Universidad CEU San Pablo
CEINDO – CEU Escuela Internacional de Doctorado

PROGRAMA en CIENCIA Y TECNOLOGÍA DE LA SALUD

Development of novel continuous flow methodologies using metal catalysts: Applications in drug synthesis

TESIS DOCTORAL

Presentada por:
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MADRID
2020

A mis padres

#Nuncadejesdecreer

This PhD has been supervised by Prof. Javier Pérez Castells and Prof. Gema Domínguez Martín. I would like to thank both their patience, closeness, and support. I want to acknowledge to Prof. Javier Pérez Castells that he always relied on me and gave me the opportunity to work in his group since I met him when I was a 3rd year Pharmacy student. I acknowledge Prof. Gema Domínguez for the way she teaches and works, so powerful, energetic, and cheerful that made the daily work easier and enjoyable.

I have to admit that I was incredibly lucky to have Dr. Jaime Blanco-Urgoiti as industrial partner. He acted as another mentor and that is something very enriching and rewarding. I would like to acknowledge him for all his teachings and guidance.

I wish to thank Prof. C. Oliver Kappe for giving me the opportunity to work in his group for 4 months, and Prof. C. A. Hone for his advices, help and support. I really appreciated my stay in Graz.

Alberto, Álex y Jose María were my lab mates during these 4 years. I would like to thank them the great experience that has been working together. The atmosphere in the laboratory has been incredible and pleasant. They have become good friends and I hope this will remain for a long time.

Moreover, I would like to thank to all the Master and undergraduate students that have passed around the lab. Especially, all the ones that have worked with me and did their bit in the work that I have done these years: Lucia M., Gilbert S., Raquel R., Elena V., Naiara P., Miryam G., Mateo C. and Javier M. In the same way, I thank the Medicinal Chemistry group for his advices and resources.

I cannot conclude this report without expressing my gratitude to my family, especially my parents for their unflagging support and comprehension since the very first day of this Ph.D. Thanks also to all my friends with whom I have shared good and bad times over these years.

This thesis, titled: '*Development of novel continuous flow methodologies using metal catalysts: Applications in drug synthesis'*, is presented as a collection of publications with the agreement of my supervisors: Prof. Javier Pérez Castells and Prof. Gema Domínguez Martín. We have followed the requirements approved by the Direction committee of CEINDO on the 30th of November of 2017. In the aim to achieve the International PhD supplement we have followed the corresponding indications and thus this report is written in English and includes a brief summary in Spanish. This Ph.D. was carried out in the Chemistry and Biochemistry department, of the Pharmacy faculty, San Pablo CEU University (Madrid, Spain).

This thesis has given rise to the following publications:

- J. García-Lacuna, G. Domínguez, J. Pérez-Castells, *ChemSusChem* **2020**, *13*, 5138-5163. DOI: 10.1002/cssc.202001372
- J. García-Lacuna, G. Domínguez, J. Blanco-Urgoiti, J. Pérez-Castells *Org. Biomol. Chem.* **2019***, 17*, 9489-9501. DOI: 10.1039/C9OB02124H
- J. García-Lacuna, G. Domínguez, J. Blanco-Urgoiti, J. Pérez-Castells *Org. Lett.* **2018***, 20*, 5219-5223. DOI: 10.1021/acs.orglett.8b02168
- J. García-Lacuna, G. Domínguez, J. Blanco-Urgoiti, J. Pérez-Castells *Chem. Commun.* **2017***, 53*, 4014-4017. DOI: 10.1039/C7CC01749A.

In addition, the following publication includes part of my work during my internship in the group of Prof. C. O. Kappe (University of Graz, Austria).

- M. Prieschl, J. García-Lacuna, R. Munday, K. Leslie, A. O'Kearney-McMullan, C. A. Hone, C. O. Kappe *Green Chem*. **2020**, *22*, 5762-5770. DOI: 10.1039/D0GC02225J

The bibliometric data on the journals were these articles have been published are presented in the corresponding chapters.

Madrid, October 2020

Prof. Gema Domínguez Martín

Prof. Javier Pérez Castells

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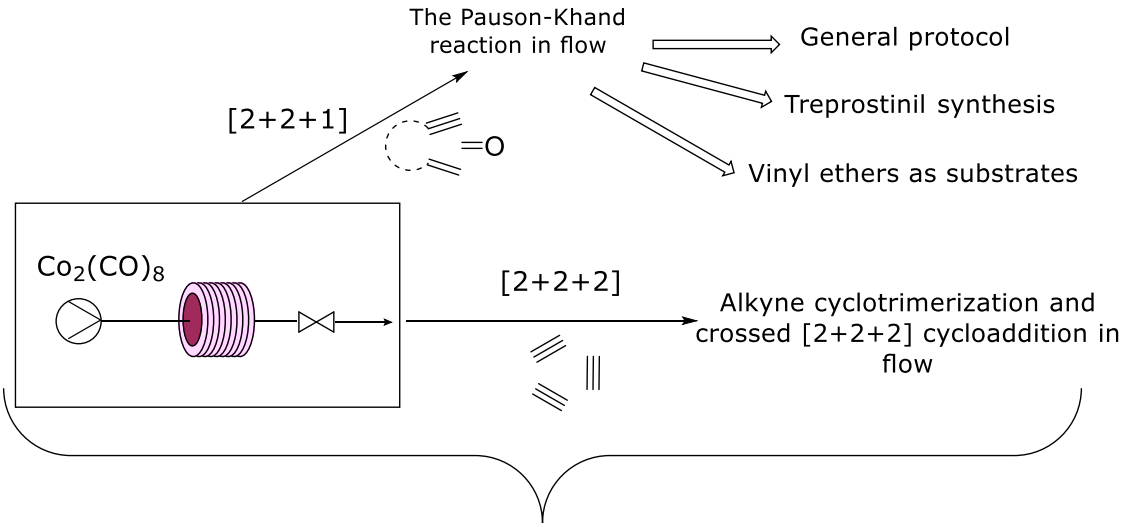
1. General introduction

The general aim of this PhD is the development of novel methodologies in continuous flow reactors in order to carry out metal catalyzed reactions. We have focused on homogeneous dicobalt octacarbonyl catalyzed cycloadditions. Applications in the synthesis of one pharmaceutical is also shown.



First, a new protocol for a cobalt catalyzed Pauson-Khand cycloaddition in a flow reactor is developed. The Pauson-Khand reaction in flow had only one precedent in the literature. However, our protocol significantly improves the previous methodology as it is is catalytic, scalable and with broader scope. Our methodology was published as a communication, in a multidisciplinary chemistry journal due to its broad interest and high applicability. Thus, we chose *Chemical Communicatios,* a high impact journal (Impact factor of 6.297 in 2017, Q1) published by the Royal Society of Chemistry. After this general study of reaction conditions and scope was finished, the novel procedure was applied to the total synthesis of the drug Treprostinil, where the key catalytic Pauson-Khand reaction (PKr) was performed in flow. This chapter includes, mainly, organic synthetic work applied to the improvement and scalability of the synthesis of this drug. Therefore, we selected the journal *Organic & Biomolecular Chemistry* (Impact factor 3.412 in 2019, Q1) for the publication, as it is specialized in new or significantly improved protocols or methodologies in total synthesis of natural products or pharmaceuticals. Furthermore, a new protocol that allows the use of vinyl ethers as substrates for the PKr is being developed, which will lead to a novel synthesis of multisubstituted tricyclic benzofurans. The results of this latter study have not been published yet.

In another chapter of this report, a new protocol that uses the same catalyst for alkyne cyclotrimerizations and crossed [2+2+2] cycloadditions using a flow reactor is developed. *Organic*

letters was the chosen journal for the publication of this work, which is a high impact journal in the field of organic chemistry (6.555 of impact factor in 2018, Q1).

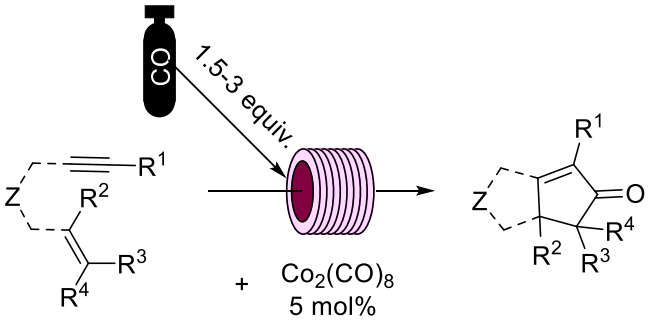
Finally, during the thesis period we carried out an extensive literature revision and analysis of all the cycloadditions performed using continuous flow methodologies. We evaluated the benefits gained by each kind of cycloaddition in flow, by comparison with traditional methodologies. The remaining challenges and the future perspectives were addressed. The resulting review manuscript was published in *ChemSusChem* journal, a high impact journal (Impact factor of 9.762 in 2019, Q1) focused on sustainable chemistry.

Furthermore, a publication which includes part of the work done during my research stay in C. O. Kappe´s group is also presented. The work involves a metal catalyzed reaction, using a gas-liquid regime, optimized using a flow reactor. This work was published in *Green Chemistry*, due to the great sustainable progress of the contribution. This journal is specialized in innovative research on the development of alternative green and sustainable technologies and had an impact factor of 9.480 in 2019 (Q1). The paper is part of a larger project that will also be published in the future.

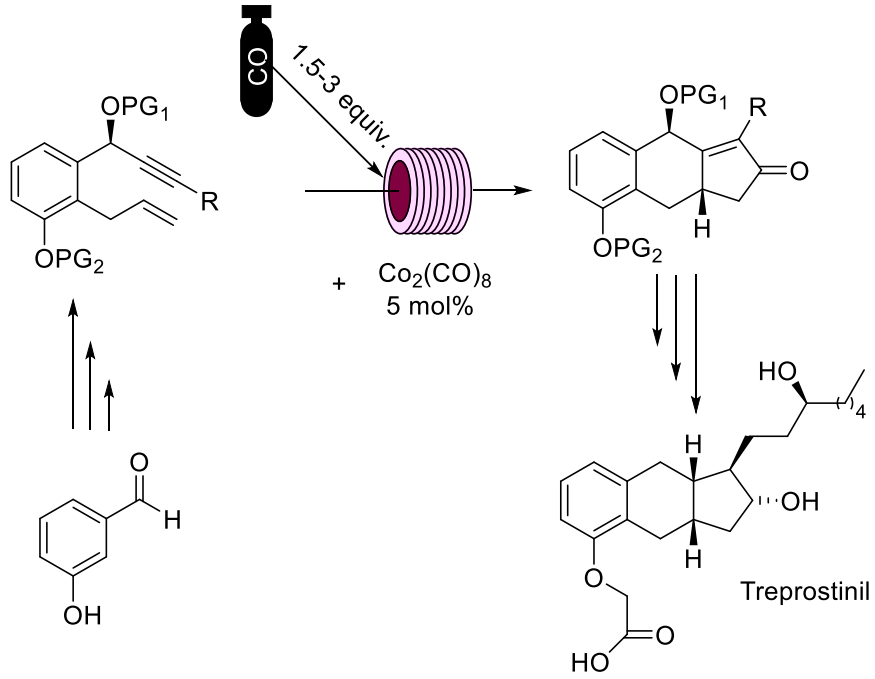
2. Aims and background

This report includes contributions that deal with two different fields of organic and organometallic synthesis performed in flow: The Pauson-Khand reaction and [2+2+2] cycloadditions. After presenting the main goals of this thesis we include a background section where we summarize the state of the art in these fields which justifies the goals proposed.

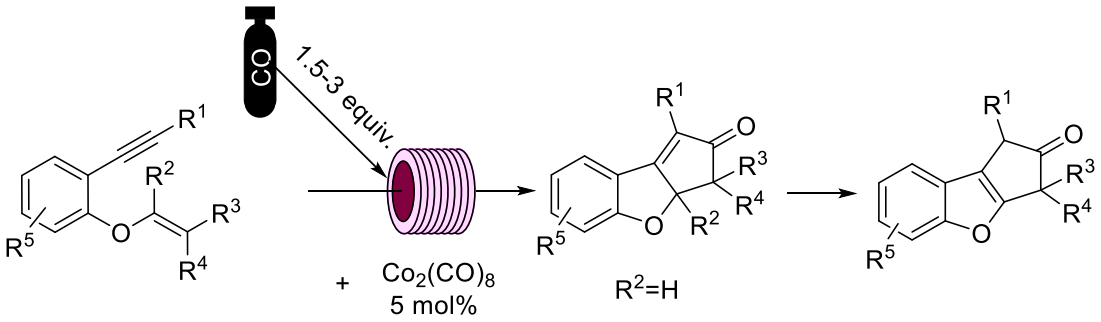
During the past 20 years, our group has made various contributions in the Pauson-Khand reaction (PKr) field. Some years ago, we decided to collaborate with *CsFlowChem,* a company specialized in continuous flow synthesis. Continuous flow reactors form part of a rapidly growing research area that is changing the way organic chemistry is performed in both academia and industrial research. Some advantages are thermal management, safer handling of hazardous chemicals, greener processes and easy scale-up. Combining the potential of these reactors and the previous experience of our group in the PKr, and other metal-catalyzed cycloadditions, we envisioned the possibility of developing flow protocols that may solve problems of safety, productivity, and scalability of these reactions.



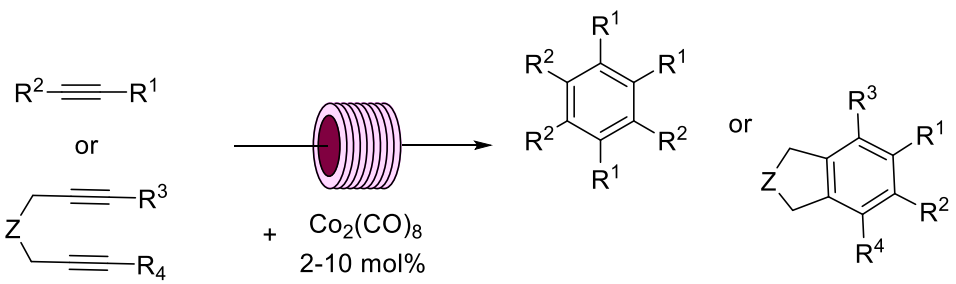
Furthermore, once the protocol for the PKr in flow was developed, the next goal was its application to the production of a drug. Treprostinil, a PGI2 analog used for the treatment of pulmonary hypertension, was chosen, due to its high cost and complex synthesis. Our novel PKr protocol in flow was used as the key step of the synthesis. In addition, new reaction pathways, the use of different protecting groups, and the possibility of performing in flow another step of the synthesis, in particular a Claisen rearrangement were explored.



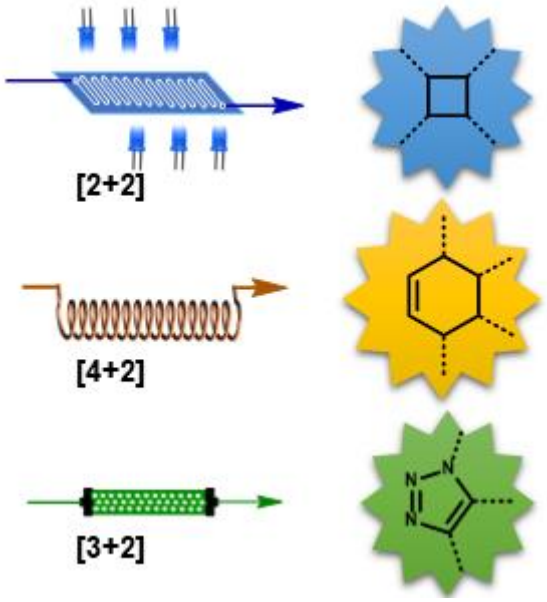
On the other hand, one kind of substrates that are historically unfavorable for the PKr are vinyl ethers. We envisioned that our flow conditions would allow the use of these substrates efficiently. Thus, we have recently been working on the optimization of the PKr in flow using vinyl ethers tethered to alkynes through aromatic rings to easily build tricyclic multisubstituted benzofurans.



Another goal has been the development of new protocols for metal catalyzed [2+2+2] cycloadditions using continuous flow. Alkyne cyclotrimerization products were detected as side products in the PKr. Therefore, we planned to benefit from the intense conditions that could be applied using flow reactors to explore the scope and versatility of [2+2+2] cycloadditions using the cheap and commercially available $Co_2(CO)_8$ as the catalyst.



The final goal was the elaboration of an extensive literature revision and analysis of all the cycloadditions performed in continuous flow, exhibiting all the benefits compared to batch protocols. Cycloadditions and flow chemistry are the two common issues in this thesis and despite the high number of reviews involving the flow chemistry field, we found a lack of a comprehensive literature revision concerning the benefits of doing cycloadditions in flow.



2.1. Flow chemistry

Over the past decade, flow reactors and microstructured devices are changing the way to perform organic reactions, moving away from the classical round-bottom flasks and other traditional techniques. The following figure shows the increase in number of publications in the field of flow chemistry applied to the synthesis of pharmaceuticals in the last 20 years. As a whole, flow technologies represent a drastic change in the way organic reactions are performed in both academia and the chemical industry. What is more, continuous flow methodologies can be combined with other enabling technologies, such as microwave irradiation, supported reagents or catalysts, photochemistry, inductive heating, electrochemistry, new solvent systems, 3D printing, or microreactor technology. These combinations allow the development of fully automated processes with increased efficiency and, in many cases, improved sustainability.

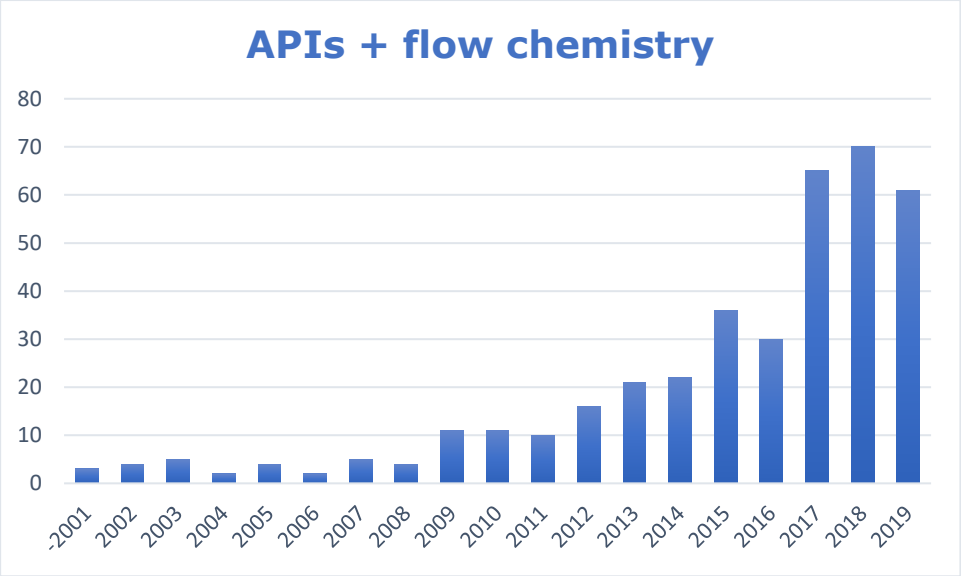
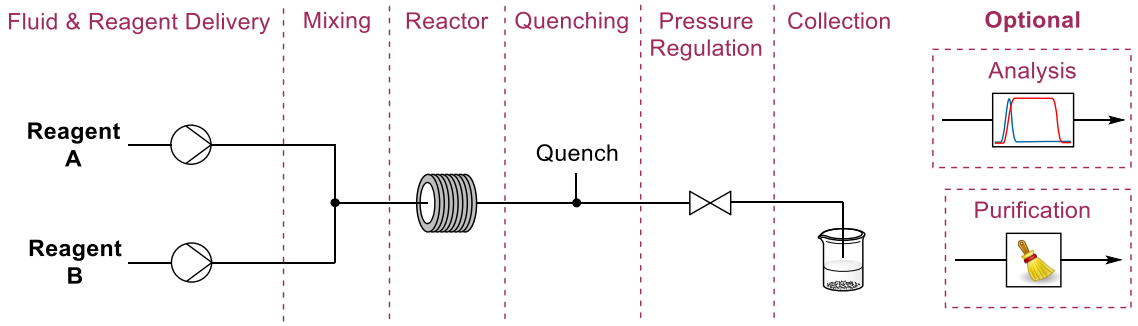


Figure 1[1]: The number of publications that share both concepts is graphed to show the growing tendency

A schematic representation of a continuous flow system is depicted in Scheme 1.

[1] Source WoS: search done 21/08/2020. “Flow chemistry” + “pharmaceutical” in all the chemistry categories but for analytical chemistry (Only articles and reviews).



Scheme 1

- Reagents: They are introduced into the system using pumps in homogenous solutions. They can be introduced separately if required. The solubility of the reagents is therefore an important issue in flow chemistry. Nevertheless, the use of oscillatory flow reactors, which may introduce particles in suspension, is growing in recent years.[2]
- Reactors: In contrast to batch methodologies flow reactors can be quite different from one protocol to another. They can vary from simple microchips with volumes in the range of microlitres to plug flow reactors with volumes in the order of litres. In the same way, they can be complex commercial systems or bespoke homemade reactors. The reactor is usually heated and/or cooled and furthermore, can be adapted to photochemistry, electrochemistry, use of gases… Inert perfluorinated polymers (PTFE, PFA, PEEK, and FEP) are the most common reactor and tubing materials as well as stainless steel. Different reactor lengths can be used to modulate the residence time which is the total time that the substate spends inside the reactor.
- Quenching: Hazardous or highly reactive reagents may be quenched in line in a controlled environment
- Pressure regulation: Back pressure regulators are often used in order to keep a constant pressure in the system. Working at high pressures allows the use of solvents in liquid state at temperatures above their boiling points. Additionally, system pressure can sometimes affect the outcome of the reaction.
- Analysis: In-line NMR, IR, HPLC might be coupled to the system to have an instantaneous monitorization of the sample. In automated platforms, data obtained can modify parameters in order to improve reaction outcome.[3]
- Purification: Techniques such as metal-scavengers, continuous separations might be used to improve the purity of the desired products.

Importantly, all of these individual parts can be arranged interchangeably and repetitively, resulting in an infinite number of possible modifications. Highly complex multistep sequences can be applied to natural product synthesis or on-demand production of pharmaceuticals.[4]

[2] P. Bianchi, J. D. Williams, C. O. Kappe *J. Flow Chem.* **2020**, *10,* 457-490.
[3] For examples of inline anaylsis and purification see: M. Baumann *Org. Biomol. Chem.* **2018**, *16*, 5946-5954.
[4] S. Mascia, P. L. Heider, H. Zhang, R. Lakerveld, B. Benyahia, P. I. Barton, R. D. Braatz, C. L. Cooney, J. M. B. Evans, T. F. Jamison, K. F. Jensen, A. S. Myerson, B. L. Trout *Angew. Chem. Int. Ed.* **2013**, *52*, 12359-12363.

Furthermore, continuous flow systems reported so far in the literature can be generally divided into four types, as suggested by Kobayashi and co-workers (Figure 2):[5]

a) Reagents are flowed through the reactor, and, at the end, the product is collected.

b) One of the reactants is supported onto a solid and confined into the reactor. The substrate is passed through the reactor, and if the reaction goes to completion, the exiting reaction mixture will contain only the desired product.

c) A homogeneous catalyst is employed; the catalyst flows through the reactor together with the reactants, so, at the end, it must be separated from the reaction product.

d) The catalyst is previously immobilized into the reactor, while the reagents are passed through. In this typology, no separation of the product from the catalyst is usually needed. In addition, the catalyst can be easily recycled and/or reused.

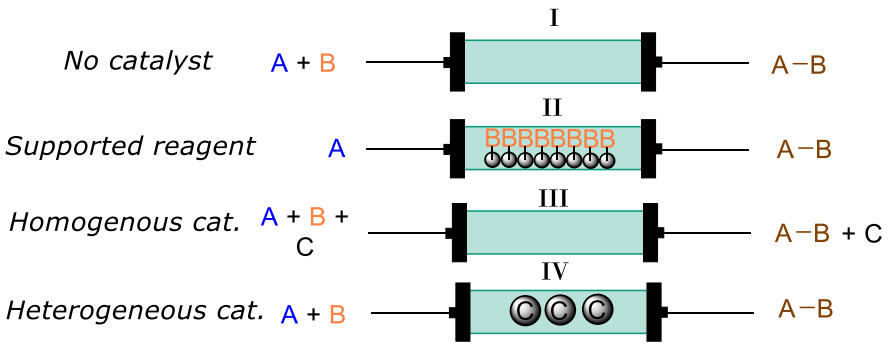


Figure 2: Reactors according to Kobayashi's classification

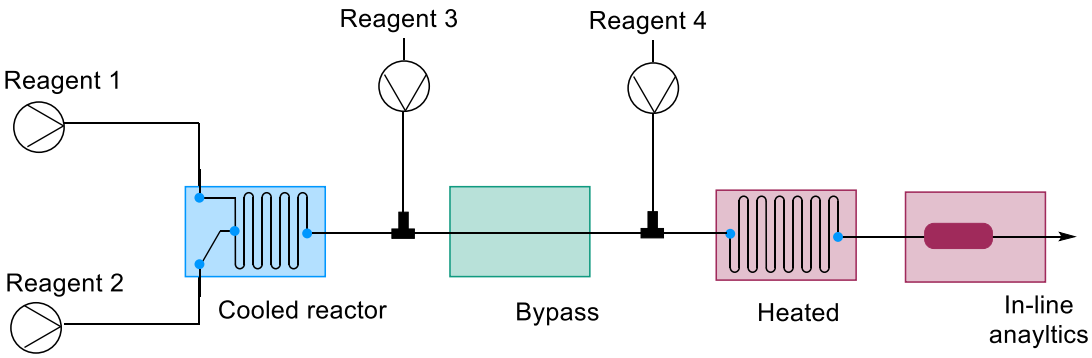
Some of the advantages of continuous flow reactors over traditional batch methodologies are summarized below:[6]

- Quick optimization of conditions: Flow chemistry enables an easy, precise, and fast change of conditions that allow a quick success in achieving the best conditions.
- Automatization: Highly automated flow synthesis platforms are used at different stages in drug development: advanced medicinal chemistry, optimization of synthetic routes, scaling up of drug candidate synthesis, and manufacturing of active pharmaceutical ingredients (APIs). The use of flow techniques in drug discovery includes library synthesis, high throughput screening, and integration of synthesis with biological test platforms. These systems, which monitor and react in real-time, are able to optimize different reaction steps and could generate thousands of individual doses of different APIs in hours (Scheme 2).[7]

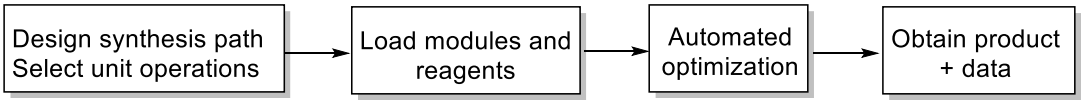
[5] T. Tsubogo, H. Oyamada, S. Kobayashi *Nature* **2015**, *520*, 329-332.

[6] For selected general reviews on flow chemistry advantages see: a) R. L. Hartman, J. P. McMullen, K. F. Jensen *Angew. Chem. Int. Ed.* **2011**, *50*, 7502-7519; b) F. Benito-López, R. J. M. Egberink, D. N. Reinhoudt, W. Verboom *Tetrahedron* **2008**, *64*, 10023-10040; c) L. Degennaro, C. Carlucci, S. De Angelis, R. Luisi *J. Flow Chem* **2016**, *6*, 136-166; d) P. Brandão, M. Pineiro, T. M. V. D. Pinho e Melo *Eur. J. Org. Chem.* **2019**, 7188-7217; e) C. Wiles, P. Watts *Green Chem.* **2012**, *14*, 38-54.

[7] a) A. Bédard, A. Adamo, K. C. Aroh, M. G. Russell, A. A. Bedermann, J. Torosian, B. Yue, K. F. Jensen, T. F. Jamison *Science* **2018**, *361*, 1220-1225; b) A. Adamo, R. L. Beingessner, M. Behnam, J. Chen, T. F. Jamison, K. F. Jensen, J. M. Monbaliu, A. S. Myerson, E. M. Revalor, D. R. Snead, T. Stelzer, N. Weeranoppanant, S. Y. Wong, P. Zhang *Science* **2016**, *352*, 61-67; c) P. Sagmeister, J. D. Williams, C. A. Hone, C. O. Kappe *React. Chem. Eng.* **2019**, *4*, 1571-1578.



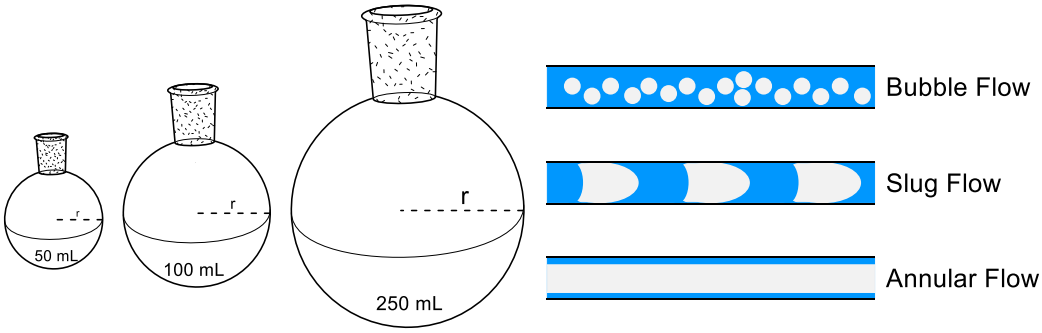
Each module may be different: Photo/cooled/heated/packed bed reactor
Liquid-liquid separators, bypass...



Scheme 2

- Better handling of hazardous reagents: The specific properties of these reactors allow an exceptionally fast heat and mass transfer. In microstructured devices of this type, virtually instantaneous mixing can be achieved for all but the fastest reactions. In the same way, hot spots and thermal runaways derived from the accumulation of heat can be avoided. As a result of the small reactor volumes, the overall safety of the process is significantly improved, even when harsh reaction conditions are used. Therefore, flow technology is the preferred choice for ultrafast reactions and highly toxic/unstable intermediates even using extreme conditions.[8]
- Use of gases: The increase of the gas-liquid interfacial area generally accelerates the reaction and improved mixing generally gives better yields. This is combined with the possibility of using high pressures safely which aids the dissolution of the gas. Interestingly, using mass-flow controllers allows determining the amount of gas used, thus permitting the use of stoichiometric quantities of the gas. In addition, if the gas used is hazardous or very toxic it benefits form handling smaller amounts in a safer way (See Figure 3).[9]

[8] A) B. Gutmann, D. Cantillo, C. O. Kappe *Angew. Chem. Int. Ed.* **2015**, *54*, 6688-6728; b) M. Movsisyan, E. I. P. Delbeke, J. K. E. T. Berton, C. Battilocchio, S. V. Ley, C. V. Stevens *Chem. Soc. Rev.* **2016**, *45*, 4892-4928.
[9] C. J. Mallia, I. R. Baxendale *Org. Process Res. Dev.* **2016**, *20*, 327-360.



Type of contactor	Interfacial area (m^2 m^{-3})
50 mL round bottom flask	60
100 mL round bottom flask	46
250 mL round bottom flask	35
Tube reactors (Horizontal/coiled)	50-700
Tube reactors (vertical)	100-2000
Stirred tank	100-2000
Gas-Liquid microchannel contactor	3400-18000

Figure 3: Interfacial area of different contactors and gas-liquid flow regimes.

Two important hazarous gases used in organic synthesis are carbon monoxide and hydrogen. Since the development of advantageous flow technologies, their use has drastically increased.

- Carbon monoxide is a colorless, odorless, tasteless, highly toxic and flammable gas; with poor solubility in most organic solvents. Thus, reactions employing this gas are most commonly carried out at elevated pressure. This makes the use of carbon monoxide a risk, especially in standard laboratories or when large quantities are needed. Nevertheless, this hazardous gas is an important C1 building block offering the possibility to install a carbonyl group into organic molecules. Continuous flow chemistry has represented in the last decade a safe and efficient tool for different carbonylations using gaseous CO.[9,10]
- Hydrogenation reactions are frequently used both in research and at production scale, not only in the pharmaceutical industry, but also in the petrochemical and food industry. Hydrogen is an extremely flammable gas, with the potential for highly exothermic detonation. In addition, most hydrogenation reactions tend to be performed under high pressures, increasing risks substantially. Hydrogenation reactions using both heterogeneous and homogeneous catalysts have been described using a wide variety of continuous flow protocols, with different catalysts and reactors.[11] The reduction of different functional groups within continuous flow reactors has been achieved,[12] but ester

[10] M. B. Plutschack, B. Pieber, K. Gilmore, P. H. Seeberger *Chem. Rev.* **2017**, *117*, 11796-11893.
[11] a) M. Irfan, T. N. Glasnov, C. O. Kappe *ChemSusChem* **2011**, *4*, 300-316; b) P. J. Cossar, L. Hizartzidis, M. I. Simone, A. McCluskey, C. P. Gordon *Org. Biomol. Chem.* **2015**, *13*, 7119-7130; c) T. Yu, J. Jiao, P. Song, W. Nie, C. Yi, Q. Zhang, P. Li *ChemSusChem* **2020**, *13*, 2876-2893.
[12] D. L. Riley, N. C. Neyt *Synthesis* **2018**, *50*, 2707-2720.

reductions needed stoichiometric amounts of reactants, like DIBAL-H (Diisobutylaluminium hydride)[13] or LDBBA (Lithium diisobutyl-*tert*-butoxyaluminum hydride)[14] to form aldehydes or borane dimethyl sulfide[15] complex to obtain alcohols. There was no flow procedures using H_2 and a catalytic amount of metal complex to reduce esters into the corresponding alcohols in robust, safe, scalable and green approach. On the other hand, several batch protocols use homogenous Ru catalysts to perform ester hydrogenation with high turnover numbers.[16] Moving those procedures into continuous flow reactors would increase the overall safety and scalability of the process, which is especially important if kilograms of the product are needed.

Another kind of reactor used for gases in continuous applications is the tube in tube reactor. It consists of a gas-addition tool for continuous processes in which the inner tube is made of a robust, but porous material such as Teflon AF-2400, which selectively allows gases to cross but not liquids. Thus, keeping a higher pressure in the gas than in the liquid phase would allow the gas to diffuse and mix with the liquid phase (Figure 4). Different gases are used, such as O_2, CO, ethylene…which are supplied through the inner tube and diffuse into an outer tube where they dissolve and react in the passing through solution.[17]

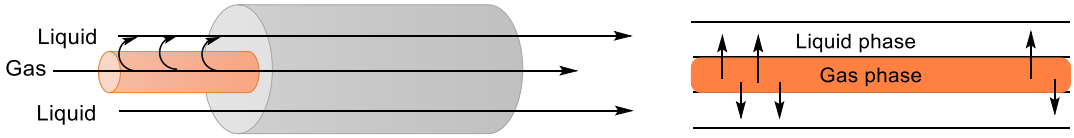


Figure 4:General picture of a tube in tube reactor

The tube-in-tube reactors are especially useful in the on-demand generation, separation, and reaction of gases. The use of gas tanks/cylinders is avoided. For instance, dry diazomethane can be formed in the inner tube *in situ* and subsequently diffuse onto the outer tube and react. Thus, this strategy completely avoids the storage and transportation of hazardous gases and significantly improves the safety of the process.[18]

- Photochemistry: Flow conditions provide efficient control of reaction conditions including uniform irradiation (Figure 5). Therefore, multigram syntheses are performed within hours instead of days. Traditional photochemical reactors have been used generally at the lab scale as the technology became unfavourable for large scale transformations. With the new advances in flow photochemistry, many photochemical reactions have become

[13] a) L. Ducry, D. M. Roberge *Org. Process Res. Dev.* **2008**, *12*, 163-167; b) D. Webb, T. F. Jamison *Org. Lett.* **2012**, *14*, 568-571; c) M. Yoshida, H. Otaka, T. Doi *Eur. J. Org. Chem.* **2014**, *2014*, 6010-6016.
[14] J. de M. Muñoz, J. Alcázar, A. de la Hoz, A. Díaz-Ortiz *Eur. J. Org. Chem.* **2012**, *2012*, 260-263.
[15] S. B. Ötvös, C. O. Kappe *ChemSusChem* **2020**, *13*, 1800-1807.
[16] S. Werkmeister, K. Junge, M. Beller *Org. Process Res. Dev.* **2014**, *18*, 289-302.
[17] F. Mastronardi, B. Gutmann, C. O. Kappe *Org. Lett.* **2013**, *15*, 5590-5593.
[18] C. A. Hone, C. O. Kappe *Chem. Eur. J.* **2020**, *Just accepted,* DOI: 10.1002/chem.202001942

greener and more scalable. What is more, continuous flow photochemistry is not only applied in organic synthesis, but also in material science, and water treatment.[19]

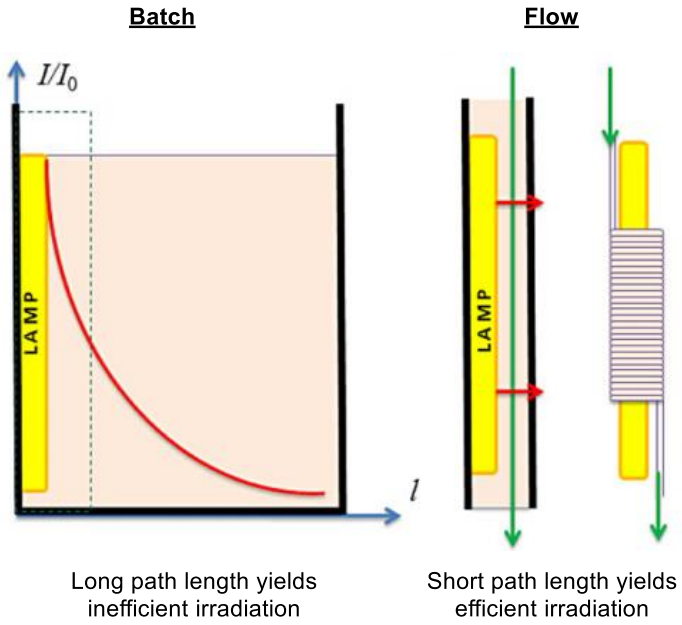


Figure 5[20]:Comparison of irradiation in batch and flow.

- Electrochemistry: The high surface area-to-volume ratios of microreactors allow effective heat and mass transportation, which can be helpful during electrosynthesis. For this reason, these devices can mitigate some of the problems associated with conventional electrosynthetic processes in batch reactors. In addition, microreactors offer higher conversions, product yields, and throughput compared to classical electrochemical reactors.[21]
- Safer control of high pressures/temperatures: The exact control of reaction conditions makes possible to work with overheated solvents and high pressures. New process windows can be explored.
- Scaling: A drug candidate entering clinical trials is needed in multigram to multikilogram amounts and scaling is often considerably easier, inexpensive, and safer through continuous processes compared with traditional batch methods. In addition, no changes in reaction conditions are generally required.

All these advantages are increasingly appreciated by the pharmaceutical industry and, thus, a growing number of companies are starting to employ continuous-flow technologies on a

[19] a) C. Sambiagio, T. Noël *Trends in Chemistry* **2020**, *2*, 92-106; b) F. Politano, G. Oksdath-Mansilla *Org. Process Res. Dev.* **2018**, *22*, 1045-1062; c) D. Cambié, C. Bottecchia, N. J. W. Straathof, V. Hessel, T. Noël *Chem. Rev.* **2016**, *116*, 10276-10341; d) R. Ciriminna, R. Delisi, Y. Xu, M. Pagliaro *Org. Process Res. Dev.* **2016**, *20*, 403-408; e) Y. Su, N. J. W. Straathof, V. Hessel, T. Noël *Chem. Eur. J.* **2014**, *20*, 10562-10589; f) M. Di Filippo, C. Bracken, M. Baumann *Molecules* **2020**, *25*, 356.
[20] K. Gilmore, P. H. Seeberger *Chem. Rec.* **2014**, *14*, 410-418.
[21] M. Atobe, H. Tateno, Y. Matsumura *Chem. Rev.* **2018**, *118*, 4541-4572.

more routine basis.[22] However, there are factors which, to date, have slowed the mainstream adoption of continuous manufacture within the chemical industries:

- Cultural change: When moving from a typical batch process to flow methodology, a critical evaluation of the chemistry is needed to determine if there is an advantage (cost analysis/suitability of process in flow).
- Management support: Flow techniques offer the ability to perform more hazardous and batch-inaccessible chemistries thereby unlocking access to products that would have been difficult to be competitive in. Changing culture and technology can be an expensive transition, but must be embraced, business cases developed, scrutinized, and driven to completion before falling behind the competition.
- Education: Lack of trained personnel has slowed the growth of the continuous manufacturing industry.

In the other hand, despite all these advantages, not all reactions are suitable to be performed in flow. The special ways in which heating, mixing, and reaction times are adjusted in the flow devices may change the composition of final products. Sometimes side reactions and decomposition can be minimized, but others, similar results than in batch are achieved. Some procedures give better yields or selectivity whereas others do not show any benefits. Finally, although scaling up is always convenient in flow, it may not justify the resources needed to use the flow methods. The recently appeared Hitchhiker's guide for flow chemistry outlines the reactions that show real benefit to be performed in flow.[10]

Ultimately, compared to batch procedures, continuous flow reactors can significantly contribute to represent a greener approach. Sustainable chemical processes rely not only on effective chemistry but also on the implementation of reactor technologies that enhance reaction performance, reduce energy consumption and improve overall safety. The main advantages of continuous flow processes that enhance this endeavour are:[23]

- Heterogeneous catalysis (Type 4 of Figure 2) and catalyst recycling.
- Telescoping multistep reactions.
- Readily accessible and scalable photochemistry.
- More data using less material and time.
- Increasing reaction efficiency through access to a wider range of reaction conditions and a faster optimization.
- Smaller energy requirements to run continuous platforms, even if extreme conditions are needed.
- Reduced solvent volumes through the elimination of large reactors.

[22] M. Baumann, T. S. Moody, M. Smyth, S. Wharry *Org. Process Res. Dev.* **2020**, *Just accepted*, DOI: 10.1021/acs.oprd.9b00524.
[23] a) S. G. Newman, K. F. Jensen *Green Chem.* **2013**, *15*, 1456-1472; b) L. Rogers, K. F. Jensen *Green Chem.* **2019**, *21*, 3481-3498.

- Safer and controlled use of extreme temperatures and pressures, including access to supercritical fluids and use of gases.

For these reasons, mainly focused on the principles of prevention, continuous manufacturing is encouraged by the ACS GCI (American Chemical Society Green Institute) Pharmaceutical Roundtable.[24] As a consequence, if implemented correctly, continuous manufacturing has the potential to reduce the time a pharmaceutical takes to reach the market. In addition, acceleration through process intensification and easier scaling up, may lead to a reduction in production costs.

As a consequence of the benefits summarized above a high number of APIs, natural products and commodity chemicals are now synthesized using multi-step continuous-flow systems.[25] These complex systems achieve sequential transformations in a mobile scaffold resembling an in vitro Nature's polyketide synthases.[26] Integrating into a single, all *in continuo* process not only the synthesis of complex molecules but the whole manufacturing process is one of the future challenges. Furthermore, an automated control system can monitor and control the process assuring product quality.[27] The main advantages would be direct transfer from development to manufacturing that will shorten the whole process time and will allow to move the products faster into the market. Furthermore, money saving, greater flexibility, small footprint, and decreased inventory may be realized through a colocation and integration of process steps in one single facility.

In spite of the high number of flow reviews published, we found a lack of literature compilation in relation to cycloadditions performed in flow. Cycloadditions are atom efficient transformations and the most common way to build carbo- and heterocycles. Advantages such as intensification of conditions, safer handling of hazardous reagents, and straightforward scaling up are especially important in several cycloadditions such as CuAAC (Copper(I)-catalyzed azide alkyne cycloaddition), Diels-Alder, ozonolysis, and [2+2] photocycloadditions. Additionally, these reactions are key steps in some pharmaceutical synthesis and their industrial application is related to a convenient flow protocol.

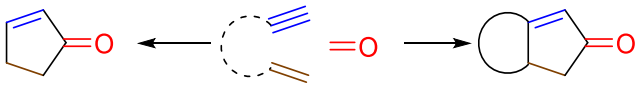
[24] P. Poechlauer, J. Colberg, E. Fisher, M. Jansen, M. D. Johnson, S. G. Koenig, M. Lawler, T. Laporte, J. Manley, B. Martin, A. O'Kearney-McMullan *Org. Process Res. Dev.* **2013**, *17*, 1472-1478.
[25] R. Porta, M. Benaglia, A. Puglisi *Org. Process Res. Dev.* **2016**, *20*, 2-25.
[26] J. Britton, C. L. Raston *Chem. Soc. Rev.* **2017**, *46*, 1250-1271.
[27] S. Mascia, P. L. Heider, H. Zhang, R. Lakerveld, B. Benyahia, P. I. Barton, R. D. Braatz, C. L. Cooney, J. M. B. Evans, T. F. Jamison, K. F. Jensen, A. S. Myerson, B. L. Trout *Angew. Chem. Int. Ed.* **2013**, *52*, 12359-12363.

2.2. The Pauson–Khand reaction (PKr)

In this report, we present three contributions in the field of the Pauson-Khand reaction (PKr): the use of vinyl ethers as substrates, the new methodology in flow reactors and its application to the synthesis of treprostinil. After presenting a general overview of the PKr, we will show the most directly related precedents for each contribution.

2.2.1. Historical overview and general considerations

The Pauson–Khand reaction (PKr) is a formal [2+2+1] cycloaddition of an alkyne, an alkene, and a carbonyl unit to give a cyclopentenone. This implies the formation of three new bonds and one or two cycles in the intermolecular or intramolecular version, respectively (Scheme 3).[28]



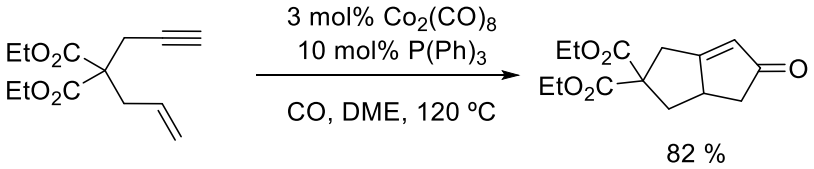
Scheme 3

First discovered as a cobalt-mediated process in the early 1970s,[29] it has remained the subject of numerous studies to improve the reaction conditions, catalysts used, broaden the scope and applications.

Although the Pauson–Khand reaction was discovered in its intermolecular form, the scope of this version in synthetic projects has always been limited by the poor reactivity and selectivity of simple alkenes. Applications have been restricted to the use of strained alkenes such as norbornene, norbornadiene, and bicyclo[3.2.0]hept-6-ene, whilst the thermodynamically more favored intramolecular version has received much more attention. The intramolecular version, introduced by Schore and Croudace in 1981,[30] avoids regioselectivity problems and has found more synthetic applications. Nevertheless, stoichiometric amounts of $Co_2(CO)_8$ were needed and the scope was limited to the formation of 5 membered rings and simple monosubstituted alkynes. In 1990, Rautenstrauch and collaborators developed an intramolecular protocol using only 0.22 mol% of $Co_2(CO)_8$. Moderate yields were achieved (around 50%) using quite extreme conditions

[28] For detailed reviews on Pauson Khand see: a) J. Blanco-Urgoiti, L. Añorbe, L. Pérez-Serrano, G. Domínguez, J. Pérez-Castells *Chem. Soc. Rev.* **2004**, *33*, 32-42; b) K. M. Brummond, J. L. Kent *Tetrahedron* **2000**, *56*, 3263-3283; c) J. D. Ricker, L. M. Geary *Topics in Catalysis* **2017**, *60*, 609-619; d) G. Dominguez, J. Pérez-Castells, in *Science of Synthesis: Metal-Catalyzed Cyclization Reactions 2* (Eds. S. Ma, S. Gao),Thieme Chem., **2017**, pp. 99-166.
[29] Early reported works on Pauson Khand reaction: a) I. U. Khand, G. R. Knox, P. L. Pauson, W. E. Watts *J. Chem. Soc. D* **1971**, 1, 36; b) I. U. Khand, G. R. Knox, P. L. Pauson, W. E. Watts *J. Chem. Soc. , Perkin Trans. 1* **1973**, 975-977; c) I. U. Khand, G. R. Knox, P. L. Pauson, W. E. Watts, M. I. Foreman *J. Chem. Soc. , Perkin Trans. 1* **1973**, 977-981; d) P. L. Pauson, I. U. Khand *Ann. N. Y. Acad. Sci.* **1977**, *295*, 2-14.
[30] N. E. Schore, M. C. Croudace *J. Org. Chem.* **1981**, *46*, 5436-5438.

(100 bar of CO, 40 bar of ethylene, and 150 ºC).[31] The first protocol of an intramolecular catalytic Pauson-Khand was developed by Jeong and coworkers in 1994. It was necessary to use additives as a way to stabilize the cobalt complexes arising from the first reaction cycle. The idea was to substitute *in situ* one or more CO ligands with different coordinating groups in order to form a more stable complex. Thus, the conversion of the catalyst onto inactive species leaving the catalytic cycle was avoided. This goal was achieved by addition of triphenylphosphine as co-ligand reaching yields between 51 and 94% (Scheme 4).[32]



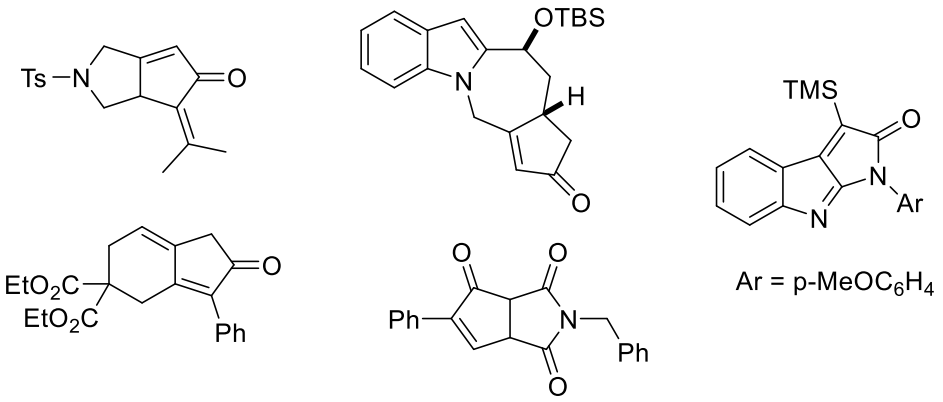
Scheme 4

Afterwards, many other additives were proposed. Thus, *N*-oxides such as TMANO (trimethylamine *N*-oxide), reduced dramatically reaction times and improved yields. However, it was used with limited substrates and stoichiometric amounts of the metal complex.[33] Good results were described by Saigo and coworkers with tributylphosphinesulfide under atmospheric pressure of CO and only 3-5 mol% of cobalt octacarbonyl.[34] A similar protocol was presented using tetramethylthiourea (TMTU) as an efficient additive. The catalytic system worked efficiently for both inter- and intramolecular examples, including the use of some internal alkynes.[35] Lewis bases with low nucleophilicity, such as 1,2-dimethoxyethane, were able to promote the cyclization. Excellent yields were obtained using this additive under a relatively high CO pressure (7 bar) using only 2-3 mol% of $Co_2(CO)_8$. Interestingly, small amounts of water also promoted the reaction.[36]

However, as the use of an additive inherently leads to the production of wastes, other activation methods have been investigated. Our group reported that molecular sieves were efficient activators for the Pauson-Khand reaction. In addition, we described a catalytic protocol using CO adsorbed in molecular sieves (zeolites) so that during the reaction there was no need to use CO gas.[37] Other techniques, such as MW heating,[38] or ultrasound,[39] which is believed to help metal-carbonyl bond cleavage,[40] remarkably accelerated the reaction. However, results concerning substrate scope or yields were not spectacular and the protocols were not catalytic.

[31] V. Rautenstrauch, P. Mégard, J. Conesa, W. Küster *Angew. Chem. Int. Ed.* **1990**, *29*, 1413-1416.
[32] N. Jeong, S. H. Hwang, Y. Lee, Y. K. Chung *J. Am. Chem. Soc.* **1994**, *116*, 3159-3160.
[33] N. Jeong, Y. K. Chung, B. Y. Lee, S. H. Lee, S. Yoo *Synlett* **1991**, *1991*, 204-206.
[34] M. Hayashi, Y. Hashimoto, Y. Yamamoto, J. Usuki, K. Saigo *Angew. Chem. Int. Ed.* **2000**, *39*, 631-633.
[35] Y. Tang, L. Deng, Y. Zhang, G. Dong, J. Chen, Z. Yang *Org. Lett.* **2005**, *7*, 593-595.
[36] T. Sugihara, M. Yamaguchi *Synlett* **1998**, *1998*, 1384-1386.
[37] a) L. Pérez-Serrano, J. Blanco-Urgoiti, L. Casarrubios, G. Domínguez, J. Pérez-Castells *J. Org. Chem.* **2000**, *65*, 3513-3519; b) J. Blanco-Urgoiti, L. Casarrubios, G. Domínguez, J. Pérez-Castells *Tetrahedron Lett.* **2002**, *43*, 5763-5765.
[38] a) M. Iqbal, N. Vyse, J. Dauvergne, P. Evans *Tetrahedron Lett.* **2002**, *43*, 7859-7862; b) S. Fischer, U. Groth, M. Jung, A. Schneider *Synlett* **2002**, *2002*, 2023-2026.
[39] J. G. Ford, W. J. Kerr, G. G. Kirk, D. M. Lindsay, D. Middlemiss *Synlett* **2000**, *2000*, 1415-1418.
[40] S. Suslick, J. W. Goodale, P. F. Schubert, H. H. Wang *J. Am. Chem. Soc.* **1983**, *105*, 5781-5785.

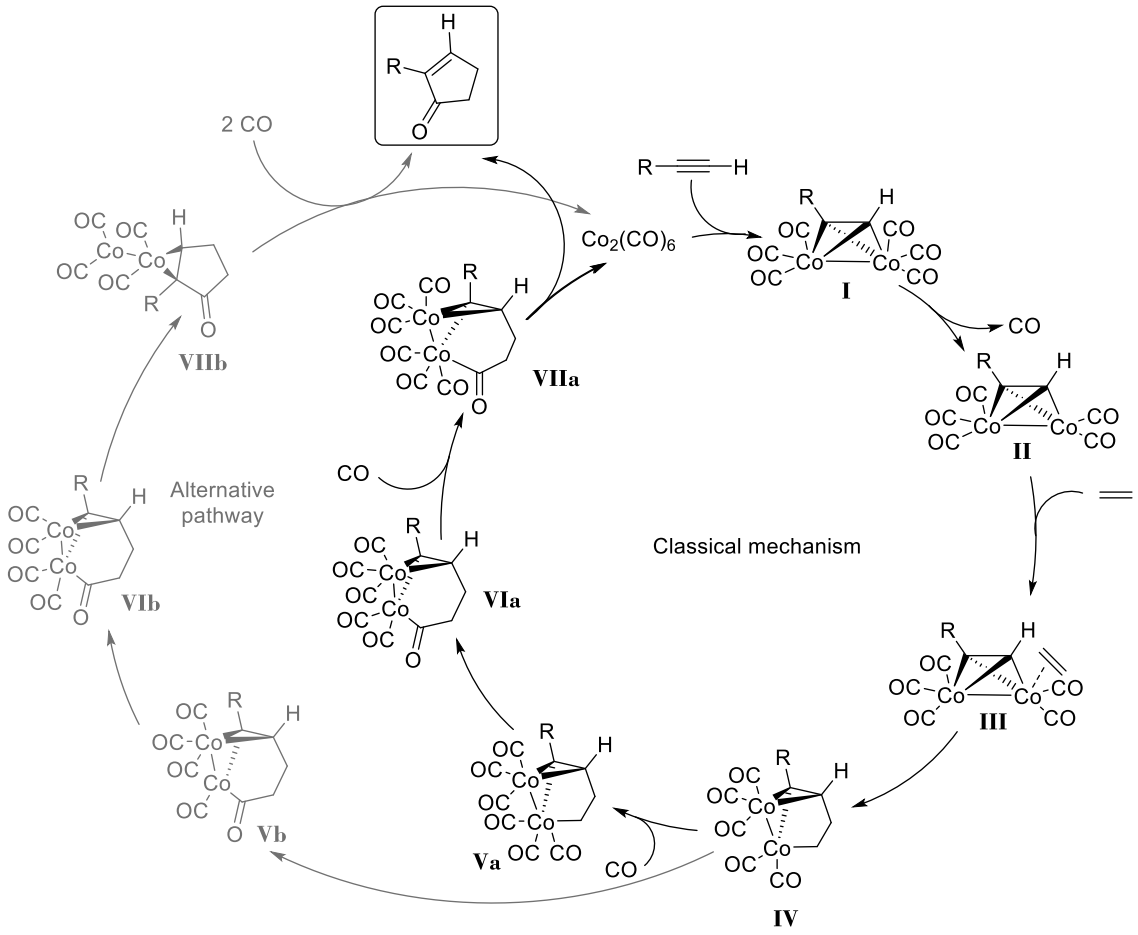
Along the years the scope of the reactions has been broadened and includes the use of allenes,[41] the formation 7-membered rings[42] the use of maleimides in the intermolecular version,[43] and an aza-Pauson−Khand-type reaction using alkynecarbodiimide derivatives[44] (Scheme 5).



Scheme 5

The generally accepted working mechanism for the PKr was proposed by Magnus and Schore in 1985.[45] However the main problem with this mechanism is that beyond the cobalt-hexacarbonylalkyne complex, it is difficult to detect further intermediates. The reaction begins with the formation of the cobalt hexacarbonyl-alkyne complex (I), and then continues with the creation of free coordination sites (II) to allow the alkene being complexed in which is considered the limiting step of the reaction. After the coordination with the olefin (III), the next step is the insertion of the double bond in a C-Co bond (IV) being the diastereoselectivity of the reaction determined at this point. The insertion of CO (Va) and a final reductive elimination yields the cyclopentenone (Scheme 6).

[41] B. Alcaide, P. Almendros *Eur. J. Org. Chem.* **2004**, *2004*, 3377-3383.
[42] a) L. Perez-Serrano, L. Casarrubios, G. Dominguez, J. Perez-Castells *Chem. Commun.* **2001**, 2602-2603; b) C. E. Madu, H. V. R. Dias, C. J. Lovely *Tetrahedron* **2017**, *73*, 6118-6137.
[43] C. L. Brantley, T. C. Coombs *Tetrahedron Lett.* **2017**, *58*, 4519-4524.
[44] C. Mukai, T. Yoshida, M. Sorimachi, A. Odani *Org. Lett.* **2006**, *8*, 83-86.
[45] a) P. Magnus, L. M. Principe *Tetrahedron Lett.* **1985**, *26*, 4851-4854; b) B. E. La Belle, M. J. Knudsen, M. M. Olmstead, H. Hope, M. D. Yanuck, N. E. Schore *J. Org. Chem.* **1985**, *50*, 5215-5222.



Scheme 6

It was not until the 2000s when comprehensive studies appeared on the full reaction mechanism performed at the DFT (Density functional studies) level with simple substrates.[46] The authors confirmed the feasibility of the Magnus mechanism. In addition, it was confirmed that the first step, the loss of one CO ligand is strongly endothermic, and therefore is the rate-determining step. On the other hand, the insertion of the olefin is the critical stereo- and regiochemical-determining step of the Pauson–Khand reaction. On other contributions, complex **II** was detected and described by NMR,[47] and intermediate **III** by X-Ray.[48] In high contrast, it was recently found that the photochemically promoted PK starts with homolytic cleavage of Co-Co, instead of CO loss.[49]

Nevertheless, this mechanism was later revised. Gimbert and coworkers reported an isotope labeling study using ^{13}CO and used mass spectrometry, in order to determine the source of the carbonyl group incorporated to the product.[50] The authors felt that intermediate **IV**, the

[46] a) M. Yamanaka, E. Nakamura *J. Am. Chem. Soc.* **2001**, *123*, 1703-1708; b) M. A. Pericàs, J. Balsells, J. Castro, I. Marchueta, A. Moyano, A. Riera, J. Vázquez, X. Verdaguer *Pure Appl. Chem.* **2002**, *74*, 167-174.
[47] M. E. Krafft, I. L. Scott, R. H. Romero, S. Feibelmann, C. E. Van Pelt *J. Am. Chem. Soc.* **1993**, *115*, 7199-7207.
[48] E. Banide, H. Müller-Bunz, A. Manning, P. Evans, M. McGlinchey *Angew. Chem. Int. Ed.* **2007**, *46*, 2907-2910.
[49] J. C. Manton, F. J. R. Cerpentier, E. C. Harvey, I. P. Clark, G. M. Greetham, C. Long, M. T. Pryce *Dalton Trans.* **2019**, *48*, 14642-14652.
[50] D. Lesage, A. Milet, A. Memboeuf, J. Blu, A. E. Greene, J. Tabet, Y. Gimbert *Angew. Chem. Int. Ed.* **2014**, *53*, 1939-1942.

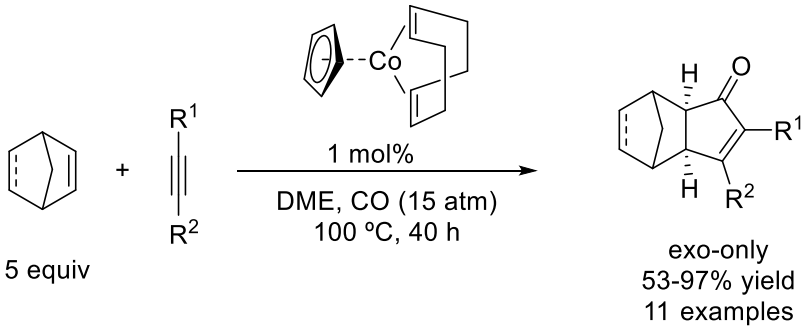
product of insertion from olefin complex (**III**), warranted investigation, and, in particular, they were curious about the feasibility of the following step, where a CO molecule returns to complex **IV** to give **Va**, which then undergoes CO insertion to give an acyl complex. Mass spectrometry ion-molecule experiments were performed on a suitably charged complex and no ^{13}C incorporation was observed in the final product. From this, the authors inferred that external CO does not return to complex **IV** to give hexacarbonyl complex **Va**. Thus, computational studies and kinetic modelling were utilized to propose a series of alternative pathways that involve internal CO transfer from the other cobalt atom (**Vb**).

Finally, this alternative pathway is to date the main accepted mechanism, although it may suffer modifications in the future. Further studies in this area will aid in refining Gimbert's hypotheses to arrive to a more definitive proposal.

Along with the initial development of the PKr, the well-known Co(0) catalyst: $Co_2(CO)_8$ was thoroughly used. This is a stable solid, but it decomposes partially after some weeks which reduces its activity. Livinghouse considered that impurities in $Co_2(CO)_8$ would induce the formation of inactive oligomers and therefore using a pure complex is an important fact for the catalytic reaction.[51] The use of $Co_4(CO)_{12}$ as a stable catalyst precursor gave excellent results mainly in the intermolecular reaction using only 0.5-1 mol% at 150 ºC and 10 bar of CO.[52] Another protocol, using only 70 ºC and 1 bar of CO, needed cyclohexylamine as additive and was applied to a set of intramolecular substrates with good yields.[53] Another alternative cobalt cluster is $Co_3(CO)_9(\mu^3\text{-CH})$, which is easily prepared from $Co_2(CO)_8$ and it increments in autooxidation stability. With only 2 mol% of this complex, excellent results were achieved at 120 ºC under 7 atm of CO.[54]

Cobalt complexes not containing carbonyl ligands were used by Chung and collaborators. This group reported the use of (Indenyl)Co(octa-1,5-diene) as a relatively stable Co(I) complex. It was used mainly for the intermolecular version, monosubstituted acetylenes even with a hydroxy group were good substrates and just 1 mol% cobalt catalyst realized an excellent yield. As for disubstituted acetylenes, the yield was moderate when using 5 mol% cobalt catalyst (Scheme 7).[55]

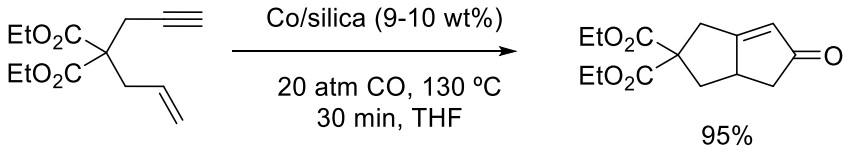
[51] D. B. Belanger, T. Livinghouse *Tetrahedron Lett.* **1998**, *39*, 7641-7644.
[52] J. W. Kim, Y. K. Chung *Synthesis* **1998**, *1998*, 142-144.
[53] M. Krafft, L. Boñaga *Angew. Chem. Int. Ed.* **2000**, *39*, 3676-3680.
[54] T. Sugihara, M. Yamaguchi *J. Am. Chem. Soc.* **1998**, *120*, 10782-10783.
[55] B. Y. Lee, Y. K. Chung, N. Jeong, Y. Lee, S. H. Hwang *J. Am. Chem. Soc.* **1994**, *116*, 8793-8794.



Scheme 7

Another approach was the use of Co(II) complexes like $Co(acac)_2$ which are more stable solids. In this case, the catalyst needs to be reduced by $NaBH_4$ for the preparation of an active species, and a pressured condition of CO is required.[56]

Heterogenous cobalt-based catalysis has also been applied,[57] in particular with the use of Co loaded onto a range of supports, such as charcoal or mesoporous silica, or by the employment of recyclable colloidal Co nanoparticles, as divulged in an extensive series of reports by Chung, Hyeon, and coworkers. One of the first efficient protocols was the use of cobalt on charcoal for intramolecular PK annulations. Albeit a relatively elevated temperature and CO pressure was needed, only 0.1 ppm of Co was bled from the support and it could be recycled several times without loss in efficiency (Scheme 8).[58] Other heterogeneous protocols used Raney cobalt,[59] poly(ethylene glycol)-Stabilized cobalt nanoparticles[60] and Co_2Rh_2 nanoparticles, which interestingly catalyzed the Pauson Khand reaction using allenes and bisallenes as reaction substrates.[61]



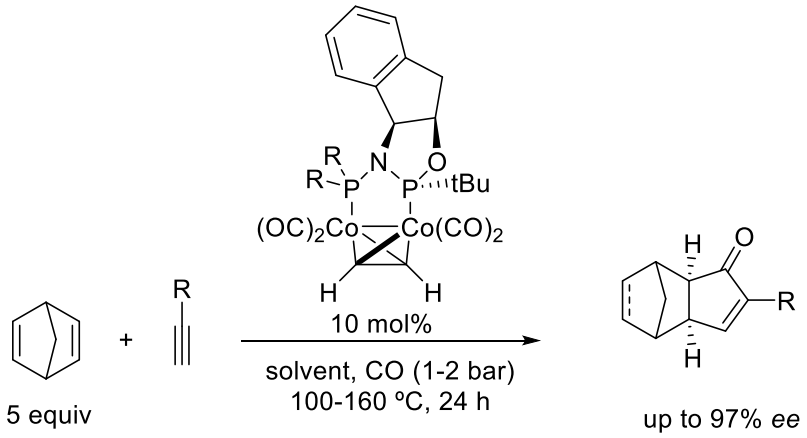
Scheme 8

These heterogeneous protocols, however, showed generally narrow scope, working well only with typical examples of the intramolecular version, limiting the intermolecular examples to the use of norbornadiene.

The asymmetric PKr with Co catalyst is limited to the intermolecular version and usually requires pre-formed chiral cobalt-substrate complexes, therefore using the metal in stoichiometric

[56] N. Y. Lee, Y. K. Chung *Tetrahedron Lett.* **1996**, *37*, 3145-3148.
[57] Y. K. Chung in *The Pauson–Khand Reaction. Scope, Variations and Applications*, (Eds. R. Rios Torres) John Wiley & Sons, **2012**, pp. 239-274.
[58] a) S. Son, S. Lee, Y. Chung *Angew. Chem. Int. Ed.* **2000**, *39*, 4158-4160; b) S. Kim, S. U. Son, S. I. Lee, T. Hyeon, Y. K. Chung *J. Am. Chem. Soc.* **2000**, *122*, 1550-1551.
[59] J. Muller, A. Rickers, W. Leitner *Adv. Synth. Catal.* **2007**, *349*, 287-291.
[60] J. Muller, J. Klankermayer, W. Leitner *Chem. Commun.* **2007**, 1939-1941.
[61] a) K. Park, Y. Chung *Adv. Synth. Catal.* **2005**, *347*, 854-866; b) J. H. Park, E. Kim, H. Kim, S. Y. Choi, Y. K. Chung *Chem. Commun.* **2008**, 2388-2390.

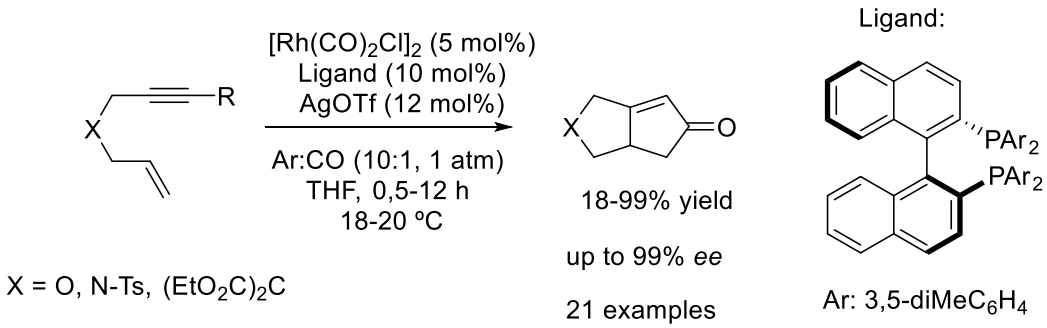
amounts. Moreover, there are only a few catalytic examples, such as that developed by the group of Riera and Verdaguer, where up to 97% of *ee* was achieved, but in moderate yield (39%) (Scheme 9).[62] In addition, an intramolecular catalytic approach, developed by Buchwald and Sturla using $Co_2(CO)_8$ and chiral biaryl phosphites gave moderate yields and *ee* in only a few cases.[63]



Scheme 9

Although cobalt is the most used metal for the PKr, there are examples which employ carbonyl clusters or other complexes of many other transition metals, such as Fe, Ir, Rh, Ru, Ti, Mo…. Among them, Rh is the most important alternative.[26] In contrast to cobalt, it is restricted to disubstituted alkynes and better results are obtained in the catalytic protocols by using only partial pressure of CO.[64]

The main advantage of using Rh is the possibility of using chiral auxiliaries to induce asymmetry. Jeong and coworkers reported a Rh(I) catalyzed protocol for the asymmetric Pauson Khand proving high yields as well as excellent enantioselectivities using mild conditions (Scheme 10).[65]



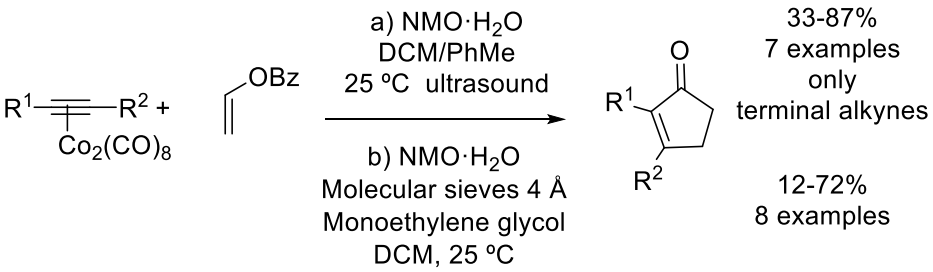
Scheme 10

[62] S. Orgué, T. León, A. Riera, X. Verdaguer *Org. Lett.* **2015**, *17*, 250-253.
[63] S. J. Sturla, S. L. Buchwald *J. Org. Chem.* **2002**, *67*, 3398-3403.
[64] T. Kobayashi, Y. Koga, K. Narasaka *J. Organometallic Chem.* **2001**, *624*, 73-87.
[65] D. E. Kim, I. S. Kim, V. Ratovelomanana-Vidal, J. Genêt, N. Jeong *J. Org. Chem.* **2008**, *73*, 7985-7989.

Since its discovery, the PKr has experienced great advances and changes in almost all aspects: catalyst loadings and promoters, broad scope, enantioselective examples, applications in natural products synthesis, understanding of the mechanism… However, its industrial applications are still limited due to the lack of a scalable, safe, and efficient protocol. Furthermore, some substrates remain challenging such as vinyl ethers.

2.2.2. Vinyl ethers as substrates for the PKr

Despite the great number of substrates used to date, vinyl ethers continue to be challenging substrates for the PKr. Only three reports where these motifs were used as PK substrates are reported. In 1981, Croudace and Schore attempted to use several vinyl ethers in an intramolecular PKr. They observed the expected reaction with cobalt complexes, but the subsequent isolation of the cyclopentenone was unsuccessful.[66] Later examples of the intramolecular version provided only moderate yields and the cleavage of the vinyl ether structure in the final product (the vinyl ether acts thus as ethylene equivalent; Scheme 11).[67]



Scheme 11

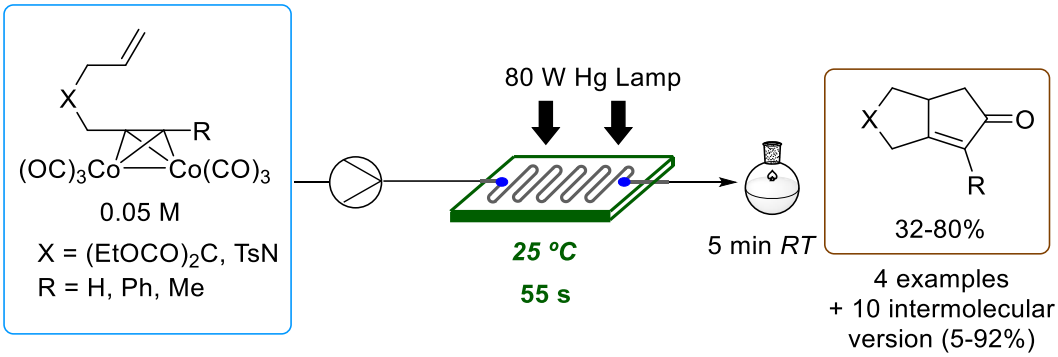
The use of 1,7-enynes tethered with an aromatic ring in the PKr has no precedents in literature. These substrates are very reactive but using flow technology specific conditions could be found to direct these substrates onto the PKr. This would provide a new efficient, scalable and versatile synthesis of tricyclic multisubstituted benzofurans.

2.2.3. The PKr in flow reactors

Yoshida and coworkers reported in 2013 the use of light irradiation as an effective, milder, and green approach for a stoichiometric PKr. Interestingly, the reactions were carried out in a flow photo-microreactor system. They claimed to have developed a method that solved the efficiency problems of other photochemical reactions allowing scaling-up.[68] The procedure consisted of passing a solution of the cobalthexacarbonyl-alkyne complex through the microchannel covered with fused quartz glass, which was irradiated by a medium pressure Hg lamp (80 W) in a residence time of 55 seconds. However, an additional stirring in a flask for 5 minutes was needed.

[66] M. C. Croudace, N. E. Schore *J. Org. Chem.* **1981**, *46*, 5357-5363.
[67] a) W. Kerr, M. McLaughlin, P. Pauson, S. Robertson *J. Organometallic Chem.* **2001**, *630*, 104-117; b) A. Cabré, X. Verdaguer, A. Riera *Synthesis* **2017**, *49*, 3945-3951.
[68] K. Asano, Y. Uesugi, J. Yoshida *Org. Lett.* **2013**, *15*, 2398-2401.

The reaction was also carried out in batch conditions as a control. The yields obtained were much better in the microreactor conditions than in batch (Scheme 12).



Scheme 12

However, this experiment provides only a few examples, some of them with very low yields and the cobalt complex needs to be previously prepared and purified. Furthermore, the scale-up method is stoichiometric, not catalytic and needs a batch step. All of these make difficult to extrapolate it into an industrial application.

2.2.4. Pauson Khand applications in total synthesis: Treprostinil

The cyclopentane ring is quite common in nature and the PK adducts are easily functionalized. This has made the PKr a useful key step in the synthesis of many interesting products such as prostaglandins, different triquinanes, polyquinanes, and diterpernes like pentalenene, epoxydictymene, paecilomycine A, ceratopicanol, furanether B, kainic acid, hirsutene, fenestranes, brefeldine A, alstonerine, loganine, xestobergsterol, spatane, daphane, iridomirmecin, dendrobin, kalmanol and β-cuparenone.[26] Among this large number of products, we will focus on the synthesis the commercialized drug Trepostinil.

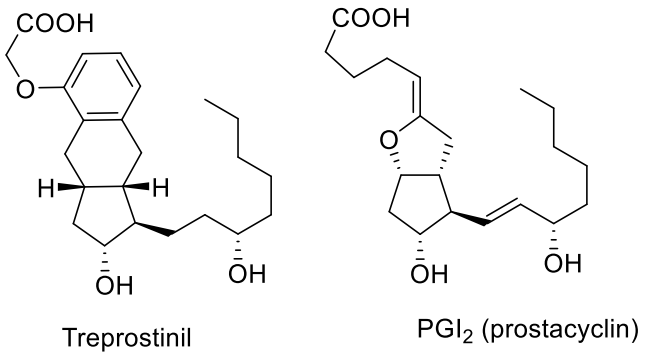


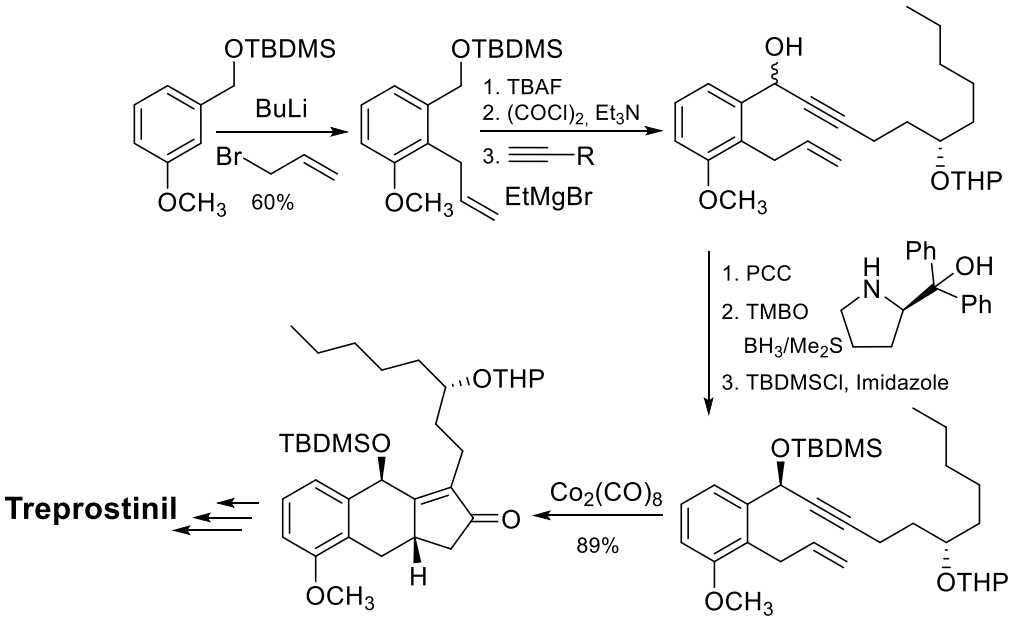
Figure 6

Treprostinil (Figure 6) is a tricyclic benzoindene analogous to prostacyclin, PGI2.[69] Its main effects are the inhibition of platelet aggregation and vasodilation, including acute pulmonary vasodilation. These biological activities are relevant for the treatment of cardiovascular diseases such as pulmonary arterial hypertension, a disease with a very poor prognosis until approximately 2010,[70] when different proteinoid therapies began to be implemented. The first therapies used intravenous administration, which entails numerous disadvantages such as difficult patient compliance. Those treatments were not chemically stable in other routes of administration due to the vinyl ether present in the PGI2. Consequently, the subsequent analogous protected the vinyl ether to acid hydrolysis. In the case of Treprostinil, the vinyl ether is embedded in a phenoxide system.

Treprostinil can be administered by inhalation, since 2013 it has been approved by the FDA as an oral drug, and in 2019, generic Treprostinil was approved, making the medication much more affordable. However, the use of oral Treprostinil is scarce and limited to inpatients.[71] One of the reasons for the high cost of the drug is its complex and expensive chemical synthesis and the high cost of its development. It is important to find new scalable syntheses processes that lower the production costs of the drug and result in less use of contaminating and harmful reagents for the environment.[72]

The most relevant published synthesis was developed by Moriarty and collaborators in 2004. The main core of the molecule was formed by an intramolecular stoichiometric Pauson–Khand reaction, of an enyne substrate which contains a bulky OTBDMS to induce stereoselectivity, as shown in Scheme 13.[73] Other later syntheses used different protecting groups[74] and ways to insert the triple bond,[75] still being the PKr the key step for the formation of the core.

[69] S. Moncada, R. Korbut, S. Bunting, J. R. Vane *Nature* **1978**, *273*, 767-768.
[70] a) J. Vachiery, R. Naeije *Expert Rev. Cardiovasc. Ther.* **2004**, *2*, 183-191; b) N. Skoro-Sajer, I. Lang, R. Naeije *Vasc. health risk manag.* **2008**, *4*, 507-513.
[71] B. Hohlfelder, A. R. Tonelli, G. A. Heresi, N. Bair, F. F. Rahaghi, S. R. Bauer *Cardiovasc. Drugs Ther.* **2020**, *34*, 547-553.
[72] Recent review of the treatment of pulmonary hypertension using treprostinil: J. Feldman, N. Habib, J. Fann, J. J. Radosevich *Future Cardiology* **2020**, *Just accepted* DOI: 10.2217/fca-2020-0021
[73] R. M. Moriarty, N. Rani, L. A. Enache, M. S. Rao, H. Batra, L. Guo, R. A. Penmasta, J. P. Staszewski, S. M. Tuladhar, O. Prakash, D. Crich, A. Hirtopeanu, R. Gilardi *J. Org. Chem.* **2004**, *69*, 1890-1902.
[74] a) K. W. Hering, G. Chambournier, G. W. Endres, V. Fedij, T. J. Krell II and H. M. Mahmoud, Methods of synthesizing a prostacyclin analog, US20150315114A1, issued Nov 5, 2015; K. W. Hering, G. Chambournier, G. W. Endres, V. Fedij, T. J. Krell II, H. M. Mahmoud, Methods of synthesizing a prostacyclin analog, WO2014089385A2, issued Jun 12, 2014; b) V. Malinin, W. Perkins, F. Leifer, D. M. Konicek, Z. Li, A. Plaunt, Preparation of prostacyclin compounds, compositions and methods of use thereof, WO2016176555A1, issued Nov 3, 2016.
[75] F. Zhang, P. Guo, W. Ji, Intermediates for synthesizing treprostinil and preparation method thereof as well as the preparation method of treprostinil thereby, WO2014094511A1, issued Jun 26, 2014.



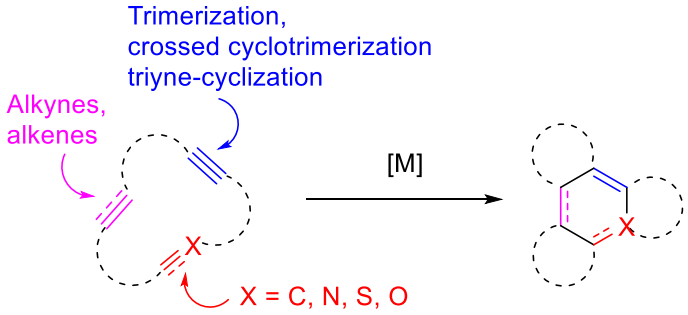
Scheme 13

Therefore, a catalytic, efficient, scalable, and green approach in this step is essential for industrial application. We envisioned the possibility of carrying out the PKr in a flow reactor to pursue these goals. In addition, the Claisen rearrangement carried out in the one of the starting steps could be developed in a flow reactor increasing its selectivity towards the desired isomer.

2.3. [2+2+2] Cycloaddition

The [2+2+2] cycloaddition is an elegant, atom-efficient, and group tolerant process to produce carbo- and heterocycles, involving the formation of several C–C bonds in a single step. Starting from various unsaturated substrates, such as alkynes, nitriles, alkenes, cumulenes, and heterocumulenes, it allows the synthesis of a great variety of aromatic and nonaromatic cycles. It is an interesting alternative to the aromatic electrophilic substitution reactions to synthesize multisubstituted aromatic rings such as benzenes and pyridines. This process is catalyzed by complexes of more than 17 different metals, being Co, Ru, and Rh the most common.[76] However, some metal-free variations have been reported in the last years, ranging from stepwise cyclization reactions of alkynes under drastic conditions (high temperatures and pressures) to trimeric condensation reactions of ketoalkynes under amine catalysis, Diels Alder type cascade reactions and cyclizations of oligoalkynes under partially mild conditions.[77]

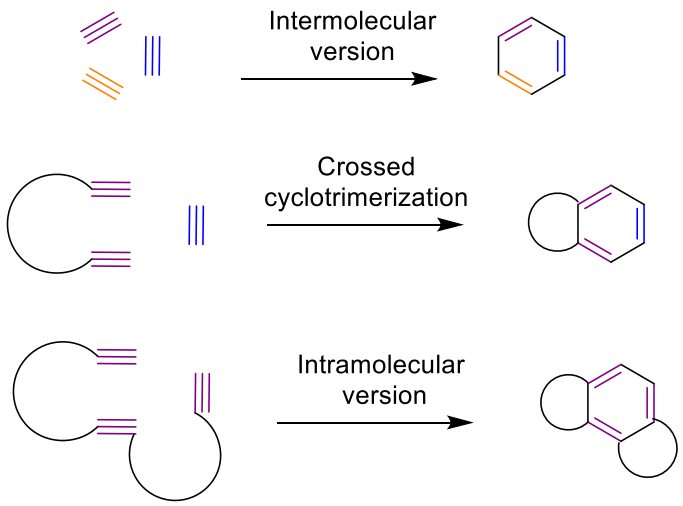
Depending on the substrate involved and its substituents, different polynuclear fused rings can be obtained (Scheme 14). Furthermore, an important problem with the [2+2+2] cycloaddition reaction is the lack of chemo and regioselectivity observed in earlier reported reactions. However, more recent contributions have attained a high degree of chemo-, regio- and even enantioselectivity.



Scheme 14

Alkynes are the most commonly used substrates, and their [2+2+2] cycloadditions can be classified into three types: the entirely intermolecular reaction or cyclotrimerization of three alkynes; the crossed cycloaddition of a diyne and an alkyne, and the totally intramolecular version, *i.e.* the cyclization of triynes (Scheme 15).

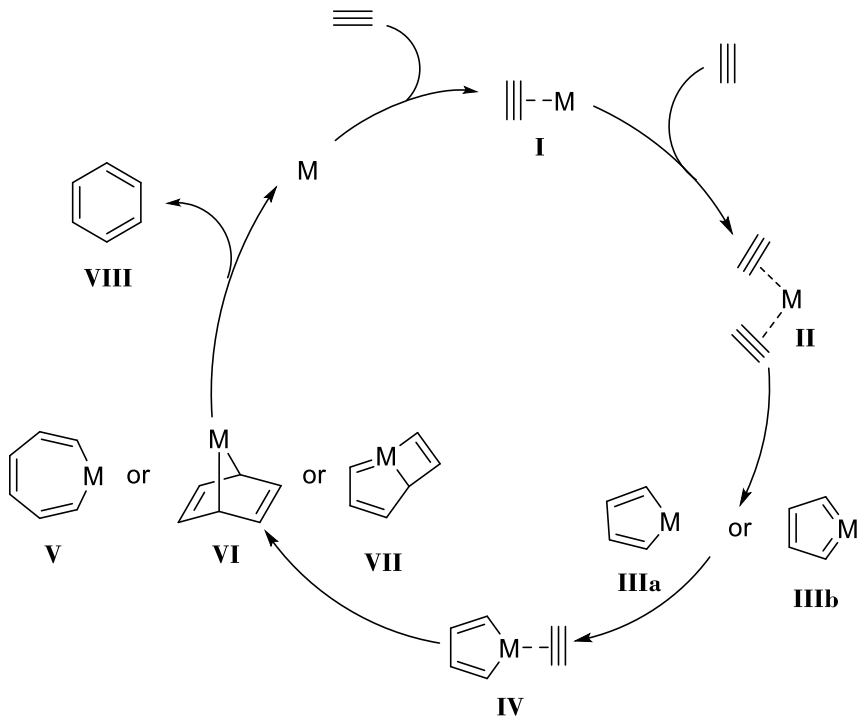
[76] a) G. Dominguez, J. Perez-Castells *Chem. Soc. Rev.* **2011**, *40*, 3430-3444; b) P. R. Chopade, L. Janis *Adv. Synth. Catal.* **2006**, *348*, 2307-2327; c) S. Kotha, K. Lahiri, G. Sreevani *Synlett* **2018**, *29*, 2342-2361.
[77] M. Hapke *Tetrahedron Lett.* **2016**, *57*, 5719-5729.



Scheme 15

The mechanism of [2+2+2] cyclotrimerizations depends on the nature of the metal and alkyne partners. The three unsaturated units that are assembled can exchange roles in the reaction sequence. Many experimental and theoretical studies have been reported, including different catalysts and unsaturated substrates. They have been summarized in a recently published review.[78] The general mechanism used to explain the transition-metal-catalyzed [2+2+2] cycloaddition reaction is shown in Scheme 16. The reaction begins with two ligand-alkyne substitution reactions. Then, the oxidative coupling of the two alkyne ligands generates a metallacyclopentadiene (**IIIa**) or a metallacyclopentatriene (**IIIb**) with a biscarbene structure. This has been found to be the rate-determining step. Intermediate **IIIa**, when M=Rh, is supported by the isolation and characterization of several derivatives. Subsequent coordination of a third alkyne ligand to the metallacyclopentadiene or **IIIb** intermediate is followed by either alkyne insertion to form metallacycloheptatriene **V** (the so-called Schore's mechanism) or metal-mediated [4+2] cycloaddition to yield the metallanorbornadiene **VI** to give a metallabicyclo[3.2.0]heptatriene **VII**. Finally, the arene **VIII** is formed by the reductive elimination of the metal.[79]

[78] A. Roglans, A. Pla-Quintana, M. Solà *Chem. Rev.* **2020**, *Just accepted,* DOI: 10.1021/acs.chemrev.0c00062.
[79] A. Dachs, A. Torrent, A. Pla-Quintana, A. Roglans, A. Jutand *Organometallics* **2009**, *28*, 6036-6043.

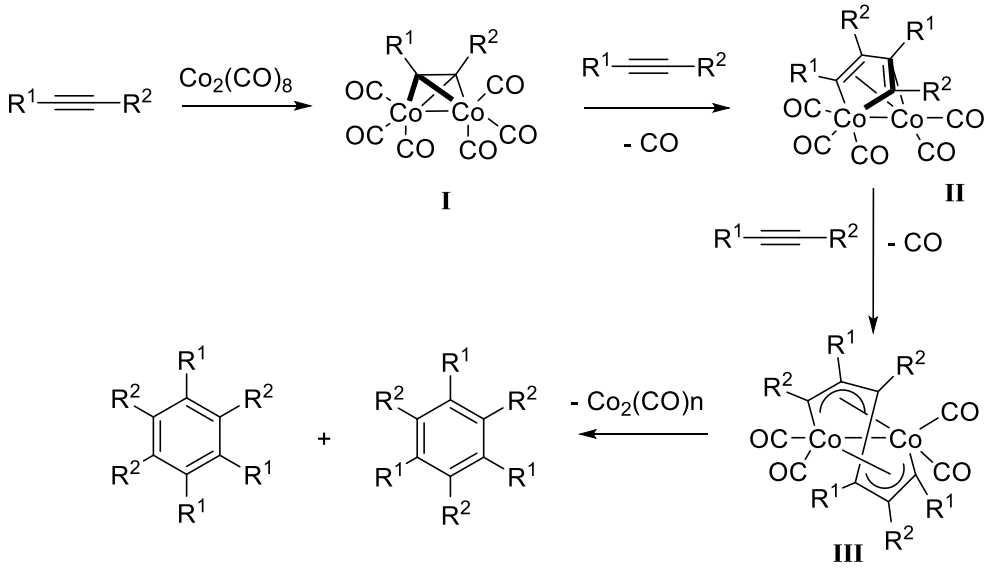


Scheme 16

Not only mononuclear complexes, but also multinuclear complexes act as catalysts for alkyne cyclotrimerization, and their reaction mechanisms have been intensively investigated toward developing highly efficient and regio- and chemo-selective catalysts. In both mononuclear and dinuclear catalytic systems, metallacyclopentadienes are considered as key intermediates.[80]

Regarding the mechanism of the $Co_2(CO)_8$, catalyzed reactions an extensive study of the mechanism, with the isolation of some intermediates and X-Ray identification, was performed by Spicer, Know, and coworkers. The reaction pathway involves an alkyne bridged dinuclear complex (**I**) as the first step of the catalytic cycle followed by a reaction with another alkyne unit which gives dimetallacyclopentadiene complex (**II**). The way this complex is formed is the key step for the regioselectivity in the final product (1,2,4, which is the most common or 1,3,5) Then, another alkyne is inserted, and the structure is reorganized forming a “flyover” cycle (which contains a C_6Co_2 ring, **III**). Finally, arenes are formed by reductive elimination of the metal, and the cobalt cluster can enter the cycle again (Scheme 17).[81]

[80] K. Yamamoto, H. Nagae, H. Tsurugi, K. Mashima *Dalton Trans.* **2016**, *45*, 17072-17081.
[81] a) R. J. Baxter, G. R. Knox, P. L. Pauson, M. D. Spicer *Organometallics* **1999**, *18*, 197-205; b) R. J. Baxter, G. R. Knox, J. H. Moir, P. L. Pauson, M. D. Spicer *Organometallics* **1999**, *18*, 206-214.

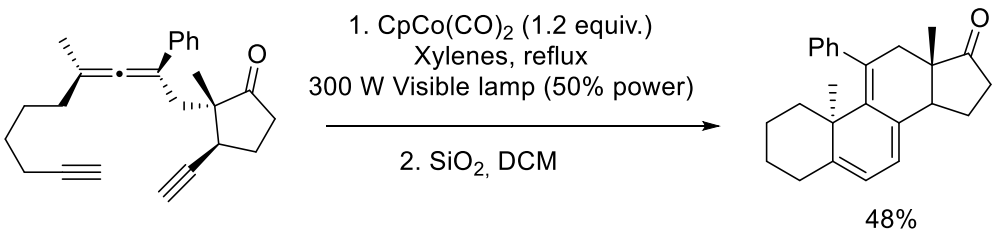


Scheme 17

2.3.1. Co catalyzed [2+2+2] cycloaddition

Cobalt complexes are one of the most utilized metal catalysts in [2+2+2] chemistry. The application of cobalt catalysts in [2+2+2] cycloaddition includes reactions of alkynes, oligoynes, alkenes, and nitriles to afford substituted benzenes, heterocycles, cyclohexadienes, and a large array of derived products.[82] The most frequently used cobalt catalysts are: Co(I) complexes like CpCo-based catalysts (Cp: Cyclopentadienyl), the commercially available and versatile $Co_2(CO)_8$, and cobalt(II) salts plus ligands as well as reductants and additives. Thus, CpCo-based catalysts can be applied under thermal as well as photochemical conditions. $CpCo(CO)_2$ is the most frequently used, due to its versatility and availability. However, harsh conditions are often needed as well as high catalyst loadings. A representative example is the synthesis of the steroid skeleton performed by the group of Aubert and Malacria. The use stoichiometric amount of $CpCo(CO)_2$, high temperature, and light irradiation for the [2+2+2] cyclization of allenediynes (Scheme 18).[83] Previously, the same group reported a cyclotrimerization coupled to a Diels Alder reaction in one step to form the core of toxoids in good yield.[84] Similar conditions were further applied to synthesize pentacyclic bis-lactones by Bessières and collaborators,[85] and 6,11-dihydroindolo[1,2-*b*]isoquinoline tetracyclic core was also produced in a 3 component [2+2+2] cycloaddition.[86] This approach is also used in natural product synthesis, such as the formation of (+)-complanadine A and lycodine derivatives.[87]

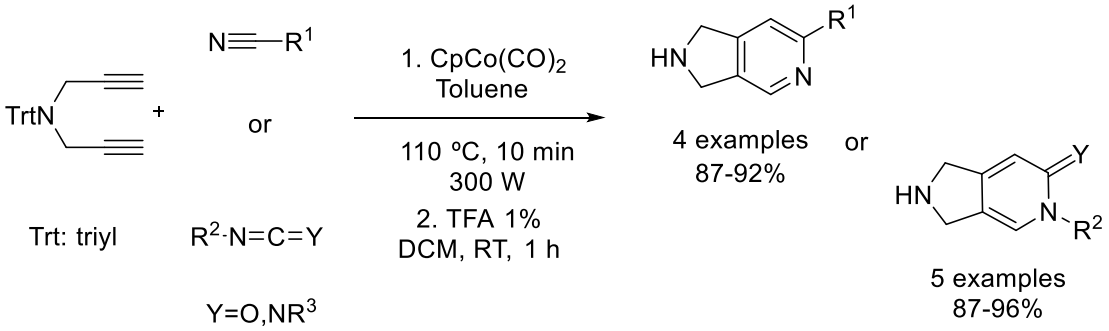
[82] T. Gläsel, M. Hapke in *Cobalt catalysis in Organic Synthesis* (Eds: M. Hapke, G. Hilt), Wiley-VCH, Weinheim, **2020**, pp. 287-335.
[83] M. Petit, C. Aubert, M. Malacria *Org. Lett.* **2004**, *6*, 3937-3940.
[84] M. Petit, G. Chouraqui, P. Phansavath, C. Aubert, M. Malacria *Org. Lett.* **2002**, *4*, 1027-1029.
[85] J. Michaux, R. Poirot, J. Einhorn, B. Bessières *Tetrahedron Lett.* **2014**, *55*, 2849-2852.
[86] A. Swami, C. V. Ramana *Synlett* **2015**, *26*, 604-608.
[87] C. Yuan, C. Chang, D. Siegel *J. Org. Chem.* **2013**, *78*, 5647-5668.



Scheme 18

Multiferrocenyl-substituted benzenes were produced by formal [2+2+2] cycloaddition combined with C–H bond activation using substoichiometric amounts of $CpCo(CO)_2$. Long reaction times and high temperatures were needed.[88] Other examples include the cycloaddition of alkyl boronates with alkenes,[89] and recently, the formation of benzo-2-siliindanes.[90]

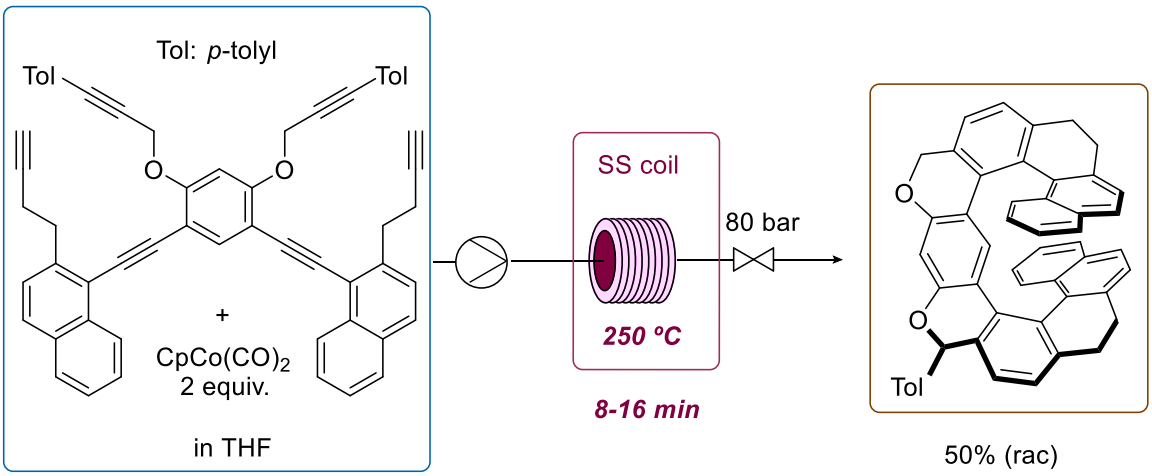
This catalyst has also been applied to synthesize heterocycles. Multisubstituted 2-aminopyridines, including macrocyclic products, were prepared by cyclotrimerization of bis-alkynes and cyanamides by Maryanoff and collaborators with 15 mol% $CpCo(CO)_2$.[91] On the other hand, a polymeric solid support combined with MW irradiation was applied by Young and Deiters to afford a wide range of pyridine, pyridone, and iminopyridine cycloadducts (Scheme 19).[92]



Scheme 19

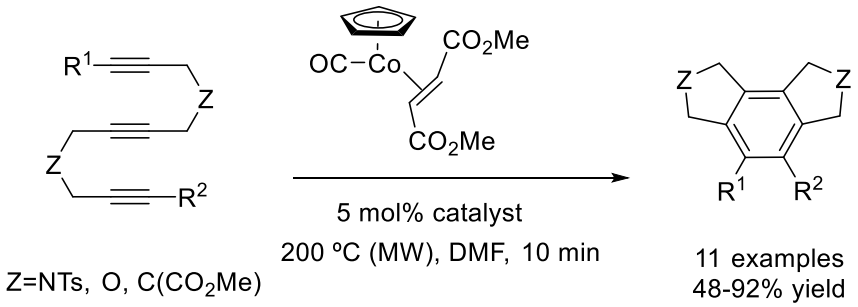
Furthermore, a different protocol was presented using a flow reactor, after testing other methodologies (MW heating, traditional batch procedure, and a light-mediated protocol). Long oxahelicenes were synthesized using stoichiometric amounts of this catalyst in short residence times (8-16 min) and high temperature (Scheme 20).[93]

[88] G. Filipczyk, A. Hildebrandt, U. Pfaff, M. Korb, T. Rüffer, H. Lang *Eur. J. Inorg. Chem.* **2014**, *2014*, 4258-4262.
[89] V. Gandon, D. Leboeuf, S. Amslinger, K. P. Vollhardt, M. Malacria, C. Aubert *Angew. Chem. Int. Ed.* **2005**, *44*, 7114-7118.
[90] T. Amakasu, K. Sato, Y. Ohta, G. Kitazawa, H. Sato, K. Oumiya, Y. Kawakami, T. Takeuchi, Y. Kabe *J. Organometallic Chem.* **2020**, *905*, 121006.
[91] L. V. R. Boñaga, H. Zhang, B. E. Maryanoff *Chem. Commun.* **2004**, 2394-2395.
[92] D. Young, A. Deiters *Angew. Chem. Int. Ed.* **2007**, *46*, 5187-5190.
[93] J. Nejedlý, M. Šámal, J. Rybáček, M. Tobrmanová, F. Szydlo, C. Coudret, M. Neumeier, J. Vacek, J. Vacek Chocholoušová, M. Buděšínský, D. Šaman, L. Bednárová, L. Sieger, I. G. Stará, I. Starý *Angew. Chem. Int. Ed.* **2017**, *56*, 5839-5843.



Scheme 20

Different transformations of this catalyst were reported by Aubert, Gandon and collaborators in order to achieve more stability and avoid the necessity of irradiation to be active. Using catalytic amounts of the novel Co-Cp derivative, a set of different cycloadducts were prepared, *via* intramolecular [2+2+2] cycloaddition (Scheme 21), alkyne cyclotrimerization and crossed [2+2+2] to form bicyclic pyridines.[94]

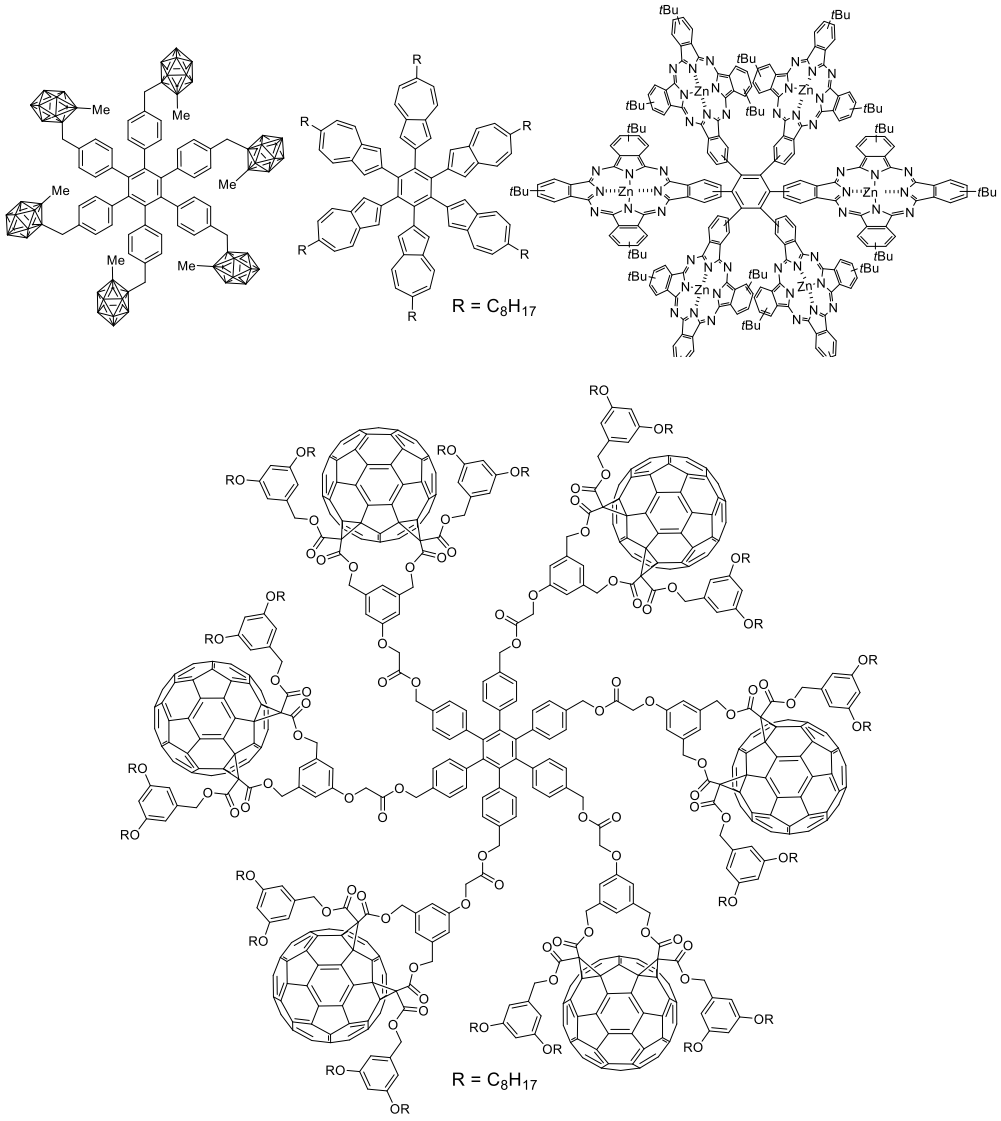


Scheme 21

The second group of cobalt catalysts are Co(0) complexes, mainly $Co_2(CO)_8$, which is a proven versatile reagent for the selective formation of multiple carbon−carbon bonds in a single chemical step.[95] The use of dicobalt octacarbonyl for alkyne cyclotrimerization has been used thoroughly for the synthesis of different star-shaped[96] molecules, such as azulene derivatives,[97]

[94] a) A. Geny, N. Agenet, L. Iannazzo, M. Malacria, C. Aubert, V. Gandon *Angew. Chem. Int. Ed.* **2009**, *48*, 1810-1813; To see more selected examples of [2+2+2] cycloadditions using Cp(Co)(L) see: b) I. Thiel, H. Jiao, A. Spannenberg, M. Hapke *Chem. Eur. J.* **2013**, *19*, 2548-2554; c) P. Garcia, Y. Evanno, P. George, M. Sevrin, G. Ricci, M. Malacria, C. Aubert, V. Gandon *Chem. Eur. J.* **2012**, *18*, 4337-4344; d) P. Garcia, Y. Evanno, P. George, M. Sevrin, G. Ricci, M. Malacria, C. Aubert, V. Gandon *Org. Lett.* **2011**, *13*, 2030-2033.
[95] Z. Zhou, M. Costa, G. P. Chiusoli *J. Chem. Soc., Perkin Trans. 1* **1992**, 1399-1406.
[96] a) B. Prasanna Dash, R. Satapathy, J. A. Maguire, N. S. Hosmane *Chem. Commun.* **2009**, 3267-3269; b) A. Idelson, C. Sterzenbach, S. Jester, C. Tschierske, U. Baumeister, S. Höger *J. Am. Chem. Soc.* **2017**, *139*, 4429-4434.
[97] S. Ito, M. Ando, A. Nomura, N. Morita, C. Kabuto, H. Mukai, K. Ohta, J. Kawakami, A. Yoshizawa, A. Tajiri *J. Org. Chem.* **2005**, *70*, 3939-3949.

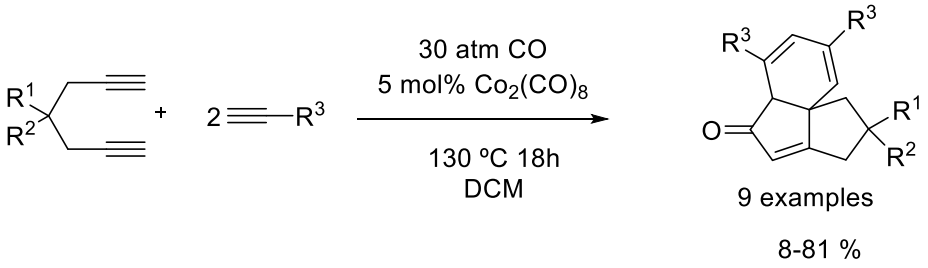
a phthalocyanine hexamer derivative,[98] fulleredendrimers,[99] benzocoronenes derivatives,[100] and others (Scheme 22).[101]



Scheme 22

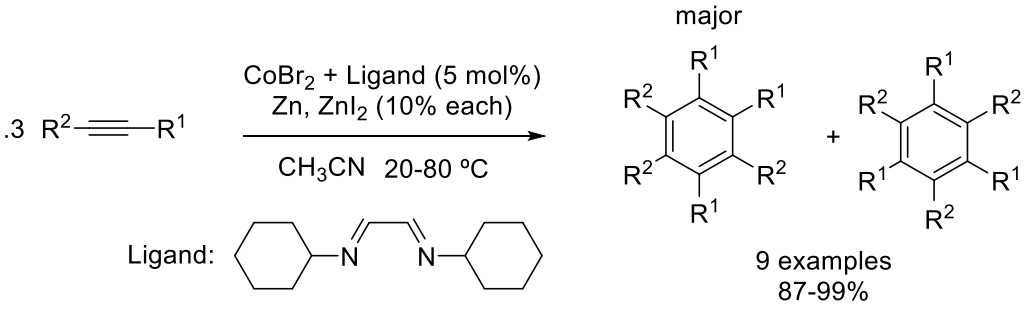
Furthermore, the group of Chung reported a tandem [2+2+2] / [4+2] cyclization using dicobalt octacarbonyl, to afford tetracycles[102] and a tandem [2+2+1] / [2+2+2] between a diyne and two phenylacetylene under CO pressure (Scheme 23).[103]

[98] G. Bottari, T. Torres *Chem. Commun.* **2004**, 2668-2669.
[99] a) U. Hahn, E. Maisonhaute, C. Amatore, J. Nierengarten *Angew. Chem. Int. Ed.* **2007**, *46*, 951-95; b) K. Nakagawa, T. Yokoyama, K. Toyota, N. Morita, S. Ito, S. Tahata, M. Ueda, J. Kawakami, M. Yokoyama, Y. Kanai, K. Ohta *Tetrahedron* **2010**, *66*, 8304-8312.
[100] a) S. Ito, M. Wehmeier, J. D. Brand, C. Kübel, R. Epsch, J. P. Rabe, K. Müllen *Chem. Eur. J.* **2000**, *6*, 4327-4342; b) Y. Zhou, M. Zhang, K. Gu, Y. Zhu, X. Fan, Z. Shen *Asian J. Org. Chem.* **2015**, *4*, 746-755.
[101] For more examples that use $Co_2(CO)_8$ in alkyne cyclotrimerization see: a) S. Hiraoka, M. Shiro, M. Shionoya *J. Am. Chem. Soc.* **2004**, *126*, 1214-1218; in crossed cyclotrimerization: b) V. Gandon, D. Leca, T. Aechtner, K. P. Vollhardt, M. Malacria, C. Aubert *Org. Lett.* **2004**, *6*, 3405-3407.
[102] D. H. Kim, Y. K. Chung *Synlett* **2005**, *12*, 1889-1892.
[103] S. U. Son, D. S. Choi, Y. K. Chung, S. Lee *Org. Lett.* **2000**, *2*, 2097-2100.



Scheme 23

The last group of catalyst are *in situ*-generated catalytic systems that use cobalt(II) salts and ligands as well as reductants and additives. These systems allow much easier and diversified generation of catalysts from simple precursor molecules, including, commercially available ligands. The general drawback is the need to reduce the cobalt(II) salt to generate the active catalyst and the sometimes less well-defined catalyst environment, which can also promote side reactions. One of the earliest protocols for alkyne cyclotrimerization using this kind of complexes was developed by Hilt and coworkers. The system was based on cobalt diimine complexes which were activated *in situ* by a combination of zinc and zinc iodide in acetonitrile (Scheme 24).[104] The regioselectivity was altered by adding disulfide ligands.[105] Recently, the same group also applied a similar methodology, using dppe (1,2-Bis(diphenylphosphino)ethane), in this case for the regioselective cyclotrimerization of (un)symmetrical 1,4-disubstituted 1,3-butadiynes.[106]



Scheme 24

Afterwards, the group of Chen and Yang reported a similar protocol, but using only 5 mol% of catalyst, TMTU as ligand to form the complex under a CO atmosphere.[107] Crossed cyclotrimerizations have also been developed by using a catalytic system based on 2-(2,6-diisopropylphenyl)iminomethylpyridine, $CoCl_2 \cdot 6H_2O$, and Zn, which is activated by phthalate derivates. Some cyclotrimerizations and a double cycloaddition were presented with good to excellent yields.[108] Fluorine-containing alkynes were used as substrates for cyclotrimerizations and crossed cycloadditions with non-fluorinated diynes using catalytic amounts of $CoCl_2$(1,4-bis(diphenylphosphino)butane) with high regioselectivity and yields.[109]

[104] G. Hilt, T. Vogler, W. Hess, F. Galbiati *Chem. Commun.* **2005**, 1474-1475.
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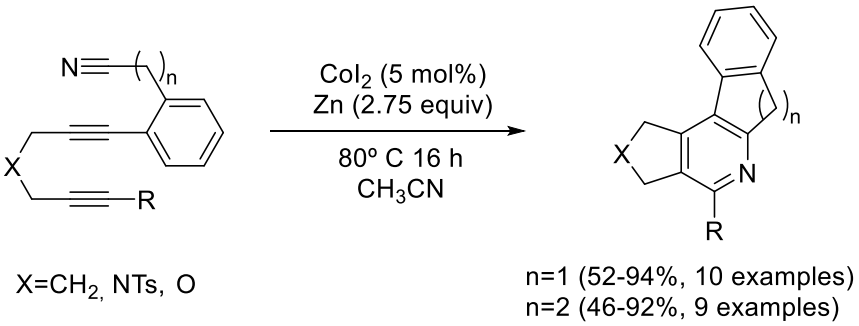
The preparation of substituted pyridines from cyanodiynes using an *in situ*-generated catalytic system was developed by Cheng and collaborators. A set of 19 different cycloadducts were produced in moderate to excellent yields (Scheme 25).[110] Afterwards, a [2+2+2] crossed cycloaddition between diynes and nitriles was developed by Okamoto and Sugiyama. However, a large excess of up to 40 equiv. of the nitrile was required.[111] A similar protocol was applied to the synthesis of ethyl picolinate derivatives, in good to excellent yields and high (>98%) regioselectivity.[112] Formation of pyridines using cobalt complexes has been widely applied in copolymerization to produce linear polymers from diyne-nitrile monomers.[113]



Scheme 25

Other less common reported catalyst is $CoCl(PPh_3)_3$, which is used for cycloaddition of triynes under mild conditions without any additive,[114] and $Co_3(CO)_9(\mu^3\text{-}CH)$, which is easily formed from $Co_2(CO)_8$, and works at low catalyst loadings (1-2 mol%) in good to excellent yields for the three types of [2+2+2] cycloadditions.[115]

Although cobalt catalysts are not the first choice for asymmetric [2+2+2] cycloadditions, there are several examples in the literature, generally using Co(I) derivatives with high temperatures and/or irradiation. Thus, atropoisomers of 2-arylpyridines were prepared using 1 mol% of a Co(I) catalyst from diynes and nitriles with high yields and up to 94% *ee* (Scheme 26).[116] Chiral diynes were used as substrates to obtain pairs of diastereomeric biaryl atropoisomers in one step, which were easily separated and functionalized.[117]

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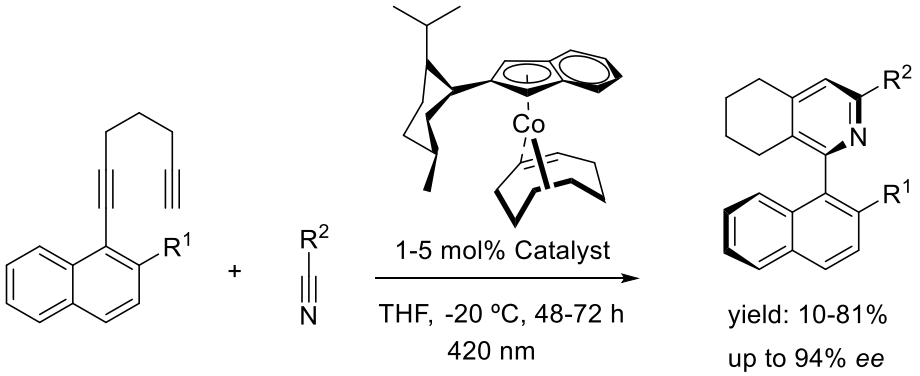
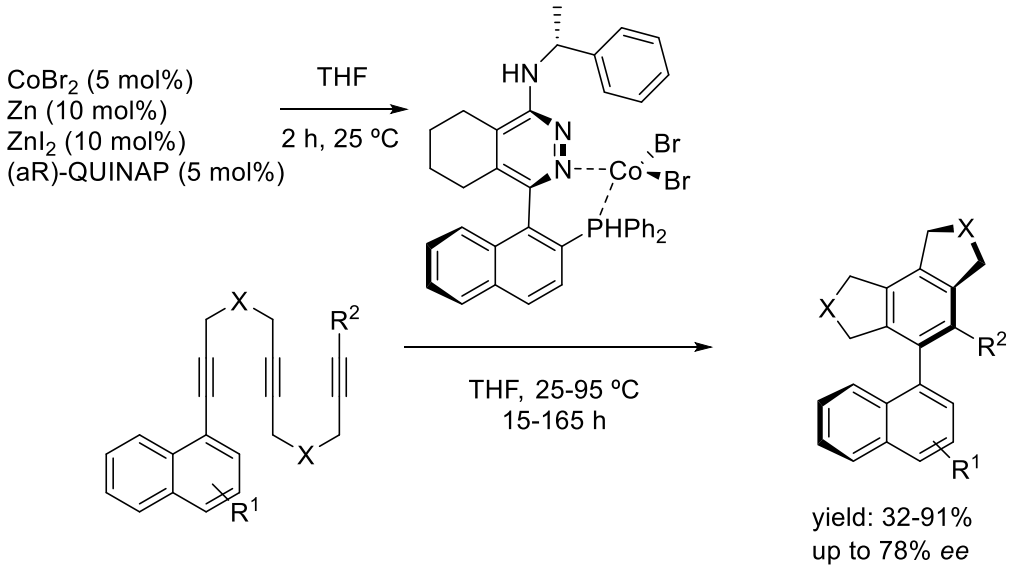


Scheme 26

On the other hand, Heller and coworkers demonstrated that conditions of the Co(I)catalyzed photochemical [2+2+2] cyclocotrimerization are suitable to prepare chiral compounds starting from chiral nitriles without any detectable loss of enantiomerical purity.[118] An example of an *in situ* formed catalyst, from a Co(II) catalyst, an additive, a reductant, and a chiral auxiliary was developed by Hapke and collaborators. They used naphthyl-substituted symmetrical and unsymmetrical triynes and isolated corresponding products in high yields and mostly moderate to high enantioselectivities (Scheme 27).[119]



Scheme 27

To sum up, [2+2+2] cycloadditions are quite powerful transformations to build 6 membered rings, and cobalt complexes are among the most frequently used to catalyze this reaction. We have shown recent examples of cyclotrimerizations, crossed [2+2+2] cycloadditions, and intramolecular [2+2+2] using cobalt catalysts, including asymmetric examples. Despite its synthetical interest, very few of these reactions have been described using flow procedures. The possibility of applying extreme conditions using the commercially available and cheap catalyst,

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$Co_2(CO)_8$, under flow conditions, is an attractive possibility that may allow us to develop a scalable, greener, catalytic and efficient protocol for alkyne cyclotrimerizations. Furthermore, new processing windows can be explored for the development of the crossed [2+2+2], which has no precedents using this catalyst.

2.4. References

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3. La reacción de Pauson-Khand en flujo continuo

Este trabajo presenta un protocolo catalítico y escalable para la realización de la reacción de Pauson-Khand, intra e intermolecular, utilizando generalmente un 5 mol% de $Co_2(CO)_8$ como catalizador en un reactor tubular, con CO introducido al sistema de manera controlada gracias a controlador másico. Se describe la síntesis de diferentes productos que incluyen anillos de 5, de 6, e incluso de 7 eslabones fusionados a la ciclopentenona formada y que presentan sustituyentes en todas las posiciones. Los sustratos más favorables reaccionan en solo 9 min a 120 ^oC, utilizando tan solo 1.5 equivalentes de CO, mientras que, para el resto, se usan condiciones que llegan a alcanzar 170 ^oC, 20 minutos y 3 equivalentes de CO.

En esta publicación, realicé todo el trabajo experimental. El Dr. Blanco-Urgoiti colaboró conmigo en la configuración y funcionamiento de los equipos de flujo. Colaboré con mis supervisores en la redacción del manuscrito, principalmente en la parte experimental y los anexos suplementarios.

Factor de impacto (2017): 6.290. **Categoría:** Química multidisciplinar (Q1 28/171). Fuente: JCR (Journal of citation reports).

Chemical Communications

COMMUNICATION

Cite this: *Chem. Commun.*, 2017, **53**, 4014
Received 7th March 2017,
Accepted 15th March 2017

DOI: 10.1039/c7cc01749a

www.rsc.org/chemcomm

A catalytic scalable Pauson-Khand reaction in a plug flow reactor.

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Abstract A catalytic, scalable intra- and intermolecular Pauson-Khand reaction protocol using generally 5 mol % of $Co_2(CO)_8$ as the catalyst in a plug flow reactor (PFR) is shown.

The Pauson–Khand reaction (PKR) is a formal [2+2+1] cycloaddition of an alkyne, an alkene and a carbonyl unit to give a cyclopentenone. Until the late nineties it was mediated by a stoichiometric amount of metal, generally cobalt.[1] Many catalytic protocols that use different cobalt and other metal complexes have appeared, some of them lacking a general scope.[2] In particular, there are few examples of intermolecular catalytic reactions. With the focus on green chemistry, it is actually impossible to think on an industrial chemical reaction, which involves transition metal complexes, that is not efficiently catalytical. In thinking on the synthetic applications of the PKR more efforts are necessary to improve the current available catalytic methodologies.

Most catalytic PKR are currently being performed under rhodium catalysis. However, cobalt still is a non expensive and efficient alternative and rhodium lacks efficient reactivity with terminal alkynes. In addition, there is a key safety issue with scalable PKR which is the use of CO gas. A limited, controllable use of this component as well as the use of low catalyst loadings is a challenge that we envisioned could be addressed through the use of flow chemistry.

Over the past two decades, continuous technology has evolved quickly and many reactions have shown great advantages when performed under flow conditions with regard to batch flask conditions.[3] In the case of gas–liquid biphasic reactions, the large gas–liquid interfacial area may allow using small amounts of gas that can be exactly measured. In addition, the environmental benefits of flow chemistry over traditional batch chemistry such as the excellent heat and mass transfer or the efficiency in mixing in small volumes, have attracted much attention.[4]

Various carbonylation reactions using a flow microreactor and continous systems have been described.[5] These include transition-metal catalyzed aminocarbonylations,[6] carbonylative Heck[7] and Sonogashira[8] reactions among others. In 2013 Yoshida's group reported the only example of a Pauson-Khand reaction in a photochemical flow microreactor. They preformed a stoichiometric reaction using previously prepared and purified cobalt hexacarbonyl-alkyne complexes.[9]

Herein we present an efficient protocol to perform catalytic, scalable intra- and intermolecular Pauson-Khand reactions using $Co_2(CO)_8$ as the catalyst in a PFR.

We used substrate **1a** to optimize conditions (Table 1).[10] The cobalt catalyzed PKR has been described in the literature using 3-10 mol % of $Co_2(CO)_8$ under 1-7 atm of CO and with the aid of additives such as phosphites,[11] phosphines,[12] tributylphosphinesulfide,[13] dimethoxyethane,[14] or a cobalt-TMTU complex.[15] These are used to substitute in situ one or more CO ligands with different coordinating groups in order to form a more stable complex that could re-enter a catalytic cycle before decomposing into unactive species.[16] We described a catalytic protocol using CO adsorbed in molecular sieves (zeolites).[17] The initial alkyne hexacarbonyl complex previoulsy prepared and purified has been used as the catalysts.[18] Our interest was to do the reaction without additives using a minimum amount of CO. The mass flow controller allows introducing into the system an accurate amount of gas. Low residence times and the possibility of working at high pressures would allow high efficiency on this process. The scheme of the system used in this work is depicted in figure 1. We first performed the reaction in batch. Entry 1 shows the best result achieved in a stainless reactor. Optimization of conditions in the PFR (entries 2-8) revealed the need to elevate the temparature up to 120 °C to achieve total conversion. Catalyst loading was first fixed at 5 mol% as with lower loadings conversions decreased (entry 5). Supply of CO could be minimized to 1.5 equiv[19] (entry 6 which shows the best conditions: 9 min of residence time, 120 °C with 1.5 equiv of CO), leading to 99% yield. In entries 7-8 we show the results of a scaled up reaction where 5 g of **1a** were efficiently transformed into **2a** in 91/82%

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Electronic Supplementary Information (ESI) available: *Spectra of new compounds. See DOI: 10.1039/c7cc01749a*

yield using 3 or 1.5 equiv of CO respectively.[20] The total time for these experiments was 38/42 min and in the latter reaction an excess of less than 300 mg of CO was used. The optimized conditions were applied to subtrates **1b-h** giving products **2b-h** in excellent yields (91-99% except **2c**). Some of these substrates are known for not giving good results in PKR. Substitution at the internal position of the olefin as in **1b**, gives generally poor yields which is not the case with our methodology (98/82%, entries 9-10). Electron poor olefins are many times uneffective.[21] However substrate **1c** only gave a good yield (68%) of **2c** with a longer residence time (17 min) and 10 mol % of catalyst (entry 14) as an only diastereomer. This product kept the *trans* stereochemistry of the starting material (see Table 1 scheme). Substrates **1d-g** reacted readily giving the corresponding cyclopentenones in excellent yields (91-95%, entries 15-20). Finally, the presence of a bulky substituent at the alkyne as in **1h** required stronger conditions (entry 24) to achieve nearly quantitative yields of product **2h**. For the scale up reaction (5 g of substrate) we used 2 equiv of CO and a 10 mol % of catalysts reaching 89% yield in 83 minutes of total time (entry 26).

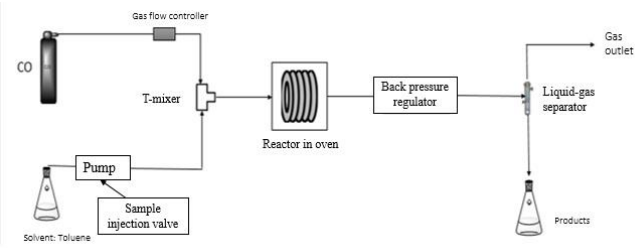
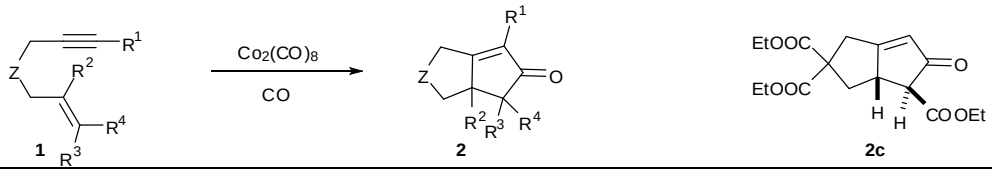
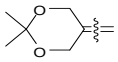


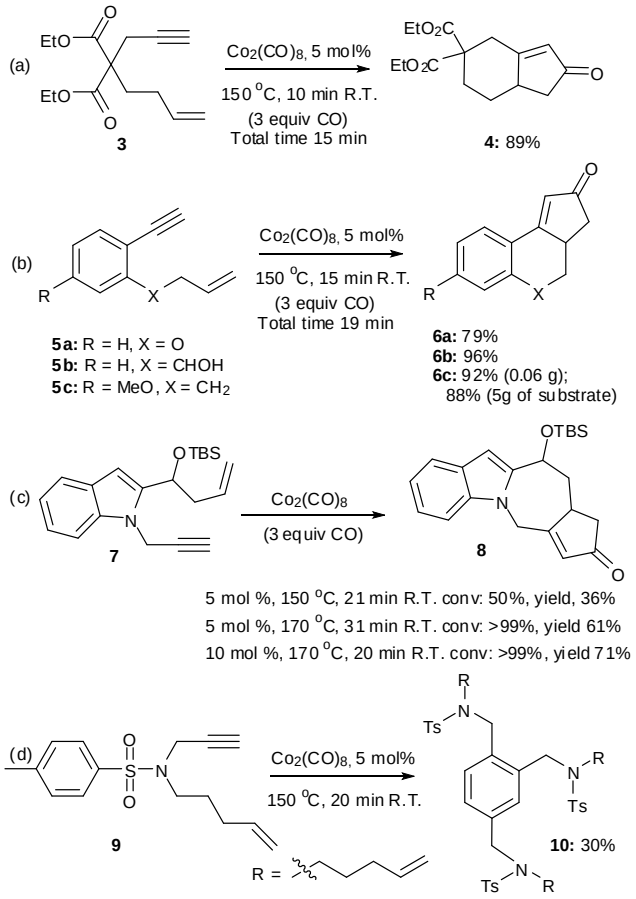
Figure 1. Scheme of the flow system used for the catalytic PKR.



Entry[a]	Starting	Z	R^1	R^2	R^3,R^4	Product	CO equiv	temp (ºC)	Residence time (min)	cat. (mol %)	Conv.[b]	Total time (min)	yield (%)[c]
1[d]	**1a**	$(EtO_2C)_2C$	H	H	H,H	**2a**	12.5[d]	120	-	5	>99	4 h[e]	78
2	**1a**	$(EtO_2C)_2C$	H	H	H,H	**2a**	3	90	11	5	51	14	35
3	**1a**	$(EtO_2C)_2C$	H	H	H,H	**2a**	3	105	10	5	>99	14	68
4	**1a**	$(EtO_2C)_2C$	H	H	H,H	**2a**	3	120	9	5	>99	13	99
5	**1a**	$(EtO_2C)_2C$	H	H	H,H	**2a**	3	120	11	2	85	14	57
6	**1a**	$(EtO_2C)_2C$	H	H	H,H	**2a**	1.5	120	9	5	>99	13	97
7[f]	**1a**	$(EtO_2C)_2C$	H	H	H,H	**2a**	3	120	9	5	>99	38	91
8[f]	**1a**	$(EtO_2C)_2C$	H	H	H,H	**2a**	1.5	120	9	5	>99	42	82
9	**1b**	$(EtO_2C)_2C$	H	Me	H,H	**2b**	3	120	9	5	>99	13	98
10	**1b**	$(EtO_2C)_2C$	H	Me	H,H	**2b**	1.5	120	9	5	>99	13	82
11	**1c**	$(EtO_2C)_2C$	H	H	CO_2Et,H	**2c**	3	120	9	5	60	13	20
12	**1c**	$(EtO_2C)_2C$	H	H	CO_2Et,H	**2c**	3	120	17	5	85	22	56
13	**1c**	$(EtO_2C)_2C$	H	H	CO_2Et,H	**2c**	3	150	17	5	>99	22	42
14	**1c**	$(EtO_2C)_2C$	H	H	CO_2Et,H	**2c**	3	120	9	10	>99	13	68
15	**1d**	TsN	H	H	H,H	**2d**	1.5	120	9	5	>99	13	94
16	**1e**	TsN	Me	H	H,H	**2e**	3	150	11	5	97	14	91
17	**1e**	TsN	Me	H	H,H	**2e**	1.5	150	11	5	97	14	79
18	**1f**	TsN	H	H	Me,Me	**2f**	3	120	10	5	>99	14	91
19	**1f**	TsN	H	H	Me,Me	**2f**	1.5	120	10	5	>99	14	79
20	**1g**		H	H	H,H	**2g**	2	120	10	5	>99	14	94
21	**1h**	O	Ph	H	H,H	**2h**	3	120	9	5	18	13	7
22	**1h**	O	Ph	H	H,H	**2h**	3	150	15	5	88	19	87
23	**1h**	O	Ph	H	H,H	**2h**	3	170	21	5	>99	27	99
24	**1h**	O	Ph	H	H,H	**2h**	1.5	170	21	5	50	27	45
25	**1h**	O	Ph	H	H,H	**2h**	2	150	21	10	75	27	70
26[f]	**1h**	O	Ph	H	H,H	**2h**	2	170	21	10	>99	83	89

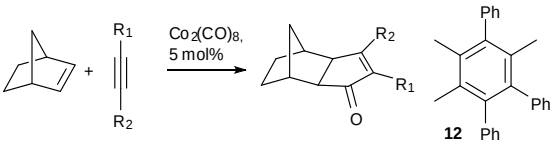
[a] Conditions for all experiments: 0.4 mmol/mL substrate concentration (0.8 mL used in each experiment), 20 bar system pressure, reactor volume: 60.63 mL. [b] by NMR. [c] in pure product. [d] Experiment in batch at 5 bar of CO, in a 30 mL stainless reactor. The CO used was 5 mmol for 0.4 mmol of substrate. [e] Reaction time. [f] Scale-up experiment with 5 g of substrate.

In view of these good results we switched to a group of substrates precursors of 6 and 7 membered rings (Scheme 1). Both with linear substrate **3** and aromatic-ring templated compounds **5** we reached 79-96% yields in products **4** and **6** (Scheme 1, a,b). The synthesis of 7 membered rings on the other hand through the PKR is possible with aromatic-templated substrates,[22] allenynes[23] or using temporary rigidifying tethers.[24] We show the synthesis of compound **8** which was obtained in 71% yield when we carried out the reaction at 170 ^{o}C and with 10 mol% of catalysts. On the contrary, under all the conditions tested with substrate **9** we did not detected the desired PKR product but isolated a moderate yield of a [2+2+2] product (**10**, 30%), as a result of a cyclotrimerization of the alkyne.



Scheme 1. Synthesis of 6- and 7-membered ring containing PK aducts.

Finally we showcase some examples of intermolecular PKR under flow conditions in Scheme 2. These results are particularly important as the catalytic intramolecular version of the PKR has found less development.[25] High pressures of CO and the use of additives are common procedures that work well only with terminal akynes.[1,2] In our hands, from norbornene and only 3 equiv of CO, we prepared different final products in a totally diastereoselective manner. The terminal alkynes (phenylacetylene and 1-hexyne) gave good yields of **11a** and **11c** respectively under the standard reaction conditions including a multigram reaction with **11a**. Internal alkynes reacted moderately and needed higher temperatures, residence times and CO equiv, but gave the disubstituted cyclopentenones **11b** and **11d** in 42 and 66% yield respectively. In addition to product **11b**, the reaction of norbornene with 1-phenylpropyne gave a 40% yield of a [2+2+2] product **12**, as a result of a cyclotrimerization process of three units of the alkyne.



Product	CO equiv	temp (°C)	R.t (min)	Total time	Yield[a]
11a: R_1 = Ph, R_2 = H	1.5	120	9	14/42	79/81%[b]
11b: R_1 = Ph, R_2 = CH_3	3	170	20	25	42%[c,d]
11c: R_1 = Bu, R_2 = H	1.5	120	10	14	83%
11d: R_1 = R_2 = CH_2OCH_3	3	170	15	20	66%[c]

[a] In pure product
[b] 0.1g/2.5 g of norbornene, scaled up reaction
[c] No reaction observed at lower temperature
[d] 40% of [2+2+2] product **12** isolated

Scheme 2. Catalytic intermolecular PKR in microreactor.

In summary we show a general protocol for both inter-and intramolecular PKR in a PFR. The use of a minimum amount of CO, the efficiency of the process, low catalysts loadings, broad scope and scalability of this method opens a new alternative that can lead to novel applications of this powerful transformation.

Funding of this project by Spanish MINECO and Fondo Europeo de Desarrollo Regional (FEDER, grant No. CTQ2015-64624-R MINECO/FEDER) and FUSP-CEU (PC17/16) is acknowledged. J. G. thanks the Fundación San Pablo-CEU for pre-doctoral fellowship.

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19 The mass flow controller used can introduce precisely up to 10 mLN/min of gas, which means 0.4 mmol/min. Thus, over 10 mLN/min, the modification of the gas flow is absolute accurate, controlling at any moment of the process the carbon monoxide equivalents. The final reaction mixture pours into a gas-liquid separator, were the excess CO gas is discarded to the atmosphere. At this point a catalyst cartridge, similar to the cars exhaust pipe could be installed so it would be transformed into CO_2.

20 Scaled up reaction, synthesis of **diethyl 5-oxo-3,3a,4,5-tetrahydropentalene-2,2(1H)-dicarboxylate, 2a:** (entries 7 and 8): 5g of **1a** and 359 mg of $Co_2(CO)_8$ (5 mol%) were dissolved in 52.52 mL of toluene. The solution was degasified with Ar, and filtered through a nylon filter of 0.45 µm. The resultant solution was set up in the pump inlet. The conditions of the system were 120 ºC, 20 bar of pressure, and 3 or 1.5 equivalents of CO. The total time was 38 and 42 minutes respectively. The crude product was filtered through celite, which was washed with chloroform (15 mL) and concentrated *in vacuo* 5.24 and 5.18 g were obtained as crude product with >99% of conversion. After purification by silica gel column chromatography (Hexane/Ethyl acetate 4:1), 5.02 g or 4.52 g of pure product were obtained (91% or 82% yield, respectively).

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4. Síntesis de Treprostinil utilizando metodología de flujo para las reacciones clave: Pauson-Khand y reordenamiento de Claisen

Se describe una nueva síntesis del fármaco Treprostinil. En ella, dos reacciones claves, un reordenamiento de Claisen y una reacción de Pauson-Khand son desarrolladas a escala de multigramo usando un reactor tubular. La primera, nos proporciona una gran mejora sobre lo descrito previamente en términos de selectividad, productividad, seguridad y separación del producto final; mientras que la segunda nos permite usar únicamente un 5 mol% de $Co_2(CO)_8$ como catalizador y 3 equivalentes de CO de manera segura. El producto de la reacción de Pauson-Khand es transformado en el Treprostinil en únicamente 3 pasos adicionales. Otra mejora que presenta el trabajo es la introducción de una cadena con un carboximetilo en el fenol para reducir los pasos de protección-desprotección. En definitiva, la síntesis consta de 12 pasos lineales desde (*S*)-epiclorhidrina y transcurre con un 14% de rendimiento global.

En esta publicación, realicé todo el trabajo experimental, incluyendo tanto las reacciones en lote como las desarrolladas en reactor de flujo. El Dr. Blanco-Urgoiti colaboró conmigo en la configuración y funcionamiento de los equipos de flujo. Colaboré con mis supervisores en la redacción del manuscrito, principalmente en la parte experimental.

Factor de impacto (2019): 3.412. **Categoría:** Química Orgánica (Q1 13/57). Fuente: JCR (Journal of citation reports)

Paper

Synthesis of treprostinil: key Claisen rearrangement and catalytic Pauson-Khand reactions in continuous flow

Cite this: *Org. Biomol. Chem.*, 2019, **17**, 9489

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Received 1st October 2019,
Accepted 15th October 2019

DOI: 10.1039/c9ob02124h

Abstract. A new synthesis of treprostinil is described using a plug flow reactor in two of the key steps. First, a Claisen rearrangement reaction is described in scaled flow at multigram amounts. Yields and selectivity of this step is sharply improved from previous syntheses. Second, the key Pauson-Khand reaction in flow is described under catalytic conditions with 5 mol % of cobalt carbonyl and only 3 equiv of CO. Scaling up of this reaction in safely ensured giving good yield of an advanced intermediate which is transformed in three steps into treprostinil. Other improvements are the introduction of the carboxymethyl chain into the phenol from the beginning to reduce the protection-deprotection steps. The synthesis is completed in 14% global yield after 12 linear steps from (*S*)-epichlorhydrinç

Introduction

Treprostinil (**1**) is a tricyclic benzoindene analogous to prostacyclin PGI_2.[1] Its main effects are the inhibition of platelet aggregation and vasodilation, including acute pulmonary vasodilation.[2] These biological activities are relevant for the treatment of cardiovascular diseases such as pulmonary arterial hypertension, a disease with a very serious prognosis until approximately 2010.[3] Since then, up to 13 prostanoid therapies have been implemented. Mostly, the continuous perfusion of a solution of the drug is used as administration route. This treatment has numerous disadvantages[4] and makes difficult the therapeutic compliance on the part of the patient. In pursuing active and stable analogues that can be administered in a less invasive way, analogues have been synthesized in which the C5-C6 double bond has been eliminated or bioisosteres have been made by replacing the cycle oxygen with a methylene group (iloprost), a sulfur atom (5Z-6,9-thiaprostacycline) or nitrogen (9-deoxy-9α,6-nitrile-PGF1). In the case of treprostinil the vinyl ether is embedded in a phenoxide system, making it resistant to acid hydrolysis (Figure 1).

Treprostinil can be administered by inhalation and since 2013 is approved by the FDA as an oral drug. The cost of the annual treatment with this drug is in a range of between 140,000 and 180,000 $. One of the causes of the high cost of the drug is its complex and expensive chemical synthesis and the high cost of its development. It is important to find new scalable synthesis processes that lower the production costs of the drug and result in less use of contaminating, and harmful reagents for the environment.

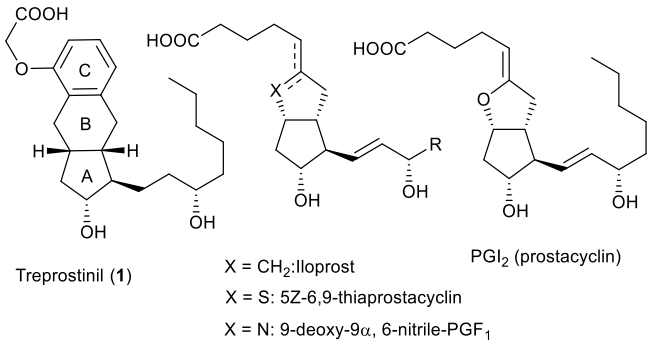

Figure 1 Prostacyclin PGI_2 and analogues used as drugs for the treatment of pulmonary arterial hypertension.

The first synthetic strategies, due to Aristoff's group used either an intramolecular Wadworth-Emmons-Wittig reaction without stereochemical control to build the cyclopentane A[5] or an intramolecular alkylation of the phenolic ring for the formation of the B ring.[6] A similar approach appeared later in the patents of Shin et al. and Gao et al.[7]

In 2004 Moriarty et al. published the first total synthesis of treprostinil based on an intramolecular stoichiometric Pauson-Khand reaction (PKR).[8] Enyne intermediate **4** is prepared by lithiation and alkylation of **2**, which is transformed into **4** in three steps. The synthetic route overcomes the problems of stereoselectivity by means of oxidation and subsequent stereoselective reduction of the enynic intermediate **4**. The resulting benzyl alcohol is protected with the bulky OTBDMS group (**5**), which serves as a temporary inducer group, achieving a totally stereoselective PKR. The PKR takes place with an 89% yield and then 6 steps are required to reach treprostinil. The route, with 15 linear steps, is said to give an overall yield of 9% (Scheme 1).

Some small variants have been disclosed based on this synthesis like the introduction of different esters in the carboxyl group of the treprostinil[9] or the use of an allyl group as a protecting

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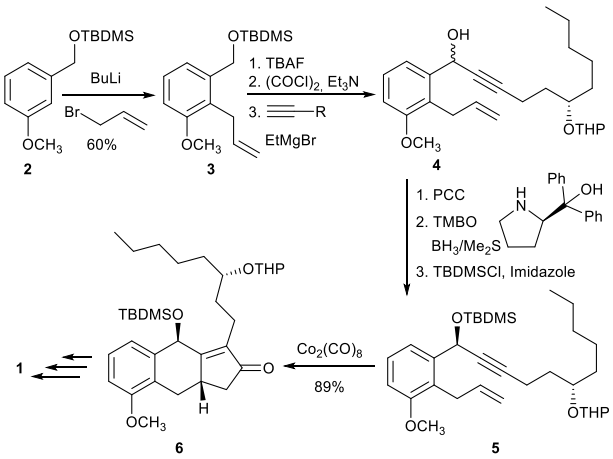
Electronic Supplementary Information (ESI) available: Spectra collection and description of the flow systems. See DOI: 10.1039/c9ob02124h

group of the phenol.[10] Different protecting groups at the hydroxyl of the side chain[11] and variations in the synthesis of the alkyne that introduces the side chain were described.[12]



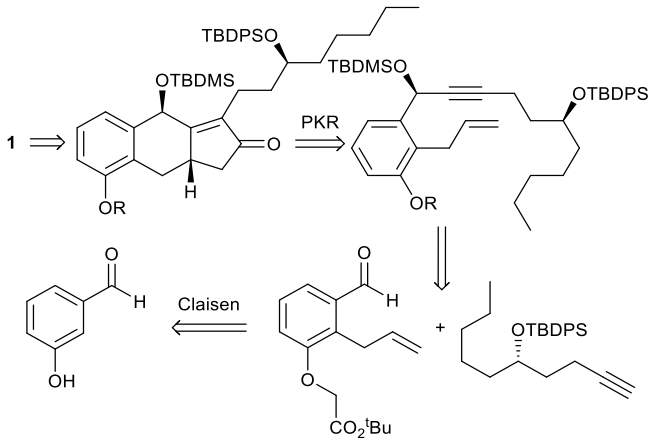
Scheme 1 Summary of the Moriarty's synthesis of treprostinil.

Flow reactors have important processing advantages including the improvement of energy and mass transfer, thermal management and the application of intense reaction conditions in a safe and controlled way, Over the past two decades, significant advances in the field of flow chemistry have permitted chemistries unachievable via conventional batch methods and helped to improve the manufacturing of Active Pharmaceutical Ingredients (APIs) via continuous processing.[13] Reactions with negative activation volumes, such as cycloadditions, condensations, and some rearrangements, including the Pauson-Khand reaction and the Claisen rearrangement, are particularly attractive for acceleration using flow technology. Application of high temperature and pressure on a reaction may lead to a chemical intensification due to the finding of novel process windows.[14] The use of gases in flow chemistry has been one of the main challenges in the development of this tool in organic synthesis. With flow systems, the amount of hazardous and toxic gas reagents, such as hydrogen or carbon monoxide, can be significantly reduced.[15] Typical examples are hydrogenation,[16] oxidation[17] and carbonylations.[18] We have published favourable preliminary results found in PKRs in a plug flow reactor (PFR).[19] Limiting the use of carbon monoxide and finding intensive condition windows was an important achievement.

A recent, very active area of research is the integration of individual process steps in the synthesis of a critical intermediate or final product into a single, fully continuous production line. Even though current pharmaceutical and fine-chemical production is by far dominated by batch processing, it is demonstrated how the tendency towards continuous processes in the pharma industry, which in addition are considered greener,[20] is increasing.[21] In this work, we highlight the benefits of the production in a continuous flow system two important steps in the treprostinil synthesis. On one side we apply our methodology to the key PKR. On the other, we use for the first time a continuous system for the other key step of the synthesis of treprostinil, the Claisen rearrangement showing the excellent performance and scalability of the flow methodology. Our method improves efficiency and selectivity while reducing risks and facilitates the isolation of the product saving time and reducing the use of solvents and energy.

Results and discussion

Scheme 2 shows the retrosynthesis of treprostinil based on the convergent synthesis of an enyne as the precursor of the PKR that gives an advanced intermediate onto the final product **1**.

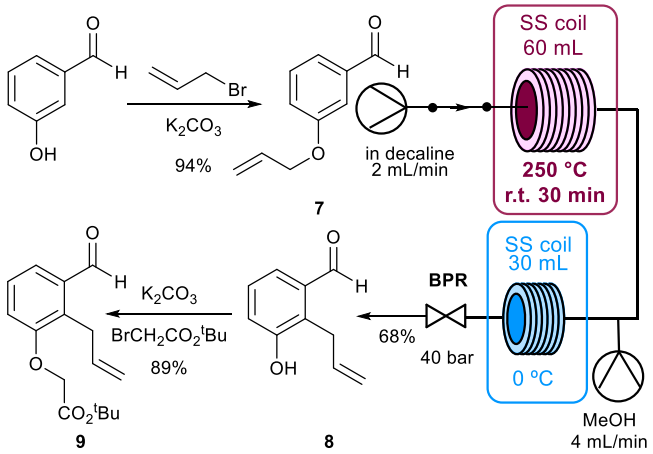


Scheme 2 Retrosynthetic analysis of treprostinil.

The first step in the synthesis is the protection of the hydroxyl group of 3-hydroxybenzaldehyde with allyl bromide in the presence of base to give 3-allyloxybenzaldehyde **7**, with a yield of 94% (Scheme 3). Then a Claisen rearrangement in the flow reactor gave **8**. The Claisen rearrangement in flow has been previously studied by several groups, including mechanistic studies but not for the synthesis of this substrate which involves two possible problems: the lability of the aldehyde group and the possible formation of regioisomers.[22]

The use of the Claisen rearrangement in batch to obtain the aldehyde **8** has been described in several patents. However, the yields are generally low and reaction times and isolation are long. Moriarty et al. described this reaction for the first time, using a temperature of 150 °C, 41 h of reaction time and numerous extractions, separations by column chromatography and a recrystallization to obtain **8** with a 25% yield.[23] Other authors described higher reaction temperatures (180 – 217 °C) and shorter reaction times (7 h), but after the long work up, yields continued to be poor (33%,[10] 42%[24] and around 50%[25]). In another contribution, a bromine atom was introduced at the *ortho* position of the allyoxide group to avoid regioselectivity problems but the isolated yield was 27% after 2 days of reaction and two days of isolation.[26] Heating with MW allowed slight increase of yield to 45% in shorter time (800 W, 240 °C, 10 minutes) to transform just 1.5 g of starting material.[27] All these previous works indicate the formation of variable amounts of

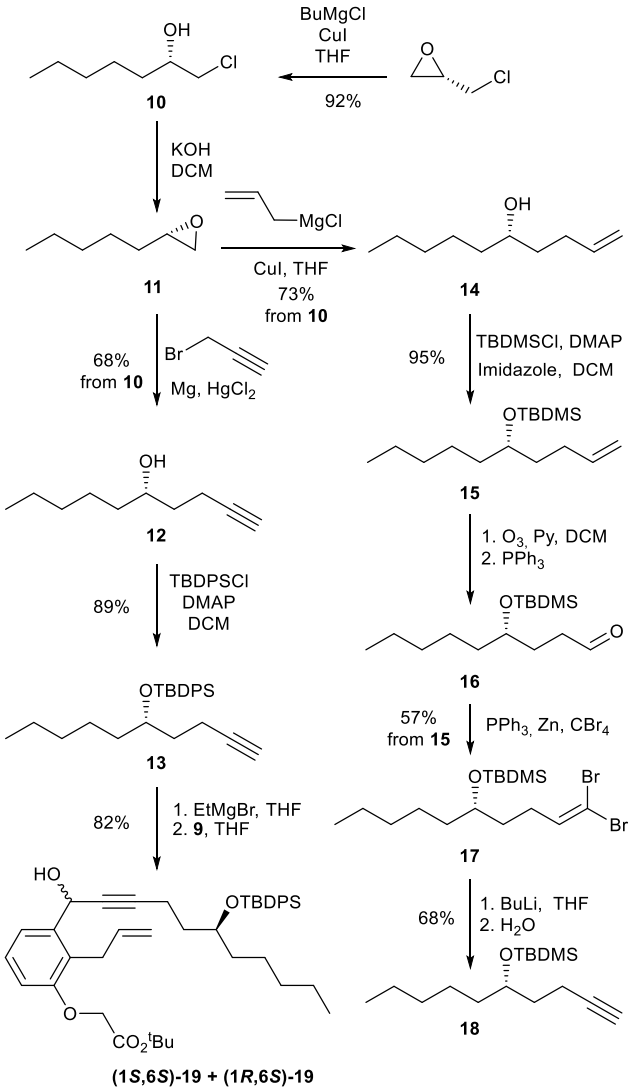
the other three possible regioisomers of the desired product **8**. Due to this poor results other group described the reaction using the methyl ester instead of the aldehyde as the starting substrate to obtain a 80% of product which had to be reduced.[28] The intensification of conditions in the flow reactor allowed in our hands the use of high temperatures and pressures that improved dramatically the yields of the desired product. Screening of conditions revealed best conversions when using a solution of **7** in 10 volumes of decalin at 250 °C with a residence time of 30 min. Decalin was selected among various solvents as it gives the best solubility of the starting material. The equipment had the configuration shown in Scheme 3. It was necessary to introduce methanol to the system to solubilize the final product, in addition to a cooling bath. The crude reaction product is collected in an Erlenmeyer flask where decalin and methanol are separated in two layers. Interestingly, the final product is mainly found in the methanol phase. With these optimized conditions, 100 g of **7** were introduced in the system and transformed into **8**. The total time of this operation was 9.5 h.[29] Partial evaporation of the methanol layer produced a precipitate, which was washed with hexane to give 74.7 g of **8**. Remarkably, the solid contained the desired regioisomer of **8** sufficiently pure to continue the synthesis (91% purity by ^{1}H NMR contaminated with other regioisomers). From the decalin layer, by addition of toluene and cooling, another precipitate of 19 g was obtained. This solid contained 28% of **8** measured by ^{1}H NMR and a mixture of other isomers. The result of this reaction is important, not only because of the total yield of final product but for the isolation process with methanol that gives high amounts of the product in an operational easy and rapid way. Next step was the formation of the product **9** by reaction of **8** with *tert*-butyl bromoacetate using potassium carbonate as the base (89% yield). Our approach introduces the final chain of treprostinil very early in the synthesis avoiding the need to deprotect and introduce the carboxymethyl chain in the last steps of the synthesis, as, for instance in Moriarty's synthesis where the phenol group is protected as methoxy. The cleavage of this group proved problematic and could only be achieved with lithium diphenylphosphine prepared in situ from diphenylphosphine and butyllithium.



Scheme 3 Synthesis of the aldehyde block 9 using a Claisen rearrangement in flow.

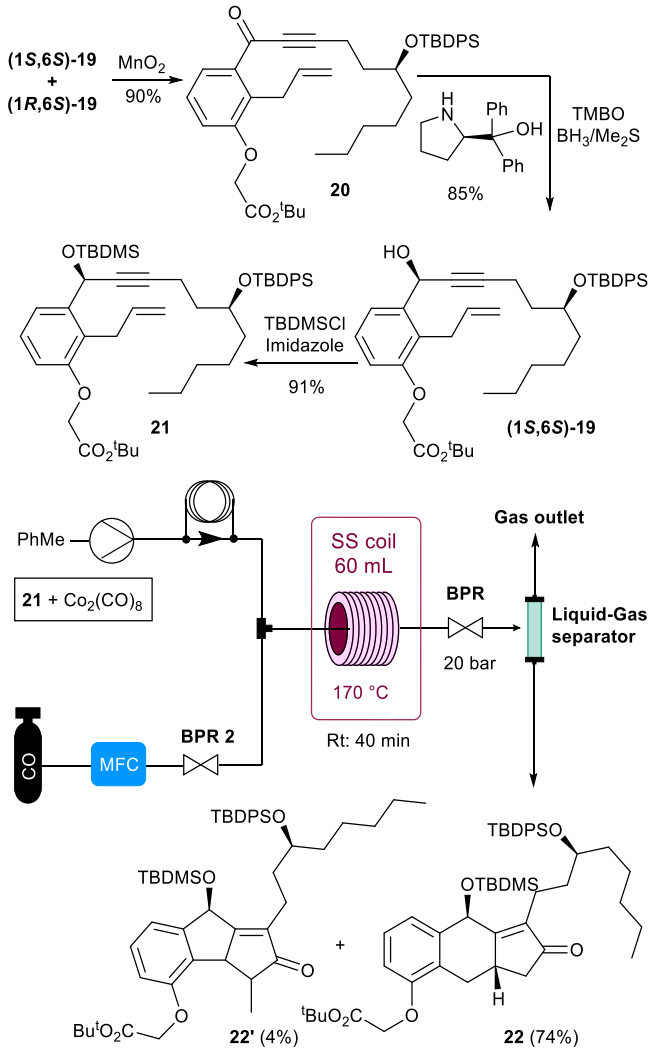
The synthesis of the long alkyne fragment has been carried out by two different routes. The reaction of epichlorhydrin with butylmagnesium chloride gave chloroheptanol **10** which upon treatment with potassium hydroxide gave epoxide **11** which was not purified. In the first approach the opening of this epoxide with a Grignard reagent formed *in situ* and catalyzed by mercury chloride gave **12** which is protected to yield **13**. The fragment is built in 4 steps with an overall yield of 56%. The second route is based on using the more reactive allylmagnesium chloride that avoids the need of mercury catalysis and gives **14** which is protected as silylderivative **16**. The triple bond is generated through an ozonolysis of intermediate **16** (catalytic osmylation with NMO and oxidative cleavage with $NaIO_4$ in basic media were used alternatively, see experimental section) and a Corey-Fuchs reaction. The intermediate **18** is reached after 7 steps from epichlorihydrin with a global yield of 25%. The overall yield of this approach is lower, but has the advantage of avoiding the use of a contaminating and highly toxic reagent such as mercury and uses a commercial Grignard reagent avoiding *in situ* formation of the propargyl derivative. The synthesis was continued with **13** which was reacted with **9** in the presence of ethylmagnesium bromide to give **19** in 82% yield as a diastereomeric mixture.

The precursor of RPK is prepared from the diastereomeric mixture (**1*S*,6*S*-19+1*R*,6*S*-19**) following the methodology of Moriarty.[8] Thus, oxidation with MnO_2 and stereoselective reduction gave enantiomerically pure (**1*S*,6*S*-19**) which was protected as TBDMS derivative (**21**). This bulky group was introduced to direct the stereochemical outcome of the subsequent PKR. Thus, **21** was prepared in three steps with a global yield of 70% from **19** diasteromeric mixture.



Scheme 4 Preparation of the alkyne containing fragment.

The Pauson-Khand reaction (PKR) was optimized in the PFR system with the aim of minimizing the use of CO and the residence time whilst achieving a good yield. Two patents had mentioned the possibility of making the PKR with catalytic amounts of cobalt and under carbon monoxide pressure.[26,30] However herein we present the first catalytic and scalable PKR in a flow reactor. Compound **21**, being an internal alkyne and producing a 6 membered ring in the PKR is not a very favorable substrate. Thus, we performed 3 reactions in batch to find starting conditions for the optimization in flow (Table 1, entries 1-3). Total conversion was achieved at 170 °C with 5 mol % of $Co_2(CO)_8$. In the PFR, using this temperature, a 0.3 M concentration of **21** and the same catalyst loading the residence time was fixed to 40 min to get total conversion of the substrate into **22** (entry 9). Some degradation products were observed but not isolated. Only 3 equiv of CO were used in each reaction. Lowering this amount of CO or the catalyst loading or decreasing the concentration of **21** precluded total conversion of this reaction (entries 7, 10, 11). System pressure was fixed at 20 bar as no improvement was observed if increasing to 25 bar (entry 8). With the optimized conditions in hand (entry 9), 7.5 g of **21** were transformed into **22** with a 74% yield in a total time of 1h 45 min (entry 12). Noteworthy is that no precipitation /decomposition of the catalyst was observed. The crude reaction mixture was very clean. However it was purified by column chromatography to eliminate cobalt impurities which in the scaled out reaction allowed the isolation of 410 mg (4% yield) of a side product which was characterized as **22'** where the emerging double bond had shifted. This was the only isolable side product. As the presence of traces of metal is a great concern in the synthesis of APIs, we performed a cobalt analysis by ICP. The crude mixture contained 3050 ppm of cobalt which was reduced to 1855 ppm after washing with HCl. Finally after purification by column chromatography, the purified product **22** contained less than 0.2 ppm of cobalt.



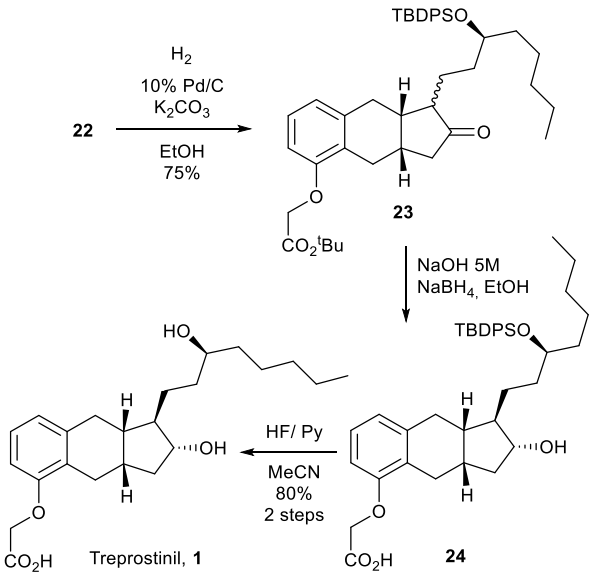
Scheme 5 Preparation of the PKR substrate 21 and its reaction in a PFR system to give intermediate 22.

Table 1 Optimization of the PKR conditions for the synthesis of **22** (entries 1-3, batch conditions; 3-12, flow conditions)

Entry [a]	CO equiv	Temp (ºC)	Res./Reac time (min/h)	cat. (mol %)	Conv.[b]	yield (%)[c]
1[d]	6[d]	150	18 h	5	65	52
2[d]	6[d]	150	18 h	10	75	65
3[d]	6[d]	170	18 h	5	>99	70
4	3.0	170	21	5	50	28
5	6.2	170	23	5	52	34
6	3.0	170	31	5	63	42
7[e]	3.0	170	31	5	40	28
8[f]	3.0	170	31	5	70	41
9	3.0	170	40	5	>99	72
10	3.0	170	40	2	70	49
11	1.5	170	40	5	92	65
12[g]	3.0	170	40	5	>99	74[h]

a) All reactions in PFR (entries 4-11) at 20 bar of system pressure, 0.3 M concentration of **21** (0.35 mmol) except otherwise indicated. b) Measured by HPLC. c) In pure product. d) Reactions in batch, in a stainless reactor at 6 bar of CO. e) Concentration of **21**: 015 M. f) System pressure 25 bar. g) Scaled out reaction with 7.5 g of **21**. Total time 1h 45 min. h) Plus 4% of **22'**.

Subsequently the benzylic alcohol group is eliminated by hydrogenolysis while reducing the double bond formed in the PKR giving **23**. The reduction of this double bond also takes place in a completely stereoselective way with regard to the stereogenic center located at the fusion, although it gives a mixture of diastereomers in the center adjacent to the ketone. However, both isomers **23** are in equilibrium in ethanolic basic solution and, due to the different rate of the reduction of the ketone with $NaBH_4$, they are balanced and finally lead to a single isomer of the product **24** with the correct stereochemistry in the 5 stereogenic centers.[8] This intermediate was treated without purification with HF/Pyridine complex to give treprostinil **1**, with a yield of 80% from **23.**



Scheme 6 Completion of the synthesis of Treprostinil.

Conclusion

A new synthesis of treprostinil is described through its intermediates, implying improvements in yields, in protective groups and, above all, the use of flow systems in two of the key steps. The carboxymethyl chain is introduced from the beginning into the phenol to reduce the protection-deprotection steps. The Claisen rearrangement is described in scaled flow at multigram amounts. Two alternative synthesis of the side chain are described. The Pauson-Khand reaction in flow is described under catalytic conditions with 5 mol % of cobalt and only 3 equiv of CO. The synthesis is completed in only three steps after the PKR. The overall yields are: 57% for the aldehyde **9**, 56% for the side chain **13**, 57% for the coupling of fragments **9** and **13** and preparation of the precursor of PK **21.** Then**,** the PK reaction and in the final stages have a yield of 44%. The overall yield of treprostinil is 14% from (*S*)-epichlorohydrin in 12 linear steps. Table 2 shows the main advantages of our synthesis compared with those described up to now using batch procedures.

Table 2 Summary of improvements reported herein due to flow technology

Reaction	Reported protocols in batch	Continuous protocol described in this paper
Claisen Rearr.	Long reaction times	30 min of R.t.
	Difficult isolation	Easy work-up
	Difficulties in achieving high T (200-250)	Easy and safe way to achieve high T. Energy saving. Ecofriendly
	22-50% yield	68% yield
Pauson-Khand reaction	Stoichiometric amounts of catalyst or Substoichometric catalyst + CO	Only 5 mol% of catalyst Using CO in a safer a controlled way
	Complex formed in DCM and reaction in AcN	Direct reaction in toluene
	Reaction time: 4–15h	40 min of res. time
	55-89 % yield	74 % yield

Experimental

All starting materials and reactants were purchased from commercial sources and used without further purification. $Co_2(CO)_8$ is a stable solid, but it decomposes partially after some weeks reducing its activity. It is advisable to use freshly opened bottles. NMR data was measured on a Bruker AM-400. Chemical shifts (δ) are expressed in ppm downfield from TMS (0.00 ppm) as an internal standard for ^1H and the central signal of $CDCl_3$ (77.0 ppm) for ^{13}C. The letters s, d, t, q, m, dd, and bs are used to indicate singlet, doublet, triplet, quadruplet, multiplet, double doublet and broad singlet respectively. Reaction progress was monitored by TLC or HPLC. IR are recorded in a Perkin-Elmer Spectrum 100 FT-IR Spectrometer. Representative signals of functional groups are given in cm^{-1}. Optical rotation is measured in an Anton Parr polarimeter MCP100. ICP analysis were performed on a ICP_AES Varian Vista-MPX. Purification

otherwise noted was made by Silica gel column chromatography using Merck silica gel 60 (0.040-0.063 mm). and eluents are indicated in each case. Melting point is measured using Stuart™ melting point apparatus SMP3.

The flow system is a PFR (Plug flow reactor, tubular reactor, composed by a 316 stainless steel tube with internal diameter of 17 mm and 25 mm of external diameter, volume = 60.6 mL) in a forced air oven, with one feeding line with a Semipreparative HPLC pump ASI Model 501. In case of the Claisen rearrangement, MeOH is introduced by another pump of the same type. The system pressure is automated controlled by a high precision needle backpressure valve and WIKA pressure sensor. In case of the Pauson Khand reaction, CO is introduced by a Bronkhorst mass flow controller calibrated for this gas, and it is mixed with the solution in a T-Shape stainless steel piece. The system has a gas liquid separator after the reactor (See SI for real pictures).

3-(Allyloxy)benzaldehyde (7)

To a solution of 3-hydroxybenzaldehyde (100 g, 0.82 mol) in ethanol (600 mL), NaI (12.3 g, 0.08 mol, 0.1 equiv), and K_2CO_3 (147.3 g, 1.07 mol,1.3 equiv) were added. Then, allyl bromide (119.1 g, 0,98 mol, 1.2 equiv) is added. The mixture was stirred at 60ºC for 3 hours. Afterwards, the mixture is filtered, and the solvent evaporated *in vacuo*. After purification in silica gel column chromatography in Hexane:Ethyl acetate (4:1), the product was obtained as a yellow oil (125.0 g, 94%). Rf: 0.63 (Hexane/AcOEt 9:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.97 (s, 1H, CHO), 7.48 – 7.38 (m, 3H, Ar), 7.22 – 7.15 (m, 1H, Ar), 6.11 – 6.02 (m, 1H, C*H*=CH_2), 5.43 (dt, J_1 = 17.3 Hz, J_2 = 1.7 Hz, 1H, CH=C*H*$_2$ *trans*), 5.32 (dt, J_1 = 10.5 Hz, J_2 = 1.6 Hz, 1H, CH=C*H*$_2$ *cis*), 4.63 – 4.56 (m, 2H, OCH_2) ppm. The spectroscopic data obtained are consistent with those reported in literature.[27]

2-Allyl-3-hydroxybenzaldehyde (8)

In an Erlenmeyer flask 100 g (0.62 mol) of 3-(allyloxy)benzaldehyde, are dissolved in decalin until a final volume of 1 L. Once the solution is perfectly clear it is placed in the inlet of the pump (pump 1). A flask with MeOH is placed in the inlet of the second pump (pump 2). MeOH was introduced after the oven to avoid precipitation of the final product. Furthermore, a cooling bath inside an ice-water bath is placed after mixing both solvents. The configuration of the system is shown in Scheme 3. The conditions of the system for this reaction were: Temperature: 250 ºC; pressure: 40 bar; residence time: 30 min; pump flow 1: 2 mL/min; pump flow 2: 4 mL/min; reactor volume: 60.6 mL; total time: 9.5 hours. The mixture of MeOH and decalin is collected in a flask. The solution was allowed to cool to room temperature, and both layers were separated. The decalin layer is stirred with MeOH (1000 mL) and both phases separated again. Both methanolic phases were joined and partially evaporated *in vacuo* until a brownish solid precipitated. The solid was washed with hexane (3x100 mL), to obtain 74.3 g of a pale-yellow solid with 91% of the desired regioisomer (determined by ^{1}H NMR). The decalin phase was placed in an ice bath with toluene (400 mL), and the solid that precipitated was filtered and washed with hexane (3x50 mL). The NMR analysis of the 19 g obtained in this way indicated the presence of a 28% of the desired regioisomer. Calculated yield of **8**: 68%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.19 (s, 1H, CHO), 7.45 (dd, J_1 = 7.7 Hz, J_2 = 1.3 Hz, 1H, Ar), 7.31 (t, J = 7.8 Hz, 1H, Ar), 7.09 (dd, J_1 = 8.0 Hz, J_2 = 1.3 Hz, 1H, Ar), 6.09-6.00 (m, 1H, C*H*=CH_2), 5.24 (s, 1H, OH), 5.13 (dd, J_1 = 10.1 Hz, J_2 = 1.6 Hz, 1H, CH=C*H*$_2$ *cis*), 5.05 (dd, J_1 = 17.2 Hz, J_2 = 1.6 Hz, 1H, CH=C*H*$_2$ *trans*), 3.91 (d, J = 5.8 Hz, 2H, C*H*$_2$CH=CH_2). The spectroscopic data obtained are consistent with those reported in literature.[27]

***tert*-Butyl 2-(2-allyl-3-formylphenoxy)acetate (9)**

To a solution of **8** (68 g, 0.42 mol, 91% purity) in 700 mL of acetone, powdered K_2CO_3 (230 g, 1.67 mol, 4 equiv) was added. Then, *tert*-butyl bromoacetate (81.9 g, 0.42 mol, 1 equiv) was slowly added. The mixture was stirred for 6 hours at 40 ºC and all the starting product was consumed (t.l.c). The mixture was cooled to room temperature and it was filtered to remove the salts. The remaining salts were washed with acetone and all the solvent was evaporated *in vacuo*. Silica gel column chromatography in Hexane:Ethyl acetate (12:1) gave 94 g of a light yellow oil (89% yield). Rf: 0.51 (Hexane/AcOEt 9:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.28 (s, 1H, CHO), 7.52 (dd, J_1 = 7.8 Hz, J_2 = 1.2 Hz, 1H, Ar), 7.32 (t, J = 8.0 Hz, 1H, Ar), 6.98 (dd, J_1 = 8.2 Hz, J_2 = 1.2 Hz, 1H, Ar), 6.11 – 5.99 (m, 1H, C*H*=CH_2), 5.02 (dq, J_1 = 10.2 Hz, J_2 = 1.6 Hz, 1H, CH=C*H*$_2$ *cis*), 4.97 (dq, J_1 = 17.1 Hz, J_2 = 1.8 Hz, 1H, CH=C*H*$_2$ *trans*), 4.57 (s, 2H, CH_2O), 3.92 (dt, J_1 = 6.0 Hz, J_2 =1.7 Hz, 2H, C*H*$_2$CH=CH_2) 1.47 (s, 9H, $(CH_3)_3C$) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 192.1 (CO), 167.6 (CO), 156.2 (C), 136.5 (CH), 135.2 (C), 131.5 (C), 127.3 (CH), 123.3 (CH), 116.7 (CH), 115.6 (CH_2), 82.5 (C), 66.4 (CH_2), 28.2 (CH_2), 28.0 (3xCH_3) ppm. IR (NaCl) ν = 2975, 2932,1750, 1735, 1601 cm^{-1}. Elemental analysis calcd for $C_{16}H_{20}O_4$: C, 69.55; H, 7.30, found: C 69.41, H 7.29.

(*S*)-1-Chloro-2-heptanol (10)

To a solution of (*S*)-(-)-epichlorohydrin (50 g, 0.54 mol) in 420 mL of tetrahydrofuran was added 7.6 g (54.05 mmol, 0.1 equiv) of CuI under argon. The reaction mixture was cooled to 0 °C, and a solution of 378 mL (0.65 mol, 1.2 equiv) of butylmagnesium chloride (20% wt in THF-toluene) was added slowly with stirring. The temperature of the reaction was controlled to be between 5-15 °C inside the flask. When the addition was finished the reaction was allowed to warm to room temperature. The solution was stirred for 10 h and all the starting product was consumed (tlc). The reaction was quenched by adding saturated NH_4Cl solution (150 mL) and HCl 1M to reach acid pH. The solid appeared was removed by filtration through celite and washed with ethyl acetate (100 mL). The aqueous phase was extracted with ethyl acetate (3x200mL). All the organic phases were combined, washed with a saturated solution of NH_4Cl (100 mL), brine (100 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. Silica gel column chromatography in Hexane:Ethyl acetate (33:1) afforded 74.3 g (92% yield) of **10** as a pale yellow oil. Rf: 0.39 (Hexane/AcOEt 9:1) ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.80 (bs, 1H, C*H*OH), 3.64 (dd, J_1 = 11.1 Hz, J_2 = 3.2 Hz, 1H, C*H*HCl), 3.47 (dd, J_1 = 11.1 Hz, J_2 = 7.1 Hz, 1H, CH*H*Cl), 2.19 (d, J = 4.1 Hz, 1H, OH), 1.56 – 1.30 (m, 8H, 4xCH_2), 0.89 (t, J = 6.8 Hz, 3H, CH_3) ppm. The spectroscopic data obtained are consistent with those reported in literature.[8]

(*S*)-2-Pentyloxirane (11)

To a solution of **10** (72 g, 0.48 mol) in DCM (280 mL) placed in an ice bath, powdered KOH (53.9 g, 0.96 mol) was slowly added. When the addition was finished the reaction was allowed to slowly warm to room temperature, and it was stirred for 3 hours. The crude reaction product was filtered through a pad of celite. Remaining salts and the pad of celite was washed with DCM (2x50 mL). The organic extracts were washed with water (200 mL), brine (200 mL), and dried (Na_2SO_4). The solvent was evaporated *in vacuo* in a 20 °C bath. 59 g of crude reaction product **11** were obtained as a clear orange oil containing DCM. The compound was taken to the next step without further purification to avoid volatilization. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.90 (m, 1H, C*H*OH), 2.75 (t, *J* = 4.5 Hz, 1H, C*H*HO), 2.47 (dd, J_1 = 5.1 Hz, J_2 = 2.7 Hz, 1H, C*H*HO), 1.53 – 1.50 (m, 2H, CH_2), 1.48 – 1.41 (m, 2H, CH_2), 1.33 – 1.31 (m, 4H, 2xCH_2), 0.90 (t, *J* = 7.1 Hz, 3H, CH_3) ppm. The spectroscopic data obtained are consistent with those reported in literature.[31]

(*S*)-Dec-1-yn-5-ol (12)

To a 2-neck flask previously dried and equipped with a condenser Mg turnings (15 equiv) were added. The metal was activated by 3 cycles of heating using a heating gun under vacuum and cooling down under argon. Then, dry Et_2O (200 mL) was added. A I_2 crystal was added to the suspension. After 20 min of stirring at room temperature $HgCl_2$ (1.59 g, 5.9 mmol, 0.06 equiv) was added and the flask was placed into an ice bath. 7.9 mL of propargyl bromide (80% propargyl bromide in toluene, 0.75 equiv) were dropwise added. The flask was transferred to a 40 °C bath and once reflux begun, it was placed into the ice bath again and the addition of propargyl bromide (44.7 mL, 4.25 equiv total 491.6 mmol) was continued dropwise. Stirring was continued for 90 minutes more at room temperature after completion of the addition. The Grignard reagent was added (*via cannula)* to a solution of the epoxide (12 g of crude **11**, ca 97.6 mmol) in dry Et_2O (300 mL) placed into an ice bath. After the addition the solution was stirred for 2 hours at room temperature and tlc showed no remaining epoxide. The reaction was quenched by adding a saturated solution of NH_4Cl until acid pH. The crude reaction mixture was filtered through a pad of celite and both phases were separated. The aqueous phase was extracted with Et_2O (3x200 mL). Organic extracts were washed with water (400 mL), brine (400 mL), dried with $NaSO_4$ and concentrated *in vacuo*. Silica gel column chromatography in Hexane:Ethyl acetate (19:1) gave **12** is obtained as a colorless oil (10.2 g, 68% yield from **10**). Rf: 0.29 (Hexane/AcOEt 9:1). $[\alpha]^{25}_D$ +2.4° (c 0.25, $HCHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.78 – 3.70 (m, 1H, C*H*OH), 2.33 (td, J_1 = 7.1 Hz, J_2 =2.7 Hz, 2H, CH_2C≡), 1.97 (t, *J* = 2.7 Hz, 1H, HC≡), 1.68 – 1.26 (m, 10H, 5xCH_2), 0.92 – 0.86 (t, *J* = 7.2 Hz, 3H, CH_3) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 84.3 (C), 70.8 (CH), 68.7 (CH), 37.4 (CH_2), 35.6 (CH_2), 31.8 (CH_2), 25.2 (CH_2), 22.6 (CH_2), 15.0 (CH_2), 14.0 (CH_3) ppm. IR (NaCl) ν = 3313, 2960, 2928, 2858 and 2119 cm^{-1}. Elemental analysis calcd for $C_{10}H_{18}O$: C, 77.87; H, 11.76. found: C 77.99, H 11.66.

(*S*)-*tert*-Butyl(dec-1-yn-5-yloxy)diphenylsilane (13)

25 g of **12** (0.16 mol) were dissolved in a mixture of DCM/DMF (360/36 mL), placed into an ice bath and dimethylaminopyridine (DMAP) (29.3 g, 0.24 mol, 1.5 equiv) was added. After 20 minutes of room temperature stirring, *tert*-butyl(chloro)diphenylsilane (TBDPSCl) (46.5 mL, 0.18 mol, 1.1 equiv) was added. The resulting mixture was stirred for 12 h at room temperature until total consumption of starting product (tlc). The reaction was quenched by adding saturated solution of NH_4Cl (150 mL). Both phases were separated, and the aqueous phase was extracted with DCM (3x200 mL), organic phases were washed with water (600 mL), and brine (600 mL). dried with Na_2SO_4, filtered, and concentrated *in vacuo*. Silica gel column chromatography in hexanes afforded 55.9 g of **13** as a light-yellow oil. (89% yield). Rf: 0.31 (Hexane), $[\alpha]^{25}_D$ +6.50° (c 0.20, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 – 7.64 (m, 4H, Ar), 7.44 – 7.34 (m, 6H, Ar), 3.80 (p, *J* = 5.7 Hz, 1H, C*H*O), 2.21 (td, J_1 = 7.7 Hz, J_2 = 2.7 Hz, 2H, CH_2C≡), 1.86 (t, *J* = 2.6 Hz, 1H, HC≡), 1.69 (td, J_1 = 7.7 Hz, J_2 = 5.6 Hz, 2H, CH_2), 1.39 – 1.35 (m, 2H, CH_2), 1.21 – 1.12 (m, 4H, 2xCH_2), 1.07 – 1.01 (m, 11H, $(H_3C)_3C$ and CH_2), 0.79 (t, *J* = 7.2 Hz, 3H, CH_3) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 135.9 (4xCH), 134.5 (C), 134.2 (C), 129.5 (CH), 129.4 (CH), 127.5 (2xCH), 127.4 (2xCH), 84.7 (C), 72.2 (CH), 68.0 (CH), 36.2 (CH_2), 35.1 (CH_2), 31.7 (CH_2), 27.1 (3xCH_3), 24.5 (CH_2), 22.5 (CH_2), 19.4 (C), 14.3 (CH_3), 14.0 (CH_2) ppm. IR (NaCl) ν = 3309, 3073, 3050, 2963, 2928, 2857, 2119, and 1589 cm^{-1}. Elemental analysis calcd for $C_{26}H_{36}OSi$: C, 79.53; H, 9.24; Si, 7.15 found: C 79.68, H 9.11.

(*S*)-Dec-1-en-5-ol (14)

To a solution of **11** (7.5 g of crude compound, ca 61.0 mmol) and CuI (0.86 g, 6.1 mmol, 0.1 equiv) in 40 mL of anhydrous THF, a solution of allylmagnesium chloride (1.7M) was slowly added in an ice bath. (53.8 mL, 91.5 mmol, 1.5 equiv). The temperature inside the flask was controlled to be below 15 ºC. When the addition was finished the reaction was stirred for 10 h and all the starting product was consumed (tlc). The reaction was quenched by adding a solution of saturated NH_4Cl to reach acid pH. The aqueous phase was extracted with ethyl acetate (3x70 mL). All the organic phases were combined, washed successively with a saturated solution of NH_4Cl (100 mL), with H_2O (100 mL), and brine (100 mL). The organic extracts were finally dried with Na_2SO_4, filtered, and concentrated *in vacuo*. The crude reaction product was purified by silica gel column chromatography in Hexane:Ethyl acetate (9:1) to afford 6.96 g of **14** as a colorless oil (73% yield from **10**). Rf: 0.25 (Hexane/AcOEt 9:1). $[\alpha]^{25}_D$ +1.3° (c 0.40, $CHCl_3$, lit +1.7).[30] ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.89 – 5.79 (m, 1H, C*H*=CH_2), 5.05 (dq, J_1 = 17.1 Hz, J_2 = 1.6 Hz, 1H, CH=CH_2 *trans*), 4.97 (dq, J_1 = 10.2 Hz, J_2 =1.6 Hz 1H, CH=CH_2 *cis*), 3.64 – 3.60 (m, 1H, C*H*OH), 2.28 – 2.09 (m, 2H, CH_2CH=), 1.53 – 1.29 (m, 10H, 5xCH_2), 0.89 (t, *J* = 6.8 Hz, 3H, CH_3) ppm. The spectroscopic data obtained are consistent with those reported in literature.[32]

(*S*)-*tert*-Butyl(dec-1-en-5-yloxy)dimethylsilane (15)

6 g of **14** (38.2 mol) were dissolved in a mixture of DCM/DMF (90/9 mL). Dimethylaminopyridine (DMAP) (2.3 g, 19.1 mol, 0.5 equiv) and imidazole (3.9 g, 57.3 mmol, 0.5 equiv) were added in an ice bath. After 20 min of room temperature stirring, *tert*-

butyldimethylsilyl chloride (TBDMSCl) (6.9 g, 45.8 mmol, 1.2 equiv) was added. The resulting mixture was stirred for 12 h at room temperature until total consumption of starting product. The reaction was quenched by adding saturated solution of NH_4Cl (60 mL). The mixture was extracted with DCM (3x60 mL), organic phases were washed with water (100 mL), and brine (100 mL), dried with Na_2SO_4, filtered, and concentrated *in vacuo*. Silica gel column chromatography in hexanes afforded 9.80 g (36.6 mmol) as a colourless liquid (95% yield). Rf: 0.48 (Hexane). $[\alpha]^{25}_D$ +2.43° (c 0.06, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.89 – 5.74 (m, 1H, C*H*=CH_2), 5.00 (dq, *J* = 17.1 Hz, J_2 = 1.6 Hz, 1H, CH=C*H*$_2$ *trans*), 4.94 (dd, J_1 = 10.1 Hz, J_2 = 1.8 Hz, 1H, CH=C*H*$_2$ *cis*), 3.70 – 3.59 (m, 1H, C*H*OTBS), 2.18 – 1.97 (m, 2H, C*H*$_2$CH=), 1.54 – 1.48 (m, 2H, CH_2), 1.45 – 1.40 (m, 2H, CH_2), 1.33 – 1.25 (m, 6H, 3xCH_2), 0.90 – 0.87 (m, 12H, C(CH_3)$_3$ and CH_3), 0.04 (s, 6H, (CH_3)$_2$Si) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 139.1 (CH), 114.1 (CH_2), 71.8 (CH), 37.0 (CH_2), 36.2 (CH_2), 32.1 (CH_2), 29.7 (CH_2), 26.0 (3xCH_3), 24.9 (CH_2), 22.7 (CH_2), 18.1 (C), 14.1 (CH_3), -4.38 (CH_3), -4.44 (CH_3) ppm. IR (NaCl) ν = 2955, 2930, 2856, 1643 cm^{-1}. Elemental analysis calcd for $C_{16}H_{34}OSi$: C, 71.04; H, 12.67 found: C 71.17, H 12.55.

(*S*)-4-((*tert*-Butyldimethylsilyl)oxy)nonanal (16)

To a cooled (-78 ºC) and stirred solution of the **15** (8 g, 29.6 mmol) in DCM (40 mL) and pyridine (2 equiv 59.2 mmol, 4.77 mL) O_3 was continuously bubbled (provided by an ozoniser and a O_2 cylinder). After 90 min of bubling tlc showed no starting product remaining. N_2 was passed though the solution for 15 minutes, then, 11.6 g of PPh_3 (1.5 equiv 44.4 mmol) were added in portions at -78 ºC. The solution was slowly warmed to room temperature until next day (16 hours) with vigorous stirring. The solvent is evaporated *in vacuo* and the residue is redissolved in hexane (50 mL) PPh_3 by-products are filtered and the solvent is evaporated *in vacuo*. The compound was taken to the next step without further purification. For small scale synthesis, osmylation and oxidative cleavage was explored. To a cooled (0 °C) and stirred solution of the alkene (500 mg, 270.2 mmol) and NMO (867 mg, 7.4 mmol, 4 equiv) in H_2O/Acetone (7/7 mL), OsO_4 (4% H_2O, 0.94 mL, 0.05 equiv) was slowly added. After overnight stirring (14 h) at room temperature TLC showed total consumption of starting material. 5 mL of a saturated solution of Na_2SO_3 were added to the crude reaction mixture in an ice bath and the acetone was evaporated *in vacuo*. The aqueous residue was extracted with MTB ether (3x10 mL), the organic phases were washed with water (15 mL), brine (15 mL) and dried with Na_2SO_4 and the solvent evaporated *in vacuo*. Then, $NaHCO_3$ (170 mg, 2.03 mmol, 1.1 equiv), and $NaIO_4$ (2.3 g, 11.1 mmol, 6 equiv) were added to the residue previously redissolved in a mixture of MeOH/H_2O (7/5 mL). After 30 min stirring at room temperature, the reaction was diluted with 10 mL of water and MeOH was evaporated *in vacuo.* The aqueous residue was extracted with MTB ether (3x10 mL). Organic extracts were washed with brine (20 mL) dried with Na_2SO_4 and concentrated *in vacuo*. The residue was purified by a short column chromatography in Hexane:Ethyl Acetate (33:1) to afford 259 mg (95% yield) of **16** as a colorless liquid. Rf: 0.52 (Hexane/AcOEt 12:1). $[\alpha]^{25}_D$ +8.5° (c 0.1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.79 (t, *J* = 1.7 Hz, 1H, CHO), 3.74 –3.67 (m, 1H, CHOTBS), 2.48 (td, J_1 = 7.5 Hz, J_2 = 1.8 Hz, 2H, C*H*$_2$CHO), 1.88 – 1.65 (m, 2H, CH_2), 1.47 – 1.23 (m, 8H, 4xCH_2), 0.92 – 0.84 (m, 12H, C(CH_3)$_3$ and CH_3), 0.04 (s, 3H, CH_3Si), 0.03 (s, 3H, CH_3Si) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 203.0 (CO), 71.1 (CH), 39.7 (CH_2), 36.9 (CH_2), 32.0 (CH_2), 28.8 (CH_2), 25.9 (3xCH_3), 24.9 (CH_2), 22.6 (CH_2), 18.1 (C), 14.0 (CH_3), -4.4 (CH_3), -4.6 (CH_3) ppm. IR (NaCl) ν = 1713 cm^{-1}. Elemental analysis calcd for $C_{15}H_{32}O_2Si$: C, 66.11; H, 11.84; found: C 66.02, H 11.95.

(*S*)-*tert*-Butyl((1,1-dibromodec-1-en-5-yl)oxy)dimethylsilane (17)

To a suspension of PPh_3 (15.5 g, 59.2 mmol, 2 equiv) and Zn (dust) (3.9 g, 59.2 mmol, 2 equiv) in dry DCM (220 mL), CBr_4 (19.6 g, 59.2 mmol, 2 equiv) was slowly added at 0ºC. After 10 minutes of stirring at 0 ºC and 15 at room temperature, a solution of **16**, (8.05 g, 29.6 mmol) in 70 mL of dry DCM was added at 0 ºC and the resulting mixture was stirred for 12 hours at room temperature. All the salts were filtered over celite, and the remaining salts were washed with hexane (80 mL). Then, the filtrate was concentrated *in vacuo*. Silica gel column chromatography in hexanes afforded 7.2 g of **17** (16.9 mmol) as a yellow oil. (57% of yield from **15**). Rf: 0.41 (Hexane). $[\alpha]^{25}_D$ +1.5° (c 0.3, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.41 (t, *J* = 7.3 Hz, 1H, CH=), 3.69 – 3.62 (m, 1H, CHOTBS), 2.22 – 2.03 (m, 2H, C*H*$_2$CH=),1.57 – 1.50 (m, 2H, CH_2), 1.44 – 1.40 (m, 2H, CH_2), 1.33 – 1.23 (m, 6H, 3xCH_2), 0.90 – 0.88 (m, 12H, C(CH_3)$_3$ and CH_3), 0.049 (s, 3H, CH_3Si), 0.047 (s, 3H, CH_3Si) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.9 (CH), 88.6 (C), 71.5 (CH), 36.9 (CH_2), 34.7 (CH_2), 32.0 (CH_2), 29.1 (CH_2), 25.9 (3xCH_3), 24.9 (CH_2), 22.7 (CH_2), 18.1 (C), 14.1 (CH_3), -4.4 (CH_3), -4.5 (CH_3) ppm. IR (NaCl) ν = 2952, 2933, 2861 and 1737 cm^{-1} Elemental analysis calcd for $C_{16}H_{32}Br_2OSi$: C, 44.87; H, 7.53; Br, 37.31; Si, 6.56; found: C 44.99, H 7.65.

(*S*)-*tert*-butyl(dec-1-yn-5-yloxy)dimethylsilane (18)

To a stirring solution of **17** (5.0 g, 11.68 mmol) in anhydrous THF (55 mL) was added dropwise n-BuLi solution (1.6 M in hexane, 15.95 mL, 25.52 mmol) at -40°C under an argon atmosphere. The solution was stirred for 15 min. at -40 ºC and then for 15 min. at 0 ºC. After completion of the reaction indicated on tlc, the reaction was quenched by dropwise addition of aqueous satured solution of NH_4Cl (25 mL) at 0 ºC and extracted with AcOEt (3 x 60 mL). The combined organic layers were washed with brine (60 mL) dried (Na_2SO_4), and product was concentrated *in vacuo*. Silica gel column chromatography in hexanes afforded 2.2 g of **18** (7.94 mmol) as a colourless oil. (68% yield). Rf: 0.50 (Hexane). $[\alpha]^{25}_D$ +18.78° (c 0.13, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.79 – 3.71 (m, 1H, CHO), 2.23 (t, *J* = 6.7 Hz, 2H, $CH_2C\equiv$), 1.93 (s, 1H, $HC\equiv$), 1.66 – 1.61 (m, 2H, CH2), 1.46 – 1.40 (m, 2H, CH_2), 1.33 – 1.25 (m, 6H,3xCH_2), 0.89 (s, 12H, (H_3C)$_3$C and CH_3), 0.06 (s, 3H, $SiCH_3$), 0.05 (s, 3H, $SiCH_3$) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 84.8 (C), 70.8 (CH), 68.1 (CH), 37.0 (CH_2), 35.6 (CH_2) 32.0 (CH_2), 25.9 (3xCH_3), 24.7 (CH_2), 22.6 (CH_2), 18.1 (C), 14.6 (CH_2), 14.0 (CH_3), -4.4 (CH_3), -4.6 (CH_3) ppm. IR (NaCl) ν = 3317, 2959, 2926, 2856, 2120, and 1470 cm-1. Elemental analysis calcd for $C_{16}H_{32}OSi$: C, 71.57; H, 12.01; Si, 10.46 found: C 72.69, H 11.13.

***tert*-Butyl 2-(2-allyl-3-((6*S*)-6-((*tert*-butyldiphenylsilyl)oxy)-1-hydroxyundec-2-yn-1-yl)phenoxy)acetate (1*S*,6*S*+1*R*,6*S*-19)**

To a stirred and refluxing solution of **13** (20 g, 50.9 mmol, 1.1 equiv) in anhydrous THF (370 mL) was slowly added a solution of EtMgBr (3M in Et_2O) (16.9 mL, 50.9 mmol) under argon. As the reaction is exothermic heating was stopped during this addition. After complete addition the reaction mixture was further refluxed for 90 min and cooled to 0 °C and then a solution **9** (12.8 g, 46.3 mmol) in anhydrous THF (40 mL) was added slowly with stirring. After complete addition, the reaction mixture was allowed to warm to room temperature and stirred for 12 h. The reaction mixture was cooled again to 0 °C, and a saturated aqueous solution of NH_4Cl was added with stirring (200 mL). The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (3x250 mL). The combined organic layers were washed with brine (600 mL) and dried (Na_2SO_4) and the solvents were removed *in vacuo*. Silica gel column chromatography in Hexane:Ethyl acetate (12:1) gave 41.7 g (82% yield) of **19** as a mixture of diastereomers.

***tert*-Butyl (*S*)-2-(2-allyl-3-(6-((tert-butyldiphenylsilyl)oxy)undec-2-ynoyl)phenoxy)acetate (20)**

To a cooled (0 °C) and stirred solution of **((1*S*,6*S*)-19+(1*R*,6*S*)-19** (20 g, 29.89 mmol) in acetone (700 mL) was added active MnO_2 (31.2 g, 0.36 mol). The reaction mixture was slowly allowed to warm to room temperature and stirred for 24 h. Then it was filtered through celite and the solid was washed with acetone. The solvents were removed *in vacuo* and 17.9 g (26.9 mmol) of **20** were obtained as a yellow oil. (90% yield) sufficiently pure to continue. A small sample was purified for characterization by silica gel column chromatography in Hexane:Ethyl acetate (9:1). Rf: 0.36 (Hexane/AcOEt 9:1). $[\alpha]^{25}_D$ -11.4 (c 0.34, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 – 7.66 (m, 5H, Ar), 7.43 – 7.32 (m, 6H, Ar), 7.23 (t, *J* = 8.0 Hz, 1H, Ar), 6.93 (dd, J_1 = 8.3 Hz, J_2 =1.2 Hz, 1H, Ar), 6.08 – 5.98 (m, 1H, C*H*=CH_2), 5.07 (dq, J_1 =17.1 Hz, J_2 = 1.8 Hz, 1H, CH=CH_2 *trans*), 4.97 (dq, J_1 = 10.1 Hz, J_2 = 1.6 Hz, 1H, CH=CH_2 *cis*), 4.56 (s, 2H, CH_2O), 3.90 – 3.82 (m, 3H, C*H*OSi and CH_2CH=), 2.49 (td, *J* = 7.2, 1.3 Hz, 2H, $CH_2\equiv$), 1.83 – 1.74 (m, 2H, CH_2), 1.49 (s, 9H, $(H_3C)_3CO$), 1.46 – 1.40 (m, 2H, CH_2), 1.28 – 1.13 (m, 6H, 3xCH_2), 1.07 (s, 9H, $(H_3C)_3CSi$), 0.80 (t, *J* = 7.2 Hz, 3H, CH_3) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 179.8 (CO), 167.7 (CO), 156.5 (C), 137.6 (C),136.6 (CH), 135.84 (2xCH), 135.80 (2xCH), 134.3 (C), 134.0 (C) 130.5 (C), 129.6 (CH), 129.5 (CH), 127.6 (2xCH), 127.5 (2xCH), 126.5 (CH), 125.5 (CH), 115.7 (CH), 115.0 (CH_2), 95.7 (C), 82.4 (C), 81.5 (C) 72.0 (CH), 66.6 (CH_2), 36.2 (CH_2), 34.2 (CH_2), 31.6 (CH_2), 29.9 (CH_2), 28.0 (3xCH_3), 27.0 (3xCH_3), 24.5 (CH_2), 22.4 (CH_2), 19.4(C), 15.0 (CH_2), 13.9 (CH_3) ppm. IR (NaCl) ν = 3069, 2956, 2932, 2858, 2210, 1754, 1731, 1648, 1574 and 1460 cm^{-1}. Elemental analysis calcd for $C_{42}H_{54}O_5Si$: C, 75.63; H, 8.16; Si, 4.21 found: C 75.77, H 8.10.

***tert*-Butyl 2-(2-allyl-3-((1*S*,6*S*)-6-((*tert*-butyldiphenylsilyl)oxy)-1-hydroxyundec-2-yn-1-yl)phenoxy)acetate ((1*S*,6*S*)-19)**

To a solution of (*R*)-methyl oxazaborolidine (26.3 mL, 1 M in toluene) was added a solution of **20** (14.6 g, 21.9 mmol) 4.845 g, 11.74 mmol) in anhydrous THF (43 mL) under argon. Then the reaction mixture was cooled to -30 °C under argon and borane-methyl sulfide complex (3.32 g, 43.8 mmol) was added slowly with stirring. After complete addition the reaction mixture was stirred at -30 °C for 1 h, then methanol (13 mL) was added carefully with stirring to quench the reaction at -10 to -15 °C. The reaction mixture was allowed to warm to room temperature and left with stirring overnight. Then it was cooled to 0 °C and 5% aqueous solution of ammonium chloride was added with stirring (20 mL). The organic layer was separated and washed with 5% aqueous ammonium chloride solution (20 mL) and brine (20 mL). The combined aqueous layers were extracted with ethyl acetate (30 mL) and washed with brine (20 mL). The combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo* to yield a viscous oil which was purified by silica gel column chromatography in Hexane:Ethyl acetate (12:1) to give 12.45 g (85%) of **(1*S*,6*S*)-19** as a pale yellow oil. Rf: 0.30 (Hexane/AcOEt 9:1). $[\alpha]^{25}_D$ -4.89 (c 0.42, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 – 7.63 (m, 4H, Ar), 7.41 – 7.31 (m, 7H, Ar), 7.19 (t, *J* = 8.0 Hz, 1H, Ar), 6.73 (dd, J_1 = 8.3 Hz, J_2 =1.1 Hz, 1H), 6.09 – 5.99 (m, 1H, C*H*=CH_2), 5.58 – 5.56 (m, 1H, C*H*OH), 5.01 – 4.96 (m, 2H, CH=CH_2), 4.53 (s, 2H, CH_2O), 3.82 (p, *J* = 5.7 Hz, 1H, C*H*OSi), 3.72 – 3.57 (m, 2H, CH_2CH=), 2.29 – 2.28 (m, 2H, $CH_2\equiv$), 2.01 (d, *J* = 5.6 Hz, 1H, OH), 1.72 – 1.67 (m, 2H, CH_2), 1.48 (s, 9H, $(H_3C)_3CO$), 1.43 – 1.37 (m, 2H, CH_2), 1.25 – 1.11 (m, 6H, 3xCH_2), 1.05 (s, 9H, $(H_3C)_3CSi$), 0.80 (t, *J* = 7.2 Hz, 3H, CH_3) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.0 (CO), 156.0 (C), 140.8 (C), 136.9 (CH) 135.90 (2xCH), 135.88 (2xCH), 134.5 (C), 134.3 (C) 129.5 (CH), 129.4 (CH), 127.5 (2xCH), 127.4 (2xCH), 127.2 (CH), 126.5 (C), 120.1 (CH), 114.9 (CH_2), 111.5 (CH), 87.3 (C), 82.2 (C), 79.7 (C),72.2 (CH), 66.4 (CH_2), 62.1 (CH), 36.2 (CH_2), 35.1 (CH_2), 31.7 (CH_2), 29.6 (CH_2), 28.0 (3xCH_3), 27.0 (3xCH_3), 24.5 (CH_2), 22.5 (CH_2), 19.4 (C), 14.8 (CH_2), 14.0 (CH_3) ppm. IR (NaCl) ν = 3517, 3072, 2953, 2930, 2857, 2332, 1753, 1734, 1588, and 1469 cm^{-1}. Elemental analysis calcd for $C_{42}H_{56}O_5Si$: C, 75.41; H, 8.44; Si, 4.21 found: C 75.59, H 8.29.

***tert*-butyl 2-(2-allyl-3-((1*S*,6*S*)-6-tert-butyldiphenylsilyloxy-1-*tert*-butyldimethylsilyloxyundec-2-yn-1-yl)phenoxy)acetate (21)**

12.45 g (18.6 mmol) of TBDMSCl (3.36 g, 22.32 mol) was added to a stirred and cooled (0 °C) solution of **(1*S*,6*S*)-19** (12.45 g, 18.6 mmol), imidazole (1.5 g, 22.32 mol), 4-(dimethylamino)pyridine (283 mg, 2.32 mmol), and DMF (1.5 mL) in dichloromethane (15 mL) under argon. The reaction mixture was slowly warmed to room temperature and stirring was continued for 15 h. The reaction mixture was washed with water (20 mL) and brine (20 mL) and concentrated *in vacuo*. The resulting viscous liquid was purified by silica gel column chromatography in Hexane:Ethyl acetate (12:1) to give 13.3 g (16.9 mmol) of **21** (91% yield). Rf: 0.53 (Hexane/AcOEt 9:1). $[\alpha]^{25}_D$ -7.14 (c 0.40, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 – 7.63 (m, 4H, Ar), 7.42 – 7.32 (m, 6H, Ar), 7.29 (dd, J_1 = 7.8 Hz, J_2 =1.1 Hz, 1H, Ar), 7.16 (t, *J* = 8.0 Hz, 1H, Ar), 6.67 (dd, J_1 = 8.2 Hz, J_2 = 1.2 Hz, 1H, Ar), 6.04 – 5.93 (m, 1H, C*H*=CH_2), 5.56 – 5.54 (m, 1H, C*H*OTBS), 4.99 – 4.94 (m, 2H, CH=CH_2), 4.51 (s, 2H, CH_2O), 3.75 (p, *J* = 5.6 Hz, 1H, CHOSi), 3.68 – 3.51 (m, 2H, CH_2CH=), 2.25 – 2.14 (m, 2H, $CH_2\equiv$), 1.70 – 1.61 (m, 2H, CH_2), 1.47 (s, 9H, $(H_3C)_3CO$), 1.38 – 1.32 (m, 2H, CH_2), 1.16 – 1.11 (m, 4H, 2xCH_2), 1.03 (s, 9H, $H_3C)_3CSi$), 0.90 (s, 9H, $(H_3C)_3CSi$), 0.92 – 0.87 (m, 2H, CH_2), 0.78 (t, *J* = 7.2 Hz, 3H, CH_3), 0.09 (s, 3H, H_3CSi) 0.08 (s, 3H, H_3CSi) ppm. ^{13}C NMR (101 MHz,

$CDCl_3$) δ 168.2 (CO), 155.9 (C) 142.4 (C), 136.5 (CH), 135.86 (2xCH), 135.84 (2xCH), 134.6 (C), 134.3 (C), 129.5 (CH), 129.4 (CH), 127.5 (2xCH), 127.4 (2xCH), 126.9 (CH), 125.4 (C), 119.4 (CH), 114.6 (CH_2), 110.7 (CH), 85.8 (C), 82.1 (C), 80.7 (C), 72.4 (CH), 66.5 (CH_2), 62.3 (CH), 36.1 (CH_2), 35.1 (CH_2), 31.7 (CH_2), 29.6 (CH_2), 28.0 (3xCH_3), 27.1 (3xCH_3), 25.9 (3xCH_3), 24.5 (CH_2), 22.5 (CH_2), 19.4 (C), 18.3 (C), 14.7 (CH_2), 13.9 (CH_3), -4.5 (CH_3), -4.8 (CH_3) ppm. IR (NaCl) ν = 2953, 2932, 2859, 2330, 1753, 1659, 1583 and 1466 cm^{-1}. Elemental analysis calcd for $C_{48}H_{70}O_5Si_2$: C, 73.61; H, 9.01; Si, 7.17 found: C 73.74, H 8.88.

tert-Butyl 2-(((4*R*,9a*S*)-4-((*tert*-butyldimethylsilyl)oxy)-3-((*S*)-3-((*tert*-butyldiphenylsilyl)oxy)octyl)-2-oxo-2,4,9,9a-tetrahydro-1*H*-cyclopenta[b]naphthalen-8-yl)oxy)acetate (22)

PKR optimization: $Co_2(CO)_8$ was dissolved in 0.5 mL of toluene. Then, 769 mg (1 mmol) of **21** is added and the solution is diluted with toluene until a final volume of 2 mL (measured in a volumetric flask). The solution is degassed with Ar for 10 min and filtered through 0.45 µm nylon filter. 0.8 mL are injected each time through a Rheodyne valve. The system is configured as shown in Scheme 5. Scale-out reaction conditions: 7.5 g of **21** (9.58 mmol) were dissolved in toluene until a final volume of 32 mL (0.3M) and 164 mg of $Co_2(CO)_8$ (0.48 mmol, 5 mol %). The solution is degassed with Ar for 15 min and filtered through 0.45 µm nylon filter. The solution is placed in the pump inlet and the conditions were: Temperature: 170 °C; pressure: 20 bar ;3 equivalents of CO; Pump flow 1: 0.66 mL/min; CO flow: 15 mLN/min; reactor volume: 60.6 mL; residence time: 40 min; total time: 1h 45 min. The solution is collected in a flask and it is washed with a 1N HCl solution (25 mL). Then, it was washed with water (25 mL), brine (25 mL), dried with Na_2SO_4, and concentrated *in vacuo*. 7.8 g of crude viscous brown oil were purified by silica gel column chromatography in a solvent gradient from hexane to Hexane: Ethyl acetate (12:1) to yield 5.75 g (74%). Samples for Co determination (by ICP) were collected, of the crude reaction mixture, after washing with HCl (1N) and of the pure compound (after column chromatography) and they are digested with nitric acid. Rf: 0.43 (Hexane/AcOEt 9:1). $[\alpha]^{25}_D$ -87.4 (c 0.42, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 – 7.59 (m, 4H, Ar), 7.42 – 7.25 (m, 6H), 7.19 (t, *J* = 7.9 Hz, 1H, Ar), 6.87 (d, *J* = 7.6 Hz, 1H, Ar), 6.66 (d, *J* = 7.7 Hz, 1H, Ar), 5.47 (s, 1H, C*H*OTBS), 4.54 (s, 2H, CH_2O), 3.75 – 3.71 (m, 1H, CHOSi), 3.62 (dd, J_1 = 17.2 Hz, J_2 = 7.5 Hz, 1H, C*H*HAr), 3.37 – 3.30 (m, 1H, C*H*), 2.67 (dd, J_1 = 18.8 Hz, J_2 = 6.4 Hz, 1H, C*H*HCO), 2.44 – 2.34 (m, 1H, C*H*HAr), 2.29 – 2.19 (m, 2H, C*H*HCO and C*H*HC=), 1.68 – 1.59 (m, 2H, C*H*HC= and C*H*H), 1.48 (s, 9H, $H_3C)_3CO$), 1.44 – 1.36 (m, 3H, CH_2 and C*H*H), 1.18 – 1.11 (m, 6H, 3xCH_2), 1.06 (s, 9H, $(H_3C)_3CSi$), 0.81 (s, 9H, $(H_3C)_3CSi$), 0.78 (t, *J* = 7.2 Hz, 3H, CH_3), 0.10 (s, 3H, H_3CSi), 0.05 (s, 3H, H_3CSi) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 209.5 (CO), 171.9 (CO), 167.9 (C), 155.2 (C), 138.7 (C), 137.6 (C), 135.87 (2xCH), 135.85 (2xCH), 134.7 (C), 134.2 (C), 129.42 (CH), 129.38 (CH), 127.4 (2xCH), 127.3 (2xCH), 127.2 (CH), 125.6 (C), 122.9 (CH), 110.2 (CH), 82.3 (C), 72.9 (CH), 65.8 (CH_2), 65.3 (CH), 42.1 (CH_2), 35.9 (CH_2), 34.5 (CH_2), 33.3 (CH_2), 32.0 (CH_2), 31.7 (CH_2), 28.0 (3xCH_3), 27.1 (3xCH_3), 25.6 (3xCH_3), 24.5 (CH_2), 22.5 (CH_2), 19.4 (C), 18.6 (C), 18.0 (CH_2), 14.0 (CH_3), -4.1 (CH_3), -4.2 (CH_3) ppm. IR (NaCl) ν = 2956, 2936, 2958, 2754, 1754, 1707, 1664, 1589, and 1475 cm^{-1}. Elemental analysis calcd for $C_{49}H_{70}O_6Si_2$: C, 72.55; H, 8.70; Si, 6.92 found: C 72.67, H 8.91. ICP (Co, measured at λ= 230.786, 238.892 and 240.725 nm): <0.2 ppm for the pure compound, 1885 for the crude reaction product, and 3300 in the sample just coming out the reactor.

tert-butyl 2-(((8*R*)-8-((tert-butyldimethylsilyl)oxy)-1-((*S*)-3-((tert-butyldiphenylsilyl)oxy)octyl)-3-methyl-2-oxo-2,3,3a,8-tetrahydrocyclopenta[a]inden-4-yl)oxy)acetate (22')

310 mg (4% yield) were isolated in the purification by column chromatography of the scale-out Pauson-Khand reaction as the only detectable side product, which is formed due to the isomerization of the double bond and PK then. Pale yellow oil. **Rf**: 0.46 (Hexane/AcOEt 9:1) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 – 7.63 (m, 4H, Ar), 7.41 – 7.32 (m, 6H, Ar), 7.22 (t, *J* = 7.9 Hz, 1H, Ar), 7.03 (d, *J* = 7.5 Hz, 1H, Ar), 6.71 (d, *J* = 8.2 Hz, 1H, Ar), 5.56 (s, 1H, CHOTBDMS), 4.57 (s, 2H, CH_2O), 3.97 (d, *J* = 4.0 Hz, 1H, C*H*CHCH$_3$), 3.75 (p, *J* = 5.6 Hz, 1H, CHOSi), 2.43 (m, 2H, C*H*CH_3 and C*H*HC=), 2.32 – 2.24(m, 1H, C*H*HC=), 1.67 – 1.60 (m, 2H, CH_2), 1.55 (d, *J* = 7.2 Hz, 3H, C*H*$_3$CH), 1.48 (s, 9H, $(H_3C)_3CO$), 1.44 – 1.35 (m, 2H, CH_2), 1.18 – 0.99 (m, 6H, 3xCH_2), 1.07 (s, 9H, $(H_3C)_3CSi$), 0.83 (s, 9H, $(H_3C)_3CSi$), 0.78 (t, *J* = 7.2 Hz, 3H, C*H*$_3$CH$_2$), 0.12 (s, 3H, CH_3Si), 0.10 (s, 3H, CH_3Si) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 211.9 (CO), 172.7 (CO), 167.6 (C), 154.4 (C), 147.1 (C), 137.2 (C), 135.91 (2xCH), 135.89 (2xCH), 134.7 (C), 134.2 (C), 131.8 (C), 129.5 (CH), 129.4 (CH), 128.8 (CH), 127.5 (2xCH), 127.3 (2xCH), 118.4 (CH), 111.4 (CH), 82.4 (C), 73.2 (CH), 69.7 (CH), 65.7 (CH_2), 51.9 (CH), 48.9 (CH), 36.2 (CH_2), 34.3 (CH_2), 31.7 (CH_2), 28.0 (3xCH_3), 27.1 (3xCH_3), 25.6 (3xCH_3), 24.4 (CH_2), 22.5 (CH_2), 20.0 (CH_2), 19.4 (C), 18.0 (C), 14.1 (CH_3), 14.0 (CH_3), -4.1 (CH_3), -4.2 (CH_3). ppm. IR (NaCl) ν = 2956, 2932, 2860, 1749, 1725, 1590 cm^{-1}. Elemental analysis calcd for $C_{49}H_{70}O_6Si_2$: C, 72.55; H, 8.70; Si, 6.92 found: C 72.72, H 8.84.

tert-Butyl 2-(((3a*S*,9a*S*)-1-((*S*)-3-((*tert*-butyldiphenylsilyl)oxy)octyl)-2-oxo-2,3,3a,4,9,9a-hexahydro-1*H*-cyclopenta[b]naphthalen-5-yl)oxy)acetate (23)

To a solution of **22** (5.6 g, 7.02 mmol) in absolute ethanol (60 mL) were added anhydrous K_2CO_3 (280 mg, 5% w/w) and 10% Pd/C (1.4 g, 50% wet, 25% w/w) and the mixture was hydrogenated at 3 bar of pressure. After 15h stirring at room temperature, the pressure was carefully released, and the reaction mixture was filtered through celite and washed with DCM (100 mL). Silica gel column chromatography in Hexane:Ethyl acetate (15:1) gave **23** as mixture of 2 stereoisomers in a 3:1 ratio measured by ^{1}H NMR. 3.60 g (75% yield). A small sample of each isomer was isolated for characterization. Major isomer: Rf: 0.51 (Hexane/AcOEt 6:1). ^{1}H NMR (400 MHz $CDCl_3$) δ 7.67 – 7.64 (m, 4H, Ar), 7.40 – 7.31 (m, 6H, Ar), 7.08 (t, *J* = 7.8 Hz, 1H, Ar), 6.71 (d, *J* = 7.6 Hz, 1H, Ar), 6.57 (d, *J* = 8.1 Hz, 1H, Ar), 4.51 (s, 2H, CH_2O), 3.73 (p, *J* = 5.1 Hz, 1H), 3.07 (dd, J_1 = 16.9 Hz, J_2 = 6.7 Hz, 1H, C*H*H), 2.87 (dd, J_1 = 16.4 Hz, J_2 = 6.6 Hz, 1H, C*H*H), 2.54 – 2.44 (m, 2H, CH and C*H*H), 2.40 – 2.33 (m, 2H, CH_2), 2.18-2.08 (m, 2H, C*H*H and CH), 1.77 – 1.73 (m, 1H, CH), 1.48 (s, 9H, $(H_3C)_3CO$), 1.51 – 1.40 (m, 6H, 3xCH_2), 1.26 – 1.08 (m, 6H, 3xCH_2), 1.05 (s, 9H, $(H_3C)_3CSi$), 0.82 (t, *J* = 7.1 Hz, 3H, CH_3) ppm. ^{13}C NMR (101 MHz $CDCl_3$) δ 220.4 (CO), 168.1 (CO), 155.1 (C) 137.2 (C), 135.9 (4xCH), 134.7 (C), 134.5 (C) 129.4 (2xCH), 127.41 (2xCH), 127.38 (2xCH), 126.2

(CH), 125.1 (C), 121.8 (CH), 108.4 (CH), 82.2 (C), 73.2 (CH), 65.8 (CH_2), 51.8 (CH), 45.1 (CH_2), 38.6 (CH), 36.0 (CH_2), 33.3 (CH_2), 31.82 (CH_2), 31.79 (CH_2), 30.5 (CH), 28.0 (3xCH_3), 27.1 (3xCH_3), 25.5 (CH_2), 24.6 (CH_2), 23.8 (CH_2), 22.5 (CH_2), 19.4 (C), 14.0 (CH_3) ppm. IR (NaCl) ν = 2955, 2930, 2856, 1737 and 1590 cm^{-1}. Elemental analysis calcd for $C_{43}H_{58}O_5Si$: C, 75.62; H, 8.56; Si, 7.17 found: C 74.90, H 8.39. Minor isomer: Rf: 0.48 (Hexane/AcOEt 6:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 – 7.64 (m, 4H, Ar), 7.41 – 7.33 (m, 6H, Ar), 7.07 (t, *J* = 7.9 Hz, 1H, Ar), 6.68 (d, *J* = 7.7 Hz, 1H, Ar), 6.55 (d, *J* = 8.1 Hz, 1H, Ar), 4.53 (s, 2H, CH_2O), 3.75 (p, *J* = 5.8 Hz, 1H, CHOSi), 3.04 – 2.84 (m, 2H, CH_2), 2.63 – 2.53 (m, 1H, CH), 2.51 – 2.29 (m, 3H, CH and CH_2), 2.20 – 2.03 (m, 2H, CH_2), 1.87 (dd, J_1 = 18.8 Hz, J_2 = 12.1 Hz, 1H, C*H*H), 1.81 – 1.72 (m, 1H, CH), 1.50 (s, 9H, $(H_3C)_3CO$), 1.50 – 1.44 (m, 3H, C*H*H and CH_2), 1.30 – 1.18 (m, 8H, 4xCH_2), 1.07 (s, 9H, $(H_3C)_3CSi$), 0.84 (t, *J* = 7.2 Hz, 3H, CH_3) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 219.2 (CO), 168.1 (CO), 155.9 (C), 136.2 (C) 135.9 (4xCH), 135.9 (C), 134.6 (C), 134.5 (C) 129.5 (CH), 129.4 (CH), 127.45 (2xCH), 127.39 (2xCH), 125.9 (CH), 122.0 (CH), 108.1 (CH), 82.2 (C), 73.3 (CH), 65.6 (CH_2), 57.0 (CH), 41.4 (CH_2), 36.3 (CH_2), 34.9 (CH_2), 34.7 (CH_2), 31.8 (CH_2), 31.4 (CH), 28.0 (3xCH_3), 27.1 (3xCH_3), 26.4 (CH_2), 24.5 (CH_2), 24.3 (CH_2), 22.6 (CH_2), 20.1(CH_2), 19.4 (C), 14.0 (CH_3) ppm. IR (NaCl) ν = 2952, 2927, 2858, 1740 and 1588 cm^{-1}. Elemental analysis calcd for $C_{43}H_{58}O_5Si$: C, 75.62; H, 8.56; Si, 7.17 found: C 75.00, H 8.41.

2-(((1*R*,2*R*,3a*S*,9a*S*)-1-((*S*)-3-((*tert*-Butyldiphenylsilyl)oxy)octyl)-2-hydroxy-2,3,3a,4,9,9a-hexahydro-1*H*-cyclopenta[b]naphthalen-5-yl)oxy)acetic acid (24)

To a cooled (-10 °C) and stirred solution of **23** (3.5 g, 5.12 mmol) in ethanol (20 mL) was added a 5M aqueous sodium hydroxide solution (10.2 mL, 51.2 mmol). The reaction mixture was stirred for 30 min and then $NaBH_4$ (203 mg, 5.38 mmol, 1.05 equiv) was added and stirring was continued at -10 °C for 1 h. An additional equiv of $NaBH_4$ (203 mg) was added and stirring was continued for another 12 h at 0 °C. Upon completion (tlc), the reaction mixture was quenched with glacial acetic acid until pH 2-3 and the solvent was removed *in vacuo*. The crude reaction mixture was dissolved in ethyl acetate (25 mL), washed with 1N HCl (20 mL), water (20 mL), brine (20 mL), dried with Na_2SO_4. and concentrated *in vacuo* to obtain 3.1 g of crude tricyclic alcohol **24** as a white solid. This was used for the next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 – 7.67 (m, 4H, Ar), 7.41 – 7.34 (m, 6H, Ar), 7.08 (t, *J* = 7.8 Hz, 1H, Ar), 6.75 (d, *J* = 7.5 Hz, 1H, Ar), 6.67 (d, *J* = 8.3 Hz, 1H, Ar), 4.66 (s, 2H, CH_2O), 3.76 – 3.70 (m, 1H, C*H*OH), 3.61 – 3.55 (d, *J* = 7.4 Hz, 1H, C*H*OSi), 2.79 (dd, J_1 = 14.8 Hz, J_2 = 6.0 Hz, 1H, C*H*H), 2.62 (dd, J_1 = 14.3 Hz, J_2 = 6.1, 1H, C*H*H), 2.52 (dd, J_1 = 14.7 Hz, J_2 =6.4 Hz, 1H, C*H*H), 2.33 (dd, J_1 = 14.2 Hz, J_2 = 6.4 Hz, 1H, C*H*H), 2.23 – 2.01 (m, 2H, C*H*H, and CH), 1.78 – 1.70 (m, 1H, CH), 1.54 – 1.42 (m, 6H, 3xCH_2), 1.29 – 1.01 (m, 8H, 3xCH_2, CH and C*H*H), 1.06 (s, 9H, $(H_3C)_3CSi$), 0.83 (t, *J* = 7.2 Hz, 3H, CH_3) ppm.^{13}C NMR (101 MHz, $CDCl_3$) δ 172.6 (CO), 153.6 (C), 140.0 (C), 134.9 (4xCH), 133.8 (C), 133.6 (C), 128.4 (2xCH), 126.6 (C), 126.4 (4xCH), 125.1 (CH), 120.9 (CH), 108.7 (CH), 76.1 (CH), 72.6 (CH), 64.5 (CH_2), 51.2 (CH), 40.0 (CH_2), 39.8 (CH), 35.1 (CH_2), 33.0 (CH_2), 32.7 (CH_2), 31.7 (CH), 30.9 (CH_2), 26.5 (CH_2), 26.1 (3xCH_3), 24.8 (CH_2), 23.7 (CH_2), 21.6 (CH_2), 18.4 (C), 13.0 (CH_3) ppm. IR (NaCl) ν = 3417, 2952, 2934, 2857, 1734 and 1585 cm^{-1}.

2-(((1*R*,2*R*,3a*S*,9a*S*)-2-Hydroxy-1-((*S*)-3-hydroxyoctyl)-2,3,3a,4,9,9a-hexahydro-1*H*-cyclopenta[b]naphthalen-5-yl)oxy)acetic acid, treprostinil (1)

To a stirring and cooled solution of the 3.1 g of the crude acid in THF (31 mL) and pyridine (1.8 mL, 3.5 equiv) in a falcon tube, HF/pyridine (1.8 mL) was carefully added dropwise. The reaction mixture was allowed to warm to room temperature and stirred overnight (15 h). The reaction was quenched adding $NaHCO_3$ until basic pH. Hexane (35 mL) was added to the mixture, and it was stirred at room temperature for 15 minutes. Organic and aqueous phases were separated, and the aqueous phase was extracted with hexane (2x30 mL). Then, HCl 1N was carefully added to the aqueous phase until pH 2-3, and it was extracted with ethyl acetate (3x40 mL). These latter organic layers were washed with water (50 mL), brine (50 mL), dried (Na_2SO_4), and concentrated *in vacuo* to give crude treprostinil which was recrystallized in EtOH:H_2O (1:1) to afford 1.6 g (80% yield from **23**) as a white solid. M.p.: 123–125 °C (lit 125–126 °C). Spectroscopical and physical data were identical to those obtained from a sample of treprostinil provided by Aldrich. (See SI for comparison) $[\alpha]^{25}_D$ +28.0 (c 0.05, EtOH, lit +34.0, c 0.45, EtOH). ^{1}H NMR (400 MHz, D_3COD) δ 7.04 (t, *J* = 7.8 Hz, 1H, Ar), 6.79 (d, *J* = 7.5 Hz, 1H, Ar), 6.69 (d, *J* = 8.3Hz, 1H, Ar), 4.62 (s, 2H, CH_2O), 3.62 (td, J_1 = 9.9 Hz, J_2 = 6.2 Hz, 1H, H2), 3.54 – 3.51 (m, 1H, H3'), 2.75 (td, J_1 = 14.8 Hz, J_2 = 6.1 Hz, 2H, H4 and H9), 2.64 (dd, J_1 = 14.7 Hz, J_2 = 5.9 Hz, 1H, H4), 2.49 (dd, J_1 =14.2 Hz, J_2 = 5.9 Hz, 1H, H9), 2.30 – 2.21 (m, 1H, H4a), 2.08 (dt, J_1 = 13.4 Hz, J_2 = 6.8 Hz, 1H, H3), 1.91 (tt, J_1 = 10.6 Hz, J_2 = 6.0 Hz, 1H, H9a), 1.96 – 1.84 (m, 1H, H1'), 1.65 – 1.27 (m, 11H, H1', 2H2', 2H4',2H5',2H6', 2H7'), 1.24 – 1.16 (m, 1H, 1H, H1), 1.14 – 1.06 (m, 1H, H3), 0.92 (t, *J* = 6.8 Hz, 3H, CH_3) ppm. ^{13}C NMR (101 MHz, D_3COD) δ 172.9 (CO), 156.5 (C), 142.2 (C), 128.7 (C), 127.2 (CH), 122.4 (CH), 110.8 (CH), 77.6 (CH), 72.9 (CH), 66.5 (CH_2), 52.7 (CH), 42.3 (CH), 42.0 (CH_2), 38.3 (CH_2), 36.0 (CH_2), 34.6 (CH_2), 34.1 (CH), 33.2 (CH_2), 29.6 (CH_2), 26.6 (CH_2), 26.5 (CH_2), 23.8 (CH_2), 14.5 (CH_3) ppm. IR (NaCl) ν = 3438, 3337, 3049, 2930, 2848 and 1737 cm^{-1}. Elemental analysis calcd for $C_{23}H_{34}O_5$: C, 70.74; H, 8.78. Found: C, 70.51; H, 8.89.

Conclusions

The conclusions section should come in this section at the end of the article, before the acknowledgements.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

Funding of this project by the Spanish MINECO, grant No. RTI2018-095588-B-I00 (Co-funded by European Regional Development Fund/European Social Fund, "Investing in your

future") and FUSP-CEU (PC17/17) is acknowledged. J. G. thanks the Fundación San Pablo-CEU for a pre-doctoral fellowship.

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5. Ciclotrimerizaciones de alquinos y cicloadiciones [2+2+2] cruzadas en un reactor de flujo

En este trabajo se describe un protocolo para realizar ciclotrimerizaciones y cicloadiciones [2+2+2] cruzadas en un reactor tubular. Se usan 2-5 mol% de $Co_2(CO)_8$ como catalizador en las ciclotrimerizaciones y un 10 mol% en las reacciones cruzadas, las cuales no tenían precedentes con dicho catalizador. Debido a los cortos periodos de tiempo (3.5–10 min), el procedimiento representa una alta productividad. Se demuestra la escalabilidad, robustez y seguridad del método con la realización de diversos escalados.

En esta publicación, realicé todo el trabajo experimental. El Dr. Blanco-Urgoiti colaboró conmigo en la configuración y funcionamiento de los equipos de flujo. Colaboré con mis supervisores en la redacción del manuscrito, principalmente en la parte experimental y los anexos suplementarios.

Factor de impacto (2019): 6.555. **Categoría:** Química Orgánica (Q1 2/57). Fuente: JCR (Journal of citation reports)

Organic Letters

Cite This: *Org. Lett.* **2018**, *20*, 5219−5223

ARTICLE

Cobalt octacarbonyl catalyzed scalable alkyne cyclotrimerization and crossed [2+2+2]-cycloaddition reaction in a plug flow reactor.

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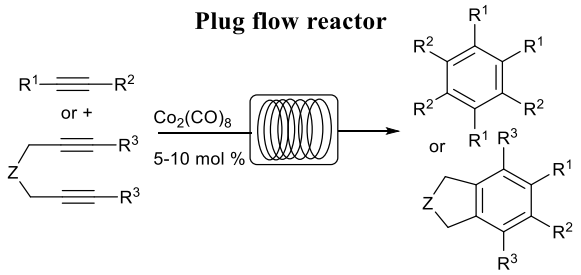
Supporting Information Placeholder



Scalable, highly efficient and broad-scope alkyne cyclotrimerization and crossed [2+2+2] cycloaddition in a plug flow reactor

ABSTRACT: Cobalt catalyzed alkyne cyclotrimerization and crossed [2+2+2] cycloadditions are developed in a plug flow reactor (PFR). The protocol uses generally 5 mol % of $Co_2(CO)_8$ and is scalable at least at multigram. Efficient, scalable use of $Co_2(CO)_8$ for crossed reactions of diynes and alkynes has hardly any precedent.

Metal catalyzed [2+2+2] cycloadditions are an atom economical and efficient way to produce highly functionalized carbo- and heterocycles. Starting from various unsaturated substrates, such as alkynes, nitriles, alkenes, cumulenes and heterocumulenes it allows the synthesis of a great variety of aromatic and non-aromatic cycles. This process is catalyzed by complexes of more than 17 different metals.[1] Cobalt complexes have proved versatile reagents in the field of [2+2+2] chemistry.[2] The cobalt mediated reactions produce cobalt-complexed products that can undergo further transformations. Vollhardt et al. reported the use of $CpCoL_2$ (L = CO or CH_2=CH_2) to effect cyclotrimerizations of alkynes,[3] including the use of alkynylboronates.[4] Double bonds forming part of aromatic heterocycles were used as unsaturated partners, in [2+2+2] cycloadditions.[5] In addition, catalytic uses of these cobalt catalysts were reported,[6] including intermolecular alkyne cyclotrimerizations using simple catalytic systems based on CoX_2[7] and, more recently, pyridine synthesis.[8] Asymmetric reactions were first reported by Heller et al. using a molecularly defined Co(I)-precatalyst, a chiral menthyl-substituted indenyl Co(I)-complex.[9] Recently, an *in situ* formed catalytic system based on cobalt(II)-salts and chiral P,N-ligands was developed by Hapke et al. for the asymmetric cyclization of triynes.[10] $Co_2(CO)_8$ is a proven versatile reagent for the selective formation of multiple carbon-carbon bonds in a single chemical step. In addition to its main synthetic application, the Pauson-Khand reaction, some [2+2+2] reactions are catalyzed by this unexpensive and easy to handle reagent.[11] Thus, cycloalkenes were used in crossed cyclizations with diynes giving tandem [2+2+2]/[4+2] cyclizations using cobalt carbonyl as the catalyst.[12] Some examples of cyclotrimerization of alkynes have been reported.[13]

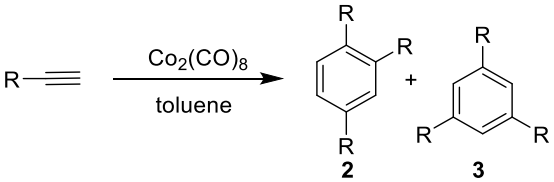
Continuous technology has shown great advantages compared with batch flask conditions, in particular for scaled up processes.[14] The environmental benefits of flow chemistry over traditional batch chemistry such as the excellent heat and mass transfer or the efficiency in mixing in small volumes, have attracted much attention.[15] In addition, these methodologies allow process intensification, for instance running reactions under extreme

process windows, using high temperatures and elevated pressures.[16] Various metal catalyzed reactions using a flow microreactor and continous systems have been described.[17] We have recently shown a general protocol for both inter-and intramolecular Pauson-Khand reaction in microreactor.[18]

Herein, we present the first scalable end efficient cobalt octacarbonyl catalyzed [2+2+2] cycloadditions performed in a plug flow stainless steel reactor. The scope includes cyclotrimerizations of terminal and internal alkynes with high selectivity and crossed reactions between diynes and alkynes.

We first explored the trimerization of phenylacetylene. When terminal alkynes are used, achieving inter-molecular reactions in a highly regioselective manner is difficult. The formation of a mixture of 1,2,4- and 1,3,5-regioisomers, being the first the major product, is common.[19] Table 1 (entries 1-9) shows the optimization study with this substrate. Total conversion was achieved with reaction temperatures over 90 ºC and catalyst loadings of 2-5 mol %. Yields were excellent under conditions of entries 3 and 6, the first with lower temperature and the latter with shorter resident time and only 2 mol % of catalyst. Batch tests were carried out for comparison. Under refluxing toluene no conversion was observed after 8 h, whereas in a sealed tube at 180 ºC the reaction was completed in 1 h (entry 8): When using MW heating and after 60 min the conversion achieved was 70% (entry 9). Once the best conditions were found, entry 10 shows the result of a scaled up reaction where 10 g of phenylacetylene were efficiently transformed into **2a** in 92% yield after a total reaction time of 105 min. For this reaction, connecting a cartridge with a metal scavenger at the end of the system allowed obtaining **2a** in 96% purity. The procedure was applied to seven terminal alkynes (entries 11-20). We could reach good yields (83-99%) in all cases. However, with some substrates (entries 16, 17 and 20) we had to elevate the reaction temperature to 230 ºC and the residence time to 5 min. The 1,2,4- isomer **2** was the exclusive product in some examples, or was greatly major, as shown by GC-MS analysis. The method is highly efficient and selective under low catalyst loadings. These are among the highest regioselectivities reported to date for this reaction. It has been proposed that the intensification conditions used in microreactors, in particular the high pressures used, may have an impact not only on the reaction kinetics but on the selectivity.[16a]

Table 1. Cyclotrimerizations of terminal alkynes

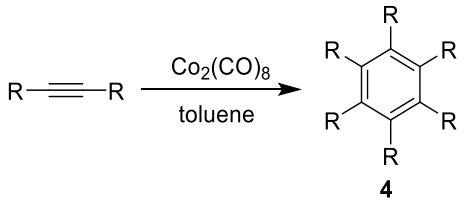


entry[a]	R	Prod.	temp (ºC)	r. t. (min)	cat. (mol %)	conv[b]	yield (%)[c]	Ratio 2:3[d]
1	Ph	2a	90	15	5	>99	88	95:5
2	Ph	2a	90	10	5	85	70	95:5
3	Ph	2a	110	10	5	>99	98	98:2
4	Ph	2a	130	10	2	93	78	98:2
5	Ph	2a	150	5	2	99	90	99:1
6	Ph	2a	180	3.5	2	>99	98	99:1
7	Ph	2a	180	1.5	2	>99	94	99:1
8[e]	Ph	2a	180	60	5	>99	80	90:10
9[f]	Ph	2a	150	60	5	70	55	92:8
10[g]	Ph	2a	180	3.5[h]	2	>99	92	99:1
11	C_4H_9	2b	180	3.5	2	>99	93	95:5
12	4-MeC_6H_4	2c	180	3.5	2	>99	94	99:1
13	4-FC_6H_4	2d	180	3.5	2	>99	99	100:0
14	4-BrC_6H_4	2e	180	3.5	2	>99	96	100:0
15	4-$Me_2NC_6H_4$	2f	180	3.5	2	15		
16	4-$Me_2NC_6H_4$	2f	230	5	5	>99	87	97:3
17	4-$NO_2C_6H_4$	2g	230	5	5	95	83	100:0
18	4-$NO_2C_6H_4$	2g	280	5	5	dec.		
19	Cy	2h	180	3.5	2	50	39	95:5
20	Cy	2h	230	5	5	>99	84	96:4

[a] Conditions for all experiments: 0.4-0.5 mmol/mL substrate concentration (1.6 mL used in each experiment), 20 bar system pressure, reactor volume: 8.1 mL. [b] By NMR. [c] in mixtures 2:3 after chromatography. [d] Determined by GC-MS. [e] Batch test in sealed tube. No conversion was observed in a reaction in refluxing toluene after 8 h [f] Batch test under MW heating in a toluene/MeOH 4:1 mixture. [g] Scale-up experiment with 10 g of substrate. [h] Total reaction time: 105 min. When the purification was achieved using a metal scavenger cartridge total time was 108 min, yield was 96%, purity of **2a** 96% by NMR with duroquinone as internal standard.

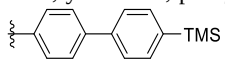
In Table 2 we summarize the reactions with internal alkynes. 4-Octyne was used to optimize conditions (entries 1-5). Using 5 mol % of catalysts, 5 min of residence time and 230 ºC we could reach a 96% yield of the final hexapropylbenzene **4a** (entry 4). There was no observable conversion in the batch tests, both under reflux (8 h) or under MW heating (150 ºC) after 1h. Under the conditions of entry 4, 10 g of the alkyne were transformed after 116 min total reaction time into the final product with an 87% yield (entry 6). The procedure was applied to four more internal alkynes (entries 7-12), achieving yields between 71 and 99 %. In some cases the residence time was increased to a maximum of 20 min and catalyst loading needed to be increased up to 10 mol % (entry 12). These reactions are known to give solubility problems as in the case of entries 8 and 12. The plug flow reactor (PFR) allows installation of a thermostated line at the exit of the reactor to solubilize the product avoiding precipitation and obstructions. Product **4e** is an interesting representative of a star shaped product and was described as a polyphenylene dendrimer precursor.[12e]

Table 2. Cyclotrimerizations of internal alkynes



Entry[a]	R	Prod.	temp (ºC)	r. t. (min)	cat. (mol %)	conv[b]	yield (%)[c]
1	$(CH_2)_2CH_3$	4a	180	3.5	5	79	60
2	$(CH_2)_2CH_3$	4a	180	10	5	86	73
3	$(CH_2)_2CH_3$	4a	200	5	5	>99	86

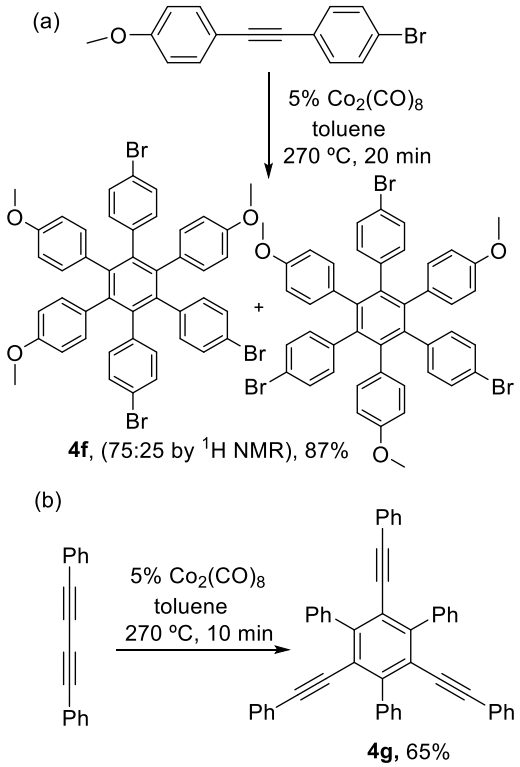
4	$(CH_2)_2CH_3$	4a	230	5	5	>99	96
5	$(CH_2)_2CH_3$	4a	230	10	2	86	78
6[d]	$(CH_2)_2CH_3$	4a	230	5[e]	5	>99	87
7	Ph	4b	230	5	5	80	68
8	Ph	4b	230	10	5	>99	94
9	CH_2OCH_3	4c	230	5	5	>99	99
10	$COOCH_3$	4d	230	15	7.5	>99	82
11[f]	$COOCH_3$	4d	270	20	5	>99	79
12	Y[g]	4e	230	20	10	85	71

[a] Conditions for all experiments: 0.5-0.3 mmol/mL substrate concentration (1.6 mL used in each experiment), 20 bar system pressure, reactor volume: 8.1 mL. [b] By NMR. [c] In pure product. [d] Scale-up experiment with 10 g of substrate. [e] Total reaction time: 116 min. When the purification was achieved using a metal scavenger cartridge total time was 119 min, yield 91%, purity of **4a** 97%. [f] 30 bar system pressure. [g] Y = 

We applied our conditions to two non-symmetric alkynes (Scheme 1). Products **4f** have been previously described as precursors of covalent organic capsules.[20] They were prepared in ca 30% yield by heating the starting alkyne in dioxane at 110 ºC during 2 weeks. We obtained an 87% yield under the conditions described in Scheme 1a. Product **4g** was prepared as a single 1,3,5-product in 65% yield (Scheme 1b).

Cobalt carbonyl has hardly been used[11] for crossed cyclotrimerization reactions between diynes and alkynes, possibly because it gives alkyne cyclotrimerization over the crossed products. However, as with the PFR conditions the reaction mixture is continuously loaded into the reactor, and we envisioned the possibility of using this catalyst for this variation of the [2+2+2] reaction. Thus, *N*,*N*-dipropargyltosylamide was reacted with phenylacetylene under different conditions (Table 3, entries 1-9). A careful selection of reaction temperature, alkyne equivalents and residence time was necessary to favor the crossed product over the alkyne or the diyne trimer **6**. The best result (72-86% yields), was achieved at 150-180 ºC, with 5-3 equiv of alkyne, 10-3.5 min of residence time and 10 mol % of catalyst (entries 2 and 3, respectively). Different metal carbonyls were used under these conditions (entries 5-11). $Rh_2(CO)_4Cl_2$ and $Co_4(CO)_{12}$ gave similar results as $Co_2(CO)_8$ (entries 7-8), leading the others to complex mixtures of decomposition products. Two batch reactions were carried out giving poor results both in sealed tube or under MW heating (entries 12-13). The method was applied to 4 different diynes (two of them substituted at the alkyne end), and three different alkynes (entries 14-25). Yields were variable, with better performance of phenylacetylene over 1-hexyne and 4-octyne. Entry 20 shows the result of a 5 g scale reaction giving **5g** in 68% yield after 210 min of total time.

Scheme 1. Regioselective synthesis of hexasubstituted benzenes.



In summary, we show a general protocol for alkyne cyclotrimerization and crossed [2+2+2] cycloadditions of diynes with alkynes in a PFR. The method uses of inexpensive $Co_2(CO)_8$, is highly efficient, has a broad scope and is easily scalable. We believe the applicability to crossed reactions is remarkable and novel. This procedure opens a new alternative that can lead to novel scaled up applications of this powerful transformation.

ASSOCIATED CONTENT

Supporting Information

Complete experimental procedures and spectroscopical data of products. Description of the equipment. Copies of ^1H NMR spectra of known products and both ^1H and ^{13}C NMR spectra of new products are included (PDF file).

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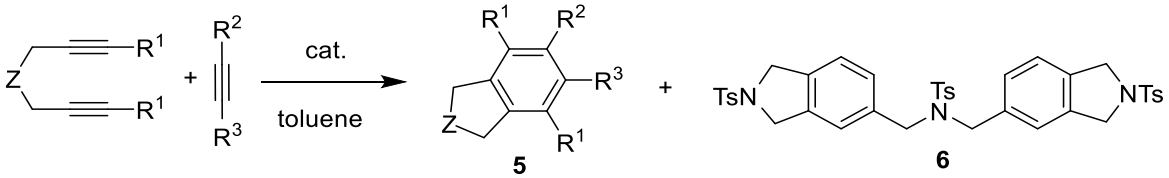
Author Contributions

The manuscript was written through contributions of all authors. / All authors have given approval to the final version of the manuscript.

ACKNOWLEDGMENT

Funding of this project by the Spanish MINECO, grant No. CTQ2015-64624-R (Co-funded by European Regional Development Fund/European Social Fund, "Investing in your future") and FUSP-CEU (PC17/17) is acknowledged. J. G. thanks the Fundación San Pablo-CEU for a pre-doctoral fellowship.

Table 3. Crossed [2+2+2] cycloadditions of diynes and alkynes



entry[a]	Z	R^1	R^2	R^3	Prod.	Cat.	cat. (mol %)	temp (ºC)	r. t. (min)	Alkyne equiv	Conv[b]	Yield(%)[c] 5 (6)
1	TsN	H	Ph	H	5a	$Co_2(CO)_8$	10	130	10	3	62	38
2	TsN	H	Ph	H	5a	$Co_2(CO)_8$	10	150	10	5	>99	72
3	TsN	H	Ph	H	5a	$Co_2(CO)_8$	10	180	3.5	3	>99	68
4	TsN	H	Ph	H	5a	$Co_2(CO)_8$	10	230	5	5	>99	20 (30)
5	TsN	H	Ph	H	5a	$Mo(CO)_6$	10	180	3.5	3	6	-
6	TsN	H	Ph	H	5a	$Co_3(CO)_9\mu^3CH$	10	180	3.5	3	>99	28 (35)
7	TsN	H	Ph	H	5a	$Co_4(CO)_{12}$	10	180	3.5	3	>99	67
8	TsN	H	Ph	H	5a	$Rh_2(CO)_4Cl_2$	10	180	3.5	3	98	71 (10)
9	TsN	H	Ph	H	5a	$Ru_3(CO)_{12}$	10	180	3.5	3	61	28
10	TsN	H	Ph	H	5a	$CpCo(CO)_2$	10	180	3.5	3	45	21
11	TsN	H	Ph	H	5a	$Cr(CO)_6$	10	180	3.5	3	<5	-
12[d]	TsN	H	Ph	H	5a	$Co_2(CO)_8$	10	180	60	3	70	35
13[e]	TsN	H	Ph	H	5a	$Co_2(CO)_8$	10	150	30	3	35	26
14	TsN	H	$(CH_2)_3CH_3$	H	5b	$Co_2(CO)_8$	10	150	10	3	>99	35
15	TsN	H	$(CH_2)_2CH_3$	$(CH_2)_2CH_3$	5c	$Co_2(CO)_8$	10	230	20	3	>99	51
16	TsN	CH_3	Ph	H	5d	$Co_2(CO)_8$	10	230	5	5	>99	70
17	TsN	CH_3	$(CH_2)_3CH_3$	H	5e	$Co_2(CO)_8$	10	230	10	5	>99	54
18	TsN	CH_3	$(CH_2)_2CH_3$	$(CH_2)_2CH_3$	5f	$Co_2(CO)_8$	10	230	10	3	>99	61
19	$(EtO_2C)_2C$	H	Ph	H	5g	$Co_2(CO)_8$	10	200	10	3	>99	85
20[f]	$(EtO_2C)_2C$	H	Ph	H	5g	$Co_2(CO)_8$	10	200	10	3	>99	68
21	$(EtO_2C)_2C$	H	$(CH_2)_3CH_3$	H	5h	$Co_2(CO)_8$	10	180	10	3	>99	82
22	$(EtO_2C)_2C$	H	$(CH_2)_2CH_3$	$(CH_2)_2CH_3$	5i	$Co_2(CO)_8$	10	230	10	3	>99	58
23	$(EtO_2C)_2C$	CH_3	Ph	H	5j	$Co_2(CO)_8$	10	230	10	5	>99	78
24	$(EtO_2C)_2C$	CH_3	$(CH_2)_3CH_3$	H	5k	$Co_2(CO)_8$	10	230	10	5	>99	75
25	$(EtO_2C)_2C$	CH_3	$(CH_2)_2CH_3$	$(CH_2)_2CH_3$	5l	$Co_2(CO)_8$	10	230	10	3	>99	70

[a] Conditions for all experiments: 0.13 mmol/mL substrate concentration, 20 bar system pressure, reactor volume: 8.1 mL. [b] By NMR. [c] In pure product. [d] Batch test in sealed tube. [e] Batch test under MW heating in a toluene/MeOH 4:1 mixture 25% of starting diyne was recovered. [f] Scale-up experiment with 5 g of substrate, total reaction time 210 min.

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6. Reacciones de cicloadición en flujo

Los reactores de química de flujo forman parte de una creciente área de investigación que ha cambiado la forma de realizar química sintética, no sólo en los laboratorios de investigación básica sino también a nivel industrial. En este trabajo de revisión, destacamos los avances más recientes relacionados con cicloadiciones realizadas en un sistema de flujo continuo. Las cicloadiciones son transformaciones que conllevan con gran economía atómica y son útiles para la formación de carbo- y heterociclos, incluyendo la construcción de esqueletos complejos de moléculas interesantes. Las principales ventajas de trasladar estas reacciones a la química de flujo son la intensificación de condiciones, manejo más seguro de gases y reactivos peligrosos, fácil optimización de condiciones y posibilidad de escalados. Estos beneficios son especialmente importantes en algunas cicloadiciones como la CuAAC (Cicloadición azida-alquino catalizada por cobre), la reacción de Diels-Alder, la ozonolisis, y la cicloadición [2+2] fotoquímica. Además, algunas de estas transformaciones son claves para la síntesis industrial de productos farmacéuticos.

En este trabajo llevé a cabo la búsqueda bibliográfica y el resumen de todos los artículos que contienen cicloadiciones en flujo. Colaboré con mis supervisores en la redacción del trabajo, y elaborando todos los esquemas.

Factor de impacto (2019): 7.962. **Categoría**: Química multidisciplinar (Q1 22/177); Ciencia y tecnología verde y sostenible (Q1 3/41). Fuente: JCR (Journal of citation reports)

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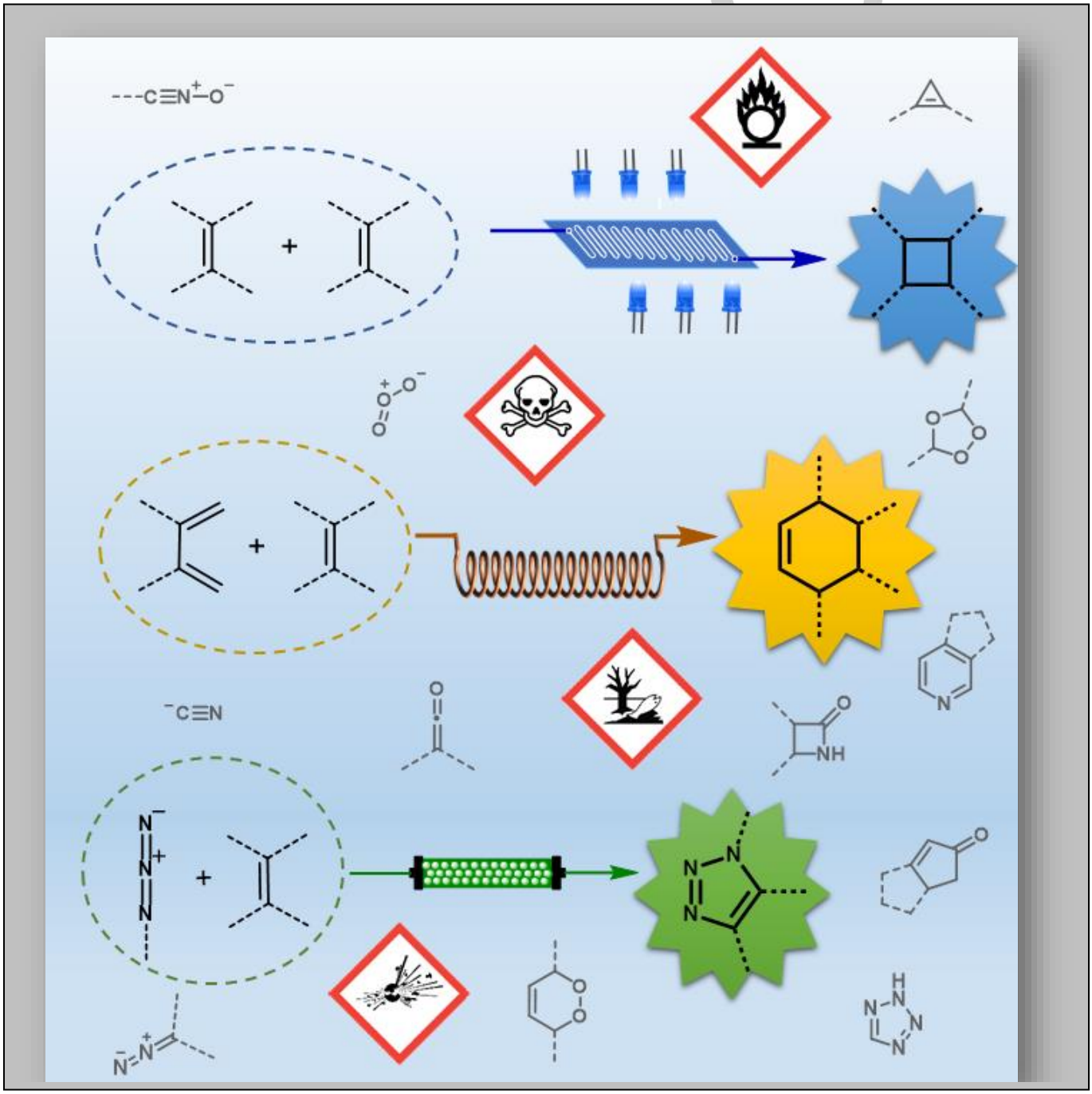
REVIEW

Flow Chemistry for Cycloaddition Reactions

Jorge García-Lacuna, Gema Domínguez and Javier Pérez-Castells*



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Abstract: Continuous flow reactors form part of a rapidly growing research area which has changed the way synthetic chemistry is performed not only in academia but also at the industrial level. In this review, we highlight the most recent advances in cycloaddition reactions performed in a flow system. Cycloadditions are atom efficient transformations for the synthesis of carbo- and heterocycles, involving the construction of challenging skeletons of complex molecules. The main advantages of translating these processes into flow include using intensified conditions, safer handling of hazardous reagents and gases, easy tuning up of reaction conditions and straightforward scaling up. These benefits are especially important in several cycloadditions, such as CuAAC, Diels-Alder, ozonolysis and [2+2] photocycloadditions. Interestingly, some of these transformations are key reactions in the industrial synthesis of pharmaceuticals.

1. Introduction

Over the past decade, flow reactors and microstructured devices are changing the way to perform organic reactions, moving away from the classical round-bottom flasks and other traditional techniques. The advantages of continuous-flow processing involve intensification of conditions, quick optimization of reactions, better handling of hazardous reagents and gases, improvement of mixing and multiphase transitions, safer control of high pressures and exothermic reactions, possibility of automatization and greener general procedures. In addition, scaling reactions with flow systems is simple and inexpensive. No changes in conditions are required as is often the case in batch. For instance, microwave scale preparations, which are generally limited to 30 mL reaction volumes, can be scaled up readily.

All these advantages are increasingly appreciated by the pharmaceutical industry and, thus, a growing number of companies are now starting to employ continuous-flow technologies on a more routine basis.[1] Highly automated flow synthesis platforms are used at different stages in drug development: advanced medicinal chemistry, optimization of synthetic routes, scaling up of synthesis of drug candidates and manufacturing of active pharmaceutical ingredients (APIs). Use of flow techniques in drug discovery includes library synthesis, high throughput screening and integration of synthesis with biological test platforms. A drug candidate entering clinical trials is needed in multigram to multikilogram amounts and scaling is generally considerably easier through continuous processes compared with traditional batch methods. Finally, manufacturing of APIs in flow, is considered greener and research to develop these processes is encouraged by the ACS GCI Pharmaceutical Roundtable.[2] In general, chemical complexity of APIs is intermediate requiring numerous, highly diverse synthetic steps.[3] However, several cases of automatized multistep procedures have been developed using specifically designed set-ups.[4] A compact, integrated and reconfigurable system was recently developed at MIT.[5] The platform is capable to generate thousands of individual doses of different APIs in hours.[6]

For the general synthesis lab, flow chemistry can be advantageous in several aspects. For instance, the reaction time, the concentration, the solvent type, and reagent flow rates, as well as the temperature can be adjusted in real time. This avoids performing numerous batch reactions to adjust conditions and is therefore highly time saving. The exact control of reaction conditions makes possible to work with overheated solvents and high pressures.[7] Thus, low boiling point solvents, easier to evaporate are usable. Another advantage is the better heat transfer and mixing which many times improve reaction yields. Due to mixing improvement, chemical transformations involving multiple phases are generally improved using flow techniques. On the other hand, if cooling is necessary, it is very efficiently done on the small tubing of flow equipment, being generally convenient to run cryogenic reactions in flow reactors. Moreover, flow technologies are well known for controlling exothermal reactions. If sudden heat emission takes place the small volumes handled at each moment prevent severe accidents.

However, not all reactions benefit from advantages when performed in flow. The special ways in which heating, mixing, and reaction times are adjusted in the flow devices may change the composition of final products. Sometimes side reactions and decomposition can be minimized, others they give similar results than in batch. Some procedures give better yields or selectivity whereas others do not show any benefits. Finally, although scaling up is always convenient in flow, it may not justify the resources needed to use the flow methods. The recently appeared Hitchhiker's guide for flow chemistry summarized the transformations that outperform in flow, as an attempt to help chemists in deciding to use continuous flow or not.[8] Cycloadditions do not usually appear among the reactions that most benefit from the advantages of flow chemistry. However, as we will see in this review, many examples demonstrate that these reactions can be enhanced in flow, primarily by taking advantage of intensified conditions, improved safety and better scaling up.[9] Application of high temperature and pressure may lead to the finding of novel process windows,[10] which is particularly useful in cycloaddition reactions such as intermolecular Diels-Alder.

When using flow chemistry, it is easier to generate intermediates *in situ* to be used immediately in a subsequent reaction. This is particularly advantageous if these reagents are unstable or hazardous. For the sake of cycloadditions, the safer handling of azides, diazocompounds or ozone is especially convenient. Flow technologies enable using these reagents even at the industrial level,[11] broadening the real scope of organic chemistry.[3]

Jorge García-Lacuna studied Pharmacy at the San Pablo-CEU University. He started his PhD in the same university in 2016, where he is currently working in continuous flow procedures, mainly gas-liquid reactions, metal-catalyzed cycloadditions such as Pauson-Khand and [2+2+2] cycloadditions and sustainable APIs synthesis.

Gema Domínguez studied Chemistry at the Universidad Complutense de Madrid (B.S. in 1982), where she received her PhD in Organic Chemistry in 1986. In 2009 she was appointed Full Professor at Universidad San Pablo-CEU. She is currently working on metal-catalysed cyclization, metathesis reactions and synthesis of new biologically active molecules.

Javier Pérez Castells received his PhD in 1994 at Universidad Complutense, Madrid. He is full professor at Universidad San Pablo-CEU since 2007, where he works on metal catalysed cyclization reactions, synthesis of new biologically active molecules and structural studies on biomacromolecules by NMR.

With regard to multiphasic systems, the main advantage of fluidic systems is the increase of the interfacial area that generally accelerates the reaction. In gas−liquid reactions, improved mixing generally gives better yields. This is combined with the possibility of using high pressures safely which aids the solution of the gas.[12] Interestingly, using mass-flow controllers allows controlling the amount of gas used, thus permitting the use of stoichiometric quantities of the gas. In addition, if the gas used is hazardous or very toxic it benefits form handling smaller amounts in a safer way. The combination of these reasons makes flow technologies very convenient for reactions involving gases. In the cycloaddition field, ozone, molecular oxygen, and ethylene are used safely and in smaller amounts in flow. A few examples use carbon monoxide in [2+2+1] reactions. In relation to molecular oxygen, the challenges pertaining to handling highly unsafe intermediates and operation within the explosive regime, especially under process-intensified conditions, can be addressed through the utilization of continuous-flow reactors.[13] Due to these facts, flow technologies are valuable for hydrogenation reactions where solid catalysis with gas-liquid mixtures are generally used.[14] In fact, flow chemistry holds great potential in sustainability and green perspectives when used with heterogenous catalysis.[15] Different modes of packing such as packed-bed or wallcoating allow performing a variety of organic reactions including enantioselective catalysis.[16] These methods have been used for [3+2] cycloadditions with heterogeneous catalysis by copper complexes[17] and for the Huisgen cycloaddition.[18]

Two types of reactions that benefit widely from the characteristics of flow reactors are electrochemical and photochemical reactions. The high surface-area to volume ratios of a flow reactor, make electrochemistry possibly scalable and cleaner, and the small dimensions eliminate the need for supporting electrolytes.[19] Regarding photochemical transformations, flow conditions provide efficient control of reaction conditions including uniform irradiation. The final products are often unstable, but as they are readily removed, the degree of degradation observed is decreased and the productivity of the processes is increased. Traditional photochemical reactors have been used generally at the lab scale as the technology became unfavourable for large scale transformations. With the new advances in flow photochemistry, many photochemical reactions become greener and more scalable.[20] Among the applications in organic synthesis, the [2+2] photocycloaddition has received high attention.[21] Furthermore, the group of Booker-Milburn developed several different flow reactors to show their advantages compared to traditional procedures, in performing variety of classical photochemical cycloadditions.[22]

Table 1. Main advantages of flow technology for cycloaddition reactions.

Key advantage using a continuous flow protocol	Applications to cycloaddition reactions.
Safer and easier use of gases: O_2, O_3, CO; Ethylene	[4+2] with singlet oxygen. Ozonolysis. Pauson-Khand. Epoxidations.
Efficient photochemistry	[2+2], [4+2] with singlet oxygen.
Safer use of azides, ozone, hydrazine.	Huisgen type cycloaddition, Ozonolysis.
Extreme temperature/pressure	Diels Alder, Kondrat'eva Reaction.
Heterogeneous catalysis	CuAAC, Cyclopropanations
Scalability issues	Related to photochemistry problems or use of dangerous materials.
Ultrafast reactions	Acid promoted [2+2], Microwave assisted Diels Alder

There are many recent reviews on flow chemistry. In addition to the mentioned general guide, and those devoted to discuss the advantages of the technique and the different designs of the equipment,[23] many works are centred on the advantages of flow technologies for the pharmaceutical industry and have been mentioned above. There are reviews dedicated to natural product synthesis,[24] and as well as heterocycles.[25] However, we believe that a review specifically dedicated to cycloadditions was missing and could be interesting for the general synthetic chemist planning to use flow methods for these types of reaction. As mentioned above, flow reactors work at relatively high pressures, which has interesting kinetic advantages in reactions with negative activation volumes, that is, in which the number of particles decrease and in those in which gases participate. Some

cycloadditions use toxic and hazardous gases such as carbon monoxide. With flow techniques the use of toxic and dangerous gases is highly restricted and controlled. Table 1 summarizes the main advantages of flow technology for cycloaddition reactions.
This review is organized attending to the ring size produced in the cycloaddition process. Due to this classification, we use the classical notation with the number of atoms involved in the cycloaddition rather than the participating electrons.

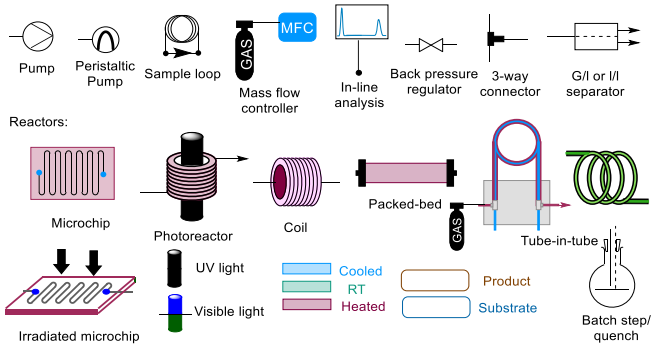
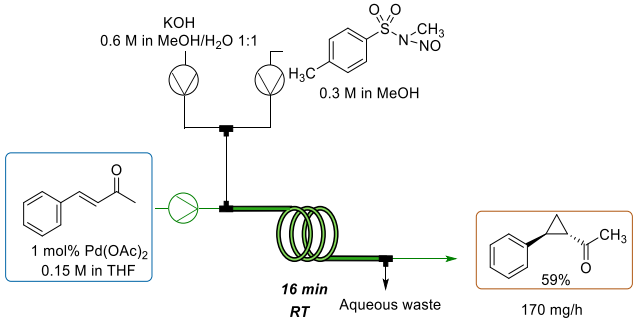


Figure 1. Diagram legend.

2. [2+1] cycloaddition: 3-membered rings

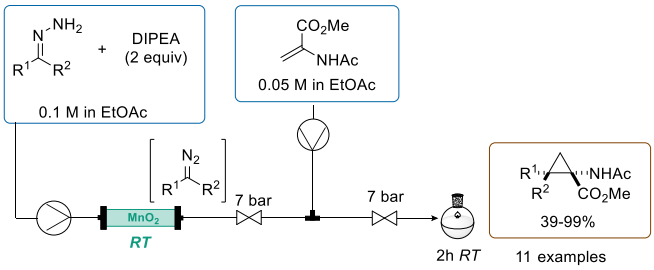
2.1. Cyclopropane synthesis

The cyclopropane moiety has a unique 3-dimensional architecture with spatially well-defined substituents, that appears in some natural products and pharmaceutically active compounds.[26] Traditional approaches by [2+1] cycloadditions include the formation of carbenes or ylides which react with alkenes through a concerted [2+1] cycloaddition.[27] Using flow chemistry, carbenes can be generated safely and their reaction with alkenes is more efficient.
Kappe and coworkers developed a continuous process for the generation, separation, and reaction of anhydrous diazomethane in a tube-in-tube reactor. The tube-in-tube device is a gas-addition tool for continuous processes whose inner tube is made of a robust, but porous material such as Teflon AF-2400, which selectively allows gases to cross, but not liquids. Using 4-phenyl-3-buten-2-one in combination with 1 mol% of $Pd(OAc)_2$ in the outer tube, the cyclopropane was obtained in 59% yield after purification. The diazomethane was generated in the inner tube of the reactor from a feed of diazald and a feed of potassium hydroxide. This technique allows safe and scalable reactions with dry diazomethane to be performed on a laboratory scale (Scheme 1).[28]



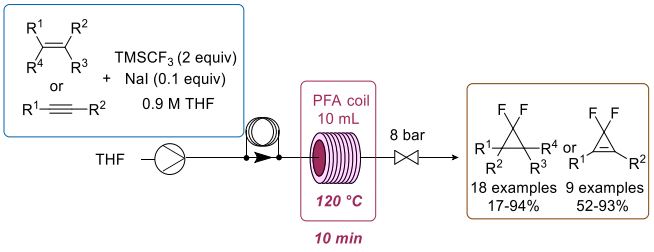
Scheme 1. Tube in tube reactor for anhydrous diazomethane synthesis.

Another approach was developed by the Ley group. Diazocompounds were generated by passing hydrazone derivatives through a column packed with activated MnO_2, which then reacted with electron poor olefins (Scheme 2). They also studied a reduction after the cyclopropanation and a telescoped cyclopropane glycine synthesis from geraniol with an in-line IR analysis to identify the diazocompound.[29]



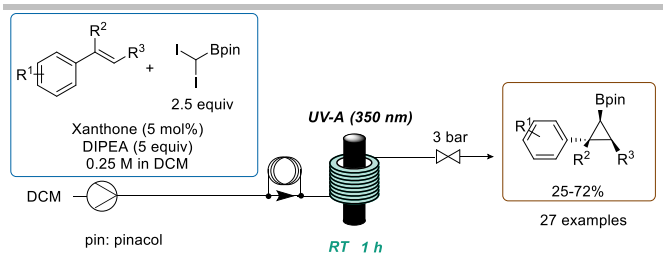
Scheme 2. Generation of diazocompounds from hydrazones and synthesis of cyclopropyl glycines.

Difluorocarbenes were generated *in situ* by Charrete and coworkers from $TMSCF_3$ and a catalytic quantity of NaI. The generated electrophilic carbene reacted smoothly with a broad range of alkenes and alkynes, allowing the synthesis of the corresponding difluorocyclopropanes and difluorocyclopropenes. The reaction proceeded cleanly with a 1 mmol/min production rate and a 10 min residence time. In batch, it needed 2 h and more equivalents of reagents, whereas it is more difficult to scale the reaction due to the gas and pressure evolution over time. (Scheme 3).[30]



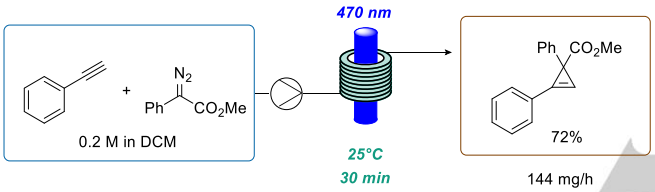
Scheme 3. Synthesis of difluorocyclopropanes and difluorocyclopropenes.

The same group reported a metal free, light-mediated, borocyclopropanation, in which a broad range of styrene derivatives were cyclopropanated in good yields within 1 h residence time to produce highly valuable cyclopropylboronate esters with modest to good diastereoselectivities. Compared to the batch procedure (18h for full conversion), reaction time was drastically reduced and yield improved. In this case, Xanthone was used as photosensitizer and DIPEA to quench the resulting iodine (Scheme 4). The resulting borocyclopropanes are versatile synthetic intermediates that can be easily diversified.[31]



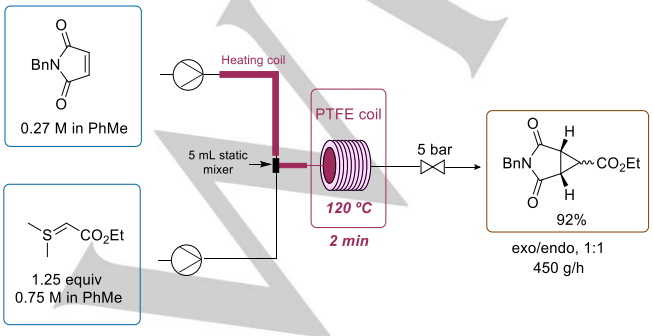
Scheme 4. Borocyclopropanation of styrene derivatives.

Carbenes can be generated photochemically. The Koenigs' group generated them from donor-acceptor diazoalkanes and blue light irradiation. In the presence of an alkyne they underwent a catalyst free cyclopropenation reaction. Two microreactors were used to produce 144 mg of the cyclopropane per hour, which is 36 times faster than the batch procedure (Scheme 5).[32] Using the same set-up, moderate to excellent yields of six cyclopropanes and good diastereoselectivity were achieved by using aryldiazoacetates with styrene as starting materials.[33]



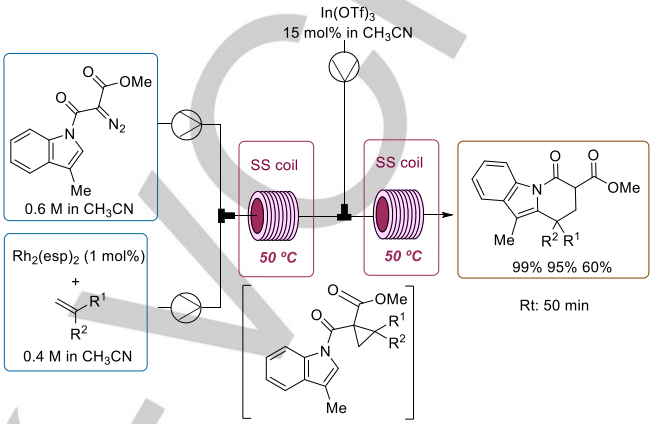
Scheme 5. Cyclopropenations from photochemically generated carbenes.

Sulfonium ylides were used to synthesize *trans*-(dioxo)-azabicyclo[3.1.0]hexane carboxylate, a key intermediate in the synthesis of complex molecules, using a flow cyclopropanation process. Ethyl (dimethylsulfuranylidene)acetate (EDSA) was used as ylide in a different feed to improve addition and it was added to a preheated solution of the alkene as it is shown in Scheme 6. This kind of addition improves selectivity and it cannot be done in batch as the rate of decomposition of EDSA is fast in toluene at high temperatures. After mixing, the reactor was heated at 120 ºC with a residence time of 2 min. Following this procedure, 3.3 kg of the desired product were produced in 7 h (92% yield). Then, it was isomerized into the pure *trans* isomer using a catalytic amount of DBU.[34]



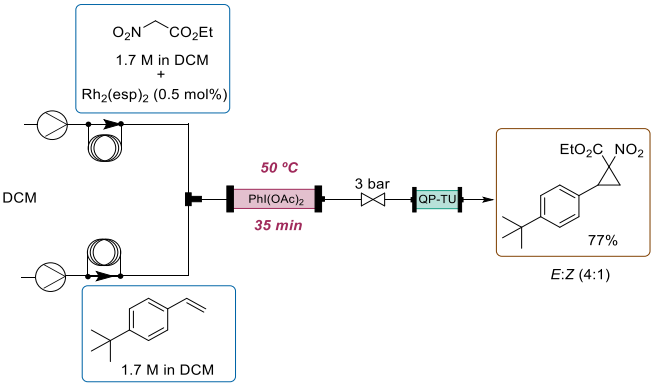
Scheme 6. Sulfonium ylides to cyclopropanate maleimides.

Two bicatalytic continuous flow reactions carried out in tandem, a cyclopropanation and an homo-Nazarov-type ring-opening cyclization, allowed preparing hydropyrido[1,2-a]indoles. Both reactions were performed in a continuous flow set up, providing 3-5 g per hour of the final isolated product in nearly quantitative yields in two of the three examples (Scheme 7). The cyclopropanation was performed with 1 mol% of $Rh_2(esp)_2$ as the catalyst.[35]



Scheme 7. Tandem cyclopropanation-homo-Nazarov-type ring-opening cyclization.

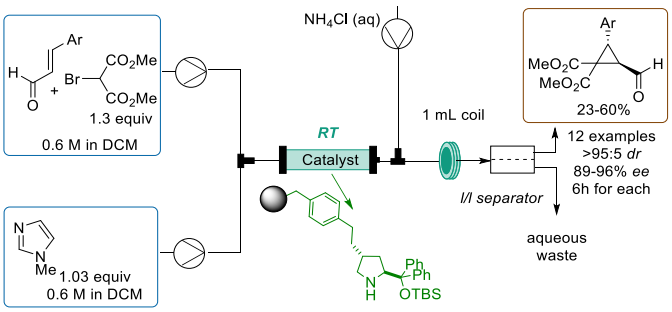
The same catalyst was used for the hypervalent iodine(III) mediated cyclopropanation. The authors did a deep study of conditions through *in situ* monitoring of carbon−carbon bond formation with benchtop NMR spectroscopy. Best results were achieved when using iodonium ylide supported in recyclable glass beds inside an Omnifit glass column (Scheme 8). Moreover, during optimization an aliquot of the reaction outflow was periodically redirected to a MS detector zone by means of a Rheodyne MRA splitting device.[36]



Scheme 8. Hypervalent iodine(III) mediated cyclopropanation.

Regarding asymmetric cyclopropanation, Pericàs and coworkers developed a solid-supported diarylprolinol catalyst for enantioselective cyclopropanation of α,β-unsaturated aldehydes. 12 different cyclopropanes were prepared in moderate yields and excellent enantioselectivity (around 90%, Scheme 9). The flow protocol is beneficial in case of electron-rich enals, where the by-

product formation is minimized. The robustness of the supported catalyst was proved by a 48 h experiment and also a two step process, in which the cyclopropanation is coupled with a Wittig reaction.[37] The same group reported a recyclable and highly efficient heterogenized copper complex for carbene transfer reactions onto various types of substrates, including the formation of a cyclopropene.[38]

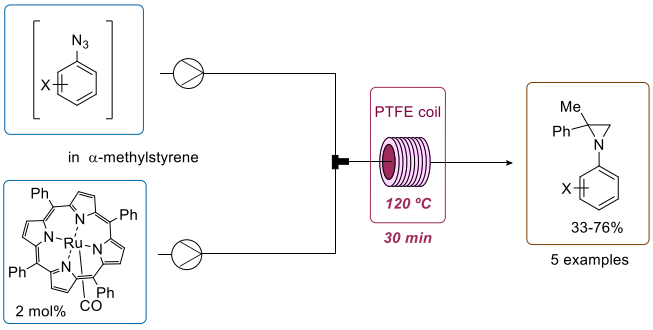


Scheme 9. Enantioselective cyclopropanation of α,β-unsaturated aldehydes.

Caselli and coworkers used supported hydrogen-bonded (SHB) chiral copper(I) complexes of pyridine containing tetraazamacrocyclic ligands Pc-L* using CO_2 as a transport vector. Cyclopropane products from both aromatic and aliphatic olefins were obtained in good yields with enantiomeric excesses up to 72%.[39]

2.2. Azidirinations

Aziridinations include nitrenation of alkenes and methylidenation of imines, generally involving metal catalysis.[40] The group of Gallo developed a straightforward two-step synthesis of *N*-arylaziridines, with Ru(porphyrin)CO as catalyst and no need of purification of the intermediate azide, which is formed from anilines in flow with an intermediate manual separation. The final *N*-arylaziridines were obtained in moderate to good yields (33–76%, Scheme 10).[41] Later, the same group compared the use of different ruthenium and cobalt based porphyrins under a traditional batch methodology and under continuous flow conditions. Cobalt-based porphyrins presented higher chemical efficiency under flow condition while higher yields were observed in traditional batch process using Ru-based ones.[42]

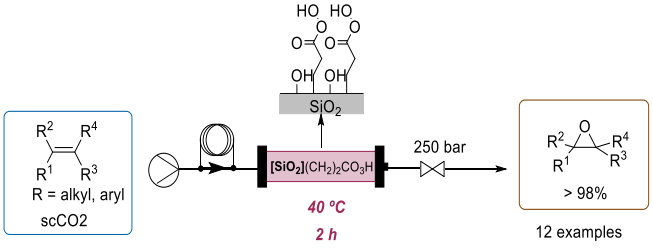


Scheme 10. Metal porphirines as catalysts for aziridinations.

2.3. Epoxidations

The synthesis of oxiranes is achieved by a wide variety of alternatives, such as the use of organic peroxy-acids, air oxidation, hypochlorites, dioxiranes or hydrogen peroxide.[43]. The large scale synthesis of ethylene oxide was described in 2002 using a stainless-steel mixing unit, with two different inlets, one for ethylene and the other for oxygen. Nitrogen was used as carrier gas. The catalytically active part of the reactor consisted of stacked and microstructured silver foils in parallel-flow geometry. The use of silver with its high thermal conductivity lead to a uniform heat distribution and therefore an enhanced process performance.[44] Afterwards, silver/α-alumina catalysts wash-coated in stainless steel microchannels were utilized. The experiments were carried out under atmospheric pressure, varying the temperature from 220 to 300 °C and the total gas flow from 5.4 to 10.5 cm^3/min.[45] The same group did a study on pretreatment strategies such as oxidative pretreatment with oxygen, reductive pretreatment with hydrogen, thermal treatment in inert gas (He) and exposing the catalyst to DCE (1 ppm) prior to a standard thermal pretreatment. Highest ethylene oxide selectivity (82.1%) at an industrially relevant ethylene conversion (7.0%) was reached with the dried catalyst pretreated with DCE.[46]

The group of González-Núñez performed an epoxidation of olefins. Anhydrous 2-percarboxyethyl-functionalized silica, a recyclable supported peracid, was used in supercritical carbon dioxide at 250 bar and 40 °C under flow conditions. This procedure simplifies the isolation of the reaction products and uses only carbon dioxide as a solvent under mild conditions. Yields were almost quantitative except for alkenes carrying strong H-bond donor/acceptor substituents, which outperforms batch methodology. Moreover, the solid reagent can be easily recycled by a reaction with 30% hydrogen peroxide in an acid medium (Scheme 11).[47]

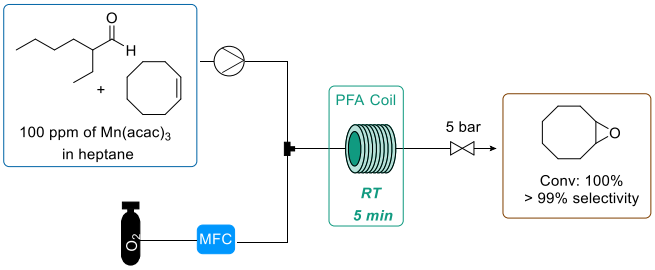


Scheme 11. Epoxidation of olefins using a recyclable supported peracid.

One traditional approach for epoxidations is the use of *m*-chloroperbenzoic acid (*m*-CPBA). However, it is shock sensitive and can deflagrate, requiring care while carrying out the reactions and during workup. Using flow methods *m*-CPBA was generated *in situ*, and converted cyclohexene into high quality cyclohexene oxide. The peracid was obtained within few seconds at room temperature by reacting *m*-chlorobenzoyl chloride with hydrogen peroxide.[48] Moreover, Gao, Chen and coworkers used either *m*-CPBA or AcOOH as oxidizing agents for asymmetric epoxidations of electron-deficient olefins in high yields (up to 90%) and excellent enantioselectivities (up to 92% *ee*).[49]

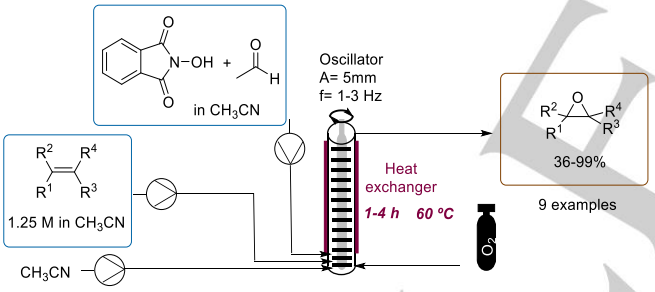
The Mukaiyama epoxidation is a very mild and selective process which is performed using molecular oxygen as the ultimate oxidant that can be performed with or without transition metal catalysis. It was studied using a segmented flow reactor evaluating different metal catalysts and catalyst loadings. Full conversion of *cis*-cyclooctene with high selectivity (>99%) into

cyclooctene oxide was reached in 5 min using 2-ethylhexanal as a sacrificial co-reductant, 100 ppm of Mn(II) as the best catalyst and 5 bar of oxygen (Scheme 12).[50] The same group did the epoxidation with methyloleate as an example of an unsaturated fatty materials. With similar conditions, a mixture of *cis*- and *trans*-epoxides of methyl oleate (25/75) were prepared in less than 4 min with a >99% selectivity toward the epoxide.[51]



Scheme 12. Mukaiyama epoxidation of cyclooctene.

An improved Minisci epoxidation process suitable for olefins was performed by Bjørsvik and coworkers. The improved process is based on the original batch protocol, redesigned, and redeveloped for continuous-flow conditions by using a novel multijet oscillating disk (MJOD). While the batch protocol requires a reaction time of 24–48 h, the continuous flow process only requires a residence time of 1–4 h for the same substrates with good yields and very high selectivity (Scheme 13).[52]

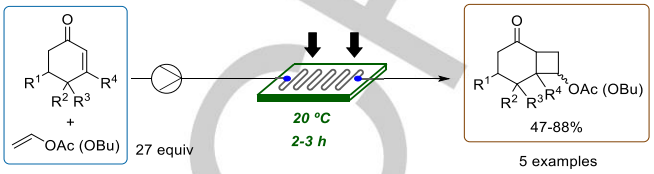


Scheme 13. Epoxidation using multijet oscillating disk (MJOD).

3. [2+2] Cycloadditions: 4-membered rings

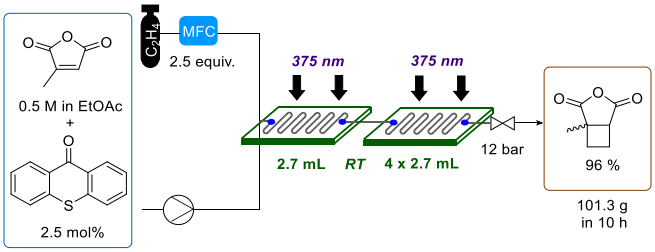
3.1. Photochemical [2+2] cycloaddition onto carbocycles

The [2+2] photocycloaddition is one of the most frequently used cycloaddition reactions to access carbocyclic products and undisputedly the most frequently used photochemical reaction. It involves two olefins, one of which is required to be excited by ultraviolet (UV) or visible light. In the last decade, it has suffered a breakthrough due to the development of flow photochemistry.[21] One of the earliest examples was reported by Ryu's group and was executed in a microflow system using glass-made microchannels. The reaction of cyclohexenones with vinyl acetates under irradiation gave [2+2] cycloaddition products in good yield with a residence time of 2 h (Scheme 14). In batch, only a 8% of conversion was achieved by that time.[53] Later, the same group studied this reaction in combination with compact light sources such as low-power black lights and UV LEDs in Foturan glass or quartz made reactors. Slightly better results were achieved using a glass-covered microreactor with a compact light source, such as a 15-W black light.[54] An intramolecular version of this process leading to similar products was recently published using an ionic liquid photosensitizer that facilitates the purification of the photocycloaddition product.[55]



Scheme 14. The [2+2] photocycloaddition into glass-made microchannels.

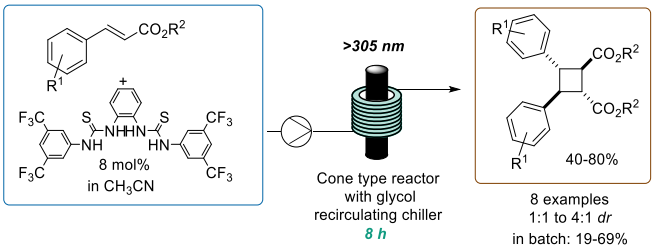
Ethylene gas, a common substrate to prepare simple cyclobutanes, further exemplifies the benefits of performing gas−liquid reactions under flow conditions. Kappe and collaborators used a flow reactor capable of gas handling and LED wavelength/power screening, to carry out reactions of ethylene with citraconic anhydride and different sensitizers. They described a scale-up process using a Corning G1 Photo Reactor with five 2.77 mL plates giving 101.3 g of the desired cyclobutane in 10 h (96% yield, Scheme 15). For these transformation, maleic anhydride has a relatively high triplet energy thus making some sensitizers ineffective in triplet transfer.[56] However, Corcoran Lévesque and coworkers found viable light sources such as monochromatic 365 nm LEDs, with which maleic anhydride reacted with ethylene producing 2.4 g/h of the cyclobutane with 85% conversion using a 140 mL reactor at -70 °C and 5 mol% of benzophenone as sensitizer.[57] Ethylene gas was used in an asymmetric [2+2] photocycloaddition reaction of a cyclohexanone at -78 °C, achieving 100% of conversion in 1 min with a *d.e.* of 52%.[58] In these cases, both the use of gases and photochemistry in flow produce a throughput which is unthinkable using batch methodologies.



Scheme 15. The [2+2] photocycloaddition of ethylene with citraconic anhydride.

The reaction between maleimides and unfunctionalized alkenes was carried out using a custom-made UV-flow reactor. Best conversions were observed when 10 mol% of the photosensitizer thioxanthone was employed. Reaction times were very short, allowing for complete conversion of the maleimide in roughly 1 min.[59] [2+2] Photocycloaddition in flow has also been applied in polymer synthesis by the same group. In the field of polymer chemistry, such reactions are often used for crosslinking.[60]

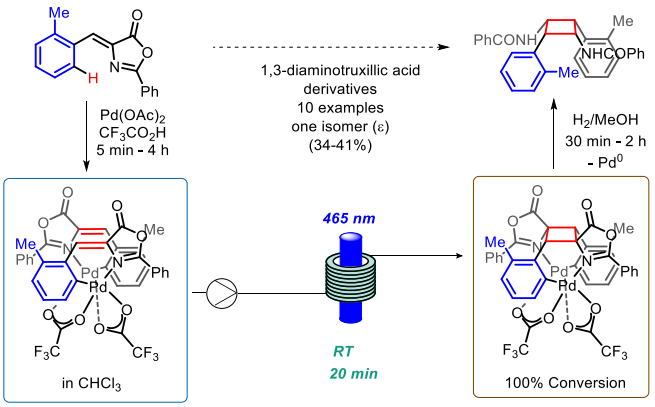
Cyclobutanes derived from the dimerization of cinnamic acids are the core scaffolds of many molecules with potentially interesting biological activities (truxillic and truxinic acid derivatives). The group of Beeler developed a flow photochemistry platform for their synthesis with a cone reactor It consist of a conical reactor, wrapped with FEP tubing which sits in small grooves that promote heat transfer, attached to a glycol recirculating chiller and irradiated by a UV source. Different cinnamate derivates were synthesized in moderate to good yields in a relatively long residence time (8 h), and 8% of the catalyst (Scheme 16). The ability of bis(thiourea) as catalyst was also proved to facilitate better reactivity and moderate diastereoselectivity in the reaction. All experiments were replicated using the flow reactor and in batch, and in the presence/absence of catalysts. Better results were achieved when using the flow reactor with bis(thiourea).[61]



Scheme 16. [2+2] Cycloaddition of cinnamic acids.

This group investigated later how to accelerate the reaction by employing liquid-liquid slug flow. In most cases, a four-fold acceleration in reaction time was observed with equivalent or superior yields. This is attributed to increased mixing that is derived from circulatory patterns within liquid-liquid slug flow regimes and a thin film that enhances photon flux by shortening the UV path length. Residence time was reduced to only 110 min, and consequently, this approach is more scalable than the previous one (productivity of 360 mg/h).[62]

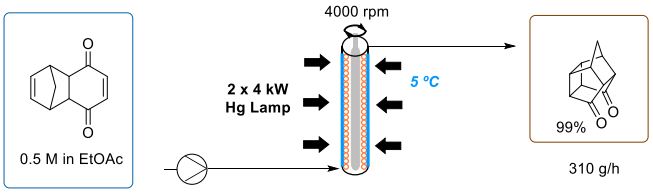
On the other hand, a wide variety of 1,3-diaminotruxillic acid derivatives were prepared as the ε-isomers, by an optimized three-step method. This procedure involves the regioselective ortho-palladation of the oxazolones, a [2+2]-photocycloaddition of the ortho-palladated complexes induced by irradiation with an LED light source, and the liberation of the truxillic acid derivatives as dialkyl esters by hydrogenation in alcoholic media. Quantitative yields were obtained when using the flow reactor in 20 min, which is faster than the batch protocol, which could only be carried out into NMR tubes (Scheme 17).[63]



Scheme 17. [2+2] Cycloaddition for the preparation of 1,3 diaminotruxillic acid derivatives.

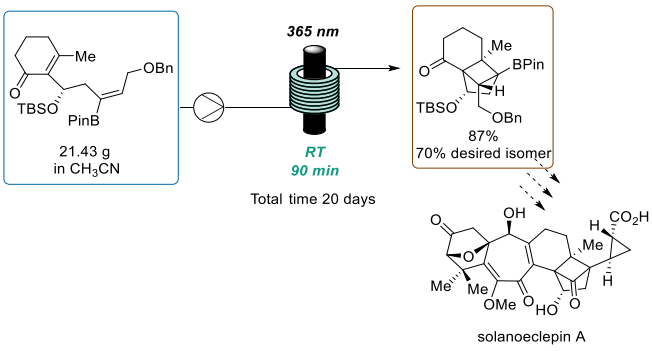
The same group disclosed a metal free cycloaddition to give 1,3-diaminotruxillic cyclobutane derivatives in very good yields. A novel setup is presented for the in-line monitoring of the continuous flow photoassisted synthesis by NMR spectroscopy, with the microreactor irradiated by LED lamps, dramatically reducing reaction times to only 30 min The mechanism of this [2+2]-photocycloaddition has been calculated by density functional theory (DFT) methods, explaining all experimental findings. The reaction takes place through a stepwise formation of two new C–C bonds through a transient diradical singlet intermediate.[64]

Recently, a novel type of reactor, namely scalable continuous Taylor vortex reactor for both UV and visible photochemistry, was used for [2+2]-photocycloadditions. The reactor consists of a transparent cylindrical outer vessel with a second smooth cylinder fitted coaxially inside it. Between the two cylinders there is a relatively narrow gap which contains the reaction solution. The inner cylinder is rotated at relatively high speed, generating so called “Taylor” or “Taylor−Couette” vortices, toroidal vortices threaded around the inner rotating cylinder (Scheme 18). Scales of up to 7.45 kg per day were obtained with nearly quantitative yields.[65]



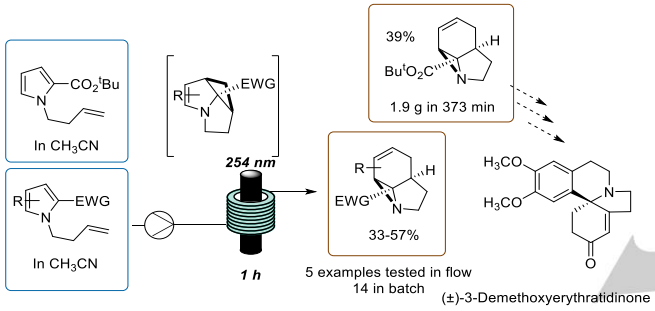
Scheme 18. A vortex reactor used for [2+2]-photocycloadditions.

Photochemical flow [2+2]-cycloadditions have been used in the enantioselective formal synthesis of solanoeclepin A. The key step was an intramolecular [2+2] photocycloaddition, performed in high yield on irradiation at 365 nm on 20 g scale in a flow system (Scheme 19). Yield (68%) and scalability were improved in flow. However, around 20 days were necessary to get full conversion (1.5 h of residence time and pump flow: 70 µL/min). The desired product was isolated after an additional step in 32% yield with a diastereoselectivity of 70%.[66]



Scheme 19. [2+2] Cycloaddition in the synthesis of Solancepin A.

A set of complex tricyclic aziridines were synthesized by the group of Booker-Milburn from pyrroles through a photocycloaddition and rearrangement that starts with a [2+2] cycloaddition. Gram quantities of these complex products could be produced by using a bespoke flow reactor. 0.91 g (51% yield) was produced in 1 h, which means a productivity of 21.8 g/day. A couple of examples were performed in the flow reactor demonstrating higher productivity and yield (Scheme 20).[67] These complex molecules, which are produced in a gram scale, could be later modified with different reactions such as Tsuji–Trost type aziridine ring-opening using carbon-nucleophiles; Pd-catalysed [3+2] cycloaddition of aldehydes and imines; or a stereo-controlled formation of tricyclic fused β-lactams.[68] What is more, the same group described a 5-step total synthesis of (±)-3-demethoxyerythratidinone, a natural alkaloid, from a simple pyrrole derivative, being the key step the formation of the tricyclic aziridine in flow. This was produced in gram quantities, which would have been very difficult to achieve in batch due to the high dilution and irradiation times required.[69]

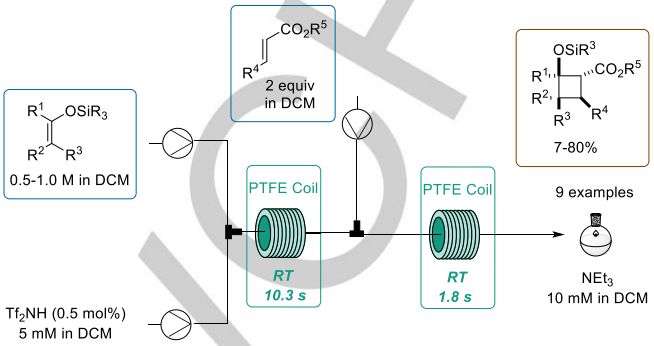


Scheme 20. Synthesis of comples tricyclic aziridines *via* [2+2] cycloaddition.

The versatility and simplicity of flow photochemistry allow its use in many different examples using homemade photoreactors. Examples found in the recent literature are: the Lophtor reactor for intramolecular [2+2] enone cycloadditions that improves yields and reduces drastically reaction times compared to batch procedures;[70] a glass-made microreactor for the cycloaddition of 2-(2-alkenyloxymethyl)naphthalene-1-carbonitriles;[71] or a meso-scale continuous flow-photochemistry platform which enabled 100 g reactions of dihydrofuranes with alkenes.[72] More recently, a flow photocycloaddition reaction system with FEP-capillary coiled around a high pressure mercury lamp was presented. It was used in intramolecular [2+2] photocycloadditions to produce oxabicycles.[73] Finally, a home-made continuous flow-photochemistry set-up with 16 UV lamps a 19 m FEP tubing reactor was used to perform an intramolecular [2+2]-photocycloaddition reaction to prepare benzobicyclo[3.2.l]octadiene, with similar yields than in batch but much higher productivity.[74]

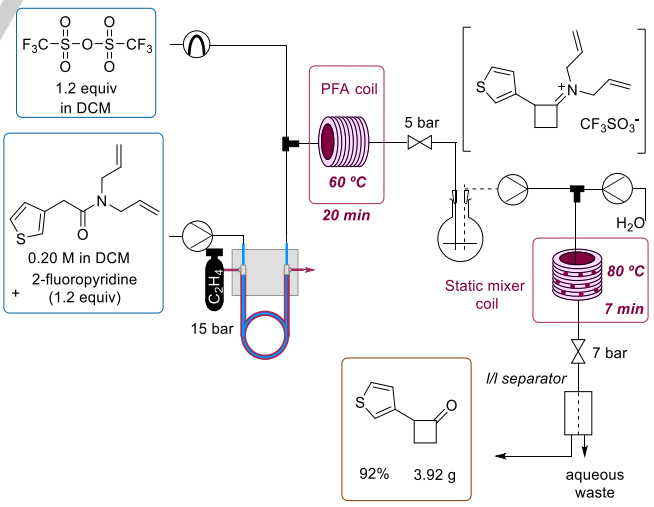
3.2. Non-photochemical [2+2] cycloaddition to carbocycles

Less common than photochemically promoted, are thermally promoted reactions between ketenes and alkenes or [2+2] cycloadditions of silyl enol ethers with alkenes catalyzed by strong acids. Using flow chemistry, we could find one example of a [2+2] cycloaddition catalyzed by the superstrong acid triflic imide (Tf_2NH) at room temperature. The microreactor method allows the [2+2] cycloaddition of unstable silyl enol ethers and acrylates. This process was unsuccessful in batch because of a number of side reactions produced due to the instability of the starting materials and products under the strong acid conditions (Scheme 21). High diastereoselectivity was only achieved at -78 ºC (96:4).[75]



Scheme 21. Acid promoted [2+2] cycloaddition.

2-Substituted cyclobutanones were prepared *via* [2+2] cycloaddition of keteneiminium salts and ethylene gas using a tube in tube reactor. Ehtylene pressure was set to 15 bar, while the system pressure was kept at 5 bar to ensure the entrance of the gas. The substrate, with 2-fluoropyridine, and triflic anhydride were injected through different pumps. Different products were synthesized after an aqueous quench in batch with moderate to excellent yields (18 examples, 47-96%). A scale-up was also performed, in which the collected solution was pumped again in order to mix it with an aqueous solution at 80 ºC. Afterwards both phases were in-line separated thanks to a Zaiput membrane. 3.92 g (92% yield) were obtained after purification (Scheme 22).[76]



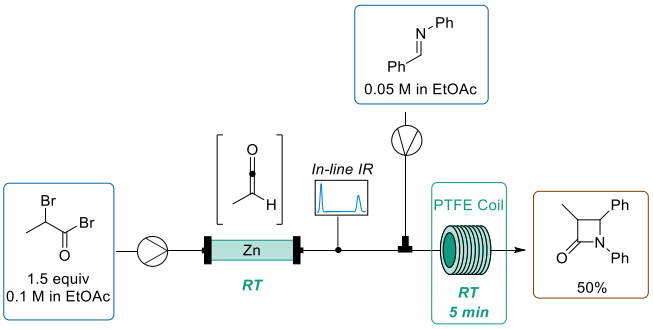
Scheme 22. [2+2] cycloaddition of keteneiminium salts and ethylene.

An emerging field of research is the development of self-optimizing reactors which consist of well-known setups equipped with monitoring technologies and the use of optimization algorithms. The [2+2] cycloaddition between ketenes and

cyclohexene was optimized by the group of Jensen and Jamison using an automated flow platform that combines different modules and in line analytics with integrated software control. After optimizing 5 different variables, a 77% yield in 11 min was achieved with a productivity of 268 mg/h of the desired product.[5] The [2+2] cycloaddition between *in situ* generated 1,3-bifunctional allenes and C_{60} was carried out using a continuous flow packed-bed reactor and silica-supported tertiary amine.[77] On the other hand, cyclobutenones were identified as secondary products when forming ketenes in flow and reacting them to form amides and esters. Without adding alcohols or amines, the cycloadduct was obtained with 95% yield in 10 min at 180 ºC.[78]

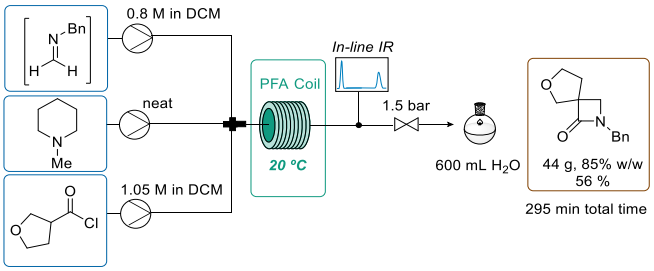
3.3. β-lactams: The Staudinger synthesis

One of the most frequently used method for the synthesis of the β-lactam ring is the venerable Staudinger synthesis. It consists of a stepwise [2+2] cycloaddition between an imine and a ketene.[79] The generation of ketenes in flow is an interesting application of continuous methods and has been reported by passing α-brominated acyl halides through a packed bed reactor, which is fulfilled with activated zinc dust and glass beads. The formation of ketenes was followed by an in-line IR spectrometer. In one case the subsequent reaction was also done under a continuous protocol, using another pump to add the imine. The final β-lactam was formed after 5 min of residence time in 50% yield (97% of yield using the continuous protocol only to prepare the ketene, Scheme 23).[80]



Scheme 23. Staudinger synthesis generating the ketene in a Zn packed bed reactor.

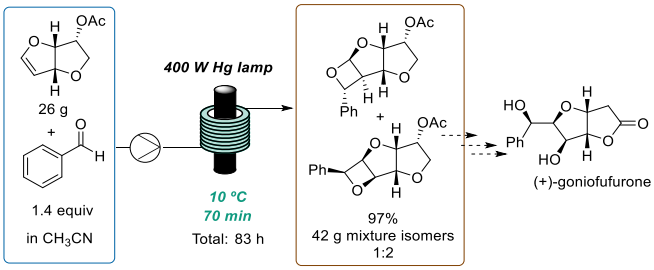
Another approach from the same group involved the *in-situ* formation of ketenes trough a Wolff Rearrangement of α-diazoketones. The reaction was performed in 7 min at 165 ºC and 80 W thanks to a continuous flow microwave apparatus.[81]
In another recent report the synthesis of a spiro β-lactam that serve as building block for MCH1 receptor antagonists was reported. This set up allowed a production of 44 g in 295 min. (56% yield, Scheme 24).[82] In these cases, flow techniques are safer (ketenes are highly reactive and toxic) and easier to scale up, even though they generally do not improve yields.



Scheme 24. Multigram β-lactam synthesis using the Staudinger reaction.

3.4. The Paternó-Büchi reaction

The Paternó-Büchi reaction is a [2+2] photocycloaddition between an electronically excited carbonyl compound and an alkene leading to oxetanes.[83] One of the earliest examples was the cycloaddition of 4-penten-1-ol with acetone in a microchannel reactor irradiated with 313 nm light in aqueous solution.[84] The group of Kakiuchi studied the asymmetric Paternò–Büchi-type photoreaction between 2,3-dimethyl-2-butene and benzoylformic acid ester with a chiral menthyl auxiliary in a continuous-flow microcapillary photoreactor. Yields and enantiomeric excess were similar to batch conditions (around 50% each), but the time needed to perform the reaction was decreased drastically using the flow reactor.[85]
The group of Booker-Milburn reported a photochemical approach to the cytotoxic lactone (+)-goniofufurone. The Paternò–Büchi photocycloaddition is performed over an enol ether, derived from the readily available sugar D-isosorbide. Although the batch irradiation proceeded in good overall yield (93%), the reaction was slow and required running at fairly high dilution which rather restricted scaling up. Using a three-layer FEP flow reactor in conjunction with a 400 W medium-pressure lamp, they were able to considerably upscale the productivity of this key reaction, enabling the formation of over 40 g of the mixture of isomers (97% isolated yield) in a single 83 h run. Interestingly, the correct stereochemistry in the major isomer was achieved (Scheme 25).[86]



Scheme 25. Multigram Paternó-Büchi reaction for (+)-goniofufurone synthesis.

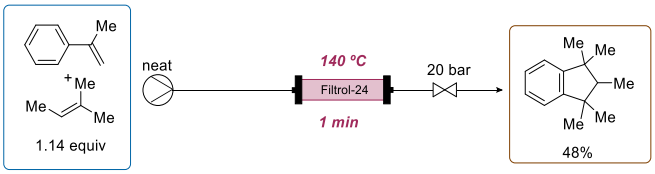
Finally, a self-optimizing photoreactor system was developed for the synthesis of oxetanes from benzophenone and furan derivatives using UV-light irradiation. The reaction mixture flow stream passed through an IR spectrometer before and after the irradiation. The recorded data was constantly analyzed by computer software which, based on this information controlled the pump unit. After setting the optimum residence time for the reaction, both substrates were pumped individually and, in the same way, concentrations were automatically optimized. A total

of 13 different products were synthesized in 83 min with generally excellent yields.[87]

4. 5-membered rings

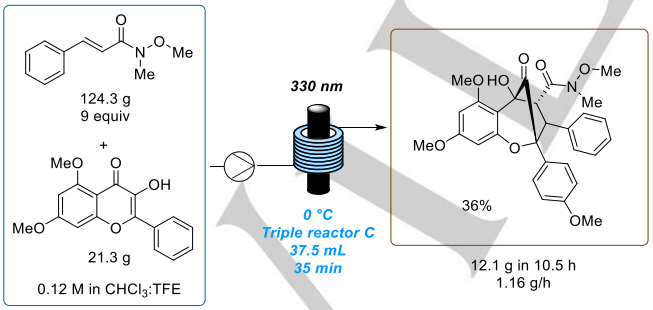
4.1. Carbocycles: [3+2] cycloadditions

An example of a [3+2] cycloaddition between isoamylene and methylstyrene in a microreactor was described in 2010, which was compared with industrial semi-batch techniques. A solid acid supported catalyst (Filtrol-24) was used as an alternative to conventional aqueous sulfuric acid catalysis, and they achieved higher yields and 5 times productivity using the microreactor system (Scheme 26).[88]



Scheme 26. [3+2] Cycloaddition affording a cyclopentane.

Beeler and coworkers reported the development of continuous flow photoreactors for large scale ESIPT (excited-state intramolecular proton transfer)-mediated [3+2]-photocycloaddition of 2-(*p*-methoxyphenyl)-3-hydroxyflavone and cinnamate- derived dipolarophiles. This reaction is difficult to scale up in batch as it requires long irradiation times (typically 12 h), low temperature (0 ºC), and high dilution (30 mM). After a study of conditions, a large scale [3+2] photocycloaddition using a triple reactor at 0 ºC was performed, with 3-hydroxyflavone and a dipolarophile (*N*-methoxy-*N*-methylcinnamamide) along 10.5 h. The desired product (12.1 g, 36%) were obtained after purification (Scheme 27). Moreover, a set of 6 different cycloadducts were synthesized in moderate yields in 35 min.[89]

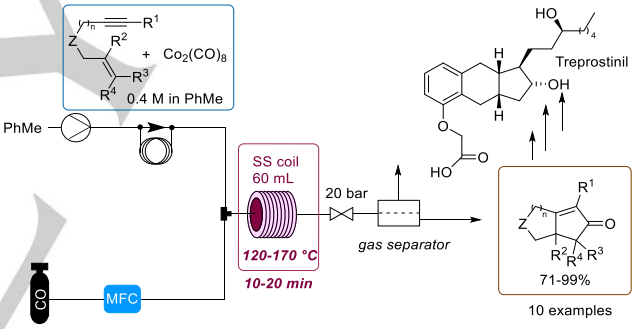


Scheme 27. [3+2] Photocycloaddition scale up.

Recently, Stephenson and coworkers presented a photochemical conversion of aminocyclopropanes into 1-aminonorbornanes *via* formal [3+2] cycloadditions initiated by homolytic fragmentation of amine radical cation intermediates. A flow protocol was presented as a viable option for this chemistry. Nevertheless, the experiments using 1 g of substrate were more successful (productivity, catalyst loading, isolated yield…) in batch than using the flow set up. The authors mentioned that they are currently searching reaction types, photocatalysts, and flow setups to develop a more robust flow protocol.[90]

4.2. Carbocycles: the Pauson-Khand reaction

The Pauson–Khand reaction is a formal [2+2+1] cycloaddition of an alkyne, an alkene and a carbon monoxide unit to give a cyclopentenone.[91] The first example of a Pauson–Khand reaction in a photochemical flow microreactor was reported using previously prepared and purified cobalt hexacarbonyl-alkyne complexes which were pumped with alkenes through a microreactor that was irradiated with a medium pressure mercury lamp.[92] Our group developed an intra- and intermolecular Pauson–Khand reaction protocol using catalytic amounts of $Co_2(CO)_8$ in a plug flow reactor. In this case, high temperatures were used instead of a photochemical induced reaction, and carbon monoxide was introduced through a MFC. Several scale ups were performed in gram scale to demonstrate the robustness and scalability of the process (Scheme 28).[93] Moreover, this protocol was also used in the key step of the synthesis of treprostinil, a PGI2 analog. Compared to batch reported synthesis, this represents a catalytic, fast and scalable procedure, with safer and controlled use of CO.[94]

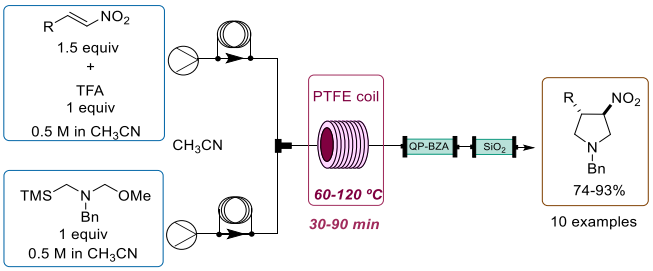


Scheme 28. General set up for the Pauson-Khand reaction in flow.

4.3. Nitrogen containing heterocycles: The Huisgen reaction

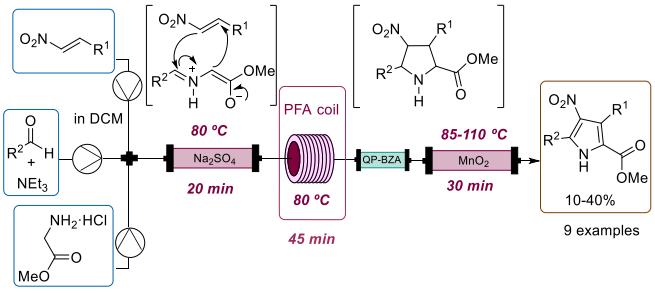
The 1,3 dipolar cycloaddition, reported by Huisgen in the 60s,[95] has experienced a great development. These reactions are known to be associated with thermal runaways and delayed exotherms, especially with nitrogen containing dipoles. Thus, they are particularly suitable for flow methodologies.[96]

5-Membered rings bearing a single nitrogen atom, can be generated from unstabilised azomethine ylides and dipolarophiles within a flow microreactor. The Ley's group used either TFA (Scheme 29) or supported $TMSCF_3$ to generate the reactive dipole and applied a series of supported metal scavengers to obtain relatively pure products. A set of 15 different pyrrolidines were produced in good to excellent yields [97]



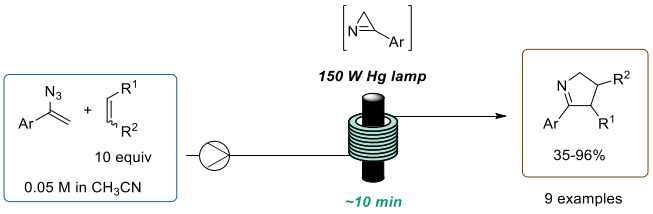
Scheme 29. Cycloaddition to afford nitropyrrolidines using homogeneous TFA.

Moreover, a library of trisubstituted drug-like pyrrolidines was prepared and further modified using microreactor technologies. Thus, after the cycloaddition, the outlet of the reactor coil was connected in series with the H-cube® system utilizing a small cartridge filled with heterogeneous Raney Ni. Pleasingly, it was found that telescoping both reactions gave the desired amino pyrrolidines in high yield (91-96%) after removal of the solvent.[98] Later, nitropyrrolidines, nitropyrrolizines (8 examples, 76-89% yield) and nitropyrroles were produced using a three-component coupling reaction between glycine esters, aldehydes, and nitro alkenes. Each of these solutions was introduced separately, mixed in a 4-way connector, and directed into a heated glass column filled with anhydrous sodium or magnesium sulfate to promote the imine formation. Then, the cycloaddition between the nitro alkene and the *in situ* formed stabilized azomethine ylide took place in the reactor. Finally, in-line work-up with the a benzylamine scavenger (QP-BZA) removed residual starting materials. Additionally, coupling another cartridge with activated MnO_2 at elevated temperatures (85-110 °C), afforded clean conversion to the corresponding pyrroles (Scheme 30).[99]



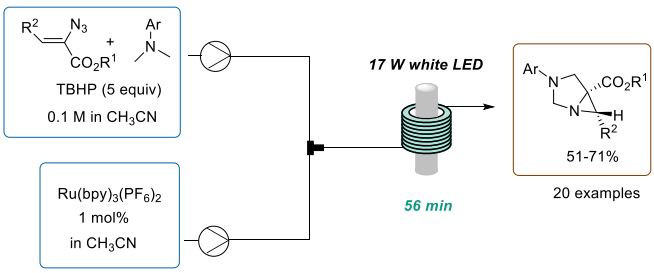
Scheme 30. Continous synthesis to pyrrolidines with [3+2] cycloaddition.

Similar conditions were applied by Fray and coworkers for [3+2] dipolar cycloaddition reactions of an unstabilised azomethine ylide precursor with electron-deficient alkenes in the presence of catalytic trifluoroacetic acid. Under optimized conditions, 30 g (87% yield, after purification) of ethyl *N*-benzylpyrrolidine-3-carboxylate were prepared in 1 h.[100] In another approach towards 2*H*-pyrroles, 2*H*-azirines were photochemically prepared *in situ* from vinylazides, and reacted with electron-deficient alkenes (Scheme 31). Furthermore, a dihydrooxazole, and a triazole were synthetized starting from hydroxypropenyl azide, and vinyl azide with diisopropyl azodicarboxylate, respectively.[101]



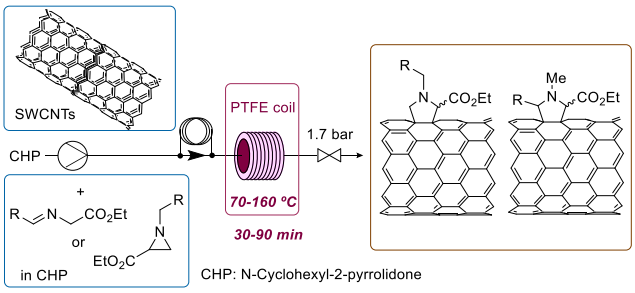
Scheme 31. [3+2] Photocycloaddition using vinyl azides.

Fused β-carbolines were synthesized *via* a visible light photoredox catalyzed oxidation/[3+2] cycloaddition/oxidative aromatization reaction. One of the examples reported was done using a flow set up with slightly better yields (75%) than in batch conditions (69%).[102] The same group presented a synthesis of an aziridine ring using a photocascade catalytic flow process catalyzed by $Ru(bpy)_3(PF_6)_2$/TBHP. The sequence consists of photosensitization, photoredox catalysis and [3+2] cycloaddition reaction.[103] Another photocatalytic flow process was used to synthesize bicyclic aziridines from *N,N*-dimethylanilines and α-azidochalcones, using the same catalyst and photosensitizer. The resulting 1,3-diazabicyclo[3.1.0]hexane derivatives were prepared in good yields (Scheme 32), which meant more selectivity and productivity than in batch (51% in 12 h).[104]



Scheme 32. Photocascade synthesis of diazabicyclo[3.1.0]hexane.

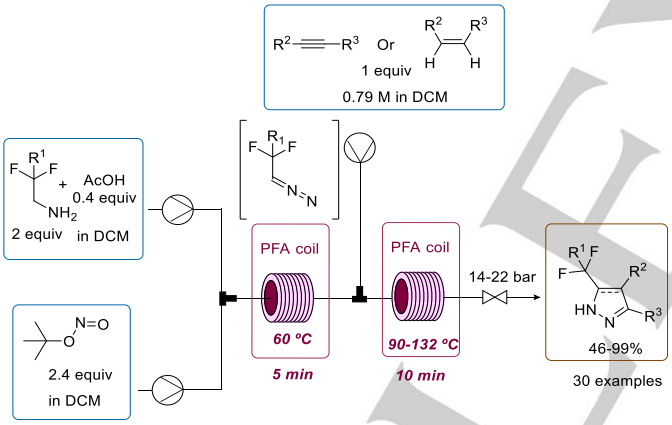
This sort of cycloadditions can also be found in carbon nanotube (CNT) functionalization. A continuous-flow cycloaddition between azomethine ylides and carbon nanotubes reduced reaction times and increased productivity compared with traditional flask synthesis (Scheme 33).[105] The flow methodology was also extended to the fast and effective addition of diazonium salts to CNTs. Besides reducing processing time, the flow approach allows to control the degree of CNTs functionalization, leading to derivatives with enhanced solubility.[106]



Scheme 33. [3+2] Cycloaddition for functionalization of SWCNTs.

Kobayashi and coworkers developed a continuous flow protocol to form 3-substituted glutamic acid derivatives by 1,4-addition of glycine derivatives to α,β-unsaturated esters. Early experiments showed poor selectivity towards the desired product, due to the competition with the pyrrolidine formation *via* [3+2] cycloaddition. Great selectivity was achieved by using $CsF{\cdot}Al_2O_3$ as a highly efficient, environmentally benign, and reusable solid-base catalyst.[107]

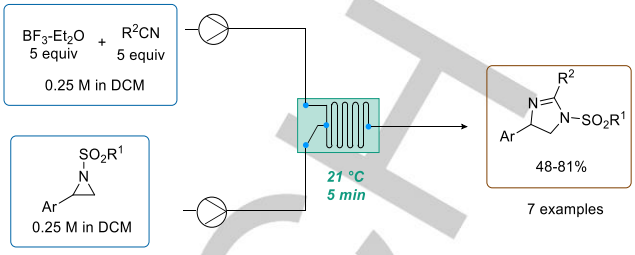
Regarding 5-membered ring diaza-heterocycles, a library of different highly substituted pyrazoles and pyrazolines were prepared by Britton and Jamison. The flow set up consist of two different modules. In the first one 2,2-difluoromethyl diazomethane or 2,2,2-trifluoromethyl diazomethane were prepared. Then, the alkane/alkyne was added and the [3+2] cycloaddition was performed in the second module. The authors demonstrated the importance of having two different modules to achieve better yields. Following this methodology 30 products were prepared in moderate to excellent yields in a total time of 15 min (Scheme 34). Moreover, a telescoped synthesis, of measles therapeutic AS-136A, was completed with 5 modules, in a total residence time of 32 min (1.76 g/h, 34% of isolated yield), where the first reaction was the cycloaddition.[108] Prior to this work, Koenigs and coworkers developed flow and batch protocols for the formation of difluoro- and trifluoro diazoalkanes. In addition to the improvement of scalability and safety, better yields were found when doing it in flow. However, the subsequent cycloaddition with vinylsulfone was performed in batch.[109]



Scheme 34. [3+2] Cycloaddition using di(tri)fluoromethyl diazomethane.

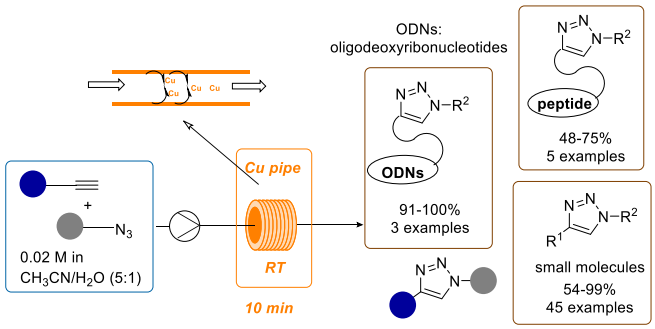
The synthesis of 1,4-disubstituted pyrazoles was achieved by the cycloaddition reaction of sydnones and terminal alkynes. The authors used a silica-supported copper catalyst which could promote the formation of the Cu-acetylide and, after cycloaddition, an exchange of the cuprous pyrazole with an alkyne to allow the catalyst recovery. Scalability of this process is limited due to the need of high dilution. In order to produce 72 mg of the desired pyrazole, 5 h were needed.[110]

Imidazolines were prepared by formal [3+2] cycloaddition of aziridines with nitriles under continuous flow. Using boron trifluoride as a Lewis acid in combination with various nitriles, imidazolines were produced in moderate to good yields from 2-aryl aziridines in 5 min (Scheme 35). A single regioisomer was seen in all cases by way of initial nucleophilic ring opening at the more substituted carbon by the nitrile, prior to ring closure. A telescoped synthesis without isolation of the aziridine was also proved.[111]



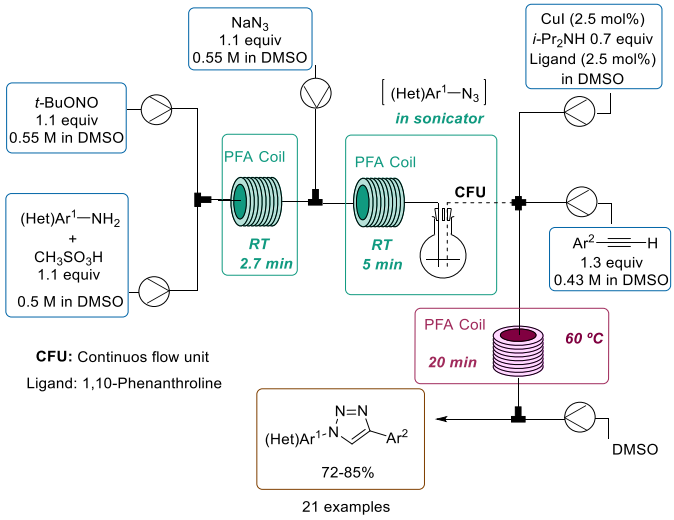
Scheme 35. [3+2] cycloaddition of aziridines with nitriles.

Triazoles have emerged as among the most exploited structures in contemporary heterocyclic chemistry. Triazole chemistry has recently received a significant impulse from the pioneering works of Sharpless[112] and Meldal[113] on Cu(I)-catalyzed alkyne–azide cycloaddition (CuAAC). Thanks to its excellent fidelity and compatibility, CuAAC has become the best definition of the "click chemistry" concept[114] and has paved the way for triazole chemistry to achieve an incredible number of applications. Furthermore, triazoles are an interesting class of heterocyclic compounds, with a broad spectrum of bioactivities. Herein, due to the great amounts of works in the field of CuAAC in flow, we will discuss only results published after the 2015 specific review of Ötvös and Fülhöp.[115] Following the classification of that review, we can differentiate these cycloadditions into two groups: Cu-free or Cu-catalyzed, including polymer bound Cu-catalysts, metal Cu, homogenous or heterogeneous catalysts. Other recent reviews have addressed the advantages of recoverable variants of the homogeneous or quasi-homogeneous catalysts of this reaction,[116] or the use of copper-made flow reactors.[117] The most relevant recent work was published by Burley, Watson and coworkers. Their protocol leveraged an engineering problem to chemical advantage: solvent-mediated Cu pipe erosion generates ppm levels of Cu *in situ* under laminar flow conditions. This was proved to be sufficient to catalyze the CuAAC reaction. The authors reported more than 50 examples, including small molecule alkynes and azides, fluorophores, marketed drug molecules, peptides, DNA, and therapeutic oligonucleotides. Using ppm amounts of Cu the reaction could not be replicated in batch, while in flow it was catalyzed in short residence time, at room temperature and without overoxidation of labile groups on the substrate. Furthermore, products contained less than 20 ppm of residual Cu (Scheme 36).[118] Approaches form other groups have included the fabrication of a copper-functionalized lignocellulosic microreactor (Cu-LμR) from bamboo culms that showed minimal leaching of copper,[119] and the design of a nanoporous AuCu membrane for the catalysis of the reaction with high throughput working at low pressure.[120]



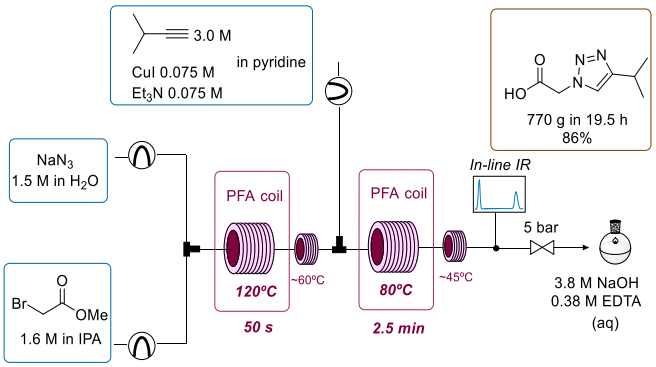
Scheme 36. CuAAC catalyzed by ppms of Cu originated due to pipe erosion.

The group of Organ and Maguire reported a telescoped three-reactor flow diazotization, azidodediazotization, and [3+2] dipolar cycloaddition process from available anilines. The CuAAC was studied in the last steps with several alkynes, and also the [3+2] cycloaddition with either malononitrile or 1,3-ciclohexadione as dipolarophiles. A set of 21 different triazoles were synthesized in good to excellent yields in only 28 min of total residence time and with no need to isolate the organic azides (Scheme 37). The continuous flow unit is a device controlled by software designed to accommodate a broad range of fluids at high pressure without pulsation.[121]



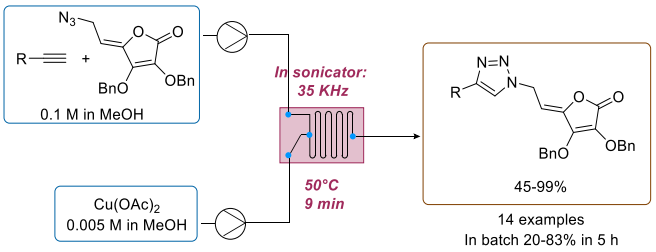
Scheme 37. Homogeneous CuAAC from anilines.

Another reported example of CuAAC in flow showed the synthesis of 2-(4-isopropyl-1*H*-1,2,3-triazol-1-yl)acetic acid using homogeneous catalysis, following Scheme 38. The procedure was tested in multigram scale, obtaining 770 g of the desired product (86% yield) including a final step in batch. Isolation of hazardous intermediates was avoided, and the evolution of the azides was monitored by in-line FT-IR.[122]



Scheme 38. Homogeneous CuAAC.

Another example of an homogeneous CuAAC, using $Cu(OAc)_2$ allowed the synthesis of novel 1,2,3-triazolyl appended 4,5-unsaturated L-ascorbic acid derivatives. The protocol implemented the use of ultrasound within the microflow device to speed up the reaction to the minute range and considerably improved the yield (Scheme 39).[123]

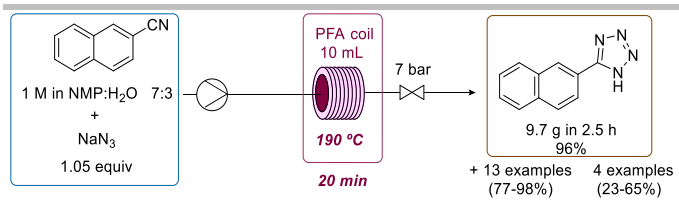


Scheme 39. Homogeneous CuAAC in sonicator.

An example of a supported copper catalyst was reported by Osako, Uozumi and coworkers. They used an amphiphilic resin-supported triazine-based polyethyleneamine dendrimer. The cycloaddition of organic azides with alkynes was completed within 22 s in the continuous-flow system to give the corresponding triazoles in up to 99% yield. Moreover, the continuous-flow system accomplished the long-term continuous-flow cycloaddition for 48 h producing 10 g of a triazole as well as the successive flow reaction producing various kinds of triazoles.[124]

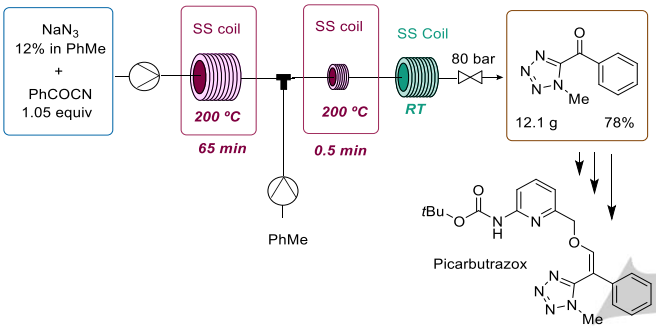
The group of Hessel prepared a Rufanamide precursor, starting from the benzylic alcohol and producing the 1,2,3-triazole in an uninterrupted continuous process. The cycloaddition between the *in situ* formed azide and 1.5 equiv. of (*E*)-methyl 3-methoxyacrylate was performed at 210 ºC within 15 min.[125]

With respect to tetrazoles, Palde and Jamison presented a safe, practical, and efficient flow synthesis of 5-substituted tetrazoles by [3+2] cycloaddition of azides to *p*-toluenesulfonyl cyanide (TsCN) in presence of $ZnBr_2$. It enjoys a broad scope in around 30 min. The hazards associated with HN_3 are essentially eliminated, shock-sensitive metal azides such as $Zn(N_3)_2$ are eschewed, and any residual NaN_3 is quenched in-line with $NaNO_2$. Another method, which was tested in gram scale, used sodium azide which reacted directly with the aryl cyanide (Scheme 40) These issues are collectively possible only because the reactions can be conducted at elevated temperature (190 ºC) in a closed environment with no head space in which HN_3 could accumulate. A closed-system batch process at 190 ºC (microwave or otherwise) would be far too hazardous.[126]



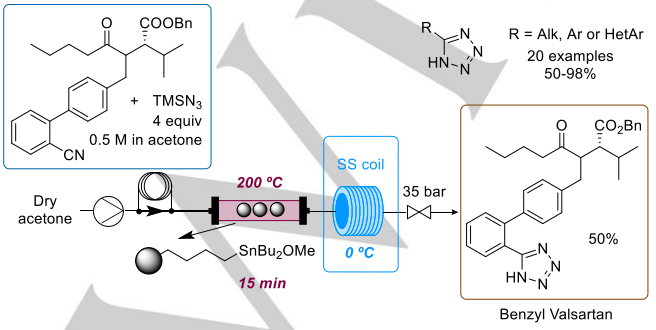
Scheme 40. Gram scale synthesis of tetrazoles in flow.

In another similar protocol, a cycloaddition between benzonitrile and dimethylammonium azide yielded 5-phenyltetrazole dimethylammonium salts.[127] On the other hand, methyl azide in solution was generated in flow, and reacted with benzoyl cyanide at 200 ºC. The resulting 1-methyl-5-benzoyltetrazole was obtained in 78% yield (12 g scale), and it is a key precursor of picarbutrazox (IX), a new potent pesticide (Scheme 41).[128]



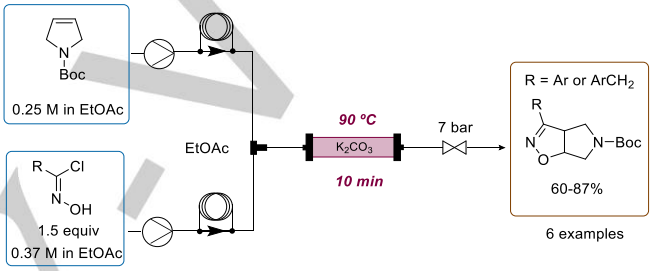
Scheme 41. Cycloaddition to afford a tetrazole precursor of picarbutrazox.

Recently, a new approach to 5-Substituted 1*H*-tetrazoles has been developed by Le Grognec and coworkers. The process involves the reaction between a polymer-supported triorganotin azide and organic nitriles. The azide is *in situ* generated from a polystyrene-supported triorganotin alkoxide and trimethylsilylazide and is immobilized in a packed bed reactor. This approach is simple, fast (7.5 to 15 min) and guarantees a low concentration of tin residues in the products (<5 ppm). The process works with aryl-, heteroaryl- and alkylnitriles and was applied for the synthesis of valsartan, an angiotensin II receptor antagonist (Scheme 42).[129]



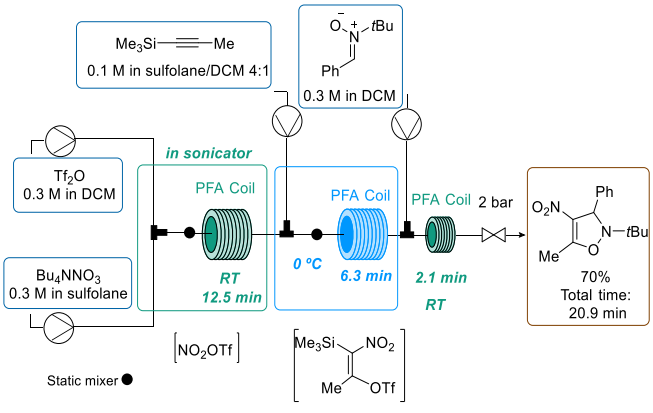
Scheme 42. Heterogeneous catalysis for tetrazole synthesis.

The [3+2] cycloaddition between nitrile oxides and alkynes represents the most important method for the synthesis of isoxazoles. One early example of this kind of cycloadditions in flow was developed by Conti´s group and consisted of a cycloaddition between chloroximes and protected pyrrolines to yield bicyclic isoxazoles, using a polymer-supported base at 90 ºC (Scheme 43). The flow methodology was compared with batch and microwave-assisted procedures. Through the flow-chemistry approach, a reduction in time (days in batch, 1.5 h MW-assisted, 10 min in flow) and an increase in yields (60-87%) were observed.[130] On the other hand, Rincón and collaborators performed an intramolecular [3+2] cycloaddition of nitrones, *in situ* generated from oximes, into bicyclic isoxazolidines. The process was intensified to a point that showed sufficient robustness, efficiency and optimal safety enhancement with moderate yields, but great productivity (120 g/h).[131]



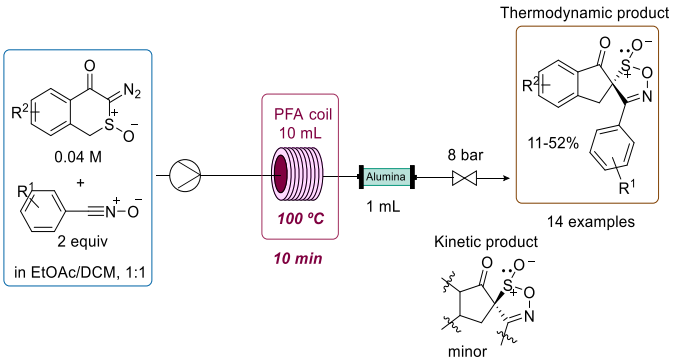
Scheme 43. [3+2] Cycloaddition towards bicyclic isoxazoles.

Morse and Jamison developed a method for overcoming the low stability of nitroalkynes through the development of nitrated vinyl silyltriflate equivalents. These silyltriflates, which were prepared *in situ*, reacted with nitrones by dipolar cycloaddition reactions to give highly substituted 4-nitroisoxazolines in high yields. The flow protocol is able to carry out the entire reaction sequence in a good yield and a short residence time, minimizing the accumulation of potentially hazardous reaction intermediates. The entire process (generation of nitronium triflate, formation of the vinyl silyltriflate intermediate and [3+2] cycloaddition) lasts 21 min and gives good yield (Scheme 44).[132]



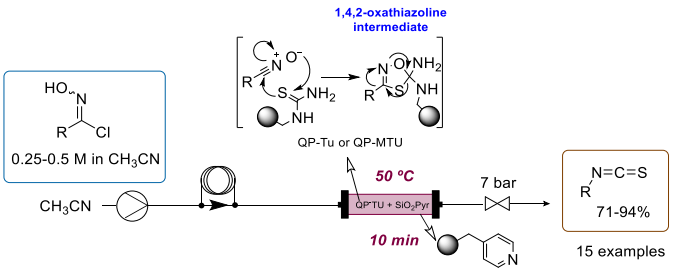
Scheme 44. Complete sequence to generate isoxazolines.

The formation of oxathiazoles reported by Maguire, Collins and coworkers involved a cycloaddition of nitrile oxide dipoles with α-oxo sulfines generated *in situ via* the α-sulfinyl carbenes derived from α-diazosulfoxides. Thermodynamic isomers were predominant using continuous flow (generation of α-oxo sulfine by thermolysis) while batch procedure led to the selective formation and isolation of the kinetic isomers (generation of α-oxo sulfine using rhodium acetate as the catalyst at 0 °C, Scheme 45).[133]



Scheme 45. [3+2] Cycloaddition towards oxothiazoles.

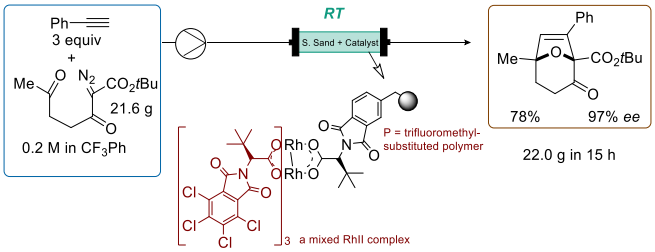
A 1,3-dipolar cycloaddition reported by Baumann and Baxendale between a nitrile oxide and a thiourea compound initially generated an unstable 1,4,2-oxathiazoline intermediate that readily rearranged into urea and the desired isothiocyanate product (Scheme 46) Interestingly, the authors found that an immobilized thiourea (QP-TU, or QS-MTU) served as an efficient source of a sulfur atom. Both the solid supported base (SiO_2-pyr) and immobilized thiourea species were blended filled into a glass column and the column inserted into a glass heating jacket which was maintained at 50 °C. The flow stream of the substrate was subsequently directed through the heated reactor column at an average residence time of 10 min. A broad range of isocyanates were produced in good to excellent yields.[134]



Scheme 46. Isocyanate synthesis through [3+2] cycloaddition and rearrangement.

4.4. Oxygen containing 5-membered heterocycles

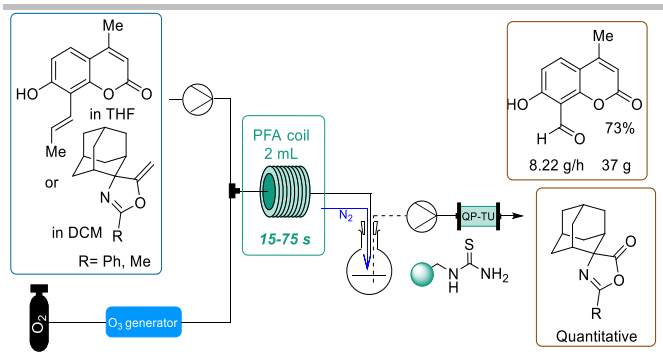
An intermolecular carbonyl ylide cycloaddition to yield a bicyclic furan was reported by Hashimoto and coworkers. The cycloaddition between 2-diazo-3,6-diketoester and styrene was catalyzed by a dirhodium(II) complex that is immobilized with 2-(trifluoromethyl)styrene and a flexible cross-linker. Up to 22 g of product were produced in high yields as well as high levels of enantioselectivity (97% *ee*) and turnover number, in a 15 h long run using phenylacetylene as dipolarophile with less than 1 mol% of catalyst (Scheme 47). The batch method provided lower yield (69%) and limited scalability.[135]



Scheme 47. Heterogeneous enantioselective cycloaddition to a afford a bicyclic furan scaffold.

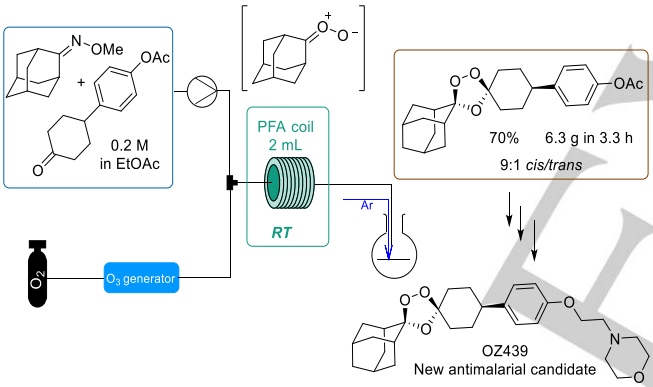
The accepted mechanism of ozonolysis consists of a 1,3-dipolar cycloaddition between the alkene and ozone to afford after several steps an ozonide, whose work up could produce a wide variety of products, including alcohols, aldehydes, ketones, acids, and amines.[136] The primary concern with ozonolysis chemistry rests on safety issues because the low molecular weight ozonides and peroxides produced, are unstable and potentially explosive. Besides, the subsequent quenching step to produce the final products is generally an exothermic process, requiring efficient temperature control.[137] Thus, flow chemistry provides a safer approach to this reaction. The first reported protocol used a silicon-Pyrex multichannel microreactor with microfabricated silicon posts where the gas-liquid regime is mixed. Ozonolysis was performed at room temperature with several model reactants with high conversion and selectivity in less than 1 s demonstrating the feasibility and safety of the process.[138] Later, the Jähnisch group studied different types of microreactors, with an online FT-IR analysis and a gas separator integrated. A successful ozonolysis of a vitamin D analog was achieved[139] and acetic acid 1-vinyl-hexyl ester.[140] Other sort of reactors that have been used for the ozonolysis, are a semipermeable teflon membrane to effect gas-liquid contact;[141] a capillary flow reactor for 1-decene ozonolysis with in line quench with triphenylphosphine;[142] and a O-Cube™ reactor with ozone leak detention, temperature control and in line quench.[143]

Similar protocols were applied for the ozonolysis step in the synthesis of 2-aminoadamantane-2-carboxylic acid[144] and coumarin-8-carbaldehyde derivatives.[145] Both included QP-TU as a solid ozonide quenching agent. The substrate was mixed with a continuous gas flow (O_2/O_3) through a T-piece. The united flow stream was then directed into a reactor coil, the reactor output which constituted a droplet spray was collected into a nitrogen blanketed purge vessel where the excess ozone was eliminated by passing a constant flow of nitrogen through the chamber. The expunged solution was continuously pumped from the chamber as it condensed through a packed bed cartridge containing an excess of the polymer-supported thiourea inducing reductive cleavage of the ozonide (Scheme 48). This protocol was also employed for an alkyne ozonolysis in the preparation of a key fragment of SR 142948A, using methanol as solvent and a MnO_2 cartridge for reducing the amounts of peroxy compounds to afford a 65% of the methyl ester product.[146] Ozonolysis flow procedures have also been applied to 1*H*-indoles for the multistep continuous flow synthesis of Ivacaftor, a cystic fibrosis drug.[147] Other examples include the ozonolysis of quinoline derivatives,[148] and fatty acids ozonolysis using liquid CO_2 as solvent.[149]



Scheme 48. Ozonolysis step QP-TU as a solid ozonide quenching agent.

Finally, a Griesbaum co-ozonolysis, which is a 1,3-dipolar cycloaddition between a ketone and an oxime derivative in the presence of ozone, to yield tetrasubsituted ozonides (1,2,4-trioxolanes), was reported.[150] Ley and coworkers produced the desired trioxolanes, which are stable and act as precursors of a drug candidate for malaria, in 70% of yield and a throughput of 1.9 g per hour. As shown in Scheme 49, a solution containing the oxime and the ketone was introduced in EtOAc in one feed, which reacted with a stream of ozone.[151]



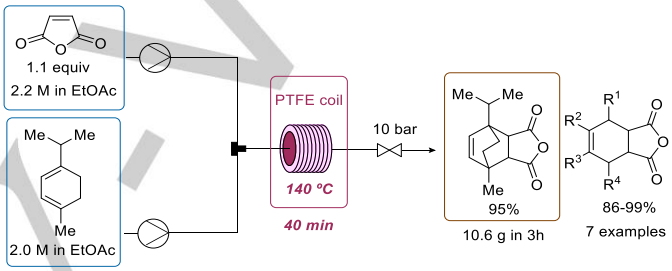
Scheme 49. Griesbaum co-ozonolysis in flow.

5. 6-membered rings

5.1. The Diels-Alder reaction

The Diels-Alder reaction is undoubtedly one of the most powerful transformations in organic chemistry which appears as the key step in numerous synthesis of natural products, APIs and agrochemicals.[152] The high pressure and temperature historically needed for the Diels-Alder reaction makes flow chemistry a favorable alternative due to the possibility of intensification of conditions and finding of new efficient process windows. This has rendered a high number of publications on this field.

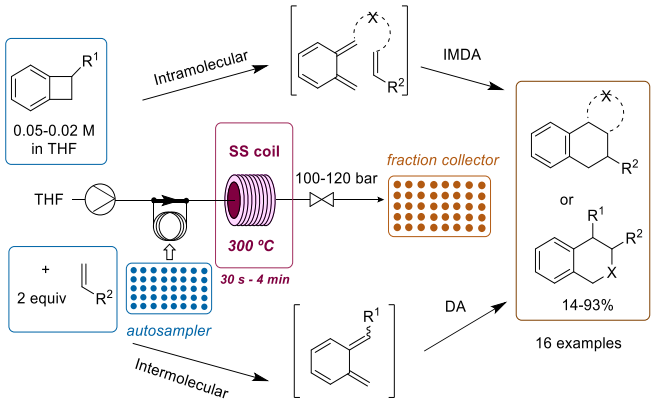
One of the earliest examples in which we can find this cycloaddition in a flow system is the reaction between cyclopentadiene with methacrolein performed by Itsuno and coworkers in 1996. They used an immobilized PS-borane catalyst to afford the cycloadduct in excellent yield and good selectivity.[153] More than 10 years later, Ley and coworkers constructed a microcapillary flow disc reactor to carry out different reactions that need high temperatures and pressures. The Diels-Alder reaction was tested at 60 ºC between maleic anhydride and isoprene reaching 93% conversion, 98% yield with a throughput of 2.73 g/min using eight parallel discs.[154] Using the same substrates, McMullen and Jensen developed an automated, silicon microreactor system that used a sequential experimentation framework driven by model-based optimization feedback for a rapid determination of reaction kinetics of the Diels-Alder. It was successfully scaled up into a Corning flow reactor (60 mL).[155] Recently, a set of compounds derived from terpenes were prepared by reaction of cyclohexadienes with maleic anhydride in excellent yields, and 3 times faster than in batch, including a scale up experiment affording 10.6 g in 3 h (Scheme 50). Furthermore, the Diels Alder reaction was combined with an heterogenous hydrogenation without purification of intermediates with successful results (80-96% yield for the two steps).[156]



Scheme 50. Diels Alder reaction of terpene derivatives with maleic anhydride.

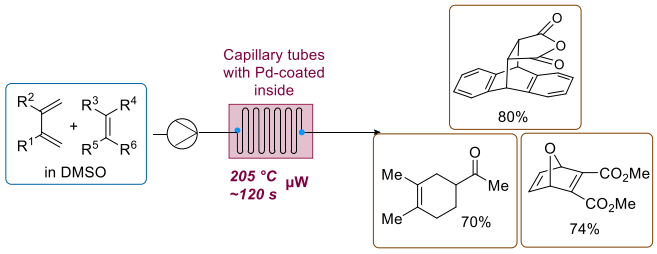
Baxendale presented a flow set up for a Baylis-Hillman reaction, acylation, thermally promoted elimination and Diels-Alder cycloaddition sequence in order to give the desired cyclohexene with a productivity of 23 g/h (isolated).[157] A microfluidic photoreactor was used for the [4+2] cycloaddition reaction of coumarins and chromones that undergo diastereoselective reactions with light-generated photoenol intermediates.[158] The solvophobic effects of reactions in core—shell double emulsions were also studied.[159] Organ and Khadra performed the reaction using ortho-trimethylsilyl triflates as substrates, which are converted *in situ* into benzyne derivates with TBAF, and reacted with different dienes to afford the desired cycloadducts in moderate yields (19–76%) in less than 2 min.[160]

A different Diels-Alder cycloaddition approach consisted of the efficient ring-opening of benzocyclobutenes and benzothiophene 2,2-dioxides followed by the [4+2] cycloaddition using a high temperature/pressure flow reactor in less than 4 min using an autosampler (Scheme 51). Attempts to reproduce this reaction in batch, using high boiling point solvents needed long reaction times and revealed problems with isolation. Using MW heating, very low conversion was observed.[161]



Scheme 51. Intra and intermolecular Diels Alder at high temperatures and pressures using autosampler.

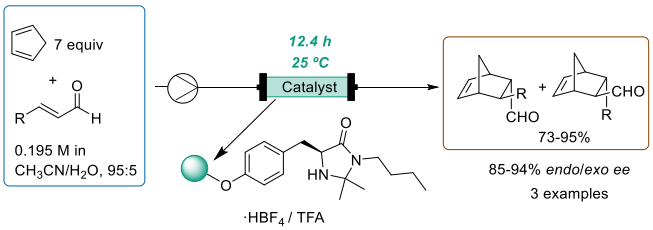
Another approach to carry out the Diels-Alder reaction is through microwave-assisted, continuous flow organic synthesis (MACOS). The group of Organ pumped the flow through capillaries with Pd colloids in its outer or inner surface. Those capillaries were heated with microwave irradiation and 3 different cycloadducts were synthetized in short residence times (around 120 s, instead of 24 h in batch) and good to excellent yield (Scheme 52).[162] The same group also used gold film capillaries to catalyze benzannulations between acetylenic aldehydes and alkynes by MACOS. 10 different products were obtained in moderate to good yields using a similar set up that the described before.[163]



Scheme 52. Diels Alder using a MACOS.

Other groups have presented equipment usable to perform microwave-assisted Diels-Alder reactions. Thus, a microwave applicator that generates a uniform electromagnetic field inside its resonant cavity, specific to continuous flow synthesis was used to carry out one Diels-Alder example with a yield of 76% in a throughput of 1 g/min. [164] Another example used a combination of microwave heating and a flow reactor. In this case a selectively heated, microwave absorbing material was part of a packed reactor bed which improved heating.[165] On the other hand, a novel non-resonance microwave applicator (non-resonant CF-MAOS) was used as the heating source in a continuous-flow synthesis system to perform the Diels-Alder reaction between 2,3-dihydronaphthalene-1,4-dione and isoprene to yield a 52% of the desired product (1.07 g/h).[166]

A stereoselective Diels Alder reaction in continuous flow was described into a chiral homemade HPLC column, packed with the MacMillan catalyst supported on silica. The authors demonstrated the possibility of working *in continuo* for more than 150 h, and the regeneration of the HPLC column. Yields up to 95% and an *ee* up to 94% were achieved. (Scheme 53).[167]

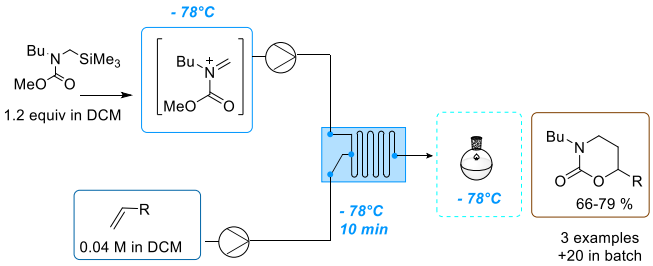


Scheme 53. Enantioselective Diels Alder reaction using heterogeneous catalyst.

Another heterogeneous approach used commercially available zeolites, reaching a high conversion (≥95%) and endo-selectivity (89:11) for the reaction of cyclopentadiene and methyl acrylate with a throughput of 0.87 g per hour (14 times heterogenous batch protocol), and the robustness of the catalyst was proved during a 7 h experiment.[168]

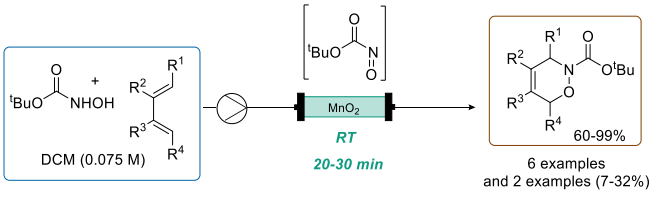
5.2. The Hetero Diels-Alder (HDA) reaction

One of the earliest examples of an HDA reaction in flow was presented in 2005.[169] Electrochemically generated *N*-acyliminium ion pools were used to perform an inverse electron demand HDA-type process that involved an electron-deficient hetero-diene with an electron-rich dienophile. Both the alkene and the generated cation pool were mixed using a micromixer cooled at -78 ºC. Compared to other reaction methods, product selectivity was increased using the microsystem (Scheme 54).[170]



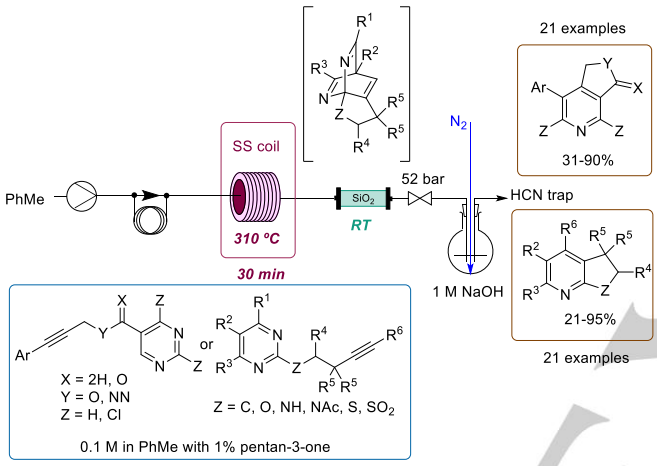
Scheme 54. Hetero Diels Alder using *N*-acyliminium ion pools.

The first example of a nitroso Diels-Alder reaction in flow was achieved by the *in-situ* formation of acyl nitroso derivatives using periodate as oxidizing agent. A total of 7 examples were tested with similar yield than in batch and a productivity of around 1 g per hour.[171] On the other hand, Nakashima and Yamamoto compared two different methods with the batch protocol. The first method used CuI as homogeneous catalysis and needed air as oxidant, the second used just one feed and it utilized a column reactor with packed MnO_2, not requiring further purification (Scheme 55). Both methods were tested in gram scale and yields were similar or slightly better than in batch but with important time saving.[172]



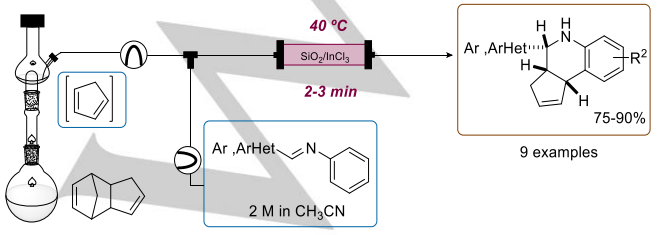
Scheme 55. Nitroso Diels Alder using supported MnO_2.

The cycloaddition between 1,3-cyclohexadiene and *N*-substituted hydroxylamine combined with further reduction of the product *in situ* with MnO_2, connected to a H-Cube® was recently disclosed.[173] A different approach allowed the synthesis of annulated pyridines in good to excellent yields through a cascade inverse-electron-demand HDA reaction and subsequent cycloreversion. The HDA reaction is assumed to occur *via* an intermediate tricyclic adduct which results from an intramolecular [4+2] cycloaddition across the C2 and C5 position of the pyrimidine ring followed by subsequent elimination of hydrogen cyanide. Using flow methodology permits controlling the formation of residual HCN working at temperatures close to 300 ºC and pressures up to 50 bar (Scheme 56).[174]



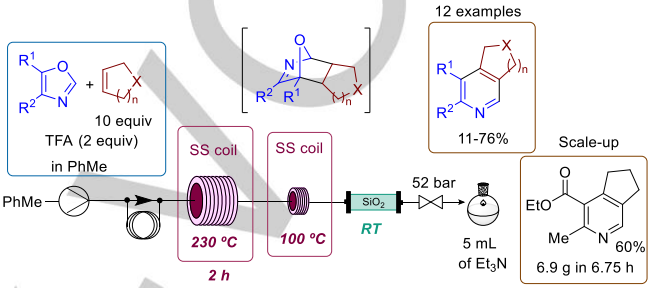
Scheme 56. Hetero Diels Alder to obtain annulated pyridines.

The Povarov reaction is a formal cycloaddition, also known as imino Diels–Alder, between an aromatic imine and an electron-rich alkene in presence of a Lewis Acid.[175] Baumann developed a continuous flow platform that integrates reagent distillation with modern flow reactor technology. That technology was applied to the successful flow synthesis of a series of tetrahydroquinolines generated through a heterogeneous $InCl_3$-catalysed Povarov reaction. Cyclopentadiene was prepared freshly from its commercially available dicyclopentadiene precursor through a high-temperature retro-cycloaddition followed by distillation, in order to avoid the exothermic dimerization. A set of 9 different examples were prepared in good to excellent yield on the gram scale within less than 1 h (Scheme 57).[176]



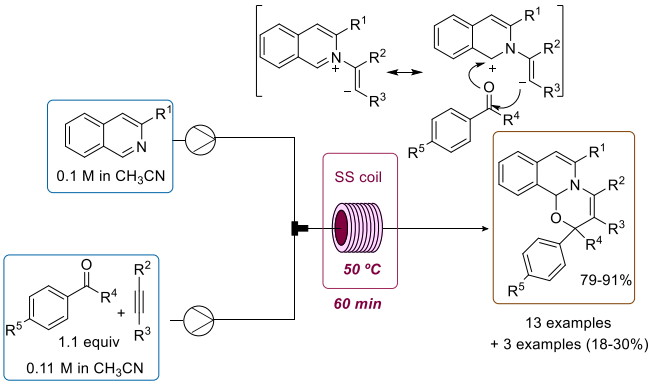
Scheme 57. Povarov reaction in flow with reactive destillation integrated.

The Kondrat'eva reaction involves a [4+2] cycloaddition between an oxazole and an alkene, followed by dehydration of the cycloadduct to afford functionalized pyridines.[177] Martin, Britton and coworkers developed a protocol to afford annulated pyridines through the inverse-electron-demand Kondrat'eva reaction in flow using cycloalkenes and inactivated oxazoles as substrates (Scheme 58). A sum of 12 different substrates were synthesized in poor to moderate yields, including a long run experiment. However, the yields were even worse using the batch procedure (only 9-11% in the MW promoted protocol) which was difficult to reproduce due to the harsh conditions needed (230 ºC and 52 bar).[178]



Scheme 58. The Kondrat'eva reaction in flow.

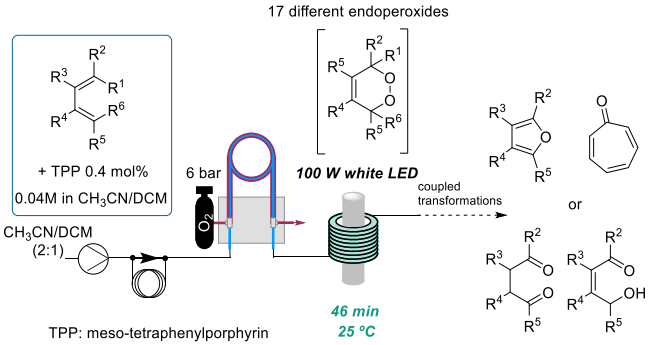
The Pericás' group published an asymmetric [4+2] cycloaddition between unsaturated heterocycles with *in situ* activated arylacetic acids. Using a polystyrene supported isothiourea, conversion of >99% and *ee* of 97% were achieved. Moreover, robustness of the catalyst was tested with no decrease in yield or *ee* after 18 h.[179] Finally, a three-component cycloaddition between an isoquinoline, an alkyne and a carbonyl compound including a [4+2] cycloaddition afforded oxazino isoquinoline derivatives in good to excellent yields. Mechanistically, the first step is the formation of 1,4-dipolar intermediate through the nucleophilic attack of the isoquinoline on the acetylenedicarboxylate. The resulting intermediate is then trapped by the carbonyl compound to generate the product (Scheme 59). In addition to the reduction of reaction times, the authors mentioned an important increase in selectivity in flow, as the cycloadduct resulting from the reaction of two alkynes was largely formed in batch.[180]



Scheme 59. 3-component [4+2] cycloaddition.

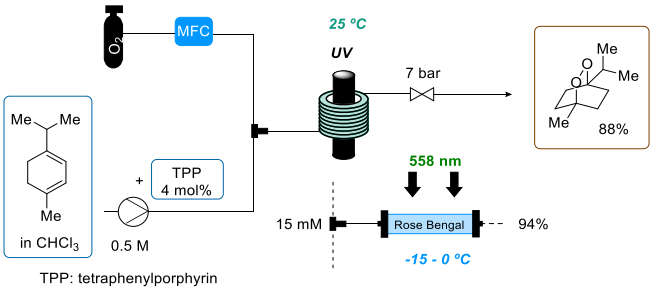
5.3. The HDA reaction with singlet oxygen

The [4+2] cycloaddition between O_2 and conjugated dienes in a photoreactor gives endoperoxides. When these are not stable, they can suffer further different rearrangements producing interesting products. Oliveira and coworkers developed a continuous flow photooxygenation of conjugated dienes to yield endoperoxides hydroxyenones, substituted furans, and 1,4-dicarbonyl derivatives after an *in cont* transformation of the endoperoxide (Scheme 60).[181] Furthermore, the group of Poliakoff and George produced a range of different products derived from the photooxygenation of pentadiene using either liquid or supercritical CO_2 as solvent.[182]



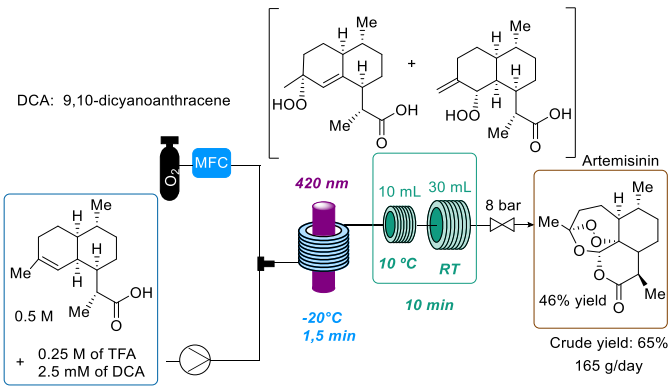
Scheme 60. [4+2] cycloadditions of conjugated dienes with singlet oxygen.

Many groups have developed [4+2] cycloadditions of α-terpinene with singlet oxygen to give a stable endoperoxide using flow methodologies. Lévesque and Seeberger used tetraphenylporphyrin (TTP) as homogeneous sensitizer in less than 1 min,[183] whereas other groups used rose Bengal either on a packed bed photoreactor system (Scheme 61)[184] or homogeneously in a Taylor vortex reactor.[185] An interesting alternative was presented by the Wirth group. Singlet oxygen was generated and trapped by using hydrogen peroxide and Li_2MoO_4 to yield quantitative amounts of ascaridole in 16 min at 40 ºC.[186] Other option was the use of a falling film microreactor to carry out an exhaustive study of all the parameters involved with which up to 89% of yield and a productivity of 3.2 M/h were achieved.[187] One study focused on the mixing of the sensitizer and substrate, with the oxygen flow. Using a monochanel microreactor, 90% yield was reached but less productivity than in batch, whereas with a tube in tube reactor, the results were 87% yield but 35 times the batch productivity.[188] Another example in which a tube in tube reactor was used with homogeneously mixed Rose Bengal at 90 ºC afforded 90% of yield (productivity of 0.77 mmol/h).[189] Recently, a polymer-supported BODIPY was used as photosensitizer with optimization by in-line NMR spectroscopy.[190]



Scheme 61. Two examples of [4+2] cycloaddition of α-terpinene with singlet oxygen.

The main application of a [4+2] photooxygenation is the synthesis of artemisinine from dihydro artemisinic acid (DHAA). Seeberger and coworkers developed a one pot photochemical continuous-flow process for the scalable semisynthesis of artemisinin from DHAA with high productivity, which starts with a singlet oxygen photooxygenation (Scheme 62).[191] Another important and green approach for this natural product is made using liquid CO_2 as solvent and a fixed bed acid photoreactor.[192]

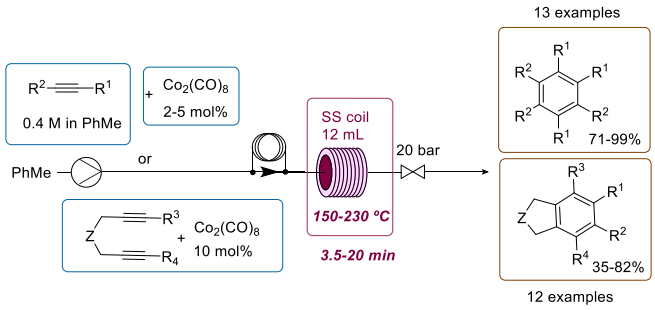


Scheme 62. [4+2] Artemisinine synthesis.

5.4. [2+2+2] Cycloaddition

The [2+2+2] cycloaddition is an elegant, atom-efficient and group tolerant process for the synthesis of carbo- and heterocycles, mostly aromatic, involving the formation of several C–C bonds in a single step. Alkynes, diynes, alkenes, imines, isocyanates, isothiocyanates, and CO_2 are common substrates for these cycloadditions to afford a broad variety of highly substituted cyclic molecules such as benzenes, pyridines, pyridones, 1,3-cyclohexadienes, pyrones, thiopyridones and cyclohexanes. It is considered an alternative to aromatic electrophilic substitution reactions to synthesize multisubstituted benzenes and pyridines.[193] Despite the high number of batch protocols for the [2+2+2] cycloaddition, there are few examples of the reaction in continuous flow so far. The first protocol was developed by Ley and coworkers. They performed the cyclotrimerization of a series of tethered trialkynes via focussed microwave irradiation to give arenes in better yield than purely thermal processes and without transition metal catalysis. They showed that it was possible to carry out this reaction in a flow process by pumping the sample through a glass coil in the microwave reaction cavity with a back-pressure regulator.[194] Oxahelicenes were prepared by polycyclization in a flow reactor.[195] On the other hand, our group

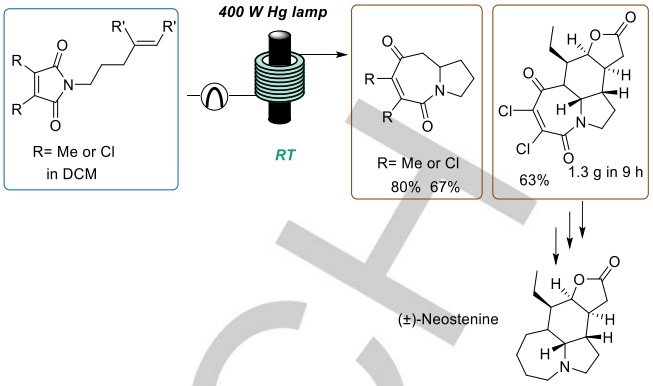
developed a protocol for homogeneous cobalt-catalyzed alkyne cyclotrimerization and crossed [2+2+2] between diynes and commercially available alkynes. The protocol generally uses 5 mol% of $Co_2(CO)_8$ and is scalable at a multigram scale (Scheme 63). A scale up of the cyclotrimerization of phenylacetylene to yield 9.2 g (92% yield) in less than 2 h was performed with only 2 mol% of catalyst and a metal scavenger cartridge was inserted at the reactor outlet to give a purity of 96%.[196]



Scheme 63. Homogeneous cyclotrimerization and crossed [2+2+2] cycloadditions at high temperatures.

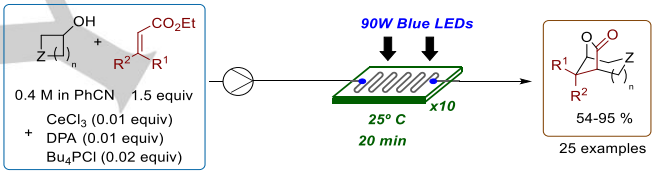
6. Miscellaneous

A formal [5+2] cycloaddition of maleimides to give azepines was reported by the group of Booker-Milburn. Although the mechanism is not clear it can be postulated following the work of Mazzocchi[197] that the reaction proceeds via direct [2+2] cycloaddition to the zwitterionic tricyclic species followed by fragmentation to the product. However, for retrosynthetic purposes, the authors consider this reaction as a diradical [5+2] cycloaddition. The same group tested the reaction under different flow photochemistry protocols.[22a] Best results were achieved when using the Vycor reactor, which contains 3 layers of FEP, and a 400 W lamp, giving an isolated yield of 80%.This highly significant result represents a 24 h yield of 178 g. However, best results with the chlorinated substrate were achieved using a Pyrex reactor with only one layer of FEP tubing (60 mL) and using the highest possible flow rate (10 mL/min). Initially, irradiation of a 0.02 M solution of the substrate in dichloromethane afforded a 67% isolated yield, representing a 24 h yield of 45 g (Scheme 64).[198] A similar protocol was applied for the total synthesis of (±)-Neostenine. In this case they used a 10 mL FEP tubing wrapped around a custom water-cooled Pyrex immersion and a irradiation of 400 W, using a high diluted sample (0.001 M), isolating the product in 63% yield with recovery of 20% unreacted starting material in a single 9 h run. Production of this amount of product by batch protocols would imply 42 successive conventional irradiations, each on a maximum scale of 50 mg and with no recovery of starting material.[199]



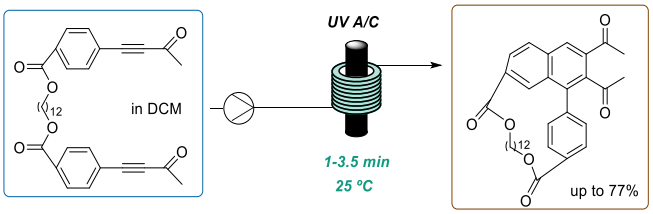
Scheme 64. Formal [5+2] Cycloaddition using flow photochemistry: synthesis of neostenine.

Zuo and coworkers performed a Cerium-catalyzed formal [5+2] cycloaddition of cycloalkanols with alkenes through dual photoexcitation. A glass microreactor was irradiated with blue-LEDs, $CeCl_3$ as catalyst, 9,10-diphenylanthracene (DPA) as cocatalyst and n-Bu_4PCl as additive. The mild catalytic manifold has been adapted to continuous flow for scale-up applications and employed for the concise synthesis of polycyclic core of 25 different bridged lactones (Scheme 65).[200]



Scheme 65. [5+2] formal cycloaddition to afford bridged lactones.

Finally, a self-made annular continuous-flow reactor was used to prepare multigram amounts of a macrocylic (1,7)-naphthalenophane through an intramolecular photo dehydro-Diels-Alder reaction. This kind of reaction in batch is characterized by applying high substrate dilutions resulting in long reaction times and consequently in over-irradiation of the corresponding products. Interestingly, the flow protocol could achieve yields up to 77% and productivities up to 4.26 g per hour (Scheme 66).[201]



Scheme 66. Intramolecular photo dehydro-Diels-Alder reaction in a flow reactor.

7. Summary and Outlook

Cycloadditions are a convenient way to build carbo- and heterocycles, many times present in pharmaceuticals and other interesting molecules. These synthetically powerful reactions often suffer from low yields and difficult scalability due to the use of hazardous reagents or gases. Although flow technology can help improve these problems, application of flow methods to cycloadditions is only reported in a minority of cases. This review aims to encourage synthetic chemists to use this technology. We show a wide variety of reactors and flow techniques with which telescoped synthesis, multigram productions and automated optimizations are possible. Furthermore, applications in the synthesis of pharmaceuticals and natural products are also presented.

All the cycloadditions gain green benefits when performed in flow: these are time saving; safe handling of hazardous reagents (azides, cyanide, toxic gases, nitrogen containing dipoles…) and energy saving when using harsh conditions (high temperatures and pressures), with less waste production. All these advantages represent a sustainable and scalable alternative, not only at industrial level, but also in academia.

Development of flow methodology is mature for certain cycloadditions. Thus, [2+2] photocycloadditions, exhibit all the benefits related to the use of photochemistry in flow, making them a scalable, energy efficient alternative with industrial applications. Huisgen type cycloadditions are performed in a safer way with impressive results. The intermolecular Diels-Alder reaction can take advantage of the use of high temperatures and pressures, so that reactions are achieved much faster with less side-products. A wide range of epoxidations and [4+2] cycloadditions with singlet oxygen are improved by the safe and optimal use of oxygen in continuous flow in. In the same way, ozonolysis procedures are successfully performed in grams per hour scale.

On the contrary, less common cycloadditions like cheletropic reactions remain unstudied under flow conditions. Moreover, examples of use of allenes as dipolarophiles, transition metal catalyzed cycloadditions, oxacycles formation and 3-component cycloadditions are still scarce compared to batch methodologies. Still, in many cases flow protocols do not exhibit an important improvement in yields, and although undoubtedly safer and easily scalable, may not justify the effort and resources needed. Moreover, there are only a few cycloadditions reported under flow conditions, that explore novel process windows, and are not observed under batch conditions.

Overall, the number of applications of flow technology in cycloaddition chemistry will continue to grow and be adopted by the chemical synthetic community and the industry in the next future.

Acknowledgements

Funding of this project by the Spanish MINECO, grant No. RTI2018-095588-B-I00 (Co-funded by European Regional Development Fund/European Social Fund, "Investing in your future") and FUSP-CEU (PC17/17) is acknowledged. J. G. thanks the Fundación San Pablo-CEU for a pre-doctoral fellowship.

Keywords: Cycloaddition • Flow chemistry • Microreactors • Heterocycles • Carbocycles

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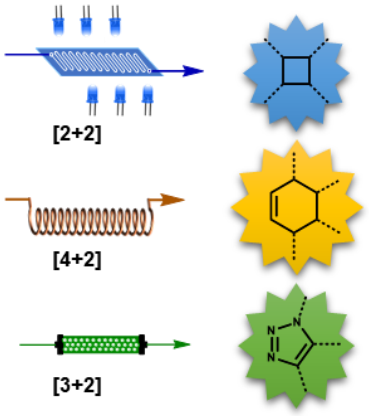

In this review we highlight the main advances in cycloadditions using flow chemistry. These powerful transformations are done in a safer way and are easily scalable under flow conditions. Thus they are usable at industrial level for the synthesis of APIs and other interesting products. Recent advances related to continuous procedures, include reactions such as the Diels-Alder, ozonolysis, Huisgen or photochemical [2+2] cycloaddition.

7. Hidrogenación de un éster en flujo catalizada por rutenio

Se describe el desarrollo de la hidrogenación de un éster en flujo continuo catalizada por rutenio usando hidrogeno (H_2). La reacción se utilizó para la reducción de un importante precursor en la síntesis del Abediterol, un agonista β2 adrenérgico, que está en fase IIa de ensayos clínicos para el tratamiento del asma y la EPOC (Enfermedad Pulmonar Obstructiva Crónica). Dicha reacción se investigó en un autoclave de química convencional usando un diseño de experimentos (DoE) para identificar el efecto de los parámetros importantes. El proceso optimizado en química de flujo operó durante 6 h con un análisis en línea de ^{19}F NMR con un *benchtop* RMN para la monitorización. El protocolo muestra un gran rendimiento (98% con 3.7 g/h) con muy poca carga catalítica (0.065 mol%). El impacto medioambiental de la hidrogenación catalizada por rutenio fue evaluado en comparación con la reducción existente utilizando cantidades estequiométricas de hidruro de litio y aluminio (LAH) y borohidruro de sodio ($NaBH_4$). La intensidad másica del proceso (PMI) de la hidrogenación catalizada por Ru (14) es más favorable en comparación con las reducciones con LAH (52) o $NaBH_4$ (133).

Contribuí en este manuscrito haciendo la búsqueda bibliográfica sobre la hidrogenación de ésteres y los experimentos preliminares de flujo. Estudiando las diferentes alternativas para la introducción del sustrato, base y catalizador en el sistema. Utilicé diferentes disolventes, catalizadores, bases e identifiqué los posibles productos secundarios y los principales parámetros involucrados en la reducción.

Factor de impacto (2019): 9.480. **Categoría**: Química multidisciplinar (Q1 20/177); Ciencia y tecnología verde y sostenible (Q1 2/41). Fuente: JCR (Journal of citation reports)

Article

Received 30th June 2020,
Accepted 11th August 2020

DOI: 10.1039/d0gc02225j

Optimization and sustainability assessment of a continuous flow Ru-catalyzed ester hydrogenation for an important precursor of a β2-adrenergic receptor agonist

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The development of a ruthenium-catalyzed continuous flow ester hydrogenation using hydrogen (H2) gas is reported. The reaction was utilized for the reduction of an important precursor in the synthesis of abediterol, a β2-adrenoceptor agonist that has undergone phase IIa clinical trials for the treatment of asthma and chronic obstructive pulmonary disorder. The reaction was investigated within a batch autoclave by using a design of experiments (DoE) approach to identify important parameter effects. The optimized flow process was successfully operated over 6 h with inline benchtop 19F NMR spectroscopy for reaction monitoring. The protocol is shown to be high yielding (98% yield, 3.7 g h−1) with very low catalyst loading (0.065 mol%). The environmental impact of the Ru-catalyzed hydrogenation was assessed and compared to an existing stoichiometric lithium aluminum hydride (LAH) reduction and sodium borohydride (NaBH4) reduction. The process mass intensity (PMI) for the Ru-catalyzed hydrogenation (14) compared favorably to a LAH reduction (52) and NaBH4 reduction (133).

The reduction of esters into their corresponding alcohols is traditionally performed in batch reactors using stoichiometric metal hydride reagents, such as LiAlH4 and NaBH4.[1] The highly reactive hydride species should be carefully handled.[2] While these reactions are often high yielding and selective, a stoichiometric reagent is necessary which consequently results in a large amount of waste that can be hazardous and expensive to destroy.[3] Moreover, the workup is particularly challenging owing to the highly exothermic hydrolysis step that forms precipitates. Catalytic reductions of esters using hydrogen gas have been demonstrated as an atom economic alternative to using stoichiometric reagents, with minimal waste generated.[4] Heterogeneous catalysts are generally limited to the use of harsh conditions and are incompatible with substrates containing sensitive functional groups.[4]

Heterogeneously catalyzed ester hydrogenations were described as early as 1931 by Adkins and co-workers.[5] Adkins-type catalysts (CuO/CuCr2O4) typically utilize very harsh conditions (>200 °C and >200 bar).[5] Despite the requirement for elevated temperatures and pressures, these catalysts are still used in modern applications for unselective reduction of fatty acids and their esters.[6] Subsequently, milder methods were developed for the reduction of the esters which also conserve olefin functionality, thus facilitating the production of unsaturated fatty alcohols.[7] More recent methods have further progressed to the use of less harsh conditions, for instance a bimetallic Ag–Au catalyst was shown to reduce dimethyl oxalate at temperatures as low as 145 °C and 30 bar pressure.[8] The heterogeneous hydrogenation of esters was recently achieved at room temperature using ruthenium-based catalysts with phosphorus ligands covalently attached to a polymeric support under 50 bar pressure.[9]

Homogeneous catalysts have been shown to perform with high turnover numbers under relatively mild conditions and display high functional group tolerance.[4,10–15] Ruthenium based catalyst systems have been demonstrated as highly efficient catalysts for ester hydrogenations.[4,12–15] In 2006, the group of Milstein introduced a new type of ruthenium catalyst utilizing pincer ligands for the hydrogenation of esters.[12] Subsequently, the Takasago International Corporation reported Ru-MACHO (A) as an efficient catalyst system.[13] RuMACHO is uninhibited by alcohols, thus is catalytically active in alcoholic solvents and is also not deactivated by the product. Gusev and co-workers reported the development of Ru-SNS (**B**) as an alternative catalyst system.[14] The benefit of Ru-SNS is that it does not use phosphine ligands, which can be relatively expensive. The switch from stoichiometric hydride reductions to Ru-catalyzed hydrogenations is estimated to reduce the E-factor (kg waste per kg product) by approximately 3 to 5-fold.[15] Currently, Ru-MACHO and Ru-SNS are the most industrially viable homogeneous ruthenium catalysts for ester hydrogenation.

The use of hydrogen gas within batch reactors generally requires the use of high pressure to ensure sufficient dissolution of gas within the liquid phase. Consequently, specialized and expensive equipment is required and scale-up can be challenging. Continuous flow reactors have been demonstrated as a safe and scalable technology for the scale-up of gas–liquid reactions.[16–18] In recent years, there has been a greater focus on developing green processes that avoid waste and hazardous compounds.[19] Sustainable chemical processes rely not only on effective chemistry but also on the implementation of reactor

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†Electronic Supplementary Information (ESI) available. See DOI: 10.1039/10.1039/d0gc02225j

technologies that enhance reaction performance, reduce energy consumption and improve overall safety. The utilization of continuous flow reactors can significantly contribute towards this endeavor.[20] Energy efficient heating enables the sustainable utilization of intensified conditions for maximizing yield and throughput. Precise parameter control, such as mixing, temperature and pressure, can improve product yield and selectivity. The safe use of highly atom efficient routes that would be inaccessible or too dangerous under traditional batch conditions is possible with continuous flow reactors.[21] The reduction of different functional groups within continuous flow reactors has been achieved by a number of research groups, and was recently reviewed by Riley and co-worker in 2018.[22,23]

Abediterol (AZD0548) (Figure 1) is a potent, long-acting inhaled β_2-adrenoceptor agonist that was first pharmacologically characterised in 2012.[24] It has undergone phase IIa trials for the treatment of asthma and chronic obstructive pulmonary disease (COPD).[25] A route for the synthesis of the lipophilic amine tail portion of abediterol was published in 2019.[26] An annual demand in the order of kilograms would be expected due to the very high potency of the drug candidate. The first step in the synthesis is a lithium aluminum hydride (LAH) reduction to afford 2,2-difluoro-2-phenylethanol (2) (Scheme 1a). An alternative protocol which uses stoichiometric NaBH4 has also been reported for the transformation.[27]

We were interested in developing a Ru-catalyzed continuous flow protocol with hydrogen gas as a sustainable, safe and scalable alternative for the synthesis of **2** (Scheme 1b). Ikariya and coworkers previously demonstrated the use of Ru-MACHO for the hydrogenation of alpha-fluorinated esters to their corresponding alcohols under batch conditions.[28]

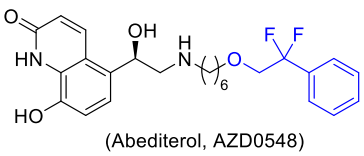
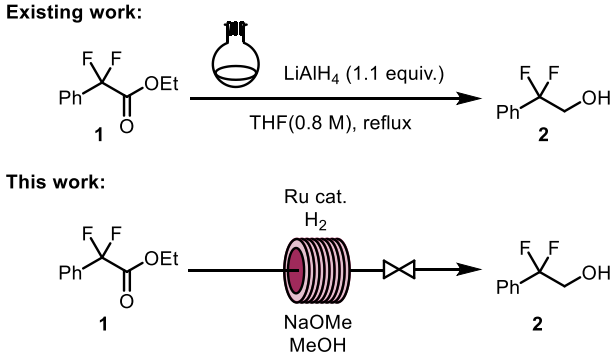


Figure 1 Structure of abediterol (AZD0548), a β_2-adrenoceptor agonist.



Scheme 1 Synthesis of 2,2-difluoro-2-phenylethanol (**2**): a) a previously reported LAH reduction (ref. 20); and b) continuous flow homogeneous Ru-catalyzed hydrogenation (this work).

Reaction optimization experiments for the hydrogenation of ethyl 2,2-difluoro-2-phenylacetate (**1**) were performed on a 5 mmol scale within a batch autoclave. Ru-MACHO (**A**) was used as catalyst and sodium methoxide (NaOMe) as base (Scheme 2). A relatively short reaction time of 1 h was used for all batch reactions to facilitate easy transfer from batch to flow. Furthermore, we were also interested in identifying conditions that dissolved all reaction components. The conversion of ester **1** (−103.9 ppm) to alcohol **2** (−106.7 ppm) could be monitored offline by ^{19}F NMR with a low field benchtop spectrometer (Spinsolve Ultra 43 MHz, Magritek). Methanol was used as solvent due to its relatively green credentials.[29] Toluene (PhMe), tetrahydrofuran (THF), methyl tetrahydrofuran (MeTHF) and tert-butyl alcohol/PhMe were also screened, but provided inferior results (Table S1†). These poorer results were probably caused by the limited base solubility in the solvent. For the batch optimization, a design of experiments (DoE) approach was selected. A four-parameter, two-level full factorial experimental design was implemented, corresponding to 19 experiments including 3 center point repeats to measure reproducibility (Table 1). Pressure was varied between 10 and 30 bar, temperature between 40 and 60 °C, catalyst loading between 0.03 and 0.10 mol% and base between 0.1 and 0.3 equivalents. During the initial experiments, an acid side product

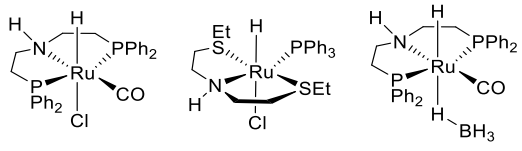
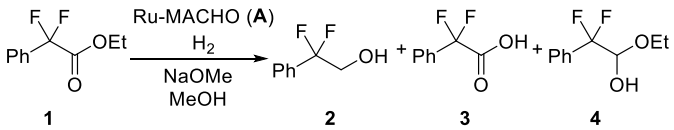


Figure 2. Hydrogenation catalysts: Ru-MACHO (**A**), Ru-SNS (**B**) and Ru-MACHO-BH (**C**)



Scheme 2. Ru-catalyzed hydrogenation of ester **1** to alcohol **2**. Acid **3** is generated as a side product and hemiacetal **4** as an intermediate.

3 (−101.3 ppm) and a hemiacetal intermediate **4** (−108.7 and −111.0 ppm) could also be identified. The methyl ester 5 derivative (−103.7 ppm) was observed from transesterification, but this did not influence the course of the hydrogenation reaction. The responses for the conversion of 1, alcohol 2, acid side product 3, and hemiacetal intermediate 4 were measured during experiments.

Gratifyingly, very high conversion and selectivity towards the desired alcohol **2** were achieved for a number of experiments (Table 1). Under milder conditions, the conversion of ester **1** and yield of alcohol **2** were lower, while intermediate **4** was observed at higher levels for these experiments. Side product **3** was observed at similar levels for all the experiments. The experimental repeats displayed very good reproducibility (entries 17–19). Furthermore, it was shown that by lowering temperature, pressure or catalyst loading (10 bar, 40 °C, 0.03

mol% A) it is possible to shift the selectivity of the reaction towards the hemiacetal intermediate **4**.

We were interested in comparing the results for the hydrogenation of ethyl 2,2-difluoro-2-phenylacetate (**1**) with less reactive methyl trifluoroacetate as substrate (Table S2†). Under similar conditions, lower conversion and higher amounts of a hemiacetal intermediate were observed as the kinetic product. The thermodynamic alcohol product could be favored under more aggressive conditions. These results suggest that a less reactive fluorinated hemiacetal is stable enough to resist further conversion to the alcohol under carefully controlled reaction conditions.

The responses from the optimization experiments, shown in Table 1, were fitted to polynomial models by using a statistical experimental design software package (Modde v12). Models were successfully fitted for the alcohol **2** and side product **3** from the ^{19}F NMR data by using multiple linear regression (MLR) (Fig. S6 and S7†). Models were generated by including all main and interaction terms and then non-significant terms were removed. A good fit was achieved for both models with $R^2 = 0.79$ and $R^2 = 0.72$ for the alcohol **2** and side product **3** respectively. The increase of pressure, temperature and catalyst loading were shown to have a positive influence on the formation of alcohol **2**. The base loading did not show an influence on the yield of **2**. The increase in pressure and catalyst loading resulted in a slight decrease in the yield of side product **3**. Temperature displayed no influence over side product **3** formation. Whereas increasing the base loading resulted in a higher yield of 3. The models generated from the DoE were used to explore the experimental design space and to identify promising initial conditions for translation to flow (Fig. 3).

Table 1. Input parameter levels and results from the design of experiments performed within a batch autoclave.[a]

[a]Standard reaction conditions: **1** (5 mmol scale) in MeOH (2.5 mL) with stirring at 600 rpm for 1 h. Conversion and product distribution were determined by integration of ^{19}F NMR. Conversion of **1** was calculated based on the combined integration of the ethyl ester **1** and methyl ester **5**.

Entry	p (bar)	T (°C)	Catalyst loading	Base (eq)	Conversion 1 (%)	Alcohol 2 (%)	Side product 3 (%)	Hemiacetal 4 (%)
1	10	40	0.03	0.1	33.0	23.3	7.3	2.3
2	30	40	0.03	0.1	72.9	66.8	5.0	1.1
3	10	60	0.03	0.1	64.7	56.9	7.3	<1
4	30	60	0.03	0.1	>99	94.9	5.1	<1
5	10	40	0.1	0.1	47.0	38.1	6.6	2.4
6	30	40	0.1	0.1	>99	96.3	3.7	<1
7	10	60	0.1	0.1	99.1	93.0	5.9	<1
8	30	60	0.1	0.1	>99	95.2	4.8	<1
9	10	40	0.03	0.3	27.7	7.7	8.0	12.1
10	30	40	0.03	0.3	71.1	57.8	7.6	5.6
11	10	60	0.03	0.3	86.6	76.9	8.9	<1
12	30	60	0.03	0.3	>99	94.2	5.8	<1
13	10	40	0.1	0.3	75.1	64.3	6.0	4.7
14	30	40	0.1	0.3	>99	94.7	5.3	<1
15	10	60	0.1	0.3	>99	94.1	5.9	<1
16	30	60	0.1	0.3	>99	94.3	5.7	<1
17	20	50	0.065	0.2	>99	93.8	6.2	<1
18	20	50	0.065	0.2	>99	94.7	5.3	<1
19	20	50	0.065	0.2	>99	95.2	4.8	<1

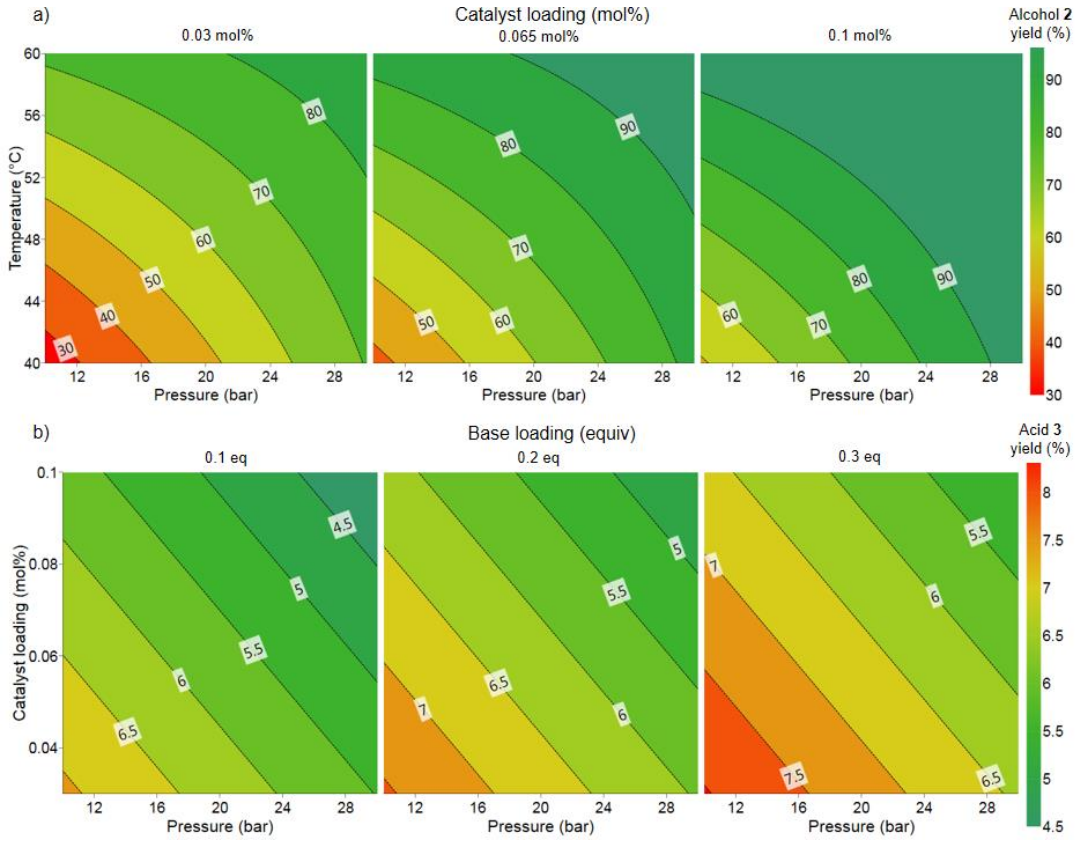


Figure 3. Model-predicted contour plots showing the influence of different parameters on: a) alcohol **2** yield; and b) side product **3** yield. Constant conditions: **1** (5 mmol scale) in MeOH (2.5 mL) with stirring at 600 rpm for 1 h.

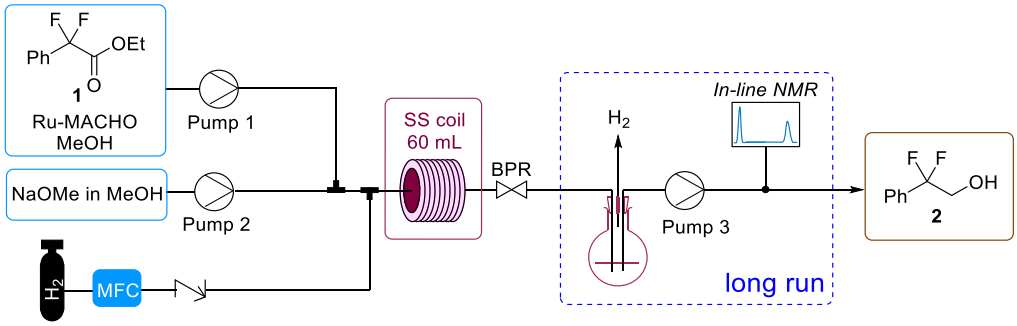


Figure 4. Continuous flow setup for the Ru-catalyzed hydrogenation of ester **1** to alcohol **2**. MFC = mass flow controller for the introduction of H_2 and BPR = back pressure regulator. The dashed blue box indicates the part of the setup utilized for the inline analysis with NMR which was implemented during the long run.

The formation of side product **3** was shown to increase with the amount of NaOMe added. Furthermore, significant heat was produced upon exposure of ester **1** to NaOMe, thus we were interested in identifying a strategy to control this exotherm. The reaction resulted in recovered starting material **1** in the absence of base, because base is necessary to form the active catalyst. Ru-MACHO-BH (**C**) has been reported to work successfully without the addition of base for pre-activation of the catalyst.[30] We attempted Ru-MACHO-BH on our system; however, Ru-MACHO-BH under base-free conditions resulted in only recovered starting material **1** (Table S4†). On addition of base, the reaction then worked successfully affording alcohol **2** in 98% yield. These results indicated that the catalyst could be decomposing during reaction preparation. We observed that Ru-MACHO-BH rapidly decomposes, with the hydrolysis of the borane group, in the presence of air (Fig. S8†). Thus, we selected Ru-MACHO (**A**) as the catalyst of choice for the flow experiments.

Flow experiments were performed using a Uniqsis FlowSyn system (Fig. 4). The two liquid feeds were introduced with high performance liquid chromatography (HPLC) pumps and hydrogen gas was introduced through a mass flow controller (MFC, Bronkhorst EL-FLOW). The two liquid feeds were mixed within an arrow-shaped mixer. Subsequently, the liquid and gas feed were combined using a Y-shaped mixer. A gas–liquid segmented (Taylor) flow regime was observed for all experiments. The reaction was performed within a heated stainless steel reactor coil (60 mL, 1/8 in. OD, 1/16 in. ID).

Pressure was applied by using an adjustable back pressure regulator (BPR). For all flow experiments, fractions were collected every 5 minutes and analyzed offline with ^{19}F NMR. In the initial flow configuration, the base and catalyst were introduced as one feed but this led to irreproducible results (Table 2, entry 1). Interestingly, the catalyst has been previously reported to slowly decompose in the presence of base.[31] Furthermore, as stated previously, the presence of a base results in the formation of side product **3**. Thus, to avoid any undesired reactions occurring within the feed solutions, the catalyst and substrate in MeOH were introduced as one feed and the NaOMe in MeOH as the second feed.

We selected to commence our flow experiments at a lower concentration (1 M) than the batch experiments to ensure the solubility of all the reaction components. A >90% product yield at 0.065 mol% catalyst loading, 20 bar pressure and 60 °C temperature was predicted from the model generated from the batch studies. A reduction in base loading had also been demonstrated in the DoE to reduce the yield of the acid side product **3** (Figure 3b), but not influence the yield of alcohol **2** (Figure 3a). The two liquid feeds were each pumped at 0.2 mL min^{-1} and the hydrogen gas at 30 mL$_n$ min^{-1}, corresponding to a residence time of approximately 50 min and 3.3 equiv. of H_2. 2 equiv. of H_2 is necessary for the transformation, therefore only a relatively small H_2 excess (1.3 equiv.) is used. A low base loading of 0.1 equivalents unexpectedly resulted in a lower conversion than expected (entry 1) and provided inconsistent results. This drop in conversion and the irreproducibility can be explained by the nature of the side reaction. The base is consumed in the presence of water by the reaction of esters **1** and **5** to the acid **3**. Thus, the reaction is very sensitive to changes in the water content at low base loadings. Full conversion and more than 90% yield of **2** could be achieved by increasing the base loading to 0.2 equivalents and the pressure to 30 bar (entry 3). More importantly, the reaction displayed good reproducibility at these conditions. The use of anhydrous MeOH and fresh NaOMe solution provided an increase in desired alcohol **2** (entry 4), whilst decreasing the formation of the acid side product **3**. The throughput could be increased by operating at a higher concentration (1.5 M), without a drop in conversion or yield observed (entry 5). The pressure could also be decreased whilst maintaining full conversion and high yield (entry 6a). residence time within the reactor setup, corresponding to 0.33 mL min^{-1} for each liquid pump and 50 mLn min^{-1} H_2 to provide 35 min residence time. These conditions resulted in >99% conversion of 1 and 87% alcohol **2**, with the remaining present as the acid **3** side product (entry 7). This result indicates that some formation of the side product **3** from remaining substrate **1** could also be occurring after the reactor within the collection vessel. We conducted control experiments using acid **3** as starting material instead of ester **1**. In these experiments only recovered acid **3** and some transesterification to the methyl ester 5 (5–7%) was observed (Table S3†). The reaction provided 91% yield of alcohol **2** even when using 2.2 equiv. of H_2 and 25 min residence time (entry 8). A reaction with Gusev's Ru-SNS catalyst (**B**) was performed as a comparison (entry 9). Under similar conditions, the use of Ru-SNS resulted in low conversion of **1**, trace amount of desired product, and high selectivity to hemiacetal **4**. A lower activity of Ru-SNS, with higher selectivity towards the hemiacetal intermediate **4** when compared to using Ru-MACHO as catalyst, has been reported by Dub and co-workers.[32]

Table 2. Results from the optimization experiments in continuous flow.[a]

Entry	p (bar)	$C_{1,0}$ [M]	Base [eq]	t_{res} [min]	Conv. **1** [%]	Yield **2** [%]
1a[b]/1b[b]	20	1.0	0.1	50	80/9	73/0
2a/2b	20	1.0	0.1	50	34/50	26/40
3a/3b	30	1.0	0.2	55	>99	91/93
4[c]	30	1.0	0.2	55	>99	95
5[c]	30	1.5	0.2	55	>99	96
6a[c]	20	1.0	0.2	55	>99	96
6b (long run)[c]	20	1.0	0.2	70	>99	98
7[c,d]	20	1.0	0.2	30	>99	87
8[c,e]	20	1.0	0.2	25	>99	91
9[f]	20	1.0	0.2	55	23	1

[a] 0.4 mL min^{-1} total liquid flow rate, both liquid feeds were pumped at equal flow rates, 30 mLn min^{-1} H^2 flow rate, 0.065 mol% catalyst loading, 60 °C temperature. Reagents were introduced for 30 min then switched to carrier solvent. [b] Pre-stirring of base and catalyst for 15 min. [c] Anhydrous MeOH and fresh NaOMe solution stored under Ar used. [d] 0.66 mL min^{-1} total liquid flow rate, 50 mLn min^{-1} H_2 flow rate. [e] 1 mL min^{-1} total liquid flow rate, 50 mLn min^{-1} H_2 flow rate. [f] Ru-SNS used as catalyst.

A long run experiment was performed over a total operation time of nearly 6 hours to demonstrate the stability of the process (entry 6b). A gas-liquid separator was incorporated into the flow setup after the BPR to enable inline analysis (Fig. 4). After separating the gas from the liquid stream, the liquid was fed using a HPLC pump through an inline flow cell (0.8 mL internal volume, max. pressure 10 bar) for monitoring by a benchtop low field NMR spectrometer (Spinsolve Ultra 43 MHz, Magritek).[33] This enabled the online monitoring of the reaction progress for all the main reaction species by ^{19}F NMR spectroscopy, with a spectrum acquired approximately every 20 s and >800 measurements taken in total. Fig. 5 shows the percentage of starting material **1**, alcohol **2** and side product **3** over operation time as determined by integration of the peaks for the spectra generated by the inline ^{19}F NMR measurements. The system performed consistently for the duration of the run. Moreover, the data points for the inline measurements very closely corresponded to the values for the data points of the collected fractions that were measured manually offline by ^{19}F NMR, thus validating the inline method. The residence time was longer for the long run due to the consumption of H_2 gas. For the optimization experiments, the feeds were injected via a sample loop (6 mL each) over 30 min. For the long run, feeds were introduced continuously through the pumps. Therefore H_2 is not consumed throughout the entire reactor for the optimization experiments, thus accounting for the difference in the observed residence time between the optimization experiments and long run (entry 6b). Overall, the process was operated at "steady-state" conditions for approximately 220 minutes. A >99% conversion of **1** and 98% selectivity towards **2** was observed for the combined fractions from operation at

"steady-state" conditions. After removal of MeOH, a simple extraction protocol was performed using ethyl acetate (EtOAc) as solvent to obtain alcohol **2** in 98% isolated yield based on "steady-state" operation. A throughput of 3.7 g h^{-1} was obtained, corresponding to a space–time yield of 1.0 g/(L min). One could envisage how the throughput could be increased by transfer to a larger scale coil reactor without a drop in performance as described elsewhere.[17a]

The flow protocol provides benefits in terms of scalability, safety and product quality over a batch autoclave protocol. The addition of reagents can be carefully manipulated to provide the desired stoichiometry. The exotherm associated with base addition can be minimized, because heat generated can be removed quickly. Typical commercial batch reactors can operate between 2 and 6 bar, therefore higher pressures require more specialized and expensive equipment. There is no headspace filled with gas within a flow reactor and a flow reactor facilitates improved safety due to the small volumes of pressurized equipment needed. Furthermore, a flow protocol operates at steady-state, therefore providing consistent product output as shown by Fig. 5. The in-line NMR also enables improved understanding the performance of the continuous process, thus aiding in waste prevention through an increase in process understanding.

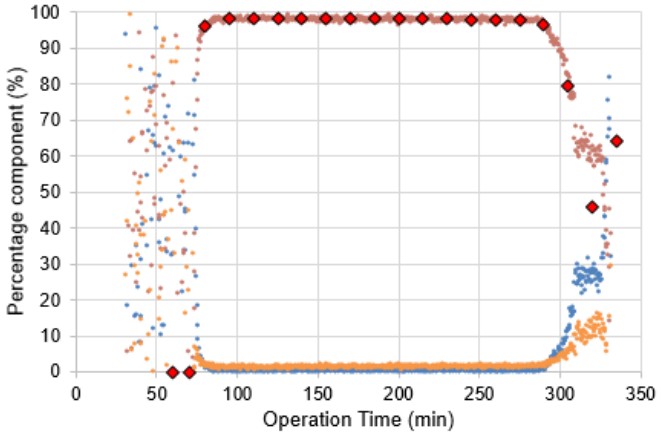


Figure 5: Results of the inline ^{19}F NMR measurements for the long run. Values are calculated by using ^{19} F NMR integrals of the peaks. Ester **1** and **5** (•), alcohol **2** (•), and side product **3** (•). Alcohol **2** (♦) measured offline for validation. Conditions used are given in Table 2, entry 6.

Table 3 shows the results from the green metrics assessment for the Ru-MACHO hydrogenation, the LAH reduction, and the NaBH4 reduction. For the comparison of the environmental impact, a green metrics toolkit developed by Clark and co-workers in 2015 was used.[34] The values used for the calculations are shown in Tables S5–S7.† All the reactions reach full conversion and provide good selectivity and yield, however; the Ru-MACHO hydrogenation reaches a higher value for yield. In addition, the Ru-MACHO protocol performs better for atom economy (AE) and reaction mass efficiency (RME), therefore has a higher optimum efficiency (OE). The Green Chemistry Institute Pharmaceutical Roundtable selected process mass intensity (PMI) as their preferred mass-based green metric.[35] PMI corresponds to the total mass used in a process divided by the mass of the product. The reaction PMI accounts for all the chemicals in the reaction, whereas the total PMI accounts for the chemicals used in the reaction and the work-up procedure. The total PMI is over 3-fold lower for the Ru-MACHO hydrogenation (14) when compared to the LAH reduction (52), and over 6-fold lower when compared to the NaBH4 protocol (133). These results demonstrate that the Ru-MACHO flow protocol is substantially more sustainable than the LAH and NaBH4 reductions. The E-factor shows the same trend, whereby a higher E factor is observed for the LAH (51) and NaBH4 (132) reductions, largely due to the high amount of solvent necessary for the work-up compared to a Ru-MACHO hydrogenation (13).

Table 3. Comparison of quantitative green metrics for the Ru-MACHO hydrogenation flow protocol and the batch protocols for the LAH and $NaBH_4$ reduction.

Metric	Ru- MACHO	LAH[a]	$NaBH_4$[a]
Conv. [%]	>99	>99	>99
Yield [%]	98	93	91
AE	78	66	66
RME	75	61	54
OE	96	91	81
PMI reaction	6	10	23
PMI work-up	8	41	110
PMI total	8	52	133
E factor	14	51	132

[a] Calculations based on LAH and NBH_4 reduction protocols reported in ref. 26 and 27 respectively.

Table 4 shows a comparison for the qualitative green metrics between the LAH and Ru-MACHO reductions. In the green metrics toolkit, colored flags (green, amber, red) are given to each reaction to assess how green they are regarding each criterion. A green flag means "preferred", amber "is acceptable-some issues" and red is "undesirable". The Ru-MACHO hydrogenation receives green flags because it is catalytic and performed in flow. On the other hand, the LAH and NaBH4 reductions require stoichiometric reagent and are currently performed in batch, which results in amber flags for these criteria. All reactions are operated within an energy efficient temperature window (0–70 °C) which results in green flags. The LAH reduction uses THF at reflux conditions and is thus less energy efficient than the Ru-MACHO reaction, which is performed below its reflux temperature. Running the LAH reaction at reflux results in an approximately 6-fold increase in energy consumption as opposed to performing the reaction at 5 °C below reflux.34,36 Due to the high amount of energy used when heating to reflux, this results in a red flag for the LAH reduction. The simple extraction for the Ru-MACHO protocol results in a green flag, whereas the LAH and NaBH4 reactions require a number of extractions and an exothermic aqueous quench (amber flag).

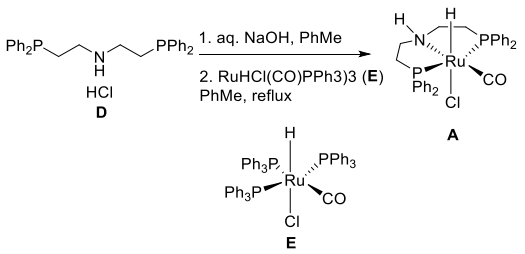
Table 4. Comparison of qualitative green measures for LAH and Ru-MACHO reduction.

Criterion	Ru-MACHO	LAH	$NaBH_4$	
Type of reaction	Catalytic	Stoichiometric	Stoichiometric	
Reactor	Flow	Batch	Batch	
T [°C]	60	66	0	
Reflux	No	Yes	No	
Workup	Extraction	Quench/Extraction	Quench/Extraction	
Solvent	MeOH/EtOAc	THF/water/MTBE	MeOH/H2O/EtOAc	
Critical element	Ru	Li, Al	Na	B

The Ru-MACHO reaction only uses green solvents (methanol and ethyl acetate), and also the NaBH4 reduction (methanol main drawback of the Ru-MACHO protocol is that ruthenium is considered a critical element, for which the supply could run out in the following 5–50 years (red flag). Although, the ruthenium catalyst is employed at a very low loading (0.065 mol%). An additional amber flag is added because the catalyst is not currently recovered. The supply of sodium is considered to be sustainable into the future, but boron supply is expected for 100–500 years so results in an amber flag. The supply for lithium and aluminum are predicted to be sufficient for 100–500 more years, which results in an amber flag.[37] However, the demand of lithium is rising rapidly due to its use in Li-ion batteries.

Currently, Ru-MACHO is not recycled as part of the continuous flow protocol, therefore we also evaluated the green metrics associated with its batch synthesis (Table 5 and Table S8†). Ru-MACHO (**A**) can be prepared from the commercially available bis[(2-diphenylphos-phino)ethyl]ammoniumchloride (**D**) and carbonyl-chlorohydridotris(triphenylphosphine)ruthenium(II) (**E**).[13,38] These metrics are very favorable, especially when considering that only 0.065 mol% of Ru-MACHO are used for the hydrogenation.

Table 5 Quantitative green metrics for the synthesis of Ru-MACHO (**A**) from bis[(2-diphenylphos-phino)ethyl]ammoniumchloride (**D**) and carbonyl-chlorohydridotris(triphenylphosphine)ruthenium(II) (**E**)



Metric	Value[a]
Conv. [%]	>99
Yield [%]	85
PMI reaction	11
PMI work-up	8
PMI total	19
E factor	18

[a] Calculations based on the batch protocol reported in ref. 13.

and ethyl acetate), while the LAH reduction uses THF and MTBE which are considered of medium concern (amber flag). The

The hydrogenation is applied to the synthesis of a precursor for a drug candidate, therefore the contamination by Ru metal should be considered. Furthermore, for executing this chemistry on industrial scale, strategies should be considered for the recovery of Ru because it is a critical element. A maximum contamination of 10 ppm is the regulatory limit for Ru metal within a pharmaceutical.[39] Hessel and co-workers reviewed strategies for the separation and recycling of homogeneous transition metal catalysts in continuous flow systems.[40] Conceivably, one of the simplest strategies is the use of scavenging agents in solution or through the incorporation of a scavenging column inline. A sustainable method for the removal of Ru was published in 2018.[41] Here, treatment of the post-reaction mixture with an isocyanide scavenger and then treatment with acid, followed by a simple filtration provided Ru levels below 5 ppm. This type of strategy could be readily incorporated inline for the current process.

Conclusions

A gas–liquid continuous flow Ru-catalyzed hydrogenation protocol was developed for the preparation of an important precursor for the β2-adrenergic receptor agonist. 2,2-Difluoro-2- phenylethanol is a key precursor to abediterol, which has undergone phase IIa clinical trials for the treatment of asthma. The reaction only consumes H_2 as a stoichiometric reagent. The flow reaction uses H_2 as an inexpensive, atom– economic, and environmentally friendly feedstock to generate gas–liquid segmented flow patterns, which allows the reaction to be completed within 1 h residence time. The flow process operates at 60 °C and 20 bar with a much smaller excess (3.3 equivalents of H_2) of gas than required for batch processes. A low catalyst loading (0.065 mol%) afforded the desired alcohol product in 98% isolated yield. In particular, the continuous flow protocol was operated for nearly 6 h run time (total duration) to produce 13.7 g of the API precursor. ^{19}F NMR was successfully incorporated inline for real-time process monitoring of the long run. The environmental impact of the hydrogenation was assessed and compared to an existing stoichiometric lithium aluminum hydride reduction (LAH). The process mass intensity of the hydrogenation represents over a 3-fold reduction when compared to the LAH reduction, and over a six-fold reduction when compared to the NaBH4 reduction. The flow protocol represents an improvement in terms of atom economy, safety and scalability, and also reduces energy consumption and solvent usage.

Acknowledgements

The CCFLOW Project (Austrian Research Promotion Agency FFG no. 862766) is funded through the Austrian COMET Program by the Austrian Federal Ministry of Transport, Innovation and Technology (BMVIT), the Austrian Federal Ministry for Digital and Economic Affairs (BMDW), and by the State of Styria (Styrian Funding Agency SFG). The INFRA FLOW project (Zukunftsfonds Steiermark no. 9003) is funded by the State of Styria (Styrian Funding Agency SFG). J. G. thanks the Banco Santander-Fundación San Pablo-CEU for a mobility fellowship.

Conflicts of interest

There are no conflicts to declare.

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8. Conclusions

- In the first chapter of this thesis a protocol for the Pauson-Khand reaction in continuous flow is presented. Catalytic amounts of unexpensive and accessible $Co_2(CO)_8$ are used in relatively extreme conditions (120-180 ºC, 20 bar), but in around only 10 minutes. Furthermore, only 1.5 to 3 equivalents of carbon monoxide are utilized, and a high scope is demonstrated. We provide examples where different ring sizes are formed including both intermolecular and intramolecular versions. The main advantage compared to the batch procedures is the overall safety of the process, using minimum quantities of catalyst and showing high efficiency and scalability.
- The second chapter includes an application of the previously developed PK flow procedure to the total synthesis of the commercialized drug Treprostinil. This is a PGI2 analog used to treat pulmonary hypertension. The main drawback of its use is associated with its high cost of production. We have developed a new efficient synthesis, changing protecting groups and optimizing some reactions. The overall yield of Treprostinil was 14% from (*S*)-epichlorohydrin in 12 linear steps. In addition to the PKr, the Claisen rearrangement was performed using a plug flow reactor. The application of flow methodology to both reactions drastically improves the overall safety, scalability, and effectiveness of the process.
- The development of the PKr in flow using as substrates vinyl ethers tethered to alkynes through aromatic rings is currently ongoing. This novel application of the PKr allows the preparation of multisubstituted tricyclic benzofurans. Vinyl ethers are generally considered unfavorable substrates for this reaction, but the flow methodology allows their transformations into the corresponding PK product.
- The third chapter consists of the development of a general protocol for alkyne cyclotrimerization and crossed [2+2+2] cycloadditions of diynes with alkynes in a plug flow reactor. The method uses unexpensive $Co_2(CO)_8$, is highly efficient, has a broad scope, and is easily scalable. Alkyne cyclotrimerizations include both terminal and disubstituted alkynes. Excellent yields were obtained in short residence times and low catalyst loadings (2-5 mol%) thanks to the possibility of applying extreme temperatures and pressures. For crossed [2+2+2] cycloadditions 10 mol% of the catalyst was needed to achieve moderate to good yields in 5-10 minutes. However, this was the first time in which the crossed cycloaddition of alkynes and diynes was carried out using $Co_2(CO)_8$ as the catalyst.
- The last part of this thesis consisted of an extensive literature search of cycloadditions performed in flow. Despite the high number of reviews about flow chemistry no revisions related to cycloadditions were reported. We found important for the future development of research in this field to summarize all the recently published progress related and

outline the advantages of performing these reactions in continuous flow and the remaining challenges.

- During the predoctoral stay at the University of Graz, in Prof. C. Oliver Kappe's group, I participated in the investigation of how to perform ester hydrogenations in continuous flow, which had no precedents in the literature. The aim was the synthesis of an interesting molecule precursor, Abediterol, which is a β2-adrenoceptor agonist. A homogeneous ruthenium catalysed ester reduction with hydrogen represents a green, scalable, and more effective approach, in comparison to existing protocols that use stoichiometric amounts of metal hydrides.

9. Resumen y conclusiones

El principal objetivo de esta tesis es el desarrollo de reacciones catalizadas por metales de transición utilizando química de flujo y su aplicación en síntesis de fármacos.

El uso de la química de flujo es pues, el punto en común de todos los capítulos, además del hecho de que ésta se aplica a la realización de cicloadiciones catalizadas homogéneamente por cobalto. En la última década, los reactores de química de flujo forman parte de un campo en rápido crecimiento que está cambiando la forma de trabajo de los químicos orgánicos, no sólo en el nivel académico, sino también en el industrial.

En los sistemas de flujo, los sustratos se introducen disueltos a través de bombas. En el caso que sea necesario, los diferentes productos de partida o catalizadores pueden introducirse de manera separada y mezclarse en las condiciones apropiadas. A continuación, la disolución pasa por un reactor, que puede variar de tamaño utilizándose desde microreactores a grandes reactores industriales. El reactor se puede calentar/enfriar/irradiar dependiendo de los requerimientos de la reacción. Generalmente, la presión del sistema se controla por un regulador de presión a la salida del reactor. Otros sistemas como el análisis en línea, el *quencheo* o la purificación en línea pueden acoplarse para la aumentar la selectividad y la pureza del producto final.

Además, las metodologías de la química de flujo en continuo se pueden combinar con otras tecnologías, como la fotoquímica, la radiación microondas, la catálisis heterogénea, la electroquímica, la impresión 3D, y/o la automatización de procesos. De este modo, la química de flujo puede ser un proceso completamente automatizado con un gran incremento en la eficiencia y, en la mayor parte de los casos, mejorando el impacto en el medio ambiente.

Las principales ventajas que presenta esta metodología, expresadas brevemente, son:

- La rápida optimización de condiciones: Debido al sencillo, preciso y ágil cambio de condiciones, la química de flujo permite estudiar rápidamente las condiciones óptimas para la reacción.
- La automatización: Las plataformas de síntesis de flujo altamente automatizadas se utilizan en diferentes etapas del desarrollo de fármacos: química médica avanzada, optimización de rutas sintéticas, síntesis de quimiotecas de candidatos a fármacos y fabricación de ingredientes farmacéuticos activos (APIs).
- Un mejor manejo de reactivos peligrosos: Las propiedades de estos reactores les confieren una transferencia de calor y masa excepcionalmente rápida. Gracias a ello, se pueden evitar los puntos calientes y fugas térmicas derivados de la acumulación de calor. Por lo tanto, la tecnología de flujo es la opción preferida para reacciones ultrarrápidas y con intermedios altamente tóxicos o inestables.
- El uso de gases: El aumento del área interfacial normalmente acelera la reacción y generalmente se obtienen mejores rendimientos. Además, el uso de controladores de

flujo másico permite determinar la cantidad de gas utilizado con exactitud pudiendo disminuir el uso de gases peligrosos o tóxicos.

- Fotoquímica: Las condiciones de flujo proporcionan una irradiación uniforme. Gracias a eso, la síntesis de cantidades grandes se realiza en horas en lugar de días.
- Electroquímica: Del mismo modo, las altas relaciones de área de superficie respecto al volumen de los microrreactores permiten un transporte efectivo de calor y masa, que lo que puede ser útil durante la electrosíntesis.
- Otras ventajas destacables son el sencillo manejo de condiciones extremas de temperaturas y presiones y el cómodo escalado, que generalmente permite extrapolar las condiciones de reacción estudiadas a cantidades de multigramo, ya sea usando reactores en línea o aumentando el tamaño de reactor.

No obstante, no todas las reacciones se benefician de estas ventajas cuando se realizan en flujo. La forma especial de ajustar los tiempos de calentamiento, mezcla, y reacción en los dispositivos de flujo pueden cambiar la composición de los productos finales. A veces, las reacciones secundarias y la descomposición se pueden minimizar, pero otras los resultados obtenidos son similares en la química por lotes. Algunos procedimientos dan mejores rendimientos o selectividad mientras que otros no muestran ningún beneficio. Por último, aunque la escalabilidad es siempre conveniente en el flujo, puede que no justifique el coste de los recursos necesarios para llevarla a cabo.

Los beneficios aludidos se evidencian en la gran cantidad de APIs y productos naturales que ahora se sintetizan mediante sistemas de flujo en continuo. Integrar en un único proceso continuo no solo la síntesis de moléculas complejas, sino también todo el proceso de fabricación es uno de los retos del futuro. Las principales ventajas serían la transferencia directa del desarrollo a la fabricación, lo cual reduciría los tiempos del proceso y el tiempo de llegada al mercado. Además de la disminución de costes, se pueden lograr una mayor flexibilidad, y una disminución del inventario mediante la colocación e integración de los pasos del proceso en una sola instalación.

Teniendo en cuenta todas estas ventajas y la experiencia previa del grupo en la reacción de Pauson-Khand (rPK), el primer objetivo de esta tesis ha sido el desarrollo de un proceso catalítico y eficiente de dicha reacción usando química de flujo.

La rPK es una cicloadición [2+2+1] en la que un alquino, un alqueno y una molécula de monóxido de carbono forman una ciclopentenona. Esto implica la formación de 3 nuevos enlaces carbono-carbono y uno o dos ciclos dependiendo respectivamente de si la reacción es intermolecular o intramolecular. Se pueden utilizar diferentes complejos metálicos como catalizadores, siendo cobalto el metal más común y $Co_2(CO)_8$ el principal catalizador usado. La rPK se descubrió en la década de 1970, pero no fue hasta mediados de los 90 cuando empezó a ser un proceso catalítico y fue aplicado a la síntesis de productos naturales y fármacos. A lo largo de los años se han utilizado diferentes estrategias para mejorar el rendimiento de la

reacción, como puede ser el uso de microondas, ultrasonidos, tamices moleculares o diferentes aditivos (*N*-óxidos, bases de Lewis…). De este modo, el alcance de la reacción se ha ampliado considerablemente. Sin embargo, la aplicación industrial de esta reacción se ha visto ralentizado, porque muchos protocolos de la rPK implican condiciones extremas, uso de CO, cantidad estequiométrica de complejos de metales de transición, y en ocasiones el uso de aditivos, que generan grandes cantidades de desechos. Por tanto, el desarrollo de un protocolo para la rPK eficiente y escalable usando química de flujo, con cantidades catalíticas de complejos metálicos y un control seguro de la cantidad de gas puede significar un avance considerable.

Únicamente se había descrito un protocolo para la rPK en el que se utilizaba química de flujo con activación fotoquímica del catalizador. Sin embargo, se trataba de un proceso estequiométrico en el que se debía preparar el complejo alquino-cobalto previamente y para lograr finalizar la reacción era necesaria la agitación en matraz una vez fuera del reactor. Por lo tanto, la aplicación industrial de esta metodología era limitada e improbable.

En el primer trabajo incluido en esta memoria, desarrollamos un protocolo catalítico y escalable en flujo para la realización de la reacción de Pauson-Khand, intra e intermolecular tras un amplio estudio de condiciones. Describimos la síntesis de diferentes productos, que incluyen anillos de 5, de 6, e incluso de 7 miembros fusionados a la ciclopentenona formada y que presentan sustituyentes en todas las posiciones. Uno de los aspectos más sobresalientes del protocolo es que sólo era necesario introducir entre 1.5 y 3 equivalentes de CO. Se trata pues de una alternativa escalable, eficiente, verde y con mayor aplicabilidad industrial.

Una vez desarrollado el protocolo de la rPK sobre diferentes sustratos modelo, el siguiente objetivo fue su aplicación a la obtención de una molécula de interés. Se eligió el treprostinil que es un benzoindeno tricíclico análogo de la prostaciclina (PGI2). Sus principales efectos son la inhibición de la agregación plaquetaria y la vasodilatación, incluyendo la vasodilatación pulmonar aguda. Actualmente se usa como tratamiento de la hipertensión pulmonar. Algunas formas de hipertensión pulmonar son afecciones graves que empeoran progresivamente y, a veces, son mortales. Si bien algunas formas de hipertensión pulmonar no pueden curarse, el tratamiento puede ayudar a disminuir los síntomas y mejorar la calidad de vida del paciente. El Treprostinil suele ser administrado por inhalación, y desde 2013 está, además, aprobado por la FDA como fármaco oral. En el año 2019, se aprobó en algunos países la forma genérica. No obstante, el uso de este fármaco continúa siendo escaso y limitado a pacientes hospitalizados. El principal motivo de su bajo uso es su elevado coste, debido, entre otras cosas, a su compleja y larga síntesis.

La principal síntesis del treprostinil fue publicada en 2004 por Moriarty y colaboradores. El núcleo tricíclico de la molécula se forma mediante una rPK intramolecular y estequiométrica, con un grupo hidroxilo protegido con un grupo voluminoso para inducir estereoselectividad. Otras síntesis posteriores han cambiado la manera de introducir el doble o el triple enlace en el precursor de la rPK, o han usado diferentes grupos protectores, aunque la rPK es el principal paso de la síntesis en la gran mayoría. Por tanto, la aplicación de nuestra metodología a ese

paso, de una manera escalable, con bajas cantidades de catalizador y un uso seguro y controlado de condiciones, en especial del uso de CO, significaría una mejor aplicación industrial.

En el segundo trabajo recogido en la memoria, desarrollamos una nueva síntesis del Treprostinil que comprendió 12 pasos lineales desde (*S*)-epiclorhidrina con un 14% de rendimiento global. Dos reacciones claves, un reordenamiento de Claisen y la reacción Pauson-Khand se realizaron a escala de multigramo en un reactor tubular siguiendo nuestro protocolo. Mejoramos la productividad, seguridad y separación del producto final en el reordenamiento de Claisen y logramos la rPK con un 5 mol% de $Co_2(CO)_8$ como catalizador y 3 equivalentes de CO. El producto de la reacción de Pauson-Khand se transformó en el treprostinil en 3 pasos adicionales.

Otros sustratos de la rPK que pueden beneficiarse de las condiciones de la química de flujo son los vinil éteres. A pesar del amplio alcance que posee la reacción, los ejemplos usando estos sustratos son escasos y generalmente se usan como equivalentes de etileno, no incorporando toda la estructura en el producto final. Además, el uso de vinil éteres anclados en un anillo aromático, podría producir benzofuranos tricíclicos polisustituidos de una manera rápida y eficiente. Hemos desarrollado la obtención de estos benzofuranos a partir de viniléteres unidos a alquinos a través de un anillo aromático en un trabajo pendiente de completar y publicar.

El siguiente objetivo de esta tesis fue el desarrollo de la reacción de cicloadición [2+2+2] usando $Co_2(CO)_8$ en química de flujo. Las reacciones de cicloadición [2+2+2] permiten sintetizar gran variedad de ciclos aromáticos y no aromáticos partiendo de diferentes tipos de sustratos insaturados que pueden ser alquinos, nitrilos, alquenos, cumulenos y heterocumulenos. Presentan una gran economía atómica pudiendo ser catalizadas por multitud de complejos metálicos. Las ciclotrimerizaciones pueden clasificarse en tres tipos diferentes dependiendo de los sustratos utilizados. En primer lugar, la ciclotrimerización de alquinos totalmente intermolecular; en segundo término, encontramos la ciclotrimerización cruzada, en la que dos de los triples enlaces están en el mismo sustrato; y finalmente tenemos la variante totalmente intramolecular, en la que los tres enlaces se encuentran dentro de la única molécula de partida.

Entre los complejos que catalizan o median en esta reacción, se encuentran los formados por cobalto, como los que poseen estructura de $CpCoL_2$ (L=CO o CH_2=CH_2). Generalmente, dichos complejos se usan en cantidades estequiométricas, acompañados de altas temperaturas e irradiación. El $Co_2(CO)_8$ representa una alternativa especialmente útil para ciclotrimerizaciones de alquinos, muy usado para la síntesis de estructuras en forma de estrella, pero sin precedentes en cicloadiciones [2+2+2] cruzadas.

La posibilidad que nos permite el fujo de usar condiciones extremas, en este caso de temperatura y presión, nos permite reducir el tiempo de reacción a minutos, e incluso segundos. Además de minimizar el uso de catalizador y ampliar el alcance a reacciones de cicloadición [2+2+2] cruzadas.

El tercer trabajo presentado en la memoria muestra el desarrollo de un protocolo para realizar ciclotrimerizaciones en un reactor tubular, usando únicamente un 2-10 mol% de $Co_2(CO)_8$ como catalizador. Se aplicó a gran variedad de alquinos mono y disubstituidos y se lograron cicloadiciones [2+2+2] cruzadas que no tenían precedentes. El procedimiento resultó ser muy efectivo con un amplio alcance y productividad, debido a sus cortos tiempos de reacción.

A continuación, se decidió realizar una revisión de todas las cicloadiciones realizadas usando química de flujo, para destacar las ventajas y los inconvenientes de trasladar este tipo de reacción al flujo continuo. Las cicloadiciones son la manera más común de construir carbo- y hererociclos. A pesar de la gran cantidad de revisiones publicadas sobre química de flujo, no existía ninguna que estudiara las ventajas y los últimos avances que aporta esta tecnología en el campo de las cicloadiciones. El cuarto trabajo recogido en la memoria es un artículo de revisión que se elaboró como consecuencia de este estudio bibliográfico.

Finalmente se incluye un trabajo que es fruto de la estancia realizada en la Universidad de Graz, en el grupo del profesor C. O. Kappe y que consiste en el estudio de la hidrogenación catalizada por rutenio de un éster precursor del Abediterol, un agonista del receptor β2 adrenérgico.

Conclusiones:

- Se ha desarrollado un protocolo para la rPK en flujo continuo. Se utilizan cantidades catalíticas de $Co_2(CO)_8$ en condiciones relativamente extremas (120-180 ºC, 20 bar) en aproximadamente 10 minutos. Además, sólo es necesario el uso de 1.5-3.0 equiv. de monóxido de carbono, y se demuestra un amplio alcance. El protocolo se aplica a la formación de distintos tipos de anillos, así como a la versión intra y a la intermolecular. La principal ventaja frente a los procedimientos convencionales es la seguridad global del proceso, usando una cantidad mínima de catalizador y demostrando una alta eficiencia y escalabilidad.
- El protocolo anterior para la rPK en flujo se aplicó a la síntesis del fármaco comercial Treprostinil, el cual es un análogo de la PGI2 utilizado para tratar la hipertensión pulmonar. El principal problema para su uso es su elevado coste de producción. Hemos desarrollado una nueva síntesis más eficiente, cambiando grupos protectores y optimizando algunas reacciones. El rendimiento global es del 14% partiendo de (*S*)-epiclorhidrina en 12 pasos lineales. Además de la reacción de Pauson-Khand, el reordenamiento de Claisen se realiza también en un reactor de flujo. La aplicación de la metodología de flujo a ambas reacciones mejora drásticamente la seguridad, escalabilidad y eficacia del proceso.
- El desarrollo la rPK en flujo utilizando como sustratos éteres vinílicos unidos a alquinos a través de anillos aromáticos está en curso. Esta nueva aplicación de la rPK permite obtener benzofuranos tricíclicos multisustituidos. Los éteres vinílicos, se consideran sustratos desfavorables para la reacción de la PK pero la metodología en flujo permite su transformación eficiente en el producto correspondiente.
- Se desarrolló un protocolo general para la ciclotrimerización de alquinos y la cicloadición [2+2+2] cruzada de diinos con alquinos en un reactor de química de flujo. El método usa $Co_2(CO)_8$ como catalizador y es eficiente, fácilmente escalable y con amplio alcance. Las ciclotrimerizaciones incluyen alquinos tanto terminales como internos. Se logran rendimientos excelentes, en cortos periodos de tiempo con baja cantidad de catalizador (2-5 mol%) gracias a la posibilidad de aplicar condiciones extremas de temperatura y presión. Para las cicloadicciones cruzadas, se necesitó un 10 mol% de catalizador para lograr rendimientos de moderados a buenos en 5-10 minutos. Sin embargo, es la primera vez que se usa este catalizador para esta transformación.
- Por último, se realizó una amplia búsqueda bibliográfica de cicloadiciones realizadas en reactores de química de flujo. A pesar la gran cantidad de artículos de revisión sobre química de flujo no había uno dedicado a cicloadiciones. Resumir y destacar las ventajas de estas transformaciones usando química de flujo en comparación con la química convencional puede resultar importante y útil para el desarrollo de la investigación en este campo.

- El trabajo realizado durante la estancia en la Universidad de Graz, en el grupo del Prof. C. Oliver Kappe, trató en parte sobre el estudio y desarrollo de la hidrogenación de un éster en flujo continuo, que no tenía precedentes en bibliografía. Se consiguió obtener un precursor del Abediterol, un agonista del receptor β2 adrenérgico. Una reducción homogénea de un éster con hidrógeno y catálisis de rutenio representa un enfoque ecológico, escalable y más eficaz, en comparación con los protocolos existentes que utilizan cantidades estequiométricas de hidruros metálicos.