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## NEW SYNTHETIC TOOLS FOR THE DEFINITION OF SUSTAINABLE CONTINUOUS- FLOW REACTORS

*The Laboratory of Green Synthetic Organic Chemistry at Perugia works on the improvement of synthetic methodologies in terms of yield and selectivity and also in terms of minimizing waste. Continuous-flow reactors operating in water or solvent-free conditions are realized to minimize waste in the large scale production of fine chemicals.*

Chemistry has an important role to play in the achieving of a sustainable civilization on Earth. A proof is given by the recent history of the US Environmental Protection Agency (US EPA), founded in 1970. Initially, US EPA adopted (as Europe) a command and control policy in the execution of environmental regulations while a shift in paradigm started in the 1980s when pollution prevention became the priority instead of end-of-pipeline control. Consequently, this approach requires to completely design ex novo the existing and necessary chemical processes making immediately evident the strategic role of synthetic chemists. With the Pollution Prevention Act, approved by the American Congress in 1990, US officially pointed the attention on the “millions of tons of pollution” and the related cost of “tens of billions of dollars per year” [1]. It is evident how the common interest of Government, industries and research institutions to cooperate is basically directed to solve obvious environmental issues

but also to reach common economic interests. Such approach will be of great benefit to the entire society allowing to keep the production in highly advanced regions (such Europe and US) and saving job positions.

The “2011 Roadmap for the Chemical Sciences” recently disclosed by the European Association for Chemical and Molecular Sciences is in fully agreement with the Green Chemistry approach. The challenge for chemists is to continue the search for new methods to maintain access to key products currently synthesized using costly procedures. An advanced region such as Europe must actively operate in this field and encourage those industries that contribute to the wealth of the society by creating new and appealing job positions.

Following the Pollution Act a growing attention has been dedicated to the so-called Green Chemistry. The “12 principles” were published by the Green Chemistry Institute in US [2] and they represent a sort of

guidelines for realizing efficient modern chemical processes. They can be summarized as follow: 1. prevent waste; 2. atom economy; 3. design safer chemicals; 4. less hazardous chemical synthesis; 5. safer or no solvents; 6. energy efficiency; 7. use renewable feedstock; 8. avoid protecting groups and derivatives; 9. catalysis; 10. design chemicals considering their degradation; 11. real-time analysis for pollution prevention; 12. inherently safer chemistry for accident prevention.

Considering that great attention must be paid to waste production, the efficiency of a chemical process cannot be correctly measured by just the yield and selectivity parameters. To evaluate the environmental impact of a synthetic procedure other metrics should be used. Among these, one of the simplest and very effective is the Environmental factor (E-factor) introduced by Sheldon [3]. This simple value is the ratio between the kg of waste produced per kg of desired product and gives the immediate idea of how an elegant and complex chemistry may result in a highly environmentally costly process. E factor, atom economy [4] and the “12 Principles” have emerged as key driving factors for the definition of sustainable chemical processes.

“Catalysis” is of key relevance to synthetic organic chemists. Catalytic methods offer numerous benefits related to sustainability, including lowered energetic reaction requirements; the use of catalytic rather than stoichiometric amounts of materials; increased selectivities; and, in many cases, the ability to use less-toxic reagents [5]. A truly crucial area concerns heterogeneous catalysis that embodies many requirements of sustainable processing by allowing the easy separation and recovery of a catalyst from the reaction products.

In addition, synthetic transformations should be preferentially performed under temperature and pressure conditions that do not require costly control equipments (minimization of energy consumption). The combination of catalysis and continuous-flow processes is the most effective solution to this issue.

Generally, continuous flow processes are performed in mini or microreactors, are more efficient than standard batch protocols and offer much higher throughput per unit volume and per unit time [6]. Most importantly, for a long time the chemical industry has relied on the continuous production of chemicals, commonly for commodities and less much for fine chemicals and pharmaceuticals. As no flow equipment on the laboratory scale was available until very recently, the chemistry developed in the laboratory was based on batch processes. This means that research was often disconnected from process chemistry which led to many problems and extra optimizations or even total redesign of the initial synthetic strategy. Anyway in our opinion, a significant step must be undertaken towards a green production. Intensified processes should be defined based on continuous-flow reactors able to drastically reduce waste and to operate in safer media taking green chemistry principles in flow. In fact, much attention should be paid to the reaction medium. The Green Chemistry principle number five points out that in view of realizing an environmentally-efficient process, the use of solvent should be made unnecessary or minimized. This is the most crucial aspect of a chemical process, both at a laboratory small-scale or in large produc-

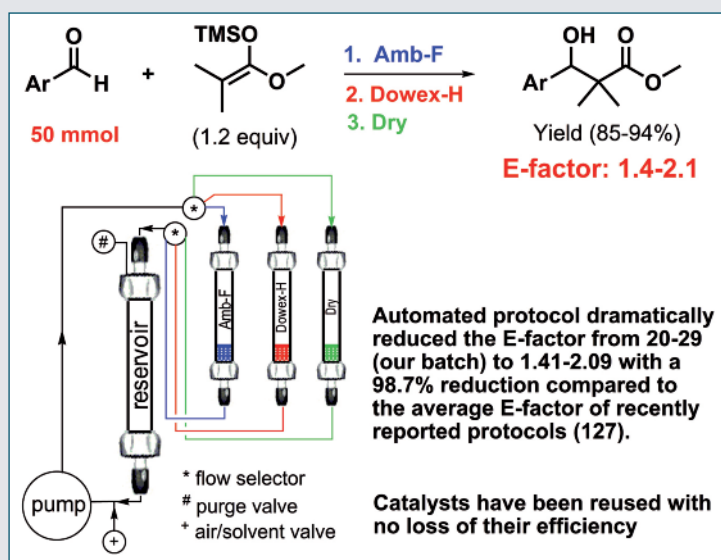
tion. Generally, the largest contribution to waste is due to the solvents used for running the reaction, isolate and purify the products [7]. Several of the solvents normally used, especially in fine chemical syntheses, are volatile and their dispersion in the environment is almost unavoidable (one example above all is given by dichloromethane, the 70% of which is inevitably dispersed). Attention is directed towards safer alternatives, supercritical fluids (mainly CO<sub>2</sub>), ionic liquids, and water are the most representatively investigated options. Anyway a careful evaluation of the actual beneficial effects of such media on the greenness of the process should be always considered before considering them “green”. A very efficient option is the use of NO SOLVENT at all (solvent-free conditions, SolFC).

In the Laboratory of *Green Synthetic Organic Chemistry* (Green SOC) at the University of Perugia, for many year we have been trying to contribute to the development of novel synthetic processes efficient from both chemical and environmental point of views [8]. We have mainly directed our attention towards the identification of chemical processes that could be realized using water as reaction medium or under solvent-free conditions (SolFC).

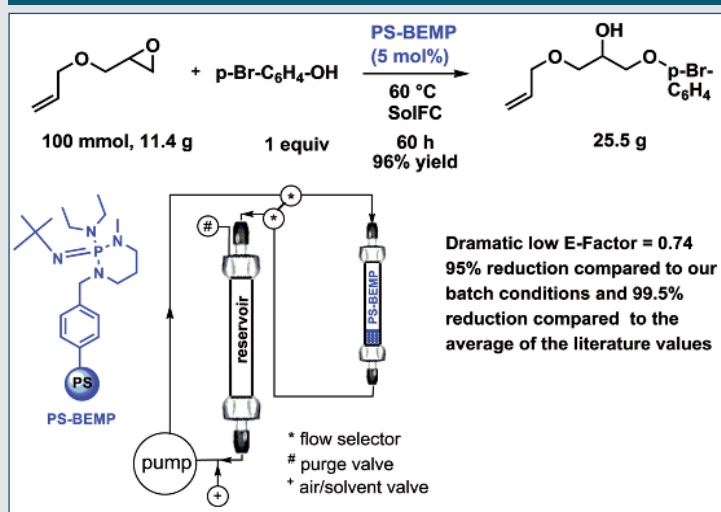
We have exploited the peculiar properties of water, and more specifically the careful control of pH, to realize efficient catalytic synthetic processes always defining the recovery and reuse of both water and catalyst [8]. Recently, we have directed our attention towards heterogeneous catalytic systems in order to realize large scale processes operating in automated continuous-flow conditions. Generally, a significant loss of catalytic efficiency is observed when a catalyst is immobilized over a solid support and often this is related to its *swelling* [9]. Such process is strongly dependant on the reaction medium employed and dramatically affects the activity of the solid catalyst, influencing the access of the reactants at the catalytic sites and also the pressure needed to “push” the reactants mixture through the solid matrix hampering the realization of continuous-flow reactors [10].

According to our experience, we have identified several crucial issues in the use of an immobilized catalyst under SolFC. Commercially available solid supports (organic or inorganic) have been developed to be used in the presence of a reaction medium and designed to deal with the related swelling processes. Mechanical stirring of the reaction mixture often causes the complete crunching of the solid catalyst hampering its recovery and reuse. In addition, an organic solvent is generally necessary to isolate the products and recover the catalyst.

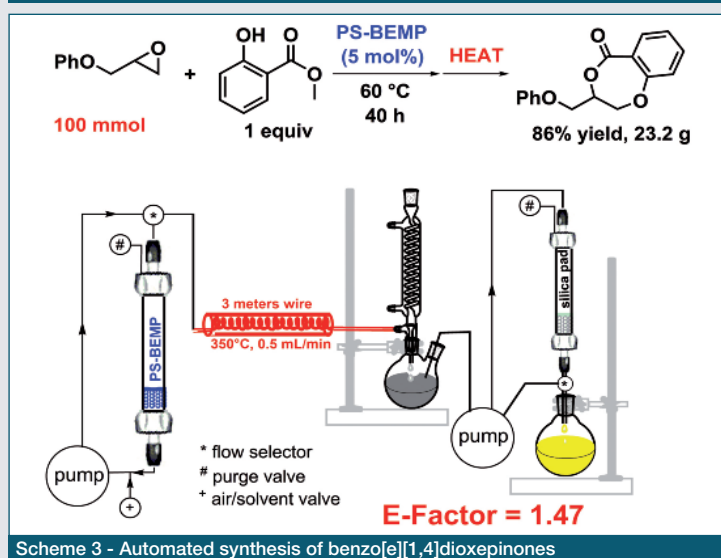
We have proposed as an alternative solution to these problems, the combined use of specifically designed catalytic systems and continuous-flow reactors able to operate under SolFC or in the presence of a dispersion medium such as water. Accordingly, novel solid supports should be designed in order to be able to operate effectively under these flow alternative conditions and consequently eliminate the problems related to the swelling and the internal pressure. This approach should allow a) the highest intimacy between the reactants and their optimal access to the catalytic sites, b) to avoid mechanical stirring and high pressures and c) the recovery of the final products using the mini-



Scheme 1 - E-factor-minimized automated preparation of  $\beta$ -hydroxy esters



Scheme 2 - Waste-minimized PS-BEMP catalyzed phenolysis of epoxide under SolFC



Scheme 3 - Automated synthesis of benzo[e][1,4]dioxepinones

mal amount of organic solvents and therefore minimizing the production of waste. Preliminarily in 2008, we have published our first paper on a continuous-flow procedure operating under SolFC for the addition of nitroalkanes to enones using commercially available solid bases [12]. This procedure allowed a 99.7% reduction of the E-factor from 250 (average literature) to 0.85 (our conditions). These results represent the first application of our current approach on the use of flow reactors under SolFC for improving the efficiency of immobilized catalysts, solve the problems related to the swelling and minimize the waste production. Another example is the E-factor minimized three-step synthesis of beta-hydroxy esters [13] featuring a 98.7% E-factor reduction from 127 (average of literature results) to 1.7 (average on our flow) (Scheme 1). This automated protocol is based on three reactors containing i) Amberlite IRA900F (Amb-F) that we have used for the first time as a solid fluoride source to promote the Mukaiyama reaction of an aldehyde and a ketene silyl acetal under SolFC, ii) DOWEX-H which is ion exchange resin that we have found to promote the desilylation step and iii) a dry-column to eliminate traces of acidic residues formed during the process. Adoption of the flow conditions has allowed to reduce the equivalents of ketene silyl acetal and also to recover and reuse the catalysts that being sealed in the reactors do not undergo to physical and chemical degradation. We have also reported the phenolysis of epoxides under SolFC catalyzed by 2-tert-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine supported on polystyrene (PS-BEMP).

In batch conditions and on a 1.0-2.0 mmol scale, products and catalyst have been isolated using the minimal amount of organic solvent (AcOEt) and E-factor values ranged between 15 and 19. When the process was performed on a flow reactor a 99.5% E-factor reduction (literature ca. 240, our flow 0.74) has been achieved (Scheme 2). We have also reported an innovative two-step synthesis of oxathiepinones featuring a very low E-factor of 1.4 (Scheme 3). The two-step flow reactor combines the PS-BEMP-catalyzed phenolysis and the thermal treatment at 350 °C (15 min.) in flow [14]. The two-step process has been performed on a multigram scale and with a very satisfactory yield. We have also developed a series of completely new polystyrene supports such as Rasta (high-loaded supports) and JandaJel (highly-spaced and flexible supports) and used in several transformations [15]. As a representative example in the case of the ring-opening of epoxides by thiols under SolFC our protocol features a 97% of the E-factor reduction from 15.3 (average of literature results under SolFC) to 0.46 (average on our flow) (Scheme 4) [15a].

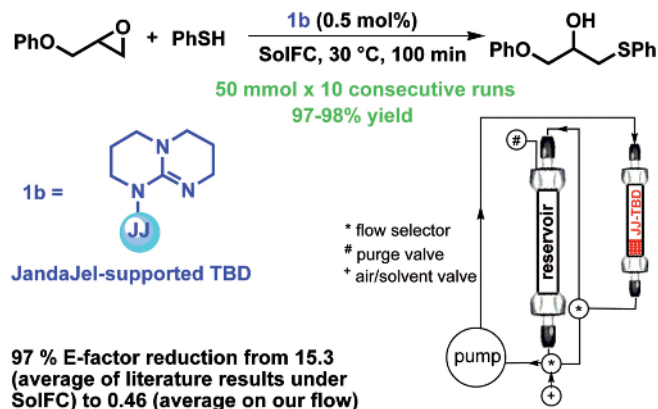
In a very recent contribution [16] we have defined an innovative and efficient protocol for the conjugate addition of azido ion to  $\alpha,\beta$ -unsaturated ketones ( $\beta$ -azidation) that represents a well-established method for the preparation of  $\beta$ -amino carbonyls [17]. In our previous report on the  $\alpha$ -azidation of  $\alpha,\beta$ -unsaturated ketone catalyzed by Amb-F, we have highlighted that adoption of SolFC was necessary to achieve the maximum efficiency of the process. Although satisfactory E-factor values were achieved (ca. 22), we also noticed that in this process the reaction mixture showed an evident tendency to stick with the polymer resin. Therefore compared to other processes studied by our group, a slightly larger amount of organic solvent was needed to isolate the products [18]. We have decided to design a novel fluoride

source which is supported on polystyrene and features a higher loading compared to those commercially available. This should allow the use of a smaller mass of catalyst and therefore should help the mixing of the reaction mixture. In addition to this and considering our experience in the use of water as reaction medium [8], we have decided to prepare a novel solid fluoride source suitable for being used in the presence of water. Our idea is to exploit water as medium to increase the reactivity of the system but also to improve dispersion of the reaction mixture. The use of specific porous solid support in water should avoid organic fouling caused by the sticking of the reaction mixture within the polymeric matrix, allowing a better catalytic efficiency and facilitating the recovery of the products from the catalyst.

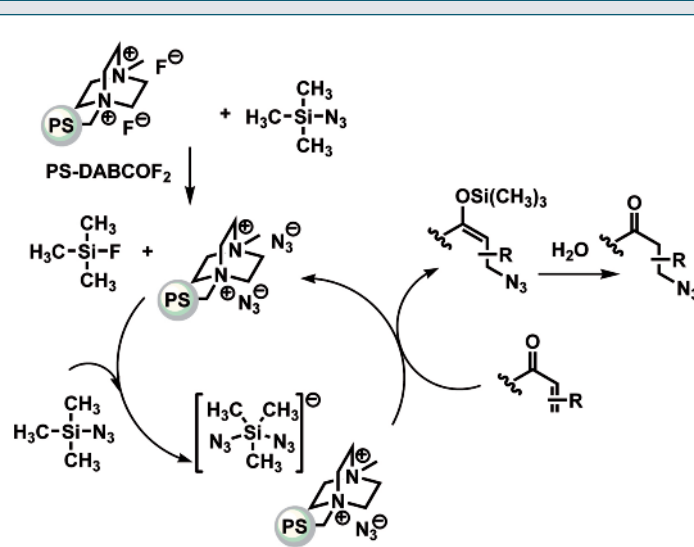
The attention has been focused on 1,4-diazabicyclo[2.2.2]octane (DABCO), an interesting diamine moiety that if supported on a polymer resin can carry a high-loading of fluoride as counter ion to two ammonium functionalities (Scheme 5). Several immobilized PS-DABCOF<sub>2</sub> catalysts were prepared with gel-type (1-2 % of divinylbenzene (DVB) as cross-linker) and porous (5.5% of DVB) polystyrene supports and with different loadings. The best results were obtained in the presence of water and with porous supports. The highest loading achieved was 7.39 mmol of F/g.

According to our previous results [18], the recovered catalysts resulted from the complete substitution of both fluorides by azido ions. Therefore the recovered catalyst was the corresponding PS-DABCO(N<sub>3</sub>)<sub>2</sub> that showed to be equally efficient. The plausible mechanism is depicted in Scheme 5. Although these preliminary reactions were conducted on a small scale (0.5-1.0 mmol), we have observed that, water has a positive influence on the dispersion of the reaction mixture facilitating the recovery of the catalyst and product. In fact, the catalyst PS-DABCOF<sub>2</sub> remains dispersed in water and by adding EtOAc (1.0 mL/mmol) to the reaction mixture the product is dissolved in the organic phase and therefore can be separated from aqueous layer by simple suction. The product can be isolated after evaporation. Both water and catalyst are therefore easily recovered and have been reused in further 10 runs with no change in the results. Under these conditions E-factor for the preparation of 4-azido-heptan-2-one is 8.6 (Scheme 6). This represents a reduction of ca. 60% compared to our previous batch protocol [18] and a 90% reduction compared to other literature procedures [19]. The protocol has been extended to several other substrates and all the E-factors values ranged between 5.9-10.5, ca. 3 times smaller than our previous procedure operating under SolFC [18].

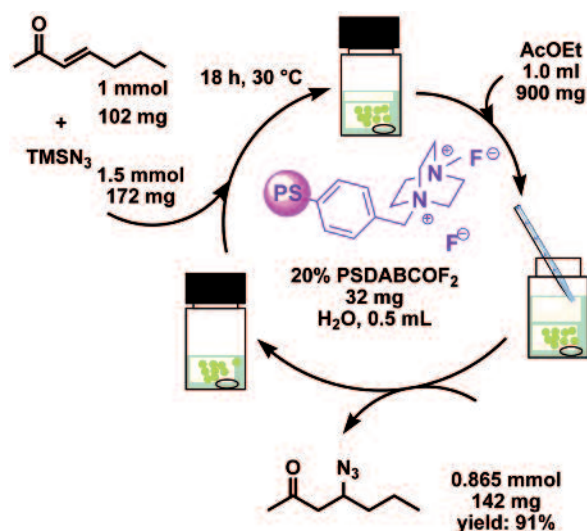
To further improve the efficiency of our approach we have also realized the azidation of representative  $\alpha,\beta$ -unsaturated ketones on a large scale by setting a continuous-flow reactor that according to our previous reports in this field, has been designed to optimize the recovery and reuse of the catalyst, to minimize waste and in particular the amount of organic solvent needed to isolate the final products. The continuous-flow protocol has allowed to further reduce the E-factor to 1.7-1.9 (Scheme 7) (ca. 80% compared to the previous batch conditions and 93-98% compared to literature procedures). The continuous-flow pro-



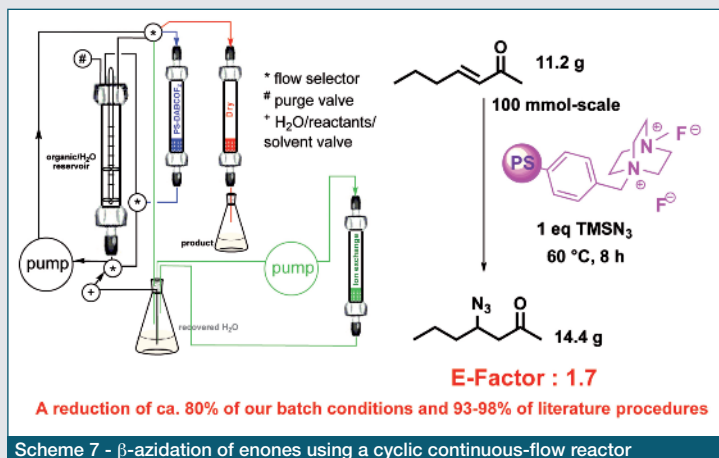
Scheme 4 - Representative example of the JandaJel-TBD catalyzed ring-opening of epoxides by thiols under SolFC



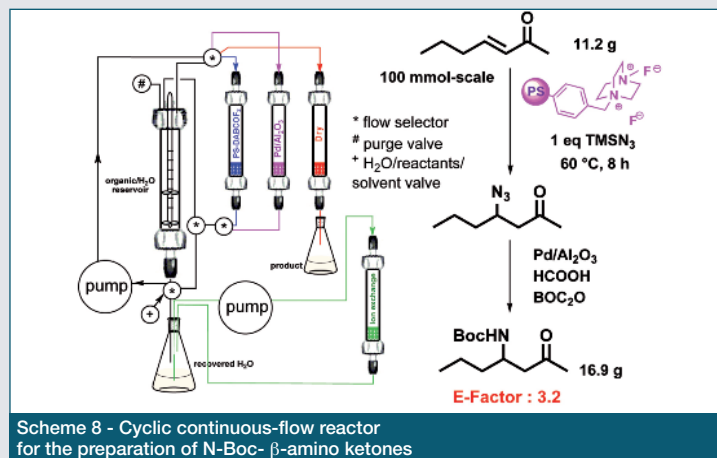
Scheme 5 - Plausible mechanism of the process involving PS-DABCO catalysts



Scheme 6 - Scheme of the small scale protocol for the  $\beta$ -azidation of enones in water with recovery and reuse of catalyst PS-DABCOF<sub>2</sub>



protocol has allowed to minimize the use of  $\text{TMSN}_3$  making the recovery and reuse of water and catalyst very efficient and simple. Finally, we have also investigated the possibility to further manipulate the  $\beta$ -azido ketone using flow-procedures. We have investigated and defined the use of a novel reduction system based on  $\text{Pd}/\text{Al}_2\text{O}_3$  (5 mol%) and an equimolar amount of  $\text{HCOOH}$ . Preliminary experiments confirmed that this catalytic system was able to reduce a  $\beta$ -azido ketone to the corresponding  $\beta$ -amino ketone but these compounds are very unstable. For this reason we have directed our efforts to set a procedure for the reduction of the azido group but in the presence of the protective agent. The reduction step was successful when performed in the presence of 1.0 equiv of  $\text{Boc}_2\text{O}$ . At this point a multistep protocol operating in continuous-flow conditions was realized and the preparation of representa-



tive *N*-Boc- $\beta$ -amino ketones starting from the corresponding enones was accomplished with a very satisfactory E-factor values (2.7-3.2) (Scheme 8).

In conclusion, with the recent examples of the research carried out in our laboratory we have tried to show that fundamental research can effectively contribute to the development of an environmentally- and chemically-efficient modern chemistry. *Green Chemistry* principles push towards the realization of novel synthetic tools that should be able to combine high chemical efficiency but also the need for minimizing production cost (mainly reducing waste). Fundamental research plays a pivotal role in this realm and is responsible for the training of a new generation of chemists able to actively contribute to the actual needs of the chemical production.

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## RIASSUNTO

### Strumenti sintetici innovativi per la definizione di reattori a flusso continui sostenibili

Il Laboratory of Green Synthetic Organic Chemistry (Green SOC) di Perugia si occupa di metodologie sintetiche innovative capaci sia di migliorare la resa e la selettività di un processo ma anche di minimizzare la produzione di rifiuti ad esso associata. Come alternativa al solvente organico si propone l'uso dell'acqua o delle condizioni di assenza di solvente. Infine per ridurre i rifiuti nella produzione della chimica fine si realizzano processi basati su reattori a flusso continuo.