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TITOLO TESI DI DOTTORATO DI RICERCA

Ecofriendly Synthetic Methodologies

in Organic Chemistry

(CHIM/06)

Coordinatore: Prof. Maurizio PETRUCCIOLI

Tutor: Dott.ssa Roberta BERNINI

Dottoranda: Maria Cristina GINNASI

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INTRODUCTION

1 Green chemistry

1.1 Definition

In recent years, scientific research has focused its efforts on the development of new technologies for pollution prevention.¹ This modern approach, based on the low environmental impact of the industrial processes, involves economic investments. In order to move in this direction, researchers must bring themselves about these changes in a way that addresses to reach a sustainable civilization. The “Pollution Prevention Act” issued in 1990 defines a national environmental policy based on the prevention of the wastes production by using a variety of methodologies and techniques obviating the need of treatment or control of chemical substances.

In this context, *green chemistry* is a important tool. According to the definition, “*green chemistry is the design of chemical products and processes which reduces or eliminates the use and the generation of hazardous substances projecting, manufacturing and producing chemical products*”.² This definition contains several recommendations: *the design of benign processes; the use and generation of safe compounds; the elimination of hazardous substances and processes*. Firstly, *the design of benign processes* assesses the effects of chemical products and processes even at the project level. Secondly, *the use and generation of safe compounds* focus on to all substances involved in the process. This principle has the aim to protect people and environment. Finally, the definition includes the concept of *elimination of hazardous substances and processes*. The fundamental basis of *green chemistry* is the incorporation of hazard minimization or elimination into all aspects of the chemistry design.

Internationally, *green chemistry* is recognized as a central point of the chemistry. Being able to combine scientific research with environmental protection, it is one of the objectives of the next millennium. For these reasons, International Union of Pure and Applied Chemistry (IUPAC) plays a key role in the promotion of *green chemistry*. This organization is working with the Organization for the Economical Cooperation and Development (OECD) in designing a sustainable chemistry that aims to promote an increased awareness of the Member States through research and development; awards; exchange of technical information; background.

1.2 Principles of green chemistry

A *green compound, reaction and process* is defined according to the following 12 principles developed by Anastas and Warner, pioneers of this new way of thinking the chemistry.³

1. Prevention

It is better to prevent wastes production than to treat or clean up them.

2. Atom economy

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

3. Less hazardous chemical synthesis

Wherever practicable, synthetic methods should be designed to use and generate substances that possess low or no toxicity for human health and environment.

4. Designing safer chemicals

Chemical products should be designed to effect their desired function while minimizing their toxicity.

5. Safe solvents and auxiliaries

The use of auxiliary substances (e.g., solvents, separation agents, etc.) should be avoided. If necessary, no hazardous chemicals should be used.

6. Design for energy efficiency

Energy requirements of chemical processes should be recognized for their environmental and economic impacts and should be minimized. If possible, synthetic methods should be carried out at room temperature and atmospheric pressure.

7. Use of renewable feedstocks

A raw material or feedstocks should be renewable rather than disposed.

8. Reduce derivatives

Unnecessary derivatization (use of blocking groups, protection/deprotection, temporary modification of physical/chemical processes) should be minimized or avoided if possible, because such steps require additional reagents and can generate wastes.

9. Catalysis

Catalytic reagents are preferred to those stoichiometric.

10. Design for degradation

Chemical products should be designed so that at the end of their function they break down into innocuous degradation products and do not persist in the environment.

11. 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.

12. Inherently safer chemistry for accident prevention

Substances used in a chemical process should be chosen to minimize the potential for chemical accidents, including releases, explosions, and fires.

1.3 Synthetic strategy to achieve green chemistry processes

1.3.1 Alternative solvents

The fifth principle highlights the elimination of auxiliaries substances, when possible. The auxiliary substances take part in the manipulation of a chemical but they are not integral part of the molecule itself. Their use should be discouraged in the development of safe processes. When unavoidable, safer solvents and auxiliaries should be used. Traditional organic solvents are hazardous for the human health and environment. Both halogenated solvents (methylene chloride, chloroform, perchloroethylene, carbon tetrachloride) and aromatic hydrocarbons are carcinogens; volatile organic compounds (VOCs) represent a wide range of hydrocarbons and their derivatives are implicated in the atmospheric ozone generation. Unfortunately, these compounds are widely used in chemistry showing excellent solvency properties. In the last few years, chemists are involved in the utilization of alternative benign reaction media. Some of them are water, supercritical fluids (e.g supercritical carbon dioxide $s\text{CO}_2$) and ionic liquids. In fact, water is the most benign solvent on the earth; ionic liquids show low volatility, chemical, physical and thermal stability, possibility to recycle and reuse.

1.3.2 Catalytic reagents

As suggested by the ninth principle of *green chemistry*, catalytic processes are preferred, when possible, because they offer several advantages compared to the stoichiometric methods including energy minimization and reduction of wastes. In fact, a catalyst lowers the activation energy of a process and experimental conditions should be less drastic. In addition, a heterogeneous catalyst is generally recovered and used for successive runs with economic and environmental benefits.

1.3.3 Renewable feedstock

Renewable feedstock are generally plant-based matter that can be used as starting materials. However, the term indicates also substances that are easily regenerated within time frames that are accessible to the human lifetime. Nowadays, there are many concerns about depleting resources as the fossil fuels: sustainability; environmental effects; economical/political effects. The use of renewable feedstocks for biofuels and bio-based products is becoming urgent even if require industrial investments. With favourable national energy policies to develop a green industry and protect the environment, plant-based biomass becomes a new focus for the production of high value added products and environmentally friendly bio-based compounds.

Since many years, the mentioned strategies to realize *green chemistry* processes have been developed in our laboratory. As a program devoted to continue this topic, in this PhD course new synthetic methodologies have been optimized in order to use ecofriendly chemicals and renewable materials as starting materials for the production of biologically active compounds and fine chemicals. In particular, we projected new fluorinated catalysts useful for the epoxidation of olefins (Chap. 6); rare amino acids were prepared by benign oxidations (Chap. 9); unreported utilizations of dimethyl carbonate were described (Chap. 7, 8); high added-value products were obtained from glycerol (Chap. 10).

2 The catalytic system Hydrogen Peroxide (H_2O_2)/Methyltrioxorhenium (CH_3ReO_3 , MTO)

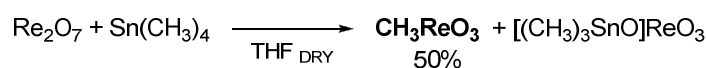
2.1 Introduction

In the oxidation reactions, catalytic processes are widely used because very often the oxidant of choice is weak and then it must be activate. A common reagent is hydrogen peroxide (H_2O_2), an ecofriendly oxidant which produces water as the only byproduct of oxidation. H_2O_2 is cheap, ease of handling, able to oxidize a wide variety of organic compounds and useful for the preparation of industrially interesting compounds with a high degree of purity useful for pharmaceutical applications. Then, it appears an attractive reagent to perform oxidation reactions in solution.⁴ Generally, metal oxides M_xO_y such as vanadium pentoxide (V_2O_5), molybdenum trioxide (MoO_3), osmium tetroxide (OsO_4) are utilized in order to activate hydrogen peroxide. However, these metallic species show several disadvantages. In fact, they are expensive, toxic and sometimes show a short lifetime.

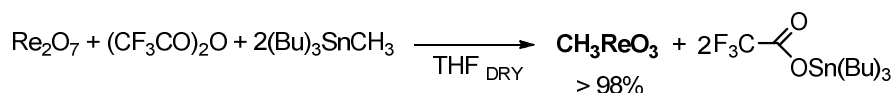
2.2 Methyltrioxorhenium (CH_3ReO_3 , MTO)

2.2.1 Synthesis

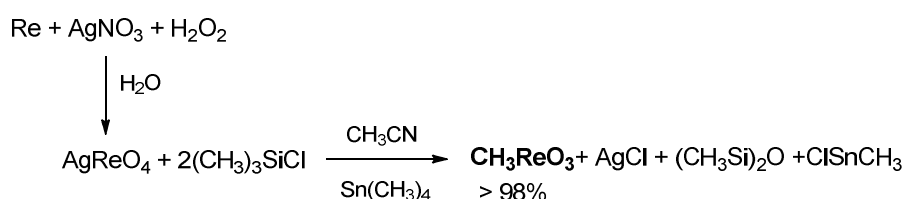
Around the 90s, with the aim to prepare new efficient, selective and easy to handle catalysts able to activate hydrogen peroxide, Herrmann and coworkers turned their attention to Rhenium (Re).⁵ Rhenium is an element exhibiting chemical properties similar to osmium and molybdenum but characterized by a lower toxicity. The first synthesized catalysts were Re-oxides (Re_xO_y) but unfortunately their efficiency in the reaction model (olefins epoxidation) were not satisfactory. Similar results were obtained by using $\text{Na}[\text{ReO}_4]$, $\text{NH}_4[\text{ReO}_4]$, $[\text{N}(\text{n-C}_4\text{H}_9)_4][\text{ReO}_4]$ and organometallic compounds such as $[(\text{CH}_3)_3\text{SnO}]\text{ReO}_3$,⁶ $[(\text{CH}_3)_3\text{SiO}]\text{ReO}_3$ ⁷ and $[(\text{C}_6\text{H}_5)_3\text{SiO}]\text{ReO}_3$. Finally, good results in term of epoxides were obtained with an organometallic specie, methyltrioxorhenium (**CH_3ReO_3 , MTO**). On the basis of its efficiency and selectivity in the oxidation reactions, Herrmann and co-workers developed several synthetic procedures in order to overcome the first synthetic difficulties and to increase the overall yield of MTO (*Schemes 1-3*). An efficient and large scale synthesis was reported in *Scheme 3*. Methyltrioxorhenium was produced in quantitative yield; the starting material was rhenium powder instead of Re_2O_7 , sensitive to the moisture.⁸



Scheme 1. Herrmann's synthesis of MTO (I)



Scheme 2. Herrmann's synthesis of MTO (II)



Scheme 3. Herrmann's synthesis of MTO (III)

2.2.2 Properties and reactivity

Methyltrioxorhenium is a colourless solid, stable at room temperature, soluble in the most common organic solvents (acetonitrile, tetrahydrofuran, ethanol, *t*-butanol, dichloromethane) and in acidic solutions. In *Figure 1*, physical, analytical and spectroscopic properties are summarized.

M.p. 106°C

IR (cm⁻¹, KBr): 1002, 950 [$\nu(\text{Re}=\text{O})$]

¹H-NMR (CDCl₃): δ (CH₃)=2.61

¹³C-NMR (CDCl₃): δ (CH₃)=19.03, $J(\text{C},\text{H})$ =138 Hz

¹⁷O-NMR (CDCl₃): 829 ppm

EI-MS: m/z =248/250 (185Re/187Re)

CH₃ReO₃: calc. C 4.82, H 1.20, O 19.26, Re 74.72; sper. C 4.84, H 1.19, O 19.30, Re 74.78

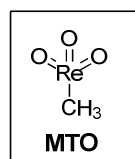
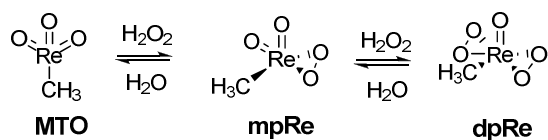


Figure 1. Properties of MTO

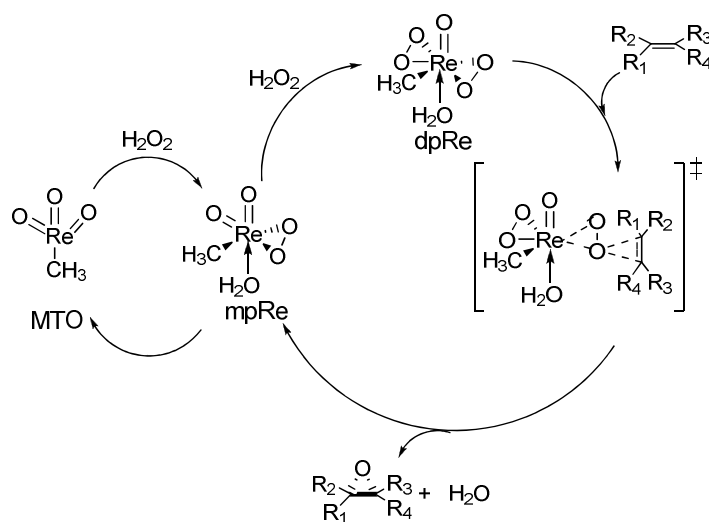
In the presence of hydrogen peroxide, MTO afford to two complexes: η^1 -monoperoxo complex $[\text{CH}_3\text{Re}(\text{O}_2)(\text{O}_2)]\text{H}_2\text{O}$ **mpRe** and η^2 -diperoxo complex $[\text{CH}_3\text{Re}(\text{O})(\text{O}_2)_2]\text{H}_2\text{O}$ **dpRe** (*Scheme 4*).⁹ The

formation of these active species is visualized by the intense bright yellow colour of the solution and determined by measurement of the absorbance at $\lambda=360\text{-}420\text{ nm}$. Their structure were confirmed by NMR spectroscopy and crystallography.



Scheme 4. Activation of H_2O_2 by MTO

Mechanistic studies showed that the active specie in the epoxidation reaction of olefins is the η^2 -diperoxo complex **dpRe** (Scheme 5).⁹



Scheme 5. Mechanism of epoxidation of olefins by MTO/ H_2O_2 system

Experimental data showed that MTO exhibits acidic properties (Lewis acid).¹⁰ Then, in the epoxidation reactions, by-products (e.g. diols) deriving from the opening of the epoxidic rings were observed. In order to decrease the acidic character of the catalyst and then the formation of these by-products, basic ligands such as pyridine¹¹ and its derivatives¹² or pyrazole¹³ were used.¹⁴ These

ligands were able to coordinate the rhenium atom of MTO increasing the stability and the lifetime of the catalyst.¹⁵ On the basis of these properties, new heterogeneous catalysts have been prepared in our laboratories. As example, MTO was supported on poly(4-vinylpyridine)cross-linked with divinylbenzene or poly(4-vinylpyridine N-oxides)cross-linked with divinylbenzene (*Figure 2*). These catalysts have been utilized to perform a large panel of oxidative transformations. An attractive feature of these catalysts is that they can be easily isolated from the reaction mixture without workup using a simple filtration to yield a solution of the pure product. They were recovered and reused for many runs without loss of efficiency and selectivity but with economic and environmental advantages.

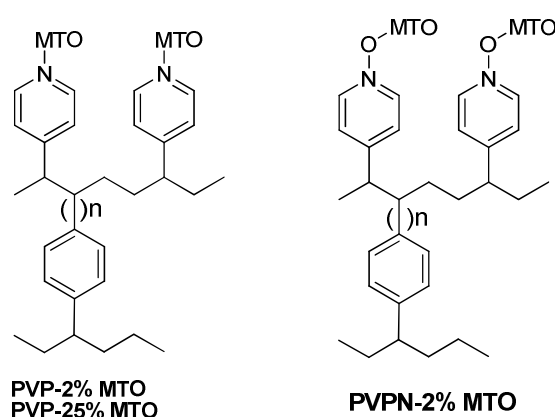
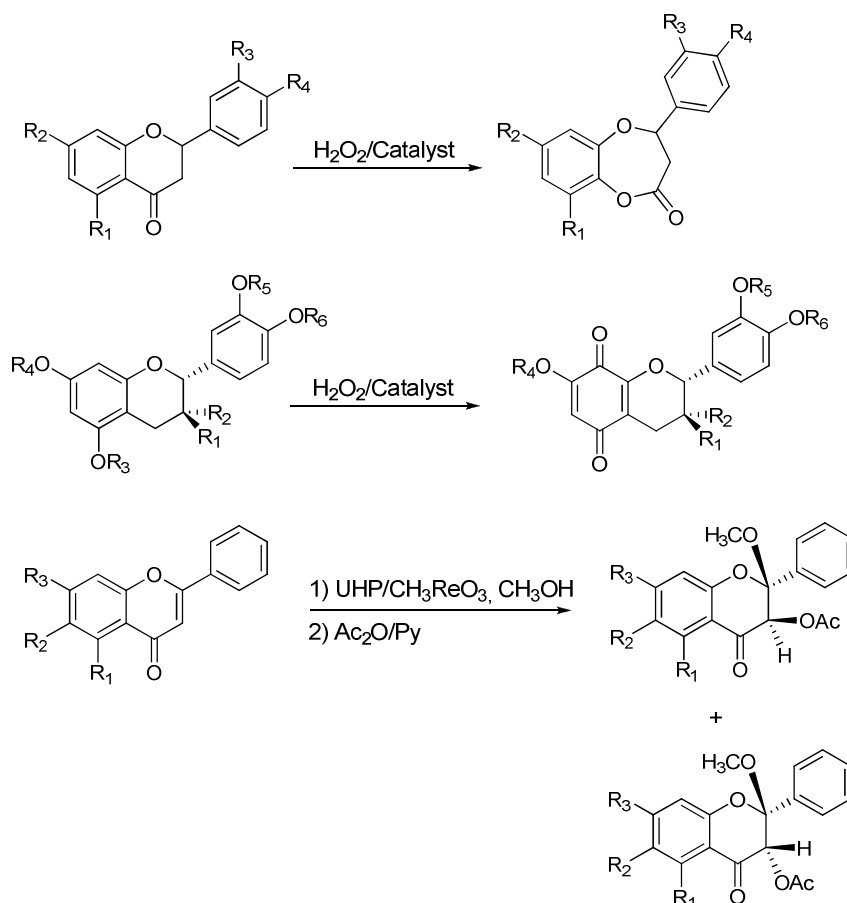


Figure 2. Polymer-supported MTO catalysts

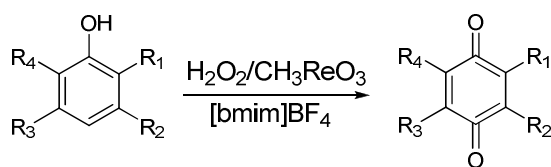
2.2.3 Oxidation of natural organic compounds

In consideration of the good results of the olefins epoxidation, the applicability of the catalytic system $\text{H}_2\text{O}_2/\text{MTO}$ was extended to a wide variety of organic compounds such as alcohols, diols, furans, amines, aromatic compounds, sugars. In the few last years, our research group investigated the efficiency and selectivity of this system in the oxidative modifications of natural organic compounds both in homogeneous and heterogeneous conditions. In particular, our research has been focused on the oxidation of flavonoids, a class of biologically active phenolic compounds in order to obtain new compounds. Lactones were synthesized from flavanones;¹⁶ *p*-benzoquinones from catechins,¹⁷ flavanones from flavones (*Scheme 6*).¹⁸ All these compounds were tested about their biological activities: lactones showed apoptotic activity on tumoral cell lines; *p*-benzoquinones and flavanones exhibited antifungal activity against three fungal strains of common saprotrophic soil and seed fungi, *Trichoderma koningii*, *Fusarium solani* and *Cladosporium herbarum*, potentially pathogenic for humans.



Scheme 6. Synthesis of new lactones by oxidation with H_2O_2 /MTO

More recently, we improved the environmentally character of the oxidations by using benign reaction media instead of traditional toxic solvents. Examples are the oxidations of alkylated phenols to the corresponding *p*-benzoquinones in ionic liquids (Scheme 7). High conversions and good yields of final products were obtained in very short reaction times.¹⁸

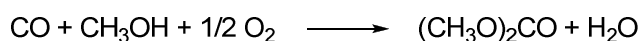


Scheme 7. Oxidation of alkylated phenols by MTO/ H_2O_2 in $[bmim]BF_4$

3 Dimethyl carbonate (DMC)

3.1 Synthesis

In the last few years, dimethyl carbonate (DMC), the simplest of all carbonates, received growing attention for its low toxicity and chemical versatility.¹⁹ DMC is synthesized by Enichem Company (Italy) through a *green* procedure based on the oxidative carbonylation of methanol and oxygen (Scheme 8). Non-hazardous materials are used and water is the only by-product of the reaction.



Scheme 8. Synthesis of DMC by Enichem Company

3.2 Physical, chemical and toxicological properties

Some physical and chemical properties of DMC are summarized in *Table 1* and *Table 2*.²⁰

Polarity and hydrogen bonding. DMC is a solvent able to form hydrogen bonds.

Miscibility with water. Although moderately polar, DMC shows good miscibility with water.

Thermal and hydrolytic stability. DMC is stable in water at room temperature and shows a thermal stability also at high temperatures.

Vapour pressure and evaporation rate. DMC is located in an intermediate position between the oxygenated solvents.

Flammability. DMC is a low flammable solvent.

Table 1. Chemical and physical properties of DMC

Properties	
Molecular weight	90
Density (Kg/l, 20°C)	1.07
Viscosity (MPa.s, 20°C)	0.6
Boiling point (°C)	90
Vapour pression (Kpa, 20°C)	5.4
Evaporation rate (20°C)	2.7
Dielectric costant (20°C)	3.1
Water miscibility (% p, 20°C)	17
Autoignition (°C)	458
Explosion limit (% v in air)	
- upper	24.5
- lower	9.5

Table 2. Solubility parameters, polarity hydrogen bonds of DMC compared to those of the common organic solvents

	α ^(a)	β ^(b)	ET30 ^(c)	DN ^(d,m)	Z ^(e,m)	δ ^(f,n)	δ ^(g,p)	δ_p ^(h)	δ_p ^(g)	δ_H ⁽ⁱ⁾	δ ^(k)	τ ^(l,p)
Esano	0.00	0.00	31.0	0.0		0.0	7.3	7.3	0.0	0.0	7.3	0.0
Toluene	0.00	0.11	33.9	0.1		0.4	8.9	8.8	0.7	1.0	9.0	0.0
THF	0.00	0.55	37.4	20.0	58.8	1.6	9.1	8.2	2.8	3.9	8.3	3.7
EtAcO	0.00	0.45	38.1	17.1	64.0	1.7	9.1	7.4	2.6	4.5	7.4	5.2
DMC	0.00	0.38	38.8	17.2	64.7	0.9	9.9	7.8	1.9	4.7	7.8	6.2
CHCl ₃	0.20	0.10	39.1	4.0	63.4	1.0	9.3	8.77	1.5	2.8	7.7	4.9
Acetone	0.08	0.43	42.2	17.0	65.7	2.7	9.9	7.6	5.1	3.4	7.7	6.1
DMF	0.00	0.69	43.8	26.6	68.4	3.8	12.1	8.5	6.7	5.5	8.3	8.1
CH ₃ CN	0.19	0.40	45.6	14.1	71.3	3.9	12.0	7.5	8.8	3.0	8.0	9.0
CH ₃ OH	0.98	0.66	55.4	30.0	83.6	1.7	14.5	7.4	6.0	10.9		

(a) Ability to make hydrogen bond as proton donor; (b)) Ability to make hydrogen bond as proton acceptor; (c) Dimroth-Reichardt's value; (d) Gutmann's value; (e) Kosower's value (f) dipole moment; (g) Hilbedrand's solubility parameter; (h) Hansen's parameter solubility, dispersion's component; (i) Hansen's parameter solubility, polarity component; (j) Prausnitz's solubility parameter, no polar component; (k) Prausnitz's solubility parameter, polar component; (m) Kcal/mole; (n) Debye; (p) cal/cm³

Table 3 reported the toxicological and ecotoxicological properties of DMC. It is characterized by a low acute toxicity for inhalation, contact and it is not irritant for skin and eyes. From the environmental point of view, it shows a very low toxicity to aquatic organisms and high biodegradability.

Table 3. Toxicological and ecotoxicological properties of DMC

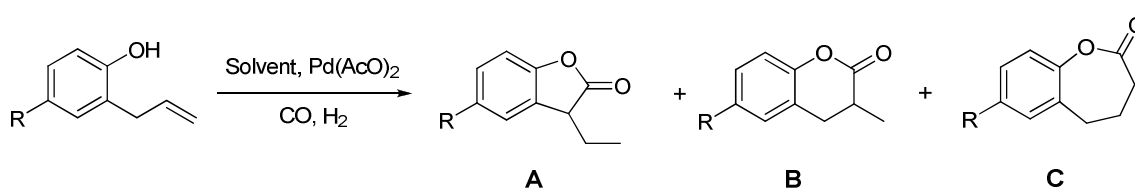
Highly toxicity	Inhalation, LC ₅₀ ^(a)	140 mg/l, 4
	Ingestion, LD ₅₀ ^(a)	13 g/Kg
	Skin contact, LD ₅₀ ^(a)	>2.5 g/Hg
Irritation	Skin (0.5 ml/4h) ^(b)	No irritant
	Eyes (400 μ l) ^(b)	Light irritant
Chronic toxicity	Ingestion (90 giorni) ^(a)	NOEL, 0.5 g/Kg/day
Mutagenesis	Citogenic mutagenesis	Negative
	Chromosomic aberration ^(c)	Negative
	DNA remediation	Negative
Biodegradation	MITI mod. (O ₂ consumption) ^(d)	Easy biodegradable (88%)
Ecotoxicity	Fish (96 h) ^(e)	LC ₅₀ > 1 g/l

(a) rat; (b) rabbit; (c) hamster culture cells in vitro;
(d) human lymphocytes culture cells in vitro; (e) *Leuciscus Idus*

Thanks to these benign properties, DMC is a good alternative to the traditional toxic solvents that can contribute to improve the relationship between application requirements and environmental compatibility and then to realize *green* processes.

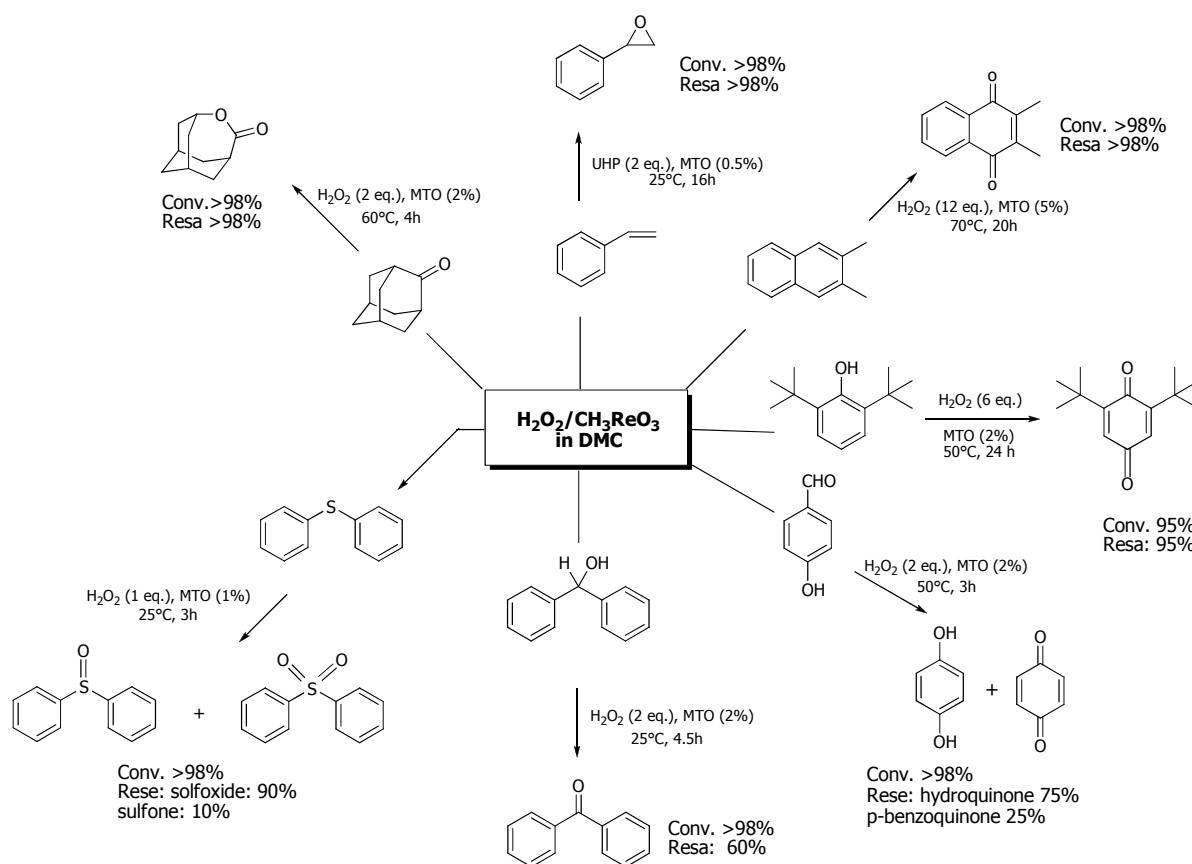
3.4 Applicability as solvent

In recent years, DMC has been largely used in the field of coatings, adhesives, aerosols, metal cleaning, degreasing in textiles and tanning. Instead, only few examples reported its use as solvent in organic synthesis. In a work, DMC was used in the oxidation reactions catalyzed by ruthenium tetroxide (RuO_4) or performed by sodium periodate (NaIO_4), sodium hypochlorite (NaClO) and ozone (O_3).²¹ A second application of DMC was reported in the Pd-catalyzed cyclocarbonylation of allyl-2-phenols for the synthesis of lactones.²² In these reactions, the solvent plays a key role in the selectivity. When the cyclocarbonylations were carried out in dichloromethane, **A** and **B** lactones were the main products; in DMC only **C** lactones were isolated (*Scheme 9*).



Scheme 9. Cyclocarbonylation of allyl-2-phenols

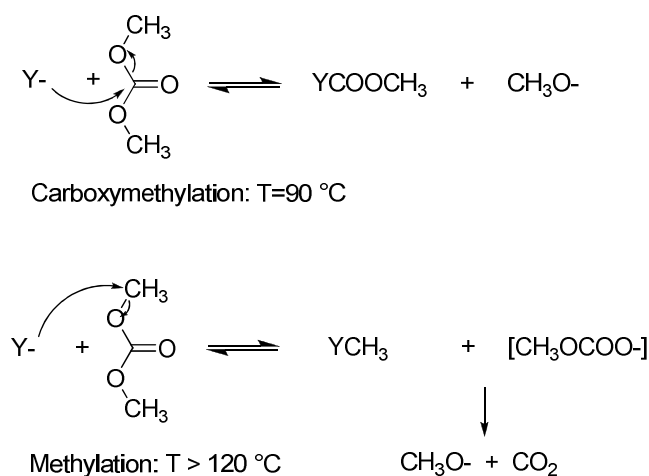
Recently, we experimented the efficiency of DMC in the oxidation with the H_2O_2 /MTO catalytic system. In *Scheme 10* are reported some of the possible applications. Reactions proceeded in very good yields and in some cases better than in dichloromethane or acetic acid.²³



Scheme 10. Catalytic oxidations of organic compounds with H_2O_2 /MTO in DMC

3.5 Applicability as reagent

DMC can be as utilized as chemical. In fact, as extensively reported by Tundo et al.,²⁴ DMC possesses two active centers (alkyl and carbonyl carbons) whose reactivity depends on the experimental conditions. Thus, in the presence of a nucleophile (Y), it may react as a methylating or as a carboxymethylating agent, depending on the reaction conditions (*Scheme 11*). At reflux temperature ($T=90^\circ\text{C}$), final products are carboxymethylated products; at higher temperatures (generally at $T=160^\circ\text{C}$), final products are methylated products. By-products were methanol (that can be distilled) and carbon dioxide. In these reactions, DMC is an environmentally benign substitute for hazardous and toxic phosgene, methyl halides and dimethyl sulfate (carcinogen).²⁵

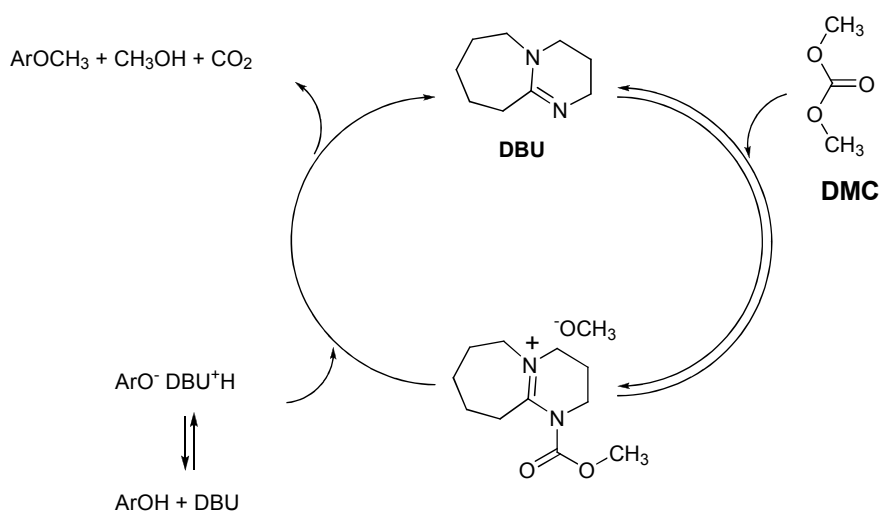


Scheme 11. Reactivity of DMC

In consideration of the high temperatures required, the reactions were generally performed under gas liquid phase-transfer catalysis (GL-PTC) conditions or in autoclave over alkali ion-exchanged zeolites, alumina, alumina-silica, CrPO_4 , AlPO_4 , $\text{CrPO}_4\text{-AlPO}_4$, $\text{AlPO}_4\text{-Al}_2\text{O}_3$, cesium carbonate.²⁶

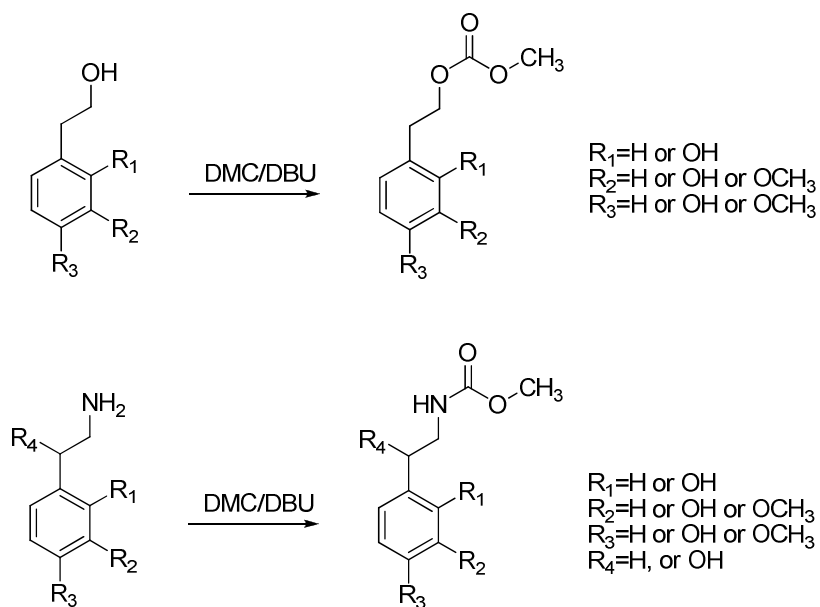
3.5.1 Reactions with DMC and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU)

In search for milder and more practical conditions to perform the methylation of phenolic compounds with DMC, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) has been proposed as a novel and active catalyst.²⁷ The reaction was carried out under atmospheric pressure at reflux temperature. According to the proposed mechanism, DBU reacts with DMC to generate a more active methylating agent which presumably reduces the activation energy required for the methylation (*Scheme 12*). The system DMC/DBU has been successfully utilized for the methylation of indoles, benzimidazoles and for the esterification of carboxylic acids.²⁸



Scheme 12. Possible catalytic mechanism for methylation of phenols by DBU/DMC system

More recently, our research group developed simple and efficient procedures to obtain new carboxymethylated phenolic derivatives ²⁹ and methyl carbamate of naturally occurring catecholamines ³⁰ (Scheme 13) by utilizing the DMC/DBU system in very good yields. In all cases, selective protections of the alcoholic or amino groups were observed under controlled conditions.



Scheme 13. Selective protection of some functionalities with DMC/DBU

4. 2-Iodoxybenzoic acid (IBX)

4.1 Introduction

The chemistry of hypervalent iodine organic reagents has experienced a great development starting from the early 1990s. This increasing interest essentially was due to the very useful oxidizing properties of these compounds, both as dehydrogenating and oxygenating reagents combined with the fact that their utilization constitutes an environmentally benign alternative to that of heavy metal-based oxidizing reagents.

More recently, 1,2-benzodioxol-3(1*H*)-one 1-hydroxy-1-oxide (2-iodoxybenzoic acid, **IBX**) found widespread applications in organic synthesis as a highly efficient and mild oxidant. It is a white crystalline solid, soluble in dimethyl sulfoxide (*Figure 3*), stable for at least 6 months also at 25 °C.³¹ Currently, a formulation of IBX, composed of a mixture of 2-iodoxybenzoic acid (49%), isophthalic acid (29%) and benzoic acid (22%), is commercially available (SIBX).³²

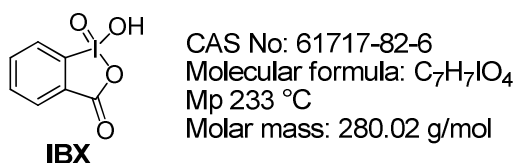
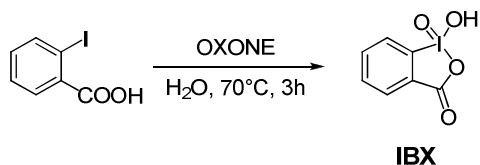


Figure 3. Chemical structure of IBX

4.2 Synthesis and properties

IBX was discovered from Hartman and Mayer in 1893. It was prepared by oxidation of 2-iodobenzoic acid with potassium bromate (KBrO₃) in 0.73 M sulphuric acid.³³ This procedure was very hazardous because, according to the international classification of substances toxicity, KBrO₃ is carcinogen (R45). In addition, the reaction produced bromine vapours, causing personal and environmental hazards. Moreover, IBX was reported to be explosive under impact or heating to >200°C.³⁴ Some authors suggested that the explosive properties of some samples of IBX were due to the presence of impurities of potassium bromate utilized during its preparation.³⁵ Then, oxidants such as potassium permanganate, peracetic acid and sodium hypochlorite were used in alternative.³⁶ In 1999, a user-friendly synthetic procedure has been described by Santagostino et al. based on the utilization of oxoneTM (2KHSO₅-KHSO₄-K₂SO₄) in water (*Scheme 14*).³⁷ This procedure offers many advantages over the previous ones: 1) experimental convenience, since it used a non toxic reagent and a benign solvent; 2) environmentally safe sulfate salts as the only by-products; 3) the

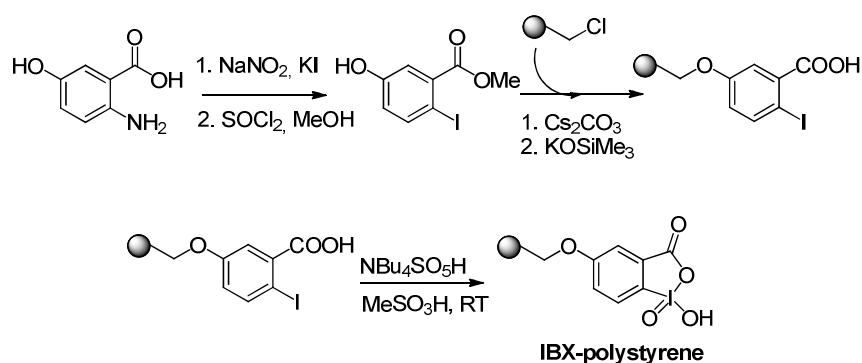
production of analytically pure ($\geq 99\%$) samples of IBX in satisfactory yield (80%); 4) the possibility to produce until 45-50 g batches of IBX.



Scheme 14. Synthesis of IBX by Santagostino et al.³⁷

The presence of IBX on the scene of the organic synthesis was limited for several years also for its remarkable insolubility in organic solvents like ethanol, acetone, acetonitrile, chloroform, methylene chloride. Recently, some studies demonstrated that IBX is reactive also in suspension. This result evaluated a wide range of applicability of IBX.

Further developments in the application of IBX include polymer-supported IBX which enable clean isolation of the product just by filtering the reaction mixture and recovery and regeneration of the separated polymer for efficient reuse for the next reaction. Among the polymer-supported IBX reagents described in the literature, IBX-polystyrene was found to be superior in the oxidative conversions of alcohols into carbonylic groups. The synthetic procedure for the preparation of IBX-polystyrene is reported in *Scheme 15*.³⁸

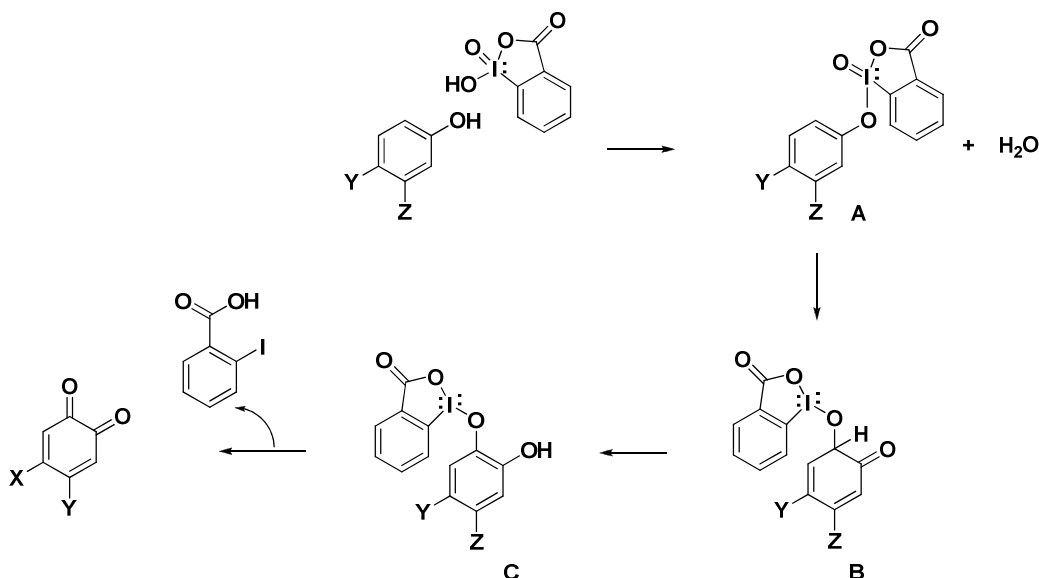


Scheme 15. Synthesis of IBX-polystyrene

4.3 Synthetic applications

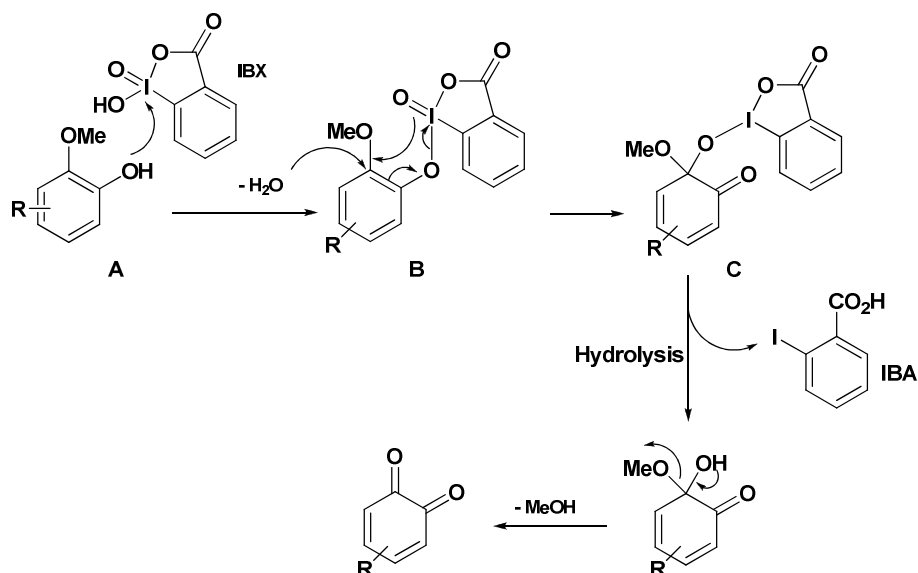
The main synthetic applications of IBX include the oxidation of alcohols to carbonyl compounds and carboxylic acids; oxidation 1,4-diols to γ -lactols; deoxygenation of oximes to carbonyl compounds; deprotection of thioacetals/thioketals, silyl ethers and THP ethers; oxidation of benzylic halides into the corresponding aldehydes or ketones; conversion of phenols into *o*-quinones; conversion of aldehyde group into cyano group; conversion of alcohols, ketones and aldehydes into the corresponding α,β -unsaturated carbonyl compounds; construction of heterocycles from functionalized anilide systems; synthesis of α -substituted carbonyl compounds.³⁹

Of particular interest is the ability of IBX to perform a regioselective oxidation of phenolic compounds possessing at least one electron-donating group in order to produce the corresponding *o*-quinones, useful reagents for Diels-Alder reactions and precursors of catecholic compounds. A plausible reaction mechanism was reported in *Scheme 16*.⁴⁰ The phenolic compounds combines with IBX to extrude H₂O affording the I^V intermediate **A**, which serves to intramolecularly deliver the oxygen to the most nucleophilic and least congested *ortho* site on the starting phenol. During this delivery process, the I^V atom is reduced to the I^{III} species **B**, which in turn tautomerizes to intermediate **C**. The catecholic compound is oxidized to the corresponding quinone by I^{III} species.



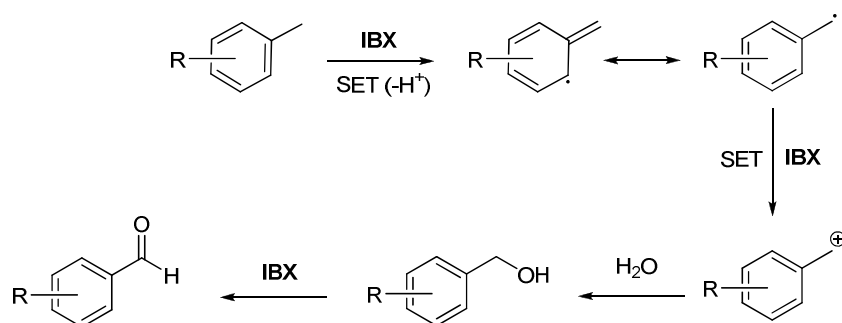
Scheme 16. Selective oxidation of phenolic compounds with IBX

With a similar mechanism, IBX is able to carry out the oxidative demethylation of methyl aryl ethers (Scheme 17). In this case, water plays a crucial role promoting the hydrolysis of the complex and the formation of the corresponding *o*-quinone.⁴¹



Scheme 17. Oxidative demethylation of methyl aryl ethers with IBX

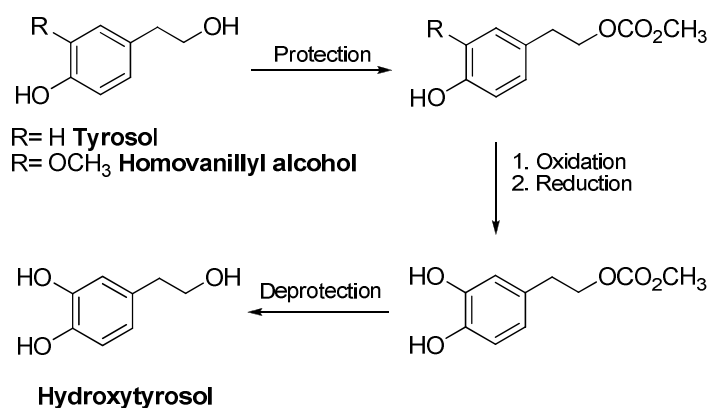
Nicolau and al. demonstrated that IBX can react also with a radical process of transferring a single electron (SET). These findings have directed their studies to other types of reactions such as dehydrogenation of aldehydes and ketones⁴² and the oxidation of benzyl systems (Scheme 18).⁴³



Scheme 18. SET mechanism of benzylic oxidation with IBX

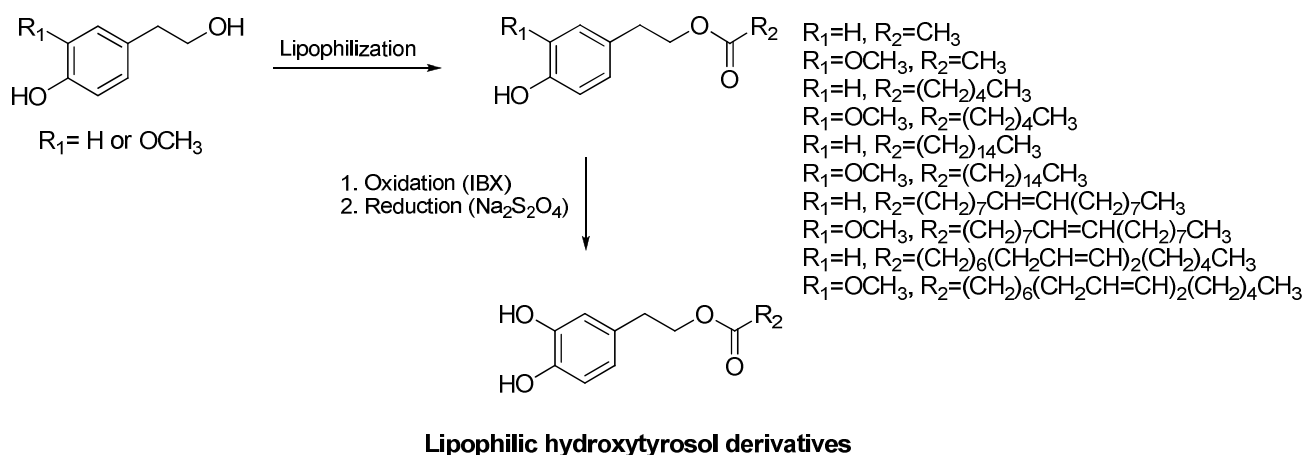
4.3.1 Synthesis of catecholic compounds

In the last few years, in our laboratory IBX was the oxidant of choice to synthesize a large panel of biologically active catecholic compounds. Hydroxytyrosol, a naturally occurred *ortho*-phenolic compound exhibiting antioxidant properties, was synthesized by a three-step high-yielding procedure from natural and low-cost compounds such as tyrosol or homovanillyl alcohol (Scheme 19).⁴⁴ At first, the efficient chemoselective protection of the alcoholic group of these compounds was performed by using dimethyl carbonate (DMC) as reagent/solvent; secondly, the oxidation with 2-iodoxybenzoic acid (IBX) and *in situ* reduction with sodium dithionite ($\text{Na}_2\text{S}_2\text{O}_4$) allowed preparing carboxymethylated hydroxytyrosol; finally, by the mild hydrolytic step, hydroxytyrosol was obtained in high yield and purity.



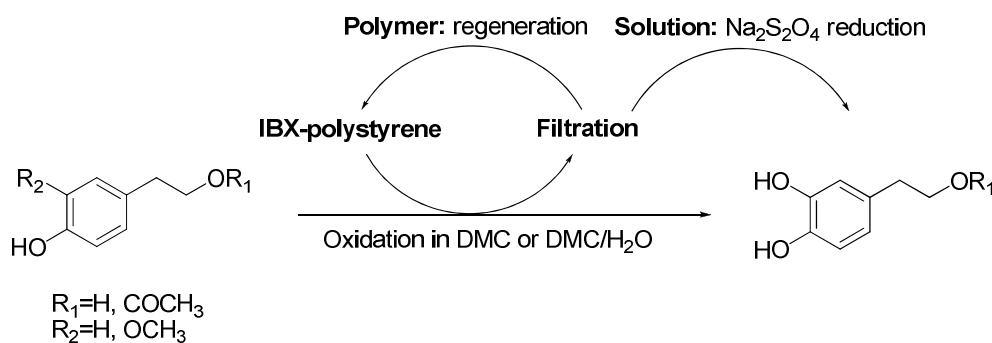
Scheme 19. Synthesis of hydroxytyrosol by homogeneous IBX

By using a similar methodology, lipophilic hydroxytyrosol derivatives, useful as additives in pharmaceutical, food and cosmetic preparations were prepared (Scheme 20). At first the chemoselective derivatization of the alcoholic group of tyrosol and homovanillyl alcohol was performed by using acyl chlorides without any catalyst to obtain the corresponding lipophilic derivatives and then these compounds were converted in good yield and high purity into the hydroxytyrosol derivatives by oxidative/reductive pathway with IBX/ $\text{Na}_2\text{S}_2\text{O}_4$ system.



Scheme 20. Synthesis of lipophilic hydroxytyrosol derivatives

In view of industrial applications, we verified the efficiency of polymer-supported IBX in the oxidative insertion of a hydroxyl into tyrosol derivatives as well as in the demethylation reaction of homovanillyl alcohol derivatives to prepare hydroxytyrosol and carboxymethylated hydroxytyrosol through an one-pot procedure (*Scheme 21*). After the work-up, final products were isolated in quantitative yields.⁴⁵



Scheme 21. Conversion of phenolic compounds into hydroxytyrosol derivatives by IBX-polystyrene

At the end, the polymeric reagent was recovered, regenerated and reused for at least five oxidation reactions without lack of efficiency to give the final products in excellent yields.

The IBX-strategy was used also for the preparation of a large panel of naturally occurring catecholic compounds (*Figure 4*).⁴⁶

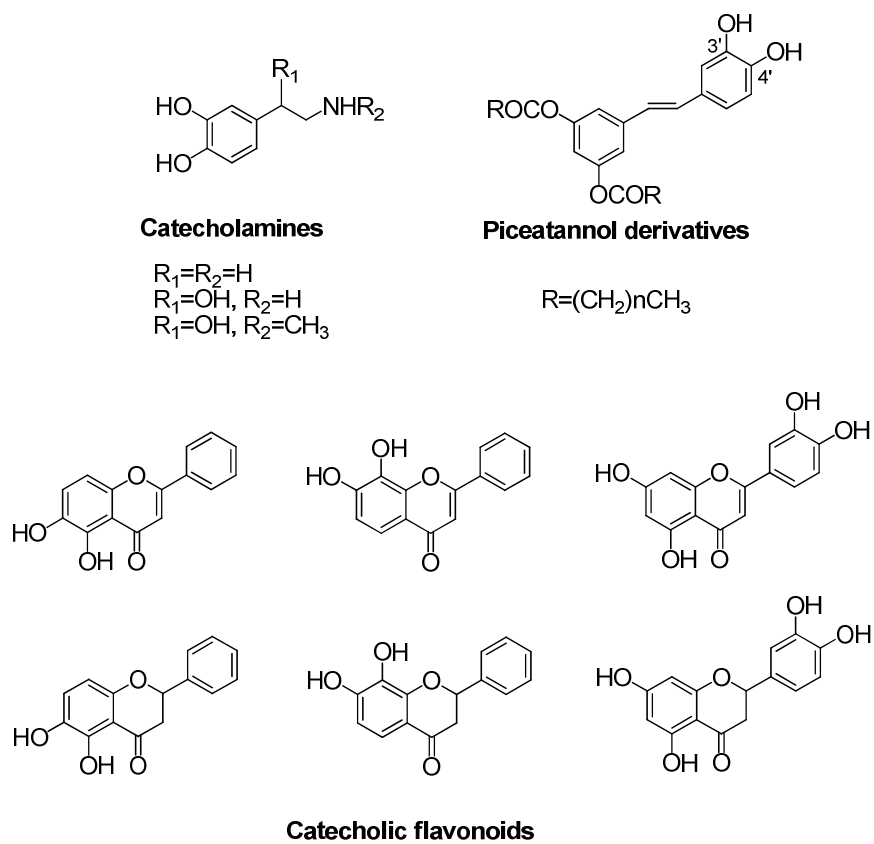


Figure 4. Catecholic compounds prepared by IBX-strategy

5. Glycerol

Introduction

Glycerol (1,2,3-propanetriol or glycerine) is a colourless, odourless, viscous and hygroscopic liquid; it is a non toxic compound, soluble in water and biodegradable. In *Figure 5* some chemical properties are described. Glycerol is an important intermediate in the metabolism of living organisms and can be synthesised by chemical and biotechnological procedures.

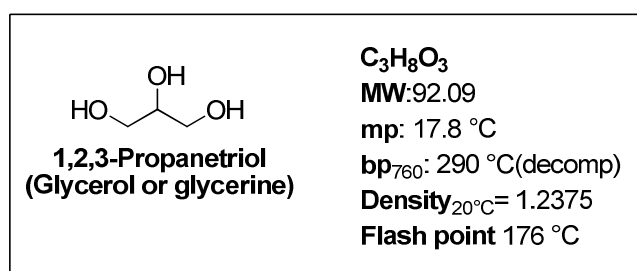
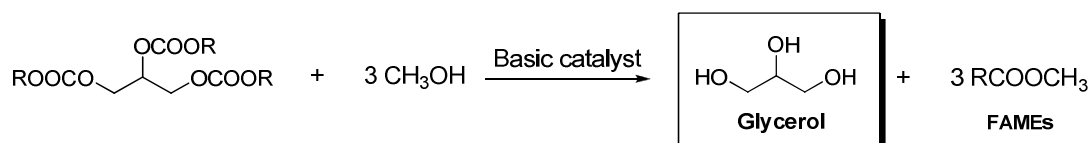


Figure 5. Some chemical properties of glycerol

This compound has been discovered in 1779 investigating the saponification products of olives by treatment with lead oxide;⁴⁷ today it is the major value-added by-product produced from oil saponification and fat transesterification reactions performed during oleochemical and biodiesel manufacturing processes. In its most common formulation, biodiesel is a mixture of methyl esters of fatty acids (FAMES), chemically obtained produced by treating soybean or rapeseed oil with an excess of methanol in the presence of a basic catalyst (*Scheme 22*). Generally, for 10 tons of biodiesel, 1 ton of glycerol is produced.⁴⁸



Scheme 22. Acyl glycerol transesterification with methanol to produce FAMES

Biodiesel is a biofuel derived from renewable resources (biomasses) exhibiting properties comparable to those of petroleum-based diesel. The utilization of the biomasses as source of energy is one of the possible strategies useful to solve the great energy crisis due to a depletion of fossil

resources and on environmental problems, e.g. the global warming. The development and utilization of these fuels is promoted in several countries in order to decrease the emission of carbon dioxide from fossil fuels, mitigate air pollution and reduce the dependence upon imported energy.

Glycerol is widely used in pharmaceutical formulations. Nowadays, these markets are generally considered mature making it difficult to absorb the glycerol surpluses. Thus, new strategies to valorise this compound and to convert it into high-value added products are an attractive challenge for industrial and academic researchers.

5.2 A biorenewable building block

Glycerol exhibits a highly functionalized nature; in fact, it presents two primary and one secondary hydroxyl groups. Then, it can be oxidized, reduced, halogenated, etherified and esterified. As shown in *Figure 6*, a wide number of high value-added chemicals can be obtained using glycerol as starting material.

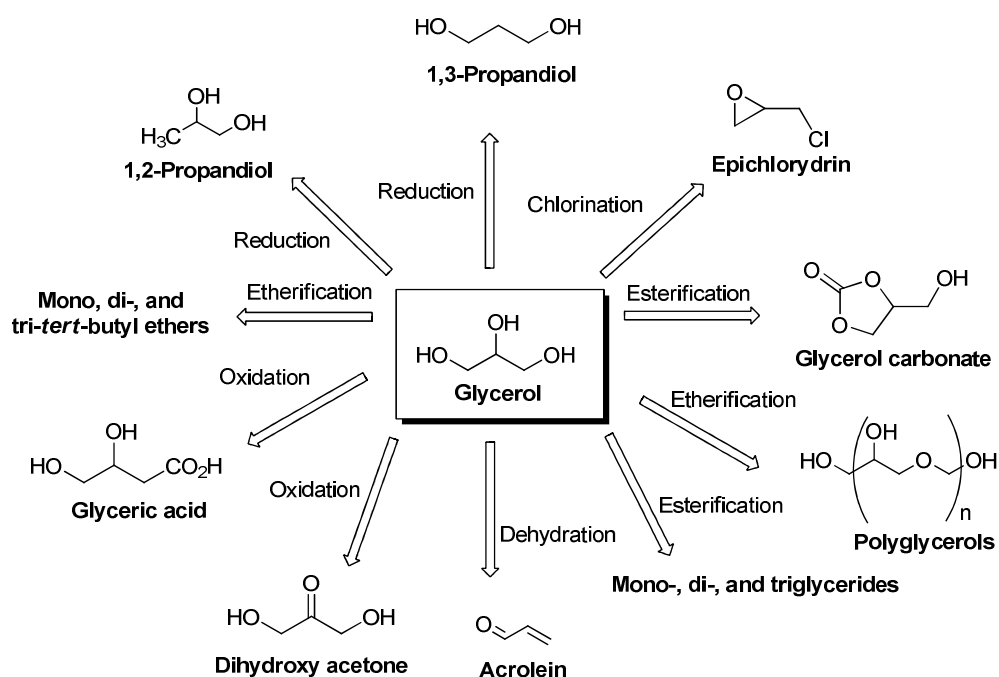


Figure 6. High added-value compounds derived from glycerol

✓ **Dihydroxy acetone** is a cosmetic ingredient in sunless tanning formulations prepared by chemoselective oxidation of glycerol's secondary hydroxyl group performed both by chemical and biocatalytic routes. Metal catalysts based on carbon-supported platinum and palladium or

microbial fermentation by *Gluconabacter oxydans*⁴⁹ are able to carry out this oxidative transformation.

- ✓ **Epichlorohydrin** is a chemical used on large scale in the production of plastics, epoxy and phenoxy resins. Today, it is industrially synthesized from Solvay by the patented “Epicerol process” based on a catalytic reaction of glycerol with hydrochloric acid followed by dehydrochlorination by sodium hydroxide. Solvay currently produces 100.000 ton/year of epichlorohydrin.⁵⁰
- ✓ **1,2-Propanediol, 1,3-propanediol** and **acrolein** are starting materials for the production of polyesters, polyethers, polyurethanes and acrylonitrile. 1,2-Propanediol, 1,3-propanediol derive from glycerol derivatives through selective hydrogenation reactions;⁵¹ acrolein is obtained by dehydration of glycerol. The selectivity of the synthesis increases in supercritical conditions and in the presence of acidic catalysts.
- ✓ **Glycerol-based polymers** such as polyglycerols and polyglycerol esters find a wide number of applications in cosmetic, pharmaceutical, food and detergent industries.⁵² They are prepared by condensation of glycerol in the presence of an alkaline catalyst. Mixture of di-, tri- and tetraglycerol derivatives are obtained varying the experimental conditions. The esterification of polyglycerol fatty acids gives polyglycerol esters. Their properties depend on the chain length and the degree of esterification.

5.3 1,2-Glycerol carbonate

5.3.1 Properties and synthesis

Among the fine chemicals that can be obtained from glycerol, 1,2-glycerol carbonate (4-hydroxymethyl-1,3-dioxolan-2-one) turned our attention (*Figure 7*). It is a colourless liquid, highly soluble in water, stable and low-toxic, relatively new for the chemical industry. It offers useful applications as a novel component of gas separations membranes, surfactants; it is used as solvent for varnishes, colours, accumulators, pharmaceuticals and ingredient in cosmetics and detergents.⁵³

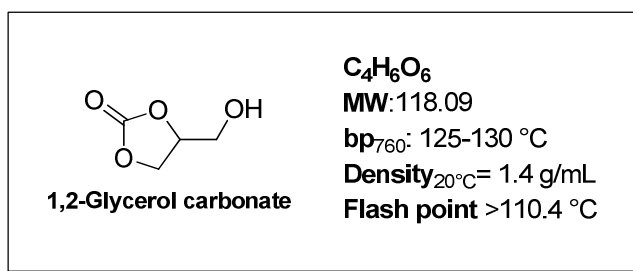
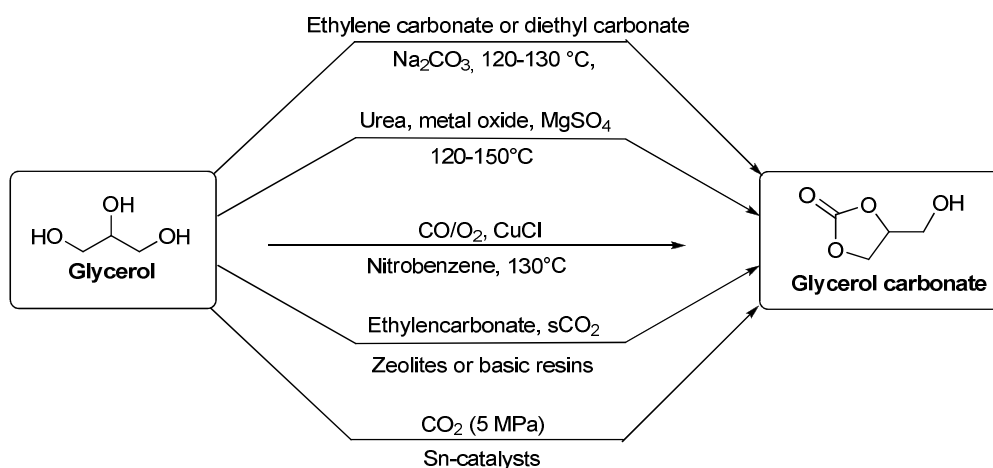


Figure 7. Some properties of 1,2-glycerol carbonate

Glycerol carbonate is synthesised by several routes. For many years, it has been prepared by reaction of epichlorohydrin with potassium hydrogen carbonate at 80 °C in the presence of 13-crown ether. Nevertheless, procedures based on the direct utilization of glycerol are more attractive (*Scheme 23*).

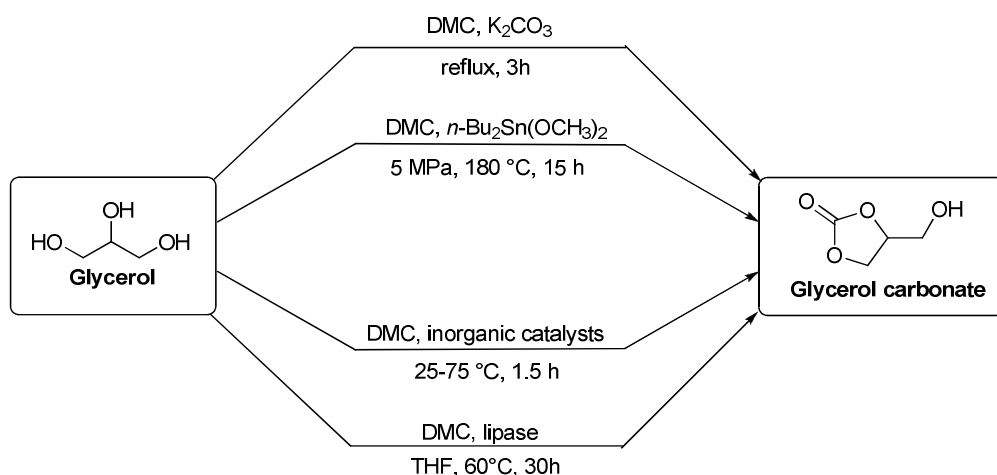


Scheme 23. Synthesis of 1,2- glycerol carbonate

A first procedure is the transesterification of glycerol with ethylene carbonate carried out at 125°C in the presence of sodium bicarbonate (yield: 81%).⁵⁴ A recent patent describes a synthesis based on the reaction between urea and glycerol. The reaction was carried out at 120-150 °C in the presence of an dehydrating agent such an anhydrous salt or molecular sieve and a catalyst (yield: 92 %).⁵⁵ A promising methodology is based on the reaction between glycerol and carbon dioxide or carbon oxide and oxygen in the presence of Cu(I) as catalyst.^{56,57} The reaction with carbon dioxide was carried out in supercritical CO₂ (sCO₂) as medium and in the presence of zeolite and ethylene carbonate as a co-source of carbonate group. Zeolites as well as strongly basic catalysts such as Amberlyst A26 enhanced the reactivity of glycerol adsorbed onto the solid catalyst and the ethylene

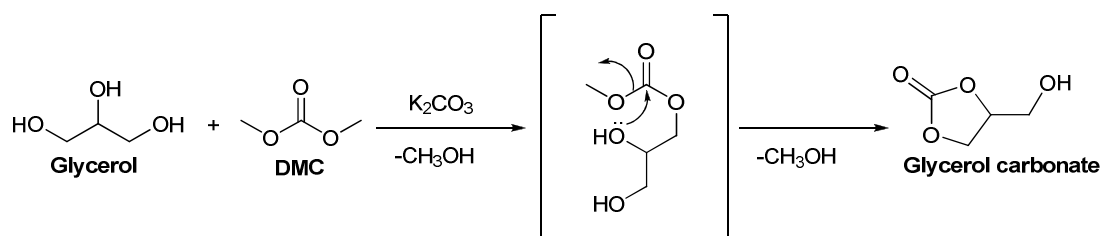
carbonate dissolved in sCO₂. Recently, Aresta et al. reported the carboxylation of glycerol with carbon dioxide in the presence of Sn-catalysts such as *n*-Bu₂Sn(OMe)₂, *n*-Bu₂SnO and Sn(OMe)₂ but only traces of 1,2-glycerol carbonate was obtained.⁵⁸

A very promising route for the production of glycerol carbonate is the reaction between glycerol and dimethyl carbonate. Some experimental conditions are described in *Scheme 24*.



Scheme 24. Several routes to prepare 1,2-glycerol carbonate from glycerol and DMC

The first example was reported by Rokicki et al.⁵⁹ When the reaction was performed under controlled conditions (70 °C, 3 h, glycerol/DMC=1/3) in the presence of K₂CO₃ as a catalyst, 1,2-glycerol carbonate was isolated in quantitative yield. A plausible mechanism of the reaction is described in *Scheme 25*. Under these experimental conditions, glycerol is carboxymethylated on the primary alcoholic group by DMC to produce an intermediate. The secondary alcoholic group of the intermediate attacks the carbonyl moiety producing glycerol carbonate and methanol.



Scheme 25. Synthesis reported by Rokicki et al.⁵⁹

Under drastic conditions, two by-products were obtained (*Figure 8*). Using DMC in a large excess (10-fold) and long reaction times (48 h), diglycerol tricarbonate **A** was observed as by-product (yield: 18%); at higher temperature (90 °C), also the third hydroxyl group of glycerol was derivatized and 4-(methoxycarbonyloxymethyl)-1,3-dioxolan-2-one **B** was isolated (yield: 34%).

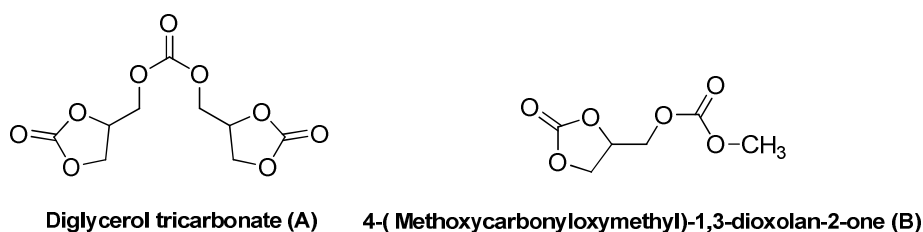


Figure 8. Main by-products of synthesis of glycerol carbonate from glycerol and DMC

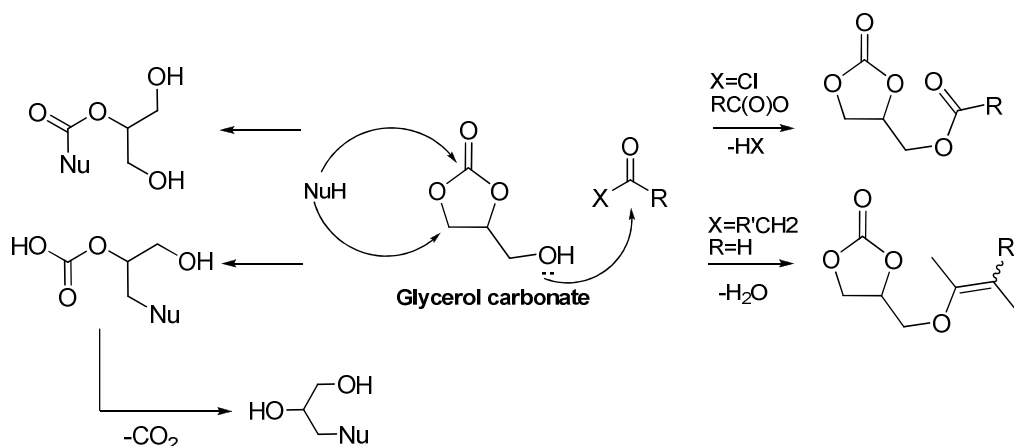
Aresta et al. performed the transesterification of glycerol with DMC in the presence of *n*-Bu₂Sn(OMe)₂ but also under these experimental conditions, the conversion rate of glycerol into glycerol carbonate was low. Recently Gomez et al. reported an extensive research focused on the optimization of the synthesis of glycerol carbonate by transesterification with a large panel of inorganic catalysts (CaO, Ca(OH)₂, CaCO₃, MgO).⁶⁰ In each case, they observed good conversions and yields and short reaction times. The order of activity of the catalysts used was CaO > Ca(OH)₂ > MgO > CaCO₃.

More recently, a biotechnological transesterification reaction of glycerol and DMC was performed in THF.⁶¹ The enzyme of choice was lipase from *Candida Antarctica* (Novozym 435) which showed high catalytic activity and provided quantitative yield of glycerol carbonate under mild conditions.

5.3.2 Reactivity

Being an inexpensive compound derived from a by-product, glycerol carbonate is of considerable interest as starting material for the production of fine chemicals. Recently, it has been utilized in the synthesis of new polymeric materials and its use in the self-condensation to oligomers has been explored as an alternative reagent to glycidol.⁶²

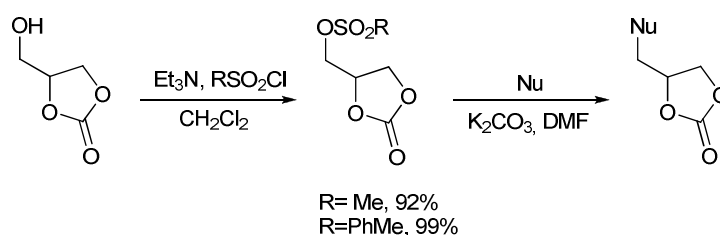
Glycerol carbonate exhibits multifunctional character. The oxygen atom of the hydroxymethyl group can be act as nucleophile, whereas both carbonyl and alkyl carbon atoms show electrophilic character (*Scheme 26*).



Scheme 26. The multiple reactivity of 1,2-glycerol carbonate

For example, the primary group of glycerol carbonate may react with aldehydes,⁶³ anhydrides,⁶⁴ isocyanates⁶⁵ to form enol ethers, esters or urethanes.⁶⁶ Also, glycerol carbonate is employed as a source of mixed carbonates which reacted with diamines to obtain polyurethanes avoiding the use of hazardous isocyanates. In alternative, glycerol carbonate may react with nucleophiles but only some examples have been reported in the literature and poor yields of final products were obtained.

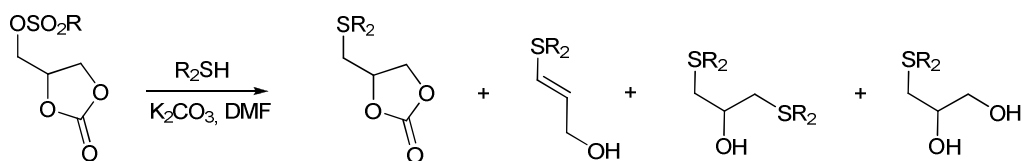
In order to increase the reactivity of glycerol carbonate toward nucleophiles, Rollin et al. activated the free alcoholic group through sulfonate formation using mesyl or tosyl chloride under basic conditions (*Scheme 27*).⁶⁷



Scheme 27. Sulfonate activation and nucleophilic substitution in glycerol carbonate

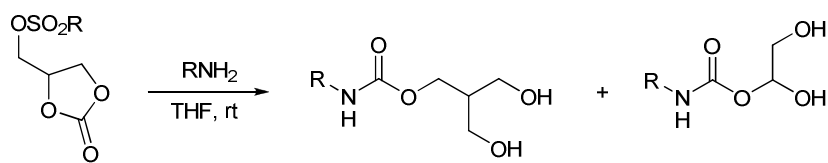
The reactivity of mesylated derivative was tested by using phenol, *meta*-methoxyphenol, aniline as nucleophiles but poor yields of final products of mono-substitution were obtained (5-30%). In the presence of thiophenol, a complex mixtures of mono-substitution, double substitution and elimination products were obtained (*Scheme 28*). The yield of the double substitution product improved increasing the amount of thiophenol and using tosylated glycerol carbonate instead of

mesylated derivative. The mono-substitution product was kept under control by using one equivalent of thiophenol.



Scheme 28. Reaction of tosylated 1,2-glycerol carbonate with thiophenol

More recently, Rousseau et al. exploited the reactivity of tosylated 1,2-glycerol carbonate toward oxygen and nitrogen nucleophiles. The results confirmed the poor reactivity of *meta*-methoxyphenol whereas primary and secondary amines showed a good reactivity (final products, yields: 71-99%, *Scheme 29*).⁶⁸



Scheme 29. Reaction of tosylated 1,2-glycerol carbonate with amines

EXPERIMENTAL DATA AND DISCUSSION

6. Synthesis of new fluorinated methyltrioxorhenium (MTO)-catalysts. Their application in the epoxidation of olefins with hydrogen peroxide

In the last few years the *fluorous catalysis* become a novel synthetic strategy in the design and reuse of both homogeneous and heterogeneous metal catalysts.⁶⁹ Two branches have been developed in this field, namely the “heavy” and the “light” fluorous catalysis.⁷⁰ In both cases ligands bearing fluorous atoms are used to coordinate the active metal species. In the “heavy” fluorous catalysis, ligands bearing 39 or more fluorines are required to allow the complete solubility of the catalyst in the fluorinate solvents in biphasic transformations. The “light” fluorous catalysis typically is performed with 9-17 fluorines to increase the solubility of catalysts in common organic solvents. In this latter case the catalyst can be easily recovered at the end of the transformation by fluorous solid-phase extraction technique (F-SPE).⁷¹ Irrespective to the nature of the fluorine catalysis, 2,2'-bipyridines with 4,4'-bis(fluorous-ponytailed) substituents are commonly used as bidentate ligands in order to maintain the geometry at the metal centre even when the metal is oxidized or reduced. Usually, methylene spacers of general formula $(\text{CH}_2)_m(\text{CF}_2)_n\text{CF}_3$ are used to insulate the active site from the electron-withdrawing fluorines.⁷² Examples of redox processes catalysed by metal/fluorous nitrogen ligands include manganese,⁷³ cobalt,⁷⁴ ruthenium,⁷⁵ and copper⁷⁶ oxidations under both “heavy” and “light” conditions.

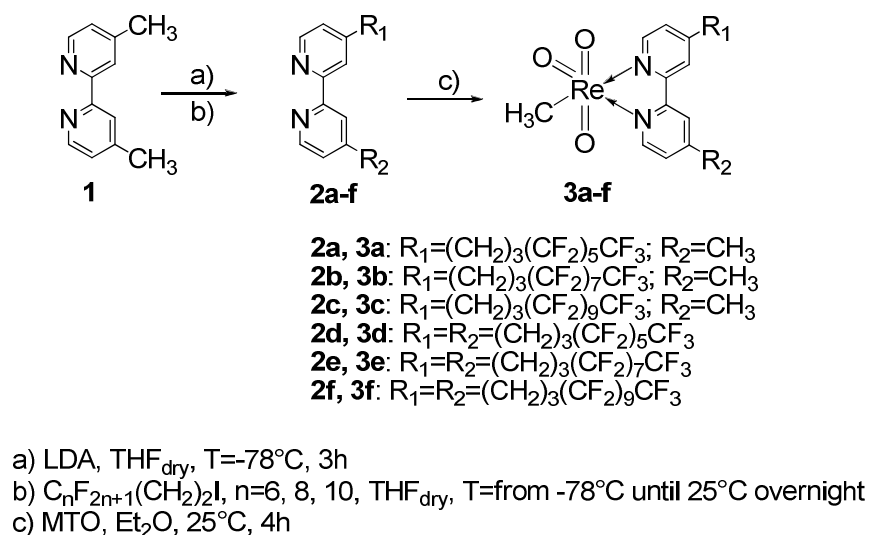
In consideration of our experience on the utilization of methyltrioxorhenium as a catalyst for the oxidation of organic compounds and on the lack of the literature data about the complexation of MTO with fluorinated nitrogen ligands, we projected the synthesis of complexes between MTO and bis(fluorous-ponytailed) 2,2'-bipyridines (MTO/bpy- F_n) characterized by different values of fluorophilicity. These catalysts were utilized for the epoxidation of olefins with hydrogen peroxide (H_2O_2).⁷⁷

Bis(fluorous-ponytailed) 2,2'-bipyridines **2a-f** (bpy- F_n) were prepared according to literature procedures starting from commercially available 4,4'-dimethyl-2,2'-bipyridine.⁷⁸ Compound **1** was treated with lithium diisopropylamide (LDA) in dry THF at low temperature (-78 °C) followed by alkylation with perfluoroalkyl iodides of general formula $\text{C}_n\text{F}_{2n+1}\text{CH}_2\text{CH}_2\text{I}$ ($n=5,7$ and 9) to afford desired mono- and bis(fluorous-ponytailed) nitrogen ligands (bpy- F_n) in acceptable yield [(Scheme 1, step a) and b)]. Freshly prepared bpy- F_n **2a-f** were successively added to a solution of MTO and the corresponding MTO/bpy- F_n catalysts **3a-f** were easily recovered in quantitative yield as yellow powder. Nuclear Magnetic Resonance analysis (^1H -NMR, ^{13}C -NMR and ^{19}F -NMR) confirmed the assigned structures. In particular, we observed a downfield shift for Re- CH_3 protons in fluorinated catalysts **3a-f** compared to the complex between MTO and 4,4'-dimethyl-2,2'-bipyridine as a

reference ($\Delta\Delta = 0.23\text{--}0.30$ ppm, see *Table 1*). Downfield shifts for H-3,3'; H-5,5' and H-6,6' protons in ^1H -NMR spectra of **3a-f** compared to ligands **2a-f** were also observed in accordance with the general behaviour previously reported for MTO complexes ($\Delta\Delta$ Ar-H 3,3'; $\Delta\Delta$ Ar-H 5,5'; $\Delta\Delta$ Ar-H 6,6', see *Table 1*).⁷⁹

Ligands **2a-f** were further characterized by evaluation of typical parameters for fluorinated species, such as the percent of fluorine content (F), the fluorous partition coefficient (FPC) and the fluorophilicity,^{80,81} $f = \ln[\text{FPC}]$. As a usual procedure, FPCs were calculated for a biphasic mixture (1:1 v/v) of perfluorooctane (FC77) and CH_2Cl_2 . These parameters are reported in *Table 2*.

On the basis of these data, ligands **2a-f** resulted useful for “light fluorous catalysis” in accordance with previous trends observed for fluorocarbon modified organics (and, in principle, the ligand **2f**, with F>60%, is also useful for “heavy fluorous catalysis”)



Scheme 1. Synthesis of MTO-fluorinated catalysts

Table 1. Chemical shifts (δ) and $\Delta\Delta$ Ar-H 3,3'; $\Delta\Delta$ Ar-H 5,5'; $\Delta\Delta$ Ar-H 6,6' of ligands **2a-f** and catalysts **3a-f** (ppm)

Entry	Ligand/Catalyst	$ReCH_3$	$\Delta\Delta$ Ar-H 3,3'	$\Delta\Delta$ Ar-H 5,5'	$\Delta\Delta$ Ar-H 6,6'
1	MTO/bpy	1.04	-----	-----	-----
2	2a	---	0.21	0.29	0.29
3	3a	1.28	---	---	---
4	2b	---	0.09	0.27	0.31
5	3b	1.27	---	---	---
6	2c	---	0.10	0.25	0.24
7	3c	1.28	---	---	---
8	2d	---	0.10	0.20	0.24
9	3d	1.33	---	---	---
10	2e	---	0.13	0.12	0.16
11	3e	1.33	---	---	---
12	2f	---	0.05	0.09	0.10
13	3f	1.34	---	---	---

Table 2. Parameters of the ligands **2a-f**.

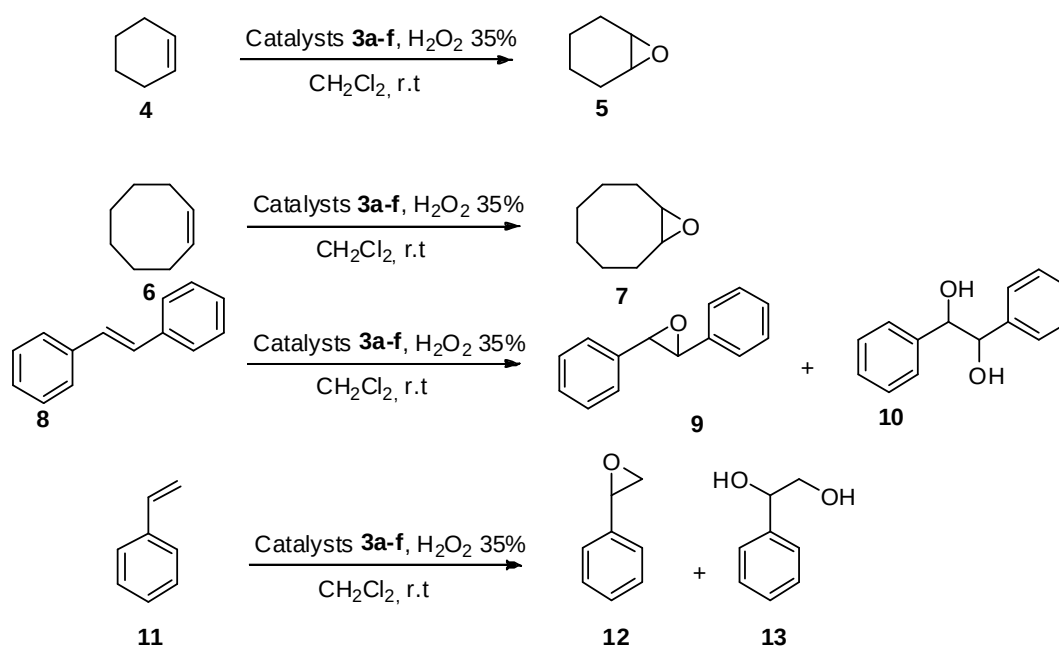
Entry	Ligand	F (%)	FPC ^a	f
1	2a	46.7	0.01	- 4.60
2	2b	51.3	0.04	- 3.20
3	2c	54.6	0.09	- 2.40
4	2d	56.4	0.25	- 2.40
5	2e	60.0	0.41	- 0.90
6	2f	62.5	2.60	+ 0.95

^aFPC= C_i fluoruous phase/ C_i organic phase; C_i is the concentration of fluorinated specie i expressed in mol/L; fluoruous phase was FC77 and organic phase was dichloromethane)

Epoxidations with MTO/bpy- F_n catalysts **3a-f** and H_2O_2 (35% aqueous solution) were investigated with cyclic aliphatic olefins, cyclohexene **4** and *cis*-cyclooctene **6** and low reactive aromatic olefins, *trans*-stilbene **8** and styrene **11**, as representative model substrates (Scheme 2). All reactions were performed applying the “light fluoruous catalysis” by using 2% in weight of **3a-f**. The epoxidation of **4** with the complex MTO/bpy was also performed as reference. The reactions were monitored by GC-MS analysis. In the absence of the catalyst, less than 5 % conversion of substrates took place under otherwise identical conditions. The results are summarized in Table 3. Noteworthy, irrespective to the presence of one or two fluorinated chains and number of fluorine atoms, MTO/bpy- F_n **3a-f** were highly efficient and selective catalysts in the epoxidation reaction of olefins **4** and **6** and the corresponding epoxides **5** and **7** were isolated in quantitative conversions and yields after only 2-5 h (Table 3, entries 2-7; 9-14). The MTO/bpy catalyst showed a similar behaviour in terms of yield and reaction time suggesting that presence of fluorine atoms in the side-chains did not interfere with the reactivity of the MTO active species (Table 3, entries 1, 8, 15 and 22).

Catalysts **3a-f** were also efficient systems in the oxidation of aromatic olefins *trans*-stilbene **8** and styrene **11** (Table 3, entries 16-21 and 23-28). In particular, in the oxidation of *trans*-stilbene **8**, the epoxide **9** was again obtained as the main reaction product in 64-92 % conversion and 45-82 % yield

(Table 3, entries 16-21). According to the known high reactivity of stilbene epoxide to give nucleophilic ring-opening reactions, significant amount of the corresponding diol **10** was observed (Table 3, entries 16-21). Noteworthy, the selectivity in the oxidation of **8** was tuned by the nature of the ligand, MTO/bpy-F_n **3b** being the most efficient catalyst (Table 3, entry 17). In the oxidation of styrene **11**, the epoxide **12** was obtained as the main product in 83-90 % conversion and 80-87 % yield (Table 3, entries 23-28), besides to unreacted substrate and traces of diol **13**. As expected, longer reaction times were required for the oxidation of **11** due to the known lower reactivity of aromatic olefins with respect to aliphatic ones (Table 1, entries 16-21 and 23-28 versus entries 2-7 and 9-14). As a general trend, the fluorophilicity *f* of the catalysts did not influenced the selectivity of the epoxidation, with the only exception of *trans*-stilbene **8**, in which case, catalysts **3a-c** bearing mono (fluorous-ponytailed).nitrogen ligands were more selective than corresponding bis(fluorous-ponytailed) systems **3d-f** (Table 3, entries 16-18 versus entries 19-21).



Scheme 2. Epoxidation reaction catalyzed by MTO MTO/bpy-F_n catalysts **3a-f**

Table 3. Experimental data of oxidation of alkenes **4-8** with perfluoroalkylated catalysts **3a-f**^a

Entry	Substrate	Catalyst	Reaction time (h)	Conv. (%) ^b	Yield (%) ^b
1	Cyclohexene 4	MTO/bpy	5	98	5 : 97
2		3a	5	97	5 : 97
3		3b	5	> 98	5 : > 98
4		3c	5	> 98	5 : > 98
5		3d	2	96	5 : 96
6		3e	3	> 98	5 : > 98
7		3f	3	> 98	5 : > 98
8	Cis-cyclooctene 6	MTO/bpy	5	> 98	7 : > 98
9		3a	5	> 98	7 : > 98
10		3b	3	> 98	7 : > 98
11		3c	5	82	7 : 82
12		3d	3	> 98	7 : > 98
13		3e	4	> 98	7 : > 98
14		3f	4	> 98	7 : > 98
15	Trans-stilbene 8	MTO/bpy	24	65	9 : 54; 10 : 11
16		3a	24	64	9 : 52; 10 : 12
17		3b	24	92	9 : 82; 10 : 10
18		3c	24	89	9 : 76; 10 : 13
19		3d	24	85	9 : 45; 10 : 40
20		3e	24	77	9 : 65; 10 : 12
21		3f	20	82	9 : 70; 10 : 12
22	Styrene 11	MTO/bpy	48	85	12 : 80; 13 : 5
23		3a	48	83	12 : 80; 13 : 3
24		3b	48	95	12 : 85; 13 : 10
25		3c	48	90	12 : 86; 13 : 4
26		3d	60	89	12 : 86; 13 : 3
27		3e	48	85	12 : 85
28		3f	48	87	12 : 87

^{a, b} Calculated by GC-MS analysis

The turnover frequencies (TOFs; moles of converted substrate per mole of catalyst per hour) of MTO/bpy-F_n catalysts **3a-f** calculated for the epoxidation of olefins **4**, **6**, **8** and **11** were found in the range of 1.0-25 depending on the experimental conditions and were similar to those of parent MTO/bpy catalyst confirming that the fluorinated chains did not modify the catalytic activity of the MTO active species.

Finally, our efforts were going to recycling catalysts. The oxidation of cyclohexene **4** with **3f** was performed as a selected example. The thermomorphic method based on the temperature-dependent solubility of the fluorous catalysts in the organic solvent was chosen as procedure to recover the catalyst. Unfortunately, the conversion of substrate and yield of epoxide **5** were dramatically decreased (25% and 20%, respectively). A better result was obtained with the light catalyst **3a** by Fluorous Solid-Phase Extraction technique (F-SPE). The column was eluted with methanol/water 80:20 to recover epoxide **5** followed by methanol to afford **3a** in appreciable yield (60%). Catalyst **3a** was used in a successive run without any further purification showing the expected reactivity (conversion: 75%; yield of epoxide **5**: 75%). Thus, in our hands the F-SPE technique was the most

efficient recycling procedure. However, a decrease of the reactivity of catalyst **3a** was observed during the successive run (conversion: 45%; yield of epoxide **5**: 45%).

In conclusion, mono- and bis(fluorous-ponytailed)/MTO catalysts were prepared for the first time in acceptable yield and applied for the activation of environmental friendly H₂O₂ in the epoxidation of aliphatic and aromatic olefins under fluorous catalysis. The epoxides were obtained in high yield and selectivity comparable to that of non fluorinated MTO complex. With the only exception of *trans*-stilbene, the fluorophilicity of the ligand did not influence the reactivity, suggesting that three carbon units in the methylene spacer effectively insulated the bipyridyl ring and the rhenium center from the electron-withdrawing effect of the fluorinated alkyl chains. The MTO/bpy-F_n catalysts can be recovered by Fluorous Solid-Phase Extraction technique and used in successive runs. Since MTO shows multi functional catalytic properties including Lewis and Brønsted activity and metathesis properties,⁸² these results are a promising entry to further exploiting the fluorine chemistry in the family of MTO based organometallic species.

Experimental section

Materials and methods

All chemicals and FluoroFlash® were purchased from Aldrich Company. Solvents were of the highest commercially available quality. Dry tetrahydrofuran was prepared according to classical procedure. Silica gel were commercially available (Merck). Thin layer chromatography was carried out using Merck platen Kieselgel 60 F254. ¹H and ¹³C NMR spectra were recorded on a Bruker (200 MHz) spectrometer; ¹⁹F NMR were utilizing a Bruker AMX 400 MHz. Chemical shift were reported in δ values. Mass spectra were recorded on a VG 70/250S spectrometer with an electron beam of 70 eV and a CP-SIL 8 CB-MS column (25m x 0.25 mm and 0.25 mm film thickness). GC analysis were performed using an isothermal temperature profile of 40 or 80 °C for 5 minutes, followed by a 10°C/min temperature gradient to 250 °C for 10 minutes. The injector temperature was 280 °C.

Preparation of 4-(perfluoroalkyl)-4'-methyl-2,2'-bipyridine (2a-c) and 4,4'-bis(perfluoroalkyl)-2,2'-bipyridine (2d-f)

The preparation was performed according to reported in literature.⁷⁸ Into a dry round bottom flask, 20 mL of dry THF were added. After cooling until to -78°C, LDA 2M (0.3 mL, 2.3 mmol), a solution 0.5 M of 4,4'-dimethyl-2,2'-bypiridine **1**, (0.198 g, 1.08 mmol) in 2 ml of dry THF were added. The mixture was kept under stirring for 3h. To the dianion obtained, the perfluoroalkyl iodide C_nF_{2n+1}CH₂CH₂I (2.3 mmol) was added and the mixture was kept under stirring for 1h at -78 °C,

then warmed up to room temperature and kept under stirring overnight. The reaction was quenched with brine (20 mL); the residue was extracted with diethyl ether (3 x 20 mL) and dried over Na₂SO₄. Evaporation of the solvent under reduced pressure, afforded crude mixture. After crystallization and, if necessary, chromatographic purification on silica gel (eluent: dichloromethane/methanol), 4-(perfluoroalkyl)-4'-methyl-2,2'-bipyridine **2a-c** and 4,4'-bis(perfluoroalkyl)-2,2'-bipyridine **2d-f** were respectively isolated in 20-40% yield. Spectroscopic data were here reported.

4-(1*H*, 1*H*, 2*H*, 2*H*, 3*H*, 3*H*-perfluorononyl)-4'-methyl-2,2'-bipyridine **2a**. Yield: 36%. Light brown solid. ¹H-NMR (200MHz, CDCl₃) δ: 8.61-8.54 (m, 2H), 8.33-8.29 (m, 2H), 7.23-7.18 (m, 2H), 2.84-2.63 (m, 2H), 2.46 (s, 3H), 2.22-1.95 ppm (m, 4H); ¹³C NMR (200 MHz, CDCl₃) δ: 156.6, 155.8, 150.5, 149.3, 149, 148.2, 122.1, 121.1, 34.5, 30.4, 21.1, 21.0. ¹⁹F (376.4 MHz, CDCl₃) δ -131.4 (2F), -128.6 (2F), -128.1 (2F), -127.2 (2F), -119.1 (2F), -86.0 (3F).

4-(1*H*, 1*H*, 2*H*, 2*H*, 3*H*, 3*H*-perfluoroundecyl)-4'-methyl-2,2'-bipyridine **2b**. Yield: 33%. Light brown solid. ¹H-NMR (200 MHz, CDCl₃) δ: 8.59-8.56 (dd, *J*=0.7 Hz, *J*=5.7 Hz, 1H), 8.53-8.50 (dd, *J*=0.5 Hz, *J*=5.0 Hz, 1H), 8.23-8.19 (m, 2H), 7.14-7.11 (dd, *J*=1.7 Hz, *J*=6.6 Hz, 2H), 2.88-2.66 (m, 2H), 2.42 (3H, s), 2.19-2.02 (m, 4H). ¹³C NMR (200 MHz, CDCl₃) δ: 156.6, 155.8, 150.6, 149.3, 149.0, 148.2, 124.8, 123.6, 121.1, 121.0, 34.6, 30.4, 21.2, 21.0. ¹⁹F (376.4 MHz, CDCl₃) δ -131.1 (2F), -128.3 (2F), -128.0 (2F), -127.7 (2F), -126.9 (4F), -119.1 (4F), -85.7 (3F).

4-(1*H*, 1*H*, 2*H*, 2*H*, 3*H*, 3*H*-perfluorotridecyl)-4'-methyl-2,2'-bipyridine **2c**. Yield: 25%. Light brown solid. ¹H-NMR (200 MHz, CDCl₃) δ: 8.59-8.57 (dd, *J*=0.7 Hz, *J*=5.0 Hz, 1H), 8.54-8.51 (dd, *J*=0.7 Hz, *J*=5.0 Hz, 1H), 8.26-8.23 (m, 2H), 7.15-7.11 (dd, *J*=1.6 Hz, *J*=6.5 Hz, 2H), 2.82-2.75 (m, 2H), 2.43 (s, 3H), 2.15-2.02 (m, 4H). ¹³C NMR (200 MHz, CDCl₃) δ: 157.9, 154.5, 151.4, 149.1, 147.8, 148.2, 125.2, 124.1, 122.8, 121.8, 34.6, 30.6, 21.4, 20.9. ¹⁹F (376.4 MHz, CDCl₃) δ -131.0 (4F), -128.0 (4F), -126.8 (4F), -122.5 (2F), -119.0 (4F), -85.7 (3F).

4,4'-bis(1*H*, 1*H*, 2*H*, 2*H*, 3*H*, 3*H*-perfluorononyl)-2,2'-bipyridine **2d**. Yield: 40%. White solid. ¹H-NMR (200 MHz, CDCl₃) δ: 8.60 (d, *J*=5.0 Hz, 2H), 8.20 (s, 2H), 7.20 (dd, *J*=1.8 Hz, *J*=1.5 Hz, 2H), 2.80 (t, *J*=7.5 Hz, 4H), 2.10 (m, 8H). ¹³C NMR (200 MHz, CDCl₃) δ: 156.4, 150.8, 149.5, 123.9, 121.3, 34.7, 30.6, 21.1. ¹⁹F (376.4 MHz, CDCl₃) δ -131.1 (4F), -128.4 (4F), -127.4 (4F), -126.9 (2F), -119.1 (4F), -85.8 (3F).

4,4'-bis(1*H*, 1*H*, 2*H*, 2*H*, 3*H*, 3*H*-perfluoroundecyl)-2,2'-bipyridine **2e**. Yield: 37%. White solid. ¹H-NMR (200 MHz, CDCl₃) δ: 8.60 (d, *J*=5.0 Hz, 2H), 8.30 (s, 2H), 7.10 (dd, *J*=1.8 Hz, *J*=1.7 Hz, 2H), 2.80 (t, *J*=7.3 Hz, 4H), 2.10 (m, 8H). ¹³C NMR (200 MHz, CDCl₃) δ: 156.4, 150.8, 149.5, 123.9, 121.3, 34.7, 30.6, 21.1. ¹⁹F (376.4 MHz, CDCl₃) δ -131.1 (4F), -128.4 (4F), -127.7 (4F), -126.9 (2F), -126.7 (4F), -119.1 (4F), -85.7 (3F).

4,4'-bis(1H, 1H, 2H, 2H, 3H, 3H-perfluorotridecyl)-2,2'-bipyridine **2f**. Yield: 30%. White solid. ¹H-NMR (200 MHz, CDCl₃) δ: 8.60 (d, *J*=5.6 Hz, 2H), 8.27 (s, 2H), 7.15 (dd, *J*=5.6 Hz, 2H), 2.84 (t, *J*=4.8 Hz, 4H), 2.15 (m, 4H), 2.05 (m, 4H). ¹³C NMR (200 MHz, CDCl₃) δ: 155.7, 150.6, 148.8, 123.1, 119.9, 34.4, 31.0, 20.6. ¹⁹F (376.4 MHz, CDCl₃) δ -131.0 (4F), -128.3 (4F), -127.6 (4F), -126.6 (2F), -119.0 (4F), -85.7 (3F).

Preparation of MTO complexes (3a-f)

0.18 mmol of perfluoroalkyl bipyridines **2a-f** were added to a solution of MTO (0.045 g, 0.18 mmol) in diethyl ether (5.0 mL). The mixture was kept under stirring for 2h at room temperature. After cooling down to 0°C, a yellow precipitate afforded. The solid was filtered off, washed with pentane and dried under flow of nitrogen until constant weight. Spectroscopic data were entirely described.

MTO/4-(1H, 1H, 2H, 2H, 3H, 3H-perfluorononyl)-4'-methyl-2,2'-bipyridine 3a. Yield: 98%. Yellow powder. ¹H-NMR (200 MHz, CDCl₃) δ=8.91-8.88 (d, *J*=5.4 Hz, 1H) 8.85-8.82 (d, *J*=5.4 Hz, 1H) 8.11 (s, 2H), 7.36-7.33 (m, 2H), 2.92-2.85 (m, 2H), 2.54 (s, 3H), 2.27-2.00 (m, 4H), 1.28 (s, 3H). ¹³C NMR (200 MHz, CDCl₃) δ=154.7, 152.3, 150.7, 150.0, 149.2, 148.8, 127.4, 126.2, 124.3, 123.4, 34.5, 30.4, 28.0, 21.4, 21.0. ¹⁹F (376.4 MHz, CDCl₃) δ= -128.8 (2F), -126.0 (2F), -125.5 (2F), -124.5 (2F), -116.7 (2F), -83.4 (3F).

MTO/4-(1H, 1H, 2H, 2H, 3H, 3H-perfluoroundecyl)-4'-methyl-2,2'-bipyridine 3b. Yield: 98%. Yellow powder. ¹H-NMR (200 MHz, CDCl₃) δ=8.90-8.87 (d, *J*= 5.5 Hz, 1H), 8.85-8.82 (d, *J*=5.5 Hz, 1H), 8.12(s, 2H), 7.36-7.34 (2dd, *J*=1.7 Hz, *J*=5.5 Hz, 2H), 2.93-2.85 (m, 2H), 2.55 (s, 3H), 2.15-2.00 (m, 4H), 1.27 (s, 3H). ¹³C NMR (200 MHz, CDCl₃) δ=156.6, 155.8, 150.6, 149.3, 149.0, 149.1, 124.8, 123.6, 121.1, 121.0, 34.6, 30.4, 28.0, 21.2, 21.0. ¹⁹F (376.4 MHz, CDCl₃) δ=-126.7 (2F), -123.9 (2F), -123.6 (2F), -123.3 (2F), -122.5 (4F), -114.7 (4F), -81.3 (3F).

MTO/4-(1H, 1H, 2H, 2H, 3H, 3H-perfluorotridecyl))-4'-methyl-2,2'-bipyridine 3c. Yield: 98%. Yellow powder. ¹H-NMR (200 MHz, CDCl₃) δ=8.83-8.76 (m, 2H), 8.41-8.29 (m, 2H), 7.42-7.34 (m, 2H), 2.94-2.87 (m, 2H), 2.58 (s, 3H), 2.13-2.07 (m, 4H), 1.28 (s, 3H). ¹³C NMR (200 MHz, CDCl₃) δ=153.6, 150.9, 149.1, 149.0, 126.6, 125.6, 124.1, 123.0, 34.6, 30.3, 26.0, 21.7, 20.9. ¹⁹F (376.4 MHz, CDCl₃) δ=-126.7 (4F), -123.7 (4F), -122.5 (4F), -118.2 (2F), -114.7 (4F), -81.4 (3F).

MTO/4,4'-bis(1H, 1H, 2H, 2H, 3H, 3H-perfluorononyl)-2,2'-bipyridine 3d. Yield: 98%. Yellow powder. ¹H-NMR (200 MHz, CDCl₃) δ=8.85 (d, 2H, J=5.4 Hz), 8.15 (s, 2H), 7.33 (d, J=5.5 Hz, 2H), 2.92-2.84 (m, 4H), 2.22-2.06 (m, 8H), 1.3 (s, 3H). ¹³C NMR (200 MHz, CDCl₃) δ=154.0, 152.7, 149.5, 125.2, 122.1, 34.6, 30.1, 23.9, 20.9. ¹⁹F (376.4 MHz, CDCl₃) δ=-128.8 (4F), -126.0 (4F), -125.5 (4F), -124.6 (4F), -116.7 (4F), -83.3 (6F).

MTO/4,4'-bis(1H, 1H, 2H, 2H, 3H, 3H-perfluoroundecyl)-2,2'-bipyridine 3e. Yield: 98%. Yellow powder. ¹H-NMR (200 MHz, CDCl₃) δ=8.76 (d, J=5.4 Hz, 2H), 8.18 (s, 2H), 7.27-7.24 (m, 2H), 2.91-2.65 (m, 4H), 2.24-1.82 (m, 8H), 1.33 (s, 3H). ¹³C NMR (200 MHz, CDCl₃) δ=156.1, 153.7, 149.4, 124.8, 122.8, 34.6, 33.8, 30.3, 23.9, 20.9. ¹⁹F (376.4 MHz, CDCl₃) δ=-126.7(4F), -124.0 (4F), -123.4 (4F), -122.6 (8F), -118.1 (4F), -114.8 (4F), -81.3 (6F).

MTO/4,4'-bis(1H, 1H, 2H, 2H, 3H, 3H-perfluorotridecyl)-2,2'-bipyridine 3f. Yield: 98%. Yellow powder. ¹H-NMR (200 MHz, CDCl₃) δ=8.70 (d, J=5.4 Hz, 2H), 8.20 (s, 2H), 7.24-7.21 (m, 2H), 2.90-2.68 (m, 4H), 2.19-2.04 (m, 8H), 1.54 (s, 3H). ¹³C NMR (200 MHz, CDCl₃) δ=156.2, 152.7, 149.5, 124.8, 122.8, 34.6, 30.1, 23.9 (CH₃-Re), 20.9; ¹⁹F (376.4 MHz, CDCl₃) δ=-126.7 (4F), -124.0 (4F), -123.6 (4F), -122.5 (16F), -118.1 (4F), -114.8 (4F), -81.4 (6F).

Determination of the partition ratio of ligands (2a-e)

This parameter was determined according to the literature [15-16]. A 5 ml bottom flask was charged with the perfluoroalkyl ligand **2a-f** (0.015 mmol), FC77 (2.0 mL) and CH₂Cl₂ (2.0 mL). The mixture was vigorously stirred for 2 h. After separation of the two phases, gravimetric measures were performed.

Epoxidation reactions

In a typical procedure the catalyst (2% referred to the substrate) was solubilized in CH₂Cl₂ (2.5 mL). Then hydrogen peroxide (35% aqueous solution, 2 equiv., 45 µL) was added and finally the substrate (0.26 mmol). The reaction mixture was kept under stirring at room temperature for 4-72 h depending on the substrate. Each 2 h, a sample was extracted; a little amount of MnO₂ was added to destroy the unreacted hydrogen peroxide and the mixture was stirred for 15 minutes. After filtration, the sample was analyzed by TLC and GC-MS to evaluate the conversion of the substrate and the yields of the final products.

Recycling experiments by using the thermomorphic mode

The crude of the oxidation reaction of cyclohexene **4** with catalyst **3f** was cooled until - 60°C. A precipitate was observed and the supernatant phase containing the oxidation product was removed. The precipitate was washed with a little amount of cold dichloromethane. Then, at room temperature a solution of substrate (0.26 mmol) in dichloromethane (2.5 mL) and hydrogen peroxide (35% aqueous solution, 2 equiv., 45 µL) was freshly introduced.

Recycling experiments by using the Fluorous Biphasic Catalysis (FBC) technique

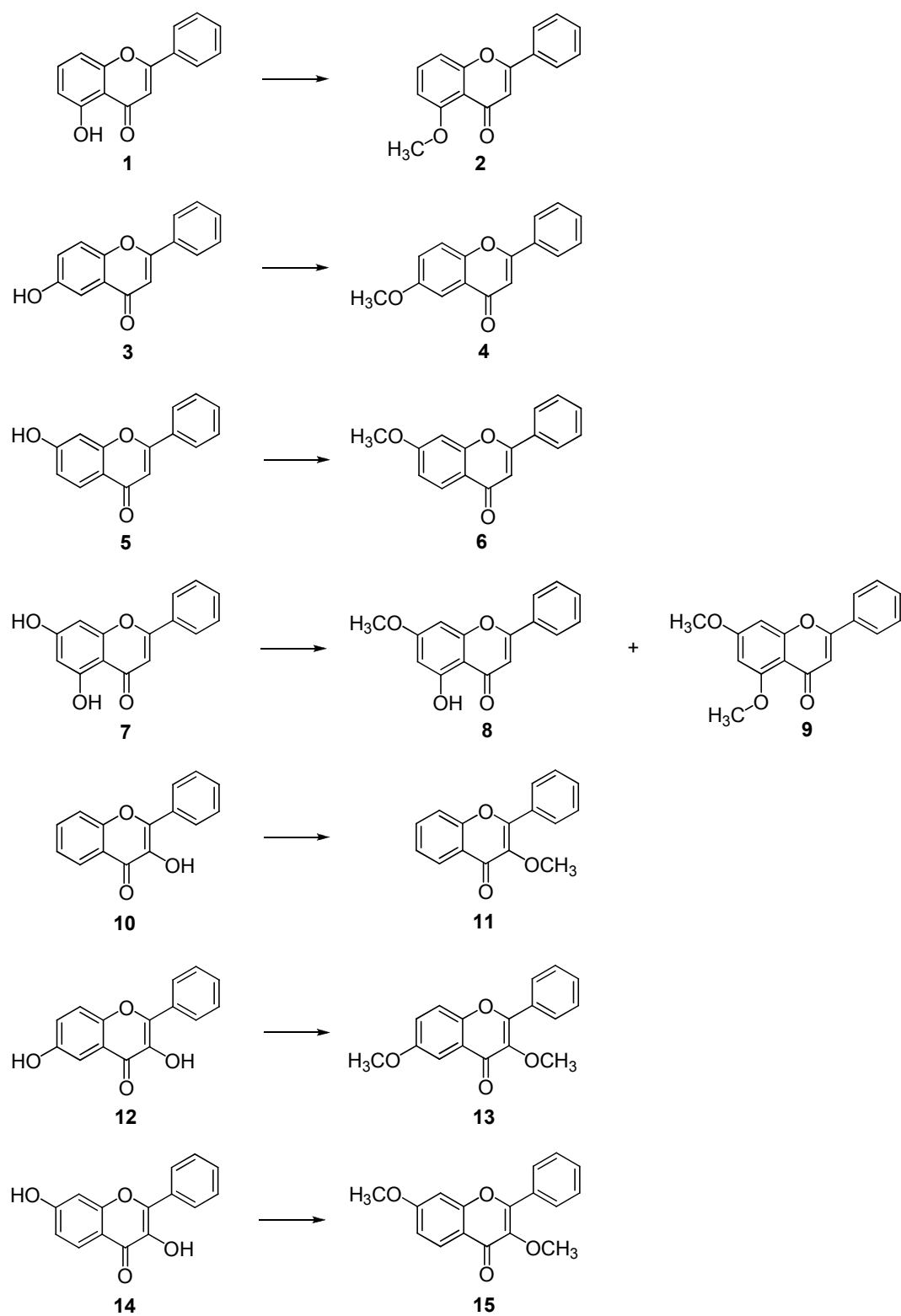
To apply the F-SPE technique, we used fluorous silica gel as solid phase (commercially available as FluoroFlash®) and a mixture of methanol/water as fluorophobic solvent and methanol as fluorophilic solvent. The oxidation of cyclohexene **4** catalyzed by **3a** was performed in dichloromethane at room temperature. The silica gel was washed with DMF and. The reaction mixture was dissolved in DMF and charged in a column with the solid phase previously preconditioned with methanol/water (80:20). Firstly, the column was eluted with methanol/water 80:20 to recover oxidation product (epoxide **9**); then with methanol to recover the fluorinated species (catalyst **3a**). Finally, the column was washed with acetone to regenerate the fluorous solid phase.

7. New applications of dimethyl carbonate. (1) Methylation of flavonoids

Flavonoids are a group of low-molecular-weight polyphenolic compounds that occur ubiquitously in all plants where they play a protective role against predators, pathogens and UV radiations.⁸³ Being present in fruits, vegetables and beverages, they are integral part of the human diet. In the last few years, dietary flavonoids have gained considerable interest because of their potential beneficial on human health.⁸⁴ Experimental studies demonstrated that they show several biological activities including radical scavenging, anti-inflammatory, antimutagenic, anti-HIV, anti-allergic, anti-platelet and antioxidant activities.⁸⁵ More recently, the potential utility of these compounds in chemoprevention of cancer has been investigated. Promising biological effects have been revealed in cell culture studies; however, when experiments have been extended to the *in vivo* experiments, in particular, in humans, these results have not been confirmed always.⁸⁶ The data have been related to very low oral bioavailability of dietary flavonoids, strictly dependent on the presence of free hydroxyl groups responsible for their susceptibility to glucuronidation, sulfation and oxidation reactions in the intestine and liver that avoids them to pass intact into the systemic circulation.⁸⁷ In contrast, methylated flavones were much metabolically stable and showed higher intestinal absorption through human colon adenocarcinoma (Caco-2) cell monolayers compared with their unmethylated analog derivatives, suggesting that methylation protects these compounds from hepatic metabolism.⁸⁸ As examples, 7-hydroxyflavone; 7,4'-dihydroxyflavone; 5,7-dihydroxyflavone (chrysin) were undetectable in tissue levels after administration to rats whereas the corresponding methylated derivatives reached high tissue levels.⁸⁹ Mono and dimethylated flavones showed potent antiproliferative activities;⁹⁰ they inhibit the carcinogenic-activating cytochrome P450 (CYP) transcription and activities,⁹¹ the benzo[a]pyrene activating enzymes and DNA binding in human bronchial epithelial BEAS-2B cells,⁹² the aromatase, an important target in hormone-sensitive cancers.⁹³ Furthermore, methylated flavonoids showed effects on multidrug resistance proteins (MRPs), transport proteins which play a central role in the defence of organism against toxic compounds;⁹⁴ they exhibit fungicidal properties.⁹⁵ The O-methylation of flavonoids is a common xenobiotic transformation occurring in plants, microbes and mammals from high selective enzymatic systems, the O-methyl transferases.⁹⁶ Chemically, the reaction was usually performed treating the corresponding phenolic compounds with dangerous and high toxic reagents such as diazomethane, dimethyl sulfate and methyl iodide.⁹⁷ In addition, their use requires stoichiometric amount of strong bases to neutralize acidic by-products resulting in the production large quantities of inorganic salts that need appropriate and expensive disposal.

In consideration both of the efficiency of the dimethyl carbonate (DMC)/1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) procedure and the biological activities of mono and dimethylated methylated flavonoids, we optimized the experimental conditions for a convenient and safe O-methylation of a large panel of flavonoids by using DMC and DBU.⁹⁸

Mono and dihydroxylated flavones **1**, **3**, **5**, **7** and flavonols **10**, **12**, **14** were the starting substrates (*Scheme 1*). O-methylation reaction was performed by using a large excess of DMC and DBU in stoichiometric amount respect to flavonoid at reflux temperature (90 °C). As reported in *Table 1*, flavonoids were converted into the corresponding methylated compounds in 12 - 72 h depending on the substrate. 5-Methoxyflavone **2** was isolated after 48 h (*Table 1*, entry 1), 6-methoxyflavone **4** after 36 h and 7-methoxyflavone **6** after only 12 h (*Table 1*, entries 2 and 3). In all cases quantitative yields of methylated products were obtained. The slow reactivity of 5-hydroxyflavone **1** may be due to the well known hydrogen bonding of 5-OH group with carbonyl group.⁹⁹ Then, as expected, the methylation of 5,7-dihydroxyflavone **7** afforded to 5-hydroxy-7-methoxy derivative **8** and 5,7-dimethoxyflavone **9** after 48 h being **8** was the main compound (*Table 1*, entry 4); prolonging the reaction time until 72 h we obtained a quantitative yield of **9** (*Table 1*, entry 5). In a similar way, we performed the O-methylation of flavonols **10**, **12**, **14** (*Table 1*, entries 6-8). Conversions and yields were quantitative after 24 h. In this case, no selectivity between phenolic and alcoholic group in C-3 was observed. It is known in the literature that 3-methoxyflavone derivatives showed high antioxidant activity,¹⁰⁰ exhibited potent neuroprotective effects on the oxidative injuries to neuronal cells.¹⁰¹ Finally, the methylation reaction was extended to several polyhydroxylated flavonoids. Unfortunately, these compounds showed a low solubility in DMC and then a poor reactivity in methylation reaction. As example, 3,5,7,3',4'-pentamethylated flavone (methylated quercetin) was isolated in only 28% after a long reaction time (72 h).



Experimental conditions:
 substrate: 0.5 mmol; DMC: 4 mL; DBU: 0.5 mmol; T= 90 °C, 12 - 72 h

Scheme 1. Methylation reaction of flavonoids with the DMC/DBU system

Table 1. Experimental data of methylation reaction of flavonoids depicted in *Scheme 2*.

Entry	Substrate	Time (h)	Conv. (%)	Yield (%)
1	1	48	> 98	2 : > 98
2	3	36	> 98	4 : > 98
3	5	12	> 98	6 : > 98
4	7	48	>98	8 : 70; 9 : 30
5	7	72	>98	9 : 95
6	10	24	> 98	11 : > 98
7	12	24	> 98	13 : > 98
8	14	24	> 98	15 : > 98

In conclusion, mono- and dimethylated flavonoids were prepared by using DMC both as solvent and reagent in the presence of DBU. Final products were isolated in high yields and high degree of purity. To the best of our knowledge, this is the first paper dealing the O-methylation of flavonoids under mild experimental conditions by using non toxic reagents in order to obtain the corresponding methylated derivatives, bioactive compounds potentially useful in cancer therapy.

Experimental section

Materials and Methods

All chemicals were purchased from Sigma-Aldrich and were of analytical grade. Silica gel 60 F254 plates and silica gel 60 were obtained from Merck. ^1H NMR and ^{13}C NMR were recorded on a Bruker 200 MHz spectrometer using CDCl_3 as solvent. All chemical shifts are expressed in ppm (δ scale) and coupling constants in Hz. GC-MS analysis was performed on a Shimatzu VG 70/250S apparatus equipped with a CP-SIL 8 CB-MS column (25 m, 0.25 mm and 0.25 mm film thickness). The analyses were performed using an isothermal temperature profile of 100 °C for 2 minutes, followed by a 10 °C/min temperature gradient for 15 minutes until 280°C. The injector temperature was 280 °C.

General procedure for the methylation reaction of flavonoids

In a typical experiment, the substrate (0.5 mmol) was dissolved in dimethyl carbonate (4.0 mL); then DBU (0.5 mmol) was added. The solution was kept at T= 90 °C under magnetic stirring and monitored by TLC. After disappearance of the substrate, the solvent was evaporated under reduced

pressure in the presence of methanol (3 mL) as an azeotropic mixture. The final products were extracted with ethyl acetate (3 x 10 mL); the reunited organic extracts were washed with a saturated solution of NaCl and dried over Na₂SO₄. After filtration, methylated compounds were purified by chromatography on column by using silica gel (230 - 400 mesh) and the mixture CH₂Cl₂/CH₃OH=9/1 as eluent and characterized by ¹H-NMR, ¹³C-NMR and GC-MS.

5-Methoxyflavone 1. Quantitative yield. White solid. Mp 130-133 °C. ¹H-NMR (200 MHz, CDCl₃): δ (ppm) 7.81-7.74 (m, 2H), 7.51-7.36 (m, 4H), 7.02 (d *J*=8 Hz, 1H), 6.72 (d, *J*=8 Hz, 1H), 6.62 (s, 1H), 3.89 (s, 3H). ¹³C-NMR (CDCl₃): δ (ppm) 178.1, 160.8, 159.6, 158.1, 133.6, 131.2, 128.7, 125.8, 114.4, 109.9, 108.8, 106.3, 56.3. MS (EI) *m/z* : 252 (M⁺).

6-Methoxyflavone 3. Quantitative yield. Yellow solid. Mp 164 °C. ¹H-NMR (200 MHz, CDCl₃): δ (ppm) 7.88-7.83 (m, 2H), 7.54-7.42 (m, 4H), 7.25 (d *J*=8Hz, 1H), 7.20 (d, *J*=8Hz, 1H), 6.76 (s, 1H), 3.85 (s, 3H). ¹³C-NMR (CDCl₃): δ (ppm) 178.1, 163.0, 156.9, 150.9, 131.7, 131.4, 128.9, 126.1, 124.4, 123.7, 119.4, 106.7, 104.7, 55.8. MS (EI) *m/z* : 252 (M⁺).

7-Methoxyflavone 5. Quantitative yield. White solid. Mp 108-110 °C. ¹H-NMR (200 MHz, CDCl₃): δ (ppm) 8.07 (d, *J*=4Hz,1H), 7.90-7.85 (m, 2H), 7.51-7.47 (m, 3H), 6.98-6.94 (m, 2H), 6.74 (s, 1H), 3.90 (s, 3H). ¹³C-NMR (CDCl₃): δ (ppm) 176.6, 162.4, 156.5, 150.1, 131.3, 131.0, 128.8, 125.9, 123.1, 119.4, 106.2, 108.8, 105.3, 55.5. MS (EI) *m/z* : 252 (M⁺).

5-Hydroxy-7-methoxyflavone 8. Yield: 70%. White solid. Mp 164-166 °C. ¹H-NMR (200 MHz, CDCl₃): δ (ppm) 7.89-7.84 (m, 2H), 7.53-7.49 (m, 3H), 6.65 (s, 1H), 6.48 (d, *J*=2.0 Hz, 1H), 6.36 (d, *J*=2.0 Hz, 1H), 3.86 (s, 3H). ¹³C-NMR (CDCl₃): δ (ppm) 182.5, 165.6, 164.6, 162.1, 157.4, 131.8, 131.3, 129.1, 126.3, 105.9, 98.2, 92.7, 55.8. MS (EI) *m/z* : 268 (M⁺).

5,7-Dimethoxyflavone 9. Quantitative yield. White solid. Mp 200-203 °C. ¹H-NMR (200 MHz, CDCl₃): δ (ppm) 7.81-7.74 (m, 2H), 7.46-7.43 (m, 3H), 6.62 (s, 1H), 6.52 (d, *J*=2Hz, 1H), 6.32 (d, *J*=2Hz, 1H), 3.90 (s, 3H), 3.86 (s, 3H). ¹³C-NMR (CDCl₃): δ (ppm) 177.5, 163.9, 160.8, 160.5, 159.8, 131.4, 131.1, 128.8, 125.8, 108.9, 96.1, 92.8, 56.3, 55.6. MS (EI) *m/z* : 282 (M⁺).

3-Methoxyflavone 10. Quantitative yield. Colourless oil. ¹H-NMR (200 MHz, CDCl₃): δ (ppm) 8.07 (d, *J*=4.0 Hz, 1H), 8.06-8.05 (m, 2H), 7.53-7.37 (m, 6H), 3.85 (s, 3H). ¹³C-NMR (CDCl₃): δ (ppm) 167.1, 150.8, 140.8, 134.1, 130.8, 131.2, 128.6, 128.3, 123.5, 118.4, 59.7. MS (EI) *m/z* : 252 (M⁺).

3,6-Dimethoxyflavone 13. Quantitative yield. Colourless oil. ¹H-NMR (CDCl₃) δ 3.87 (s, 3H), 3.89 (s, 3H), 7.27 (m, 1H), 7.47 (m, 4H), 7.590 (d, *J*= 3.0 Hz, 1H), 8.07 (m, 2H). ¹³C-NMR (200 CDCl₃) δ 55.9, 60.1, 104.5, 119.4, 123.9, 124.8, 128.4, 128.5, 130.6, 131.0, 141.1, 150.2, 155.4, 156.6, 174.9. MS (EI) *m/z*: 282 (M⁺).

3,7-Dimethoxyflavone **15**. Quantitative yield. Colourless oil. $^1\text{H-NMR}$ (CDCl_3) δ 3.86 (s, 3H), 3.89 (s, 3H), 6.95 (m, 2H), 7.45 (m, 3H), 8.00 (m, 3H). $^{13}\text{C-NMR}$ (200 CDCl_3) δ 55.8, 60.1, 99.9, 114.4, 119.0, 127.1, 128.3, 128.4, 128.5, 128.6, 130.5, 131.0, 141.5, 155.2, 158.0, 164.0, 175. GC-MS (m/z): 282, 150, 105, 89, 77, 63, 51. MS (EI) m/z : 282 (M^+).

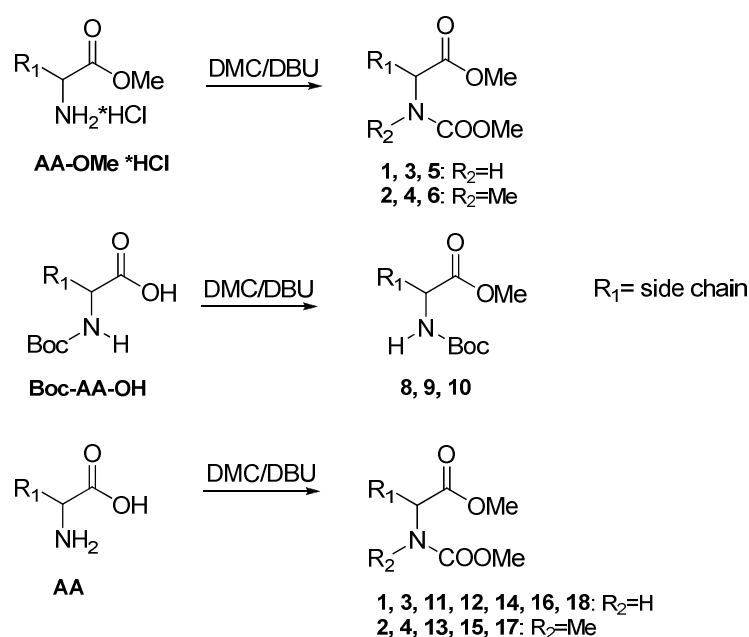
8. New applications of dimethyl carbonate. (2) Protection of the amino acids functionalities

Synthetic organic chemistry is based on the rational combination of reagents in order to prepare molecules. More research has been devoted to perform the synthesis with high selectivity. Protecting groups are required to prevent the formation of undesired bonds and side reactions. A particular attention has been turned to the protection of amino acids functionalities in peptide chemistry in order to avoid the polymerization of amino acids and to modify their branched chains.

An “ideal” protecting group is easily introduced into the functional group; stable in a broad range of experimental conditions; easily removed at the end of the synthetic process.

The most common protecting groups of amino acids are 9-fluorenylmethoxycarbonyl (Fmoc), *tert*-butyloxycarbonyl (Boc), 2-nitrophenylsulfenyl (Nps), 2-(4-biphenyl)isopropoxycarbonyl (Bpoc), benzyloxycarbonyl (Z), carbamoylmethyl (Cam), benzyl (Bn), 9-fluorenylmethyl (Fm), 2-trimethylsilylethyl (TMSE), trityl (Trt).¹⁰² Often, harmful reactants are required to introduce or remove them.

During this PhD course we optimized a new ecofriendly procedure to protect amino and/or acidic group of amino acids by using the DMC/DBU system. A large panel of amino acid derivatives were utilized as starting materials (*Scheme 1, Figure 1*). Experimental are reported in *Table 1*.



Scheme 1. Protective methodology of amino acids by using DMC/DBU

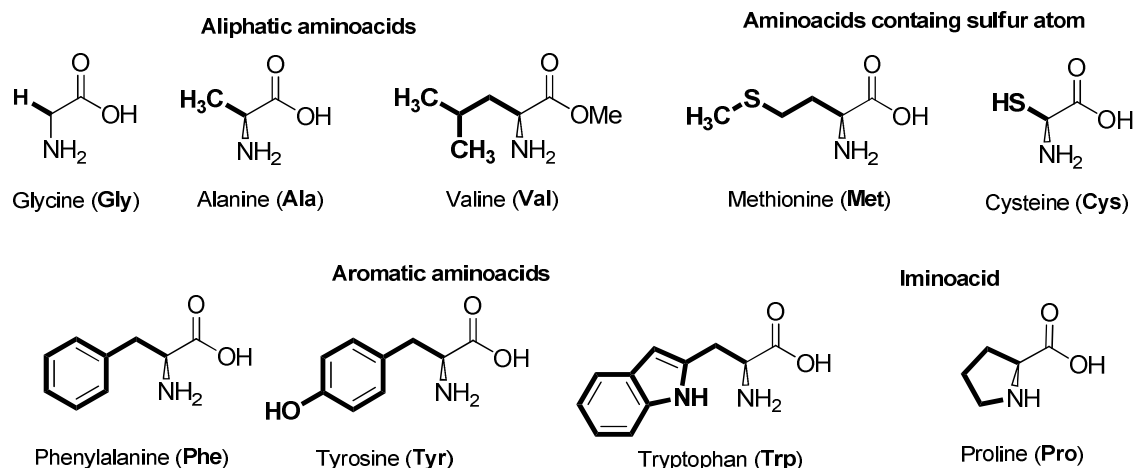


Figure 1. Selected natural L-amino acids

Table 1. Experimental data

Entry	Amino acid	Product ($R_2 =$)	Yield (%)
1	Gly-OMe*HCl	1: H; 2: CH ₃	1: 68; 2: 21
2	Ala-OMe*HCl	3: H; 4: CH ₃	3: 65; 4: 15
3	Val-OMe*HCl	5: H; 6: CH ₃	5: 55; 6: 10
4	Boc-Gly-OH	7: H	7: 70
5	Boc-Met-OH	8: H	8: 60
6	Boc-Trp-OH	9: H	9: 40
7	Boc-Pro-OH	10: H	10: 96
8	Gly	1: H; 2: CH ₃	1: 67; 2: 10
9	Ala	3: H; 4: CH ₃	3: 74; 4: 9
10	Met	11: H	11: 45
11	Phe	12: H; 13: CH ₃	12: 49; 13: 10
12	Tyr	14: H; 15: CH ₃	14: 65; 15: 15
13	Trp	17: H; 18: CH ₃	17: 50; 18: 10
14	Pro	21: H	21: 42

Firstly, we tested the efficiency of the DMC/DBU system to protect the α -amino or α -acid group on representative amino acids.

After 24 h of reaction at reflux temperature, **Gly-OMe*HCl**, **Ala-OMe*HCl** and **Val-OMe*HCl** afforded to the corresponding carboxymethylated derivatives **1**, **3** and **5** (Table 1, entries 1-3). Traces of by-products **2**, **4** and **6** deriving from the N-methylation were observed even stopping the reaction after 8 h. Under these experimental conditions, the conversion of the substrates was lower.

The α -acid group of **Boc-Gly-OH**, **Boc-Met-OH**, **Boc-Trp-OH** and **Boc-Pro-OH** was esterified by DMC/DBU affording to the corresponding methyl esters **7**, **8**, **9**, **10** in 40-96% yield depending on the amino acid (*Table 1, entries 4-7*).

Finally, we extended the protective methodology to free amino acids. As showed in *Table 1*, the reactivity of the aliphatic amino acids **Gly** and **Ala** is similar. The corresponding protected products **1** and **3** were isolated in satisfactory yields (70%, *Table 1, entries 8 and 9*). Traces of N-methylated compounds **2** and **4** as by-products were observed (yields: 10 and 9%, respectively). Amino acids containing sulphur atom **Met** and **Cys** were tested. Unfortunately, **Cys** was not soluble in DMC whereas **Met** afforded to the corresponding compound **11** in 45% yield (*Table 1, entry 10*). Between aromatic amino acids (**Phe**, **Tyr** and **Trp**), **Phe** showed a reactivity similar to that of aliphatic amino acids **Gly** and **Ala**. In fact, the main product was the full protected amino acid **12** and the by-product the N-methylated derivative **13** (*Table 1, entry 11*). **Tyr** showed less selectivity than **Phe**. In fact, in addition to the expected product **14** and to the N-methylated byproduct **15** (*Table 1, entry 13*), traces of O-methylated by-product **16** deriving from the methylation of the phenolic group was observed (*Figure 2*). However, reducing time reactions till 8 h, the formation of compound **16** was avoided.

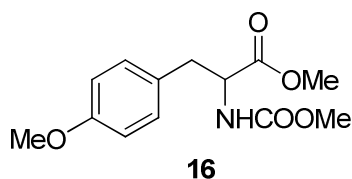


Figure 2. The O-methylated by-product deriving from **Tyr**

Our methodology did not show selectivity for **Trp**. In fact, we observed a mixture of products: the expected tryptophan derivative **17**, the N-methylated by-product **18** (*Table 1, entry 13*) and traces of compounds **19** and **20** deriving from carbomethoxylation and methylation of the heterocyclic cycle present into the side chain (*Figure 3*).

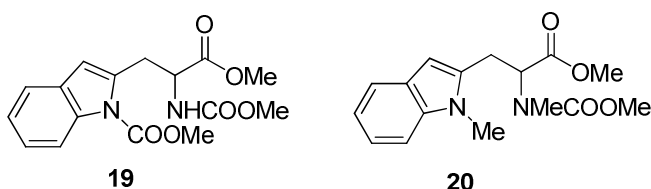
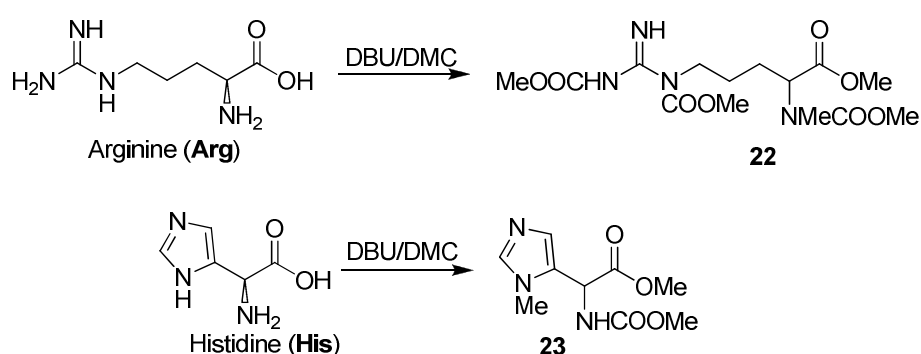


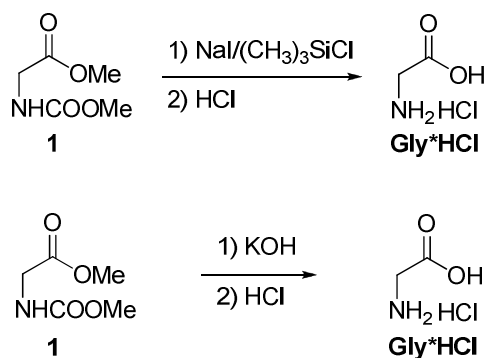
Figure 3. By-products deriving from the protection reaction of **Trp**

The iminoacid proline (**Pro**) showed a moderate reactivity affording to the corresponding protected product **21** in 42% yield (*Table 1, entry 14*). Other amino acids have been tested. As representative basic amino acids, arginine (**Arg**) and histidine (**His**) have been tested. Unfortunately, the DMC/DBU system showed a low selectivity and complex mixtures of reaction afforded. Between possible products, we isolated amino acid derivatives **22** and **23** deriving from methylation and carbomethoxylation reactions into the guanidinic and imidazolic group (*Scheme 2*). Asparagine (**Asn**) and glutamine (**Gln**) showed a very low solubility in DMC and then a very poor reactivity.



Scheme 2. Protective methodology of DMC/DBU of **Arg** and **His**

Finally, we tested the experimental conditions to remove the protecting group. **Gly-OMe*HCl** was chosen as representative substrate (*Scheme 3*).¹⁰³ Two different procedures were experimented. Firstly, we used iodotrimethylsilane generated in situ by reaction of sodium iodide and chlorotrimethylsilane. Adding hydrochloric acid, the corresponding **Gly*HCl** afforded in 76% yield. Under basic hydrolysis, **Gly*HCl** was isolated in 90% yield. Work is in progress to verify if the protecting/removal procedures maintain the chirality of natural amino acids.



Scheme 3. Deprotection methodologies for glycine derivative **1**

In conclusion, we optimized a new simple and ecofriendly procedure to protect α -amino and α -acid group of a large panel of amino acids by using the DMC/DBU system. The corresponding protected derivatives were isolated in moderate to good yields depending on the amino acid. Usually, traces of the corresponding N-methylated was observed as by-products. The removal of the protecting group was optimized. These results encourage us to extend this procedure to peptides.

Experimental section

Materials and Methods

All chemicals were purchased from Aldrich Company (Milan, Italy). Solvents were of the highest commercially available quality. Dry acetonitrile was prepared refluxing the solvent on NaH under nitrogen atmosphere. Reactions were monitored by Thin Layer Chromatography (TLC) analysis on silica gel plates (Kieselgel 60 F254). The spots were visualized with UV light and, when necessary, using a ninidrine solution. Column chromatography was performed on silica gel 60 commercially available from Merk using mixtures of petroleum ether /ethyl acetate or dichloromethane and methanol. ¹H-NMR, ¹³C-NMR spectra were recorded on a Bruker spectrometer (200 MHz). Chemical shift (δ) are reported in parts per million; coupling constants (J) are reported in Hertz. GC-MS analysis was performed on a Shimatzu VG 70/250S spectrometer with an electron beam of 70 eV and a CP-SIL 8 CB-MS column (25m, 0.25 mm and 0.25 mm film thickness). GC-MS analysis were recorded using an isothermal temperature profile of 100 °C for 2 minutes, followed by a 10 °C/min temperature gradient for 15 minutes until 280°C. The injector temperature was 280 °C.

Typical procedure to protect amino acids by the DMC/DBU system

In a typical reaction, amino acid (1.0 mmol) was dissolved in DMC (10 mL) and DBU (1-2 eq.) was stirred at reflux for 24 h. The reaction was monitored by GC-MS and, when possible, by TLC. At the end, the mixture was cooled to room temperature and DMC evaporated under vacuum as an azeotropic mixture with methanol; the residue was solubilized in ethyl acetate and added of HCl 1N; finally, the organic phases were washed with brine solution and dried on Na₂SO₄. After filtration, the organic extracts were concentrated under vacuum. The purification of the crude mixture by chromatography on silica gel (eluent: ethyl acetate/petroleum ether= 2/1) afforded to final products which were characterized by ¹H-NMR, ¹³C-NMR and GC-MS. Yields of the reactions of **Gly** and **Gly-OMe** were calculated by GC-MS analysis using amino acid derivative **7** as internal standard. Yields of other amino acids were calculated after chromatographic purification.

Methyl N-(methoxycarbonyl)glycinate 1. Yields: 67-68%. Colourless oil. ¹H-NMR (200 MHz, CDCl₃): δ (ppm) 3.96 (d, *J*=6.0 Hz, 2H), 3.74 (s, 3H), 3.68 (s, 3H). ¹³C-NMR (CDCl₃): δ (ppm) 172.4, 154.3, 52.5, 52.3, 42.6. MS (EI) *m/z*: 147 (M⁺).

Methyl N-(methoxycarbonyl)-N-methylglycinate 2. Yields: 10-20%. Light yellow oil. ¹H-NMR (200 MHz, CDCl₃): δ (ppm) 3.93 (d, *J*=6.0 Hz, 2H), 3.71 (s, 3H), 3.67 (s, 3H), 2.94 (s, 3H). ¹³C-NMR (CDCl₃): δ (ppm) 170.0, 156.0, 52.9, 52.4, 35.2. MS (EI) *m/z*: 161 (M⁺).

Methyl N-(methoxycarbonyl)alaninate 3. Yields: 65-74%. Colourless oil. ¹H-NMR (200 MHz, CDCl₃): δ (ppm) 4.38-4.31 (m, 1H), 3.72 (s, 3H), 3.66 (s, 3H), 1.40, 1.36 (s, 3H). ¹³C-NMR (CDCl₃): δ (ppm) 173.5, 156.2, 52.4, 52.3, 49.6, 18.7. MS (EI) *m/z*: 161 (M⁺).

Methyl N-(methoxycarbonyl)-N-methylalaninate 4. Yields: 9-15%. Colourless oil. ¹H-NMR (200 MHz, CDCl₃): δ (ppm) 4.38-4.31 (m, 1H), 3.72 (s, 3H), 3.66 (s, 3H), 3.01 (s, 3H), 1.40, 1.36 (s, 3H). ¹³C-NMR (CDCl₃): δ (ppm) 173.5, 156.2, 52.4, 52.3, 49.6, 29.7, 18.7. MS (EI) *m/z*: 175 (M⁺).

Methyl N-(methoxycarbonyl)valinate 5. Yield: 55%. Colourless oil. ¹H-NMR (200 MHz, CDCl₃): δ (ppm) 3.35-4.38 (m, 1H), 3.71 (s, 3H), 3.63 (s, 3H), 2-1.90 (m, 1H), 0.85 (s, 3H), 0.82 (s, 3H). ¹³C-NMR (CDCl₃): δ (ppm) 172.5, 156.7, 58.8, 56.7, 51.8, 31.0, 18.7. MS (EI) *m/z*: 189 (M⁺).

Methyl N-(tert-butoxycarbonyl)glycinate 7. Yield: 70%. Yellow oil. ¹H-NMR (200 MHz, CDCl₃): δ (ppm) 3.88 (d, *J*=6.0 Hz, 2H), 3.72 (s, 3H), 1.42 (s, 9H). ¹³C-NMR (CDCl₃): δ (ppm) 170.1, 155.7, 79.9, 52.2, 42.3, 28.2. MS (EI) *m/z*: 189 (M⁺).

Methyl N-(tert-butoxycarbonyl)methioninate 8. Yield: 60%. Yellow oil. ¹H-NMR (200 MHz, CDCl₃): δ (ppm) 4.44-4.37 (m, 1H), 3.71 (s, 3H), 2.50 (t, *J*=7.5 Hz, 2H), 2.17-1.79 (m, 2H), 2.07 (s, 3H), 1.41 (s, 3H). ¹³C-NMR (CDCl₃): δ (ppm) 172.8, 156.7, 52.8, 52.4, 32.2, 29.9, 28.3, 15.5. MS (EI) *m/z*: 263 (M⁺).

Methyl N-(tert-butoxycarbonyl)-1-(methoxycarbonyl)tryptophanate 9. Yield: 40%. White solid. ^1H -NMR (200 MHz, CDCl_3): δ (ppm) 8.15-8.12 (m, 2H), 7.50-7.20 (m, 2H), 4.71-4.62 (m, 1H), 4.01 (s, 3H), 3.67 (s, 3H), 3.23-3.17 (m, 2H), 1.27 (s, 9H). ^{13}C -NMR (CDCl_3): δ (ppm) 172.3, 155.1, 150.4, 137.5, 133.5, 124.9, 123.6, 122.9, 119.0, 115.2, 105.9, 53.8, 53.6, 52.5, 31.0, 28.3. MS (EI) m/z : 376 (M^+).

1-tert-Butyl 2-methyl pyrrolidine-1,2-dicarboxylate 10. Yield: 96%. Yellow oil. ^1H -NMR (200 MHz, CDCl_3): δ (ppm) 4.28-4.30 (m, 1H), 3.73 (s, 3H), 3.45-3.38 (m, 2H), 2.14-1.70 (m, 4H), 1.43 (s, 9H). ^{13}C -NMR (CDCl_3): δ (ppm) 171.1, 153.5, 79.7, 57.4, 52.0, 46.1, 30.7, 28.0, 23.5. MS (EI) m/z : 229 (M^+).

Methyl N-(methoxycarbonyl)methioninate 11. Yield: 45%. Yellow oil. ^1H -NMR (200 MHz, CDCl_3): δ (ppm) 4.47-4.41 (m, 1H), 3.70 (s, 3H), 3.67 (s, 3H), 2.51 (t, $J=7.5$ Hz, 2H), 2.22-1.88 (m, 2H), 2.08 (s, 3H). ^{13}C -NMR (CDCl_3): δ (ppm) 172.5, 156.5, 53.1, 52.5, 31.9, 30.7, 15.5. MS (EI) m/z : 221 (M^+).

Methyl N-(methoxycarbonyl)phenylalaninate 12. Yield: 49%. Yellow oil. ^1H -NMR (200 MHz, CDCl_3): δ (ppm) 7.32-7.07 (m, 5H), 4.67-4.58 (m, 1H), 3.71 (s, 3H), 3.69 (s, 3H), 3.10-3.07 (m, 2H). ^{13}C -NMR (CDCl_3): δ (ppm) 172.1, 156, 135.7, 129.2, 128.6, 127.1, 54.7, 52.0, 38.2. MS (EI) m/z : 237 (M^+).

Methyl N-(methoxycarbonyl)-N-methylphenylalaninate 13. Yield: 10%. Yellow oil. ^1H -NMR (200 MHz, CDCl_3): δ (ppm) 7.32-7.07 (m, 5H), 4.67-4.58 (m, 1H), 3.71 (s, 3H), 3.69 (s, 3H), 3.10-3.07 (m, 2H), 2.75 (s, 3H). ^{13}C -NMR (CDCl_3): δ (ppm) 172.1, 156.3, 135.7, 129.2, 128.6, 127.1, 54.7, 52.3, 38.2, 29.7. MS (EI) m/z : 251 (M^+).

Methyl N-(methoxycarbonyl)tyrosinate 14. Yield: 65%. Yellow oil. ^1H -NMR (200 MHz, CDCl_3): δ (ppm) 7.46-7.20 (m, 2H), 7.12-7.07 (m, 2H), 4.67-4.57 (m, 1H), 3.70 (s, 3H), 3.64 (s, 3H), 3.09-3.07 (m, 2H). ^{13}C -NMR (CDCl_3): δ (ppm) 172, 156.2, 154.6, 135.7, 129.2, 128.5, 54.8, 52.3, 38.3. MS (EI) m/z : 251 (M^+).

Methyl N-(methoxycarbonyl)-N-methyltyrosinate 15. Yield: 15%. Yellow oil. ^1H -NMR (200 MHz, CDCl_3): δ (ppm) 7.30-7.25 (m, 2H), 7.22-7.17 (m, 2H), 4.67-4.57 (m, 1H), 3.64 (s, 3H), 3.54 (s, 3H), 3.09-2.8 (m, 2H), 2.38 (s, 3H). ^{13}C -NMR (CDCl_3): δ (ppm) 171.8, 156.2, 154.8, 130.4, 127.9, 116.2, 62.8, 52.7, 51.9, 35.4, 30.0. MS (EI) m/z : 267 (M^+).

N-(methoxycarbonyl)-O-methyltyrosine 16. Yield: 6%. Yellow oil. ^1H -NMR (200 MHz, CDCl_3): δ (ppm) 7.04-6.97 (m, 2H), 6.84-6.76 (m, 2H), 4.59-4.56 (m, 1H), 3.76 (s, 3H), 3.69 (s, 3H), 3.64 (s, 3H), 3.03-3.00 (m, 2H); ^{13}C -NMR (CDCl_3): δ (ppm) 171.9, 158.8, 156.2, 130.3, 125.6, 114.1, 55.2, 54.6, 52.0, 37.8. MS (EI) m/z : 267 (M^+).

Methyl N-(methoxycarbonyl)tryptophanate **17**. Yield: 50%. Yellow oil. $^1\text{H-NMR}$ (200 MHz, CDCl_3): δ (ppm) 8.15-8.14 (m, 2H), 7.54-6.98 (m, 2H), 4.70-4.63 (m, 1H), 3.66 (s, 3H), 3.64 (s, 3H), 3.30-3.27 (m, 2H). $^{13}\text{C-NMR}$ (CDCl_3): δ (ppm) 173.8, 158.3, 139.2, 128.5, 124.6, 120.5, 119.3, 119.5, 112.8, 106.8, 54.5, 52.1, 50.1, 28.4. MS (EI) m/z : 276 (M^+).

Methyl N-(methoxycarbonyl)-N-methyltryptophanate **18**. Yield: 10%. Yellow oil. $^1\text{H-NMR}$ (200 MHz, CDCl_3): δ (ppm) 8.15-8.14 (m, 2H), 7.55-7.25 (m, 2H), 7.20-7.05 (m, 2H), 3.93 (s, 3H), 3.63 (s, 3H), 3.72-3.53 (m, 1H), 3.16-2.70 (m, 2H), 2.43 (s, 3H). $^{13}\text{C-NMR}$ (CDCl_3): δ (ppm) 172.0, 157.7, 138.2, 128.0, 124.6, 121.3, 119.4, 118.0, 109.8, 107.8, 61.6, 53.8, 52.7, 30.1, 27.0. MS (EI) m/z : 290 (M^+).

Methyl N,1-bis(methoxycarbonyl)tryptophanate **19**. Yield: 9.6%. Yellow oil. $^1\text{H-NMR}$ (200 MHz, CDCl_3): δ (ppm) 8.15-8.14 (m, 2H), 7.54-7.10 (m, 2H), 6.98-6.99 (m, 1H), 4.71-4.67 (m, 1H), 4.01 (s, 3H), 3.64 (s, 3H), 3.22-3.20 (m, 2H). $^{13}\text{C-NMR}$ (CDCl_3): δ (ppm) 174.0, 158.2, 150.4, 137.4, 128.0, 124.5, 123.4, 122.3, 119.5, 115.8, 105.8, 54.5, 52.6, 52.1, 50.1, 29.3. MS (EI) m/z : 334 (M^+).

Methyl N-(methoxycarbonyl)-N,1-dimethyltryptophanate **20**. Yield: 7.4%. Yellow oil. $^1\text{H-NMR}$ (200 MHz, CDCl_3): δ (ppm) 7.52-7.48 (m, 2H), 7.33-7.05 (m, 3H), 4.70-4.62 (m, 1H), 3.73 (s, 3H), 3.67 (s, 3H), 3.65 (s, 3H), 3.28-3.26 (m, 2H), 2.56 (s, 3H). $^{13}\text{C-NMR}$ (CDCl_3): δ (ppm) 172.0, 157.7, 137.5, 128.0, 121.4, 120.6, 120.4, 118.5, 107.8, 104.9, 61.6, 53.8, 52.7, 32.5, 30.1, 27.3. MS (EI) m/z : 304 (M^+).

Dimethyl pyrrolidine-1,2-dicarboxylate **21**. Yield: 42% yield. Yellow oil. $^1\text{H-NMR}$ (200 MHz, CDCl_3): δ (ppm) 4.29-4.18 (m, 1H), 3.63 (s, 3H), 3.58 (s, 3H), 3.45-3.38 (m, 2H), 2.14-1.88 (m, 4H). $^{13}\text{C-NMR}$ (CDCl_3): δ (ppm) 171.1, 159.5, 57.4, 52.4, 52.0, 46.5, 30.7, 23.4. MS (EI) m/z : 187 (M^+).

Methyl N^5 -{imino[(methoxycarbonyl)amino]methyl}- N^2,N^5 -bis(methoxycarbonyl)ornithinate **22**. Yield: 30%. Yellow oil. $^1\text{H-NMR}$ (200 MHz, CDCl_3): δ (ppm) 4.29-4.32 (m, 1H), 4.09-3.83 (m, 2H), 3.95 (s, 3H), 3.92 (s, 3H), 3.72 (s, 3H), 3.67 (s, 3H), 2.0-2.05 (m, 2H), 1.85-1.67 (m, 2H). $^{13}\text{C-NMR}$ (CDCl_3): δ (ppm) 175.7, 163.2, 156.8, 156.7, 153.5, 53.3, 52.7, 51.4, 48.8, 45.5, 30.7, 25.6. MS (EI) m/z : 362 (M^+).

Methyl N,3-bis(methoxycarbonyl)histidinate **23**. Yield: 20%. Yellow oil. $^1\text{H-NMR}$ (200 MHz, CDCl_3): δ (ppm) 7.35-7.40 (m, 1H), 6.61-6.67 (m, 1H), 5.2-5.18 (m, 1H), 3.71 (s, 3H), 3.65 (s, 3H), 3.56 (s, 3H), 3.34-3.15 (m, 2H), 2.90 (s, 3H). $^{13}\text{C-NMR}$ (CDCl_3): δ (ppm) 175.0, 157.5, 138.5, 119.2, 112.8, 63.3, 52.7, 52.1, 30.9, 30.0, 26.6. MS (EI) m/z : 255 (M^+).

Deprotection of methyl N-(methoxycarbonyl)glycinate (**1**)

Procedure a). A mixture of methyl N-(methoxycarbonyl)glycinate **1** (0.3 mmol, 44 mg), chlorotrimethylsilane (0.6 mmol, 0.040 mL) and sodium iodide (0.9 mmol, 70.3 mg) in dry acetonitrile (5 mL) was kept under reflux in nitrogen atmosphere. The reaction was monitored by TLC using a ninidrine solution as detector. Then, the mixture was cooled to room temperature; 3 mL of methanol saturated with HCl was carefully added and the mixture was stirred for 15 min. The solvents were removed under vacuum; the solution was washed with MeCN, MeOH, and CH₂Cl₂ for a complete removal of excess reagents and soluble by-products. The white solid was dried under high vacuum pump (23 mg, yield: 71%) and characterized by ¹H, ¹³C NMR spectroscopy and GC-MS.

Procedure b). Methyl N-(methoxycarbonyl)glycinate **1** (1.0 mmol, 147 mg) was solubilised in MeOH/H₂O=3/1 (12 mL), then a solution of 10% KOH was added (10 mL). The mixture was kept at room temperature and monitored by TLC using the ethanolic ninidrine solution. After 40 minutes the substrate disappeared. Then, methanol saturated with HCl was added (4 mL) and the mixture was stirred for 15 min. The solvents were removed under vacuum; the solution was washed with MeCN, MeOH, and CH₂Cl₂ for a complete removal of excess reagents and soluble by-products. The white solid was dried under high vacuum pump (130 mg, yield: 90%) and characterized by ¹H, ¹³C NMR spectroscopy and GC-MS.

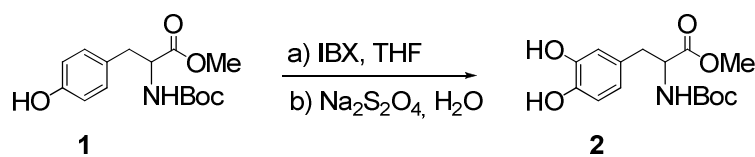
Glycine hydrochloride. ¹H-NMR (200 MHz, CD₃OD): δ (ppm) 2.29 (s, NH), 18.6-1.82 (m, 2H). ¹³C-NMR (CDCl₃): δ (ppm) 169.7, 41.0. MS (EI) m/z : (silylated product) 219 (M⁺).

9. Synthesis of L-3,4-dihydroxyphenylalanine (L-DOPA) derivatives with 2-iodoxybenzoic acid (IBX)

The synthesis of unnatural amino acids and peptides is of pivotal importance for the development of a selective chemical engineering of proteins.¹⁰⁴ According to general methods employed for these transformations, the amino acids and peptides can be modified at the backbone of the molecule as well as in their side-chains. Backbone modifications include changes at any one of the three repeating moieties, that are NH, CO and α -CH bonds.¹⁰⁵ Side-chain modifications are in general performed by oxidation of low redox potential residues.¹⁰⁶ In this latter case, a different selectivity is observed depending on the nature of the oxidant. As for example, the selective oxidation of methionine (Met), cysteine (Cys) and tryptophan (Trp) in the presence of other potentially oxidizable residues has been performed with the methyltrioxorhenium (MTO)/hydrogen peroxide catalytic system.¹⁰⁷ High redox potential residues, aliphatic side-chain amino acids, require most powerful oxidants. Thus, leucine (Leu) and leucine residues are oxidized by dimethyldioxirane (DMD) at γ -CH bond to obtain the corresponding 4,4-dimethyl-4-butanolide derivatives without backbone modifications.¹⁰⁸

Tyrosine (Tyr) is the only α -amino acid bearing the phenolic moiety. The catechol derivative of Tyr is 3,4-dihydroxyphenylalanine (DOPA). DOPA is an unusual amino acid derived from post-translational modification of tyrosine.¹⁰⁹ It is well known that DOPA is rarely included in proteins. However, it is found in marine biological tissues, including coral reef structures,¹¹⁰ eggshells¹¹¹ seashells¹¹² and adhesives produced by mollusks.¹¹³ It has been postulated that the adhesive and cohesive properties of mussel adhesive proteins in sea water is due to the catechol moiety present into DOPA and DOPA residues.¹¹⁴ Cross-linked structures having DOPA residues create hardened matrices useful as biomaterials.¹¹⁵ Since the late 1960s, DOPA is the most successful therapeutic agent in the treatment of Parkinson's disease.¹¹⁶ It is as building block for design and synthesis of biologically active compounds.¹¹⁷ Thus, research in the design of novel synthesis of DOPA peptides is a high priority. In this PhD course, we described an efficient and selective *ortho*-hydroxylation of Tyr and Tyr containing peptides to corresponding DOPA derivatives with IBX.¹¹⁸

Firstly, we turned our attention on the oxidation of tyrosine. In order to avoid possible competitive side reactions, we need to protect the amino group. We utilized the N-Boc derivative **1** as starting material.¹¹⁹ The oxidation of **1** with a small excess of IBX in THF afforded a quantitative conversion of substrate after 40 min. Boc- DOPA-OMe derivative **2** was obtained in 95% yield as the only product (*Scheme 1*; *Table 1*, entry 1). The structure of **2** was unambiguously assigned by comparison with authentic sample.¹²⁰ Compound **2** showed a value of the optical rotatory power $[\alpha]_D +7.0^\circ$ (methanol, $c=1.0$, $T=22^\circ\text{C}$) according to authentic L-enantiomer.²⁴



Scheme 1. Oxidative conversion of Boc-Tyr-OMe **1** into Boc-DOPA-OMe **2** with IBX/Na₂S₂O₄ system

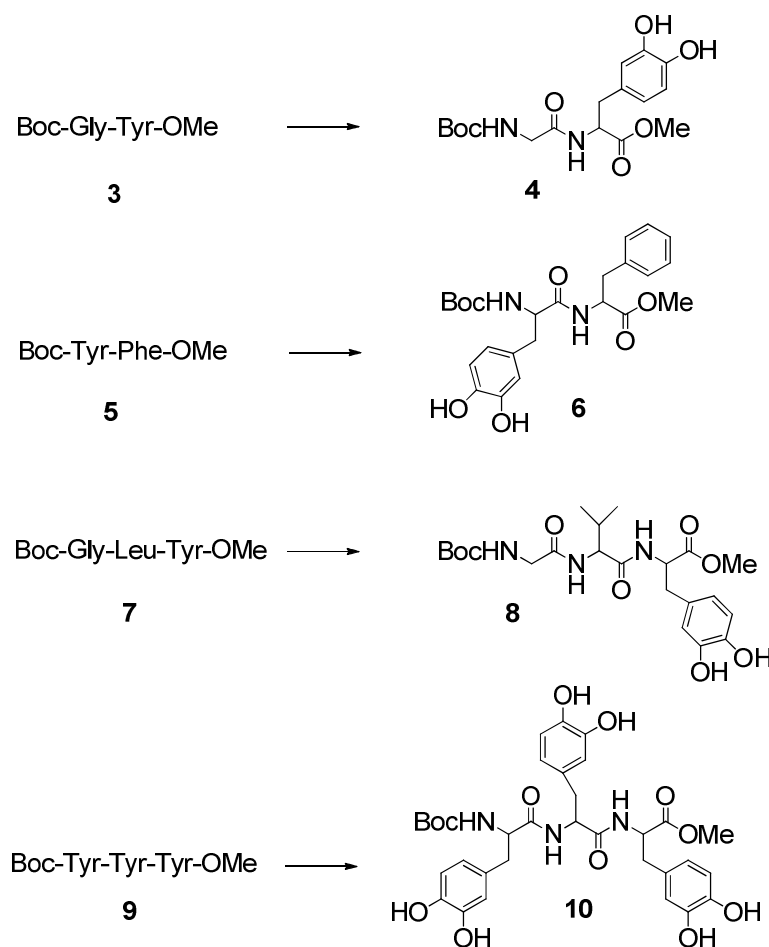
These experimental data demonstrated that the stereochemical integrity of the final product was not compromised during the oxidative/reductive step of Boc-L-Tyr-OMe **1**. According to the previously reported mechanism, the oxidation reaction with IBX probably proceeded with an ionic pathway.^{40,41} It is interesting to note that the IBX/Na₂S₂O₄ system mimed the activity of naturally occurring mushroom tyrosinase (EC 1.14.18.1).¹²¹

Table 1. Experimental data of oxidations depicted in *Schemes 1 and 2*.

Entry	Substrate	Product	Conv. (%)	Yield (%)
1	1	2	>98	95
2	3	4	90	85
3	5	6	88	84
4	7	8	85	80
5	9	10	80	75

On the basis of the efficiency observed in the oxidation of **1** we extended the IBX procedure to a panel of selected Tyr-containing dipeptides and tripeptides bearing amino acids with different aliphatic or aromatic side-chain residues (*Scheme 2*). The oxidation of Boc-Gly-Tyr-OMe **3** with IBX afforded Boc-Gly-DOPA-OMe **4** in good conversion and yield (*Table 1, entry 2*), besides to a low amount of unreacted substrate. In a similar way, treatment of Boc-Tyr-Phe-OMe **5** gave the corresponding Boc-DOPA-Phe-OMe **6** in satisfactory conversion and yield (*Table 1, entry 3*). The transformations reported were found to be selective, and the possible oxidation of the benzylic position¹²² in phenylalanine (Phe) residue as well as that of the amide group¹²³ in the backbone were not observed in our experimental conditions. Finally, the oxidation of tripeptides Boc-Gly-Leu-Tyr-OMe **7** bearing one reactive Tyr residue, and Boc-Tyr-Tyr-Tyr-OMe **9** bearing three reactive Tyr residues, was studied. In the case of **7** the Tyr residue was selectively oxidized to give Boc-Gly-Leu-DOPA-OMe **8** in good conversion and yield (*Table 1, entry 4*). The treatment of Boc-Tyr-Tyr-Tyr-OMe **9** with 1.2 equiv. of IBX afforded a complex mixture of reaction products probably due to a low selectivity in the oxidation of different Tyr residues. According to this hypothesis, the reaction

repeated in the presence of a large excess of IBX (4.0 equiv.) gave the highly functionalized tripeptides Boc-DOPA-DOPA-DOPA-OMe **10**, in which all Tyr residues are functionalized, in satisfactory yield (*Table 1, entry 5*). The shifts of the absorptions of the nine aromatic protons at 6.26-6.62 ppm in the ^1H NMR spectrum of **10** compared to the absorptions of the twelve aromatic protons at 6.56-6.86 ppm of **9** and the appearance of three new quaternary carbon atoms in the ^{13}C NMR spectrum of **10** confirmed the assigned structure.



Scheme 2. Oxidative modification of dipeptides **3**, **5** and tripeptides **7**, **9** with IBX/Na₂S₂O₄ system

As selected examples, the stereochemical integrity of peptides **4** and **10** was confirmed by comparison of the optical rotatory power with authentic samples after deprotection procedure above described [Gly-L-DOPA: found $[\alpha]_{\text{D}}$ +46.0°, reported +46.07°; L-DOPA-L-DOPA-L-DOPA: found $[\alpha]_{\text{D}}$ +13.7, reported +13.76 (1M HCl, c=1.0, T=25°C).^{124,125}

In view of technological applications of the IBX-procedure for the oxidative conversion of tyrosine derivatives into DOPA residues, we worked under heterogeneous conditions using polymer-supported IBX, specifically IBX polystyrene already applied successful by us for the synthesis of hydroxytyrosol^{44,45} and catecholamines.¹²⁶ As selected model compound, we tested the oxidation of Boc-Tyr-OMe derivative **1**. Good results in terms of conversion of substrate and yield of **2** were obtained with an excess of the oxidant (conversion: 95%, yield: 90%). Recycling experiments proceeded with success. When the substrate disappeared, the polymeric reagent was recovered and IBX polystyrene was regenerated according to the previously reported⁴⁵ and reused in oxidations. As shown, IBX polystyrene was used for at least five cycles of oxidation without loss of efficiency to give **2** (Table 2, entries 1-5). With the sixth recycling experiment, conversions and yields decreased but no side-chain products were isolated demonstrating that the oxidations proceeded again with a high chemo- and regio-selectivity (Table 2, entries 6-10).

Table 2. Experiment of recycling of IBX polystyrene in the oxidation of **1**.

Entry	Run	Conv. (%)	Yield (%)
1	1	95	90
2	2	95	88
3	3	95	90
4	4	94	89
5	5	95	88
6	6	75	72
7	7	72	70
8	8	70	68
9	9	72	70
10	10	70	68

In conclusion, our results showed that IBX and IBX polystyrene were efficient reagents in the oxidative conversion of tyrosine and tyrosine derivatives into DOPA and DOPA residues. The stereochemical integrity of the final product was not compromised during the reactions. Usually, DOPA peptides are prepared under solid phase synthesis that sometimes requires complex reaction conditions. To the best of our knowledge this is the first example of an one-pot synthesis of DOPA peptides starting from already available substrates. This procedure opens a novel way for the synthesis of modified proteins having DOPA residues in their structure.

Experimental section

Materials and methods

All chemicals were purchased from Sigma-Aldrich and were of analytical grade. Silica gel 60 F254 plates were obtained from Merck. ^1H NMR and ^{13}C NMR were recorded on a Bruker 200 MHz spectrometer using CDCl_3 as solvent. All chemical shifts are expressed in ppm (δ scale) and coupling constants in Hz.

Oxidation of tyrosine derivatives

The appropriate substrate (**1**, **3**, **5**, **7**, **9**, 1.0 mmol) was dissolved in THF (8.0 mL) with a small excess of IBX (1.2 eq., 336.0 mg). The solution was stirred at room temperature until disappearance of the substrate followed by *in situ* reduction with sodium dithionite ($\text{Na}_2\text{S}_2\text{O}_4$, 2.0 equiv.) in water (8.0 mL), afforded to correspondent DOPA derivative in high yield (**2**, **4**, **6**, **8**, **10**, 75-95%). No chromatographic purifications needed.

Methyl N-(tert-butoxycarbonyl)-3-hydroxytyrosinate **2** (Boc-DOPA-OMe). Yield: 95%. Yellow oil. ^1H -NMR (200 MHz, CDCl_3): δ (ppm) 6.98-6.75 (m, 2H), 4.19-4.17 (m, 1H), 3.69 (s, 3H), 3.70 (s, 3H), 3.19-3.07 (m, 2H), 1.30 (s, 9H). ^{13}C -NMR (CDCl_3): δ (ppm) 171.9, 155.8, 146.8, 143.9, 127.1, 122.5, 116.7, 115.8, 79.5, 54.6, 52.0, 38.0, 28.3. MS (EI) m/z : 251 (M^+).

Methyl N-(tert-butoxycarbonyl)glycyl-3-hydroxytyrosinate **4** (Boc-Gly-Tyr-OMe). Yield: 85%. Yellow oil. ^1H -NMR (200 MHz, CDCl_3): δ (ppm) 6.74-6.65 (m, 2H), 4.87-4.84 (m, 1H), 3.89 (s, 2H), 3.70 (s, 3H), 3.03-2.91 (m, 2H), 1.39 (s, 9H). ^{13}C -NMR (CDCl_3): δ (ppm) 173.5, 170.2, 158.7, 145.3, 142.2, 130.2, 122.9, 116.2, 115.2, 79.1, 52.4, 49.1, 44.1, 37.1, 28.2. MS (EI) m/z : 251 (M^+).

Methyl N-(tert-butoxycarbonyl)-3-hydroxytyrosylphenylalaninate **6** (Boc-DOPA-Phe-OMe). Yield: 84%. Yellow oil. ^1H -NMR (200 MHz, CDCl_3): δ (ppm) 7.38-7.18 (m, 6H), 6.73-6.75 (m, 2H), 4.91-4.84 (m, 2H), 3.55 (s, 3H), 3.11-2.96 (m, 4H), 1.4 (s, 9H). ^{13}C -NMR (CDCl_3): δ (ppm) 172.0, 170.2, 157.8, 146.6, 144.2, 136.1, 129.5, 128.5, 126.5, 122.5, 116.6, 115.7, 81.0, 55.4, 52.9, 50.1, 37.6, 37.5, 28.9. MS (EI) m/z : 251 (M^+).

Methyl N-(tert-butoxycarbonyl)glycylvalyl-3-hydroxytyrosinate **8** (Boc-Gly-Leu-DOPA-OMe). Yield: 80%. Yellow oil. ^1H -NMR (200 MHz, CDCl_3): δ (ppm) 6.67-6.73 (m, 3H), 4.56-4.59 (m, 2H), 3.92 (s, 2H), 3.55 (s, 3H), 3.03-2.91 (m, 2H), 2.23 (m, 1H), 1.39 (s, 9H), 0.96-0.81 (m, 6H). ^{13}C -

NMR (CDCl₃): δ (ppm) 170.2, 169.5, 155.3, 145.3, 142.2, 127.8, 122.9, 116.2, 115.2, 78.5, 56.4, 55.0, 52.5, 42.2, 36.9, 30.3, 28.2, 18.21, 17.0. MS (EI) m/z : 251 (M^+).

Methyl N-(tert-butoxycarbonyl)-3-hydroxytyrosyl-3-hydroxytyrosyl-3-hydroxytyrosinate **10** (Boc-DOPA-DOPA-DOPA-OMe). Yield: 75%. Yellow oil. ¹H-NMR (200 MHz, CDCl₃): δ (ppm) 6.83-6.51 (m, 9H), 4.70-4.51 (m, 3H), 3.65 (m, 3H), 2.90-2.74 (m, 6H), 1.33 (s, 9H). ¹³C-NMR (CDCl₃): δ (ppm) 172.2, 171.5, 170.8, 155.9, 144.4, 144.3, 144.1, 143.6, 129.6, 127.9, 127.7, 127.3, 120.7, 116.1, 115.8, 115.2, 80.6, 60.5, 53.6, 52.2, 37.1, 36.9, 36.6, 28.0.

Determination of rotatory power of Boc-DOPA-OMe (2)

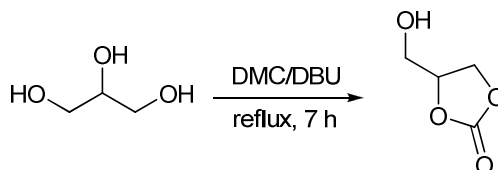
In order to further confirm the chirality of Boc-DOPA-OMe derivative **2**, it was deprotected by HCl-saturated ethyl acetate and 10% KOH solution in methanol to give free DOPA which was subjected to chiral HPLC analysis (CHIROBIOTIC T, Aldrich) using commercial L-DOPA and D,L-DOPA as previously reported.¹²⁷ The presence of the peak attributable to L-DOPA and the absence of the D-DOPA in the HPLC profile of the sample prepared according to our procedure confirmed the chirality of the product. Compound **2** showed a value of the optical rotatory power $[\alpha]_D +7.0^\circ$ (methanol, $c=1.0$, $T=22^\circ\text{C}$) according to authentic L-enantiomer.

Recycling experiments of oxidative procedure of Boc-Tyr-OMe (1)

After each run the polymeric reagent was recovered by filtration and the remaining solution was treated with Na₂S₂O₄. IBX polystyrene was regenerated and reused in oxidations after adding fresh substrate.). Derivative **2** afforded as the only product for 10 runs in good yields (68-90%).

10. New high added-value products from glycerol

On the basis of our previous experience on the utilization of the DMC/DBU system, first of all we synthesized 1,2-glycerol carbonate (*Scheme 1*). Glycerol was solubilized in DMC and DBU was added. The mixture was kept at reflux temperature (90 °C). Monitoring the reaction via gas-chromatography (GC-MS), we isolated the expected product after 7 h (yield: 70%).



Scheme 1. Synthetic procedure of glycerol carbonate with DMC/DBU system

Moreover, we observed the formation of by-products **A** and **B** (yields: 10 and 15%, *Figure 1*). Prolonging the reaction time until 24 h, compound **B** was the only product recovered in quantitative yield.

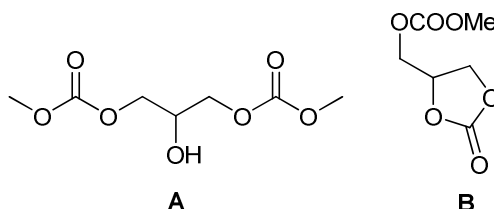


Figure 1. By-products A and B obtained from the synthesis of 1,2-glycerol carbonate

In order to increase the green character of this synthesis, we utilized polymer-bound DBU (1% cross linked with divinylbenzene). After 9 h of reaction, we obtained 1,2-glycerol carbonate in 75% yield, comparable to that obtained in homogeneous conditions. Also the two by-products were isolated in similar yields. After the reaction, polymer-bound DBU was recovered and reused for a new synthesis adding fresh glycerol and DMC. DBU was used until the third run but a decrease of the efficiency was observed since the second run (*Figure 2*).

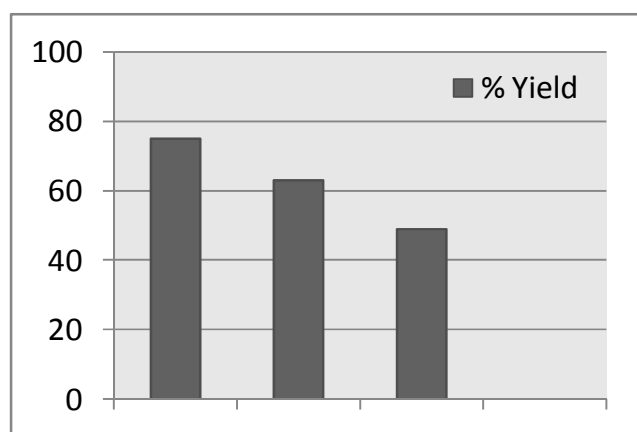
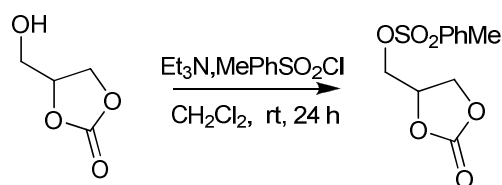


Figure 2. Recycling of polymer-bound DBU

Then, we converted glycerol carbonate into tosylated glycerol carbonate by the procedure already reported in the literature (*Scheme 2*). Glycerol carbonate was dissolved in CH_2Cl_2 , after triethylamine and tosyl chloride were added. The expected product was isolated in quantitative yield.



Scheme 2. Sulfonate activation of glycerol carbonate

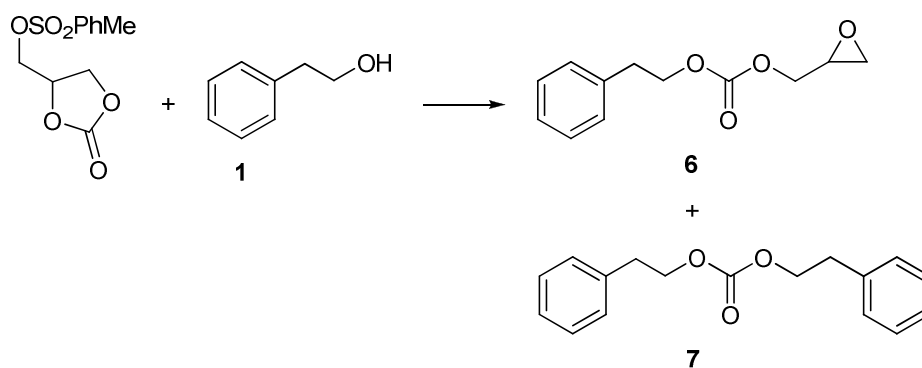
The chemical versatility of tosylated glycerol carbonate appeared to us particularly promising in order to synthesised new molecules containing the glycerol-skeleton by nucleophilic substitutions. In particular we projected the synthesis of novel phenolic and catecholic compounds with potential antioxidant activity. On the basis of our previous experience,^{44,45} we chose 2-phenethylalcohol **1**, 2-(4-hydroxyphenyl)ethanol **2** (tyrosol), 4(3-hydroxypropyl)phenol **3**, 3-(2-hydroxyethyl)phenol **4** and 4-hydroxy-3-methoxyphenethanol **5** (homovanillyl alcohol) as nucleophilic reagents. The reaction between tosylated glycerol carbonate and 2-phenethylalcohol **1** was the model reaction (*Scheme 3*). All experimental conditions are reported in *Table 1*.

Table 1. Influence of reaction parameters in nucleophilic substitution of tosylated glycerol carbonate

Entry	1 (eq.)	Solvent	Base (eq.)	T (°C)	t (h)	6 (yield %)	7 (yield %)
1	3	DMF	NaHCO ₃ (6.0)	90	24	--	--
2	3	DMF	Et ₃ N (6.0)	90	24	--	--
3	1	DMF	K ₂ CO ₃ (3.0)	90	7	22	16
4	1	DMF	K ₂ CO ₃ (3.0)	90	24	15	21
5	3	DMF	K ₂ CO ₃ (6.0)	90	7	30	18
6	3	DMF	K ₂ CO ₃ (6.0)	90	24	19	42
7	1.2	THF _{dry}	NaH (1.2)*	-78 to rt	2	50	15

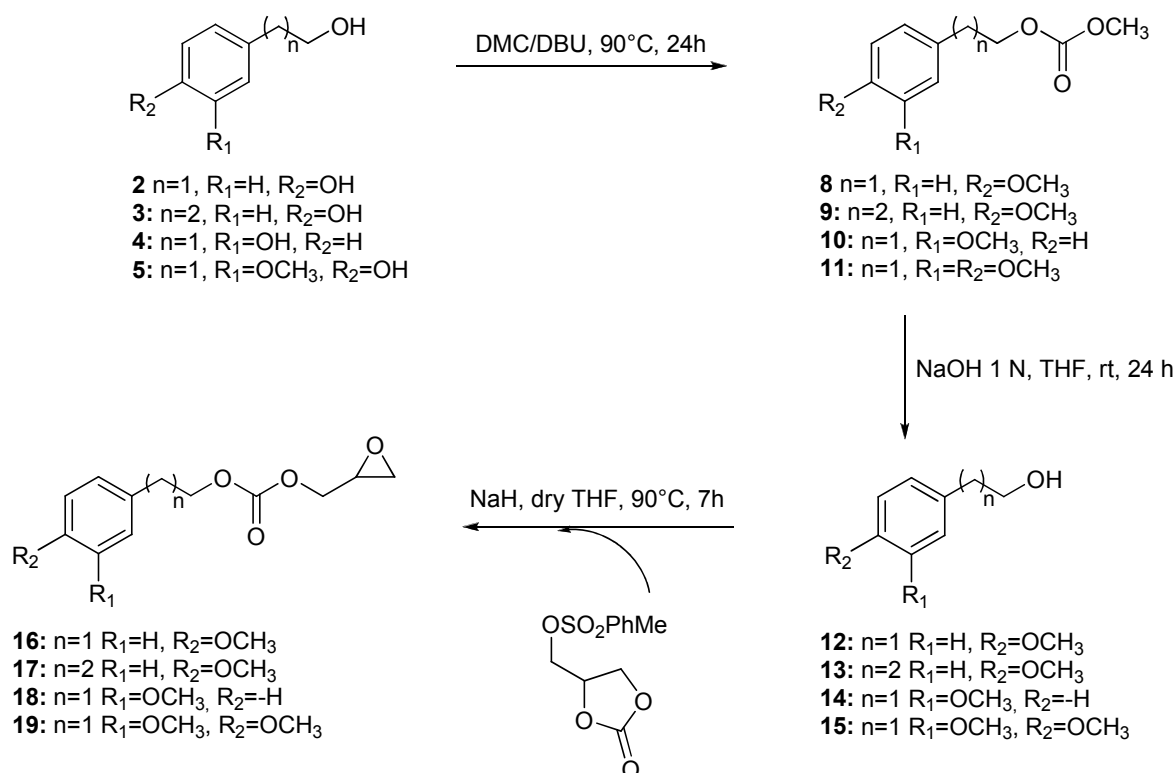
* In the presence of catalytic amount of tetrabutylammonium bromide (TBAB)

Firstly, we carried out the reaction in DMF with sodium hydrogen carbonate or triethylamine as bases for 24 h and the presence of a large excess of bases and phenethyl alcohol **1** (Table 1, entries 1 and 2). Unfortunately, no products were observed. With potassium carbonate, a mixture of products **6** and **7** was obtained in 16-42% yields depending on the experimental conditions (Table 1, entries 3-6). The highest yield of the expected product **6**, even if again moderate, was obtained with a large excess of phenethyl alcohol **1** and base after 7 h (Table 1, entry 5). Under the same experimental conditions but prolonging time reaction until 24 h, the main compound was **7** (Table 1, entry 6). A satisfactory yield of compound **6** was obtained by using sodium hydride as base and a catalytic amount of tetrabutylammonium bromide (TBAB) in dry THF (Table 1, entry 7).

**Scheme 3.** Reaction between tosylated glycerol carbonate and 2-phenethylalcohol **1**

Then, we applied these experimental conditions with tyrosol **2**, 4(3-hydroxypropyl)phenol **3**, 3-(2-hydroxyethyl)phenol **4** and homovanillyl alcohol **5**. Unfortunately, when glycerol carbonate reacted with these nucleophiles, complex mixtures of reaction were obtained, probably for possible competitive reactions of the phenolic moiety. In order to avoid the side reactions, we protected the phenolic group with a procedure already optimized by us, based on two steps (Scheme 4).¹²⁸ First, we protected the alcoholic and phenolic groups by a carboxymethylation/methylation with DMC/DBU

system to obtain the corresponding compounds **8-11** in quantitative yields; then, we hydrolyzed the carbonate moiety under basic conditions in order to obtain methylated derivatives **12-15** (yields: 90-95%). Then, we performed the reaction of these derivatives with tosylated glycerol carbonate in dry THF and in the presence of sodium hydride and TBAB, as previously described. Compounds **16-19** were isolated in 42-50% yields. The different alkyl chain length of derivatives **12** and **13** and the position of the methoxy group into the aromatic ring of **14** and **15** did not influence the course of the reaction.

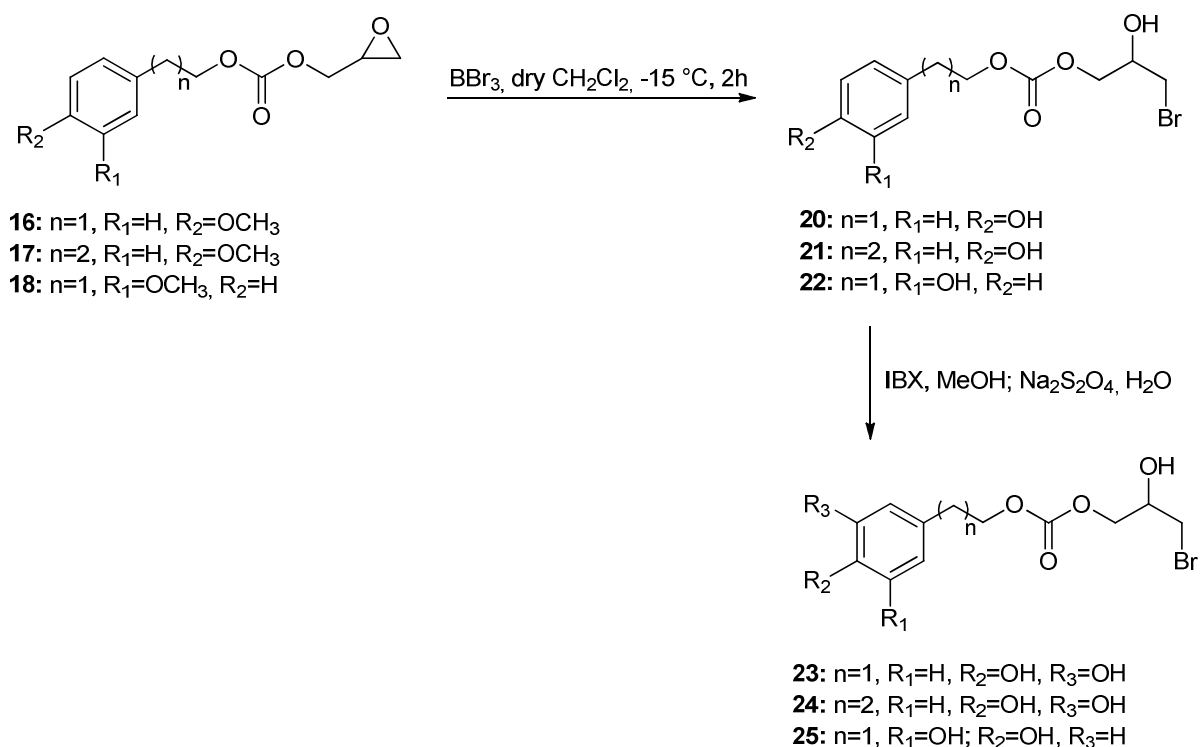


Scheme 4. Preparation of compounds **16-19**

Then, we demethylated compounds **16-18** by using a dichloromethane solution of BBr_3 in order to obtain the corresponding hydroxylated compounds **20-22** (yields: 40-55%, *Scheme 5*). Unfortunately, during these methylation reactions, BBr_3 opened also the epoxidic rings. Finally, compounds **20-22** were hydroxylated on the aromatic ring by using the IBX/ $Na_2S_2O_4$ procedure.^{44,45} Products **23-25** were isolated in moderate yields (43-49%).

Work is in progress about the evaluation of the antioxidant activity of these new compounds by using the 2,2-diphenyl-1-picrylhydrazyl (DPPH $\cdot$) radical test assay.¹²⁹ The antioxidant activity was defined as the amount of compound necessary to decrease the initial DPPH $\cdot$ concentration by 50%

and expressed as EC₅₀ (Efficient Concentration=mmol isochroman/mmol DPPH[•]). The reduction of DPPH[•] was followed by monitoring the decrease in the absorbance at $\lambda=516$ nm of known solutions of compounds to be tested until reaching the steady state. Preliminary data of EC₅₀ of compounds **6**, **16**, **20**, **23** showed that the antioxidant activity follows the order **23** > **20** > **16** > **6**. As a consequence, both the phenolic and catecholic moiety is essential to increase the antioxidant activity, as already reported in the literature¹³⁰ and observed by us for similar compounds.⁴⁴⁻⁴⁶



Scheme 5. Synthesis of hydroxylated derivatives of glycidyl carbonates

In conclusion, glycerol carbonate was obtained in satisfactory yield from renewable starting material, glycerol, and dimethyl carbonate, an ecofriendly chemical in the presence of DBU. We explored the versatility of tosylated glycerol carbonate toward a series of phenolic compounds in order to prepare new compounds. This route is a green alternative to the use of glycidol and epichloridrin in order to prepare compounds containing the oxyranly moiety, a key structural segment in organic synthesis. Finally, after the regioselective hydroxylation of aromatic with IBX/Na₂S₂O₄ system, we isolate new catecholic compounds with potential antioxidant activity.

Experimental section

Materials and Methods

All chemicals were purchased from Aldrich Company (Milan, Italy). Solvents were of the highest commercially available quality. Dry THF was prepared refluxing on KOH and after on potassium under nitrogen atmosphere. Dry CH_2Cl_2 was obtained refluxing the solvent on CaH_2 . Reactions were monitored by Thin Layer Chromatography (TLC) analysis on silica gel plates (Kieselgel 60 F254). The spots were visualized with UV light and, when necessary, iodine vapours. Column chromatography was performed on silica gel 60 commercially available from Merk using mixtures of petroleum ether /ethyl acetate or dichloromethane and methanol. ^1H -NMR, ^{13}C -NMR spectra were recorded on a Bruker spectrometer (200 MHz). Chemical shift (δ) are reported in parts per million; coupling constants (J) are reported in Hertz. GC-MS analysis was performed on a Shimadzu VG 70/250S spectrometer with an electron beam of 70 eV and a CP-SIL 8 CB-MS column (25m, 0.25 mm and 0.25 mm film thickness). GC-MS analysis were recorded using an isothermal temperature profile of 100 °C for 2 minutes, followed by a 10 °C/min temperature gradient for 15 minutes until 280°C. The injector temperature was 280 °C.

Synthesis of 1,2-glycerol carbonate (4-hydroxymethyl-1,3-dioxolan-2-one)

Procedure a). Glycerol (92 mg, 1.0 mmol) was dissolved in DMC (6.0 mL), then DBU (1.0 eq.) was added; the mixture was stirred at reflux for 7 h. The reaction was monitored by GC-MS analysis and by TLC, using UV and iodine vapours as detectors. At the end, the mixture was cooled to room temperature. DMC was evaporated under vacuum as an azeotropic mixture with methanol and the crude mixture was purified by chromatography on silica gel (eluent: $\text{CH}_2\text{Cl}_2/\text{MeOH}=9/1$). 1,2-Glycerol carbonate (yield: 70%), diglycerol tricarboxylate **A** (yield: 10%) and 4-(methoxycarbonyloxymethyl)-1,3-dioxolan-2-one **B** (yield: 15%) were characterized by ^1H -NMR, ^{13}C -NMR and GC-MS.

Procedure b). Glycerol (92 mg, 1.0 mmol) was dissolved in DMC (6.0 mL), then polymer-bound DBU (1.0 eq., N loading: 1.15 mmol/g) was added; the mixture was stirred at reflux for 9 h. The reaction was monitored by GC-MS and by TLC using UV and iodine vapours as detectors. At the end, the mixture was cooled to room temperature; polymer-bound was filtered, DMC was evaporated under vacuum as an azeotropic mixture with methanol and the crude mixture was purified by chromatography on silica gel (eluent: $\text{CH}_2\text{Cl}_2/\text{MeOH}=9/1$). 1,2-Glycerol carbonate (yield: 75%),

diglycerol tricarboxylate **A** (yield: 12%) and 4-(methoxycarbonyloxymethyl)-1,3-dioxolan-2-one **B** (yield: 10%) were characterized by ^1H -NMR, ^{13}C -NMR and GC-MS.

Glycerol 1,2-carboxylate (4-hydroxymethyl-1,3-dioxolan-2-one). Colourless oil. ^1H -NMR (200 MHz, $\text{CDCl}_3/\text{CD}_3\text{OD}$): δ (ppm) 4.70-4.60 (m, 1H), 4.42 (dd, $J_1=8.0$ Hz, $J_2=8.4$ Hz, 1H), 4.27 (dd, $J_1=8.0$ Hz, $J_2=6.0$ Hz, 1H) 3.72 (ddd, $J_1=2.0$ Hz, $J_2=4.0$ Hz, $J_3=8.0$ Hz, 1H) 3.48 (ddd, $J_1=2.0$ Hz, $J_2=4.0$ Hz, $J_3=8.0$ Hz, 1H). ^{13}C -NMR ($\text{CDCl}_3/\text{CD}_3\text{OD}$): δ (ppm) 115.6, 77.4, 66.3, 61.3. MS (EI) m/z (silylated glycerol carbonate): 189 ($\text{M}^+ - 1$).

Diglycerol tricarboxylate A. Colourless oil. ^1H -NMR (200 MHz, CDCl_3) δ (ppm) 4.84-4.77 (m, 2H), 4.48 (dd, J_1 and $J_2=8.6$ Hz, 1H), 4.39 (dd, $J_1=13.2$ Hz, $J_2=3.2$ Hz, 1H), 4.34 (dd, $J_1=6.0$ Hz, $J_2=2$ Hz, 1H), 4.29 (dd, $J_1=4.2$ Hz, $J_2=2.4$ Hz, 1H). ^{13}C -NMR: (CDCl_3): δ (ppm) 156.0, 155.5, 70.3, 67.3, 65.1. MS (EI) m/z : 262 ($\text{M}^+ - 1$).

4-(Methoxycarbonyloxymethyl)-1,3-dioxolan-2-one B. White solid. ^1H -NMR (200 MHz, CDCl_3) δ (ppm) 4.88-4.77 (m, 1H), 4.44 (t, J_1 and $J_2=8.6$ Hz, 1H), 4.32 (dd, $J_1=13.2$ Hz, $J_2=3.2$ Hz, 1H), 4.25 (dd, $J_1=6.0$ Hz, $J_2=2$ Hz, 1H), 4.16 (dd, $J_1=4.2$ Hz, $J_2=2.4$ Hz, 1H) 3.65 (s 3H). ^{13}C -NMR: (CDCl_3): δ (ppm) 155.1, 154.4, 73.6, 66.1, 65.8, 55.4. MS (EI) m/z : 177 ($\text{M}^+ + 1$).

Synthesis of 3-O-tosylated-1,2-glycerol carbonate

1,2-Glycerol carbonate (1.0 g, 8.5 mmol) was dissolved in CH_2Cl_2 (10 mL), after triethylamine (1.0 eq.) and tosyl chloride (2 g, 10.2 mmol, 1.2 eq.) were added. The mixture was stirred at room temperature for 24h. The reaction was monitored by TLC. At the end, CH_2Cl_2 was evaporated under vacuum. The crude product was washed with cold methanol and dried at high vacuum pump. 3-O-Tosylated-1,2-glycerol carbonate was isolated in quantitative yield and characterized by ^1H -NMR, ^{13}C -NMR and GC-MS.

3-O-Tosylated-1,2-glycerol carbonate. White solid. ^1H -NMR (200 MHz, $\text{CDCl}_3/\text{CD}_3\text{OD}$) δ (ppm) 7.80-7.74 (m, 2H), 7.40-7.24 (m, 2H), 4.93-4.82 (m, 1H), 4.56 (dd, $J_1=8.0$ Hz, 1H); 4.34 (dd, $J_1=6.0$ Hz; $J_2=2.0$ Hz, 1H) 4.20 (dd, $J_1=2.0$ Hz, 2H); 2.45 (s, 3H). ^{13}C -NMR: ($\text{CDCl}_3/\text{CD}_3\text{OD}$): δ (ppm) 155.6, 145.3, 133.0, 129.9, 128.0, 72.1, 70.3, 77.3, 21.8. MS (EI) m/z (silylated glycerol carbonate): 272 (M^+).

Preparation of compounds (8-11)

The appropriate phenol **2-5** (1.0 mmol) was solubilised in DMC (6.0 mL), then DBU (1.2 eq., 178 μL) was added and the mixture was heated to reflux (90 $^\circ\text{C}$) for 24 h. The reaction was monitored by

TLC and GC-MS. After the disappearance of the substrate, the reaction mixture was cooled to room temperature and DMC was evaporated under vacuum with methanol. The residue was solubilised with dichloromethane (10 mL) and treated with HCl 1N (5.0 mL). The aqueous phase was extracted with dichloromethane (3x5 mL). The reunited organic phases were washed with a saturated solution of NaCl (10 mL) and dried over Na₂SO₄. Compounds **8-11** were isolated in quantitative yields and characterized by ¹H-NMR, ¹³C-NMR and GC-MS.

2-(4'-Methoxyphenyl)ethyl methyl carbonate 8. Colourless oil. ¹H-NMR (200 MHz, CDCl₃) δ (ppm) 7.16-7.09 (m, 2H), 6.86-6.75 (m, 2H), 4.28 (t, *J*=7.1 Hz, 2H), 3.77 (s, 3H), 3.74 (s, 3H), 2.90 (t, *J*=7.1 Hz, 2H). ¹³C-NMR (CDCl₃): δ (ppm) 158.0, 155.6, 131.3, 131.2, 112.3, 67.8, 55.2, 55.1, 35.3. MS (EI) *m/z*: 210 (M⁺).

3-(4'-Methoxyphenyl)propyl methyl carbonate 9. Colourless oil. ¹H-NMR (200 MHz, CDCl₃): δ (ppm) 7.14-7.09 (m, 2H) 6.86-6.74 (m, 2H), 4.14 (t, *J*=7.1 Hz, 2H), 3.77 (s, 3H), 3.75 (s, 3H) 2.63 (t, *J*=8 Hz, 2H); 1.91-1.82 (m, 2H). ¹³C-NMR (CDCl₃): δ (ppm) 157.1, 155.7, 134.4, 130.3, 114.5, 68.8, 55.2, 55.1, 31.4, 30.4. MS (EI) *m/z*: 224 (M⁺).

2-(3'-Methoxyphenyl)ethyl methyl carbonate 10. Colourless oil. ¹H-NMR (200 MHz, CDCl₃): δ (ppm) 7.20-7.16 (m, 1H) 6.81-6.74 (m, 3H), 4.32 (t, *J*=7.1 Hz, 2H), 3.75 (s, 3H), 3.73 (s, 3H) 2.93 (t, *J*=7.1 Hz, 2H). ¹³C-NMR (CDCl₃): δ (ppm) 158.8, 155.6, 141.71, 129.2, 121.3, 113.2, 112.6, 67.8, 55.5, 55.1, 35.7. MS (EI) *m/z*: 210 (M⁺).

2-(3',4'-Dimethoxyphenyl)ethyl methyl carbonate 11. Colourless oil. ¹H-NMR (200 MHz, CDCl₃): δ (ppm) 6.85-6.67 (m, 3H), 4.28 (t, *J*=7.1 Hz, 2H), 3.84 (s, 6H), 3.75 (s, 3H) 2.88 (t, *J*=7.1 Hz, 2H). ¹³C-NMR (CDCl₃): δ (ppm) 155.6, 150.2, 149.1, 133.2, 123.2, 114.8, 121.3, 67.8, 55.5, 55.1, 35.7. MS (EI) *m/z*: 240 (M⁺).

Preparation of compounds (12-15)

The appropriate compounds **8-11** (1.0 mmol) was solubilised in tetrahydrofuran (4.0 mL), then a solution of 1N NaOH (4.0 mL) was added. The reaction mixture was stirred at room temperature for 24 h and monitored by TLC. At the end of the reaction, the solvent was removed under vacuum. The residue was neutralized with HCl 1N. Then, the aqueous phase was extracted with dichloromethane (3x5 mL). The organic phases were washed with a saturated solution of NaCl (10 mL) and dried over Na₂SO₄. After the evaporation of the solvent, products **12-15** were isolated in quantitative yields and characterized by ¹H-NMR, ¹³C-NMR and GC-MS.

2-(4'-Methoxyphenyl)ethanol **12**. Colourless oil. $^1\text{H-NMR}$ (200 MHz, CDCl_3) δ (ppm) 7.14-7.09 (m, 2H), 6.87-6.81 (m, 2H), 3.76 (t, $J=7.1$ Hz, 2H), 3.76 (s, 3H), 2.77 (t, $J=7.1$ Hz, 2H); $^{13}\text{C-NMR}$ (CDCl_3): δ (ppm) 158.0, 131.3, 131.0, 112.5, 63.0, 55.2, 38.9; MS (EI) m/z : (silylated product) 224 (M^+).

3-(4'-Methoxyphenyl)propan-1-ol **13**. Colourless oil. $^1\text{H-NMR}$ (200 MHz, CDCl_3): δ (ppm) 7.13-7.08 (m, 2H) 6.86-6.80 (m, 2H), 3.76 (s, 3H), 3.62(t, $J=7.1$ Hz, 2H), 2.63 (t, $J=8$ Hz, 2H), 1.91-1.80 (m, 2H). $^{13}\text{C-NMR}$ (CDCl_3): δ (ppm) 157.2, 134.3, 129.3, 113.9, 62.4, 55.2, 34.5, 22.8; MS (EI) m/z (silylated product) 238 (M^+).

2-(3'-Methoxyphenyl)ethanol **14**. Colourless oil. $^1\text{H-NMR}$ (200 MHz, CDCl_3): δ (ppm) 7.26-7.17 (m, 1H) 6.82-6.75 (m, 3H), 3.80 (t, $J=7.1\text{Hz}$, 2H), 3.78 (s, 3H), 2.82 (t, $J=7.1$ Hz, 2H). $^{13}\text{C-NMR}$ (CDCl_3): δ (ppm) 159.1, 141.4, 129.4, 128.9, 113.0, 112.6, 64.4, 55.5, 39.2. MS (EI) m/z : 224 (M^+).

2-(3',4'-Dimethoxyphenyl)ethanol **15**. Colourless oil. $^1\text{H-NMR}$ (200 MHz, CDCl_3): δ (ppm) 6.78-6.68 (m, 3H), 3.82 (s, 6H), 3.76 (t, $J=7.1\text{Hz}$, 2H), 2.74 (t, $J=7.1$ Hz, 2H). $^{13}\text{C-NMR}$ (CDCl_3): δ (ppm) 150.4, 149.1, 133.4, 121.4, 113.9, 113.3, 64.5, 55.6, 38.7; MS (EI) m/z : (silylated product) 242 (M^+).

Synthesis of alkyl glycidyl carbonates (**16-19**)

The appropriate compound **12-15** (2.0 mmol) was solubilized in dry THF (4 mL) and NaH (1.2 equiv.) was added. The mixture was kept under stirred at -70°C under nitrogen atmosphere for 15 minutes. Then, a solution of tosylated 1,2-glycerol carbonate (0.5 g, 1.84 mmol) and $n\text{-Bu}_4\text{NBr}$ (59 mg, 0.183 mmol) in dry THF (5 mL) was slowly added. The reaction was monitored by TLC. After 2 h at -70°C under stirring, the mixture was allowed to slowly warm up to room temperature; after 1h THF was evaporated under vacuum and the crude mixture was solubilised in ethyl acetate and water. The organic layer was washed with water and brine, then dried over Na_2SO_4 . After filtration and concentration of the solution in vacuum, the residue was purified by flash column chromatography (petroleum ether/ethyl acetate=3/1). At the end, glycidyl carbonate **6**, **16-19** were isolated in 42-50% yields and characterized by $^1\text{H-NMR}$, $^{13}\text{C-NMR}$ and GC-MS.

Oxiran-2'-ylmethyl 2-phenylethyl carbonate **6**. Colourless oil. $^1\text{H-NMR}$ (200 MHz, CDCl_3) δ (ppm) 7.33-7.18 (m, 5H), 4.35 (dd, $J_1=12.0$ Hz, $J_2=4.0$ Hz, 1H), 4.34 (t, $J=8$ Hz, 2H), 4.00 (dd, $J=6.0$ Hz, 1H), 3.24-3.16 (m, 1H), 2.97 (t, $J=7.1$ Hz, 2H) 2.82(t, J_1 and $J_2=4$ Hz, 1H), 2.63 (dd, $J=2.4$ Hz, 1H). $^{13}\text{C-NMR}$: (CDCl_3): δ (ppm) 154.9, 137.1, 128.9, 128.6, 126.7, 68.6, 68.2, 49.1, 44.6, 35.1. MS (EI) m/z : 222 (M^+).

2-(4'-Methoxyphenyl)ethyl oxiran-2-ylmethyl carbonate **16**. Colourless oil. $^1\text{H-NMR}$ (200 MHz, CDCl_3) δ (ppm) 7.14-7.08 (m, 2H), 6.85-6.78 (m, 2H), 4.35 (dd, $J_1=3.2$ and $J_2=8.0$ Hz, 1H), 4.28 (t,

$J=8.0$ Hz, 2H), 3.98 (dd, $J=6.0$ Hz, 1H), 3.75 (s, 3H), 3.22-3.14 (m, 1H), 2.89 (t, $J=7.1$ Hz, 2H), 2.80(t, J_1 and $J_2=4.5$ Hz, 1H), 2.63 (dd, $J=2.4$ Hz, 1H). ^{13}C -NMR: (CDCl_3): δ (ppm) 158.4, 154.9, 129.9, 129.1, 114.0, 68.9, 68.1, 55.2, 49.0, 44.6, 34.2. MS (EI) m/z : 252 (M^+).

3-(4'-Methoxyphenyl)propyl oxiran-2-ylmethyl carbonate 17. Colourless oil. ^1H -NMR (200 MHz, CDCl_3) δ (ppm) 7.24-7.06 (m, 2H), 6.85-6.78 (m, 2H), 4.38 (dd, $J_1=3.3$ Hz, $J_2=8.8$ Hz, 1H), 4.14 (t, $J=6$ Hz, 2H), 4.02 (dd, $J=6.0$ Hz, 1H), 3.76 (s, 3H), 3.27-3.19 (m, 1H), 2.84 (t, J_1 and $J_2=4.0$ Hz, 1H), 2.66 (dd, $J=2.4$ Hz, 1H), 2.89 (t, $J=7.1$ Hz, 2H), 2.02-1.88 (m, 2H). ^{13}C -NMR: (CDCl_3): δ (ppm) 157.9, 155.0, 132.9, 129.3, 113.9, 68.1, 67.6, 55.2, 49.0, 44.6, 30.9, 30.4. MS (EI) m/z : 266 (M^+).

2-(3'-Methoxyphenyl)ethyl oxiran-2-ylmethyl carbonate 18. Colourless oil. ^1H -NMR (200 MHz, CDCl_3) δ (ppm) 7.24-7.17 (m, 1H), 6.82-6.75 (m, 3H), 4.39 (dd, 1H, $J_1=2.0$ Hz, $J_2=12.0$ Hz, 2H), 4.34 (t, $J=7.2$ Hz, 2H), 4.01 (dd, $J=6.0$ Hz, 1H), 3.78 (s, 3H), 3.25-3.17 (m, 1H), 2.95 (t, $J=7.2$ Hz, 2H), 2.83(t, J_1 and $J_2=4.5$ Hz, 1H), 2.64 (dd, $J=2.4$ Hz, 1H). ^{13}C -NMR: (CDCl_3): δ (ppm) 160.0, 159.7, 138.6, 129.6, 121.3, 114.7, 112.1, 68.5, 68.2, 55.2, 49.0, 44.6, 35.1. MS (EI) m/z : 252 (M^+).

2-(3',4'-Dimethoxyphenyl)ethyl oxiran-2-ylmethyl carbonate 19. Colourless oil. ^1H -NMR (200 MHz, CDCl_3) δ (ppm) 6.82-6.72 (m, 3H), 4.37 (dd, $J_1=3.2$ Hz, $J_2=8.0$ Hz, 1H), 4.31 (t, $J=8.0$ Hz, 2H), 3.99 (dd, $J=6.0$ Hz, 1H), 3.84 (s, 3H), 3.24-3.16 (m, 1H), 2.90 (t, $J=7.2$ Hz, 2H), 2.82(t, J_1 and $J_2=4.0$ Hz, 1H), 2.63 (dd, $J_1=2.0$ Hz, $J_2=4.0$ Hz, 1H). ^{13}C -NMR (CDCl_3): δ (ppm) 155.5, 150.0, 149.0, 129.6, 120.9, 112.2, 111.4, 68.8, 68.2, 55.8, 49.0, 44.5, 34.7). MS (EI) m/z : 282 (M^+).

Preparation of demethylated glycidyl carbonates (20-22)

The appropriate substrate **16-18** was dissolved in fresh dry dichloromethane (12 mL). Then the mixture was cooled at -15°C and boron tribromide solution 1M in dichloromethane (2.0 mmol) was added. At the end, the mixture was brought to room temperature and ice was added; after stirred at room temperature for 5 min; the organic phase was washed with a saturated solution of NaHCO_3 (10 mL). The aqueous phase was extracted with dichloromethane (3x6 mL); then the organic phase was washed with a saturated solution of NaCl (20 mL) and dried over Na_2SO_4 . After filtration the solvent was removed under vacuum, the residue was purified by flash chromatography (petroleum ether/ethyl acetate=2/1) and products **20-22** were isolated in 40-55% yields.

3-Bromo-2-hydroxypropyl 2-(4'-hydroxyphenyl)ethyl carbonate 20. Yield: 40%. Yellow oil. ^1H -NMR (200 MHz, CDCl_3) δ (ppm) 7.14-7.08 (m, 2H), 6.78-6.71 (m, 2H), 4.27 (dd, $J_1=6.0$, $J_2=12.0$, 1H), 4.23 (t, $J=6$ Hz, 2H), 4.08 (dd, $J=6.0$ Hz, 1H), 3.54-3.36 (m, 1H), 3.49 (dd, $J_1=2.0$, $J_2=4.0$, 1H),

3.46 (dd, $J_1=2.0$, $J_2=4.0$, 1H), 2.87 (t, $J=7.1$ Hz, 2H). ^{13}C -NMR: (CDCl_3): δ (ppm) 155.1, 154.5, 130.1, 129.8, 115.5, 69.1, 69.0, 68.9, 34.2, 34.1. MS (EI) m/z : (silylated **20**) 462 (M^+-1).

3-Bromo-2-hydroxypropyl 3-(4-hydroxyphenyl)propyl carbonate 21. Yield: 50%. Yellow oil. ^1H -NMR (200 MHz, CDCl_3) δ (ppm) 7.04-6.98 (m, 2H), 6.77-6.70 (m, 2H), 4.24 (dd, $J=6$, 1H), 4.14 (t, $J=4$ Hz, 2H), 4.14 (dd, $J=6.0$ Hz, 1H), 3.58-3.41 (m, 1H), 3.48 (t, $J_1=J_2=6.0$ Hz, 1H), 3.55 (dd, $J=2.4$, 1H), 2.62 (t, $J=7.6$ Hz, 2H), 2.03-1.87 (m, 2H). ^{13}C -NMR: (CDCl_3): δ (ppm) 154.5, 153.3, 132.2, 114.7, 68.4, 68.2, 67.2, 35.6, 30.3, 29.7. MS (EI) m/z : (silylated **21**) 476 (M^+-1).

3-Bromo-2-hydroxypropyl 2-(3-hydroxyphenyl)ethyl carbonate 22. Yield: 44%. Yellow oil. ^1H -NMR (200 MHz, CDCl_3) δ (ppm) 7.20-7.12 (m, 1H), 6.78-6.68 (m, 3H), 4.34 (t, $J=7.0$ Hz, 2H), 4.23 (d, $J=6$, 2H), 4.10-4.0 (m, 1H), 3.47 (dd, $J_1=4$; $J_2=1$, 2H), 2.92 (t, $J=7.0$ Hz, 2H). ^{13}C -NMR: (CDCl_3): δ (ppm) 155.7, 155.0, 138.8, 129.8, 121.3, 115.8, 113.8, 69.0, 69.8, 68.6, 49.0, 34.9, 34.4. MS (EI) m/z : 462 (M^+-1).

Synthesis of compounds (23-25)

The appropriate substrate **20-22** (1.0 mmol) was dissolved in MeOH (8 mL), then IBX (336 mg, 1.2 equiv) was added. The solution was stirred at 0°C until disappearance of the substrate (2 h). At the end, water (8 mL) and $\text{Na}_2\text{S}_2\text{O}_4$ (348 mg, 2.0 mmol) were added, and the solution was stirred for 5 min at room temperature. After evaporation of the solvent under vacuum the residue was solubilised with ethyl acetate and treated with a saturated solution of NaHCO_3 . The aqueous phase was extracted with ethyl acetate. The organic phases were washed with a saturated solution of NaCl and dried over Na_2SO_4 . After filtration the solvent was evaporated under vacuum, the residue was purified by flash chromatography (petroleum ether ethyl acetate, 2:1) and the corresponding hydroxylated products affording in satisfactory yield.

3-bromo-2-hydroxypropyl 2-(3',4'-dihydroxyphenyl)ethyl carbonate 23. Yield: 48%. Yellow oil. ^1H -NMR (200 MHz, CDCl_3) δ (ppm) 6.80-6.72 (m, 1H), 6.65-6.60 (m, 2H), 4.30 (t, $J=7.0$ Hz, 2H), 4.23 (d, $J=4.0$ Hz, 2H), 4.10-4.00 (m, 1H), 3.51 (dd, $J_1=4.0$ Hz, $J_2=6.0$ Hz, 1H), 3.43 (dd, $J_1=6.0$ Hz, $J_2=4.0$ Hz, 1H), 2.85 (t, $J=7.0$ Hz, 2H). ^{13}C -NMR: (CDCl_3): δ (ppm) 155.0, 143.7, 142.6, 129.8, 121.3, 116.0, 115.5, 69.1, 69.0, 68.8, 68.2, 31.0, 29.7. MS (EI) m/z : (silylated **23**) 462 (M^+-1).

3-Bromo-2-hydroxypropyl 3-(3',4'-dihydroxyphenyl)propyl carbonate 24. Yield: 49%. Yellow oil. ^1H -NMR (200 MHz, CDCl_3) δ (ppm) 6.78-6.72 (m, 1H), 6.67-6.55 (m, 2H), 4.25 (d, 1H, $J=4$), 4.12 (t, $J=6.4$ Hz, 2H), 4.17-4.08 (m, 1H), 3.54 (dd, $J_1=4.0$ Hz, $J_2=2.0$ Hz, 1H), 3.46 (dd, $J_1=J_2=5.0$ Hz, 1H), 2.58 (t, $J=7.5$ Hz, 2H), 2.01-1.82 (m, 2H). ^{13}C -NMR (CDCl_3): δ (ppm) 155.2, 143.6, 141.9, 133.7, 120.7, 115.4, 115.3, 74.0, 68.8, 34.3, 30.0, 29.7. MS (EI) m/z : (silylated **24**) 476 (M^+-1).

3-Bromo-2-hydroxypropyl 2-(3',4'-dihydroxyphenyl)ethyl carbonate 25. Yield: 43%. Yellow oil. ¹H-NMR (200 MHz, CDCl₃) δ (ppm) 6.80-6.72 (m, 1H), 6.65-6.60 (m, 2H), 4.30 (t, $J=7.0$ Hz, 2H), 4.23 (d, $J=4.0$ Hz, 2H), 4.10-4.00 (m, 1H), 3.51 (dd, $J_1=4.0$ Hz, $J_2=6.0$ Hz, 1H), 3.43 (dd, $J_1=6.0$ Hz, $J_2=4.0$ Hz, 1H), 2.85 (t, $J=7.0$ Hz, 2H). ¹³C-NMR (CDCl₃) δ (ppm) 155.0, 143.7, 142.6, 129.8, 121.3, 116.0, 115.5, 69.1, 69.0, 68.8, 68.2 31.0, 29.7. MS (EI) m/z : (silylated **25**) 462 ($M^{+}-1$).

CONCLUSIONS

As a part of the research carried out in our laboratory devoted to *green chemistry* processes, during this PhD course new ecofriendly methodologies useful in organic chemistry have been optimized.

Mono- and bis(fluorous-ponytailed)/methyltrioxorhenium catalysts (bpy-F_n/MTO) have been prepared for the first time in acceptable yield and characterized by spectroscopic data. Their application in the epoxidation of olefins with the environmental friendly oxidant hydrogen peroxide has been tested. The corresponding epoxides have been obtained in high yields and selectivities similar to those obtained using traditional MTO catalysts. Experiments on the recovery and recycling of MTO/bpy-F_n catalysts have been not satisfactory.

Dimethyl carbonate (DMC), an ecofriendly chemical, has been widely utilized both as solvent and reagent in several reactions. In particular, its efficiency in the methylation of flavonoids has been verified in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU). In these reactions, DMC has been an alternative reagent to hazardous and carcinogen chemicals. Final products are bioactive compounds potentially useful in cancer therapy. However, the methodology is limited to mono or dihydroxylated flavonoids being high hydroxylated flavonoids insoluble in DMC.

An efficient and ecofriendly procedure to protect α -amino and α -acid group of a large panel of amino acids by using the DMC/DBU system has been optimized; the corresponding protected derivatives have been isolated in moderate to good yields depending on the amino acid. The removal of the protecting group has been optimized. This procedure will be extended to peptides.

2-Iodoxybenzoic acid (IBX) has been employed as selective and efficient oxidant as an alternative to toxic oxidizing heavy metals to synthesize rare amino acids DOPA and DOPA peptides from tyrosine derivatives. Yields have been very satisfactory. IBX-polystyrene has been very efficient and its use could afford to economic and environmental benefits.

An unreported route for the preparation of 1,2-glycerol carbonate we described from glycerol, a renewable starting material, and DMC. The reactivity of tosylated glycerol carbonate toward a series of phenolic compounds in order to prepare new potential antioxidants have been explored.

Products of this Ph.D activity

Published Papers

1. Bernini, R.; Barontini, M.; Crisante, F.; **Ginnasi, M. C.**; Saladino, R. "A novel and efficient synthesis of DOPA and DOPA peptides by oxidation of tyrosine residues with IBX", *Tetrahedron Lett.* **2009**, 50, 6519 - 6521
2. Saladino, R.; **Ginnasi, M. C.**; Collalto, D.; Bernini, R.; Crestini, C. "An Efficient and Selective Epoxidation of Olefins with Novel Methyltrioxorhenium(fluorous ponytailed)2,2'-bipyridines Catalysts" *Adv. Synth. Cat.* **2010**, 352, 1284 - 1290
3. Bernini, R.; Crisante, F.; **Ginnasi, M. C.** "A convenient and safe O-methylation of flavonoids with dimethyl carbonate" *Molecules* **2011**, doi:103390/molecules150x000x

Oral and poster communications

1. Bernini, R.; **Ginnasi, M. C.**; Mincione, E.; Saladino, R.; "Bis(fluorous-ponytailed)2,2'-bipyridines as ligands for methyltrioxorhenium(CH₃ReO₃, MTO)catalyzed epoxidation of olefins with hydrogen peroxide" *XVI International Symposium on Homogenous Catalysis (ISHC-XVI)*, poster communication, Firenze, **6 - 11 luglio 2008**
2. Bernini, R.; **Ginnasi, M. C.**; Mincione, E.; Saladino, R.; "New fluorinated catalysts of MTO in ecofriendly epoxidation with H₂O₂" *XXIII Convegno Nazionale della Società Chimica Italiana*, poster communication, Sorrento, **5 - 10 luglio 2009**
3. Bernini, R.; Barontini, M.; Crisante, F.; **Ginnasi, M. C.**; Provenzano, G. "Agro-industrial waste: a source of bioactive phenolic compounds useful for the production of fine chemicals" oral communication, *Ecomondo*, Rimini, **28 - 31 ottobre 2009**
4. Bernini, R.; Barontini, M.; Crisante, F.; Ginnasi, M. C.; Mincione, E.; Fabrizi, G. "A novel use of the recyclable IBX polystyrene: efficient chemo- and regioselective aromatic hydroxylation of natural phenolic compounds", *3rd International Conference on Hypervalent Iodine Chemistry*, oral communication, Bordeaux (France), **4 - 7 Luglio 2010**
5. Barontini, M.; Bernini, R. Crisante, F.; **Ginnasi, M. C.**; Saladino, R. "Dimethyl carbonate (DMC): an ecofriendly reagent useful for the protection of amino acids" *XXXIII Convegno Nazionale della Divisione di Chimica Organica Società Chimica Italiana*, poster communication, San Benedetto del Tronto, **12-16 settembre 2010**
6. Bernini, R.; Barontini, M.; Crisante, F.; **Ginnasi, M. C.**; Fabrizi, G. "2-Iodoxybenzoic Acid (IBX): an old but modern reagent useful for the preparation of biologically active catecholic compounds" *XXXIII Convegno Nazionale della Divisione di Chimica Organica Società Chimica Italiana*, oral communication, San Benedetto del Tronto, **12-16 settembre 2010**

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