (s, 3H), 3.19 (ddd, *J* = 10.3, 7.9, 5.3 Hz, 1H), 3.02-2.94 (m, 1H), 2.44 (br s, 1H), 2.19-2.11 (m, 1H), 1.97-1.80 (m, 2H), 1.70-1.62 (m, 1H). **^{13}C{^{1}H} NMR** (150 MHz, $CDCl_3$): δ 158.6, 136.9, 127.7, 113.9, 62.3, 55.4, 47.0, 34.4, 25.7.[1]

(*S*)-2-(4-Fluorophenyl)pyrrolidine (2c): general procedure with IRED-44 starting from **1c**. Purification by flash column chromatography (EtOAc/MeOH 9/1 v/v + 1.0 % Et_3N) gave **2c** as a yellow oil (11.1 mg, 48%, R_f = 0.25 EtOAc/MeOH 9/1 v/v + 1% Et_3N). % *ee*: >99. $[\alpha]_{25}^{D}$: - 47.9 (c = 0.5, CH_2Cl_2). **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.32 (dd, *J* = 8.5, 5.6 Hz, 2H), 6.99 (t, *J* = 8.7 Hz, 2H), 4.09 (t, *J* = 7.7 Hz, 1H), 3.19 (ddd, *J* = 10.2, 7.8, 5.1 Hz, 1H), 3.01 (ddd, *J* = 10.1, 8.4, 6.7 Hz, 1H), 2.21-2.11 (m, 1H), 1.97-1.76 (m, 3H), 1.66-1.57 (m, 1H). **^{13}C{^{1}H} NMR** (150 MHz, $CDCl_3$): δ 161.9 (d, *J* = 244.3 Hz, 1C), 140.6, 128.1 (d, *J* = 7.8 Hz, 1C), 115.2 (d, *J* = 21.1 Hz, 1C), 62.0, 47.0, 34.6, 25.6. **^{19}F{^{1}H} NMR** (564 MHz, $CDCl_3$): δ -116.4 (s, 1F).[1]

(*S*)-2-Phenylpiperidine (4a): general procedure with IRED-72 starting from **3a**. Purification by flash column chromatography (Et_2O/Et_3N 99/1 v/v) gave **4a** as a yellow oil (11.3 mg, 50%, R_f = 0.1 Et_2O/Et_3N 99/1 v/v). % *ee*: 97. $[\alpha]_{25}^{D}$: - 33.1 (c = 0.5, CH_2Cl_2). **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.37 (d, *J* = 6.6 Hz, 2H), 7.33-7.29 (m, 2H), 7.25-7.21 (m, 1H), 3.62-3.55 (m, 1H), 3.19 (d, *J* = 11.3 Hz, 1H), 2.80 (td, *J* = 11.6, 2.7 Hz, 1H), 1.93 (br s, 1H) superimposed to 1.91-1.87 (m, 1H), 1.82-1.77 (m, 1H), 1.69-1.61 (m, 1H), 1.60-1.45 (m, 3H). **^{13}C{^{1}H} NMR** (150 MHz, $CDCl_3$): δ 145.5, 128.5, 127.2, 126.8, 62.5, 47.9, 35.0, 26.0, 25.5.[1]

(*S*)-2-(4-Methoxyphenyl)piperidine (4b): general procedure with IRED-72 starting from **3b**. Purification by flash column chromatography (EtOAc/MeOH 9/1 v/v + 1.0 % Et_3N) gave **4b** as a yellow oil (22.5 mg, 84%, R_f = 0.25, EtOAc/MeOH 9/1 v/v + 1.0 % Et_3N). % *ee*: >99. $[\alpha]_{25}^{D}$: -45.4 (c = 0.6, $CHCl_3$). **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.28 (d, *J* = 8.2 Hz, 2H), 6.85 (d, *J* = 8.7 Hz, 2H), 3.79 (s, 3H), 3.53 (dd, *J* = 10.7, 2.6 Hz, 1H), 3.21-3.14 (m, 1H), 2.79 (td, *J* = 11.7, 2.7 Hz, 1H), 1.91-1.85 (m, 1H), 1.80-1.69 (m, 2H), 1.67-1.61 (m, 1H), 1.58-1.45 (m, 3H). **^{13}C{^{1}H} NMR** (150 MHz, $CDCl_3$): δ158.7, 138.0, 127.8, 113.8, 61.9, 55.4, 48.0, 35.1, 26.0, 25.6.[1]

(*S*)-2-(4-Fluorophenyl)piperidine (4c): general procedure with IRED-72 starting from **3c**. Purification by flash column chromatography (EtOAc/MeOH 9/1 v/v + 1.0 % Et_3N) gave **4c** as a yellow oil (20.3 mg, 81%, R_f = 0.25, EtOAc/MeOH 9/1 v/v + 1.0 % Et_3N). % *ee*: >99. $[\alpha]_{25}^{D}$: - 9.4 (c = 0.2, CH_2Cl_2). **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.35-7.29 (m, 2H), 7.01-6.96 (m, 2H), 3.59-3.54 (m, 1H), 3.21-3.15 (m, 1H), 2.79 (td, *J* = 11.7, 2.7 Hz, 1H), 1.92-1.85 (m, 1H), 1.77-1.73 (m, 1H) superimposed to 1.72 (br s, 1H), 1.68-1.63 (m, 1H), 1.57-1.44 (m, 3H). **^{13}C{^{1}H} NMR** (150 MHz, $CDCl_3$): δ 162.0 (d, *J* = 244.7 Hz, 1C), 141.5, 128.2 (d, *J* = 8.0 Hz, 1C), 115.2 (d, *J* = 20.7 Hz, 1C), 61.8, 47.9, 35.2, 26.0, 25.5. **^{19}F{^{1}H} NMR** (564 MHz, $CDCl_3$): δ -115.8 (s, 1F).[1]

(*S*)-2-Phenylazepane (6a): general procedure with IRED-72 starting from **5a**. Purification by flash column chromatography (PE/Et_2O 7:3 + 1.0 % Et_3N) gave **6a** as a yellow oil (16.2 mg, 66 %, R_f = 0.25, PE/Et_2O 7:3 + 1.0 % Et_3N). % *ee*: >99. $[\alpha]_{25}^{D}$: - 50.3 (c = 0.6, CH_2Cl_2). **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.36-7.33 (m, 2H), 7.30 (t, *J* = 7.7 Hz, 2H), 7.24-7.19 (m, 1H), 3.75 (dd, *J* = 10.2, 3.7 Hz, 1H), 3.14 (dt, *J* = 13.6, 5.2 Hz, 1H), 2.85 (ddd, *J* = 13.2, 9.1, 3.5 Hz, 1H), 1.97 (ddt, *J* = 14.1, 7.1, 3.6 Hz, 1H), 1.88-1.55 (m, 8H). **^{13}C{^{1}H} NMR** (150 MHz, $CDCl_3$): δ 147.3, 128.5, 126.8, 126.5, 65.1, 48.4, 39.2, 31.1, 27.0, 26.3.[2]

(*S*)-2-(4-Methoxyphenyl)azepane (6b): general procedure with IRED-72 starting from **5b**. Purification by flash column chromatography (PE/EtOAc 7:3 v/v) gave **6b** as a yellow oil (6.3 mg, 22%, R_f = 0.23 PE/EtOAc 7:3 v/v). % *ee*: >99. $[\alpha]_{25}^{D}$: - 62.3 (c = 0.5, CH_2Cl_2). **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.26 (d, *J* = 8.8 Hz, 2H), 6.84 (d, *J* = 8.7 Hz, 2H), 3.79 (s, 3H), 3.69 (dd, *J* = 10.2, 3.7 Hz, 1H), 3.16-3.09 (m, 1H), 2.87-2.79 (m, 1H), 1.93 (ddt, *J* = 14.0, 7.1, 3.6 Hz, 1H), 1.85-1.64 (m, 8H). **^{13}C{^{1}H} NMR** (150 MHz, $CDCl_3$): δ 158.5, 139.6, 127.6, 113.9, 64.6, 55.4, 48.5, 39.3, 31.0, 27.0, 26.2.[1]

(*S*)-2-(4-Fluorophenyl)azepane (6c): general procedure with IRED-72 starting from **5c**. Purification by flash column chromatography (PE/EtOAc 7:3 v/v) gave **6c** as a yellow oil (12.7 mg, 47%, R_f = 0.25, PE/EtOAc 7:3 v/v). % *ee*: >99. $[\alpha]_{25}^{D}$: - 53.8 (c = 0.5, CH_2Cl_2). **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.32-7.27 (m, 2H), 6.99-6.95 (m, 2H), 3.74 (dd, *J* = 10.1, 3.8 Hz, 1H), 3.15-3.08 (m, 1H), 2.88-2.79 (m, 1H), 1.94 (ddt, *J* = 13.9, 6.9, 3.5 Hz, 1H), 1.86-1.62 (m, 8H). **^{13}C{^{1}H} NMR** (150 MHz, $CDCl_3$): δ 161.8 (d, *J* = 244.3 Hz, 1C), 143.0, 128.0 (d, *J* = 7.8 Hz, 1C), 115.2 (d, *J* = 21.1 Hz, 1C), 64.3, 48.3, 39.4, 31.0, 27.0, 26.2. **^{19}F{^{1}H} NMR** (564 MHz, $CDCl_3$): δ -112.3 (s, 1F).[2]

(*R*)-2-propylpiperidine, (−)-Coniine (4d): general procedure with IRED-18 starting from **3d**. Purification by flash column chromatography (EtOAc/MeOH 98:2 v/v + 1.0 % Et_3N) gave **4d** as a colorless oil (11.8 mg, 66%, R_f = 0.12, EtOAc/MeOH 98:2 v/v + 1.0 % Et_3N). % *ee*: >99 (*via* derivatization with TsCl).[39] $[\alpha]_{25}^{D}$: - 4.1 (c = 1.0, $CHCl_3$). **^{1}H NMR** (600 MHz, $CDCl_3$): δ 3.00 (d, *J* = 11.5 Hz, 1H), 2.56 (td, *J* = 11.8, 2.7 Hz, 1H), 2.41-2.34 (m, 1H), 1.71 (d, *J* = 11.1 Hz, 1H), 1.59 (d, *J* = 13.3 Hz, 1H), 1.52 (d, *J* = 14.0 Hz, 1H) superimposed to 1.49 (br s, 1H), 1.37-1.21 (m, 6H), 1.06-0.94 (m, 1H), 0.85 (t, *J* = 5.5 Hz, 3H). **^{13}C{^{1}H} NMR** (150 MHz, $CDCl_3$): δ 56.7, 47.3, 39.8, 33.1, 26.7, 25.0, 19.1, 14.3.[40]

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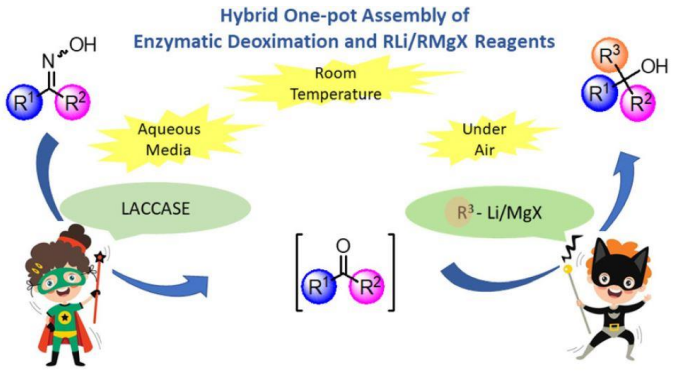
CHAPTER 6: From oximes to tertiary alcohols: hybrid one-pot tandem assembly of enzymatic deoximation and RLi/RMgX reagents

The research presented in this chapter was realized during the period spent at the Organic and Inorganic Chemistry Department (IUQOEM), University of Oviedo in the research group of Prof. Joaquín García-Álvarez as visiting scholar. Part of the results presented in this chapter are published in *Org. Biomol. Chem.* **2023**, *21*, 4414-4421 (DOI:10.1039/D3OB00285C).

The highly efficient biodeoximation of aromatic ketoximes, promoted by the enzymatic oxidative system laccase/TEMPO/O_2 has been successfully assembled, for the first time, with the fast and chemoselective addition of highly polar *s*-block organometallic reagents (RLi/RMgX) *en route* to highly substituted tertiary alcohols.

By using this hybrid one-pot tandem protocol, tertiary alcohols have been selectively synthesized in good yields and, importantly, under *greener* and mild reaction conditions (room temperature, absence of protecting atmosphere and aqueous media; conditions traditionally forbidden for polar organometallic reagents). The overall hybrid one-pot tandem transformation amalgamates two distant organic synthetic tools (RLi/RMgX reagents and enzymes) without the need of tedious and energy/solvent-consuming intermediate isolation/purification steps, thus in good agreement with the principles of the so-called Green Chemistry.



6.1 Introduction

In the framework of Green Chemistry[1] and during the last decades, the use of enzymes as alternatives to highly toxic and expensive transition-metal-based catalysts has played a significant role in the development of more sustainable organic processes.[2] Importantly, enzymes are produced from renewable resources

and are biodegradable and essentially non-hazardous and non-toxic. Additionally, other subsequent costs, like the removal of noble-metal traces from the final products are avoided. At this point, it is also worth mentioning that enzymatic reactions are generally performed under mild conditions (room temperature, atmospheric pressure) and in water, often without the need for functional-group activation, protection or deprotection steps.[3]

As previously discussed, all these environmental and operational benefits have contributed to an exponential increase in the use of biocatalytic methods as alternative and *greener* synthetic tools in organic synthesis. In this perspective, their use in hybrid chemoenzymatic one-pot tandem protocols appears highly desirable and it is currently considered a hot topic.[4]

In this vein, other research groups have previously reported the possibility to design one-pot tandem protocols in which the laccase from *Trametes Versicolor* could be fruitfully amalgamated with other synthetic tools under sustainable reactions conditions (room temperature, under air and using water as an environmentally friendly solvent).[5]

Laccases are copper-containing enzymes belonging to the group of oxidoreductases. In nature, laccases are involved in biological processes such as lignification in plants or lignin degradation in fungi, and catalyse the oxidation of substrates such as phenols, polyphenols and anilines by means of four-electron transfer processes.[5-6] Examples of catalytic networks in which laccases have also been combined with other enzymes such as lipases, oxidoreductases, ω-transaminases or enoate reductases have been reported.[7]

It is also worth highlighting that the laccase-mediated biooxidation only demands O_2 as oxidant, thus generating only water as by-product, which perfectly fits our quest for eco-friendly oxidation processes.

In recent years the design of multistep one-pot synthetic protocols has attracted great attention since their implementation allows to increase the sustainability of the global chemical process under study.[8] As a matter of fact, the use of one-pot tandem protocols (in substitution of traditional and tedious stepwise processes) permits to avoid the employment of purification protocols, usually needed for the isolation of reaction intermediates (with the concomitant reduction of chemical waste and energy/time costs), thus making simpler the practical aspects of the desired synthetic methodology.

Moreover, these one-pot procedures are also the synthetic tool of choice when it is not possible to isolate highly-reactive or transitory-formed species as intermediates.[9] Although they have been successfully exploited to create a wide

variety of natural products and other complex molecular architectures under the banner of Green Chemistry, there are currently few successful examples of their hybrid versions in which the combination of enzymatic, organocatalytic, and transition-metal or main-group-mediated processes have been successfully assembled within the different reaction steps.[10]

These hybrid approaches are particularly appealing when these multistep protocols try to amalgamate two different and distant synthetic approaches, like enzymatic reactions (which intrinsically use water as natural reaction medium, under aerobic conditions and at room temperature),[11] and the chemistry of highly reactive and polar organolithium (RLi) or Grignard (RMgX) reagents, which usually requires the use of dry, often toxic and volatile organic solvents, under inert atmosphere (N_2 or Ar) and at low temperature (ranging from 0 to -78 ºC).[12]

The possibility to merge these two "segregated" synthetic methodologies traditionally set apart (enzymes and RLi/RMgX reagents) into a combined hybrid one-pot tandem protocol started to be achievable owing to the previous works reported by several research groups, which revealed the possibility to promote organolithium- or organomagnesium-mediated organic reactions in protic solvents such as water, glycerol or DESs, at room temperature and without the need of protecting atmosphere (*i.e.*, under air).[13] Our main contribution to this topic can be highlighted by the following publications:

- "Directed *ortho*-metalation–nucleophilic acyl substitution strategies in deep eutectic solvents: The organolithium base dictates the chemoselectivity"[14]
- "Lateral lithiation in deep eutectic solvents: Regioselective functionalization of substituted toluene derivatives"[15]
- "A fast and general route to ketones from amides and organolithium compounds under aerobic conditions: synthetic and mechanistic aspects"[16]
- "Chemo- and Regioselective Anionic Fries Rearrangement Promoted by Lithium Amides under Aerobic Conditions in Sustainable Reaction Media"[17]

The use of RLi/RMgX reagents under these bench-type reaction conditions has allowed the design of new hybrid one-pot tandem protocols that implement the combination of highly polar organometallic reagents with either transition metal-[13a, 13b, 14, 16, 18] or organocatalysed[13w] protocols under more sustainable reaction conditions.

However, the aforementioned combination of enzymes and organolithium/Grignard reagents has been scarcely studied. To the best of our knowledge, only two protocols have reported to date the combination of enzymes and polar organometallic chemistry:

a. Lithium carbenoid homologation reaction merged with an enzymatic reduction;[19]

b. Catalytic oxidation of secondary alcohols by the laccase/TEMPO system followed by the addition of organolithium reagents to the in-situ formed ketones.[5a]

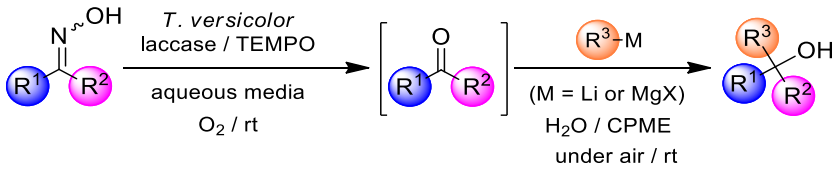
The latter methodologies, in particular, present several shortcomings related to:

1. Limited scope of the reaction as the catalytic bio-oxidation tolerates only a few alcohols;

2. Low to moderate isolated yields of the resulting tertiary alcohols;

3. Ineffectiveness of Grignard reagents in this hybrid tandem protocol.

As an alternative methodology aimed at increasing the substrate scope, herein is reported a hybrid one-pot tandem methodology capable to transform ketoximes into non-symmetric tertiary alcohols by combining the biodeoximation reaction[5b, 5c, 6] (by means of a laccase/TEMPO/O_2 system),[5b] with the subsequent fast, chemoselective and air-, moisture-, and room temperature-compatible addition of highly polar RLi/RMgX organometallic reagents (Scheme 6.1).



Scheme 6.1. Design of a hybrid one-pot tandem protocol by combining enzymes (laccase from *Trametes versicolor*) with highly polar *s*-block organometallic reagents (RLi/RMgX) in aqueous medium, at room temperature and under air.

The (amid)oxime function, starting material for this approach (Scheme 6.1), is ubiquitous in nature and can be found in the structure of several natural and synthetic bioactive compounds (Figure 6.1) as well as in several metabolic pathways.[20]

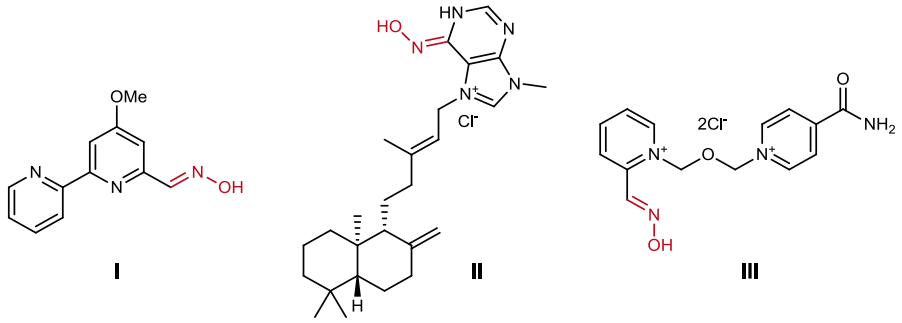


Figure 6.1. Complex bioactive oximes (oxime function marked in red). (I) Caerulomycin-A isolated from *Streptomyces caeruleus* is an example of an oxime from microbial specialized metabolism.[21] (II) Agelasine-D oxime, an anti-fouling compound.[22] (III) HI-6 has the potential to remediate nerve agent poisoning as it is able to reverse acetylcholinesterase inhibition caused by intoxicating organophosphates.[23]

Oximes are considered valuable synthetic precursors which give access to a wide variety of other functionalities such as amines, carboxylic acids or nitriles, although usually under harsh conditions (*i.e.*, using reduction with metals or hydrides or hydrolysis reactions catalysed by inorganic salts).[24]

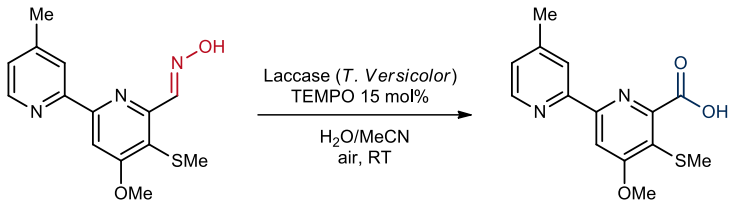
Moreover, the deoximation reaction into the corresponding carbonyl compounds is one of the most important transformations in organic synthesis and for fine chemical production.[24a] Since oximes are stable compounds they can be used for storage purposes, protection-deprotection as synthetic intermediates, purification, and characterization of carbonyl compounds in organic synthesis, especially for the synthesis of active pharmaceutical ingredients (APIs) as well as natural products.

Deoximation methods by using stoichiometric reagents or metal based procedures are mature and can produce the related carbonyl products in high yields with broad substrate application scopes.[24a] Among these approaches $SnCl_2/TiCl_3$ combinations,[25] Si_2Cl_6,[26] $Ce(SO_4)_2$,[27] $Fe(NO_3)_3$,[28] $RuCl_3$,[29] $NaNO_2$[30] as well as organo di- and hydroperoxy- selenides have been reported.[24a] These methods clearly suffer from the sustainability point of view, given the chemical hazards of the reagents/catalysts and the solvent toxicity (i.e. dichloromethane, chloroform, toluene and THF).[31]

Consequently, for environment-protection considerations as well as production cost-controlling purposes in fine chemical industry, the development of novel catalytic deoximation methods has emerged as a new research trend in recent years.[24a]

The first example of Laccase promoted deoxymation-oxidation protocol was reported by González-Sabín *et al*. where Collismycin precursors, including oxime

derivatives **IV**, were successfully oxidized by air to produce the related carboxylic acids **V** (Scheme 6.2).[5b] This room temperature reaction required 15 mol% of 2,2,6,6-tetramethylpiperidin-1-oxyl (TEMPO) as co-catalyst and were performed in H_2O/MeCN (10/1 v/v) solvent. The protocol was also applied on a series of oximes bearing aryl-, alkyl- or heterocycle moieties to produce the related ketones or carboxylic acids under mild conditions.[5b]



IV **V** (95%)

Scheme 6.2. Laccase-promoted biodeoxymation-oxidation protocol.[5b]

With this idea, the following *greener* features of the abovementioned hybrid one-pot tandem protocol proposed in this chapter (Scheme 4.1) are remarkable:

1. Aqueous medium is the solvent of choice to accomplish the combination of both biocatalysed and main-group-promoted organic transformations;

2. Global one-pot tandem protocol proceeds at room temperature and under aerobic conditions;

3. No isolation of any reaction intermediate (ketones in this case) is mandatory, thus reducing the chemical waste and energy/time costs;

4. Is an effective and chemoselective methodology for the synthesis of highly-substituted tertiary alcohols which are often considered components of Active Pharmaceutical Ingredients (APIs), natural products, agrochemicals or synthetic materials.[32]

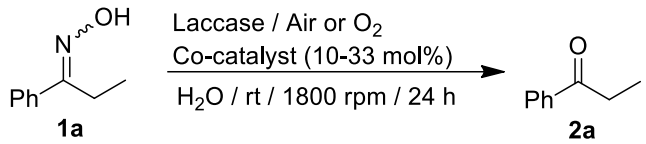
6.2 Optimization of the enzymatic deoximation

We started our investigation by focusing our attention on the deoximation of aromatic ketoximes under mild reaction conditions promoted by the system laccase/TEMPO/O_2 (Table 6.1). Thus, we selected as model reaction the biodeoximation of (*Z*/*E*)-1-phenylpropan-1-one oxime (**1a**) in pure water as solvent, promoted by the laccase/TEMPO system and using aerial O_2 as co-oxidant during 24 h.

Firstly, we observed an important effect of the stirring speed on the reaction, with a dramatic increase in the conversion of **1a** into the corresponding propiophenone (**2a**) when moving from 800 rpm to 1800 rpm (47% to 84%; entries 1-2, Table 6.1). This experimental observation has been previously reported in biooxidation processes promoted with the catalytic system laccase/TEMPO/O_2 and is related to the increase of solubility of the required O_2 in the reaction medium.[5b]

Once the stirring speed was fixed at 1800 rpm, we decided to optimize the amount of the co-catalyst (TEMPO in this case) observing an important increase in activity by moving from 10 to 33 mol% (compare entries 2 and 3). Trying to achieve quantitative conversion into the desired propiophenone (**2a**), we carried out the biocatalytic oxidation reaction in oxygen atmosphere by using an external oxygen balloon (1 atm). By employing this simple experimental variation, we achieved the complete and chemoselective conversion of ketoxime **1a** into the desired ketone **2a** (no by-products were detected, entry 4), at room temperature and after 24 h.

Table 6.1. Deoximation of propiophenone oxime **1a** into ketone **2a** promoted by the system laccase/TEMPO/O_2 in aqueous medium at room temperature after 24 hours. [a]



1a **2a**

Entry	Laccase[b,c]	Co-catalyst	Oxidant	Conv.(%)[d]
1	*T. Versicolor*	TEMPO (33 mol%)	Air	47[e]
2	*T. Versicolor*	TEMPO (33 mol%)	Air	84
3	*T. Versicolor*	TEMPO (10 mol%)	Air	40
4	*T. Versicolor*	TEMPO (33 mol%)	O_2	>99
5	*Rhus Vernicifera*	TEMPO (33 mol%)	O_2	1
6	$CuCl_2 \cdot 2H_2O$/TMEDA	TEMPO (33 mol%)	O_2	2
7	*T. Versicolor*	AZADO (33 mol%)	O_2	>99
8	*T. Versicolor*	TEMPO (33 mol%)	O_2	>99[f]
9	-	TEMPO (33 mol%)	O_2	0
10	*T. Versicolor*	-	O_2	2

[a] General conditions: 24 h of reaction at room temperature and at 1800 rpm, using 0.73 mmol of **1a** in 1 mL of water, oxidant: 1 atm. [b] 280 mg of *T. Versicolor* (0.5 U/mg); 2.8 mg of *Rhus Vernicifera* (50 U/mg) were employed. [c] U/mg = Units of activity per mg of enzyme. [d] Determined by GC, no significant amount of by-products was detected. [e] Stirring speed: 800 rpm. [f] 100 µL of CH_3CN were added as co-solvent.

The effectiveness of a different commercially available laccase (*Rhus Vernicefera*) was also studied (50 U/mg), but no activity in the deoximation process

was observed (entry 5). Interestingly, an archetypical transition-metal based catalytic oxidation system (*i.e.*, $CuCl_2 \cdot 2H_2O$/TMEDA; TMEDA = *N*,*N*,*N*´,*N*´-tetramethylethylenediamine) is not capable to replicate the activity observed when using our biocatalytic system (entry 6).[33] At this point, we should mention that the biooxidation system under study tolerates the use of other co-catalysts like AZADO (2-azaadamantane *N*-oxyl, entry 7) or water-miscible co-solvents like acetonitrile (entry 8).

Finally, no biocatalytic reaction was observed in the absence of catalytic amounts of the laccase (entry 9) or co-catalyst (TEMPO in this case, entry 10). These experimental findings testify that the biocatalytic system laccase/TEMPO/O_2 is responsible for the catalytic activity observed in the deoximation reaction of **1a**.

6.3 Optimization of the hybrid one-pot tandem transformation

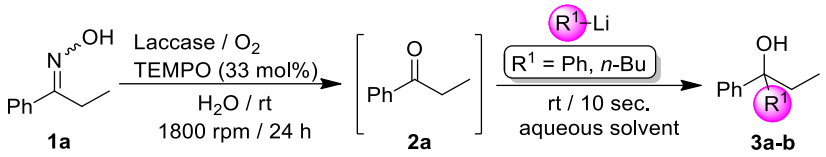
After setting up the best conditions for the biodeoximation process of **1a** into the desired ketone **2a** (water as solvent, room temperature and 24 h of reaction, 1800 rpm, oxygen atmosphere), we investigated its combination with the chemoselective addition of RLi/RMgX reagents to the intermediate ketone **2a** without any intermediate purification/isolation step, in the presence of the biocatalytic system laccase/TEMPO/O_2, and working at room temperature, under air and in aqueous medium, a trio of reactions conditions usually forbidden in traditional polar organometallic chemistry.[12]

With this idea in mind, the laccase/TEMPO/O_2 deoximation of **1a** into the corresponding ketone **2a** was followed by the direct addition of a variety of RLi/RMgX reagents to the resulting aqueous-based reaction mixture (no isolation/purification of any intermediate was required, see Table 6.2).

Initially, the reaction mixture formed by the ketoxime **1a** and the biooxidation system (laccase/TEMPO) was allowed to react in bulk water, at room temperature and under O_2 to trigger the desired deoximation reaction.

As soon as the complete conversion of **1a** into propiophenone (**2a**) was achieved (24 h, confirmed by GC analysis), PhLi was directly added to the reaction mixture in the absence of any protecting atmosphere and at room temperature (entry 1, Table 6.2). Under these bench-type reaction conditions, we observed that PhLi added almost immediately (10 s) to the *in-situ* formed propiophenone (**2a**) leading to the desired tertiary alcohol **3a** with total chemoselectivity, as no by-products were detected even in the presence of the enzyme (laccase) and the co-catalyst (TEMPO).

Table 6.2. Hybrid one-pot tandem transformation of ketoxime **1a** into tertiary alcohols **3a-b** promoted by combination of the laccase/TEMPO/O_2 system with the chemoselective addition of RLi reagents (R = Ph or *n*-Bu) in aqueous medium, at room temperature under air.[a]



Entry	R^1Li	Eq.	Solvent	Product	Conv.(%)[b]
1	PhLi	3	H_2O	**3a**	67
2	PhLi	3	H_2O/CPME	**3a**	79
3	PhLi	2	H_2O/CPME	**3a**	60
4	PhLi	3	H_2O/2-MeTHF	**3a**	65
5	*n*-BuLi	2	H_2O/CPME	**3b**	28
6	*n*-BuLi	3	H_2O/CPME	**3b**	62
7	*n*-BuLi	3	H_2O/2-MeTHF	**3b**	37

[a] General conditions: 24 h of reaction at room temperature and at 1800 rpm; laccase from *T. Versicolor* (0.5 U/mg, 280 mg) for 0.73 mmol of **1a**, 1 atm O_2, 0.33 eq. TEMPO in 1 mL of water were used. Then 1 mL of the co-solvent and the RLi reagent [R = Ph (1.9 M in *n*-Bu_2O) or *n*-Bu (2.5 M in hexanes)] were added without any isolation/purification of **2a**. [b] Determined by GC, no significant amount of by-products were detected.

Here, it is important to mention that the possible side reaction between the organolithium reagent and TEMPO was not detected,[34] thus disclosing a new example in which the addition reaction of the RLi reagent to carbonyl compound is faster than any other side reactions or hydrolysis.[13a-q, 14-17]

With the aim to increase the yield of the final product **3a** and taking into account the positive effect associated with the use of biphasic mixtures of water and sustainable ethereal solvents [like cyclopentyl methyl ether (CPME)][35] in the addition of RLi reagents to organic electrophiles in protic solvents,[13a-e, 14-17] we investigated the use of this mixture in our tandem protocol.

An important increase in the final yield of the tertiary alcohol **3a** was observed in this case (79%, entry 2). On the other hand, when the equivalents of PhLi were decreased from 3 to 2, a lower yield (60%) in the final aromatic alcohol **3a** was achieved (entry 3). Similarly, by replacing CPME with another sustainable ethereal solvent like 2-MeTHF,[36] the yield of **3a** could not be increased either (entry 4).

Finally, we decided to study the scope of the reaction by investigating:

1. The nature of the **organolithium reagent** (comparing aromatic PhLi with aliphatic *n*-BuLi)
2. The **co-solvent** in which these commercially available solutions of RLi reagents are accessible [an ethereal donor solvent for PhLi (*n*-Bu_2O) and an aliphatic and non-coordinating solvent for *n*-BuLi (hexanes)].

Thus, the comparison between entries 2-4 (for PhLi, synthesis of alcohol **3a**) and 5-7 (for *n*-BuLi, synthesis of alcohol **3b**) in Table 6.2 clearly indicates that higher yields are always observed when an ethereal-based solution of RLi is employed. These experimental observations could be related to the capability of the ethereal solvent (*n*-Bu_2O) present in the commercial solution of PhLi to break down less reactive aggregates (oligomers) usually present in RLi solutions.[37]

6.4 Hybrid one-pot tandem transformation of ketoximes into tertiary alcohols

Given the best conditions for the formation of tertiary alcohols **3a**,**b** upon addition of the polar organolithium reagent at room temperature, under air, in the biphasic H_2O/CPME mixture and stirring this reaction media for 10 s, we extended our studies to other highly-polar organometallic reagents (RLi/RMgX, see Table 6.3).

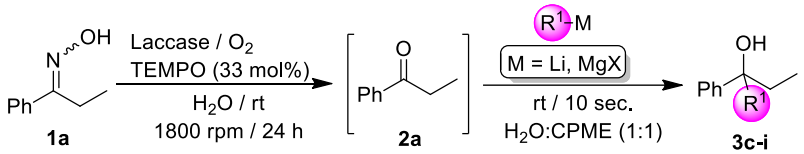
Firstly, we observed almost quantitative conversion into tertiary alcohol **3c** (91%, entry 1) when using MeLi (commercial solution in Et_2O) as nucleophilic reagent. As expected, both gradual increase of steric hindrance (thus decreasing their nucleophile character) from EtLi to *s*-BuLi and *t*-BuLi and using all these commercially available solutions of RLi reagents in hydrocarbon solvents produced a concomitant reduction of the yield (from 73 to 53%) in the alcohols **3d-f** (entries 2-4).

However, it is important to mention the total chemoselectivity of our hybrid protocol, as no side products (aside from the unreacted ketone **2a** and the desired alcohol **3d**-**f**) were observed. These results are especially remarkable when considering highly reactive RLi compounds (*i.e.*, *s*-BuLi and *t*-BuLi, which are usually stored and employed at low temperatures), as these reagents are known to be prone to undergo a fast *β*-hydride elimination.[12h]

Moreover, we should mention that not only aliphatic and primary RLi reagents but also heteroaryllithiums [like 2-thienyl lithium (thienylLi); **3g**; entry 5] can be employed in our hybrid one-pot tandem protocol, working at room temperature and under air.

Finally, with the aim to build up a full picture of the effect of the nature of the polar organometallic reagent in this hybrid protocol, we also studied the usefulness of Grignard reagents, like allylMgBr (entry 6) and benzylMgCl (entry 7) under the previously optimized reaction conditions (room temperature, under air) and in the presence of the enzyme (laccase) and the co-factor (TEMPO). Satisfactorily, we found that magnesium-based polar organometallic reagents can promote the Grignard reaction even under biocatalytic conditions giving rise to the desired tertiary alcohols **3h**,**i** in moderate to good yields (33-50%; entries 6-7).

Table 6.3. Hybrid one-pot tandem transformation of ketoxime **1a** into tertiary alcohols **3c-i** promoted by the combination of the laccase/TEMPO/O_2 system with the chemoselective addition of RLi/RMgX in aqueous medium, at room temperature under air.[a]



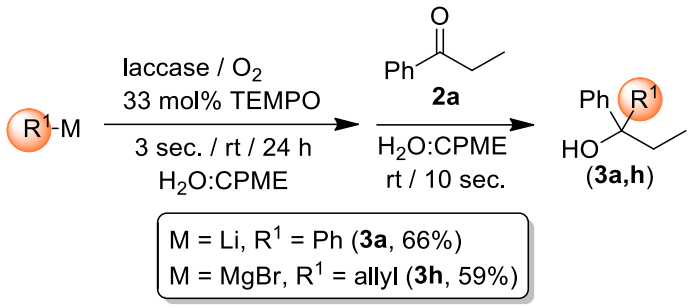
Entry	R-M (3 eq)	Product	Conv.(%)[b]	Yield(%)[c]
1	MeLi	**3c**	91	82
2	EtLi	**3d**	73	66
3	*s*-BuLi	**3e**	69	64
4	*t*-BuLi	**3f**	53	40
5	ThienylLi	**3g**	55	46
6	AllylMgBr	**3h**	62	50
7	BenzylMgCl	**3i**	46	33

[a] General conditions: 24 h of reaction at room temperature and at 1800 rpm; laccase from *T. Versicolor* (0.5 U/mg, 280 mg) for 0.73 mmol of **1a**, 1 atm O_2, 0.33 eq. TEMPO in 1 mL of water were used. Then 1 mL of the co-solvent and the RLi [R = Me (1.6 M in Et_2O); Et (0.5 M in benzene/cyclohexane); *s*-Bu (1.4 M in cyclohexane); *t*-Bu (1.7 M in pentane); 2-thienyl (1.0 M in THF/hexanes)] or RMgX [R = allyl (1.0 M in Et_2O); benzyl (2.0 M in THF)] reagents were added without any isolation/purification. [b] Determined by GC, no significant amount of by-products were detected. [c] Isolated yields.

As previously observed for RLi reagents, both reactions proved to be totally chemoselective giving rise to the expected alcohols as the sole products after only 10 seconds before quenching. These results are particularly remarkable taking into account other previous studies which reported complete protonation of the Grignard reagents in competition with carbonyl addition.[38]

Highlighting the exciting potential of using highly polar *s*-block organometallic reagents under biocatalytic conditions (air, aqueous media, room temperature) and in the presence of enzymes/co-factors, we decided to design

control experiments which could corroborate the observed ability of RLi/RMgX reagents to survive under the aforementioned biocatalytic conditions. Thus, when the addition order of the reagents was reversed and PhLi or allyMgBr were firstly introduced in the reaction mixture containing water/CPME, TEMPO and laccase (*i.e.*, in the absence of the intermediate ketone **2a**, being this mixture stirred for 3 seconds under air and at room temperature before addition of the propiophenone (**2a**), products **3a** and **3h** were still obtained in remarkable yields (66 and 59%, respectively, see Scheme 6.3). Indeed, after 6 seconds of stirring under the biodeoximation conditions in the absence of **2a** the formation of **3a-h** is totally suppressed. These control experiments are in total agreement with previous control studies on the addition of RLi reagents into imines[13p] or nitriles[13o] in protic reaction media, and reinforce the ability of RLi/RMgX to promote the very fast and chemoselective addition reaction into the desired unsaturated organic electrophiles before their expected hydrolysis reaction with moisture or the reaction media.

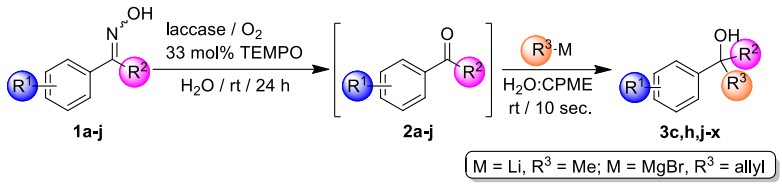


Scheme 6.3. Control experiments for assessing the capability of RLi/RMgX reagents to work under biocatalytic conditions and in the presence of enzymes/co-factors.

6.5 Reaction substrate scope

Trying to find the limits of our new study on the combination of enzymes and polar organometallic reagents, we decided to test a series of ketoximes (**1a-j**, Table 6.4) by employing either MeLi or allylmagnesium bromide as alkylating/allylating reagents (best conversions were observed when using these polar organometallic reagents; see entries 1 and 6, Table 6.3) working at room temperature, in aqueous medium and under air.

Table 6.4. Hybrid one-pot tandem transformation of ketoximes **1a**-**j** into tertiary alcohols **3c**,**h**,**j**-**x** promoted by combination of the laccase/TEMPO/O_2 system with the chemoselective addition of MeLi/AllylMgBr in aqueous medium, at room temperature and in the presence of air.[a]



Entry	R^1	R^2	R^3M	Product	Yield(%)[b]
1	H (**1a**)	Et	MeLi	**3c**	82
2	H (**1a**)	Et	AllylMgBr	**3h**	50
3	*p*-Cl (**1b**)	Et	MeLi	**3j**	83
4	*p*-Cl (**1b**)	Et	AllylMgBr	**3k**	58
5	*p*-OMe (**1c**)	Et	MeLi	**3l**	72
6	*p*-OMe (**1c**)	Et	AllylMgBr	**3m**	52
7	*p*-Me (**1d**)	Et	MeLi	**3n**	54
8	*p*-Me (**1d**)	Et	AllylMgBr	**3o**	36
9	H (**1e**)	Me	MeLi	**3p**	74
10	H (**1e**)	Me	AllylMgBr	**3q**	43
11	*p*-Cl (**1f**)	Me	MeLi	**3r**	78
12	*m*-Cl (**1g**)	Me	MeLi	**3s**	29
13	*o*-Cl (**1h**)	Me	MeLi	**3t**	11
14	*p*-Cl (**1f**)	Me	AllylMgBr	**3u**	16
13	*m*-OMe (**1i**)	Me	MeLi	**3v**	40
14	*m*-OMe (**1i**)	Me	AllylMgBr	**3w**	28
15	*p*-OMe (**1j**)	Me	MeLi	**3x**	88

[a] General conditions: 24 h of reaction at room temperature and at 1800 rpm; laccase from *T. Versicolor* (0.5 U/mg, 280 mg) per 0.73 mmol of **1a-i**, 1 atm O_2, 0.33 eq. TEMPO in 1 mL of water were used. Then 1 mL of the co-solvent and 3 eq. of MeLi (1.6 M in Et_2O) or AllylMgBr (1.0 M in Et_2O) reagents were added without any isolation/purification. [b] Isolated yields.

Firstly, we should mention that in all cases studied the biooxidative system formed by laccase/TEMPO/O_2 was able to convert quantitatively all the starting ketoximes **1a**-**j** into the corresponding ketones **2a-j** (99% conversions, GC analysis) after 24 h reaction time, independently from: *a*) the nature [electron-withdrawing (like Cl- in **1b**,**f**-**h**) or electron-donating (MeO- or Me- in **1c**-**d**,**i**-**j**)]; or *b*) the position of the substituent in the aromatic ring (*o*-, *m*- and *p*-positions are tolerated).

Secondly, it was always possible to add directly the desired polar organometallic reagents (MeLi or allylMgBr) to the biocatalytic reaction medium (in the presence of the enzyme and TEMPO), working at room temperature, under air

and in aqueous media, thus yielding the desired tertiary alcohols **3c**,**h**,**j**-**x** in only 10 s of reaction time (Table 6.4).

Therefore, we found that our hybrid one-pot tandem protocol tolerates a variety of functional groups in the aromatic ring, being compatible with either electron-withdrawing (Cl-, entries 3 and 4) or electron-donating groups (Me- or OMe-, entries 5-8) at the *para*-position. As expected, higher yields were always observed when MeLi was used as the organometallic reagent in place of allylMgBr.

At this point, it is also worth mentioning the high chemoselectivity of our hybrid protocol, as the following side reactions were not observed:

1. Li- or Mg-chloride exchange reaction in ketoxime **1b**;
2. *Ortho*-metalation in ketoxime **1c**;
3. Metalation of benzylic positions in substrate **1d**.

Moreover, we have proved that not only propiophenone-type ketoximes (**1a**-**d**) but also acetophenone-based ketoximes **1e**-**j** can be used in our hybrid one-pot tandem protocol. In this case, we explored the effect (steric hindrance) of the position of the same substituent (Cl-) in the three different positions of the aromatic ring, finding a higher yield for the *para*-derivative **3r** (78%, entry 11) and lower yield in the case of the hindered *ortho*-derivative **3t** (11%, entry 13). As expected, the *meta*-derivative **3s** was formed in an intermediate yield of 29% (entry 12). These experimental observations support a strong influence of the steric effects in the addition reaction of RLi/RMgX reagents in our hybrid one-pot tandem protocol.

Finally, it is also noteworthy that our new hybrid one-pot tandem system is compatible with acetophenone-type ketones **2e**-**j** (Table 6.4), whereas previously reported addition reactions of RLi/RMgX towards such water-soluble substrates were totally ineffective in aqueous media.[13w, 18a] We correlate this experimental observation with the presence of an immiscible ethereal solvent (CPME) in the aqueous mixture which could decrease the partition of acetophenone-type substrates in water.

6.6 Conclusion

In this work, we have demonstrated the possibility to combine enzymatic-promoted organic transformation with the chemistry of highly polar organometallic compounds (RLi/RMgX), working in aqueous media and under bench-type reactions conditions (room temperature and absence of any protecting atmosphere) which

are conditions typically employed in biocatalytic chemistry but for long, previously forbidden for polar organometallic reagents (RLi/RMgX).

Moreover, it is important to mention that our new hybrid one-pot tandem protocol permits the simple experimental connection between a biocatalytic deoximation procedure (mediated by the laccase/TEMPO/O_2 system) and the chemoselective and fast addition of RLi/RMgX reagents on transiently-formed ketones giving rise to the desired and highly-substituted tertiary alcohols without the need of any intermediate step (i.e., tedious and time/energy consuming purifications/isolations).

In addition, the following key points are worth mentioning:

1. We established a new synthetic route to diversely functionalized tertiary alcohols in up to 82% yield from oximes and polar organometallic compounds with a good substrate scope in terms of both oximes and organometallics (organolithium and Grignard reagents);

2. All reactions were found to proceed under *green* and bench-type conditions leading to the desired tertiary alcohols.

These results demonstrate the possibility to merge polar organometallic chemistry based on RLi/RMgX reagents with other synthetic tools from the organic reaction toolbox such as biocatalytic transformations while working under environmentally friendly and bench-type reaction conditions. This certainly paves the way for disclosing new synergistic synthetic methodologies relying on hybrid one-pot tandem protocols.

6.7 Experimental section

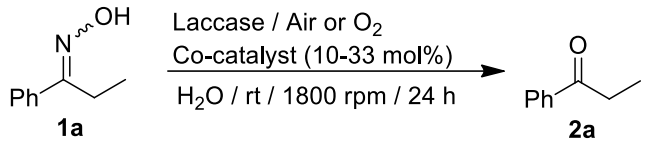
6.7.1 Experimental details

Materials and methods. All reagents were obtained from commercial suppliers and used without further purification. Laccase from *Trametes Versicolor* or *Rhus Vernicifera*, TEMPO and AZADO were purchased from Sigma Aldrich. Organometallic reagents were purchased from Sigma Aldrich: i) 2.5 M solution of *n*-BuLi in hexanes; ii) 1.6 M solution of MeLi in Et2O; iii) 1.4 M solution of *s*-BuLi in cyclohexane; iv) 1.7 M solution of *t*-BuLi in pentane; v) 1.9 M solution of PhLi in dibutyl ether; vi) 2.0 M solution of BnMgCl in THF; vii) 1.0 M solution of 2-thienyllithium in THF/hexanes; viii) 1.0 M solution of allylmagnesium bromide in Et_2O. Concentrations of all organolithium reagents were determined by titration with L-menthol,[39] and for the Grignard reagents titration against iodine was employed.[40] All the rest of reagents and solvents were of the highest quality available. Ketoximes **1a**-**j** were synthesized according to the procedure reported in the literature.[41] Reactions were monitored by GC-FID analysis or by thin-layer chromatography (TLC) carried out on 0.25 mm silica gel coated aluminum plates (60 Merck F_{254}) with UV light (254 nm) or *p*-anisaldehyde indicator[42] as visualizing agents. R_f values refer to TLC carried out on silica gel plates. Chromatographic separations were carried out under pressure on silica gel (40-63 μm, 230-400 mesh) using flash-column techniques. Full characterization data have been presented for the known compounds.

Instrumentation. ^{1}H NMR (600 MHz) and $^{13}C\{^1H\}$ (150 MHz) NMR spectra were recorded on a Jeol ECZR600 spectrometer at room temperature. ^{1}H NMR (300 MHz) and $^{13}C\{^1H\}$ (75 MHz) NMR spectra were recorded on a Bruker DPX-300 spectrometer at room temperature. Calibration was made on the signal of the residual solvent (^{1}H $CHCl_3$: 7.26 ppm; $^{13}C\{^1H\}$ $CDCl_3$: 77.16 ppm). Chemical shifts (δ) are given in parts per million (ppm) and coupling constants (*J*) in Hertz (Hz). Multiplicities are reported as follows: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br (broad). Gas chromatography (GC) analyses were performed on an Agilent Technologies 7820A chromatographic system equipped with a HP-5 (30 m x 0.32 mm x 0.25 μm) column. Melting points were determined on a Stuart Scientific SMP3 melting point apparatus.

*6.7.2 Deoximation of propiophenone oxime **1a** into ketone **2a***

General procedure. All reactions were performed at room temperature. In an 8 mL vial equipped with a magnetic stirrer Laccase and co-catalyst (eq.) were added to a 0.73 mmol (109 mg) suspension of propiophenone oxime **1a** in water (1 mL) and the mixture was stirred under the selected atmosphere for 24 h. Then, the reaction mixture was extracted with dichloromethane (3 x 5 mL), the organic layers were combined, washed with brine (1 x 5 mL), dried with Na_2SO_4 and the solvent removed *in vacuo*. Conversions of **1a** into propiophenone **2a** (Table 6.1) were determined by GC-FID analysis of the crude reaction mixtures. A sample of **1a** was synthesized according to the procedure reported in the literature[41] and used as reference for GC-FID analyses. A sample of commercial **2a** (Sigma-Aldrich 99%) was analyzed and used as reference for GC-FID analyses of the reaction crudes.

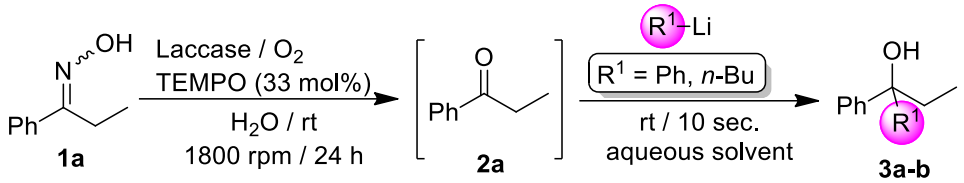


1-Phenylpropan-1-one oxime (1a): white solid (R_f = 0.23 hexane/EtOAc 8/2 v/v), mp 50.2−51.6 °C (hexane). Mixture of *E* and *Z* stereoisomers (*E*/*Z* = 10/1). **^{1}H NMR** (300 MHz, $CDCl_3$, mixture of *E* and *Z* stereoisomers): δ 7.88 (br s, 2H, *E* + *Z*), 7.68-7.51 (m, 4H, *E* + *Z*), 7.50-7.28 (m, 6H, *E* + *Z*), 2.84 (q, *J* = 7.6 Hz, 2H, *E*), 2.63 (q, *J* = 7.4 Hz, 2H, *Z*), 1.19 (t, *J* = 7.6 Hz, 3H, *E*) superimposed to 1.12 (t, *J* = 7.6 Hz, 3H, *Z*). **^{13}C{^{1}H} NMR** (75 MHz, $CDCl_3$, mixture of *E* and *Z* stereoisomers): δ 160.9 (*E*), 159.7 (*Z*), 135.7 (*E*), 133.7 (*Z*), 129.3 (*E*), 129.0 (*Z*), 128.7 (*E*), 128.4 (*Z*), 127.9 (*Z*), 126.4 (*E*), 29.1 (*Z*), 19.9 (*E*), 11.3 (*Z*), 11.0 (*E*).[43]

1-Phenylpropan-1-one (2a): colorless liquid (R_f = 0.25 hexane/Et_2O 9/1 v/v). **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.97 (d, *J* = 7.4 Hz, 2H), 7.55 (t, *J* = 7.3 Hz, 1H) superimposed to 7.46 (t, *J* = 7.3 Hz, 2H), 3.01 (q, *J* = 7.2 Hz, 2H), 1.23 (t, *J* = 7.2 Hz, 3H). **^{13}C{^{1}H} NMR** (75 MHz, $CDCl_3$): δ 200.9, 137.1, 133.0, 128.7, 128.1, 31.9, 8.4.[44]

*6.7.3 Hybrid one-pot tandem transformation of ketoxime **1a** into tertiary alcohols **3a-b***

General procedure. *T. versicolor* laccase (280 mg, 0.5 U/mg) and TEMPO (38 mg, 33 mol%) were added to a 0.73 mmol (109 mg) suspension of propiophenone oxime **1a** in water (1 mL) and the mixture was stirred vigorously (1800 rpm) in an 8 mL vial under oxygen atmosphere for 24 h. Once the biodeoximation reaction was completed (GC-FID analysis, 24 h), 1 mL of ethereal co-solvent was added to form a biphasic reaction medium (apart from Table 6.2, entry 1). Next, the corresponding organolithium reagent (RLi, selected equivalents) was rapidly spreaded over the reaction mixture at room temperature, under air. After 10 s, a saturated solution of NH_4Cl_{aq} (2.5 mL) was added, and the mixture was extracted with dichloromethane (3 x 5 mL). The combined organic phases were washed with brine (1 x 5 mL), dried over anhydrous Na_2SO_4, and the solvents were removed *in vacuo*. Conversion of **1a** into tertiary alchols **3a**-**b** was determined by GC-FID analysis of the crude reaction mixtures. The crude products obtained with the optimized conditions (Table 6.2, entry 2 for **3a**; Table 6.2, entry 6 for **3b**) were purified by flash column chromatography and characterized by ^1H and $^{13}C\{^1H\}$ NMR.

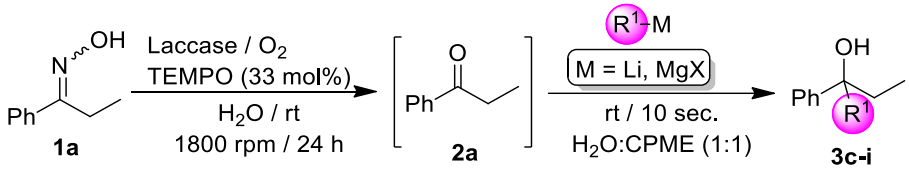


1,1-Diphenylpropan-1-ol (3a): flash column chromatography (hexane/Et_2O 9/1 v/v) gave product **3a** as a white solid (70%, R_f = 0.19 hexane/Et_2O 9/1 v/v), mp 93.2–94.6 °C (hexane). **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.44 (d, *J* = 8.0 Hz, 4H), 7.33 (t, *J* = 7.6 Hz, 4H), 7.28-7.18 (m, 2H), 2.35 (q, *J* = 7.3 Hz, 2H), 2.06 (br s, 1H), 0.91 (t, *J* = 7.3 Hz, 3H). **^{13}C{^{1}H} NMR** (75 MHz, $CDCl_3$): δ 147.0, 128.2, 126.9, 126.2, 78.6, 34.6, 8.2.[13w]

3-Phenylheptan-3-ol (3b): flash column chromatography (hexane/Et_2O 9/1 v/v) gave product **3b** as a colorless oil (57%, R_f = 0.29 hexane/Et_2O 9/1 v/v). **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.48-7.34 (m, 4H), 7.33-7.23 (m, 1H), 2.02-1.76 (m, 4H), 1.67 (br s, 1H), 1.40-1.22 (m, 3H), 1.18-1.00 (m, 1H), 0.90 (t, *J* = 6.9 Hz, 3H), 0.82 (t, *J* = 7.3 Hz, 3H). **^{13}C{^{1}H} NMR** (75 MHz, $CDCl_3$): δ 145.7, 127.6, 125.8, 124.9, 41.9, 35.0, 25.2, 22.7, 13.6, 7.4.[13w]

*6.7.4 Hybrid one-pot tandem transformation of ketoxime **1a** into tertiary alcohols **3c-i***

General procedure. *T. versicolor* laccase (280 mg, 0.5 U/mg) and TEMPO (38 mg, 33 mol%) were added to a 0.73 mmol (109 mg) suspension of propiophenone oxime **1a** in water (1 mL) and the mixture was stirred vigorously (1800 rpm) in an 8 mL vial under oxygen atmosphere for 24 h. Once the biodeoximation reaction was completed (GC-FID analysis, 24 h), 1 mL of CPME was added as co-solvent to form a biphasic reaction medium. Next, the corresponding organolithium (RLi, 3.0 eq) or Grignard (RMgX, 3.0 eq) reagent was rapidly spread over the reaction mixture at room temperature, under air. After 10 s, a saturated solution of NH_4Cl_{aq} (2.5 mL) (2.5 mL) was added, and the mixture was extracted with dichloromethane (3 x 5 mL). The combined organic phases were washed with brine (1 x 5 mL), dried over anhydrous Na2SO4, and the solvents were removed *in vacuo*. Conversion of **1a** into tertiary alcohols **3c-i** was determined by GC-FID analysis of the crude reaction mixtures. The crude products were purified by flash column chromatography and characterized by ^1H and $^{13}C\{^1H\}$ NMR spectroscopy. Yields refer to isolated products (Table 6.3).



2-Phenylbutan-2-ol (3c): flash column chromatography (hexane/Et_2O 9/1 v/v) gave product **3c** as a colorless oil (82%, R_f = 0.16 hexane/Et_2O 9/1 v/v). **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.51-7.42 (m, 2H), 7.41-7.32 (m, 2H), 7.30-7.22 (m, 1H), 1.87 (qd, *J* = 7.3, 3.8 Hz, 2H), 1.77 (br s, 1H), 1.58 (s, 3H), 0.82 (t, *J* = 7.4 Hz, 3H). **^{13}C{^{1}H} NMR** (75 MHz, $CDCl_3$): δ 147.9, 128.2, 126.6, 125.0, 75.1, 36.8, 29.8, 8.4.[13w]

3-Phenylpentan-3-ol (3d): flash column chromatography (hexane/Et_2O 9/1 v/v) gave product **3d** as a colorless oil (66%, R_f = 0.22 hexane/Et_2O 9/1 v/v). **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.47-7.32 (m, 4H), 7.30-7.20 (m, 1H), 2.00-1.77 (m, 4H), 1.69 (br s, 1H), 0.80 (t, *J* = 7.4 Hz, 6H). **^{13}C{^{1}H} NMR** (75 MHz, $CDCl_3$): δ 145.7, 127.9, 126.2, 125.4, 77.3, 34.9, 7.7.[13i]

4-Methyl-3-phenylhexan-3-ol (3e): flash column chromatography (hexane/Et_2O 95/5 v/v) gave product **3e** as a colorless oil (64%, R_f = 0.21 hexane/Et_2O 95/5 v/v). Mixture of diastereomers (dr = 1:1). **^{1}H NMR** (300 MHz, $CDCl_3$, mixture of diastereoisomers): δ 7.46-7.31 (m, 8H), 7.30-7.20 (m, 2H), 1.95 (dq, *J* = 14.4, 7.4 Hz, 4H), 1.86-1.68 (m, 2H), 1.59 (br s, 2H), 1.44-1.23 (m, 2H), 1.05-0.64 (m, 18H). **^{13}C{^{1}H} NMR** (75 MHz, $CDCl_3$, mixture of diastereoisomers): δ 144.7, 144.4, 127.0, 126.9, 125.3, 125.2, 125.1, 79.1, 78.9, 44.0, 43.8, 31.3, 31.0, 23.3, 22.4, 12.9, 11.9, 11.8, 7.1.[13w]

2,2-Dimethyl-3-phenylpentan-3-ol (3f): flash column chromatography (hexane/Et_2O 95/5 v/v) gave product **3f** as a colorless oil (40%, R_f = 0.26 hexane/Et_2O 95/5 v/v). **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.38 (d, *J* = 7.7 Hz, 2H), 7.33-7.28 (m, 2H), 7.24-7.19 (m, 1H), 2.23 (dq, *J* = 14.8, 7.4 Hz, 1H), 1.87 (dq, *J* = 14.5, 7.3 Hz, 1H), 1.68 (s, 1H), 0.91 (s, 9H), 0.68 (t, *J* = 7.4 Hz, 3H). **^{13}C{^{1}H} NMR** (150 MHz, $CDCl_3$): δ 143.0, 127.9, 127.2, 126.3, 81.4, 38.5, 27.0, 26.0, 8.3.[45]

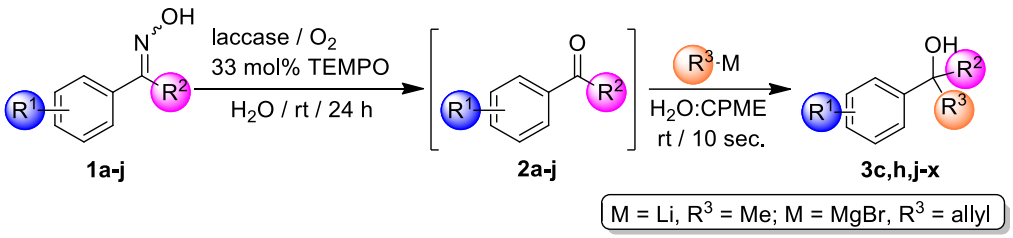
1-Phenyl-1-(thiophen-2-yl)propan-1-ol (3g): flash column chromatography (hexane/Et_2O 9/1 v/v) gave product **3g** as a pale yellow oil (46%, R_f = 0.23 hexane/Et_2O 9/1 v/v). **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.51 (d, *J* = 7.0 Hz, 2H), 7.42-7.21 (m, 4H), 7.00-6.89 (m, 2H), 2.38 (q, *J* = 7.5 Hz, 2H) superimposed to 2.33 (s, 1H), 0.94 (t, *J* = 7.3 Hz, 3H). **^{13}C{^{1}H} NMR** (75 MHz, $CDCl_3$): δ 153.2, 145.7, 128.2, 127.2, 126.7, 125.9, 124.8, 124.1, 77.5, 36.5, 8.4.[46]

3-Phenylhex-5-en-3-ol (3h): flash column chromatography (hexane/Et_2O 9/1 v/v) gave product **3h** as a colorless oil (50%, R_f = 0.23 hexane/Et_2O 9/1 v/v). **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.41 (d, *J* = 7.1 Hz, 2H), 7.36 (t, *J* = 7.6 Hz, 2H), 7.27-7.22 (m, 1H), 5.65-5.53 (m, 1H), 5.19-5.07 (m, 2H), 2.74 (dd, *J* = 13.9, 6.0 Hz, 1H), 2.52 (dd, *J* = 13.8, 8.6 Hz, 1H), 1.99 (br s, 1H), 1.92-1.80 (m, 2H), 0.79 (t, *J* = 7.4 Hz, 3H). **^{13}C{^{1}H} NMR** (150 MHz, $CDCl_3$): δ 145.3, 133.2, 127.6, 126.0, 125.0, 119.1, 75.5, 46.5, 34.8, 7.4.[47]

1,2-Diphenylbutan-2-ol (3i): flash column chromatography (hexane/Et_2O 9/1 v/v) gave product **3i** as a colorless oil (33%, R_f = 0.25 hexane/Et_2O 9/1 v/v). **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.37-7.31 (m, 4H), 7.27-7.23 (m, 1H), 7.22-7.19 (m, 3H), 7.00-6.95 (m, 2H), 3.18 (d, *J* = 13.4 Hz, 1H), 3.08 (d, *J* = 13.3 Hz, 1H), 2.01 (dq, *J* = 14.8, 7.5 Hz, 1H), 1.85 (dq, *J* = 14.5, 7.3 Hz, 1H), 1.76 (br s, 1H), 0.79 (t, *J* = 7.4 Hz, 3H). **^{13}C{^{1}H} NMR** (150 MHz, $CDCl_3$): δ 145.1, 136.1, 130.3, 127.7, 127.6, 126.3, 126.1, 125.2, 76.6, 49.1, 34.1, 7.5.[48]

*6.7.5 Hybrid one-pot tandem transformation of ketoximes **1a-j** into tertiary alcohols **3c,h,j-x***

General procedure. *T. versicolor* laccase (280 mg, 0.5 U/mg) and TEMPO (38 mg, 33 mol%) were added to a 0.73 mmol (109 mg) suspension of the corresponding ketoxime **1a-j** in water (1 mL) and the mixture was stirred vigorously (1200 rpm) in an 8 mL vial under oxygen atmosphere for 24 h. Then 1 mL of CPME was added as co-solvent to form a biphasic reaction medium. Next, MeLi (3.0 eq, 1.6 M in Et_2O) or allylMgBr (3.0 eq, 1.0 M in Et_2O) was rapidly spreaded over the reaction mixture at room temperature, under air. After 3 s, a saturated solution of NH_4Cl_{aq} (2.5 mL) was added, and the mixture was extracted with dichloromethane (3 x 5 mL). The combined organic phases were washed with brine (1 x 5 mL), dried over anhydrous Na_2SO_4, and the solvents were removed *in vacuo*. The crude tertiary alcohols **3c,h,j-x** products obtained were purified by flash column chromatography and characterized by ^1H and $^{13}C\{^1H\}$ NMR. Yields (Table 6.4) refer to isolated products.



2-(4-Chlorophenyl)butan-2-ol (3j): flash column chromatography (hexane/Et_2O 9/1 v/v) gave product **3j** as a colorless oil (83%, R_f= 0.21 hexane/Et_2O 9/1 v/v). **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.37 (d, *J* = 8.6 Hz, 2H) superimposed to 7.30 (d, *J* = 8.6 Hz, 2H), 1.90-1.75 (m, 2H) superimposed to 1.72 (br s, 1H), 1.54 (s, 3H), 0.80 (t, *J* = 7.4 Hz, 3H). **^{13}C{^{1}H} NMR** (75 MHz, $CDCl_3$): δ 146.2, 132.2, 128.1, 126.4, 74.6, 36.6, 29.7, 8.2.[49]

3-(4-Chlorophenyl)hex-5-en-3-ol (3k): flash column chromatography (hexane/Et_2O 9/1 v/v) gave product **3k** as a colorless oil (58%, R_f= 0.20 hexane/Et_2O 9/1 v/v). **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.40 (d, *J* = 8.7 Hz, 2H) superimposed to 7.37 (d, *J* = 8.7 Hz, 2H), 5.70-5.56 (m, 1H), 5.25-5.14 (m, 2H), 2.75 (dd, *J* = 13.8, 5.9 Hz, 1H), 2.55 (dd, *J* = 13.7, 8.4 Hz, 1H), 2.00-1.81 (m, 3H), 0.83 (t, *J* = 7.2 Hz, 3H). **^{13}C{^{1}H} NMR** (150 MHz, $CDCl_3$): δ 143.2, 132.0, 131.1, 127.0, 125.9, 118.8, 74.6, 45.8, 34.1, 6.6.[50]

2-(4-Methoxyphenyl)butan-2-ol (3l): flash column chromatography (hexane/Et_2O 9/1 v/v) gave product **3l** as a colorless oil (72%, R_f= 0.19 hexane/Et_2O 9/1 v/v). **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.35 (d, *J* = 8.8 Hz, 2H), 6.87 (d, *J* = 8.8 Hz, 2H), 3.81 (s, 3H), 1.82 (qd, *J* = 7.3, 2.4 Hz, 2H), 1.70 (br s, 1H), 1.53 (s, 3H), 0.79 (t, *J* = 7.4 Hz, 3H). **^{13}C{^{1}H} NMR** (75 MHz, $CDCl_3$): δ 158.3, 140.0, 126.2, 113.5, 74.7, 55.3, 36.8, 29.7, 8.5.[51]

3-(4-Methoxyphenyl)hex-5-en-3-ol (3m): flash column chromatography (hexane/EtOAc 95/5 v/v) gave product **3m** as a colorless oil (35%, R_f = 0.11 hexane/EtOAc 95/5 v/v). **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.32 (d, *J* = 8.7 Hz, 2H), 6.89 (d, *J* = 8.7 Hz, 2H), 5.68-5.54 (m, 1H), 5.19-5.08 (m, 2H), 3.83 (s, 3H), 2.72 (dd, *J* = 13.5, 6.0 Hz, 1H), 2.49 (dd, *J* = 13.5, 6.0 Hz, 1H), 1.90-1.77 (m, 2H), 1.61 (br s, 1H), 0.78 (t, *J* = 7.5 Hz, 3H). **^{13}C{^{1}H} NMR** (150 MHz, $CDCl_3$): δ 158.1, 137.9, 133.8, 126.6, 119.4, 113.3, 75.8, 55.2, 46.9, 35.3, 7.9.[52]

2-(*p*-Tolyl)butan-2-ol (3n): flash column chromatography (hexane/Et_2O 9/1 v/v) gave product **3n** as a colorless oil (54%, R_f = 0.18 hexane/Et_2O 9/1 v/v). **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.32 (d, *J* = 8.1 Hz, 2H), 7.15 (d, *J* = 7.9 Hz, 2H), 2.34 (s, 3H), 1.83 (qd, *J* = 7.2, 3.2 Hz, 2H), 1.69 (br s, 1H), 1.54 (s, 3H), 0.80 (t, *J* = 7.4 Hz, 3H). **^{13}C{^{1}H} NMR** (75 MHz, $CDCl_3$): δ 145.0, 136.2, 128.9, 125.0, 74.9, 36.8, 29.8, 21.1, 8.5.[50]

3-(*p*-Tolyl)hex-5-en-3-ol (3o): flash column chromatography (hexane/Et_2O 9/1 v/v) gave product **3o** as a colorless oil (36%, R_f = 0.24 hexane/Et_2O 9/1 v/v). **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.29-7.24 (m, 2H), 7.15 (d, *J* = 7.8 Hz, 2H), 5.66-5.51 (m, 1H), 5.17-5.04 (m, 2H), 2.74-2.64 (m, 1H), 2.53-2.44 (m, 1H), 2.34 (s, 3H), 1.97 (br s, 1H), 1.89-1.76 (m, 2H), 0.77 (t, *J* = 7.4 Hz, 3H). **^{13}C{^{1}H} NMR** (150 MHz, $CDCl_3$): δ 142.9, 136.0, 133.9, 128.9, 125.5, 119.5, 76.0, 47.0, 35.4, 21.1, 8.0.[53]

2-Phenylpropan-2-ol (3p): flash column chromatography (hexane/Et_2O 9/1 v/v) gave product **3p** as a colorless oil (74%, R_f = 0.21 hexane/Et_2O 9/1 v/v). **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.51-7.48 (m, 2H), 7.37-7.32 (m, 2H), 7.27-7.23 (m, 1H), 1.79 (br s, 1H), 1.60 (s, 6H). **^{13}C{^{1}H} NMR** (150 MHz, $CDCl_3$): δ 149.2, 128.4, 126.8, 124.5, 72.7, 31.9.[54]

2-Phenylpent-4-en-2-ol (3q): flash column chromatography (hexane/Et_2O 9/1 v/v) gave product **3q** as a colorless oil (43%, R_f = 0.25 hexane/Et_2O 9/1 v/v). **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.47-7.42 (m, 2H), 7.37-7.32 (m, 2H), 7.27-7.22 (m, 1H), 5.63 (dddd, *J* = 16.9, 10.3, 8.3, 6.4 Hz, 1H), 5.17-5.08 (m, 2H), 2.69 (dd, *J* = 13.7, 6.5 Hz, 1H), 2.51 (dd, *J* = 13.6, 8.4 Hz, 1H), 2.06 (br s, 1H), 1.56 (s, 3H). **^{13}C{^{1}H} NMR** (150 MHz, $CDCl_3$): δ 147.7, 133.8, 128.3, 126.7, 124.9, 119.6, 73.7, 48.6, 30.0.[55]

2-(4-Chlorophenyl)propan-2-ol (3r): flash column chromatography (hexane/EtOAc 9/1 v/v) gave product **3r** as a colorless oil (78%, R_f = 0.25 hexane/EtOAc 9/1 v/v). **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.41 (d, *J* = 8.0 Hz, 2H), 7.29 (d, *J* = 8.0 Hz, 2H), 1.56 (s, 6H). **^{13}C{^{1}H} NMR** (150 MHz, $CDCl_3$): δ 147.7, 132.5, 128.3, 125.9, 72.2, 31.8.[51]

2-(3-Chlorophenyl)propan-2-ol (3s): flash column chromatography (hexane/EtOAc 9/1 v/v) gave product **3s** as a colorless oil (29%, R_f = 0.25 hexane/EtOAc 9/1 v/v). **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.49 (t, *J* = 1.6 Hz, 1H), 7.36 (d, *J* = 8.0 Hz, 1H), 7.27 (t, *J* = 8.0 Hz, 1H), 7.22 (d, *J* = 8.0 Hz, 1H), 1.57 (s, 6H). **^{13}C{^{1}H} NMR** (150 MHz, $CDCl_3$): δ 151.4, 134.9, 129.4, 126.7, 124.9, 122.7, 72.2, 31.6.[51]

2-(2-Chlorophenyl)propan-2-ol (3t): flash column chromatography (hexane/EtOAc 9/1 v/v) gave product **3t** as a colorless oil (11%, R_f = 0.25 hexane/EtOAc 9/1 v/v). **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.69 (d, *J* = 7.5 Hz, 1H), 7.38 (d, *J* = 7.5 Hz, 1H), 7.28 (t, *J* = 7.5 Hz, 1H), 7.21 (t, *J* = 7.5 Hz, 1H), 2.68 (brs, 1H), 1.76 (s, 6H). **^{13}C{^{1}H} NMR** (150 MHz, $CDCl_3$): δ 144.8, 131.3, 131.2, 128.1, 126.8, 72.9, 29.3.[51]

2-(4-Chlorophenyl)pent-4-en-2-ol (3u): flash column chromatography (hexane/EtOAc 8/2 v/v) gave product **3u** as a pale yellow oil (16%, R_f = 0.26 hexane/EtOAc 8/2 v/v). **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.40–7.34 (m, 2H), 7.32–7.27 (m, 2H), 5.62–5.58 (m, 1H), 5.18–5.08 (m, 2H), 2.63 (dt, *J* = 18.6, 9.3 Hz, 1H), 2.48 (dd, *J* = 13.8, 8.2 Hz, 1H), 2.23–2.08 (m, 1H), 1.52 (s, 3H). **^{13}C{^{1}H} NMR** (150 MHz, $CDCl_3$): δ 146.2, 133.3, 132.2, 128.3, 126.3, 119.8, 73.5, 48.5, 30.1.[56]

2-(3-Methoxyphenyl)propan-2-ol (3v): flash column chromatography (hexane/EtOAc 8/2 v/v) gave product **3v** as a colorless oil (40%, R_f= 0.21 hexane/EtOAc 8/2 v/v). **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.27 (d, *J* = 8.0 Hz, 1H), 7.07 (t, *J* = 8.0 Hz, 2H), 6.80 (dd, *J* = 8.0, 2.4 Hz, 1H), 3.82 (s, 3H), 1.58 (s, 6H). **^{13}C{^{1}H} NMR** (150 MHz, $CDCl_3$): δ 159.6, 150.9, 129.2, 116.8, 111.8, 110.6, 72.4, 55.2, 31.6.[51]

2-(3-Methoxy-phenyl)-pent-4-en-2-ol (3w): flash column chromatography (hexane/EtOAc 8/2 v/v) gave product **3w** as a colorless oil (28%, R_f= 0.21 hexane/EtOAc 8/2 v/v). **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.26 (t, *J* = 8.0 Hz, 1H), 7.01 (t, *J* = 8.0 Hz, 2H), 6.78 (t, *J* = 4.0 Hz, 1H), 5.67–5.57 (m, 1H), 5.16–5.11 (m, 2H), 3.83 (s, 3H), 2.69 (q, *J* = 6.8 Hz, 1H), 2.48 (q, *J* = 6.8 Hz, 1H), 2.05 (s, br, 1H), 1.53 (s, 3H). **^{13}C{^{1}H} NMR** (150 MHz, $CDCl_3$): δ 159.9, 149.5, 133.6, 129.1, 119.6, 117.2, 111.7, 110.5, 73.5, 55.3, 48.4, 29.9.[56]

2-(4-Methoxyphenyl)propan-2-ol (3x): flash column chromatography (hexane/EtOAc 8/2 v/v) gave product **3x** as a colorless oil (88%, R_f= 0.26 hexane/EtOAc 8/2 v/v). **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.41 (d, *J* = 6.0 Hz, 2H), 6.87 (d, *J* = 6.0 Hz, 2H), 3.80 (s, 3H), 1.56 (s, 6H). **^{13}C{^{1}H} NMR** (150 MHz, $CDCl_3$): 154.4, 137.4, 121.6, 109.5, 68.2, 51.3, 27.9, 27.8.[13i]

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