TANDEM REACTIONS IN ORGANIC SYNTHESIS: THE ARTISTIC APPROACH IN MODERN ORGANIC CHEMISTRY

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REACCIONES TÁNDEM EN SÍNTESIS ORGÁNICA: EL AVANCE ARTÍSTICO EN LA QUÍMICA ORGÁNICA MODERNA.

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ABSTRACT

The rise of the processes involving sequential reactions (tandem) is mainly due to its advantages. Although it is required high inventiveness and synthetic knowledge, this provides synthetic pathways and processes whose atomic economy is high, in addition to being inexpensive, since it can avoid many purification and separation steps during synthesis. They are also environmentally generous, avoiding the use and production of toxic substances, and the possibility to build complex molecules with high stereoselectivity. This review aims to give a few examples, from existing plethora so far, allowing illustrating and clarifying aspects related to processes involving sequential reactions with an inventiveness that borders on a level that it would be considered as art.

Keywords: Tandem, Domino, Michael, aldol, multicomponent, chiral auxiliary.

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RESUMEN

El auge de los procesos con reacciones secuenciales (tándem) se debe principalmente a sus ventajas. Aunque requiere de alto ingenio y conocimiento sintético, proporciona rutas de síntesis y procesos en los que la economía atómica es elevada, además de ser de bajo costo, ya que se pueden evitar muchos pasos de purificación y separación en el transcurso de la síntesis. Además son ecológicamente generosos, evitando el uso y la producción de sustancias tóxicas y, por si fuera poco, con los cuales se puede llegar a construir moléculas complejas, con alto nivel de estereoselectividad. Este documento de revisión pretende dar algunos pocos ejemplos, de la plétora existente a la fecha, que permitan ilustrar, y de cierta manera aclarar, aspectos relacionados con procesos en los que se involucren reacciones secuenciales, con un ingenio tal que bordea en niveles que se considerarían como arte.

Palabras clave: Tándem, Dominó, Michael, aldol, multicomponente, Auxiliar quiral.

INTRODUCTION

In the time elapsed since the 90s to currently, organic synthesis has ceased to be a practice that mixed inventiveness, understanding, knowledge, and some luck, to a modern science that can increasingly use a great number of chemical conversions and transformations in a logical and efficient manner. This approach allows the construction of highly complex molecules assuming an enormous challenge to the experimenter. Thus, the synthesis of compounds still has a double category of science and art (Nicolau and Sorensen, 1996).

The relationship between the structural complexity and the smallest number of steps in a synthetic procedure is pursued to be continuously improved. Now it is habitual to avoid those synthetic routes require many steps, since this promotes economically or environmentally situations. Current methods therefore must properly handle resources and time, as well as reduce the amount of wastes formed and avoid reactive and toxic solvents. However, the fact to achieve very complex structures would not be possible without the growing and development of new methodologies to examine novel synthetic ideas.

Therefore, a primary objective for the contemporary organic synthesis - which is closely related to the preparation of naturally-occurring compounds, drugs, agrochemicals and other important materials - is the improvement of efficiency, among other mentioned requirements (vide supra), and one of the ways to satisfy these aspirations is the development and fine-tuning of those methods known as tandem (Grigg *et al.*, 1996), consisting of several sequential reactions that efficiently allow the creation of compounds with complex structures starting from simple, modest substrates (Semreen *et al.*, 2013).

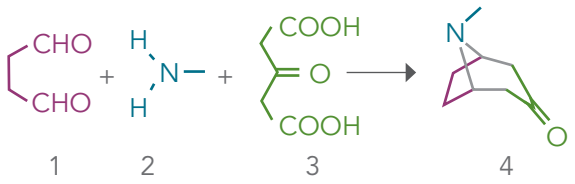
Protocols involving tandem (Grigg *et al.*, 1996; Semreen *et al.*, 2013) and multicomponent (Dyker, 1997; Jieping and Hughes, 2005) reactions are those that allow building complex molecules in few steps, representing an area of exploration with great

interest. However, the words tandem, sequential, domino, cascade, among others, sometimes communicate ambiguities, although in many papers are used as synonyms. Likewise, an urged demand to modern organic synthesis is focused to decrease the formation of unwanted products, with a direct environmental impact. Such transformations seek to support the "atom economy", a term fixed by Barry Trost to indicate that the clear intention is that most of the atoms or fragments in the starting materials are integrated into the product (Trost, 1995). It is clear that few processes satisfy this additional principle, but today there are a vast number of attempts to achieve this noble purpose (Marson, 2012).

SEQUENTIAL REACTIONS

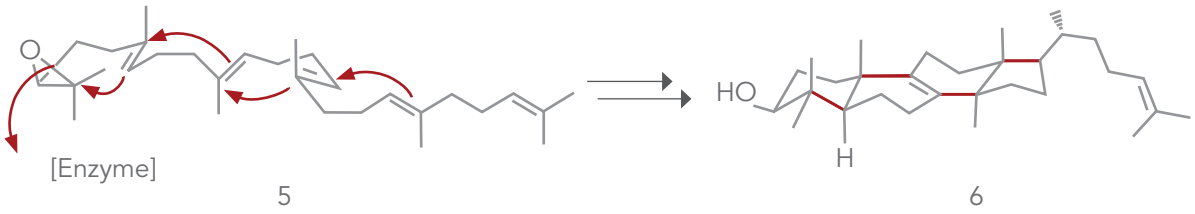
Sequential reactions (also known as "one-pot") are those that all reagents and substrates are placed into a flask to give the final product without further additions, isolates or manipulations (excepting of course the final isolation of the desired product) (Fraile *et al.*, 2011). They are characterized by their elegance, high stereoselectivity and the simple way to perform them. Those reactions allow constructing complex molecules in a few synthetic steps and often are characterized by a lack of collateral products, becoming as environmentally friendly alternatives. In addition, the amount of solvent required for one-pot process is comparatively much lower to that of multistage processes. This kind of reaction has extensively been studied in recent years and, due to its favorable qualities, most likely will be the "process key" of the organic chemistry (Marson, 2012).

Clearly appreciated is that, although in the laboratory it is no common to perform sequential reactions, the nature frequently uses them and they are very common in enzymatic pathways. In this way, nature is not only very selective, but also very effective because several bonds are formed or broken without isolation of any intermediate. This kind of process appears, e.g., in the biosynthesis of alkaloids, terpenes, and steroids. Taking biogenesis as a prototype, we can "discover" important sequential transformations. Thus, by a double Mannich reaction of a pyrroline salt (in turn formed from ornithine) with an acetoacetate is obtained the bicyclic tropane skeleton, an important constituent of many alkaloids such as ecgonine and atropine. This biogenetic analysis led to Robinson design a stylish synthesis of tropinone (4) through a sequential reaction by mixing succinaldehyde (1), methylamine (2), and 3-ketopentanedicarboxylic acid (3) (Scheme 1) (Fleming, 1973). This synthesis of tropinone by Robinson in 1917 within a test tube (another chemist, Willstätter, needed to use many synthetic steps), gave him international recognition by revealing a new form of synthetic thinking (Vanderwal and Sorensen, 2004).



Scheme 1. Synthesis of tropinone

Another fascinating illustration from Nature is the cyclization of squalene oxide (5) to produce lanosterol (6), a precursor for the synthesis of steroids (Scheme 2) (Corey *et al.,* 1992). In this case, a first reaction triggers the sequence of following steps, so often it is mentioned as "cascade cyclization", another expression usually applied to these reactions. The scientific literature also describes these cyclizations as "zipper reactions", since cyclization processes seem to close down as an acyclic skeletons zipper (Balova *et al.*, 2003).



Scheme 2. Squalene oxide (5) cyclization to produce lanosterol (6).

An evident interrogation would appear is how should properly termed the sequential reactions. Unfortunately, we can't categorically answer that question because, although there are a plethora of proposed terms, the authors do not fully agree about the meaning of them. Consequently, it is possible to find in the literature two or more different names for the same type of reaction.

Many papers widely use the expression "tandem" reaction. Tandem literally means "one after another" and particularly applies to a kind of vehicle whose drive elements are spatially located next to each other. However, the tandem concept associates an idea of temporality: the elements are positioned behind each other but are simultaneously moved. Other authors prefer to name these processes as "domino reaction" (Tietze, 1996). A domino reaction "is a process that involves two or more transformations forming bonds (usually C-C), taking place under the same reaction conditions without adding further reagents or catalysts, and the following reactions acquire functionality from the previous step" (Fresner *et al.*, 1989). It is clear to state that for this kind of reactions, the preliminary formation of a reactive intermediate, such as a carbocation or carbanion, is not considered as a step reaction (Tietze, 1996).

Hence, the formation of a diene by retro-Diels-Alder reaction and subsequent cycloaddition is also considered as a tandem or domino reaction (Winkler, 1996). In a tandem (or domino) reaction is ideally pursued that the individual steps have comparable reaction rates in order to avoid the reaction can enrich in an intermediate, giving undesirable reactions such as self-condensation. Thus, a "stationary state" concentration must be achieved for the intermediate formed (Tietze and Beifuss, 1993). In fact, the tandem process of a Knoevenagel-hetero-Diels-Alder reaction has been followed by NMR confirming that concept (Tietze, 1984). Tietze has also used the concept of consecutive reaction as a process when a reagent, additive, or catalyst is added after the first transformation, but without first-formed product isolation, whose new reaction leads to the final product (Tietze and Beifuss, 1993). In these cases the two reactions can be performed under different reaction conditions, e.g., at different temperatures, although this parameter should not be taken as a requirement. Finally, reactions or iterative processes could be mentioned, consisting of the repetition of a transformation that can also be performed as tandem reaction, sequentially or individually. From the above-mentioned concepts, the tandem (or domino) reaction undoubtedly involves the most simple and elegant transformation. Formation of a cycloadduct could then be accomplished by concerted reaction or by two sequential reactions. Hence, the concerted reaction could be therefore considered as a two-step tandem process (Winkler, 1996). However, the domino reaction designation - for this kind of reactions - appears to be more accurate (associates a sense of temporality) as often happens in chemical reactions, i.e., the individual reactions occur one after another

as a result of the above. However, the tandem concept is more extensive. In any case, it is expected that both expressions are used for a long time in the scientific literature as synonyms.

The words such as cascade, consecutive and sequential are usually used in order to specify how reactions happen (Denmark *et al.*, 1996). With these conventions it is possible to distinguish three broad categories: (1) *tandem cascade reactions*, whose reactions are intrinsically coupled, i.e., each subsequent stage happens under structural change provided by the previous step under the same reaction conditions (equivalent definition to the domino reaction, *vide supra*) (Tietze and Beifuss, 1993), (2) *tandem consecutive reactions*, where the first reaction is necessary but not enough to lead a tandem process, i.e., other reagents are necessary to be added or modify the conditions to facilitate the propagation reaction, and (3) *tandem sequential reactions*, where the second stage requires the addition of substrates, starting materials or a new reagent (Denmark *et al.*, 1996).

Types of Tandem reactions

Tandem reactions have been classified into four families: cationic, anionic, radical, and pericyclic depending on the nature of the first step, each one can be further classified into four subgroups in response to the second step (Bunce, 1995; Tietze and Beifuss, 1993). If the tandem process involves more than two transformations, this system can be extended. Photochemical, carbene or carbenoid-involving, and transition metal-induced or catalyzed sequences must also be added. The latter ones are undoubtedly the most fruitful and promising research areas, because new tandem reactions are discovering and/or inventing each day (Fraile *et al.*, 2011).

As mentioned above, the criterion of this classification is based on that species generally formed in the first reaction could be cations, anions, or radicals. The cation expression here is synonymous to "electrophile" and anion to "nucleophile". Thus, the addition of a nucleophile to a double bond C=C or C=X is considered as an anionic transformation. In this regard, the Mannich reaction, one of the oldest domino reactions, is an anionic-anionic process. For most tandem reactions, the first two changes involve the same kind of reaction, mostly anionic-anionic type. In recent years many pericyclic-pericyclic tandem reactions have been described. Additionally, in most multistage tandem reactions, the second and subsequent steps usually are intramolecular, a fact that all synthetic researcher recognize as advantage (Nicolaou *et al.*, 2003).

Pericyclic sequences are an excellent strategy for building complex skeletons, because the tandem process usually produces several bonds, new rings and potentially several stereogenic centers (Pellissier, 2006a). Besides pericyclic-pericyclic sequences such as Diels-Alder/Diels Alder, Diels-Alder/retro-Diels-Alder, Diels-Alder/ene, Diels-Alder/1,3-dipolar, Cope/Claisen, oxy-Cope/Claisen, oxi-Cope/Cope, Claisen/Diels-Alder, Claisen/ene, among others, it is possible to find pericyclic-cationic, anionic-pericyclic, and pericyclic-radical combinations (Winkler, 1996; Back *et al.*, 2010).

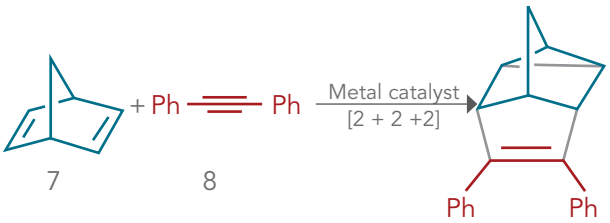
Tandem Cycloadditions

A field that allows accessing to many natural products, and their analogues, giving versatility and stereochemical advantages is tandem cycloadditions. A review on the Diels-Alder cycloaddition coupled in tandem was published many years ago (Winkler 1996). This review classifies the reactions considering that the first reaction involves the masking (or not) to the diene and dienophile for the second cycloaddition. Thus, the extrusion of carbon dioxide from a pyrone generates a second diene (e.g., 1,3-cyclohexadiene), which can then undergo a second cycloaddition. The non-interrupted reactions can be classified in turn as:

(a) simultaneous reactions whose diene and dienophile are present in the starting compounds and

(b) sequential reactions whose first cycloaddition generates a new diene or dienophile that undergoes a second cycloaddition.

Other multicomponent cycloadditions are comprised under the name of cycloadditions [2+2+2] that allow the formation of carbocyclic and heterocyclic systems (Geis and Schmalz, 1998) (Scheme 3). Once more, the expression cycloaddition has a formal sense, since these reactions do not involve real one-stage cycloadditions for all three components. Rather the "cycloaddition" implicates the reaction between a transition metal complex and one or two of the components causing a metallacycle intermediate, whose reaction with the remaining components leads to the final ring system. A particular case of this kind of reaction involving two real tandem cycloaddition reactions, the first one as Diels-Alder and the second one as 1,3-dipolar, especially in its asymmetric version using a chiral heterodiene, was reported some years ago (Coutts and Wallece, 1994; Thorarensen and Denmark, 1996).



7 8 9

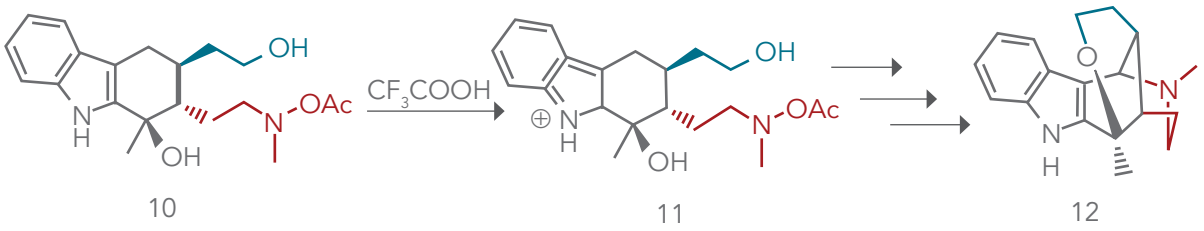
Scheme 3. [2+2+2]-type cycloaddition

USES OF TANDEM REACTIONS IN ASYMMETRIC SYNTHESIS

Quality and importance of a tandem reaction can be correlated between the number of bonds generated in the total process and the structural complexity of the product. This transformation can be given as mono, di or multicomponent. Then, the most of the known multicomponent processes, but not all, can be defined as a subset of domino or tandem reactions (Marson, 2012). The use of this kind of reactions in asymmetric synthesis is constantly increasing. This fact is due since single-step reactions enable synthesis of a wide range of structurally diverse compounds through an efficient, economical way by using reasonably simpler processes. The reactions can be carried out in solution, as well as on solid supports and provide easy access to highly diverse molecules, even including the possibility of automated synthesis (Tietze *et al.*, 1998; García-Ruano *et al.*, 2008).

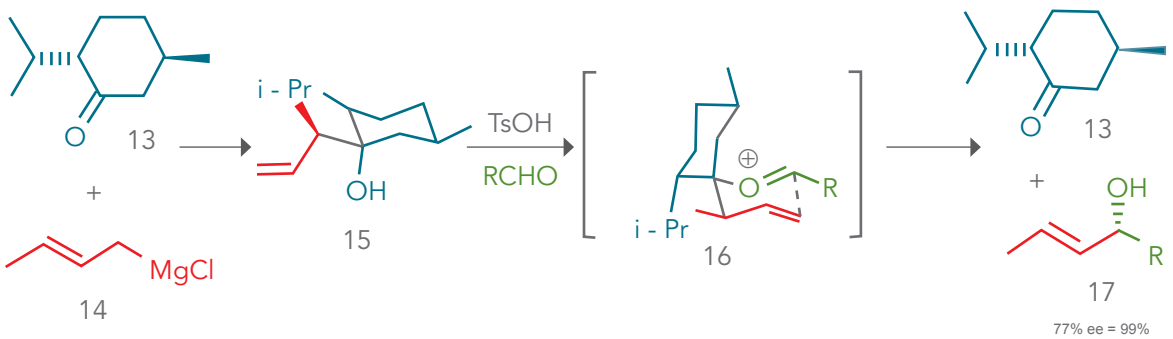
Cationic sequences

Cationic sequences are one of the oldest known tandem reactions. In this process, a carbocation is formed. This carbocation can be formed by removing or adding a positive species such as a proton. The carbocation then reacts with a nucleophile to form a new carbocation that undergo one or more additional transformations within a cation-cation process, being eventually captured by a nucleophile or stabilized by a proton elimination. Biomimetic cyclization of polyenes is of great importance. An application of steroid synthesis was published many years ago, demonstrating the effectiveness of a fluorinated C-8 atom as an auxiliary carbocation stabilizer to increase the polyene cyclization (Johnson *et al.*, 1993). Several versions of this kind of cascade reactions have been developed, e.g., reaction applied for the synthesis of (-)-gilbertine (Scheme 4) (Jiricek and Blechert, 2004), where the formation of a cation (10) (as ammonium) is generated from an appropriately substituted indole (11). Once the ammonium is formed, the molecule undergoes a set of rearrangements and nucleophilic additions to reach the desired structure (12), corresponding to the tetracyclic alkaloid, (-)-gilbertine.



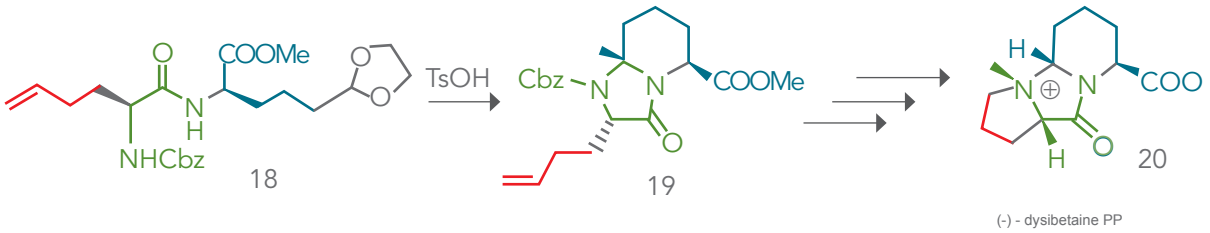
Scheme 4. Synthesis of (-)-gilbertine by asymmetrically sequential reactions.

Another example is the process called Ferrier Rearrangement, which has been used to prepare pyrano[2,3-*b*][1]benzopyrans by a cation-mediated sequential process. Reaction of 2-*C*-acetoxymethylgalactal with *p*-chlorophenol in the presence of $BF_3.Et_2O$ resulted in a Ferrier exocyclic rearrangement, followed by intramolecular cyclization toward the pyrano[2,3-*b*][1]benzopyran (Booma and Balasubramanian, 1993). A crotylation of aldehydes mediated by menthone (13) was also developed (Nokami *et al.*, 2000). The reaction mechanism starts with a hemiacetal formation and an oxonium ion is then generated by dehydration in acid medium. This intermediate rearranges, adopting a half-chair transition state (16), by a oxonia-Cope-type [3,3]-sigmatropic process affording the crotylated product (17) (Scheme 5).



Scheme 5. Menthone-mediated Asymmetric crotylation of aldehydes.

An interesting intermolecular cationic tandem reaction was used as the key step in the asymmetric synthesis of the natural product (-)-dysibetaine PP. The reaction is useful when L-allysine-derived dipeptide (18) are treated with TsOH (catalytic amount) leads to the bicyclic *N,N*-acetal (19) formation through cascade cationic cyclizations in good yields and diastereoselectivities. Once the bicyclic was formed, it was further converted into (-)-dysibetaine PP (20) (IJzendoorn *et al.*, 2006).



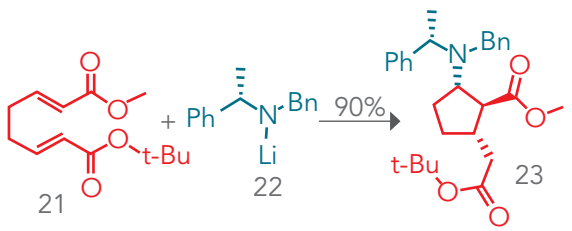
Scheme 6. (-)-dysibetaine PP-targeted intermolecular cationic tandem cyclization.

The endocyclization of various acyclic polyunsaturated terpenoids-derived polyepoxides, including geraniol, farnesol and geranylgeraniol, is another example of cationic sequence, which provides an efficient, stereoselective synthesis of substituted oxepanes and fused polyoxepanes. This process conducts toward Boron trifluoride etherate-promoted polyepoxide oxacyclization (McDonnald *et al.*, 2002). Similarly, BF_3.Et_2O-promoted protocols lead to some interesting transformations such as the cyclizing rearrangement of (+)-arenarol forming (+)-Aureol (Nakamura *et al.*, 2002) and the synthesis of the tetracyclic core (+)-stachyflin, a potent antiviral against influenza A, which is characterized by BF_3.Et_2O-inducted epoxide opening, leading to cyclization as key step (Nakatani *et al.*, 2002).

Anionic sequences

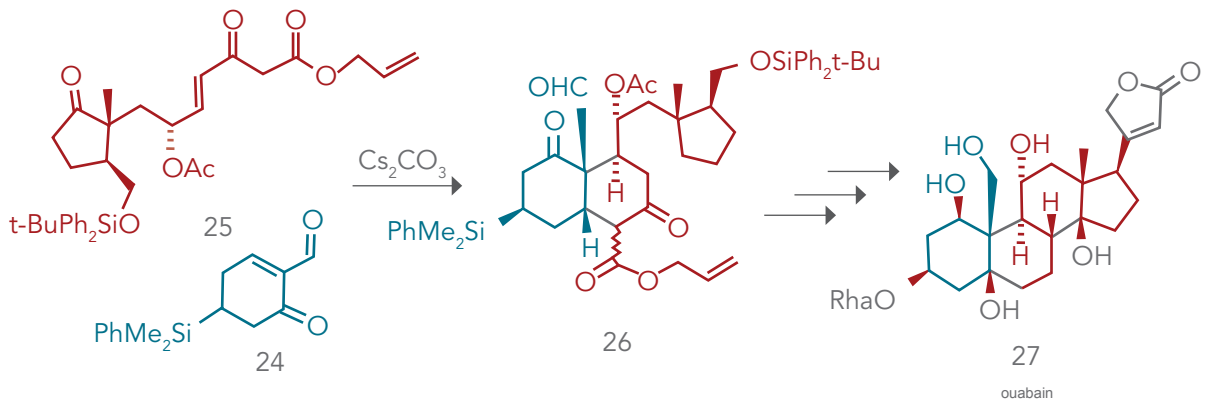
The largest family of tandem reactions is the process that involves anionic intermediates. In such reactions, the first step is the formation of an anion or a nucleophile. Most cases involve the deprotonation of a CH group with the formation of a carbanion, which then reacts with an electrophile to form a new anionic functionality. The latter anion attacks another electrophile in an anionic-anionic process. The sequence is completed by reaction with an electrophile, such as a proton, or by removal of a group $X^{(-)}$. In the case of an anionic-pericyclic process, the anion formed in the anionic step is converted to a multiple bond-containing compounds, which is then able to undergo a pericyclic reaction. Finally, a third class of anionic sequences is represented by the processes when the second step is not anionic or pericyclic. Family tandem reactions involving anionic intermediates have been used extensively in total synthesis (Hashimoto *et al.* 2002; Slana *et al.*; 2006 Li *et al.*, 2007).

A typical case of anionic-anionic sequences are those when there is a Michael's initiator or terminator to generate a cyclic structure. The tandem Michael-Michael reactions are a powerful tool for the formation of ring systems common in natural products. Several elegant applications of Michael-double asymmetric intramolecular reaction have been designed for the synthesis of oxygenated derivatives of diterpene alkaloids such as atisine (Ihara *et al.*, 1992). Another illustration is the asymmetric synthesis of 2-*N*-benzyl-*N*-α-methylbenzylamino-5-carboxymethyl-cyclopentane-1-carboxylate (23), achieved by asymmetric Michael addition and subsequent intramolecular 5-exo-trig cyclization (Scheme 7) (Urones *et al.*, 1997).



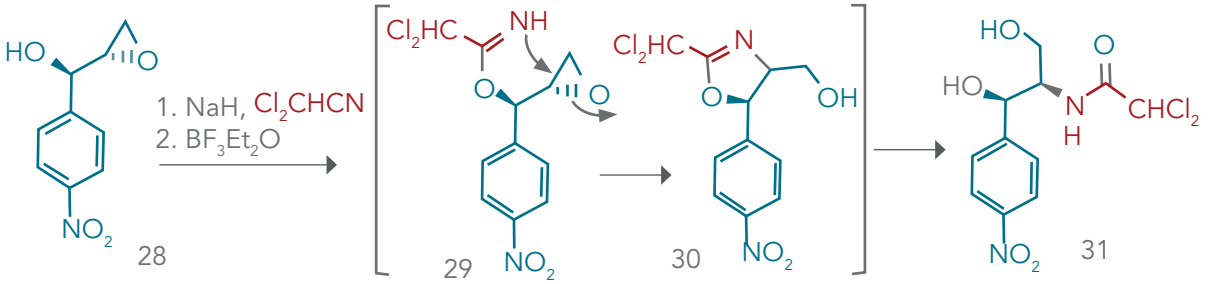
Scheme 7. Michael addition in anionic tandem reactions

A recent fascinating example of the anionic sequence is the first and long-awaited total synthesis of the natural cardioactive glycosylated steroid ouabain (Zhang *et al.*, 2008). This transformation was achieved on the basis of a polyanionic cyclization strategy, providing a tricyclic domino intermediate (26) in good yield (85%) (Scheme 8). The intermediate is formed from an asymmetric tandem Michael/Michael reaction occurring between chiral cyclohexenone (24) and chiral Nazarov substrate (25) in the presence of C_s2CO_3, whose product (26) was finally converted into expected ouabain (27).



Scheme 8. Ouabain (27) synthesis through a polyanionic cyclization strategy.

In addition, some asymmetric variations for the Mannich-Michael reaction have also been developed, such as those involving amino acid-derived imine esters as chirality mediators using Danishefsky's dienes, which release the corresponding chiral enaminone (Waldmann and Braun, 1992). This methodology was applied to the synthesis of highly functionalized tetracyclic indole bases corresponding to the skeleton of yohimbine and reserpine-like alkaloids (Lock and Waldmann, 1996). Finally, an interesting example of an anionic reaction through *N*-containing intermediates is that used to the enantioselective synthesis of (-)-chloramphenicol (31), based on the $BF_3.Et_2O$-mediated cascade reaction involving a chiral epoxydichloroimidate opening (29) and *in situ* hydrolysis of the oxazoline (30) (Scheme 9) (Bhaskar *et al.*, 2004).



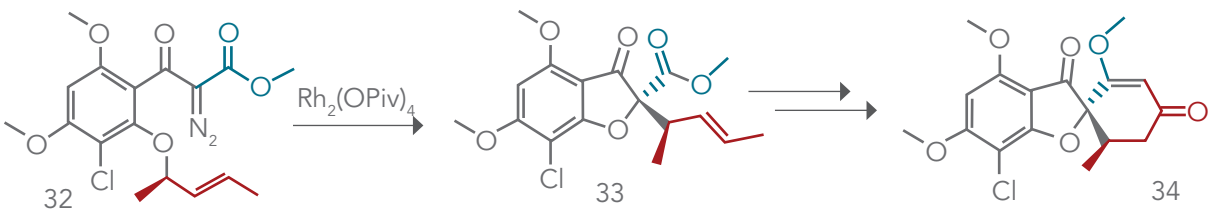
Scheme 9. Enantioselective synthesis of (-)-chloramphenicol (31).

Pericyclic, Radical and Carbene sequences

Pericyclic reactions such as Diels-Alder, ene, Claisen, Cope or electrocyclic reactions are themselves extremely useful for transformations. By combining two or more pericyclic reactions, the effect can be multiplied. There are considerable advances in the use of pericyclic processes to start inter and intramolecular sequences. In particular, tandem sequences involving asymmetric cycloaddition reactions are highly effective processes for the rapid elaboration of complex polycyclic systems, since each cycloaddition event generates a new ring and two new covalent bonds. In this set of reactions, there are sequences often including a Diels-Alder reaction in the first step (Pellissier, 2006a). Likewise, the pericyclic processes are more easily engageable to anionic processes, because several rearrangements required deprotonation as requirement in the reaction. The product of these sequences frequently incorporates enolates or other nucleophilic group which will further react with electrophilic reagents (Saito *et al*., 1992).

On the other hand, the potential of the radical-involving sequences is very high due to the mild conditions where radicals are generated. These mild reaction conditions tolerate a wide range of functionality in substrates, allowing that complex synthetic targets can be prepared with minimal use of protecting groups. Most transformations in this category involve radical-radical tandem processes. As an example, carbohydrates are converted to their next lowest homologue by means of ß-fragmentation-mediated cyclization sequence (Malacria, 1996). The high selectivity of the reaction, along with the chiral nature of the sugars, makes it a highly valuable procedure as a source of chiral building blocks for organic synthesis.

Tandem reactions using carbene intermediates have been a productive area of discovery in recent years (Burling *et al*., 2007). Carbenoid and carbene can react with a number of functional groups. A more reactive intermediate (perhaps an ylide) often is formed which can undergo further subsequent reactions. It was demostrated that the use of oxygen-containing chiral auxiliaries induces a modest enantioselectivity in Cope cyclopropanation reactions (Davies and Huby, 1992). This asymmetric approach is given by blocking of one of the faces at carbenoid through intramolecular coordination, as the case of carbene-based tandem reaction toward the enantioselective synthesis of the antifungal agent, (+)-griseofulvin (34) (Scheme 10) (Pirrung *et al*., 1991). A review with numerous interesting examples of radical, pericyclic and carbene-based sequences was recently published (Pellissier, 2013).



Scheme 10. Asymmetric carbene-based tandem reaction toward (+)-griseofulvin synthesis

Multicomponent reactions

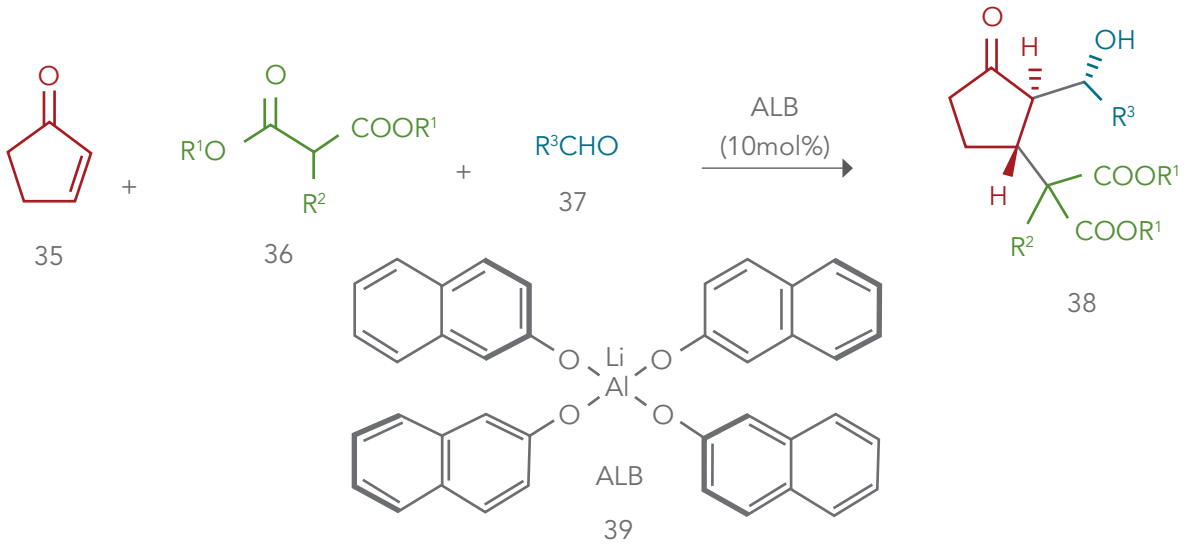
Multicomponent reactions (MCRs) are those in which three or more reactants come together (or close together) in a single reaction vessel to form a new product, which contains portions of all components (Pellissier, 2006a). The MCRs directly convert more than two substrates in its product by "one-pot" reaction. Starting materials for this kind of transformation are rich in functional groups. Typically, MCRs provide complex products by reaction of structurally simple starting materials. The MCRs proceed according to the tandem principle, since subsequent transformations are a consequence of the functionalities produced in the previous transformation. These reactions are highly flexible, (chemo)-selective, convergent, and they are efficient atomic processes with high exploratory power. Inspired by the mode of action of nature, many research groups have published the simple operation to build complex molecules, where several bonds are formed in a sequence without isolation of intermediates. Such processes, commonly referred to tandem reactions, led to the ecologically and economically favorable production of a wide range of organic compounds.

Ugi reaction is one of the emblematic cases of a MCR. This reaction has been studied extensively being a typical four-component condensation between a carboxylic acid, an oxo compound, an C-isocyanide, and an amine affording an α-aminoamide (Domling and Ugi, 2000). Ugi reaction has been applied to the asymmetric synthesis of amino acids. Another example is the Biginelli synthesis of dihydropyrimidines consisting of a condensation of urea, an aldehyde, and a 1,3-ketoester. The first asymmetric versions of this reaction were developed since 2001 using galactose-derived aldehydes as chiral auxiliaries (Dondoni *et al.*, 2001). Finally, Petasis reaction is the condensation between carbonyl compounds, amines, and aryl or vinylboronic derivatives. This reaction has been improved with the three possible chiral reagents. Thus, various chiral amines have been implicated as phenylglycinol, phenylethylamine, morpholin - 2 - one derivatives, and aminodiols. In this way it has demonstrated the possibility of using chiral aldehydes as chiral auxiliaries, giving excellent yield and stereoselectivity (Petasis and Zavialov, 1997).

Employing chiral catalysts

Reactions employing an organic molecule as catalyst in order to create enantiomer-enriched products are much more innovative, artistic approaches with great potential that minimize formation of by-products, operating costs, and environmental deterioration (Zhou, 2010). Since a few years, the field of asymmetric catalysis, previously dominated by metal catalysis and biocatalysis, has been complemented by organocatalysis using small amounts of organic molecules as a third powerful tool. The organocatalysts are usually non-toxic, highly efficient and selective, rapidly available, metal-free and robust. These advantages explain the growing interest in their use in organic synthesis (Dalko and Moisan, 2004; Seayed and List, 2005).

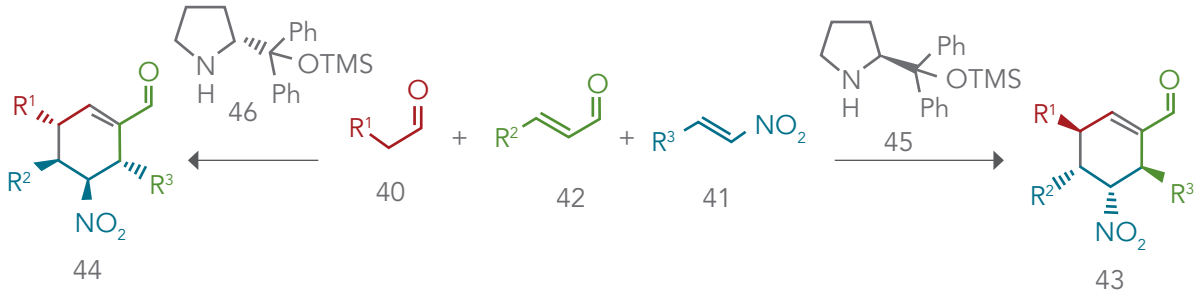
The first asymmetric catalyzed Michael-aldol tandem reaction was reported in 1996 (Arai *et al.*, 1996). This tandem reaction was favored by the catalytic use of a asymmetric multifunctional heterobimetallic complex such as AlLibis[(R)-binaftoxido] (ALB) (39) (Scheme 11). The probable mechanism of this catalytic asymmetric reaction starts when the diethyl malonate (36) react with ALB giving the corresponding enolate. This enolate then reacts with the cyclopentenone (35), coordinated by the aluminum, to give an enantioselectively aluminum-enolate adduct. The reaction of the latter enolate with an aldehyde (37) produces an alkoxide. Although it remains unclear whether an aluminum or lithium alkoxide is generated, but the resulting alkoxide captures a proton from the acidic OH group to give the coupled product of three components and ALB is regenerated, completing the catalytic cycle (Arai *et al.*, 1996).



Scheme 11. The first asymmetric catalyzed Michael-aldol tandem reaction.

So far, a large number of tandem reactions using chiral auxiliaries have been described. Such reactions comprise, e.g., organocatalytic tandem reactions with high enantio and diastereoselectivity such as Michael-aldol of β-diketones, β-ketosulfones, and β-keto esters with α,β-unsaturated ketones, as well as O-nitroso Aldol-Michael reactions catalyzed by a tetrazole attached to a pyrrolidine. Former auxiliar promoted a nitroso Diels-Alder adduct. L-proline-catalyzed Robinson anullations as one-pot process, the synthesis of optically active functionalized chromans by Michael-Friedel-Crafts tandem, and the asymmetric Mannich reaction, useful for the construction of nitrogen-containing molecules, are excellent models of chiral auxiliary-catalyzed asymmetric protocols, among many others (Pellissier, 2006b). A good tutorial review, covering numerous examples discussing the structural diversity and stereocontrol arising from one-pot combinations of at least three components, had been recently published (Marson, 2012).

One of the most interesting synthetic approaches is that reported for the development of an organocatalyzed asymmetric reaction for the synthesis of tetrasubstituted cyclohexenecarbaldehydes by three-component tandem reaction (Enders *et al.*, 2006). The triple cascade reaction proceeds via a sequence involving a Michael/Michael/aldol condensation providing products with good yields. This catalytic cascade reaction condenses three components such as an aldehyde (40), an nitroalkene (41), an α,β-unsaturated aldehyde (42), using a chiral secondary amine (45 or 46), capable to catalyze each step on the triple cascade (Scheme 12). In the first step, the catalyst (S)-45 activates component 40 by forming an enamine which is then selectively added to the nitroalkene 41 in a Michael-like reaction. The subsequent hydrolysis releases the catalyst being now able to form the iminium ion from the α,β-unsaturated aldehyde 42 in order to achieve the conjugate addition with the nitroalkane formed. The third subsequent step will further lead to the activation of the resulting enamine to perform an intramolecular aldol condensation. The hydrolysis returns the catalyst for a new cycle, releasing the desired product, the tetrasubstituted cyclohexenecarbaldehyde (43).



Scheme 12. Three-component tandem reaction reaction for the synthesis of tetrasubstituted cyclohexenecarbaldehydes.

During this sequence, four stereogenic centers are formed with high diastereoselectivity and complete enantioselectivity. Moreover, the reaction allows variation of the starting materials in order to obtain many polyfunctional cyclohexenes derivatives, which can be used as building blocks in organic synthesis. The reason for the high stereoselectivity is the first Michael addition known to proceed with high diastereo and enantioselectivity (Enders *et al.*, 2006). Clearly, this selectivity is maintained or increased in the second step by a sterically favorable interaction between iminium and nitroalkane species.

CONCLUSIONS

Classification of tandem processes is mainly given according to the type of species formed in the first and second step. Therefore, sequences could be classified as cationic-cationic, where both first and second step generate cations, commonly known as electrophiles. The important parameter at the time to propose a tandem process is the individual steps must have comparable reaction rates in order to prevent the reaction can be enriched in one of the intermediaries, generating undesirable products.

Although sequential processes are currently used in a more frequent manner, in the literature is usual to find for the same process a different classification or name. However, the expression tandem is the most used and the most welcome is, having as synonyms domino and cascade. The rise in the use of tandem processes is mainly due to its advantages. Despite it requires high inventiveness and synthetic knowledge, it provides synthetic pathways and processes with high atom economy, low cost, and minimizing purification and separation steps during synthesis. They are also environmentally generous, avoiding the use and production of toxic substances.

This synthetic inventiveness comes from a more accurate and appropriate knowledge on the reactions occurring in living organisms to generate metabolites, whose occurrence is in agreement to tandem processes. Therefore, complex molecules can be generated with high stereoselectivity, with the aim of obtaining the pure stereoisomer (or high enantiomeric or diastereomeric excess) having a more favorable specific activity. This approach remains in the border of the artistic levels, because a complex structure is usually related to a fascinating, elegant method to achieve that structure such as the painter creates his artwork or the musician generates his masterpiece.

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