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Organic Synthesis: New Vistas in the Brazilian Landscape

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ABSTRACT

In this overview, we present our analysis of the future of organic synthesis in Brazil, a highly innovative and strategic area of research which underpins our social and economical progress. Several different topics (automation, catalysis, green chemistry, scalability, methodological studies and total syntheses) were considered to hold promise for the future advance of chemical sciences in Brazil. In order to put it in perspective, contributions from Brazilian laboratories were selected by the citations received and importance for the field and were benchmarked against some of the most important results disclosed by authors worldwide. The picture that emerged reveals a thriving area of research, with new generations of well-trained and productive chemists engaged particularly in the areas of green chemistry and catalysis. In order to fulfill the promise of delivering more efficient and sustainable processes, an integration of the academic and industrial research agendas is to be expected. On the other hand, academic research in automation of chemical processes, a well established topic of investigation in industrial settings, has just recently began in Brazil and more academic laboratories are lining up to contribute. All these areas of research are expected to enable the future development of the almost unchartered field of scalability.

Key words: organic synthesis, frontiers, overview, brazilian scenario.

INTRODUCTION

Almost 30 years ago, Dieter Seebach attempted to review the important advances in the domain of organic synthesis over the twenty five preceding years and to project the future in this area (Seebach 1990). The ideas and thoughts put forth in that paper were the subject of much debate over the coming years as some have taken his words as if organic synthesis had matured and stagnation was awaiting ahead.

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* Contribution to the centenary of the Brazilian Academy of Sciences.

The major points made by Seebach were that function, more than the structure of molecules, would lead the synthetic efforts and that novel reactions would most likely come from biological and organometallic chemistry, shifting the attention to catalytic and asymmetric methodologies, and these points appear to be, to a large extent, confirmed. In addition, the author anticipated improvements in experimental procedures and the broader application of special techniques, leading to undreamed levels of efficiency and selectivity with respect to known procedures.

Synthetic chemistry is a highly creative discipline due to its ability to create its object of

investigation, to invent new methodologies as well to contribute to fundamental and applied knowledge, underpinning our social and economical progress with the discovery of new drugs, contributing to food supply, providing new polymers and materials with novel properties and functions with a direct impact on the welfare of the world population.

Recently, Brocksom and coworkers reviewed the important changes that have taken place in the last twenty to thirty years on the directions and objectives of organic synthesis worldwide (Brocksom et al. 2015), and in this paper we decided to take a bird's-eye view of the scenario of organic synthesis in Brazil while benchmarking it against the most relevant accomplishments worldwide.

This is not meant to be a review paper on the academic research nor a comprehensive coverage of all areas of research underway in the area of chemical synthesis in Brazil. We decided to focus on the most promising areas of academic research which, in our viewpoint, are bound to contribute for the future progress in synthetic chemistry, namely: 1) green chemistry, 2) catalysis, 3) automation and 4) scalability, as well as, 5) the development of new and improvement of known methodologies and applications to the total synthesis of natural products and pharmaceutical ingredients. We selected few representative examples in these areas from leading groups worldwide as well as from Brazilian laboratories guided by the number of citations received, as well as their novelty and pioneering nature in the Brazilian scenario. The authors apologize for any missing reference even those that would be included if other benchmarks were adopted as the overview nature of this paper and limitations of time and space allowed only a limited number of illustrative examples to be included.

GREEN CHEMISTRY

According to IUPAC, green chemistry can be defined as the invention, design and application of chemical products and processes to reduce or to eliminate the use and generation of hazardous substances (Tundo et al. 2000, Corrêa et al. 2013). The main areas of research are the use of alternative feedstocks and solvents (Rinaldi and Schüth 2009, Sheldon 2014), the use of innocuous reagents and bio-based transformations, the design of safer chemicals, the development of alternative reaction conditions and minimization of energy consumption (Tundo et al. 2000, Corrêa et al. 2013). In practice, this would include the incorporation of catalytic reactions in the process, maximize incorporation of the atoms of the reagents in the final product and to avoid unnecessary derivatization, functional group interconversion and changes in the redox state.

The most widely used metrics for measuring the environmental impact of a chemical process are the E factor, defined as the mass ratio of waste to the mass of the desired product, and the atom economy, defined as the molecular weight of the desired product divided by the sum of the molecular weights of all substances produced in the stoichiometric equation, expressed as a percentage (Sheldon 1992, 1997, Tundo et al. 2000, Corrêa et al. 2013).

As an illustration of this last concept, the production of propylene oxide, a chemical feedstock for the production of polyols and polyurethanes, can be achieved through the chlorohydrin or the propylene process. The former process takes place with 25% atom economy and employs chlorine as the oxidizing agent and produces hydrochloric acid, calcium chloride and water as by-products while the second route (the propylene process) is a one-step process which employs hydrogen peroxide as the oxidation agent, and produces only water as by-product with 76% of atom economy (Russo et al. 2013) (Figure 1).

The oxidation of alcohols is a key transformation in the chemical sciences and the best solution would be the use of oxygen or hydrogen peroxide as the oxidation agent

in the presence of a proper catalyst. While the use of chromium (VI) salts has been banned from industrial applications, there are still some general oxidation methodologies which can not be considered ecofriendly as their atom economy is not even moderate (Mancuso et al. 1978, Dess and Martin 1983). As a green alternative, the use of Pd(II)/phenanthroline complex in the presence of molecular oxygen has been described in the oxidation of a wide range of alcohols (ten Brink et al. 2000) while a Pd(II)/bisquinoline complex was shown to promote the oxidation of benzylic alcohols in water (Buffin et al. 2008) (Figure 2).

The use of 2,2,6,6-tetramethylpiperidinyloxyl radical (TEMPO) as an organocatalyst in the presence of sodium hypochlorite (household bleaching) and 10% sodium bromide solution in biphasic solvent (dichloromethane/water) is a general methodology which complies with some of the green chemistry principles (Anelli et al. 1987). In order to improve the greeness of such process, other environmentally benign solvent systems (methyl and isopropyl acetate) (Janssen et al. 2011), as well as the use of recycable oligomeric nitroxyl radicals (Dijksman et al. 2000) and the substitution of sodim hypochlorite for bipiridyl-Cu(II) complex which allowed complete selectivity for the oxidation of a primary alcohol in the presence of a secondary one were implemented (Gamez et al. 2003, 2004).

Fine chemicals can be also produced from renewable feedstock as described by Spanevello and coworkers for the production of levoglucosene from cellulose, an useful building block in asymmetric synthesis and catalysis (Sarotti et al. 2007, Sheldon et al. 2015, Sheldon and Sanders 2015, Domine et al. 2015) (Figure 3).

Hydrogenation is one of the key industrial processes with applications in the fine chemicals, food and petrochemical industries. It is usually carried out under catalytic conditions with platinum, palladium and nickel being the metals of choice for

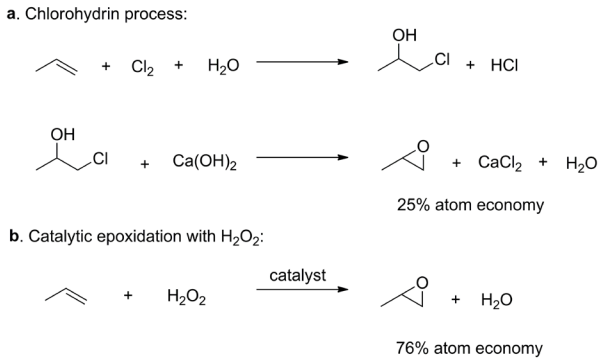


Figure 1 - The chlorohydrin and the propylene processes for the production of propylene oxide (Russo et al. 2013).

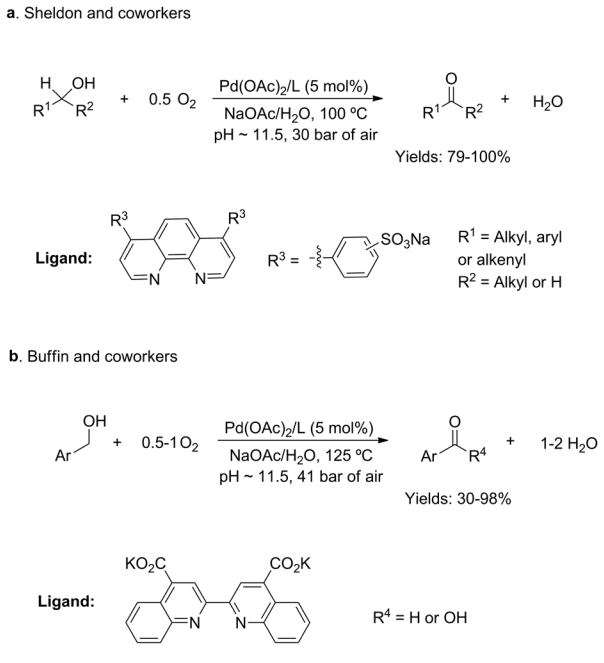


Figure 2 - Oxidation of alcohols using Pd(II)/phenanthroline and Pd(II)/bisquinoline as a greener alternative (ten Brink et al. 2000, Buffin et al. 2008).

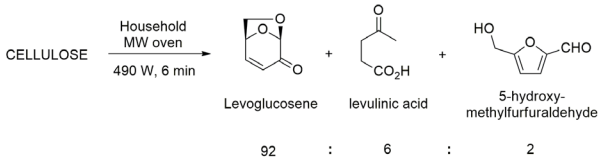


Figure 3 - Production of levoglucosene as the main product from microwave pyrolysis of cellulose (Sarotti et al. 2007).

heterogeneous processes while rhodium, ruthenium and iridium are widely used under homogeneous conditions.

Rossi and coworkers described a magnetically recoverable palladium catalyst, prepared by immobilization of palladium over silica-coated magnetite nanoparticles, which was reduced by molecular hydrogen to produce palladium nanoparticles distributed and stabilized in the magnetizable support surfaces, which was shown to convert cyclohexene to cyclohexane under mild reaction conditions (75 ºC and 6 atm) with a turnover frequency (TOF) of 11 500 h^{-1} (Rossi et al. 2007) (Figure 4).

Sousa-Aguiar, Lopez-Sanchez and coworkers (Romano et al. 2016) have shown that a cheap, active, stable and sustainable catalyst (Cu/TiO_2) efficiently promotes the hydrogenation of furfural under low hydrogen pressure (10 bar) and temperature (125 ºC) when a green solvent (cyclopentyl methyl ether) was used under microwave irradiation (Figure 4). Fraga et al. have studied the oxidation in aqueous phase of 5-hydroxymethylfurfural employing Pt/ZrO_2 catalysts (da Silva et al. 2016).

Alkene epoxidation was accomplished using chromatography alumina and hydrogen peroxide under nearly anhydrous conditions. By conducting the reaction under Dean–Stark conditions, commercially available 60% hydrogen peroxide could be used thus avoiding the use of moderately concentrated and shock-sensitive hydrogen peroxide (van Vliet et al. 2001) (Figure 5).

Schuchardt and coworkers have demonstrated that sol-gel alumina calcinated at 400 ºC is a very efficient catalyst for the epoxidation of cyclohexene and cyclooctene with 70 wt % aqueous hydrogen peroxide (Rinaldi et al. 2004). Rossi and coworkers developed a catalyst based on the immobilization of Au(III) on the surface of core–shell silica-coated magnetite nanoparticles, followed by metal reduction, which provided Au(0) NPs which were able to promote the aerobic oxidation of alcohols at mild temperature with a distinct selectivity for benzylic alcohols (Oliveira et al. 2010).

The use of greener conditions for the esterification reaction has attracted the interest of several Brazilian laboratories. Barbosa and coworkers reported on the solvent-free esterification of aliphatic and aromatic carboxylic acids with ethanol and 2-methyl-1-butanol catalyzed by solid Lewis acids ($ZnCl_2$, $FeSO_4$) supported on silica or alumina (Barbosa et al. 2006). Rossi and coworkers described the preparation of esters from the corresponding primary alcohols using molecular oxygen as a green oxidant and a SiO_2-supported gold nanoparticle catalyst thus avoiding the use of non-benign oxidants or an excess of reagents or continuous product removal in order to shift the equilibrium to the esterification product (Oliveira et al. 2009) (Figure 6).

Alternative reaction media such as solvent-free conditions, environmentally benign solvents, water and ionic liquids have been extensively explored in many Brazilian laboratories. This topic has been reviewed by de Andrade and coworkers (Andrade and Alves 2005) while Senra and coworkers reviewed the use of non-conventional reaction media, alternative activation modes and catalytic systems in the Buchwald-Hartwig and Ullmann-type reactions (Senra et al. 2011).

Moved by the availability of glycerol from the biodiesel production, several groups have studied its derivatization and use as reaction medium seeking to increase the greenness of the processes. Mota and coworkers reported on the acetalization of glycerol using zeolite Beta and no solvent (da Silva et al. 2009). Silveira and coworkers reported on the preparation of bis-indolyl methanes by using glycerol and hydrated cerium (III) chloride at 75 ºC (Silveira et al. 2009). Later, Lenardão and coworkers reported on the use of ammonium niobium oxalate as the catalyst in water (50 ºC) or in glycerol (sonication, 110 ºC) for the preparation

of the same family of compounds (Mendes et al. 2015) (Figure 7).

The thioketalization of aliphatic and aromatic aldehydes and ketones was achieved by Perin and coworkers in glycerol at 90 ºC in good to excellent yields (Perin et al. 2010). Ricordi and coworkers reported on the use of glycerol as the solvent in the copper-catalyzed cross-coupling reaction of diaryl diselenides with arylboronic acids using CuI and DMSO as additive which could be directly reused for further cross-coupling reactions (Ricordi et al. 2012). The use of CuI/Zn/glycerol as a recyclable catalytic system for the preparation of (*E*)-1,2-bis-chalcogen alkenes from terminal alkynes has been described (Gonçalves et al. 2014).

The use of choline chloride:urea (1:2) as a deep euthetic solvent was described by Lenardão and coworkers for the synthesis of vinyl selenides (Lopes et al. 2015).

Dupont and coworkers pioneered the use of ionic liquids in Brazil and his laboratory has led the pace of research in this area worldwide, particularly regarding the use of 1,3-dialkylimidazolium cation as a new class of solvents for extraction and separation processes, organic synthesis and catalysis (Dupont 2004, 2011, Dupont et al. 2000, 2002, Dupont and Spencer 2004, Migowski and Dupont 2007). Ionic liquids were shown to be a suitable media for the generation and stabilization of soluble metal nanoparticles which proved to be efficient green catalysts for several reactions in multiphase conditions and also novel materials for chemical sensors (Dupont and Scholten 2010). Some of the contributions of Dupont and coworkers in the domain of catalytic reactions in ionic liquids will be highlighted in the next section of this document ("Catalysis").

In 2009, Braga et al. reported the synthesis of diaryl selenides via an eco-friendly cross-coupling reaction of aryl and alkyl bromides with diselenides using a catalytic amount of CuO nanopowder as catalyst and an ionic liquid as a recyclable solvent

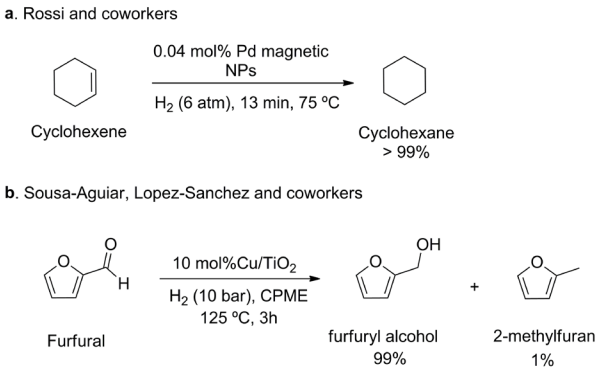


Figure 4 - Hydrogenation of cyclohexene and furfural using Pd magnetic nanoparticles (NPs) and Cu/TiO_2, respectively (Rossi et al. 2007, Romano et al. 2016).

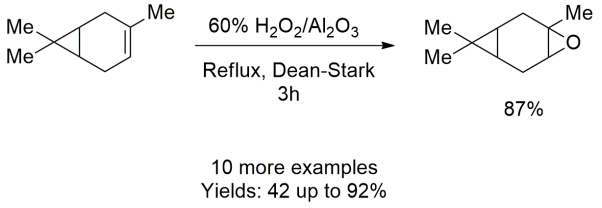


Figure 5 - Alkene epoxidation using 60% H_2O_2/Al_2O_3 and Dean-Stark conditions (van Vliet et al. 2001).

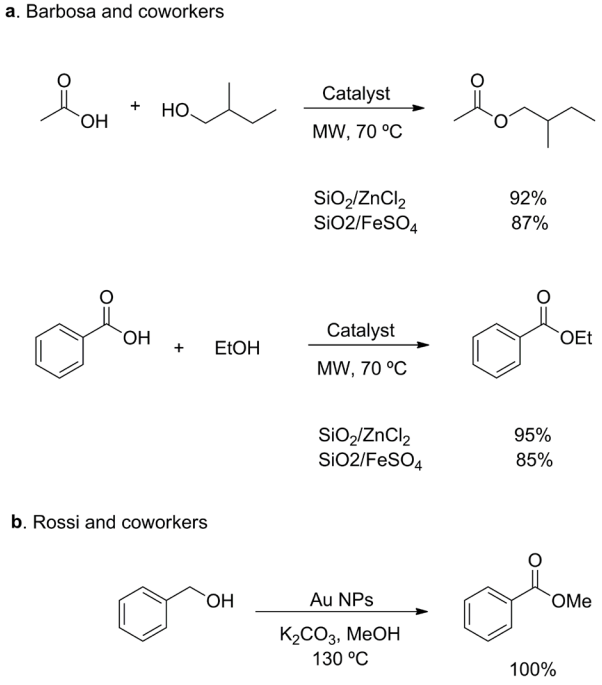


Figure 6 - Green esterification processes developed by Barbosa and Rossi (Barbosa et al. 2006, Oliveira et al. 2009).

(Singh et al. 2009). CuO nanoparticles were also shown to be an efficient and recyclable catalyst for cross-coupling reactions of organic diselenides with aryl boronic acids (Alves et al. 2009). The same laboratory also employed BMIM-BF_4 in the preparation of a series of diorganyl diselenides under neutral reaction conditions (Narayanaperumal et al. 2010) (Figure 8).

Stefani and coworkers developed a mild, convenient and improved protocol for the preparation of imines by ultrasound irradiation in excellent yields and short reaction times (Guzen et al. 2007) while de Andrade and coworkers carried out the preparation of imines in ionic liquids (Andrade et al. 2004). Parise-Filho and coworkers developed a one-pot protocol for the synthesis of sulfonyl hydrazones under mild, cheap and environmentally safe conditions with the reduction of the amount of hydrazine employed (Cunha et al. 2016).

Da Silva et al. developed the use of propylene carbonate (PC) as an alternative solvent as illustrated by the preparation of 2,4,5-triaryl imidazoles from aromatic aldehydes, benzyl and ammonium acetate (Muñoz et al. 2016). PC offers advantages not only in the yield of the reaction but also in the isolation of the product, which consists of a simple filtration followed by washes with warm water. Russowsky, Schneider and coworkers reported on the preparation of triazoles in water media via click chemistry using a recoverable and recyclable Cu/SiO_2 composite as catalyst (Radatz et al. 2014) (Figure 9).

Bieber and coworkers pioneered the studies of organometallic reactions with carbonyl compounds in water such as the propargylation of aldehydes in the presence of zinc powder in concentrated aqueous salt solutions in moderate to good yields (Bieber et al. 1998).

Recently, Malvestiti and coworkers described the use of a mechanochemical method for the potassium allyltrifluoroborate salt addition to aromatic and aliphatic aldehydes using water for the liquid-assisted griding of the reagents (de Souza et al. 2016). This methodology could be extended to the allylation of ketones by the use of a europium complex. Considering the allylation agent and its by-products, aqueous media, energy efficiency and use of catalyst, the methodology meets several of the green chemistry principles. Martins and coworkers have synthesized NH-pyrazoles by grinding β-dimetilaminovinylketones with solid hydrazine sulfate in the presence of p-toluenesulfonic acid (Longhi et al. 2010).

In 2002, Mattos has explored the use of trichloroisocyanuric acid in aqueous acetone as a safer and cost effective methodology for the preparation of epoxides (Wengert et al. 2002) and trihaloisocyanuric acid/NaX (X=Cl, Br) for the dihalogenation of alkenes with the use of molecular bromine (Tozetti et al. 2007).

Regarding minimization of waste production, tackling the amount and nature of the solvent employed, the formation of by-products and the use of excess amounts of reagents and additives are the major challenges to be faced. As mentioned before, the use of benign and easily recoverable solvents is an obvious solution although the best solution, particularly for large scale production, is a solvent-free process. Recently, de Andrade and Dar reviewed the use of solvent-free and alternative solvents, microwave and ultrasound irradiation, and flow chemistry as a tool to simplify work-up conditions (Andrade and Dar 2016).

Despite the plethora of reaction conditions that might be considered for a chemical transformation, a large step towards greenness can be taken by implementing catalytic technologies which are poised to mitigate the environmental impact of a chemical process.

CATALYSIS

Over the last decades, chemists have realized that one of the most powerful ways to improve synthetic processes was through catalysis. The use of catalysis can provide several benefits such as: i) shorter reaction times; ii) increase of yield; iii) milder reaction conditions; iv) higher selectivity; and v) possibility to develop stereoselective procedures. More recently, catalytic processes have been recognized as one of the principles of green chemistry.

In organic chemistry, catalysis plays a pivotal role in several types of synthetic transformation. The preparation of an ester from an alcohol and a carboxylic acid is taken as a reliable transformation because of acid catalysis, as is the addition of molecular hydrogen across a double bond, only possible when a metal catalyst (most often, Pd, Ni or Pt) is present. In industrial settings, one of the most important examples of catalysis is the synthesis of ammonia, from molecular hydrogen and dinitrogen, known as the Haber-Bosch process: under normal conditions N_2 is an unreactive gas and without the presence of an iron-based metallic catalyst this reaction would not be feasible. Despite being the most efficient way to produce ammonia, the Haber-Bosch synthesis requires an extremely high pressure of starting materials and high temperature. Nowadays, chemists are more and more interested in the development of catalytic systems that allow for the use of mild reaction conditions combined to high efficiency (high yield, selectivity, etc).

Among the several classes, metal catalysts are the most used. They have been applied to a wide range of transformations such as substrate activation by Lewis acid interaction, oxidation reactions, hydrogenation, radical reactions, and others. Another area of catalysis which has proven to be of great importance in the last few years is organocatalysis. This mode of catalysis makes use

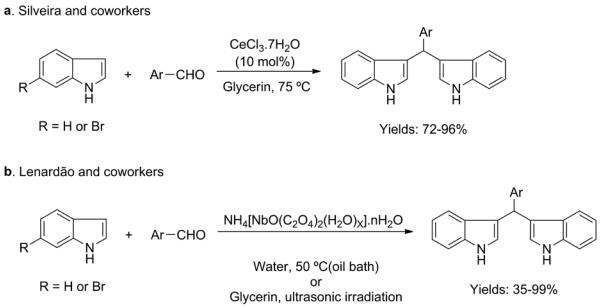


Figure 7 - Synthesis of bis-indolyl methanes using $CeCl_3.7H_2O$) or $NH_4[NbO(C_2O_4)_2(H_2O)_X].nH_2O$ (Silveira et al. 2009, Mendes et al. 2015).

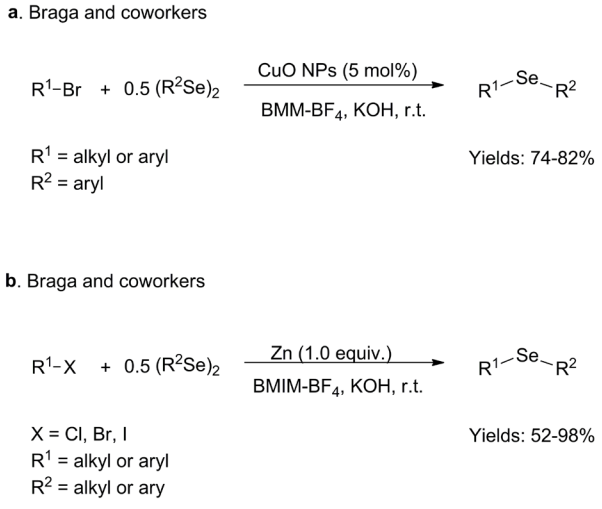


Figure 8 - Cross-coupling of diselenides using CuO nanoparticles and Zn (Singh et al. 2009, Narayanaperumal et al. 2010).

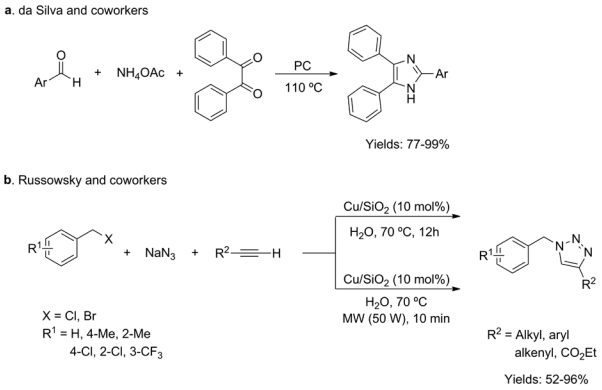


Figure 9 - Synthesis of 2,4,5-triaryl imidazoles 1,2,3-triazoles (Muñoz et al. 2016, Radatz et al. 2014).

of small chiral organic molecules which are capable of activating substrates toward nucleophiles or electrophiles in an asymmetric fashion.

The use of light to promote chemical reactions is a phenomenon known for several decades since the discovery of photosynthesis. Until a few years ago, almost 100% of all photochemical reactions used in organic synthesis were restricted to the use of UV light. Recently, a new mode of catalysis known as Visible Light Photoredox Catalysis (VLPC) has taken the attention of several research groups, which are using it as a highly efficient tool for the preparation of complex compounds.

Enzymatic transformations represent an attractive alternative to conventional chemical reactions due to several reasons such as the low environmental impact, capacity of discriminating between enantiomers of the same substrate, regio and enantioselectivity, and mild reaction conditions.

CATALYSIS BY METALLIC SPECIES

Nowadays, one of the most relevant uses of metals in organic synthesis relies on the development of non-activated C-H bond functionalization reactions. For several decades, chemists have pursued the ideal synthesis, starting from almost unfunctionalized starting materials and placing the correct functionalities in the right positions without having to deal with functional group manipulations. Since the beginning of this century, scientific community has witnessed a great development in this area, which is entirely based on metal catalysis.

Perhaps one of the earliest and most striking examples in this area came from the group of M. Christina White. In 2007, White's group reported the use of an iron catalyst for the selective hydroxylation of aliphatic non-activated C-H bonds (Chen and White 2007) (Figure 10). Despite the moderate yields, this work represented a breakthrough since it described a selective functionalization based on small electronic differences between C-H bonds. Reports on stereoselective versions of this kind of reaction are truly sparse, and Davis group has recently reported a site-selective and stereoselective functionalization of non-activated C–H bonds by using chiral dirhodium catalysts (Liao et al. 2016) (Figure 11).

Although non-activated C-H functionalization is taken as the highest challenge within this area, other types of C-H functionalization involving $C(sp^2)$-H and activated $C(sp^3)$-H can be found in the literature (Cramer 2012, Peng and Maulide 2013, Gensch et al. 2016, Usman et al. 2017).

Publications in indexed journals in the field of catalysis applied to chemical processes by Brazilian laboratories have started to appear regularly in the literature during 1990's and have grown steadily ever since, almost doubling the number of articles published in indexed journals over the last five years with fifty-six of these original papers receiving fifty-six or more citations. In the area of catalysis applied to organic chemistry, approximately twenty original articles were published over the last five years produced by Brazilian laboratories.

Metallic species have dominated the scenario of catalytic chemical processes originated from Brazilian laboratories. Due in part to its obvious industrial applications, the hydrogenation reaction has been investigated as the hydrogenation of cyclohexene catalyzed by rhodium complexes in ionic liquids (Suarez et al. 1996), the hydrogenation of arenes by Rh(0) and Ir(0) nanoparticles stabilized in ionic liquids (Fonseca et al. 2003), the partial hydrogenation of benzene to cyclohexene by ruthenium nanoparticles in imidazolium ionic liquids (Silveira et al. 2004), the partial hydrogenation of 1,3-butadiene to 1-butene (Suarez et al. 1997) and the hydrogenation of ketones by iridium nanoparticles under mild conditions (Fonseca et al. 2004). Hydroformylation of 1-alkenes was performed under solventless conditions using rhodium nanoparticles prepared

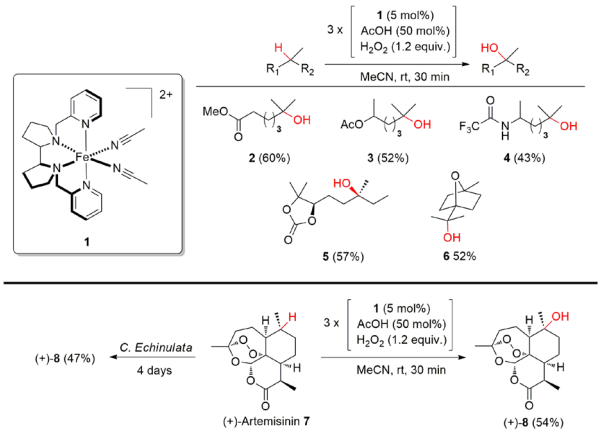


Figure 10 - Non-activated C-H functionalization mediated by an iron catalyst (Chen and White 2007).

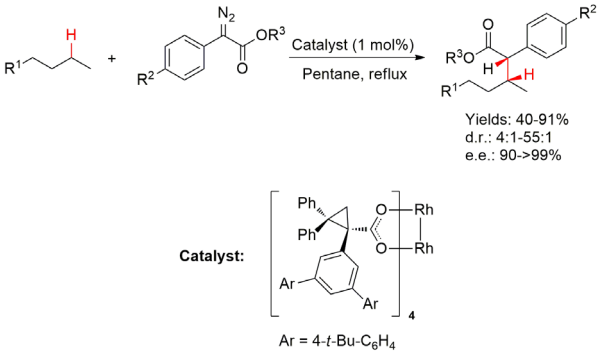


Figure 11 - Asymmetric non-activated C-H functionalization mediated by a chiral rhodium catalyst (Liao et al. 2016).

in imidazolium ionic liquids as catalysts (Bruss et al. 2006).

The selective oxidation of hydrocarbons processes have received less attention so far despite its potential in the chemical industry. A binuclear Fe(III) complex was conceived as a mimetic of monoamine oxygenase and it was shown to convert cyclohexane to cyclohexanol and cyclohexanone (19.2% overall yield) when hydrogen peroxide was employed as the oxidant (Esmelindro et al. 2005). Immobilization of metalloporphyrins in nanotubes of natural halloysite was explored in the oxidation of octane, cyclohexane and n-heptane (Machado et al. 2008).

The generation of metallic nanoparticles in ionic liquids for catalytic processes stands out as the most prolific area of catalytic processes in academic laboratories in our country and the contributions from Dupont and coworkers are among the most cited papers from Brazilian laboratories (Dupont et al. 2000, 2002, Dupont and Scholten 2010, Scholten et al. 2012).

A representative example of Dupont's contribution for catalytic processes is the study of the kinetics and reaction mechanism of the Heck reaction promoted by CN-palladacycles where it was found that palladacycles act as a Pd(0) reservoir which undergoes oxidative addition of the aryl halide on its surface, followed by lixiviation of homogeneous Pd(II) species. Reversible coordination of the olefin to the product of oxidative addition enables the reductive elimination of the Heck adduct, regenerating the homogeneous Pd(0) species (Consorti et al. 2005) (Figure 12).

Other examples came from the group of Gusevskaya who described the use of Pd (or Pt)-based catalysts for the functionalization of monoterpenes (Rocha et al. 1998, Foca et al. 2000, 2002). In one of these examples, the group reported a stereoselective tandem-oxidative coupling of camphene using $Pd(NO_3)Cl/LiNO_3$ or $Pd(OAc)_2/LiNO_3$ as catalysts (da Silva and Gusevskaya 2001).

In 2002, Pilli and coworkers have explored the use of organometallic catalytic processes, particularly the intramolecular Heck reaction for the synthesis of indolizidinone, quinolizidinone and benzoazepinone heterocycles (Santos and Pilli 2002) and the Sonogashira reaction for the synthesis of 1-ferroceneyl-2-aryl(heteroaryl) acetylenes and 2-ferrocenylindol derivatives (Torres et al. 2002).

Regarding asymmetric metal catalysis, pioneering work in Brazil was conducted by Dupont in the end of 1990's when the group reported the use of a $RuCl_2$-(S)-BINAP]$_2$ complex dissolved in 1-*n*-butyl-3-methylimidazolium tetrafluoroborate ($BMI{\cdot}BF_4$) molten salt for the asymmetric hydrogenation of 2-phenylacrylic acid (Monteiro et al. 1997) (Figure 13a). Later on, the same group

reported higher values of enantioselectivity for hydrogenation reactions using a chiral rhodium complex in BMI·BF_4, under higher hydrogen pressures (Berger et al. 2001) (Figure 13b).

In 2003, Braga and coworkers described that oxazolidines derived from L-serine and L-threonine efficiently catalyzed the addition of diethylzinc to aldehydes (Braga et al. 2003). Later on, the same laboratory described that pyrrolidinyl methanols catalyzed the zinc-promoted addition of arylboronic acids to aromatic aldehydes with the reactive arylzinc species being generated *in situ* via a boron-zinc Exchange (Braga et al. 2005).

Correia, Eberlin and coworkers studied the mechanism of the Heck-Matsuda arylation employing arenediazonium salts by ESI-MS. The authors were able to disclose several cationic intermediates of the oxidative addition step and to propose a more detailed mechanism for the Heck-Matsuda reaction (Sabino et al. 2004). The diastereo- and enantioselective variant of the Heck-Matsuda reaction has been developed by Correia and coworkers who recently achieved high enantiomeric excess by using chiral pyrimidine- and pyrazine-oxazolines as chiral *N*,*N* ligands for highly site- and enantioselective palladium-catalyzed arylations of trisubstituted olefins using aryldiazonium salts as aryl-transfer agents (Meira et al. 2007, Oliveira et al. 2013, 2015) (Figure 14).

The development of phosphine-free catalysts for the Heck reaction has been a topic of active research with the contribution of several Brazilian laboratories (Consorti et al. 2003, Senra et al. 2007, 2008, 2009, Rosa and Rosa 2012, dos Santos et al. 2014).

The Suzuki coupling has also attracted the interest of Brazilian chemists who explored, among other aspects, the use of palladium on calcium carbonate in ethanol-water as the solvent medium (Oliveira and Antunes 2007), acceleration under microwave irradiation (Martins et al. 2011) or using palladium nanoparticles and a phosphine-functionalized support as catalyst (Costa et al. 2010). Palladacycles have been shown to act as the source of Pd(0) active catalyst in the coupling of terminal alkynes with aryl bromides and iodides under mild reaction conditions (Consorti et al. 2006). Stefani and coworkers explored the Suzuki-Miyaura cross-coupling reaction of potassium aryltrifluoroborate salts and aryl tellurides to produce the corresponding biaryls (Cella et al. 2006) as well as the Pd(0)-catalyzed cross-coupling reactions between potassium aryl- and vinyltrifluoroborate salts and aryl- and vinylic tellurides to afford the corresponding stilbenes in good to excellent yields (Cella and Stefani 2006).

Petragnani and Comasseto have trained a large number of students and post-doctoral coworkers in the domain of the chemistry of chalcogenides, particularly organoselenium and organotellurium compounds (Petragnani and Comasseto 1986, Comasseto and Barrientos-Astigarraga 2000, Petragnani and Stefani 2007, Comasseto 2010). Several of them have successfully established their own research groups and continued to explore the organochalcogen territory (Cella et al. 2006, Cella and Stefani 2006, Zeni et al. 2006, Braga et al. 2006).

Of particular interest to this overview on organometallic catalysis, is the coupling of Z-vinylic tellurides with alkynes catalyzed by $PdCl_2$/CuI to provide Z-enynes or Z-enediynes which was described by Comasseto and Zeni (Zeni and Comasseto 1999). Later on, the same group described the coupling of vinylic tellurides with alkynes catalyzed by $PdCl_2$ (Raminelli et al. 2004). CuO nanoparticles have been described as a recycable catalyst for cross-coupling of organic diselenides and aryl boronic acids (Alves et al. 2009). Terminal alkynes were shown to undergo mild and efficient amidoalkylation with aqueous formaldehyde and secondary amines under CuI catalysis to provide tertiary propargylamines (Bieber and da Silva 2004). Cysteine- and

methionine-derived oxazolidine and thiazolidine were shown to be good ligands for the palladium catalyzed asymmetric allylation reaction (Schneider et al. 2004).

Another metal which has been object of intense exploration by some Brazilian research groups is niobium. Brazil holds 86% of the world niobium reserves and this is one of the reasons why this metal became popular around here. Niobium(V) pentachloride has been employed as a very efficient Lewis acid in esterification reactions (de Sairre et al. 2005, Aranda et al. 2009), Diels-Alder (Constantino et al. 2006), intramolecular Friedel-Crafts (Polo et al. 2008), multicomponent reactions (de Andrade et al. 2015) and others (Lacerda et al. 2012) (Figure 15).

Pilli and coworkers have explored the use titanium and iridium for the asymmetric allylation of aldehydes and primary alcohols, respectively, as an approach to the synthesis of natural products and molecules with relevant biological activities, such as (*R*)-Fluoxetine (de Fátima and Pilli 2003, 2004, 2005a, b, Novaes et al. 2015a, b).

Organocatalysis

The Hajos-Parrish-Eder-Sauer-Wiechert reaction is considered the pioneer work on asymmetric aldol reaction of pratical use in synthetic organic chemistry. It involves the cyclization of a triketone promoted by an organic catalyst (L-Proline) and it was independently reported in 1971 by two groups: Hajos and Parrish from Hoffman-LaRoche Inc. (Hajos and Parrish 1971, 1974) and Eder, Sauer and Wiechert from Schering AG (Eder et al. 1971a, b, c) (Figure 16).

In 2000, List, Lerner and Barbas III recognizing the mechanistic similarities between the aldolase catalytic antibodies they have previously developed and the intramolecular asymmetric aldol reaction above, described the use of 30 mol% of L-proline in the asymmetric aldol condensation between

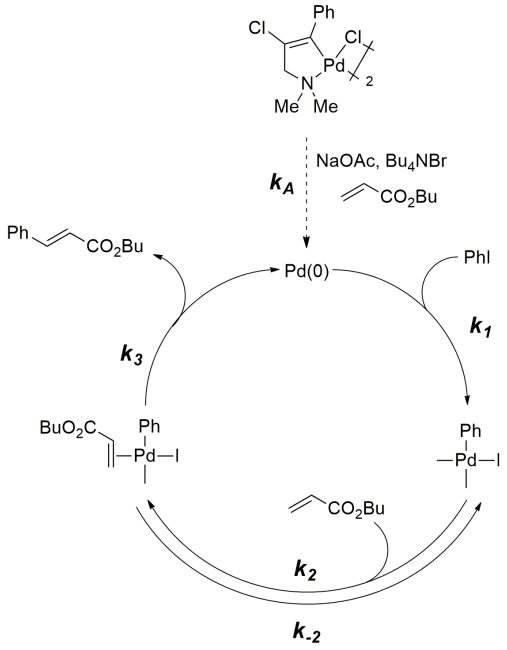


Figure 12 - Postulated Heck reaction mechanism (Consorti et al. 2005).

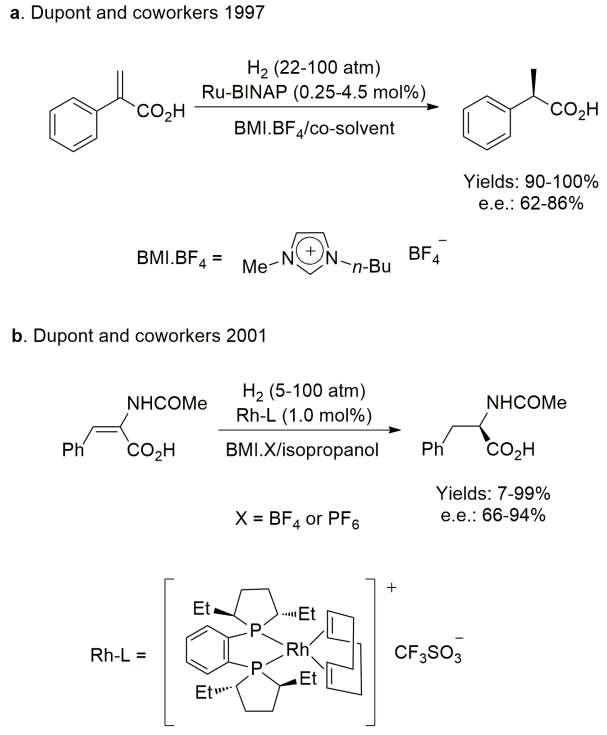


Figure 13 - Asymmetric hydrogenation reported by Dupont and coworkers (Monteiro et al. 1997, Berger et al. 2001).

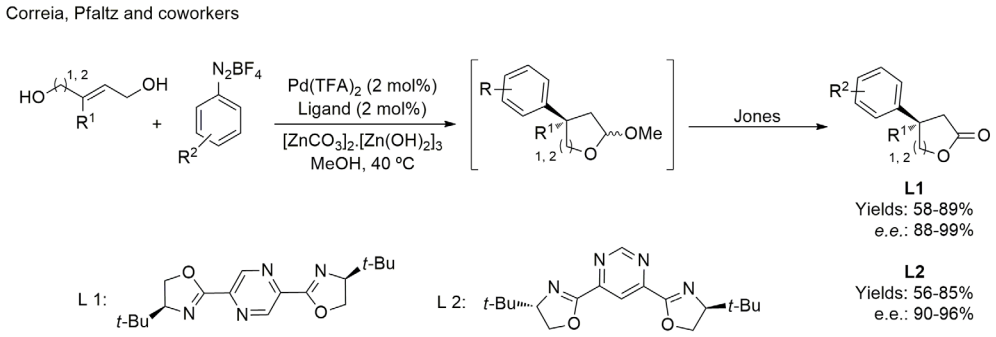


Figure 14 - Enantioselective Heck-Matsuda reaction developed by Correia and coworkers (Meira et al. 2007, Oliveira et al. 2013, 2015).

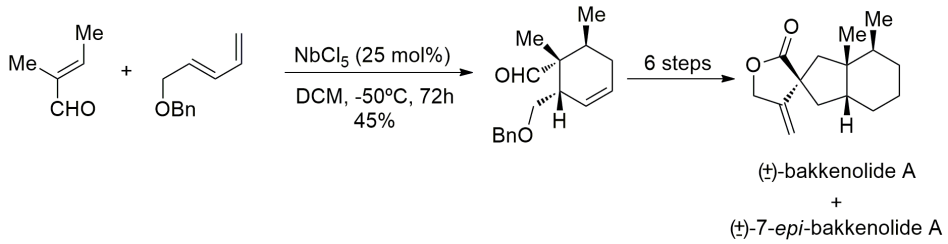


Figure 15 - Niobium catalyzed Diels-Alder reaction (Constantino et al. 2006).

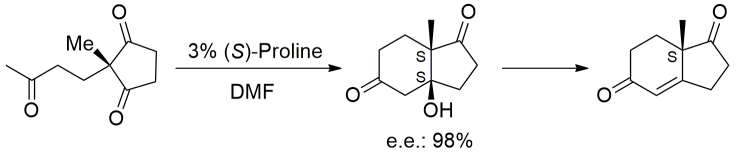


Figure 16 - The Hajos-Parrish-Eder-Sauer-Wiechert reaction (Hajos and Parrish 1971, 1974, Eder et al. 1971a, b, c).

acetone and aldehydes with yields ranging from 54-97% and enantiomeric excesses from 60-96% (List et al. 2000). From that point on, the area of asymmetric organocatalysis flourished and the readers are directed to review articles for a broad coverage of this topic (Seayad and List 2005, Pellissier 2007, Govender et al. 2016, Meninno and Lattanzi 2016, Phillips 2016, Vetica et al. 2017, Zhan et al. 2017, Liu and Wang 2017).

Currently, the most outstanding examples involve cascade reactions that increase molecular complexity with strict control of stereochemistry. In one example published in 2013, Melchiorre research group reported a three-component triple domino reaction between aliphatic aldehydes, 2,4-dienals and unsaturated oxindoles using a proline derivative as catalyst (Chatterjee et al. 2013) (Figure 17). The authors demonstrated high levels of control over relative and absolute stereochemistry for six-membered ring formation, quite an accomplishment for such a complex system.

More recently, Jørgensen group reported an aza-Diels-Alder/ring-closing cascade reaction for the obtainment of bicyclic azaheterocycles with a unique structural scaffold similar to compounds with important biological activities like the natural product (+)-lentiginosine and perindopril, a drug used in the treatment of hypertension (Li et al. 2017) (Figure 18).

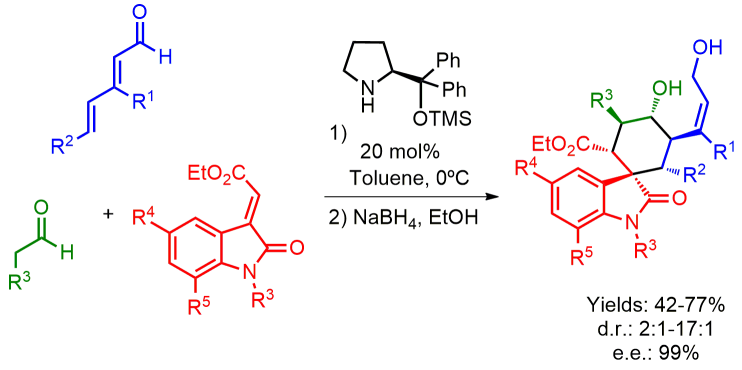


Figure 17 - Organocatalyzed three-component triple domino reaction described by Melchiorre (Chatterjee et al. 2013).

In Brazil, one of the earliest reports on asymmetric organocatalysis was disclosed in 2008 by Lüdtke, Paixão and coworkers (Schwab et al. 2008). The authors explored the use of cysteine-derived prolinamides as organocatalysts for the asymmetric aldol reaction between acetone and aromatic aldehydes (Figure 19).

By changing the proline moiety, this methodology was further extended by Schneider and coworkers to allow the use of cyclic ketones as nucleophiles (Rambo et al. 2015). The addition of small amounts of water to the proline-catalyzed aldol addition of acetone to isatin led to an increase in the enantioselectivity of the reaction, as reported by Garden, Tomasini and coworkers (Angelici et al. 2009).

Later on, Paixão reported an asymmetric Michael addition of malonates to α,β-unsaturated aldehydes using a modified Jørgensen–Hayashi organocatalyst and EtOH:brine as solvent (Feu et al. 2013). The products were obtained in good yield and high enantioselectivity (Figure 20). Furthermore, the products served as building blocks for the synthesis of chiral indoles, known to be core structures in biologically active molecules.

In collaboration with Havana University, the same group also reported a stereoselective synthesis of natural-product-like hybrids by merging organocatalysis and the Ugi four component reaction (Echemend et al. 2015) (Figure 21). The organocatalytic part involves the addition of cyclic 1,3-diketones to α,β-unsaturated aldehydes using a L-Proline derived catalyst. After the reaction is finished, amine and isocyanide were added and the Ugi reaction took place, leading to a mixture of compounds. By choosing the appropriate conditions, the authors were able to selectively drive the reaction toward formation of the desired product with excellent diastereo- and enantioselectivity.

Amarante and coworkers reported the desymmetrization of dibenzylideneacetones using a sugar-based organocatalyst with the creation of two stereogenic centers, one of which is quaternary. The methodology was proven highly diastereoselective and the products might serve as precursor for the synthesis of functionalized amino acids by acid treatment (Pinheiro et al. 2016).

Photocatalysis

Over the past decades, the use of photocatalysis was mainly restricted to some rearrangements, cycloadditions and electrocyclization reactions, most of which required the use of UV light. In the last two decades, the scientific community has witnessed the renaissance of photocatalysis when some laboratories started to explore the use of visible light to promote useful synthetic

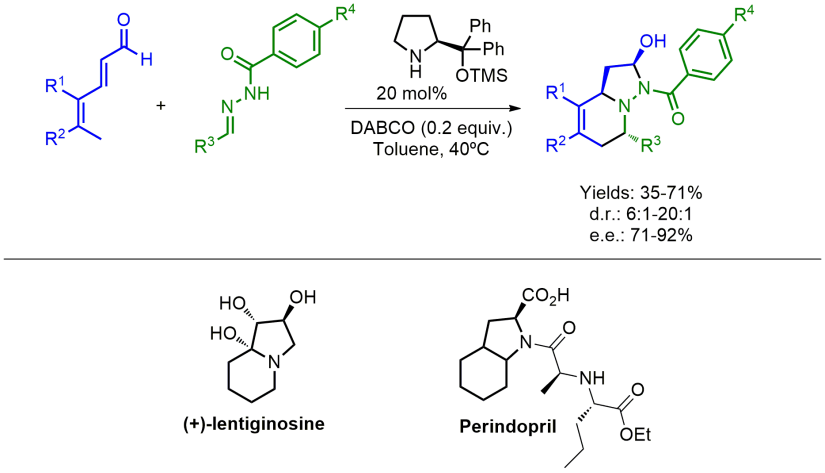


Figure 18 - Organocatalyzed aza-Diels-Alder/ring-closing cascade reaction reported by Jørgensen (Li et al. 2017).

transformations. This young field was named "visible-light photoredox catalysis (VLPC)", once the exited catalyst acts as an oxidant/reductant that generates reactive radical species by engaging in single electron transfer processes with the substrates (Prier et al. 2013, Angnes et al. 2015, Romero and Nicewicz 2016).

Stephenson reported the generation of a carbon-centered pyrroloindoline-derived radical, followed by coupling with a substituted indole as the key step in the synthesis of (+)-gliocladin (Furst et al. 2011). Xiao described cycloadditions between dipolarophiles and 1,3-dipoles generated from tetrahydroisoquinolines using VLPC and Ru(II) as the photoredox catalyst (Zou et al. 2011). The trifluoromethylation of ketones, esters, amides and arenes was enabled by coupling with photogenerated trifluoromethyl radicals, as reported by MacMillan (Nagib and MacMillan 2011, Pham et al. 2011).

Many research groups have merged photoredox catalysis with other types of catalysis, such as metal catalysis and organocatalysis, in order to achieve asymmetric transformations. MacMillan research group has published several works where they report the concomitant use of photoredox and organocatalysis for the asymmetric functionalization of aldehydes (Welin et al. 2015) (Figure 22).

In another example, Meggers group merged photoredox catalysis with Lewis acid catalysis using chiral-at-metal Ir/Rh complexes as asymmetric catalysts (Huo et al. 2016) (Figure 23). The same strategy was used by Yoon to promote the asymmetric addition of α-aminoradicals to α,β-unsaturated oxazolidinones, without using chiral-at-metal complexes but a combination of $Sc(OTf)_3$ and a chiral ligand (Espelt et al. 2015). Stephenson and Jacobsen demonstrated that asymmetric addition of nucleophiles to chiral iminium ions was possible when using an anion binding organocatalyst (Bergonzini et al. 2014). More examples of asymmetric photoredox transformations can be found in specialized reviews (Meggers 2015, Shaw et al. 2016, Zhang and Meggers 2017).

In 2015, Paixão and coworkers reported the combination of tris(trimethylsilyl)silane and visible-light for the synthesis of indoles and oxindoles. The methodology used no photocatalyst and went through the formation of donor-acceptor complexes (EDA) between the silane and the aromatic substrates (da Silva et al. 2015) (Figure

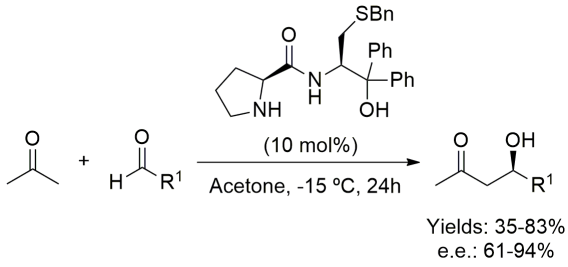


Figure 19 - Asymmetric aldol reaction reported by Lüdtke, Paixão and coworkers (Schwab et al. 2008).

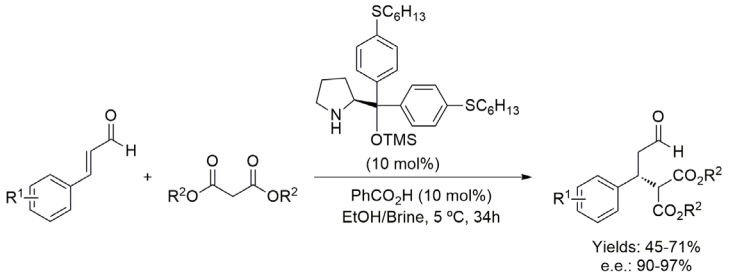


Figure 20 - Asymmetric Michael addition reported by Paixão and coworkers (Feu et al. 2013).

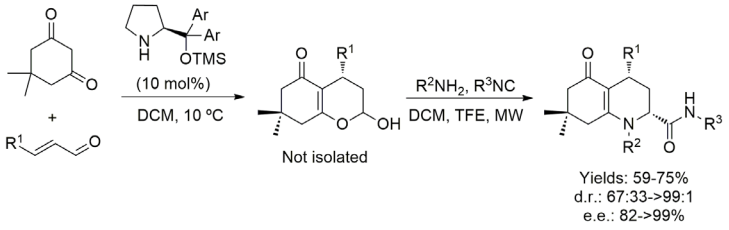


Figure 21 - Combination of organocatalysis and Ugi four component reaction reported by Paixão, Rivera and coworkers (Echemend et al. 2015).

24). In the next year, in collaboration with Florida State University, de Oliveira and coworkers reported a methodology for the photooxygenation of electron-rich aromatic systems under continuous flow conditions (de Oliveira et al. 2016). The authors used meso-tetraphenylporphyrin (TPP) as the photocatalyst in only 0.3 mol% and molecular oxygen as the stoichiometric oxidant (Figure 25).

Biocatalysis

Biocatalysis has been used as a green alternative to toxic reagents in synthetic useful transformations. A representative example is the biocatalyzed enantioselective dihydroxylation of alkenes. Chiral diols are important building blocks in organic synthesis and the most common way to prepare these compounds is through asymmetric Sharpless dihydroxylation, which uses OsO_4, $K_3[Fe(CN)_6]$ and chiral quinine or quinidine derived ligands. Such transformation has been reported employing a biocatalysed cascade sequence which consists of a lipase (Novozyme 435) mediated enantioselective epoxidation, followed by ring opening by an epoxide hydrolase (EH) (Xu et al. 2011) (Figure 26).

Biocatalytic processes have also been used in the synthesis of active pharmaceutical ingredients (APIs). GDC-0994 is a potent, selective and highly efficient inhibitor of ERK1/2 kinases, a group of

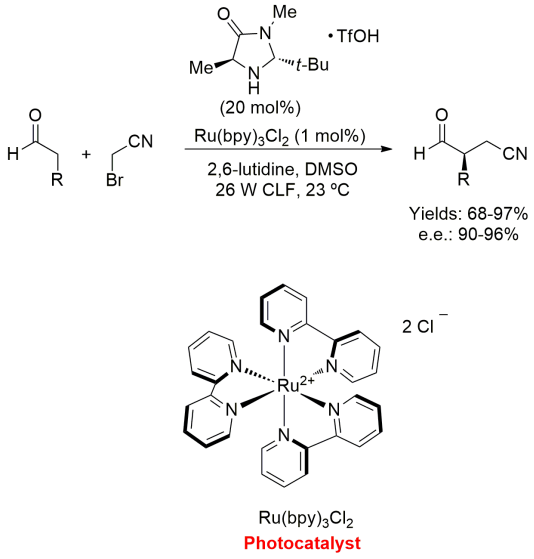


Figure 22 - Photocatalyzed reaction between aldehydes and α-bromonitriles (Welin et al. 2015).

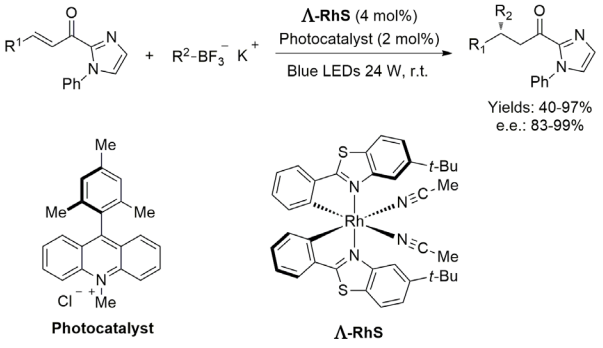


Figure 23 - Asymmetric photocatalyzed reaction using chiral-at-metal Rh complex as Lewis acid (Huo et al. 2016).

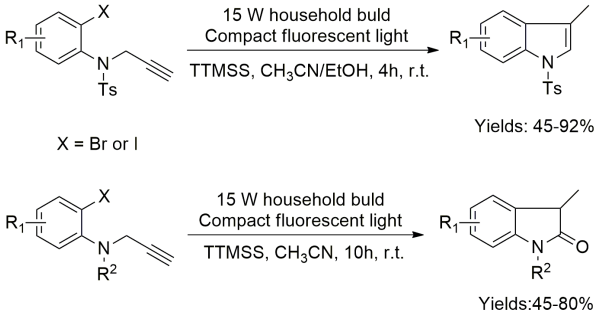


Figure 24 - Photocatalyzed synthesis of indoles and oxindoles reported by Paixão and coworkers (da Silva et al. 2015).

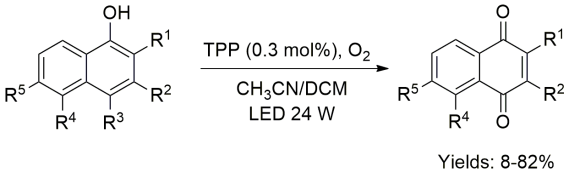


Figure 25 - Photocatalyzed photooxygenation of hydroquinones under flow condotions reported by de Oliveira and McQuade (de Oliveira et al. 2016).

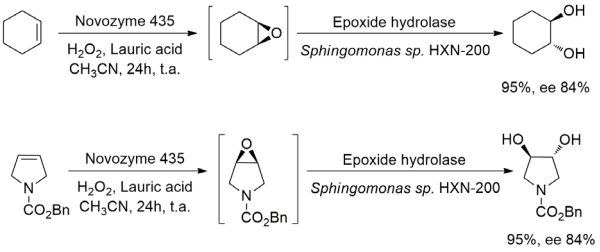


Figure 26 - Biocatalyzed asymmetric dihydroxylation (Xu et al. 2011).

enzymes that are involved in cancer development. The original version of GDC-0994 synthetic route featured an asymmetric Sharpless dihydroxylation as the key step (Blake et al. 2013, Ren et al. 2015) (55% yield after protection and 94% e.e.) (Figure 27a). In order to increase the optical purity of the final compound, Linghu and coworkers developed a new synthetic route where the deprotected diol (which is synthetically equivalent to the final compound in the first route) was obtained by a ketoreductase (KRED)-mediated enantioselective ketone reduction (Linghu et al. 2017) (Figure 27b).

In Brazil, several groups focus on the development of biocatalytic reactions and processes. Rodrigues and coworkers, in the early 1990's, reported on the stereoselective reduction of 1-phenyl-1,2-propanedione to the corresponding (1*R*,2*S*)-diol by baker's yeast immobilized on chrysotile and montmorillonite. The methodology was also successfully used for the asymmetric synthesis of 2-amino-1-phenylethanol and (*R*)- or (*S*)-1-phenyl-2-chloroethanol (Sorrilha et al. 1992).

Andrade and coworkers reported on the reduction of organochalcogen acetophenones with carrot roots and described the production of *ortho*-organochalcogeno-α-methylbenzyl alcohols via enzymatic kinetic resolution catalyzed by a lipase in organic media (Comasseto et al. 2004). Lemos and coworkers reported on the stereoselective reduction of aldehydes and ketones using cells from *Manihot esculenta* and *Manihot dulcis* roots, also with e.e. >90% (Machado et al. 2006).

In another example of kinetic resolution, dos Santos reported the use of lipase B from Candida antarctica (CALB) for the resolution of hydroxy tellurides (dos Santos et al. 2006) (Figure 28). The products were obtained with excellent values of enantiomeric excess (98% or higher) and conversion (47-50%).

The same enzyme was used by Porto for the resolution of *N*-hydroxypropargyl piperidones which are important building blocks in organic synthesis (Melgar et al. 2010) (Figure 29).

Marsaioli and coworkers have investigated the use of *Candida albicans* CCT 0776 whole cells for the stereoinversion of alcohols (Mantovani et al. 2009) (Figure 30). A racemic mixture of 1-phenylethanol is completely converted into the *R* isomer and the process is actually a cascade composed by selective oxidation of the *S* enantiomer, followed by selective reduction. The reaction proceeds with almost quantitative conversion and e.e. up to 99%. The same enzyme was used in the deracemization of 1,2-octanediol (Chena et al. 2008).

De Souza research group has published on the use of lipases as synthetic tools for derivatization of organic molecules (Junior et al. 2012, Sutili et al. 2013, Costa et al. 2014). In one example, the group demonstrated that lipases can also catalyze the Michael addition of primary and secondary amines to acrylonitrile (de Souza et al. 2009) (Figure 31).

AUTOMATION

Organic synthesis is and will continue to be a labor-intensive enterprise as the preparation of raw materials and the purification and characterization of the desired products, among others operations, will always demand time and resources. At the same time, organic synthesis will continue to be expected to deliver the requested amount of a chemical entity at the lowest cost and the least time.

In order to cope with such an ever-increasing demand, new technologies will have to be incorporated to research and industrial labs. In fact, there seems to be a gap between the research developed at academic settings and the needs of process chemists as, more often than not, problems related to downstreaming, safety and scalability have to be solved before a fundamental discovery can be translated to an industrial process. On a more philosophical tone, the hardly acquired skills and training of a synthetic organic chemist would be better appropriated by the society when he/she works on unchartered territory of science and not on more mundane tasks.

As previously remarked by professor Steven Ley, a pioneer in the implementation of automated process in academic settings, most of the apparatus and glassware used in research laboratories these days are not fundamentally different from those familiar to the chemists of the last century. Modern life has incorporated the integration and connectivity of equipments and devices and the internet of things is now a reality. Therefore, it seems natural that the technology put to serve the society as a whole, should also be of value to assist and control processes and operations in academic laboratories, leaving more time for chemists to engage in creative activities (Ley et al. 2015a, b, Fitzpatrick et al. 2016).

Machines can (and already do) assist chemists on several different operations such as safe handling and preparing hazardous materials, controlling

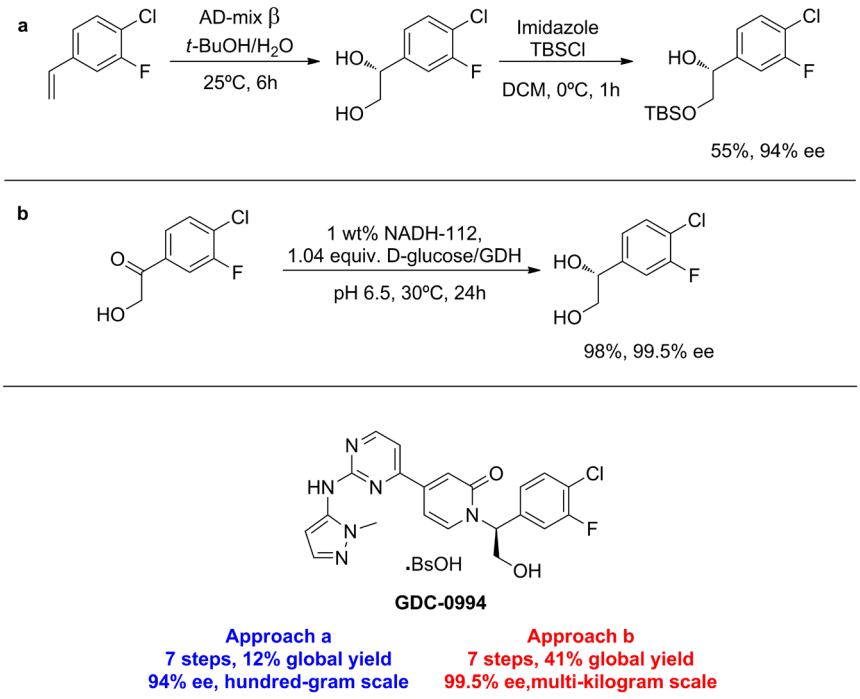


Figure 27 - (**a**) Sharpless dihydroxylation (Blake et al. 2013 and Ren et al. 2015) and (**b**) Biocatalytic asymmetric ketone reduction (Linghu et al. 2017).

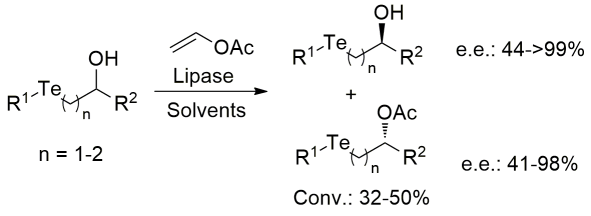


Figure 28 - Kinetic resolution of hydroxy tellurides reported by dos Santos and coworkers (dos Santos et al. 2006).

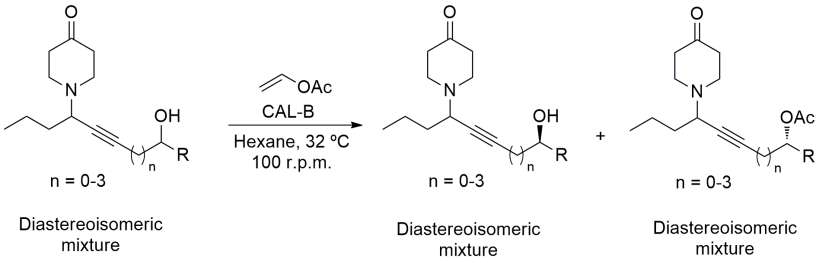


Figure 29 - Kinetic resolution of hydroxypropargylpiperidones reported by Porto and coworkers (Melgar et al. 2010).

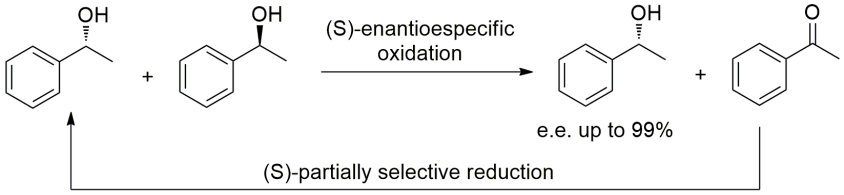


Figure 30 - Biocatalized stereoinversion of alcohols reported by Marsaioli and coworkers (Mantovani et al. 2009).

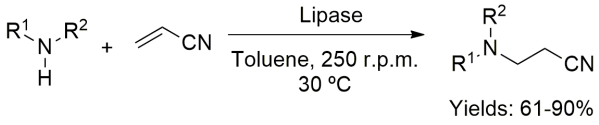


Figure 31 - Michael addition of amines to acrylonitrile catalyzes by lipase (de Souza et al. 2009).

processes occurring at very low or very high temperatures, in-line filtration, evaporation and solvent-switching, liquid-liquid extractions and chromatographic separation, crystallization and several others operations. While machine-assisted tasks are commonplace in industrial settings, some academic laboratories have successfully incorporated such technologies over the recent years in Brazil and elsewhere.

A particularly instructive example is the production of the *E* and *Z* forms of the anticancer drug tamoxifen using an experimental reactor to produce 220 g/day, corresponding to 20,000 daily doses of the drug (Murray et al. 2013) (Figure 32).

A three-step process was successfully implemented using continuous-flow process to prepare about 8 g/hour of the non-steroidal anti-inflammatory drug ibuprofen using a 250 microliter flow reactor (Snead and Jamison 2015) (Figure 33). Over the last two decades, pharmaceutical research and process laboratories saw a rapid increase in laboratory automation and robotics, which led to the extensive implementation of enabling technologies. Additionally, reconfiguration of the industrial R&D activities led to the extensive outsourcing of the synthesis of candidates and final active pharmaceutical intermediates (APIs), particularly those involved in precompetitive R&D projects. The reconfiguration of R&D activities in pharma companies has provided additional impetus to the development and implementation of enabling technologies, including collaborations with academic groups (Michaudel et al. 2015).

A representative case is the continuous production of aliskiren hemifumarate, a renin inhibitor used for the treatment of hypertension. The synthetic route starts with the reaction of the γ-butyrolactone depicted bellow to the final active pharmaceutical ingredient (Mascia et al. 2013) (Figure 34). The continuous flow setup provides a nominally 45 g/hour of aliskiren hemifumarate which corresponds to 2.7 x 10^6 tablets/year. The plant layout is compact, with a 2.4 x 7.3 m^2 footprint, and contained within enclosures where all the intermediate reactions, separations, crystallizations, drying, and formulation leading to the final tablet are carried out.

Seeberger and coworkers implemented a continuous flow process to prepare artemisinin, the most effective antimalarial drug in clinical use, from dihydroartemisinic acid (DHAA), a secondary metabolite produced by *Artemisia annua*, which can be converted to artemisin by oxidation with photochemically generated singlet oxygen, followed by acid treatment (Kopetzki et al. 2013) (Figure 35).

Using a HPLC pump, a solution of dihydroartemisinic acid (DHAA), the photosensitizer (9,10-dicyanoanthracene, DCA) and trifluoroacetic acid (TFA) was reacted with at least two equivalents of oxygen. The photoreactor was kept at -20 ºC and after passing through it, the mixture passed through

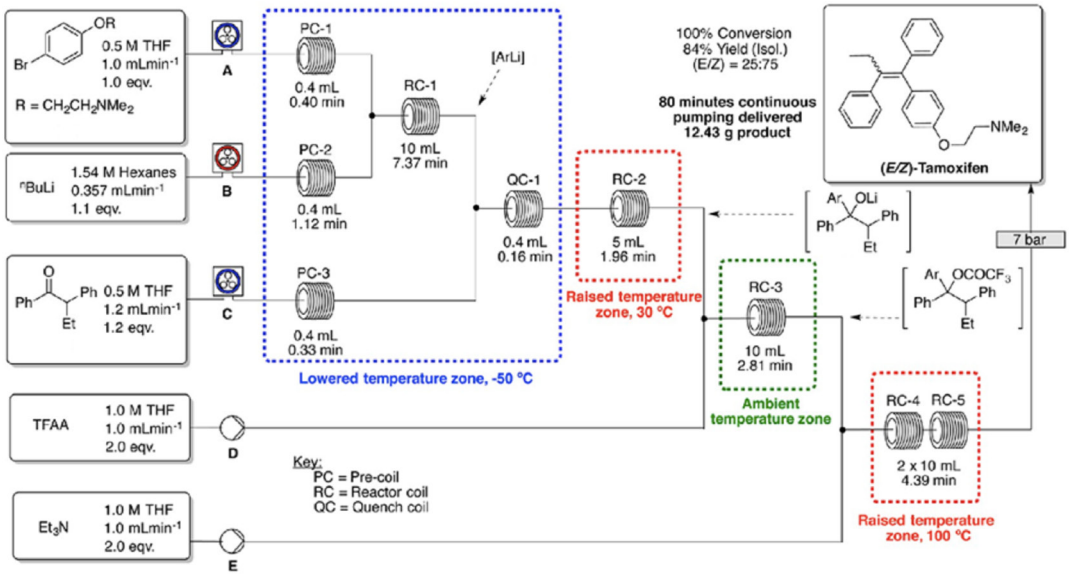


Figure 32 - Continuous-flow telescoped synthesis of (E/Z)-tamoxifen reported by Ley. Adapted with permission from Murray et al. (2013).

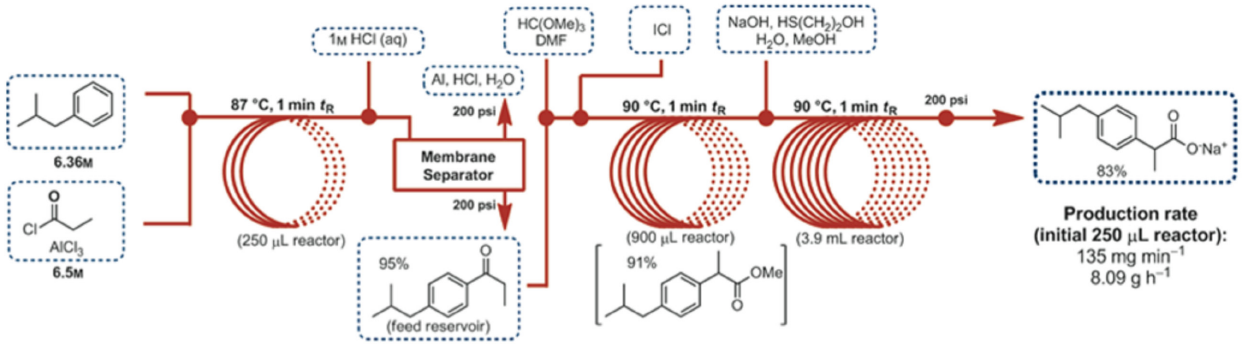


Figure 33 - Continuous flow, three-minute synthesis of ibuprofen reported by Jamison. Adapted with permission from Snead et al. (2015).

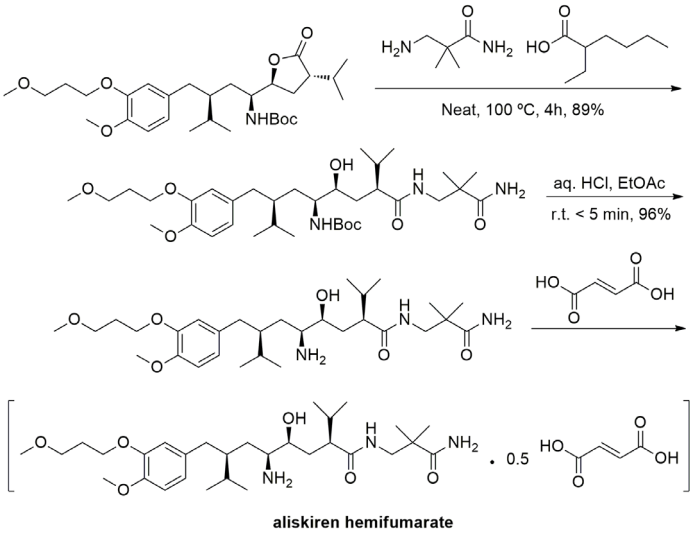


Figure 34 - End-to-end continuous production of aliskiren hemifumarate (Mascia et al. 2013).

two additional tube reactors kept at 10 and 20 ºC, respectively, before the final product is collected.

Ley and coworkers devised a multi-step flow synthesis of imatinib, the active pharmaceutical ingredient of Gleevec, marketed by Novartis AG for the treatment of chronic myeloid leukaemia (CML) and gastrointestinal stromal tumors, which also could be adapted to produce imatinib analogues for further biological evaluation (Hopkin et al. 2013).

De Oliveira and coworkers have recently reported the combination of batch and continuous flow processes for the preparation of curcumin, a compound with a growing demand in the pharmaceutical industry due to its high diversity of biological activities (Carmona-Vargas et al. 2017) (Figure 36). The same strategy was used for the syntheses of other curcuminoids related to curcumin.

The first step in the synthesis is the preparation of a boron complex, starting from acetylacetone and B_2O_3/B(O-*n*-Bu)$_3$ which was better performed in conventional batch apparatus because of slurry formation. The second and third steps were executed in continuous flow manner. In the second step, the initially formed boron complex reacts with vanillin via four aldol condensations, to furnish a second boron complex. The last step involves boron decomplexation through use of HCl, followed by integrated phase separation. The overall yield for curcumin is 63% and 7.5 g sample was obtained after 7 h of process, space-time yield (STY) equal to 25.5 g per day.

Organocatalytic reactions have also been adapted to continuous flow platforms through anchoring of the organocatalyst on a solid support. Paixão and Cass have demonstrated the use of a proline functionalized silica column to catalyze the Michael addition of aldehydes to nitroolefins when the reaction mixture was passed through it (Scatena et al. 2014) (Figure 37). The outcome of the reactor was integrated with a chromatographic column for product separation and, in the sequence, with a chiral polysaccharide column for stereoselectivity quantification, making the entire system fully automated.

In the field of biocatalysis, some groups have turned their attention to the development of continuous-flow platforms using immobilized enzymes in order to obtain biocatalized processes that are more prone to scale-up, easy of handling and less time consuming. In collaboration with the Massachusetts Institute of Technology, Andrade research group reported the use of a lipase (CAL-B) packed-bed reactor for the conversion of esters and amines into carboxamides under continuous flow conditions (Andrade et al. 2016) (Figure 38). The yields obtained for carboxamide production under continuous flow were much higher than for batch conditions, and the reaction times were also a little shorter.

De Souza group reported the use of Novozyme 435 for kinetic resolution of racemic 1-phenylethylamine (de Miranda et al. 2013) (Figure 39). The products were obtained with high enantiomeric ratios and conversions. When compared to the batch procedure, flow mode provided products in shorter reaction times, and with higher productivity and easier wok-up.

Another work using Novozyme 435 for kinetic resolution under flow conditions was published by Piovan and coworkers who described the resolution of secondary alcohols by acylation and deacylation reactions. In this case, the greatest advantage of the flow platform was to enable a scale-up from 7 to 18 fold higher than conventional batch reactor (Thomas et al. 2017).

SCALABILITY

Over the last decades, the field of organic synthesis has experienced an enormous growth as our capacity to create new synthetic methodologies and synthesize complex molecules has reached a level of excellence. At the same time, the mutually

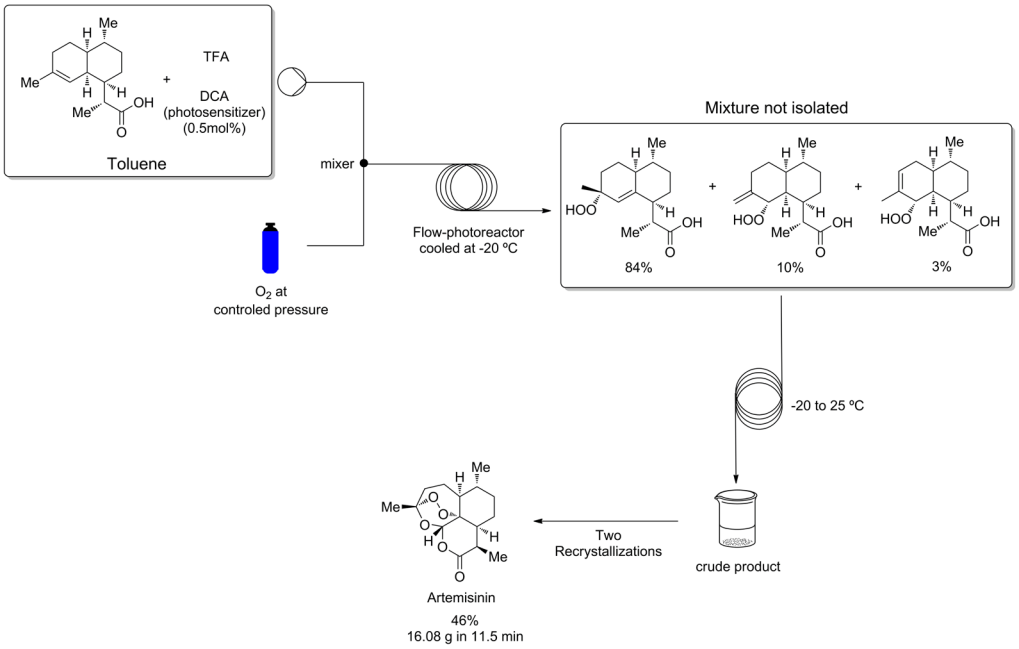


Figure 35 - Continuous flow semi-synthesis of artemisinin reported by Seeberger and coworkers (Kopetzki et al. 2013).

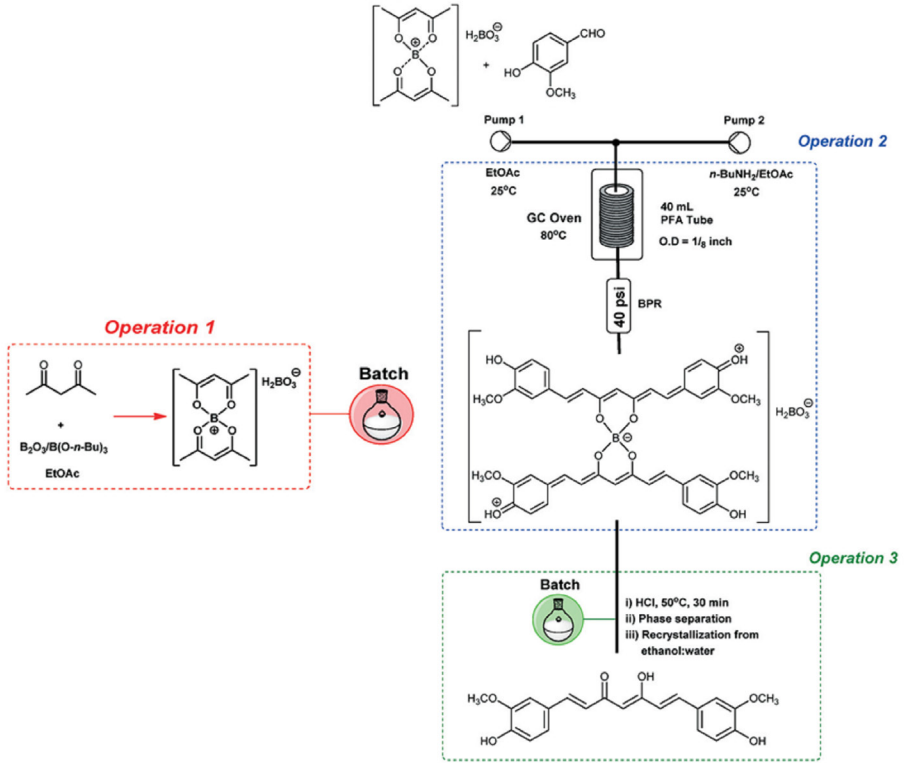


Figure 36 - Synthesis of curcuminoids by combination of batch and continuous-flow conditions reported by de Oliveira and coworkers. Adapted with permission from Carmona-Vargas et al. (2017).

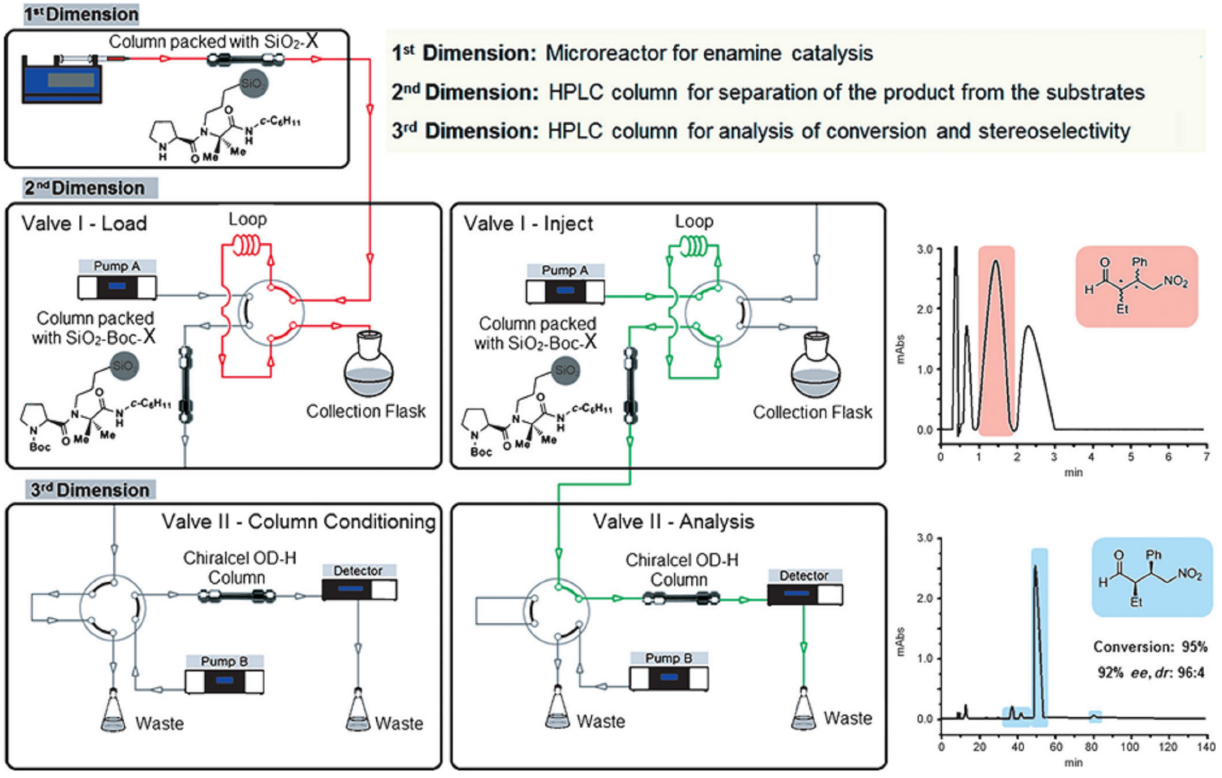


Figure 37 - Monitoring-integrated continuous-flow reactor reported by Paixão, Cass and coworkers. Adapted with permission from Scatena et al. (2014).

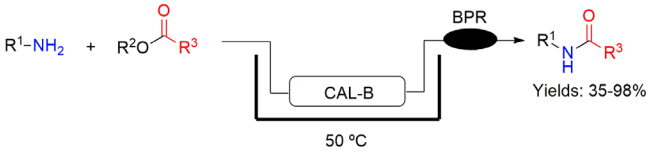


Figure 38 - Continuous-flow synthesis of carboxamides using immobilized lipase reported by Andrade and Jamison (Andrade et al. 2016).

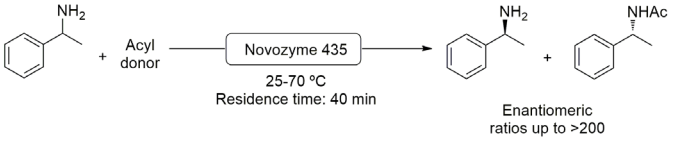


Figure 39 - Kinetic resolution of racemic 1-phenylethylamine reported by de Souza and coworkers (de Miranda et al. 2013).

beneficial synergy between curiosity-driven research (academic and non-proprietary industrial research) and problem-solving research (developed both at industrial and academic settings) has greatly enhanced the societal role of chemistry although it has not necessarily led to an integration of goals and values among chemical sciences (Chemistry and Chemical Engineering). More often than not, chemical endeavours at academic settings allowed the preparation of small amounts of complex target structures, usually in the range of few miligrams, while it would be up to the process chemists at industrial settings to solve the problems associated to scaling-up the process.

Currently, the concern on the development of applied chemistry has become a matter of great importance. From the viewpoint of a synthetic organic chemist, applicability means that you have a synthetic route for the production of large quantities of a compound, which displays a high socio-economical interest. Until a few years ago, only people working in industry were worried about scalability of synthetic procedures, but now this kind of concern is being implemented at the early stages of synthetic developments in academia.

An efficient, large scale synthetic route of a complex organic molecule is a challenge which depends on many factors, such as: i) step counting; ii) level of complexity of the final product; iii) stereochemical control; iv) stability of each intermediate; v) number of operational processes and its complexity (extraction, purification, handling of hazardous chemicals, etc); and vi) overall yield. Even at common laboratory scale, these issues are not easy to address, and this has forced the scientific community to search for synthetic processes more and more close to the ideality (Gaich and Baran 2010). Avoiding protecting groups by using more selective methodologies (Young and Baran 2009) and functional group and redox state manipulation through use of C-H activation (Newhouse and Baran 2011, Gutekunst and Baran 2011, Brückl et al. 2012) are some of the approaches adopted in order to target a scalable synthesis, as well as adherence to green chemistry principles, as much as possible. Of course, the notion of scalability in academic settings is different from its industrial counterpart. In academia, high scale synthesis generally means the production of gram-quantities of the final product or of an important intermediate while in industry, chemists and chemical engineers are targeting kilograms or even tons of the desired chemical entity.

Examples of large-scale complex syntheses

A well-devised, carefully planned synthetic route is key for the implementation of an efficient and scalable approach to complex structures. Those acquainted with the field of chemical synthesis, highly appreciate earlier demonstrations that highly complex molecular architecture could be efficiently constructed, such as the synthesis of Daphniphyllum alkaloids by Heathcock and coworkers (Heathcock 1992, Piettre and Heathcock 1990), the total synthesis of strychinine by Rawal and Iwasa (Rawal and Iwasa 1994), Novartis route to discodermolide (Mickel et al. 2004) and Baran approach to the taxane framework, present in the life saving drug paclitaxel (Taxol®), which provided a functionalized taxadienone skeleton in gram-scale (Mendoza et al. 2012).

One of the most amazing examples of scalability in a synthesis of a complex molecule is the synthesis of the API used in Halaven® (E7398, INN eribulin mesylate), a drug used to treat breast cancer and liposarcoma. This compound is an analog of halichondrin B, a macrolide isolated from some species of marine sponges with very limited availability (Towle et al. 2001, Zheng et al. 2004). In order to support its clinical development, a highly efficient large-scale synthesis was required (Chase et al. 2013, Austad et al. 2013a, b). Chemists at Eisai Inc. developed a process encompassing 34

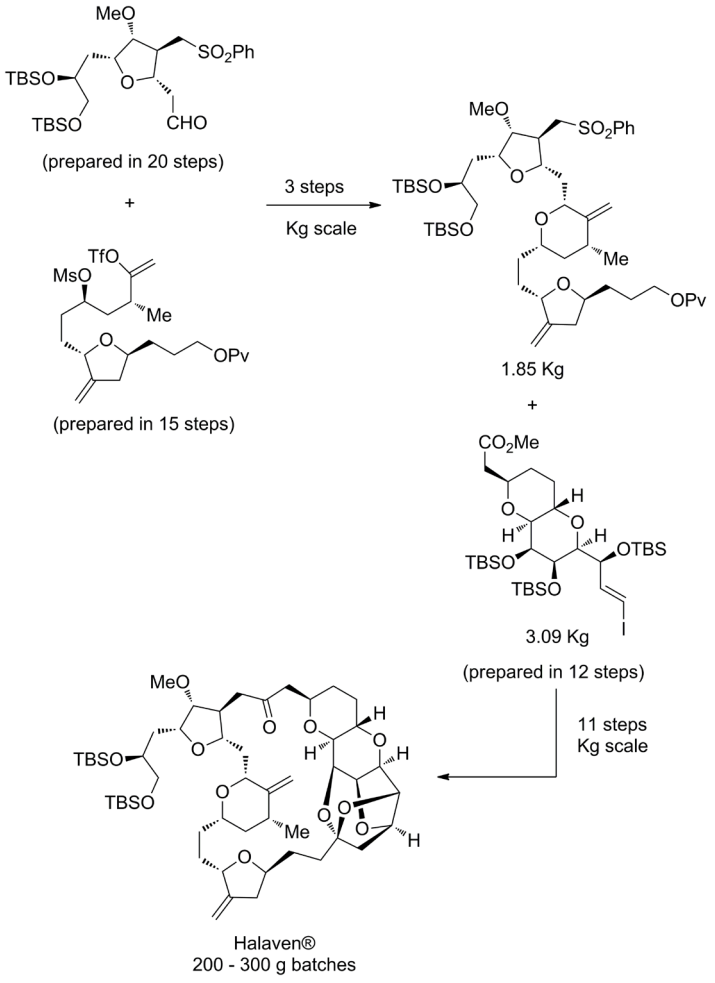


Figure 40 - The commercial synthesis of Halaven®, a landmark achievement in process chemistry (Chase et al. 2013, Austad et al. 2013a, b).

steps in the longest linear route, based on previously studies carried out in the 1990s by Professor Y. Kishi, Harvard University, which delivered 200-300 g of Halaven® in one batch (Figure 40).

Another great example was published by Baran's group, where the authors reported the scalable synthesis of axinellamines, compounds that belong to the natural products class of pyrrole−imidazole alkaloids (PIA) (Su et al. 2008, Yamaguchi et al. 2008) (Figure 41).

These compounds display a broad-spectrum antibacterial activity against Gram-positive and Gram-negative bacteria. In their first reports in 2008, Baran's group reported the syntheses of such compounds in a milligram-scale serving as a proof of concept (O'Malley et al. 2008). Six years later, they published a revised synthesis capable of delivering these compounds on a gram-scale (Rodriguez et al. 2014). The key factor for this improvement was the re-evaluation of the synthetic strategy to access a highly functionalized guanidine-spirocycle that serves as template for the obtainment of axinellamines. In the first generation syntheses, the synthetic pathway to reach this compound was long and laborious, consisting of 20 steps, 12 chromatographic separations and overall yield of <1%. In the new synthetic route, the number of steps and chromatographic purifications was reduced to 8

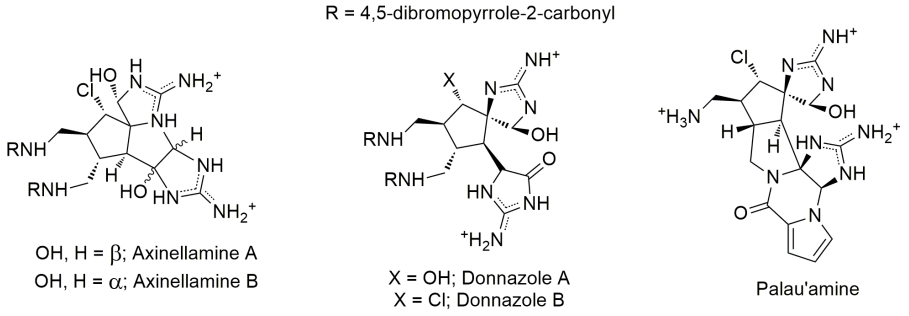


Figure 41 - Structures of axinellamine antibiotics.

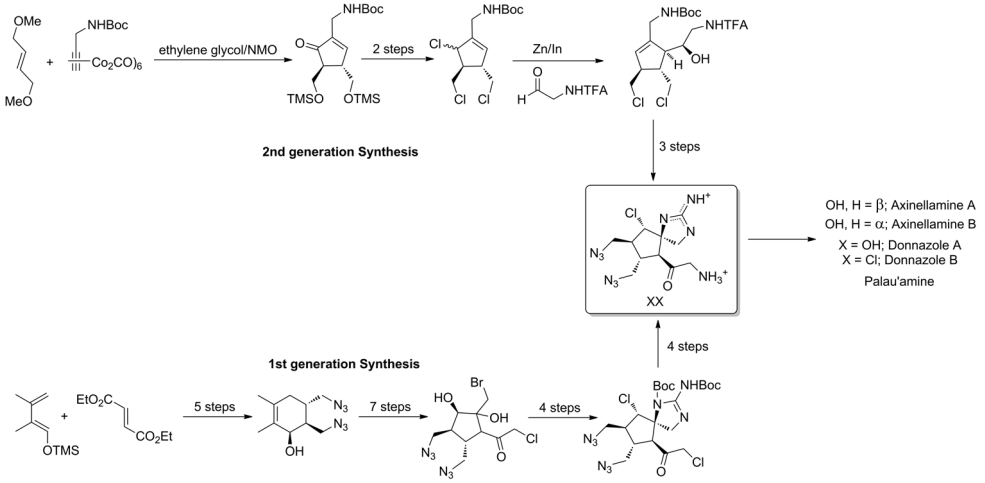


Figure 42 - First and second generation syntheses of the highly functionalized guanidine-spirocycle intermediate (O'Malley et al. 2008, Rodriguez et al. 2014).

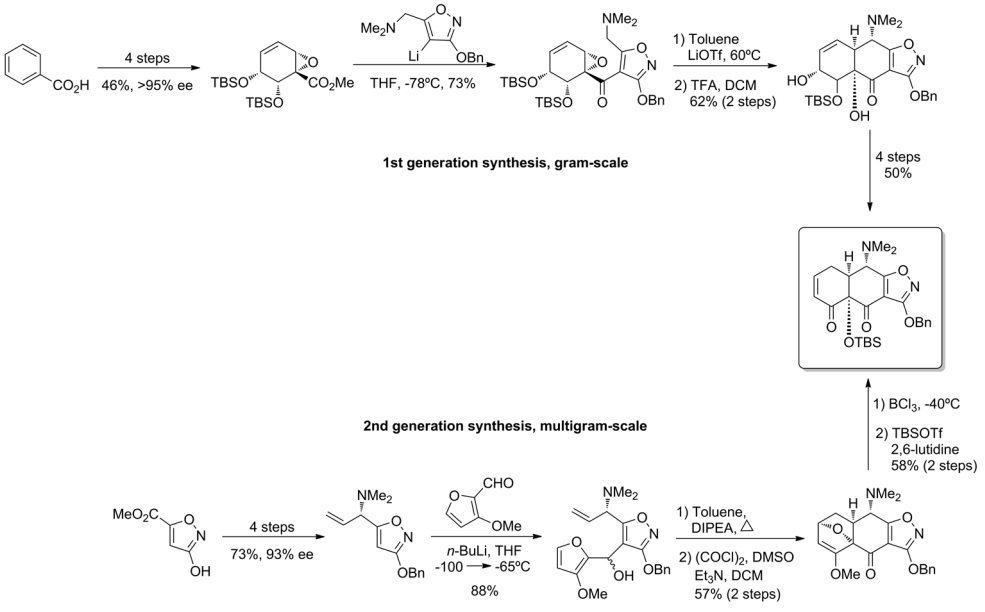


Figure 43 - First and second generation syntheses of the intermediate used in the synthesis of tetracyclines (Charest et al. 2005, Brubaker and Myers 2007).

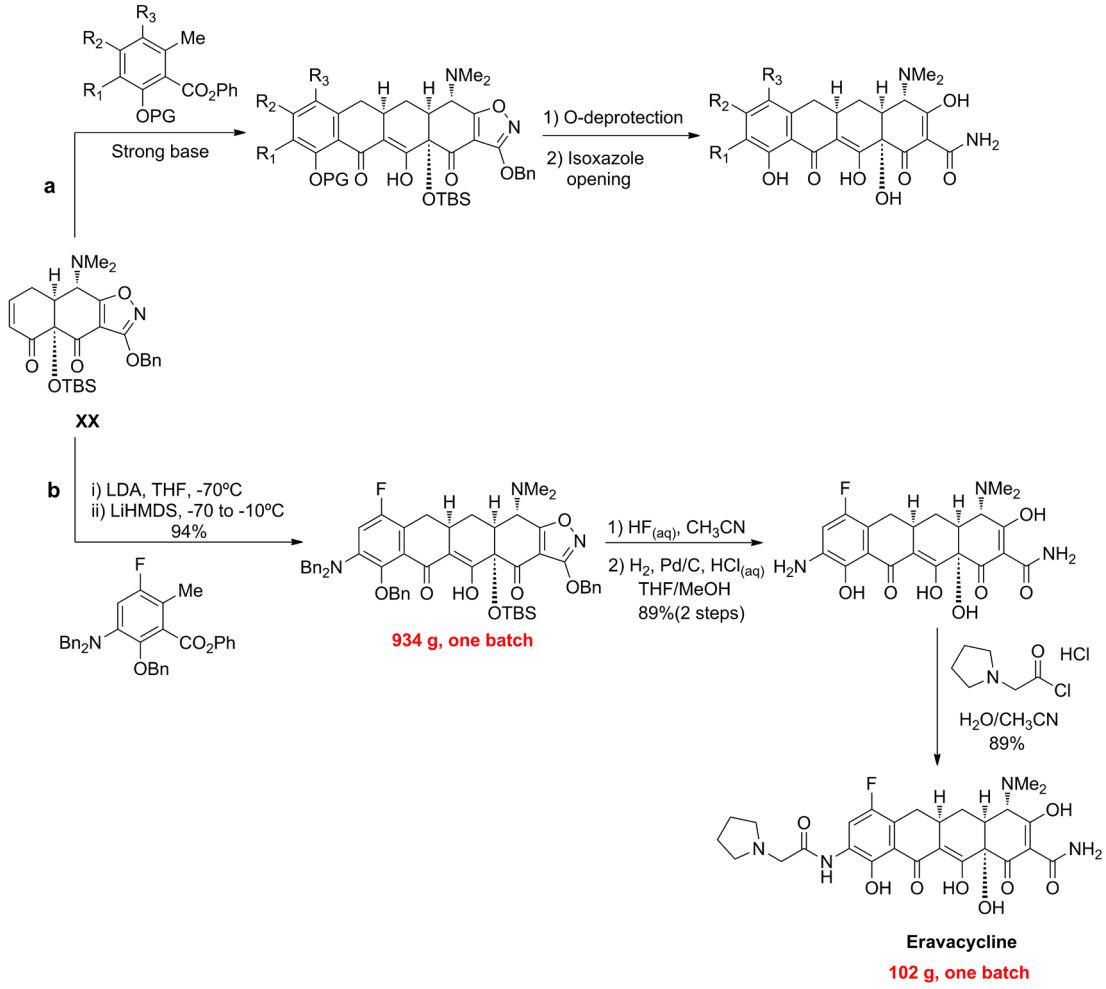


Figure 44 - a) General approach for the synthesis of new tetracycline derivatives (Kummer et al. 2011); **b**) syntheses of eravacycline (Ronn et al. 2013).

and 4, respectively, and the overall yield increased more than 10 times (13%) (Figure 42).

In some cases, scalability can work as an instrument to enable the discovery of new drug candidates. A good example of this is the synthesis of tetracyclines, another class of compounds with antibiotic properties. As in the case of axinellamines, efforts were directed to improve the synthesis of a template compound that enables the obtainment of tetracycline derivatives in a few steps. In 2005, Myers group demonstrated the obtainment of intermediate in a gram-scale from readily available benzoic acid in 11 steps and 10% overall yield (Charest et al. 2005) (Figure 43). Two years later, the same group published another synthetic approach to the synthesis of the same compound with two steps less, twice the yield and amenable to multigram production (Brubaker and Myers 2007).

A third and fourth generation syntheses were also developed but the number of steps, yield or production capacity were not so different from the second one. The advantages for these new-generation routes are: i) all synthetic intermediates are crystalline or solid, avoiding the need of chromatographic purification; and ii) the fourth route is more amenable to structural modification. The general approach to new tetracycline derivatives involves Michael-Dieckmann reaction

of the template compound with a benzylic anion of a left-hand piece (LHP), followed by oxygen deprotection and isoxazole opening (Figure 44a) (Kummer et al. 2011). Using this strategy, Tetraphase Pharmaceuticals team was able to produce the first fully synthetic tetracycline antibiotic under clinical development, named eravacycline, which was produced in more than 100 g in one batch (Ronn et al. 2013) (Figure 44b).

The quest to develop more efficient antibiotics in order to fight back resistance by pathogenic microorganisms led Myers and coworkers to devise a synthetic plataform, which employs simple building blocks (commercially available or prepared in few steps in gram quantities) and a highly convergent assembly process through which a collection of more than 300 structurally diverse 14- and 15-membered macrolide antibiotic candidates were prepared, including some novel scaffolds, thus enabling investigation of diverse macrolides that exhibit potent activities against bacterial strains resistant to erythromycin, azithromycin and other currently prescribed antibiotics.

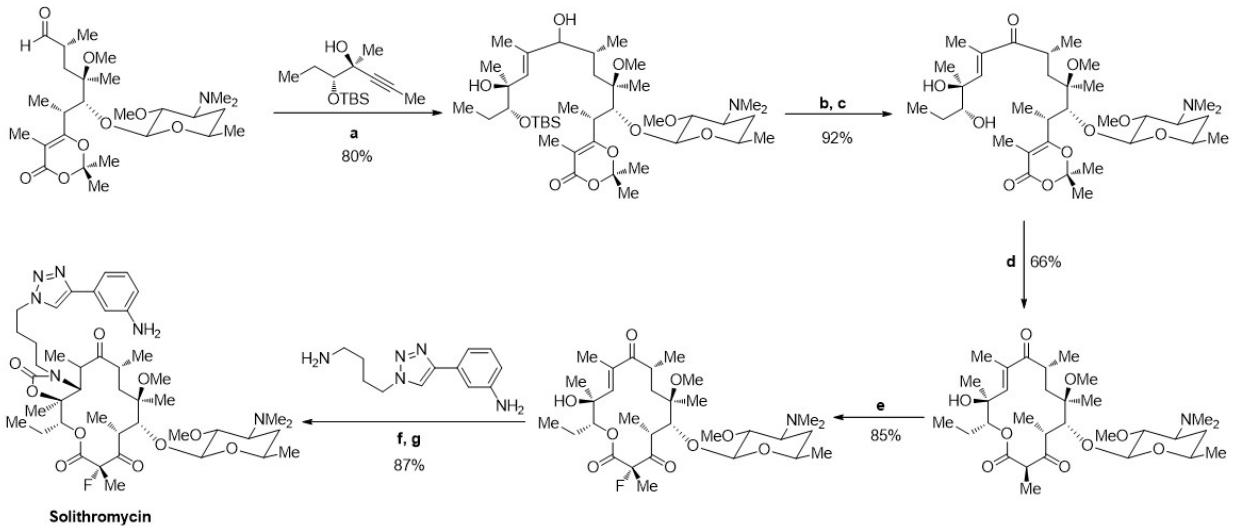
This approach is illustrated by the total synthesis of Solithromycin, a next-generation oral and intravenous fluoro 14-membered macrolide which is in Phase 3 clinical trials for the treatment of bacterial pneumonia and urethritis (Seiple et al. 2016) (Figure 44).

In collaboration with LEO Pharma, Baran's group has recently reported a scalable synthesis of (−)-Thapsigargin, a highly complex natural product that works as a potent inhibitor of the SERCA-pump protein, which makes it suitable for application in several medical areas (Chu et al. 2017). In a previous report, (−)-Thapsigargin was synthesized in 42 steps (Ball et al. 2007). In the new approach, the compound was obtained in only 11 steps (Figure 46). It is important to mention that (−)-Thapsigargin itself was not obtained in a gram-scale due to safety reasons, once this compound is highly toxic. The gram-scale endpoint is a highly advanced intermediate that allows rapid obtainment of (−)-Thapsigargin or any other derivative that can be used in structure-activity relationship (SAR) studies.

In Brazil, most of the concerning about scalability relies inside industrial environment. Part of the synthetic community has started to embrace the importance of this concept due to the popularization of continuous-flow reactors and its advantages over conventional batch apparatus, among which the scaling up of chemical synthesis under safe conditions is a highlight.

De Oliveira and coworkers have reported a safer, scalable and more efficient synthesis of *meso*-substituted porphyrin derivatives under continuous-flow conditions (Momo et al. 2015) (Figure 47). The compounds were produced with yields beyond those obtained for batch reactors in a gram scale.

In 2015, Brocksom and Ley reported the development of a deca-gram ring expansion of (*R*)-(−)-carvone to a seven-membered ring derivative that might serve as the structural core for the synthesis of guaiane sesquiterpenes, terpenoid alkaloids and other related compounds (Alves et al. 2015). The first step in the synthesis, the Corey–Chaykovsky epoxidation of (*R*)-(−)-carvone, was first devised in batch conditions reaching 95% yield and capable of delivering more than 23 g of crude product with satisfactory purity. In flow conditions, the same yield was found as well as high productivity and easiness of operation at larger scales. The next steps were all conduct in batch apparatus at large scales. 8.1 g of the final cycloheptenone (41% overall yield) was obtained from 18.0 g of (*R*)-(−)-carvone in four steps with minimal necessity of chromatography purification (Figure 48).



Conditions: **a**) Cp_2TiCl_2, cyclopentylmagnesium bromide, 80%; **b**) Dess–Martin periodinane, **c**) Bu_4NF; **d**) 132 °C, 0.5 mM, PhCl; **e**) KOtBu, $FN(SO_2Ph)_2$; **f**) Im_2CO, DBU; **g**) imidazole hydrochloride, 60°C.

Figure 45 - Total synthesis of solithromycin (Seiple et al. 2016).

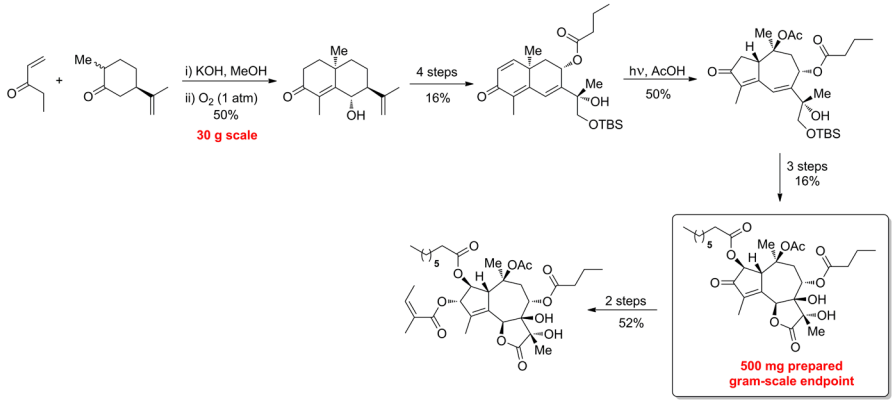
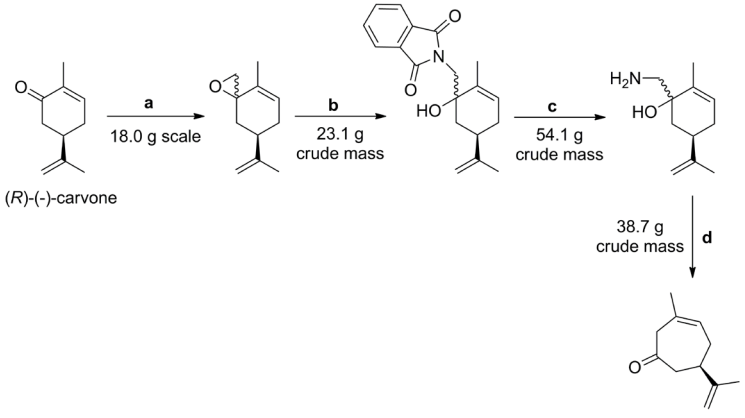


Figure 46 - Synthesis of (−)-Thapsigargin devised by Baran's group (Chu et al. 2017).



Reagents and conditions: **a**) $Me3S^+I^-$, *n*-BuLi, DMSO-THF, 90–95%, **b**) K-phthalimide, phthalimide, DMF, 155–160 °C, 3 h, **c**) $NH_2NH_2{\cdot}H_2O$, EtOH, 80–85 °C, 2 h, 64% for 2 steps **d**) $NaNO_2$ 1.25 M, AcOH 10% (v/v), 0–4 °C, 4 h, 35–71%.

Figure 48 - Deca-gram ring expansion of (*R*)-(−)-carvone reported by Brocksom and Ley (Alves et al. 2015).

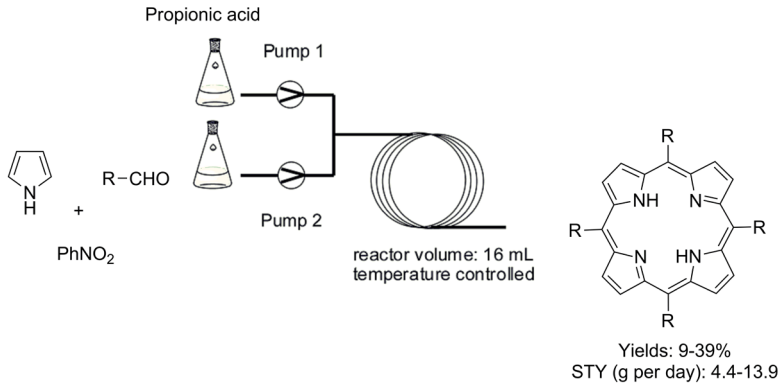


Figure 47 - Scalable synthesis of porphyrins under continuous-flow conditions reported by de Oliveira and coworkers (Momo et al. 2015).

Figure 49 - Sulfenylation and selenylation of lithium enolates of esters (Brocksom et al. 1974).

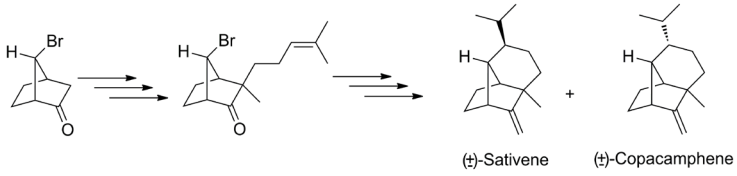


Figure 50 - Bakuzis total syntheses of (±)-sativene and (±)-copacamphene (Bakuzis et al. 1976).

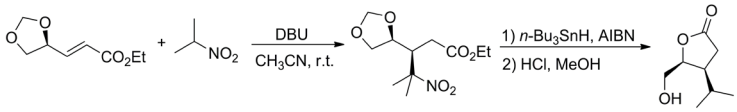


Figure 51 - Stereoselective Michael addition of nitrocompounds to enoates according to Costa and coworkers.

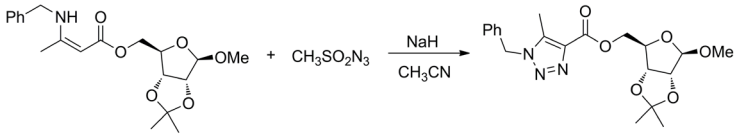


Figure 52 - Sinthesis of 1-benzyl-1*H*-1,2,3-triazoles according to Ferreira and coworkers (da Silva et al. 2009).

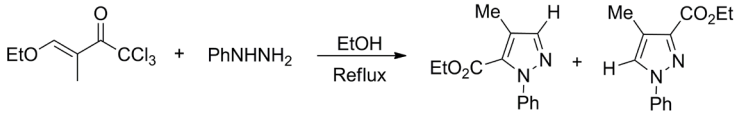


Figure 53 - Preparation of ethoxycarbonyl pyrazoles by Martins and coworkers (Martins et al. 1995).

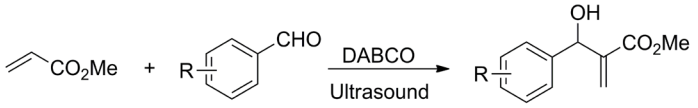


Figure 54 - Baylis-Hilmann reaction promoted by ultrasound irradiation, according to Coelho and coworkers (Coelho et al. 2002).

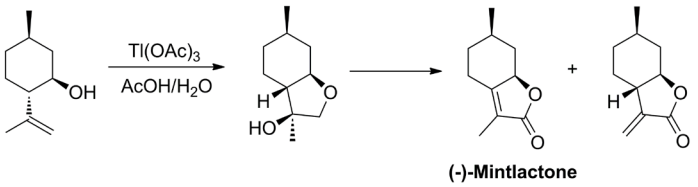


Figure 55 - Ferraz's total synthesis of (-)-mintlactone (Ferraz et al. 2000).

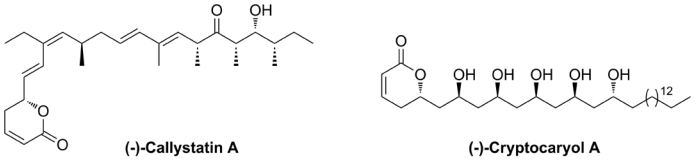


Figure 56 - Some of the natural products prepared by Dias and coworkers using stereoselective boron aldol reactions (Dias and Meira 2005, Dias et al. 2015).

METHODOLOGICAL STUDIES AND TOTAL SYNTHESIS

Since the work of Brocksom and Petragnani on the alkylation of lithium enolates of esters with electrophiles, including diphenyldisulfide and phenylselenelyl bromide, in the mid-1970's (Brocksom et al. 1974) (Figure 49), and the pioneer total synthesis of sativene and copacamphene via a radical cyclization by Bakuzis (Bakuzis et al. 1976) (Figure 50), the area of synthetic methodology in Brazil has grown steadly over the last five decades.

Petragnani and Comasseto have enlarged the field of organoselenium and organotellurium chemistry and have trained generations of organic chemistry dedicated to this area, some of them already mentioned in previous sections (Comasseto et al. 1997).

The contributions by Kascheres on the reactivity of strained cyclopropenones and cyclopropenimines (Kascheres and Rodriges 1975) and by Kover on the rearrangement of terpenoids (Pinto et al. 1988) also underpinned the training and inspired generations of chemists many of them still active in the field.

The frontiers of organic chemistry in Brazil have expanded since then and several groups have established themselves around the country, spreading areas of competence all over the topics of major research interests in the decades after the seminal work of the pioneer groups. Groups dedicated to methodological studies (several of them previously mentioned) and to the total synthesis of natural and biologically active compounds, including active pharmaceutical ingredients, achieved international status.

Costa and coworkers reported on the *syn*-selective Michael addition of a series of substituted primary and secondary nitromethane derivatives to chiral enoates in the presence of TBAF.3H_2O or DBU (Costa et al. 1997) (Figure 51).

Ferreira and coworkers described the synthesis of several 1-benzyl-1*H*-1,2,3-triazoles attached to different carbohydrate templates and their *in vitro* inhibitory profile against HIV-1 reverse transcriptase. The syntheses of these compounds were performed by diazo group transfering to enamines (da Silva et al. 2009) (Figure 52).

Martins and coworkers reported a one-pot synthesis of ethoxycarbonyl pyrazoles by the cyclocondensation of β-alkoxyvinyl trichloromethyl ketones with hydrazine hydrochloride under milder conditions (Martins et al 1995) (Figure 53).

Coelho and coworkers have extended the scope of the Baylis-Hillman reaction including the utilization of ultrasound radiation to promote the reaction of several aromatic and aliphatic aldehydes and different α,β-unsaturated eletrophiles and have shown that DABCO was much more effective for catalyzing a Baylis-Hillman reaction under the influence of ultrasound irradiation (Coelho et al. 2002) (Figure 54). Studies on the mechanism of the of the Baylis-Hilmann reaction by ESI-MS were also reported (Santos et al. 2004) and have applied this methodology to the diastereoselective synthesis of styryl lactones (Paioti and Coelho 2011).

Several Brazilian laboratories have contributed to the development of synthetic methodologies and have demonstrated their application of the total syntheses of natural products and/or pharmaceutical ingredients.

As mentioned previously, Constantino and coworkers described a highly regioselective and stereoselective one-step synthesis of eremophilanes and bakkanes through a niobium catalyzed Diels-Alder reaction which was applied to the total synthesis of bakkenolide A (Constantino et al. 2006), while Ferraz and coworkers described the synthesis of (-)-mintlactone employing thallium triacetate (TTA)-mediated cyclization of (-)-isopulegol (Ferraz et al. 2000) (Figure 55).

Dias and coworkers have employed stereoselective boron aldol reactions as the key methodology for the total syntheses of several natural products such as callystatin A (Dias and Meira 2005), among others, and have demonstrated the 1,5-*anti* stereocontrol on the boron aldol reaction of β-alkoxy methyl ketones with aldehydes (Dias et al. 2002, Dias and Aguilar 2008) which was applied to the total synthesis of natural products, such as (-)-cryptocaryol A (Dias et al. 2015), and the pharmaceutical ingredient Atorvastatin^{R} calcium salt (Dias et al. 2016) (Figure 56).

The reaction of *N*-acyliminium ions with a variety of soft nucleophiles have allowed Pilli and coworkers to contribute for the total syntheses of representatives of the pyrrolizidine, indolizidine and quinolizidine alkaloid families, as well as their application to the asymmetric synthesis of pharmaceutical ingredients such as levobupicaine and methyl phenidate, among others, in optically pure forms (Pilli and Russowksy 1996, Pilli et al. 1995, Klitzke 2001, Santos and Pilli 2003) (Figure 57).

A promising future for the area of synthetic methodologies applied to organic molecules seems to be warranted as a new generation of experimentalists starts to offer their contributions

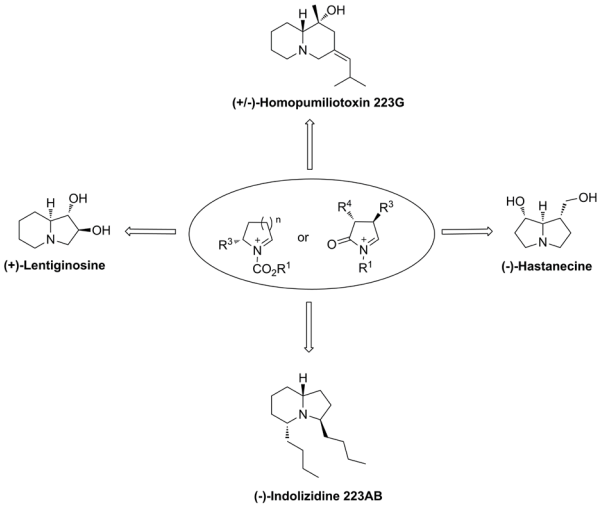


Figure 57 - Some representative pyrrolizidine, indolizidine and quinolizidine alkaloids prepared by Pilli and coworkers (Pilli and Russowksy 1996, Pilli et al. 1995, Klitzke 2001, Santos and Pilli 2003).

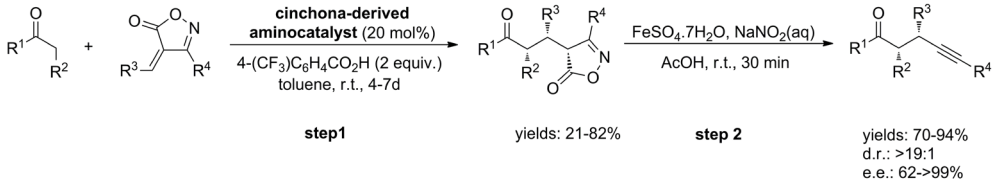


Figure 58 - Stereoselective synthesis of β-alkynylketones using alkylidene isoxazol-5-ones (Jurberg 2017).

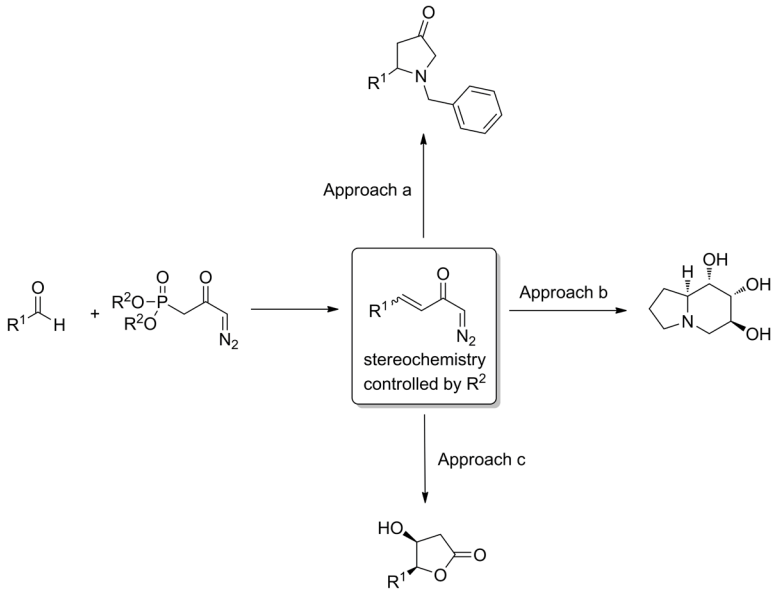


Figure 59 - Contributions from Burtoloso's research group to the chemistry of diazoketones (Pinho and Burtoloso 2011, Bernardim et al. 2012, Talero and Burtoloso 2017).

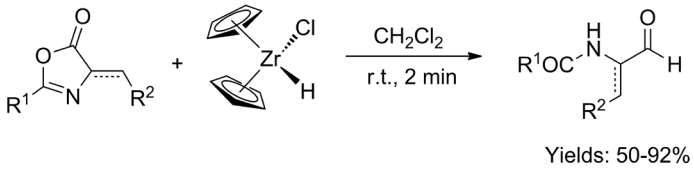


Figure 60 - Chemoselective reduction of azlactones using Schwartz's reagent reported by Amarante (Pinheiro et al. 2017).

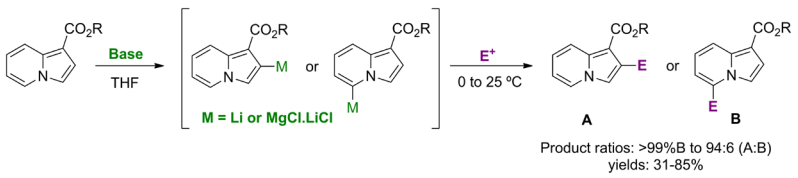


Figure 61 - Regioselective metalation/functionalization of 1-ester-substituted indolizines reported by Clososki (Amaral et al. 2015).

to the field bringing novel concepts, ideas, and approaches to secure progress in the area.

Jurberg group has explored the use of alkylidene isoxazol-5-ones for the functionalization of carbonyl compounds, followed by downstream structure diversification. In a recent work, the group described a two-step reaction sequence for the asymmetric formal α-propargylation of ketones (Jurberg 2017a) (Figure 58). Other examples of the utility of isoxazol-5-ones have been reported by the group and includes the synthesis of substituted pyridines (Stivanin et al. 2017) and 2,3-dihydro-6H-1,3-oxazin-6-ones (Jurberg and Davies 2017b).

Contributions to the chemistry of diazoketones have been made by Burtoloso and coworkers. In 2011, the group reported a new method for the preparation of α,β-unsaturated diazoketones from aldehydes and a Horner-Wadsworth-Emmons reagent. This new strategy was applied to the synthesis of important nitrogen heterocycles such as pyrrolidinones (Pinho and Burtoloso 2011) (Figure 59, approach a) and piperidines (Rosset and Burtoloso 2013) used by the pharmaceutical industry, as well as alkaloid natural products (Bernardim et al. 2012) (Figure 59, approach b). More recently, the group has reported the Sharpless asymmetric dihydroxylation of α,β-unsaturated diazoketones as a new approach for the obtainment of disubstituted furanones (Talero and Burtoloso 2017) (Figure 59, approach c).

Other examples of synthetically useful methodologies came from the Amarante's research group as they have recently reported a highly chemoselective addition of Schwartz's reagent to azalactones as a method for the preparation of challenged functionalized α-amino aldehydes in a 2-minute reaction time (Pinheiro et al. 2017) (Figure 60).

Other important contributions from this group include a catalyst free decarboxylative trichloromethylation of aldimines (Ávila et al. 2016) and an innovative method that uses DMSO as the methylsulfenylation agent of electrophilic carbon atoms (Pereira et al. 2017).

In the field of organometallic chemistry, Clososki's group has reported some interesting methodologies such as the control of regioselectivity in the metalation of 1-ester-substituted indolizines by appropriate choice of base and electrophile (Amaral et al. 2015) (Figure 61).

The use of mixed lithium-magnesium organometallic species have also been reported by the same group (Nishimura et al. 2013, Batista et al. 2015).

Lüdtke's group has reported interesting transformations involving organozinc species such as the influence of substrate structure on the stereochemical outcome of the addition of arylzinc reagents to α-amino aldehydes (Martins and Lüdtke 2014, Martins et al. 2017) (Figure 62a). The same group has also published interesting work regarding the *in situ* generation of lithium selenocarboxylates and its reaction with sugar azides (Silva et al. 2016) (Figure 62b).

In the field of chalcogen chemistry, Menezes and Freitas have demonstrated how these elements can be applied in the synthesis of (*Z*)-1,3-enynes pseudoglycosides (Dantas et al. 2016) (Figure 63). The same group, in collaboration with Oliveira, has recently reported two simple and efficient methods for the synthesis of sulfinate esters and thiosulfonates from sodium salts of sulfinic acids (Tranquilino et al. 2017).

As important as metals and chalcogens, the synthetic utility of hypervalent iodine also attracted the interest of da Silva Junior and coworkers. His group reported on this topic on several occasions and one of the most recent and relevant contribution to the field was a new method for the electrophilic α-alkynylation of ketones using hypervalent iodine (Utaka et al. 2014) (Figure 64). Other important contributions involve new protocols for synthetic useful transformations (Ahmad et al. 2013) and the application of hypervalent iodine based

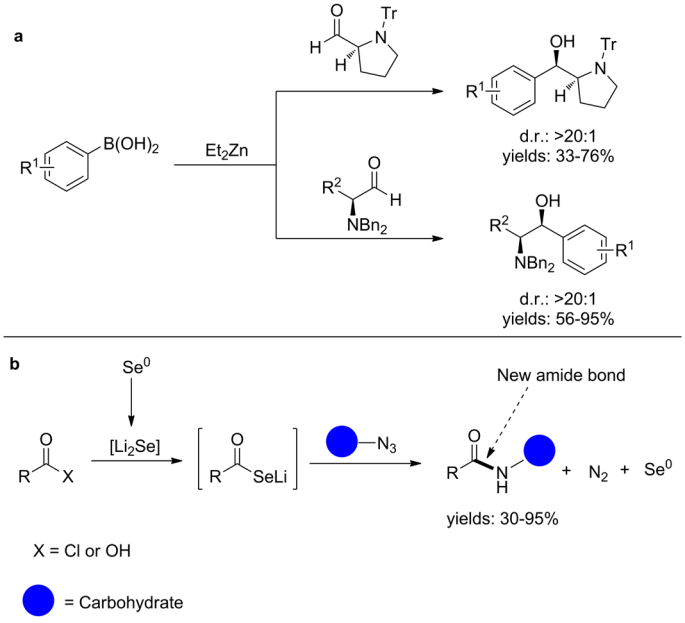


Figure 62 - Addition of arylzinc reagents to aldehydes (**a**) and synthesis of glycosyl amides using *in situ* generated lithium selenocarboxylates (**b**) reported by Lüdtke (Martins and Lüdtke 2014, Martins et al. 2017, Silva et al. 2016).

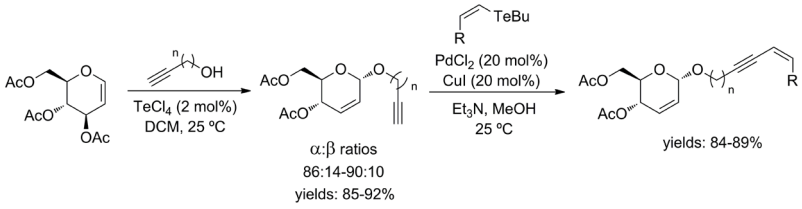


Figure 63 - Addition of (*Z*)-1,3-enynes pseudoglycosides reported by Menezes (Dantas et al. 2016).

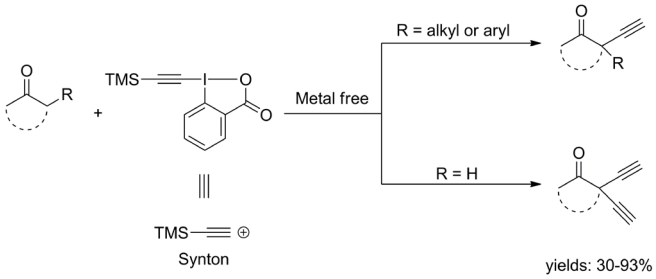


Figure 64 - Electrophilic α-alkynylation of ketones reported by da Silva Jr (Utaka et al. 2014).

methodologies in the synthesis of pharmaceutical ingredients (Silva Jr et al. 2007).

Reports on green chemistry methodologies appeared as the result of collaborative work of Raminelli's and Pizzuti's groups mainly focusing on the use of ultrasound and environmentally friendly solvents. A recent example involve the iodination of aromatic and heteroaromatic compounds (Ferreira et al. 2014) (Figure 65), synthesis of 5-(3,3,3-trifluoro-2-oxopropylidene)pyrrolidin-2-ones (Franco et al. 2015) and 3-(thiophen-2-yl)-4,5-dihydro-1H-pyrazole-1-carboximidamides (dos Santos et al. 2016).

N. da Silva Júnior, in collaboration with J. F. Bower, University of Bristol, UK, have reported a Rh catalyzed activation of 1,4-benzoquinones toward reaction with electrophiles. C−H iodination, bromination, and phenylselenylation were achieved (Jardim et al. 2016a) (Figure 66). This was the first method that can achieve direct C−H phenylselenylation of this compound class. This methodology was further extended for naphthoquinones derivatization (Jardim et al. 2016b).

Other researchers like de Andrade and Paixão have also contributed to the development of novel useful synthetic methods. We will just provide a few more references for the readers (Andrade and Azevedo 2001, Barreto et al. 2016, de la Torre et al. 2016) since other reports have been outlined in the previous sections.

Recently, Andrade and coworkers reported on the tandem radical addition/cyclization employing $FeSO_4.7H_2O$ as catalyst to prepare oxindoles (Correia et al. 2017) (Figure 67).

CONCLUSIONS

Chemistry, in general, and synthetic organic chemistry, in particular, have been highly successful in the 20th century offering novel and on-demand solutions to society which depends on the products of the chemical industry to maintain its current standard of living and improve quality of life.

At the same time, public awareness of the hazardous substances that are present in many chemical processes led society to question some of the benefits offered by the chemical enterprise.

Although the output of the academic research can not be regulated, we can strive in the years to come to ensure that high standard chemical research will continue to produce cutting-edge scientific knowledge and to serve humankind even better.

This is to imply that we may expect to see an even greater flow of results on the production of chemicals from renewable resources, the use of greener solvents and catalytic processes that will turn out environmentally cleaner chemical processes, enhancing atom utilization, securing the replacement of over-stoichiometric and hazardous reagents and the implementation of automated processes as an enabling technology.

Some research topics such as regio- and stereoselective C-H activation, catalytic oxidation using air as the oxidizing agent, milder and less energy demanding hydrogenation protocols, particularly its asymmetric version, the use of bi- and even triphasic processes in order to facilitate the workup of the reaction and the implementation of cascade processes to increase complexity in one-pot transformations are expected to receive increasing attention.

The current Brazilian scenario reveals a promising future for the chemical sciences as a well trained and talented young generation of chemists have come to play over the last decades. Several of these groups have perceived the importance of contributing to promising areas such as green chemistry, catalysis and, more recently, to automation of chemical processes, as well to push forward the limits of synthetic methodologies.

It is clear from the selected information collected in this overview that the area of scalability is not yet included in the academic research

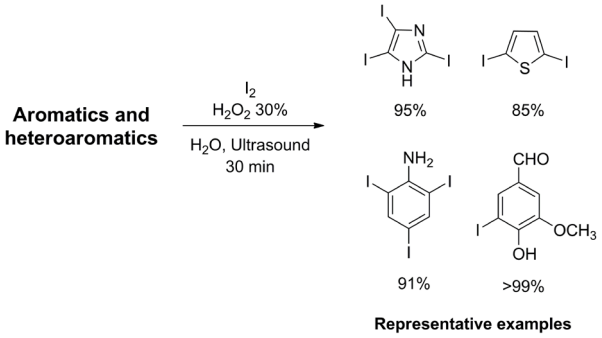


Figure 65 - Iodination of aromatics and heteroaromatics promoted by ultrasound in water reported by Raminelli and Pizzuti (Ferreira et al. 2014).

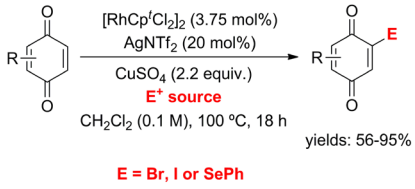


Figure 66 - Rh catalyzed C−H iodination, bromination, and phenylselenation of 1,4-benzoquinones reported by N. da Silva Júnior and Bower (Jardim et al. 2016a).

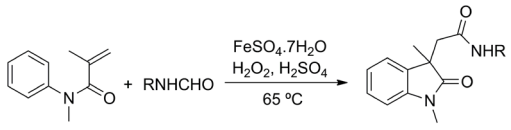


Figure 67 - Preparation of oxindoles reported reported by Andrade (Correia et al. 2017).

agenda. As the full potential of the chemical sciences will only be realized if novel knowledge translates to some extent into industrial processes, it is imperative integration of the academic and industrial research agendas.

Out of the promising areas covered in this overview, catalysis, green chemistry and methodology development at large, stand out as the more productive ones but in the years to come academic and industrial laboratory have to share their expertises if the promise these areas hold is to be realized. Less risky and less innovative research ("me-too" research proposals) should give room to innovative and cutting-edge ideas that have the potential of a tranformative impact on the output of the chemical enterprise. The same rational applies to automation and scalability of chemical process in academic research.

Needless to say, for harvesting the expected fruits of a more articulated research agenda, a continuous and reliable flow of funding and a world-class peer reviewing and assessment of results have to prevail in the Brazilian scenario.

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REFERENCES

AHMAD A, SCARASSATI P, JALALIAN N, OLOFSSON B AND SILVA JR LF. 2013. Oxidative rearrangement of alkenes using *in situ* generated hypervalent iodine(III) Tetrahedron Lett 54: 5818-5820.

ALVES D, SANTOS CG, PAIXÃO MW, SOARES LC, DE SOUZA D, RODRIGUES OED AND BRAGA AL. 2009. CuO nanoparticles: an efficient and recyclable catalyst for cross-coupling reactions of organic diselenides with aryl boronic acids. Tetrahedron Lett 50: 6635-6638.

ALVES LC, DESIDERÁ AL, DE OLIVEIRA KT, NEWTON S, LEY SV AND BROCKSOM TJ. 2015. A practical decagram scale ring expansion of (R)-(−)-carvone to (R)-(+)-3-methyl-6-isopropenyl-cyclohept-3-enone-1. Org Biomol Chem 13: 7633-7642.

AMARAL MFZJ, BAUMGARTNER AA, VESSECCHI R AND CLOSOSKI GC. 2015. Directed metalation of 1-ester-substituted indolizines: base/electrophile-controlled regioselective functionalization. Org Lett 17: 238-241.

ANDRADE CKZ AND ALVES LM. 2005. Environmentally Benign Solvents in Organic Synthesis: Current Topics. Curr Org Chem 9: 195-218.

ANDRADE CKZ AND AZEVEDO NR. 2001. Niobium(V) chloride-mediated allylation of aldehydes. Scope and stereoselectivity. Tetrahedron Lett 42: 6473-6476.

ANDRADE CKZ AND DAR AR. 2016. Applying green processes and techniques to simplify reaction work-ups. Tetrahedron 72: 7375-7391.

ANDRADE CKZ, TAKADA SCS, ALVES LM, RODRIGUES JP, SUAREZ PAZ, BRANDÃO RF AND SOARES VCD. 2004. Molecular sieves in ionic liquids as an efficient and recyclable medium for the synthesis of imines. Synlett: 2135-2138.

ANDRADE LH, SOUSA BA AND JAMISON TF. 2016. Confining a biocatalyst for highly efficient and selective synthesis of carboxamide derivatives under continuous-flow conditions. J Flow Chem 6: 67-72.

ANELLI L, BIFFI C, MONTANARI F AND QUICI S. 1987. Fast and selective oxidation of primary alcohols to aldehydes or to carboxylic acids and of secondary alcohols to ketones mediated by oxoammonium salts under two-phase conditions. J Org Chem 52: 2559-2562.

ANGELICI G, CORRÊA RJ, GARDEN SJ AND TOMASINI C. 2009. Water influences the enantioselectivity in the proline or prolinamide-catalyzed aldol addition of acetone to isatins. Tetrahedron Lett 50: 814-817.

ANGNES RA, LI Z, CORREIA CRD AND HAMMOND GB. 2015. Recent synthetic additions to the visible light photoredox catalysis toolbox. Org Biomol Chem 13: 9152-9167.

ARANDA DAG, GONÇALVES JA, PERES JS, RAMOS ALD, DE MELO CAR, ANTUNES OAC, FURTADO NC AND TAFT CA. 2009. The use of acids, niobium oxide, and zeolite catalysts for esterification reactions. J Phys Org Chem 22: 709-716.

AUSTAD BC ET AL. 2013a. Commercial manufacture of Halaven®: chemoselective transformations en route to structurally complex macrocyclic ketones. Synlett: 333-337.

AUSTAD BC ET AL. 2013b. Process development of Halaven®: synthesis of the C14–C35 fragment via Iterative Nozaki–Hiyama–Kishi Reaction–Williamson Ether Cyclization. Synlett, p. 327-332.

ÁVILA EP, DE SOUZA IF, OLIVEIRA AVB, KARTNALLER V, CAJAIBA J, DE SOUZA ROMA, CORRÊA CC AND AMARANTE GW. 2016. Catalyst free decarboxylative trichloromethylation of aldimines. RSC Adv 6: 108530-108537.

BAKUZIS P, CAMPOS OOS AND BAKUZIS MLF. 1976. Total synthesis of sativene and copacamphene via a free radical cyclization. J Org Chem 41: 3261-3264.

BALL M, ANDREWS SP, WIERSCHEM F, CLEATOR E, SMITH MD AND LEY SV. 2007. Total Synthesis of Thapsigargin, a Potent SERCA Pump Inhibitor. Org Lett 9: 663-666.

BARBOSA SL, DABDOUB MJ, HURTADO GR, KLEIN SI, BARONI ACM AND CUNHA C. 2006. Solvent free esterification reactions using Lewis acids in solid phase catalysis. Appl Catal A: General 313: 146-150.

BARRETO AFS, DOS SANTOS VA AND ANDRADE CKZ. 2016. Synthesis of acylhydrazino-peptomers, a new class of peptidomimetics, by consecutive Ugi and and hydrazino-Ugi reactions. Beilstein J Org Chem 12: 2865-2872.

BATISTA JHC, DOS SANTOS FM, BOZZINI LA, VESSECCHI R, OLIVEIRA ARM AND CLOSOSKI GC. 2015. Directed functionalization of halophenyl-2-oxazolines with TMPMgCl·LiCl. Eur J Org Chem 5: 967-977.

BERGER A, DE SOUZA RF, DELGADO MR AND DUPONT J. 2001. Ionic liquid-phase asymmetric catalytic hydrogenation: hydrogen concentration effects on enantioselectivity. Tetrahedron-Asymmetry 12: 1825-1828.

BERGONZINI G, SCHINDLER CS, WALLENTIN C-J, JACOBSEN EM AND STEPHENSON CRJ. 2014. Photoredox activation and anion binding catalysis in the dual catalytic enantioselective synthesis of bamino esters. Chem Sci 5: 112-116.

BERNARDIM B, PINHO VD AND BURTOLOSO ACB. 2012. α,β-Unsaturated diazoketones as platforms in the asymmetric synthesis of hydroxylated alkaloids. Total synthesis of 1-deoxy-8,8a-diepicastanospermine and 1,6-dideoxyepicastanospermine and formal synthesis of pumiliotoxin 251D. J Org Chem 77: 9926-9931.

BIEBER LW AND DA SILVA MF. 2004. Mild and efficient synthesis of propargylamines by copper-catalyzed Mannich reaction. Tetrahedron Lett 45: 8281-8283.

BIEBER LW, DA SILVA MF, DA COSTA RC AND SILVA LOS. 1998. Zinc barbier reaction of propargyl halides in water. Tetrahedron Lett 39: 3655-3658.

BLAKE JF ET AL. 2013. Serine/threonine kinase inhibitors. WO2013130976A1.

BRAGA AL, LÜTDKE DS, SCHNEIDER PH, VARGAS F, SCHNEIDER A, WESSJOHANN LA AND PAIXÃO MW. 2005. Catalytic enantioselective aryl transfer: asymmetric addition of boronic acids to aldehydes using pyrrolidinylmethanols as ligands. Tetrahedron Lett 46: 7827-7830.

BRAGA AL, LÜDTKE DS, VARGAS F AND BRAGA RC. 2006. Catalytic applications of chiral organoselenium compounds in asymmetric synthesis. Synlett, p. 1453-1466.

BRAGA AL, RUBIM RM, SCHREKKER HS, WESSJOHANN LS, DE BOLSTER MWG, ZENI G AND SEHNEM JA. 2003. The facile synthesis of chiral oxazoline catalysts for the diethylzinc addition to aldehydes. Tetrahedron: Asymmetry 14: 3291-3295.

BROCKSOM TJ, DESIDERÁ AL, DE CARVALHO ALVES L AND DE OLIVEIRA KT. 2015. The new directions of organic synthesis. Curr Org Synth 12: 496-522.

BROCKSOM TJ, PETRAGNANI N AND RODRIGUES R. 1974. Ester enolates. New preparation of malonates, phosphonoacetates, and .alpha.-selenyl and sulfinyl esters. J Org Chem 39: 2114-2116.

BRUBAKER JD AND MYERS AG. 2007. A practical, enantioselective synthetic route to a key precursor to the tetracycline antibiotics. Org Lett 9: 3523-3525.

BRÜCKL T, BAXTER RD, ISHIHARA Y AND BARAN PS. 2012. Innate and guided C–H functionalization logic. Acc Chem Res 45: 826-839.

BRUSS AJ, GELESKY MA, MACHADO G AND DUPONT J. 2006. Rh(0) nanoparticles as catalyst precursors for the solventless hydroformylation of olefins. J Mol Catal A-Chem 252: 212-218.

BUFFIN BP, BELITZ NL AND VERBEKE SL. 2008. Electronic, steric, and temperature effects in the Pd(II)-biquinoline catalyzed aerobic oxidation of benzylic alcohols in water. J Mol Catal A: Chem 284: 149-154.

CARMONA-VARGAS CC, ALVES LC, BROCKSOM TJ AND DE OLIVEIRA KT. 2017. Combining batch and continuous flow setups in the end-to-end synthesis of naturally occurring curcuminoids. React Chem Eng 2: 366-374.

CELLA R, CUNHA RLOR, REIS AES, PIMENTA DC, KLITZKE CF AND STEFANI HA. 2006. Suzuki−Miyaura cross-coupling reactions of aryl tellurides with potassium aryltrifluoroborate salts. J Org Chem 71: 244-150.

CELLA R AND STEFANI HA. 2006. Ultrasound-assisted synthesis of Z and E stilbenes by Suzuki cross-coupling reactions of organotellurides with potassium organotrifluoroborate salts. Tetrahedron 62: 5656-5662.

CHAREST MG, LERNER CD, BRUBAKER JD, SIEGEL DR AND MYERS AG. 2005. A convergent enantioselective route to structurally diverse 6-deoxytetracycline antibiotics. Science 308: 395-398.

CHASE CE, FANG FG, LEWIS BM, WILKIE GD, SCHNADERBECK MJ AND ZHU X. 2013. Process development of Halaven®: synthesis of the C1–C13 fragment from d-(–)-gulono-1,4-lactone. Synlett, p. 323-326.

CHATTERJEE I, BASTIDA D AND MELCHIORRE P. 2013. Vinylogous Organocatalytic Triple Cascade Reaction: Forging Six Stereocenters in Complex Spiro-Oxindolic Cyclohexanes. Adv Synth Catal 355: 3124-3130.

CHEN MS AND WHITE MC. 2007. A predictably selective aliphatic C-H oxidation reaction for complex molecule synthesis. Science 318: 783-787.

CHENA LS, MANTOVANI SM, DE OLIVEIRA LG, DUARTE MCT AND MARSAIOLI AJ. 2008. 1,2-Octanediol deracemization by stereoinversion using whole cells. J Mol Catal B-Enzym 54: 50-54.

CHU H, SMITH JM, FELDING J AND BARAN PS. 2017. Scalable synthesis of (−)-thapsigargin. ACS Cent Sci 3: 47-51.

COELHO F, ALMEIDA WP, VERONESE D, MATEUS CR, LOPES ECS, ROSSI RC, SILVEIRA GPC AND PAVAM CH. 2002. Ultrasound in Baylis–Hillman reactions with aliphatic and aromatic aldehydes: scope and limitations. Tetrahedron 58: 7437-7447.

COMASSETO JV. 2010. Selenium and tellurium chemistry: historical background. J Braz Chem Soc 21: 2027-2031.

COMASSETO JV AND BARRIENTOS-ASTIGARRAGA RE. 2000. Add a little tellurium to your synthetic plans. Aldrichimica Acta 33: 66-78.

COMASSETO JV, LING LV, PETRAGNANI N AND STEFANI HA. 1997. Vinylic selenides and tellurides – preparation, reactivity and synthetic applications. Synthesis, p. 373-403.

COMASSETO JV, OMORI AT, PORTO ALM AND ANDRADE LH. 2004. Preparation of chiral organochalcogeno-α-methylbenzyl alcohols via biocatalysis. The role of Daucus carota root. Tetrahedron Lett 45: 473-476.

CONSORTI CS, FLORES FR AND DUPONT J. 2005. Kinetics and mechanistic aspects of the Heck reaction promoted by a CN−palladacycle. J Am Chem Soc 127: 12054-12065.

CONSORTI CS, FLORES FR, ROMINGER F AND DUPONT J. 2006. A simple and efficient copper-free catalytic system based on a palladacycle for the arylation of alkynes. Adv Synth Catal 348: 133-141.

CONSORTI CS, ZANINI ML, LEAL S, EBELING G AND DUPONT J. 2003. Chloropalladated propargyl amine: a highly efficient phosphine-free catalyst precursor for the Heck reaction. Org Lett 5: 983-986.

CONSTANTINO MG, DE OLIVEIRA KT, POLO EC, DA SILVA GVJ AND BROCKSOM TJ. 2006. Core structure of eremophilanes and bakkanes through niobium catalyzed diels−alder reaction: synthesis of (±)-Bakkenolide A. J Org Chem 71: 9880-9883.

CORRÊA AG, ZUIN VG, FERREIRA VF AND VAZQUEZ PG. 2013. Green chemistry in Brazil. Pure App Chem 85: 1643-1653.

CORREIA VG, ABREU JC, BARATA CAE AND ANDRADE LH. 2017. Iron-Catalyzed Synthesis of Oxindoles: Application to the Preparation of Pyrroloindolines Org Lett 19: 1060-1063.

COSTA ICR, SUTILI FK, DA SILVA GVV, LEITE SGF, MIRANDA LSM AND DE SOUZA ROMA. 2014. Lipase catalyzed ascorbyl palmitate synthesis under microwave irradiation. J Mol Catal B-Enzym 102: 127-131.

COSTA JS, DIAS AG, ANHOLETO AL, MONTEIRO MD, PATROCINIO VL AND COSTA PRR. 1997. Syn-selective Michael addition of nitromethane derivatives to enoates derived from (R)-(+)-glyceraldehyde acetonide. J Org Chem 62: 4002-4006.

COSTA NJS, KIYOHARA PK, MONTEIRO AL, COPPEL Y, PHILIPPOT K AND ROSSI LM. 2010. A single-step procedure for the preparation of palladium nanoparticles and a phosphine-functionalized support as catalyst for Suzuki cross-coupling reactions. J Catal 276: 382-389.

CRAMER N. 2012. Teaching enantioselectivity to C–H bond functionalizations: initial steps of a rather long shot. Chimia 66: 869-872.

CUNHA MR, TAVARES MT, CARVALHO CF, SILVA NAT, SOUZA ADF, PEREIRA GJV, FERREIRA FF AND PARISE-FILHO R. 2016. Environmentally safe condition for the synthesis of aryl and alkyl sulfonyl hydrazones via one-pot reaction. ACS Sustainable Chem Eng 4: 1899-1905.

DA SILVA CXA, GONÇALVES VLC AND MOTA CJA. 2009. Water-tolerant zeolite catalyst for the acetalisation of glycerol. Green Chem 11: 38-41.

DA SILVA ED, GONZALEZ WA AND FRAGA MA. 2016. Aqueous-phase oxidation of 5-hydroxymethylfurfural over Pt/ZrO_2 catalysts: exploiting the alkalinity of the reaction medium and catalyst basicity. Green Process Synth 5: 353-364.

DA SILVA FC ET AL. 2009. Synthesis, HIV-RT inhibitory activity and SAR of 1-benzyl-1H-1,2,3-triazole derivatives of carbohydrates. Eur J Med Chem 44: 373-384.

DA SILVA GP, ALI A, DA SILVA RC, JIANG H AND PAIXÃO MW. 2015. Tris(trimethylsilyl)silane and visible-light irradiation: a new metal- and additive-free photochemical process for the synthesis of indoles and oxindoles. Chem Commun 51: 15110-15113.

DA SILVA MJ AND GUSEVSKAYA EV. 2001. Palladium-catalyzed oxidation of monoterpenes: novel tandem oxidative coupling–oxidation of camphene by dioxygen. J Mol Catal A: Chem 176: 23-27.

DANTAS CR, DE FREITAS JJR, BARBOSA QPS, MILITÃO GCG, SILVA TDS, DA SILVA TG, PAULINO AAS, FREITAS JCR, OLIVEIRA RA AND MENEZES PH. 2016. Stereoselective synthesis and antitumoral activity of Z-enyne pseudoglycosides. Org Biomol Chem 14: 6786-6794.

DE ANDRADE A, DOS SANTOS GC AND DA SILVA-FILHO LC. 2015. Synthesis of quinoline derivatives by multicomponent reaction using niobium pentachloride as lewis acid. J Heterocyclic Chem 52: 273-277.

DE FÁTIMA A, KOHN LK, ANTONIO MA, DE CARVALHO JE AND PILLI RA. 2005a. (R)-Goniothalamin: total syntheses and cytotoxic activity against cancer cell lines. Bioorg Med Chem 13: 2927-2933.

DE FÁTIMA A, KOHN LK, ANTONIO MA AND PILLI RA. 2004. Enantioselective syntheses of (R)- and (S)-argentilactone and their cytotoxic activities against cancer cell lines. Bioorg Med Chem 12: 5437-5442.

DE FÁTIMA A, LAPIS AAM AND PILLI RA. 2005b. Concise total synthesis of (R)-fluoxetine, a potent and selective serotonin reuptake inhibitor. J Braz Chem Soc 16: 495-499.

DE FÁTIMA A AND PILLI RA. 2003. Total syntheses of (R)-argentilactone and (R)-goniothalamin via catalytic enantioselective allylation of aldehydes. Tetrahedron Lett 44: 8721-8724.

DE LA TORRE AF, RIVERA DG, CONCEPCIÓN O, ECHEMENDIA R, CORREA AG AND PAIXÃO MW. 2016. Multicomponent synthesis of cyclic depsipeptide mimics by ugi reaction including cyclic hemiacetals derived from asymmetric organocatalysis. J Org Chem 81: 803-809.

DE MIRANDA AS, MIRANDA LSM AND DE SOUZA ROMA. 2013. Ethyl acetate as an acyl donor in the continuous flow kinetic resolution of (±)-1-phenylethylamine catalyzed by lipases. Org Biomol Chem 11: 3332-3336.

DE OLIVEIRA KT, MILLER LZ AND MCQUADE DT. 2016. Exploiting photooxygenations mediated by porphyrinoid photocatalysts under continuous flow conditions. RSC Adv 6: 12717-12725.

DE SAIRRE MI, BRONZE-UHLE ES AND DONATE PM. 2005. Niobium(V) oxide: a new and efficient catalyst for the transesterification of β-keto esters. Tetrahedron Lett 46: 2705-2708.

DE SOUZA ROMA, MATOS LMC, GONÇALVES KM, COSTA ICR, BABICS I, LEITE SGF, OESTREICHER EG AND ANTUNES OAC. 2009. Michael additions of primary and secondary amines to acrylonitrile catalyzed by lipases. Tetrahedron Lett 50: 2017-2018.

DE SOUZA VP, OLIVEIRA CK, DE SOUZA TM, MENEZES PH, ALVES JR S, LONGO RL AND MALVESTITI I. 2016. A green approach for allylations of aldehydes and ketones: combining allylborate, mechanochemistry and lanthanide catalyst. Molecules 21: 153.

DESS DB AND MARTIN JC. 1983. Readily accessible 12-I-5 oxidant for the conversion of primary and secondary alcohols to aldehydes and ketones. J Org Chem 48: 4155-4156.

DIAS LC AND AGUILAR AM. 2008. 1,5-Asymmetric induction in boron-mediated aldol reactions of β-oxygenated methyl ketones. Chem Soc Rev 37: 451-469.

DIAS LC, BAÚ RZ, DE SOUZA MA AND ZUKERMAN-SCHPECTOR J. 2002. High 1,5-anti stereoinduction in boron-mediated aldol reactions of methyl ketones. Org Lett 4: 4325-4327.

DIAS LC, KUROISHI PK AND DE LUCCA EC. 2015. The total synthesis of (−)-cryptocaryol A. Org Biomol Chem 13: 3575-3584.

DIAS LC AND MEIRA PRR. 2005. Total synthesis of the potent antitumor polyketide (−)-callystatin A. J Org Chem 70: 4762-4773.

DIAS LC, VIEIRA AS AND BARREIRO EJ. 2016. The total synthesis of calcium atorvastatin. Org Biomol Chem 14: 2291-2296.

DIJKSMAN A, ARENDS IWCE AND SHELDON RA. 2000. Polymer immobilised TEMPO (PIPO): an efficient catalyst for the chlorinated hydrocarbon solvent-free and bromide-free oxidation of alcohols with hypochlorite. Chem Commun, p. 271-272.

DOMINE ME, MARINAS A AND SHELDON RA. 2015. Biomass valorization into fuels, energy, materials and chemicals (UBIOCHEM-IV). Catal Today 257: 151-153.

DOS SANTOS AA, DA COSTA CE, PRINCIVAL JL AND COMASSETO JV. 2006. Lipase-catalyzed kinetic resolution of (RS)-hydroxy tellurides. Tetrahedron Asymmetry 17: 2252-2259.

DOS SANTOS EFS, CURY NM, DO NASCIMENTO TA, RAMINELLI C, CASAGRANDE GA, PEREIRA CMP, SIMIONATTO E, YUNES JÁ AND PIZZUTI L. 2016. Ultrasound-promoted synthesis of 3-(thiophen-2-yl)-4,5-dihydro-1H-pyrazole-1-carboximidamides and anticancer activity evaluation in leukemia cell lines. J Braz Chem Soc 28: 217-224.

DOS SANTOS MR, CORIOLANO R, GODOI MN, MONTEIRO AL, DE OLIVEIRA HCB, EBERLIN MN AND SILVEIRA NETO BAD. 2014. Phosphine-free Heck reaction: mechanistic insights and catalysis “on water” using a charge-tagged palladium complex. New J Chem 38: 2958-2963.

DUPONT J. 2004. On the solid, liquid and solution structural organization of imidazolium ionic liquids. J Braz Chem Soc 15: 341-350.

DUPONT J. 2011. From molten salts to ionic liquids: a “nano” journey. Acc Chem Res 44: 1223-1231.

DUPONT J, CONSORTI CS AND SPENCER J. 2000. Room temperature molten salts: neoteric “green” solvents for chemical reactions and processes. J Braz Chem Soc 11: 337-344.

DUPONT J, DE SOUZA RF AND SUAREZ PAZ. 2002. Ionic liquid (molten salt) phase organometallic catalysis. Chem Rev 102: 3667-3692.

DUPONT J AND SCHOLTEN JD. 2010. On the structural and surface properties of transition-metal nanoparticles in ionic liquids. Chem Soc Rev 39: 1780-1804.

DUPONT J AND SPENCER J. 2004. On the noninnocent nature of 1,3-dialkylimidazolium ionic liquids. Angew Chem Int Ed 43: 5296-5297.

ECHEMEND R, DE LA TORRE AF, MONTEIRO JL, PILA M, CORRÊA AG, WESTERMANN B, RIVERA DG AND PAIXÃO MW. 2015. Highly stereoselective synthesis of natural-product-like hybrids by an organocatalytic/multicomponent reaction sequence. Angew Chem Int Ed 54: 7621-7625.

EDER U, SAUER G AND WIECHERT R. 1971a. Neuartige asymmetrische cyclisierung zu optisch aktiven steroid-cd-teilstücken. Angew Chem 83: 492-493.

EDER U, SAUER G AND WIECHERT R. 1971b. New type of asymmetric cyclization to optically active steroid cd partial structures. Angew Chem Int Ed Engl 10: 496-497.

EDER U, SAUER G AND WIECHERT R. 1971c. Optically active 1,5-indanone and 1,6-naphthalenedionene. Ger Pat: DE 2014757.

ESMELINDRO MC, OESTREICHER EG, MARQUEZ-ALVAREZ H, DARIVA C, EGUES SMS, FERNANDES C, BORTOLUZZI AJ, DRAGO V AND ANTUNES OAC. 2005. Catalytic oxidation of cyclohexane by a binuclear Fe(III) complex biomimetic to methane monooxygenase. J Inorg Biochem 99: 2054-2061.

ESPELT LR, MCPHERSON IS, WIENSCH EM AND YOON TP. 2015. Enantioselective conjugate additions of α-amino radicals via cooperative photoredox and lewis acid catalysis. J Am Chem Soc 137: 2452-2455.

FERRAZ HMC, GRAZINI MVA, RIBEIRO CMR, BROCKSOM U AND BROCKSOM TJ. 2000. A Short route to (−)-mintlactone by thallium(iii)-mediated cyclization of (−)-isopulegol. J Org Chem 65: 2606-2607.

FERREIRA IM, CASAGRANDE GA, PIZZUTI L AND RAMINELLI C. 2014. Ultrasound-promoted rapid and efficient iodination of aromatic and heteroaromatic compounds in the presence of iodine and hydrogen peroxide in water. Synth Commun 44: 2094-2102.

FEU KS, DEOBALD AM, NARAYANAPERUMAL S, CORRÊA AG AND PAIXÃO MW. 2013. An eco-friendly asymmetric organocatalytic conjugate addition of malonates to α,β-unsaturated aldehydes: application on the synthesis of chiral indoles. Eur J Org Chem: 5917-5922.

FITZPATRICK DE, BATTILOCCHIO C AND LEY SV. 2016. Enabling technologies for the future of chemical synthesis. ACS Cent Sci 2: 131-138.

FOCA CM, DIAS AO, AUGUSTI R, DOS SANTOS EM AND GUSEVSKAYA EV. 2000. Platinum/tin catalyzed hydroformylation of naturally occurring monoterpenes. J Mol Catal A: Chem 152: 15-24.

FOCA CM, DOS SANTOS EM AND GUSEVSKAYA EV. 2002. Diastereoselective hydroformylation of camphene catalyzed by platinum/tin complexes. J Mol Catal A: Chem 185: 17-23.

FONSECA GS, SCHOLTEN JD AND DUPONT J. 2004. Iridium nanoparticles prepared in ionic liquids: an efficient catalytic system for the hydrogenation of ketones. Synlett, p. 1525-1528.

FONSECA GS, UMPIERRE AP, FICHTNER PFP, TEIXEIRA SR AND DUPONT J. 2003. The use of imidazolium ionic liquids for the formation and stabilization of Ir^0 and Rh^0 nanoparticles: efficient catalysts for the hydrogenation of arenes. Chem Eur J 9: 3263-3269.

FRANCO MSF, CASAGRANDE GA, RAMINELLI C, MOURA S, ROSSATTO M, QUINA FH, PEREIRA CMP, FLORES AFC AND PIZZUTI L. 2015. Ultrasound-promoted environmentally friendly synthesis of 5-(3,3,3-trifluoro-2-oxopropylidene)pyrrolidin-2-ones. Synth Commun 45: 692-701.

FURST L, NARAYANAM J AND STEPHENSON C. 2011. Total synthesis of (+)-gliocladin c enabled by visible-light photoredox catalysis. Angew Chem Int Ed 50: 9655-9659.

GAICH T AND BARAN PS. 2010. Aiming for the ideal synthesis. J Org Chem 75: 4657-4673.

GAMEZ P, ARENDS IWCE, REEDIJK J AND SHELDON RA. 2003. Copper(II)-catalysed aerobic oxidation of primary alcohols to aldehydes. Chem Commun: 2414-2415.

GAMEZ P, ARENDS IWCE, SHELDON RA AND REEDIJK J. 2004. Room temperature aerobic copper-catalysed selective oxidation of primary alcohols to aldehydes. Adv Synth Catal 346: 805-811.

GENSCH T, HOPKINSON MN, GLORIUS F AND WENCEL-DELORD J. 2016. Mild metal-catalyzed C–H activation: examples and concepts. Chem Soc Rev 45: 2900-2936.

GONÇALVES LCC, VICTÓRIA FN, LIMA DB, BORBA PMY, PERIN G, SAVEGNAGO L AND LENARDÃO EJ. 2014. CuI/glycerol mediated stereoselective synthesis of 1,2-bis-chalcogen alkenes from terminal alkynes: synthesis of new antioxidants. Tetrahedron Lett 55: 5275-5279.

GOVENDER T, ARVIDSSON PI, MAGUIRE GEM, KRUGER HG AND NAICKER T. 2016. Enantioselective organocatalyzed transformations of β-ketoesters. Chem Rev 116: 9375-9437.

GUTEKUNST WR AND BARAN PS. 2011. C-H functionalization logic in total synthesis. Chem Soc Rev 40: 1976-1991.

GUZEN KP, GUAREZEMINI AS, ÓRFAO ATG, CELLA R, PEREIRA CMP AND STEFANI HA. 2007. Eco-friendly synthesis of imines by ultrasound irradiation. Tetrahedron Lett 48: 1845-1848.

HAJOS ZG AND PARRISH DR. 1971. Asymmetric synthesis of optically active polycyclic organic compounds. Ger Pat: DE 2102623.

HAJOS ZG AND PARRISH DR. 1974. Asymmetric synthesis of bicyclic intermediates of natural product chemistry. J Org Chem 39: 1615-1621.

HEATHCOCK CH. 1992. Die faszinierenden alkaloide aus yuzuriha. Angew Chem 104: 675-691.

HOPKIN MD, BAXENDALE IR AND LEY SV. 2013. An expeditious synthesis of imatinib and analogues utilising flow chemistry methods. Org Biomolec Chem 11: 1822-1839.

HUO H, HARMS K AND MEGGERS E. 2016. Catalytic, enantioselective addition of alkyl radicals to alkenes via visible-light-activated photoredox catalysis with a chiral rhodium complex. J Am Chem Soc 138: 6936-6939.

JANSSEN MHA, CASTELLANA JFC, JACKMAN H, DUNN PJ AND SHELDON RA. 2011. Towards greener solvents for the bleach oxidation of alcohols catalysed by stable N-oxy radicals. Green Chem 13: 905-912.

JARDIM GAM, BOWER JF AND DA SILVA JÚNIOR EN. 2016a. Rh-Catalyzed reactions of 1,4-benzoquinones with electrophiles: C−H iodination, bromination, and phenylselenation. Org Lett 18: 4454-4457.

JARDIM GAM, DA SILVA JÚNIOR EN AND BOWER JF. 2016b. Overcoming naphthoquinone deactivation: rhodium-catalyzed C-5 selective C–H iodination as a gateway to functionalized derivatives. Chem Sci 7: 3780-3784.

JUNIOR II, FLORES MC, SUTILI FK, LEITE SGF, MIRANDA LSM, LEAL ICR AND DE SOUZA ROMA. 2012. Fatty acids residue from palm oil refining process as feedstock for lipase catalyzed monoacylglicerol production under batch and continuous flow conditions. J Mol Catal B-Enzym 77: 53-58.

JURBERG ID. 2017a. An aminocatalyzed stereoselective strategy for the formal α-propargylation of ketones. Chem Eur J 23: 9716-9720.

JURBERG ID AND DAVIES HML. 2017b. Rhodium- and non-metal-catalyzed approaches for the conversion of isoxazol-5-ones to 2,3-dihydro-6H-1,3-oxazin-6-ones. Org Lett 19: 5158-5161.

KASCHERES AJ AND RODRIGUES JAR. 1975. Reaction of diphenylcyclopropenone with 2-aminopyridines. Synthetic and mechanistic implications. J Org Chem 40: 1440-1444.

KLITZKE CF AND PILLI RA. 2001. Enhanced trans diastereoselection in the allylation of cyclic chiral N-acyliminium ions. Synthesis of hydroxylated indolizidines. Tetrahedron Lett 42: 5605-5608.

KOPETZKI D, LÉVESQUE F AND SEEBERGER PH. 2013. A continuous-flow process for the synthesis of artemisinin. Chem Eur J 19: 5450-5456.

KUMMER DA, LI D, DION A AND MYERS AG. 2011. A practical, convergent route to the key precursor to the tetracycline antibiotics. Chem Sci 2: 1710-1718.

LACERDA V, DOS SANTOS DA, DA SILVA LC, GRECO SJ AND DOS SANTOS RB. 2012. The growing inpact of niobium in organic synthesis and catalysis. Aldrichim Acta 45: 19-27.

LEY SV, FITZPATRICK DE, INGHAM RJ AND MYERS RM. 2015a. Organic synthesis: march of the machines. Angew Chem Int Ed 54: 3449-3464.

LEY SV, FITZPATRICK DE, MYERS RM, BATTILOCCHIO C AND INGHAM RJ. 2015b. Machine-assisted organic synthesis. Angew Chem Int Ed 54: 10122-10137.

LI Y, BARLØSE C, JØRGENSEN J, CARLSEN BD AND JØRGENSE KA. 2017. Asymmetric catalytic aza-diels–alder/ring-closing cascade reaction forming bicyclic azaheterocycles by trienamine catalysis. Chem Eur J 23: 38-41.

LIAO K, NEGRETTI S, MUSAEV DG, BACSA J AND DAVIES HML. 2016. Site-selective and stereoselective functionalization of unactivated C–H bonds. Nature 533: 230-234.

LINGHU X, WONG N, IDING H, JOST V, ZHANG H, KOENIG SG, SOWELL CG AND GOSSELIN F. 2017. Development of a practical synthesis of ERK inhibitor GDC-0994. Org Process Res Dev 21: 387-398.

LIST B, LERNER RA AND BARBAS CF. 2000. Proline-catalyzed direct asymmetric aldol reactions. J Am Chem Soc 122: 2395-2396.

LIU J AND WANG L. 2017. Recent advances in asymmetric reactions catalyzed by proline and its derivatives. Synthesis 49: 960-972.

LONGHI K, MOREIRA DN, MARZARI MRB, FLOSS VM, BONACORSO HG, ZANATTA N AND MARTINS MAP. 2010. An efficient solvent-free synthesis of NH-pyrazoles from β-dimethylaminovinylketones and hydrazine on grinding. Tetrahedron Lett 51: 3193-3196.

LOPES EF, GONÇALVES LC, VINUEZA JCG, JACOB RG, PERIN G, SANTI C AND LENARDÃO EJ. 2015. DES as a green solvent to prepare 1,2-bis-organylseleno alkenes. Scope and limitations. Tetrahedron Lett 56: 6890-6895.

MACHADO GS, CASTRO KADF, WYPYCH F AND NAKAGAKI F. 2008. Immobilization of metalloporphyrins into nanotubes of natural halloysyte toward selective catalysts for oxidation reactions. J Molec Cat A: Chem 283: 99-107.

MACHADO LL, SOUZA JSN, DE MATTOS MC, SAKATA SK, CORDELL GA AND LEMOS TLG. 2006. Bioreduction of aldehydes and ketones using Manihot species. Phytochemistry 67: 1637-1643.

MANCUSO AJ, HUANG S-L AND SWERN D. 1978. Oxidation of long-chain and related alcohols to carbonyls by dimethyl sulfoxide "activated" by oxalyl chloride. J Org Chem 43: 2480-2482.

MANTOVANI SM, ANGOLINI CFF AND MARSAIOLI AJ. 2009. Mechanistic investigation of the Candida albicans CCT 0776 stereoinversion system and application to obtain enantiopure secondary alcohols. Tetrahedron Asymmetry 20: 2635-2638.

MARTINS BS AND LÜDTKE DS. 2014. Boron/zinc exchange reaction in the diastereoselective arylation of N-protected L-prolinal. Eur J Org Chem: 5364-5369.

MARTINS BS, MORO AV AND LÜDTKE DS. 2017. Stereoselective arylation of amino aldehydes: overriding natural substrate control through chelation. J Org Chem 82: 3334-3340.

MARTINS DL, AGUIAR LCS AND ANTUNES OAC. 2011. Microwave promoted Suzuki reactions between aroyl chlorides and boronic acids catalyzed by heterogeneous and homogeneous phosphine-free palladium catalysts. J Organomet Chem 696: 2845-2849.

MARTINS MAP, FREITAG R, FLORES AFC AND ZANATTA N. 1995. One-Pot Synthesis of 3(5)-Ethoxycarbonylpyrazoles. Synthesis, p. 1491-1492.

MASCIA S ET AL. 2013. End-to-end continuous manufacturing of pharmaceuticals: integrated synthesis, purification, and final dosage formation. Angew Chem Int Ed 52: 12359-12363.

MEGGERS E. 2015. Asymmetric catalysis activated by visible light. Chem Commun 51: 3290-3301.

MEIRA PRR, MORO AV AND CORREIA CRD. 2007. Stereoselective Heck-Matsuda arylations of chiral dihydrofurans with arenediazonium tetrafluoroborates; an efficient enantioselective total synthesis of (-)-isoaltholactone. Synthesis, p. 2279-2286.

MELGAR GZ, WENDLER EP, DOS SANTOS AA AND PORTO ALM. 2010. First stereocontrolled acetylation of a hydroxypropargylpiperidone by lipase CALB. Tetrahedron Asymmetry 21: 2271-2274.

MENDES SR, THUROW S, PENTEADO F, DA SILVA MS, GARIANI RA, PERIN G AND LENARDÃO EJ. 2015. Synthesis of bis(indolyl)methanes using ammonium niobium oxalate (ANO) as an efficient and recyclable catalyst. Green Chem 17: 4334-4339.

MENDOZA A, ISHIHARA Y AND BARAN PS. 2012. Scalable enantioselective total synthesis of taxanes. Nature 4: 21-25.

MENINNO S AND LATTANZI A. 2016. Organocatalytic asymmetric reactions of epoxides: recent progress. Chem Eur J 22: 3632-3642.

MICHAUDEL Q, ISHIHARA Y AND BARAN PS. 2015. Academia–industry symbiosis in organic chemistry. Acc Chem Res 48: 712-721.

MICKEL SJ, NIEDERER D, DAEFFLER R, OSMANI A, KUESTERS E, SCHMID E, SCHAER K AND GAMBONI R. 2004. Large-scale synthesis of the anti-cancer marine natural product (+)-Discodermolide. Part 5: linkage of fragments C_{1-6} and C_{7-24} and finale. Org Proc Res Dev 8: 122-130.

MIGOWSKI P AND DUPONT J. 2007. Catalytic applications of metal nanoparticles in imidazolium ionic liquids. Chem Eur J 13: 32-39.

MOMO PB, BELLETE BS, BROCKSOM TJ, DE SOUZA ROMA AND DE OLIVEIRA KT. 2015. Exploiting novel process windows for the synthesis of meso-substituted porphyrins under continuous flow conditions. RSC Adv 5: 84350-84355.

MONTEIRO AL, ZINN FK, DE SOUZA RF AND DUPONT J. 1997. Asymmetric hydrogenation of 2-arylacrylic acids catalyzed by immobilized Ru-BINAP complex in 1-n-butyl-3-methylimidazolium tetrafluoroborate molten salt. Tetrahedron: Asymmetry 8: 177-179.

MUÑOZ JAH, DE CARVALHO EM, JONES JR J AND DA SILVA FM. 2016. Propylene carbonate as a solvent in the eco-friendly synthesis of highly substituted imidazoles through the Radziszewski reaction. Curr Org Synth 13: 432-439.

MURRAY PRD, BROWNE DL, PASTRE JC, BUTTERS C, GUTHRIE D AND LEY SV. 2013. Continuous flow-processing of organometallic reagents using an advanced peristaltic pumping system and the telescoped flow synthesis of (E/Z)-tamoxifen. Org Process Res Dev 17: 1192-1208.

NAGIB DA AND MACMILLAN DWC. 2011. Trifluoromethylation of arenes and heteroarenes by means of photoredox catalysis. Nature 480: 224-228.

NARAYANAPERUMAL S, ALBERTO EE, GUL K, RODRIGUES OED AND BRAGA AL. 2010. Synthesis of diorganyl selenides mediated by zinc in ionic liquid. J Org Chem 75: 3886-3889.

NEWHOUSE T AND BARAN PS. 2011. If C-H bonds could talk: selective C-H bond oxidation. Angew Chem Int Ed 50: 3362-3374.

NISHIMURA RHV, TOLEDO FT, LOPES JLC AND CLOSOSKI GC. 2013. Efficient synthesis of chlorohydrins using ClCH2MgCl·LiCl. Tetrahedron Lett 54: 287-290.

NOVAES LFT, SAROTTI AM AND PILLI RA. 2015a. Total synthesis and stereochemical assignment of cryptolatifolione. RSC Adv 5: 53471-53476.

NOVAES LFT, SAROTTI AM AND PILLI RA. 2015b. Total synthesis and tentative structural elucidation of cryptomoscatone e3: interplay of experimental and computational studies. J Org Chem 80: 12027-12037.

OLIVEIRA BL AND ANTUNES OAC. 2007. Miyaura-Suzuki cross coupling reactions: the role of $Pd/CaCO_3$ as catalyst reservoir. Lett Org Chem 4: 13-15.

OLIVEIRA CC, ANGNES RA AND CORREIA CRD. 2013. Intermolecular enantioselective Heck–Matsuda arylations of acyclic olefins: application to the synthesis of β-aryl-γ-lactones and β-aryl aldehydes. J Org Chem 78: 4373-4385.

OLIVEIRA CC, PFALTZ A AND CORREIA CRD. 2015. Quaternary stereogenic centers through enantioselective Heck arylation of acyclic olefins with aryldiazonium salts: application in a concise synthesis of (R)-Verapamil. Angew Chem Int Ed 54: 14036-14039.

OLIVEIRA RL, KIYOHARA PK AND ROSSI LM. 2009. Clean preparation of methyl esters in one-step oxidative esterification of primary alcohols catalyzed by supported gold nanoparticles. Green Chem 11: 1366-1370.

OLIVEIRA RL, KIYOHARA PK AND ROSSI LM. 2010. High performance magnetic separation of gold nanoparticles for catalytic oxidation of alcohols. Green Chem 12: 144-149.

O'MALLEY DP, YAMAGUCHI J, YOUNG IS, SEIPLE IB AND BARAN PS. 2008. Total synthesis of (+/-)-axinellamines A and B. Angew Chem Int Ed 47: 3581-3583.

PAIOTI PHS AND COELHO F. 2011. A Morita–Baylis–Hillman adduct allows the diastereoselective synthesis of styryl lactones. Tetrahedron Lett 52: 6180-6184.

PELLISSIER H. 2007. Asymmetric organocatalysis. Tetrahedron 63: 9267-9331.

PENG B AND MAULIDE N. 2013. The redox-neutral approach to C-H functionalization. Chem Eur J 19: 13274-13287.

PEREIRA AA, PEREIRA AS, DE MELLO AC, CARPANEZ AG, HORTA BAC AND AMARANTE GW. 2017. methylsulfenylation of electrophilic carbon atoms: reaction development, scope, and mechanism. Eur J Org Chem: 1578-1582.

PERIN G, MELLO LG, RADATZ CS, SAVEGNAGO L, ALVES D, JACOB RG AND LENARDÃO EJ. 2010. Green, catalyst-free thioacetalization of carbonyl compounds using glycerol as recyclable solvente. Tetrahedron Lett 51: 4354-4356.

PETRAGNANI N AND COMASSETO JV. 1986. Synthetic applications of tellurium reagents. Synthesis, p. 1-30.

PETRAGNANI N AND STEFANI HA. 2007. Tellurium in organic synthesis, 2nd ed., Elsevier, 398 p.

PHAM PV, NAGIB DA AND MACMILLAN DWC. 2011. Photoredox catalysis: a mild, operationally simple approach to the synthesis of α-trifluoromethyl carbonyl compounds. Angew Chem Int Ed 50: 6119-6122.

PHILLIPS AMF. 2016. Organocatalytic asymmetric nitro-michael reactions. Curr Org Synth 13: 687-725.

PIETTRE S AND HEATHCOCK CH. 1990. Biomimetic total synthesis of proto-daphniphylline. Science 248: 1532-1534.

PILLI RA, DIAS LC AND MALDANER OA. 1995. One-Pot Preparation of Quinolizidin-2-one and Indolizidin-7-one Ring Systems. Concise Total Syntheses of (.+-.)-Myrtine, (.+-.)-Lasubine II, and (-)-Indolizidine 223AB. J Org Chem 60: 717-722.

PILLI RA AND RUSSOWKSY D. 1996. Addition of a chiral boron enolate to cyclic N-acyliminium ions. Stereocontrolled synthesis of the pyrrolizidine ring system. J Org Chem 61: 3187-3190.

PINHEIRO DLJ, ÁVILA EP, BATISTA GMF AND AMARANTE GW. 2017. Chemoselective reduction of azlactones using Schwartz's reagent. J Org Chem 82: 5981-5985.

PINHEIRO DLJ, BATISTA GMF, GONÇALVES JR, DUARTE TN AND AMARANTE GW. 2016. Sugar-based organocatalyst for the diastereoselective desymmetrization of dibenzylideneacetones. Eur J Org Chem, p. 459-462.

PINHO VD AND BURTOLOSO ACB. 2011. Preparation of α,β-Unsaturated Diazoketones Employing a Horner−Wadsworth−Emmons Reagent. J Org Chem 76: 289-292.

PINTO AC, ABLA MA, RIBEIRO N, PEREIRA AL, KOVER WB AND AGUIAR AP. 1988. Rearrangement of Terpenoids with Boron Trifluoride-Ether. J Chem Res (S): 88.

POLO EC, DA SILVA-FILHO LC, DA SILVA GVJ AND CONSTANTINO MG. 2008. Síntese de 1-indanonas através da reação de acilação de Friedel-Crafts intramolecular utilizando $NbCl_5$ como ácido de Lewis. Quim Nova 31: 763-766.

PRIER CK, RANKIC DA AND MACMILLAN DWC. 2013. Visible light photoredox catalysis with transition metal complexes: applications in organic synthesis. Chem Rev 113: 5322-5363.

RADATZ CS, SOARES LA, VIEIRA ER, ALVES D, RUSSOWSKY D AND SCHNEIDER PH. 2014. Recoverable Cu/SiO_2 composite-catalysed click synthesis of 1,2,3-triazoles in water media. New J Chem 38: 1410-1417.

RAMBO RS, JACOBY CG, DA SILVA TL AND SCHNEIDER PH. 2015. A highly enantio- and diastereoselective direct aldol reaction in aqueous medium catalyzed by thiazolidine-based compounds. Tetrahedron: Asymmetry 26: 632-637.

RAMINELLI C, PRECHTL MHG, SANTOS LS, EBERLIN MN AND COMASSETO JV. 2004. Coupling of vinylic tellurides with alkynes catalyzed by palladium dichloride: evaluation of synthetic and mechanistic details. Organometallics 23: 3990-3996.

RAWAL VH AND IWASA S. 1994. A short, stereocontrolled synthesis of strychnine. J Org Chem 59: 2685-2686.

REN L ET AL. 2015. Discovery of highly potent, selective, and efficacious small molecule inhibitors of ERK1/2. J Med Chem 58: 1976-1991.

RICORDI VG, FREITAS CS, PERIN G, LENARDÃO EJ, JACOB RG, SAVEGNAGO L AND ALVES D. 2012. Glycerol as a recyclable solvent for copper-catalyzed cross-coupling reactions of diaryl diselenides with aryl boronic acids. Green Chem 14: 1030-1034.

RINALDI R AND SCHÜTH F. 2009. Design of solid catalysts for the conversion of biomass. Energy Environ Sci 2: 610-626.

RINALDI R, SEPÚLVEDA J AND SCHUCHARDT U. 2004. Cyclohexene and cyclooctene epoxidation with aqueous hydrogen peroxide using transition metal-free sol-gel alumina as catalyst. Adv Synth Catal 346: 281-285.

ROCHA LL, DIAS AO, AUGUSTI R, DOS SANTOS EM AND GUSEVSKAYA EV. 1998. Palladium/tin catalyzed alkoxycarbonylation of naturally occurring bicyclic monoterpenes. J Mol Catal A: Chem 132: 213-221.

RODRIGUEZ RA, BARRIOS STEED D, KAWAMATA Y, SU S, SMITH PA, STEED TC, ROMESBERG FE AND BARAN PS. 2014. Axinellamines as broad-spectrum antibacterial agents: scalable synthesis and biology. J Am Chem Soc 136(43): 15403-15413.

ROMANO PN, DE ALMEIDA JMAR, CARVALHO Y, PRIECEL P, SOUSA-AGUIAR EF AND LOPEZ-SANCHEZ JA. 2016. Microwave-Assisted Selective Hydrogenation of Furfural to Furfuryl Alcohol Employing a Green and Noble Metal-Free Copper Catalyst. ChemSusChem 9: 3387-3392.

ROMERO NA AND NICEWICZ DA. 2016. Organic photoredox catalysis. Chem Ver 116: 10075-10166.

RONN M ET AL. 2013. Process R&D of eravacycline: the first fully synthetic fluorocycline in clinical development. Org Process Res Dev 17: 838-845.

ROSA GR AND ROSA DS. 2012. NCP pincer palladacycle as a phosphine-free catalyst precursor for the Heck–Mizoroki coupling of aryl halides. RSC Advances 2: 5080-5083.

ROSSET IG AND BURTOLOSO ACB. 2013. Preparation of Z-α,β-unsaturated diazoketones from aldehydes. Application in the construction of substituted dihydropyridin-3-ones. J Org Chem 78: 9464-9470.

ROSSI LM, SILVA FP, VONO LLR, KIYOHARA PK, DUARTE EL, ITRI R, LANDERS R AND MACHADO G. 2007. Superparamagnetic nanoparticle-supported palladium: a highly stable magnetically recoverable and reusable catalyst for hydrogenation reactions. Green Cheem 9: 379-385.

RUSSO V, TESSER R, SANTACESARIA E AND DI SERIO M. 2013. Kinetics of propene oxide production via hydrogen peroxide with ts-1. Ind Eng Chem Res 52: 1168-1178.

SABINO AA, MACHADO AHL, CORREIA CRD AND EBERLIN MN. 2004. Probing the mechanism of the Heck reaction with arene diazonium salts by electrospray mass and tandem mass spectrometry. Angew Chem Int Ed 43: 2514-2518.

SANDERS JPM AND SHELDON RA. 2015. Comparison of the sustainability metrics of the petrochemical and biomass-based routes to methionine. Catal Today 239: 44-49.

SANTOS LS, PAVAM CH, ALMEIDA WP, COELHO F AND EBERLIN MN. 2004. Probing the mechanism of the Baylis–Hillman reaction by electrospray ionization mass and tandem mass spectrometry. Angew Chem Int Ed 43: 4330-4333.

SANTOS LS AND PILLI RA. 2002. The intramolecular heck reaction and the synthesis of indolizidinone, quinolizidinone and benzoazepinone derivatives. Synthesis, p. 87-93.

SANTOS LS AND PILLI RA. 2003. Studies towards the construction of alkylidene quinolizidines. The total synthesis of homopumiliotoxin 223G. J Braz Chem Soc 14: 982-993.

SAROTTI AM, SPANEVELLO RA AND SUÁRES AG. 2007. An efficient microwave-assisted green transformation of cellulose into levoglucosenone. Advantages of the use of an experimental design approach. Green Chem 9: 1137-1140.

SCATENA GS, DE LA TORRE AF, CASS QB, RIVERA DG AND PAIXÃO MW. 2014. multicomponent approach to silica-grafted peptide catalysts: a 3D continuous-flow organocatalytic system with on-line monitoring of conversion and stereoselectivity. Chem Cat Chem 6: 3208-3214.

SCHNEIDER PH, SCHREKKER HS, SILVEIRA CC, WESSJOHANN LA AND BRAGA AL. 2004. Multicomponent approach to silica-grafted peptide catalysts: A 3 D continuous-flow organocatalytic system with on-line monitoring of conversion and stereo-selectivity. Eur J Org Chem 12: 2715-2722.

SCHOLTEN JD, LEAL BC AND DUPONT J. 2012. Transition metal nanoparticle catalysis in ionic liquids. ACS Catalysis 2: 184-200.

SCHWAB RS, GALETTO FZ, AZEREDO JB, BRAGA AL, LÜDTKE DS AND PAIXÃO MW. 2008. Organocatalytic asymmetric aldol reactions mediated by a cysteine-derived prolinamide. Tetrahedron Lett 49: 5094-5097.

SEAYAD J AND LIST B. 2005. Asymmetric organocatalysis. Org Biomol Chem 3: 719-724.

SEEBACH D. 1990. Organic synthesis—where now? Angew Chem Int Ed 29: 1320-1367.

SEIPLE IB ET AL. 2016. A platform for the discovery of new macrolide antibiotics. Nature 533: 338-345.

SENRA JD, AGUIAR LCS AND SIMAS ABC. 2011. Recent progress in transition-metal-catalyzed c-n cross-couplings: emerging approaches towards sustainability. Curr Org Synt 8: 53-78.

SENRA JD, MALTA LFB, DA COSTA MEHM, MICHEL RC, AGUIAR LCS, SIMAS ABC AND ANTUNES AOC. 2009. Hydroxypropyl-α-cyclodextrin-capped palladium nanoparticles: active scaffolds for efficient carbon-carbon bond forming cross-couplings in water. Adv Synth Catal 351: 2411-2422.

SENRA JD, MALTA LFB, DE SOUZA ALF, MEDEIROS ME, AGUIAR LCS AND ANTUNES OAC. 2007. Phosphine-free Heck reactions in aqueous medium using hydroxypropylated cyclodextrins as supramolecular hosts. Tetrahedron Lett 48: 8153-8156.

SENRA JD, MALTA LFB, SOUZA ALF, AGUIAR LCS AND ANTUNES AOC. 2008. palladium on calcium carbonate combined to 2-hydroxypropyl-α/β-cyclodextrins: a selective catalytic system for aqueous Heck coupling and hydroarylation. Adv Synth Catal 350: 2551-2558.

SHAW MH, TWILTON J AND MACMILLAN DWC. 2016. Photoredox catalysis in organic chemistry. J Org Chem 81: 6898-6926.

SHELDON RA. 1992. Organic synthesis; past, present and future. Chem Ind (London) 23: 903-906.

SHELDON RA. 1997. Catalysis and pollution prevention. Chem Ind (London), p. 12-15.

SHELDON RA. 2014. Green and sustainable manufacture of chemicals from biomass: state of the art. Green Chem 16: 950-963.

SHELDON RA AND SANDERS JPM. 2015. Toward concise metrics for the production of chemicals from renewable biomass. Catal Today 239: 3-6.

SHELDON RA, SANDERS JPM AND MARINAS A. 2015. Sustainability metrics of chemicals from renewable biomass. Catal Today 239: 1-2.

SILVA JR LF, SIQUEIRA FA, PEDROZO EC, VIEIRA FYM AND DORIGUETTO AC. 2007. Iodine(III)-promoted ring contraction of 1,2-dihydronaphthalenes: a diastereoselective total synthesis of (±)-Indatraline. Org Lett 9: 1433-1436.

SILVA L, AFFELDT RF AND LÜDTKE DS. 2016. Synthesis of glycosyl amides using selenocarboxylates as traceless reagents for amide bond formation. J Org Chem 81: 5464-5473.

SILVEIRA CC, MENDES SR, LÍBERO FM, LENARDÃO EJ AND PERIN G. 2009. Glycerin and $CeCl_3 \cdot 7H_2O$: a new and efficient recyclable medium for the synthesis of bis(indolyl)methanes. Tetrahedron Lett 50: 6060-6063.

SILVEIRA ET, UMPIERRE AP, ROSSI LM, MACHADO G, MORAIS J, SOARES GV, BAUMVOL IJR, TEIXEIRA SR, FICHTNER PFP AND DUPONT J. 2004. The partial hydrogenation of benzene to cyclohexene by nanoscale ruthenium catalysts in imidazolium ionic liquids. Chem Eur J 10: 3734-3740.

SINGH D, ALBERTO EE, RODRIGUES OED AND BRAGA AL. 2009. Eco-friendly cross-coupling of diaryl diselenides with aryl and alkyl bromides catalyzed by CuO nanopowder in ionic liquid. Green Chem 11: 1521-1524.

SNEAD DR AND JAMISON TF. 2015. A three-minute synthesis and purification of ibuprofen: pushing the limits of continuous-flow processing. Angew Chem Int Ed 54: 983-987.

SORRILHA AEPM, MARQUES M, JOEKES I, MORAN PJS AND RODRIGUES JAR. 1992. Reduction of phenylketones by immobilized baker's yeast. Bioorg Med Chem Lett 2: 191-196.

STIVANIN ML, DUARTE M, SARTORI C, CAPRETI NMR, ANGOLINI CFF AND JURBERG ID. 2017. An Aminocatalyzed Michael Addition/Iron-Mediated Decarboxylative Cyclization Sequence for the Preparation

of 2,3,4,6-Tetrasubstituted Pyridines: Scope and Mechanistic Insights. J Org Chem 82: 10319-10330.

SU S, SEIPLE IB, YOUNG IS AND BARAN PS. 2008. Total syntheses of (±)-massadine and massadine chloride. J Am Chem Soc 130: 16490-16491.

SUAREZ PAZ, DULLIUS JEL, EINLOFT S, DE SOUZA RF AND DUPONT J. 1996. The use of new ionic liquids in two-phase catalytic hydrogenation reaction by rhodium complexes. Polyhedron 15: 1217-1219.

SUAREZ PAZ, DULLIUS JEL, EINLOFT S, DE SOUZA RF AND DUPONT J. 1997. Two-phase catalytic hydrogenation of olefins by Ru(II) and Co(II) complexes dissolved in 1-n-butyl-3-methylimidazolium tetrafluoroborate ionic liquid. Inorg Chim Acta 255: 207-209.

SUTILI FK, RUELA HS, LEITE SGF, MIRANDA LSM, LEAL ICR AND DE SOUZA ROMA. 2013. Lipase-catalyzed esterification of steric hindered fructose derivative by continuous flow and batch conditions. J Mol Catal B-Enzym 85-86: 37-42.

TALERO AG AND BURTOLOSO ACB. 2017. Sharpless asymmetric dihydroxylation on α,β-unsaturated diazoketones: a new entry for the synthesis of disubstituted furanones. Synlett 28: 1748-1752.

TEN BRINK G-J, ARENDS IWCE AND SHELDON RA. 2000. Green, catalytic oxidation of alcohols in water. Science 287: 1636-1639.

THOMAS JC, BURICH MD, BANDEIRA PT, DE OLIVEIRA ARM AND PIOVAN L. 2017. Biocatalysis in continuous-flow mode: a casestudy in the enzymatic kinetic resolution of secondary alcohols via acylation and deacylation reactions mediated by Novozym 435®. Biocatalysis 3: 27-36.

TORRES JA, PILLI RA, VARGAS MD, VIOLANTE FA, GARDEN SJ AND PINTO AC. 2002. Synthesis of 1-ferrocenyl-2-aryl(heteroaryl)acetylenes and 2-ferrocenylindole derivatives via the Sonogashira–Heck–Cassar reaction. Tetrahedron 58: 4487-4492.

TOWLE MJ ET AL. 2001. *In vitro* and *in vivo* anticancer activities of synthetic macrocyclic ketone analogues of halichondrin B. Cancer Res 61: 1013-1021.

TOZETTI SDF, DE ALMEIDA LS, ESTEVES PM AND DE MATTOS MCS. 2007. Trihaloisocyanuric acids/NaX: an environmentaly friendly system for vicinal dihalogenation of alkenes without using molecular halogen. J Braz Chem Soc 18: 675-677.

TRANQUILINO A, ANDRADE SRP, DA SILVA APM, MENEZES PH AND OLIVEIRA RA. 2017. Non-expensive, open-flask and selective catalytic systems for the synthesis of sulfinate esters and thiosulfonates. Tetrahedron Lett 58: 1265-1268.

TUNDO P, ANASTAS P, BLACK DSTC, BREEN J, COLLINS T, MEMOLI S, MIYAMOTO J, POLYAKOFF M AND TUMAS W. 2000. Synthetic pathways and processes in green chemistry. Introductory overview. Pure App Chem 72: 1207-1228.

USMAN M, REN Z-H, WANG Y-Y AND GUAN Z-H. 2017. Recent developments in cobalt catalyzed carbon–carbon and carbon–heteroatom bond formation via C–H bond functionalization. Synthesis 49: 1419-1443.

UTAKA A, CAVALCANTI LN AND SILVA JR LF. 2014. Electrophilic alkynylation of ketones using hypervalent iodine. Chem Commun 50: 3810-3813.

VAN VLIET MCA, MANDELLI D, ARENDS IWCE, SCHUCHARDT U AND SHELDON RA. 2001. Alumina: a cheap, active and selective catalyst forepoxidations with (aqueous) hydrogen peroxide. Green Chem 3: 243-246.

VETICA F, CHAUHAN P, DOCHAIN S AND ENDERS D. 2017. Asymmetric organocatalytic methods for the synthesis of tetrahydropyrans and their application in total synthesis. Chem Soc Rev 46: 1661-1674.

WELIN ER, WARKENTIN AA, CONRAD JC AND MACMILLAN DWC. 2015. Enantioselective α-alkylation of aldehydes by photoredox organocatalysis: rapid access to pharmacophore fragments from β-cyanoaldehydes. Angew Chem Int Ed 54: 9668-9672.

WENGERT M, SANSEVERINO AM AND DE MATTOS MCS. 2002. Trichloroisocyanuric acid: an alternate green route for the transformation of alkenes into epoxides. J Braz Chem Soc 13: 700-703.

XU Y, LI A, JIA X AND LI Z. 2011. Asymmetric trans-dihydroxylation of cyclic olefins by enzymatic or chemo-enzymatic sequential epoxidation and hydrolysis in one-pot. Green Chem 13: 2452-2458.

YAMAGUCHI J, SEIPLE IB, YOUNG IS, O'MALLEY DP, MAUE M AND BARAN PS. 2008. Synthesis of 1,9-dideoxy-pre-axinellamine. Angew Chem Int Ed 47: 3578-3580.

YOUNG IS AND BARAN PS. 2009. Protecting-group-free synthesis as an opportunity for invention. Nat Chem 1: 193-205.

ZENI G AND COMASSETO JV. 1999. Coupling of Z-vinylic tellurides with alkynes catalysed by $PdCl_2CuI$: synthesis of Z-enynes and Z-enediynes. Tetrahedron Lett 40: 4619-4622.

ZENI G, LÜDTKE DS, PANATIERI RB AND BRAGA AL. 2006. Vinylic tellurides: from preparation to their applicability in organic synthesis. Chem Rev 106: 1032-1076.

ZHAN G, DU W AND CHEN YC. 2017. Switchable divergent asymmetric synthesis via organocatalysis. Chem Soc Rev 46: 1675-1692.

ZHANG L AND MEGGERS E. 2017. Steering asymmetric lewis acid catalysis exclusively with octahedral metal-centered chirality. ACC Chem Res 50: 320-330.

ZHENG WJ ET AL. 2004. Macrocyclic ketone analogues of halichondrin B. J Bioorg Med Chem Lett 14: 5551-5554.

ZOU Y-Q, LU L-Q, FU L, CHANG N-J, RONG J, CHEN J-R AND XIAO W-J. 2011. Visible-light-induced oxidation/[3+2] cycloaddition/oxidative aromatization sequence: a photocatalytic strategy to construct pyrrolo[2,1-a] isoquinolines. Angew Chem Int Ed 50: 7171-7175.