Chemo-differentiating ABB′ multicomponent reactions. Privileged building blocks

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Multicomponent reactions (MCRs) designated as ABB′ are defined as those reactions that introduce into the final product one molecule of component A and two molecules of component B in a chemo-differentiating manner. This ability to discriminate the incorporation of component B ensures that these processes maintain the advantages of using multicomponent reactions in diversity-oriented molecular construction. Furthermore, they benefit from the fact that only two reagents need to be mixed together. Component B can be therefore considered to be a privileged building block, and the reactions in which it participates, chemo-differentiating multicomponent reactions. Among the reduced set of compounds capable of acting as such building blocks, we discuss the use of ketenes, terminal conjugated alkynoates, enolisable carbonyl compounds, cyclic enol ethers and cyclic enamines.

Introduction

Although the availability of novel multicomponent reactions (MCRs) has increased dramatically over the last decade, they cover a limited amount of the chemical space and much still remains to be accomplished.[1–9] There is no doubt that some of these transformations are important cornerstones in the diversity-oriented construction of molecular complexity due to their ability to incorporate, in a fast and efficient manner, three or more components into a single product. This means that the structure of the product can be easily modified by small systematic variations of each of the starting materials. MCRs generally benefit from other aspects such as atom-economy, the use of readily available starting materials, resource effectiveness and bond-forming efficiency, which render these reactions useful environmentally friendly alternatives, in keeping with the greener direction in which organic chemistry is proceeding. In addition, because MCRs are one-pot processes with simpler experimental conditions that do not require the isolation of intermediates, they are perfect candidates for combinatorial, automated synthesis and drug discovery.

Over the years, there have been various classification systems for MCRs, *e.g.* according to the components involved, the type of reaction or the reversibility of reactions leading to intermediary products. In terms of the components involved,

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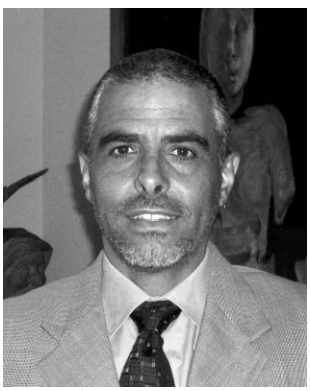


Fernando García-Tellado

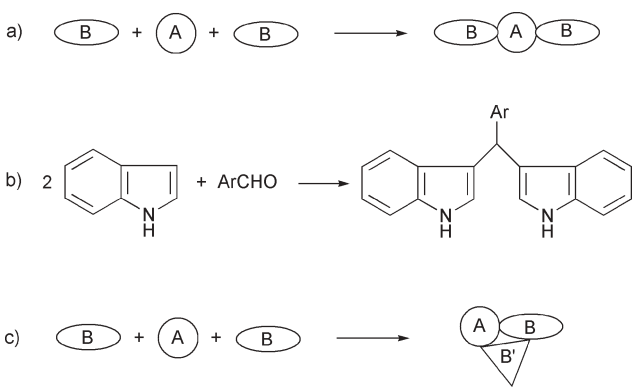
Fernando García-Tellado was born in Tenerife, Spain in 1957. He studied chemistry at the University of La Laguna where he later obtained his PhD in 1983 under the supervision of Professors Antonio González González, B. M. Fraga and Melchor García Hernández. After completing a post-doctoral work with Professor James R. Hanson at the University of Sussex, UK (1985–1986), he received a permanent position at the Spanish Consejo Superior de Investigaciones Científicas in 1986. Since then, he has maintained a tenured scientist position at the Instituto de Productos Naturales y Agrobiología. Since 2000, he has been also an associate researcher of the Instituto Canario de Investigación del Cáncer. He was a Fulbright visiting researcher at the group of Professor Andrew G. Hamilton at the University of Pittsburgh, USA (1989–1991). His research is mainly focused on the development of new efficiency-based synthetic methodologies, organocatalysis, aqueous chemistry and chemistry of cancer.

multicomponent reactions that utilise, for example, three components (3CR) can be divided into three different categories depending on the nature of the starting materials. ABC designates a multicomponent reaction involving three different reagents; ABB (or AB_2), a reaction that involves one molecule of reagent A and two molecules of reagent B (Scheme 1a); and finally, AAA, a reaction that involves three molecules of the same reagent. It appears reasonable that in order to achieve the highest possible complexity and diversity in the final products, the ideal multicomponent reaction would fall into the first category (ABC) although this is not strictly necessary as evidenced by a few selected examples that have appeared in the literature over the last decade and that will be highlighted in this article. The key to this particular category of multicomponent reactions that can be designated ABB′ is the chemo-differentiating incorporation of the component B in two distinct manners (B and B′), which ensures the complexity and functional diversity of the final product (Scheme 1c).[10] We use the term chemo-differentiating to signify that each chemical function incorporated into the product is chemically different from the other. All of the selected examples share a common chemical property: they perform a chemical process able to transform a small set of reagents into a final product whose structure incorporates each reagent several times and in the form of differentiated chemical functions. In terms of diversity-generation, it means that two identical starting units construct highly functionalized products containing a broader set of chemical functionalities or structural motifs. Furthermore, there are two more beneficial aspects that arise from the fact that only two reagents need to be mixed together: (a) the reaction processing becomes simpler, saving time and equipment, and (b) since one of the drawbacks of MCRs is that all the starting materials must tolerate the initial reaction conditions, obviously, there is a higher possibility that only two starting materials tolerate those conditions rather than three.

The chemical realization of this design concept is contingent on two factors. First, the construction of a suitable chemo-differentiating reaction network, and second, the chemical availability of the suitable starting reagents. This ability is denoted only by a short number of chemical functionalities. We refer to them as *privileged building blocks* to highlight this reactivity-based property (the term *privileged* is used to signify an advantageous reactivity profile more than a universal one). Among the reduced set of compounds displaying this particular reactivity profile, we will highlight the use of ketenes, terminal conjugated alkynoates, enolisable carbonyl compounds, cyclic enol ethers and cyclic enamines.

The examples that have appeared in the literature are not all three-component chemo-differentiating MCRs. Following the same reasoning that we have applied to 3C MCRs, other examples involving more components can be easily catalogued into new categories such as AABB′, ABB′C, *etc.* Examples falling into some of these more complex categories are scarcer and they will also be discussed in this review.

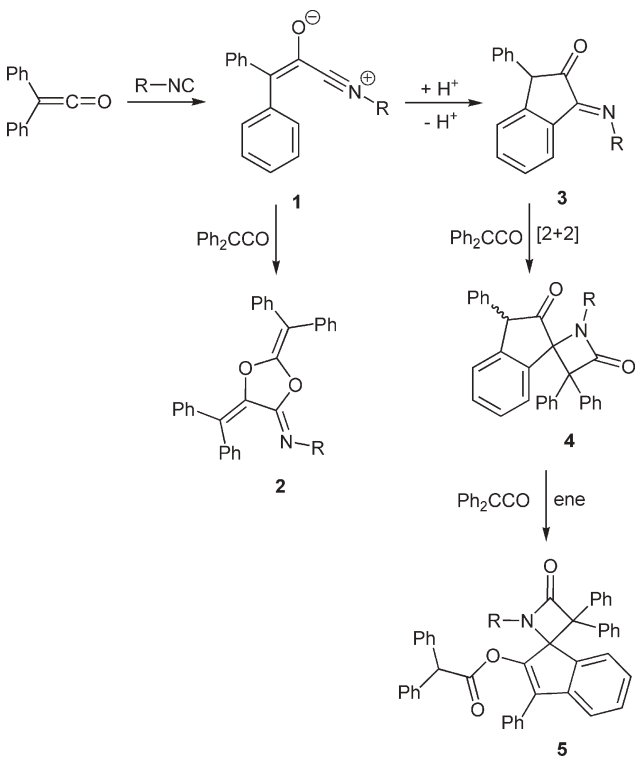
Finally, many of the reactions appearing in this article had not been originally presented as multicomponent reactions and this has made it more difficult to search for them in keyword databases. Although a careful inspection has been conducted to find examples which would reflect the objectives of this review, it does not intend to be fully comprehensive, but rather, a conceptual overview of a selected group of examples which will most likely aid in the search for new MCRs and that will benefit both academic and industrial scientists.



Scheme 1 (a) ABB (or AB_2) 3CR. Both molecules of component B are incorporated into the product in a similar manner. (b) Example of an ABB 3CR. Synthesis of bis(indolyl)methanes from indole and aromatic aldehydes. (c) ABB′ 3CR. Two molecules of component B are introduced into the product as different building blocks. The product gains structural complexity and diversity.

Ketenes

It has been known for some time that ketenes react with isocyanides in an ABB (or AB^2) 3CR to form 2,5-dialkylidene-4-imino-1,3-dioxolane derivatives[11] **2** (Scheme 2). Although in this reaction three new bonds and one ring are formed, it appears obvious from observing the structure of the product



Scheme 2 Ketene-based ABB′ 3CR.

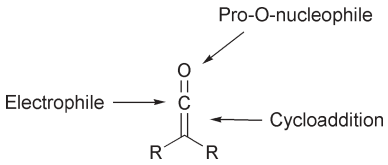


Fig. 1 Reactivity profile of ketenes.

that the ketene building blocks contribute limited functional diversity to the final product. This occurs because both ketenes are incorporated following similar nucleophilic additions. The first one involves the addition of the initial isocyanide and the second one the enolate of the zwitterionic intermediate **1**.

A very recent example shows the versatility of ketenes as privileged building blocks (Fig. 1), and at the same time allows us to show again the difference between an ABB MCR and a chemo-differentiating ABB′ MCR.

Robertson *et al.* have recently shown[12] that under controlled experimental conditions (low practical concentrations of ketene and presence of TMSCl), intermediate **1** can rearrange and, more importantly, undergo a [2 + 2] cycloaddition with another ketene molecule to give the more elaborated product **4** as a mixture of two diastereomers (Scheme 2). The increased structural complexity and diversity are mainly a result of the new ABB′ 3CR in which the ketene building blocks are introduced into the product in two different manners: *via* a nucleophilic addition and a cycloaddition. The mechanism proposed by the authors includes the electrocyclisation of zwitterion **1** in the absence of a high concentration of diphenylketene, tautomerisation and the successive [2 + 2] cycloaddition that generates the β-lactam ring. Key to the formation of product **4**, instead of 1,3-dioxolane derivative **2**, is the slow addition of the diphenylketene to avoid its intermolecular reaction with intermediate **1**. Overall, this process generates four new bonds and two rings in a single operation.

A further modification in the experimental conditions, which includes an additional equivalent of diphenylketene, brings about the transformation of **4** into product **5** *via* an ene reaction. In this new ABBB′ 4CR, the additional ketene building block is also introduced into the final product through a nucleophilic addition, generating an additional carbon–oxygen bond and ester functionality. BBB′ denotes therefore that only two out of the three type B building blocks are incorporated in a similar manner.

Terminal conjugated alkynoates

Terminal conjugated alkynoates are small molecules with an extremely high degree of chemical complexity (Fig. 2). These

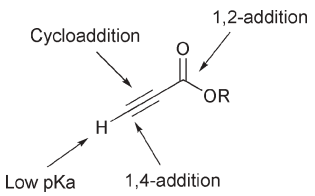
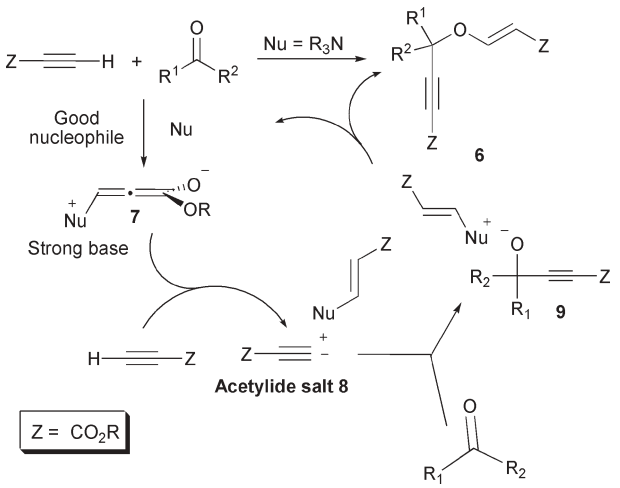


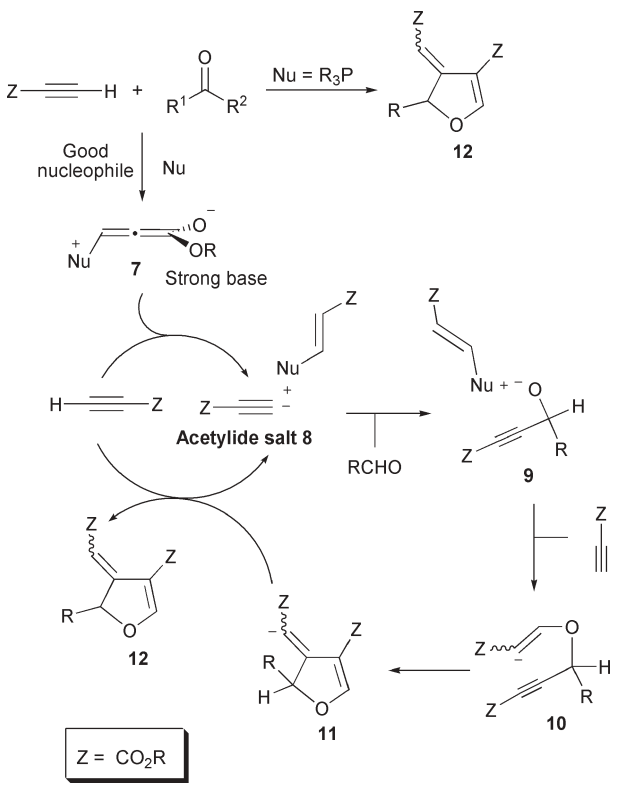
Fig. 2 Reactivity profile of terminal conjugated alkynoates.



Scheme 3 Conjugated acetylide-driven ABB′ 3CR.

molecules can react with a wide range of reagents that include for example nucleophiles, strong bases, dienes or dipoles.

Our own contributions to this chemistry combine the two main chemical properties of terminal conjugated alkynes: their relatively high acidity ($pK_a < 18.8$)[13] and their good Michael-acceptor character.[14] Interestingly, this means that this privileged building block can act as a nucleophile and an electrophile in the same MCR. Depending on the catalyst and the reaction conditions, one molecule of an aliphatic aldehyde or certain α-dicarbonyl compounds and two molecules of a terminal conjugated alkynoate may be combined to yield enol-protected propargylic alcohols **6** (Scheme 3) or 1,2-dihydrofuran derivatives **12** (Scheme 4).[15,16]



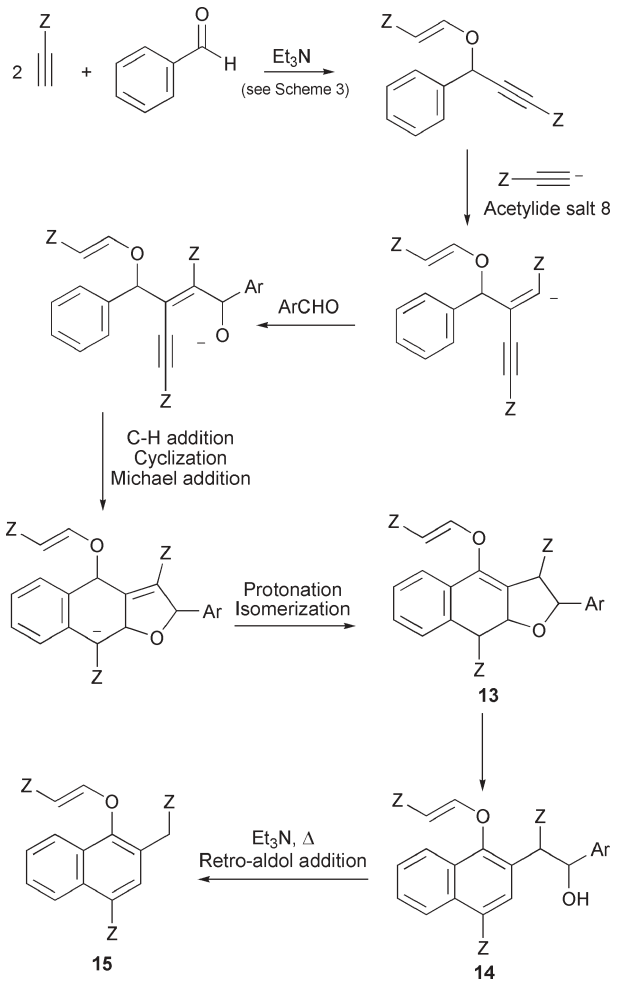
Scheme 4 Another conjugated acetylide-driven ABB′ 3CR.

Both processes represent examples of ABB′ 3CRs and have a common starting point. The energetically favoured nucleophilic addition on the terminal conjugated alkyne generates the zwitterionic allenolate **7**, which deprotonates the starting conjugated alkyne to generate the reactive acetylide salt **8**. Overall, a catalytic amount of a good nucleophile generates a catalytic amount of a strong base. Once formed, the reactive acetylide salt **8** adds to an electrophile present in the reaction medium to give the expected addition products. Aldehydes or α-dicarbonyl compounds bearing no protons more acidic than the terminal alkynoate itself are good electrophiles and their adducts, propargylic alkoxides **9** are themselves good nucleophiles, to give Michael addition on either the reactive conjugated alkene counterion affording enol-protected propargylic alcohol derivatives **6**, or a free starting terminal conjugated alkynoate affording the corresponding 1,2-dihydrofuran **12**. The formation of heterocyclic compound **12** is the result of an intramolecular Michael addition in intermediate **10** and the protonation of **11** by the starting alkynoate. As a result this MCR generates three new bonds (two C–C and one C–O) and one ring.

Interestingly, the nucleophilic catalyst plays at least two important roles. It not only triggers the acetylide generation, but it is also crucial in determining the outcome of the reaction. Under the appropriate reaction conditions, tertiary amines funnel the process towards **6** while tertiary phosphines afford **12**. In both cases, one building block is introduced as an acetylide ion (nucleophile) due to its increased acidity and one as a Michael-acceptor (electrophile).

Finally, as it can be anticipated by the use of multicomponent reactions, the products (**6** and **12**) constitute highly functionalized units which are well suited for using as scaffolds for further diversity-oriented molecular construction. In this regard we have already explored some of the possibilities of product **6** in the efficient synthesis of 1,3-oxazolidines[17] and polysubstituted pyrroles.[18] The simplicity of the first ABB′ MCR, coupled with another domino process has allowed us to build small libraries of compounds in a programme aimed at the discovery of bioactive substances for cancer treatment.[19,20]

More recently, a similar-in-origin triethylamine-catalysed AABBB′ type 5CR of an alkyl propiolate with aromatic aldehydes has been described.[21] This temperature-dependent sequence of cascade reactions generates, at a first stage, 2,3,9,9*a*-tetrahydronaphtha[2,3-*b*] furans **13** with an impressive bond-forming efficiency of seven new bonds (five C–C and two C–O) in a single operation (Scheme 5). Upon warming, these products can be selectively transformed into naphthalene derivatives **14** or **15**. The mechanism proposed by the authors involves the formation of the enol-protected propargylic alcohol **6** (already described in Scheme 3) which undergoes a further acetylide addition to generate an intermediate that is able to react with another molecule of the initial aldehyde. This is followed by a series of rearrangements and protonation to afford **13**. The cascade of reactions has been able to incorporate two molecules of aromatic aldehydes and three molecules of ethyl propiolate into the product. Both aldehyde units are incorporated following similar 1,2-additions on the carbonyl moiety (AA) but the ethyl propiolate units are



Scheme 5 Conjugated acetylide-driven AABBB′ 5CR.

incorporated in two different ways: two as sources of acetylide nucleophiles and one as a Michael-acceptor (BBB′).

Enolizable carbonyl compounds

There are two well-known reactivity sites in this group of compounds (Fig. 3). The increased acidity of α-hydrogens, which leads to the formation of enolate ions, and the electrophilicity of the carbonyl group give rise to the aldol reaction. The corresponding β-hydroxycarbonyl compound (or the α,β-unsaturated derivative) can subsequently be used in a further reaction to give a more elaborated product. When both reactions are combined in a one-step process, the bases are obtained for an ABB′ type MCR. Not surprisingly, there

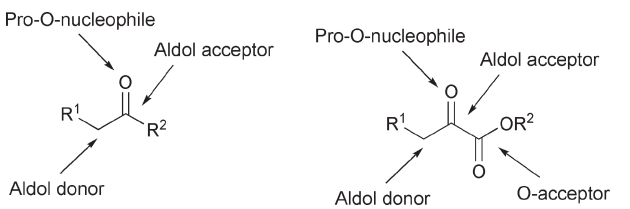
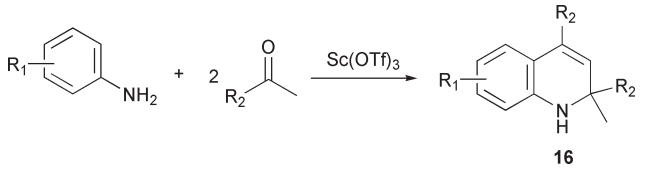
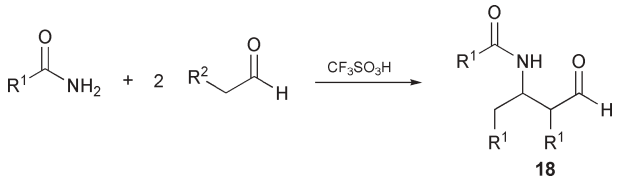


Fig. 3 Reactivity profiles of simple enolisable carbonyl compounds and enolisable α-ketoesters.



Scheme 6 Sc-catalysed ABB′ 3CR synthesis of dihydroquinolines.



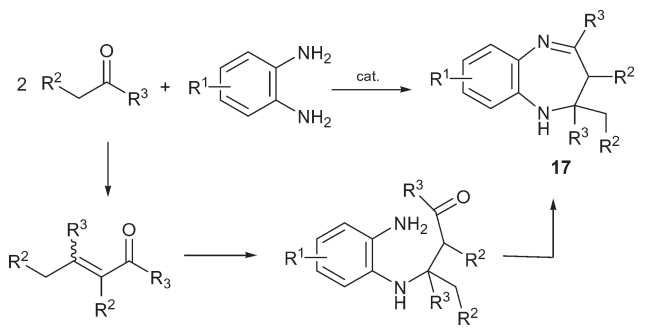
Scheme 8 Trifluoromethanesulfonic acid-catalysed ABB′ 3-C synthesis of β-amido aldehydes.

are a considerably higher number of examples that include the use of enolisable carbonyl compounds as the privileged building blocks.

The first two examples show the reaction of ketones with aromatic amines. Theoclitou and Robinson have recently developed an ABB′ 3C synthesis of polysubstituted 1,2-dihydroquinolines **16** *via* a modified Skraup reaction that uses ketone and the desired aniline as the starting materials (Scheme 6).[22] This $Sc(OTf)_3$-catalysed reaction proceeds under much milder conditions than the original Skraup cyclisation (at 145 °C under pressure for 2–3 days in the presence of iodine), while allowing to expand the scope of the substituents in both the aromatic amine and the ketone.

When *o*-phenylenediamine is used as the aromatic amine, the result is the formation of 1,5-benzodiazepine derivatives **17** *via* another ABB′ 3CR as has been described by various groups under a wide range of different reaction conditions (Scheme 7).[23] Aliphatic ketones (cyclic and acyclic), and substituted acetophenones have all been used as the privileged building blocks in these transformations. The originally proposed mechanism[24] involves the formation of the α,β-unsaturated carbonyl compound followed by two consecutive additions (one Michael addition and one 1,2-addition) of the amino groups on the aldol intermediate. The number of catalysts used to promote this reaction is large and includes Lewis and protic acids, microwave conditions, use of ionic liquids and solid supports.

There are other examples showing 3C or even 4C chemodifferentiating MCRs of aldehydes with either amides or aliphatic amines. Interestingly, the reaction of aldehydes and amides can give a number of products depending on the reaction conditions. The simplest case is the ABB′ 3-C trifluoromethanesulfonic acid-catalysed condensation of a primary amide with two equivalents of an aldehyde to give the corresponding β-amido aldehyde **18** as a mixture of two diastereomers (Scheme 8).[25] The authors propose the *in situ* formation of the imine from an amide and an aldehyde,



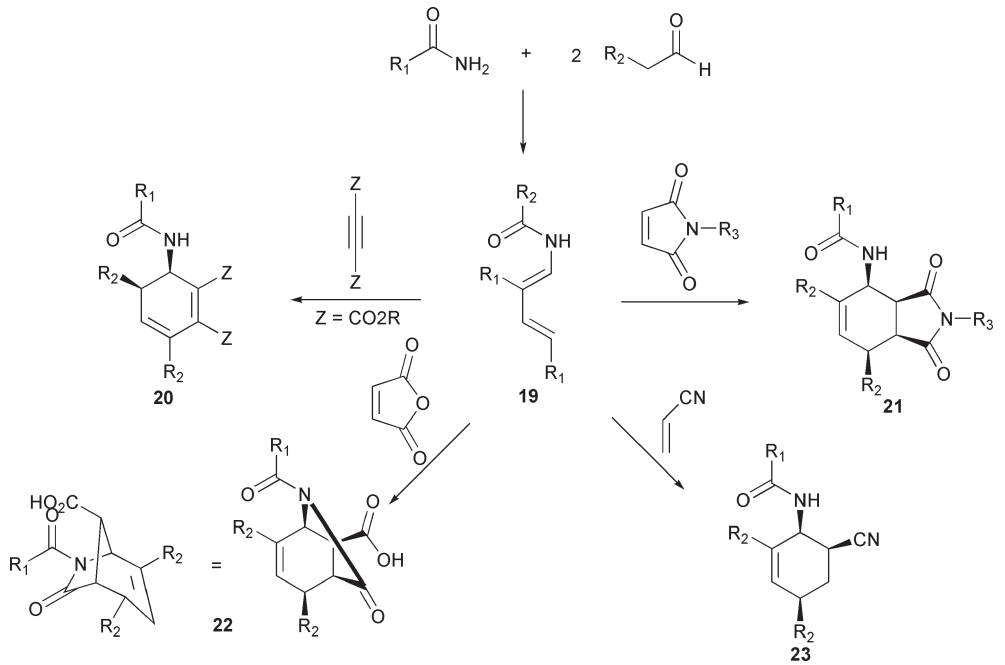
Scheme 7 ABB′ 3C synthesis of 1,5-benzodiazepine derivatives.

followed by an amidoalkylation with a second molecule of aldehyde. Experiments with α,β-unsaturated aldehydes and amides under the same reaction conditions did not lead to the expected product, ruling out the possibility of a direct aldol condensation followed by dehydration and conjugate addition. The β-amido aldehydes obtained are of synthetic value because they are relatively stable derivatives of β-amino aldehydes which are more difficult to isolate. It should also be added that these authors developed a similar methodology under different acidic conditions with the use of acetals as the source of the corresponding aldehydes.[26]

More appealing seems the ABB′C 4C coupling of amides, aldehydes and dienophiles (Scheme 9). Beller *et al.* further developed this methodology, which involves the Diels–Alder reaction of a 1-acylamino-1,3-diene intermediate **19** with different dienophiles (dialkyl acetylenedicarboxylates, acrylonitrile, maleic anhydride or maleimides), to efficiently prepare highly functionalized cyclohexene and cyclohexadiene derivatives **20–23** in a diastereoselective manner.[27] Remarkably, although up to four stereogenic centres are created, the authors only observe the formation of one diastereomer in each case. This reaction features the formation of four new bonds (three carbon–carbon and one carbon–nitrogen) and one new ring. Additionally, when maleic anhydride is used as the dienophile, the expected product undergoes a rearrangement through a subsequent intramolecular amidation of one carboxylic moiety to give bicyclic products **22**. The key to this MCR (coined by the authors as the AAD reaction: amide–aldehyde–dienophile) is that although there are numerous side reactions which could likely proceed under these conditions, there is a selective formation of the 1-acylamino-1,3-diene intermediate **19** which is trapped by the appropriate dienophile.

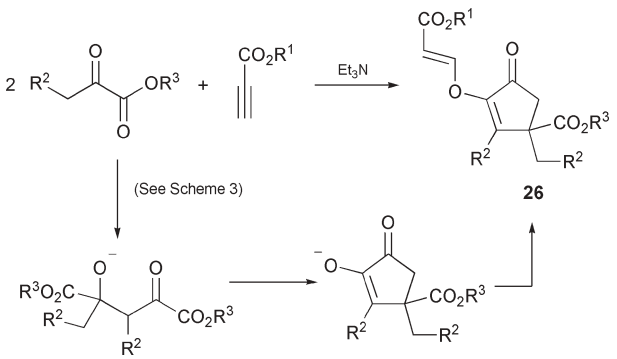
Similarly, the group of Ishii reported the preparation of polysubstituted pyrroles **24** *via* a samarium trichloride ($SmCl_3$)-catalysed ABB′C 4-C coupling of amines, aldehydes and nitroalkanes (Scheme 10).[28] As before, the aldehyde acts as the privileged building block in the formation of a key α,β-unsaturated imine intermediate **25**. Addition of the nitroalkane to **25** is followed by a rearrangement and elimination of H_2O and HNO to give the pyrrole **24**. The authors clearly show that the only role of the catalyst is to form the α,β-unsaturated imine because, in a separate experiment, the coupling of a preformed α,β-unsaturated imine with a nitroalkane takes place in the absence of $SmCl_3$ to form the expected product.

The last example in this category of enolisable carbonyl compounds also comes from our laboratory and is based on the ABB′ 3C organocatalysed homoaldolic condensation of α-ketoesters (Fig. 3) in the presence of terminal conjugated

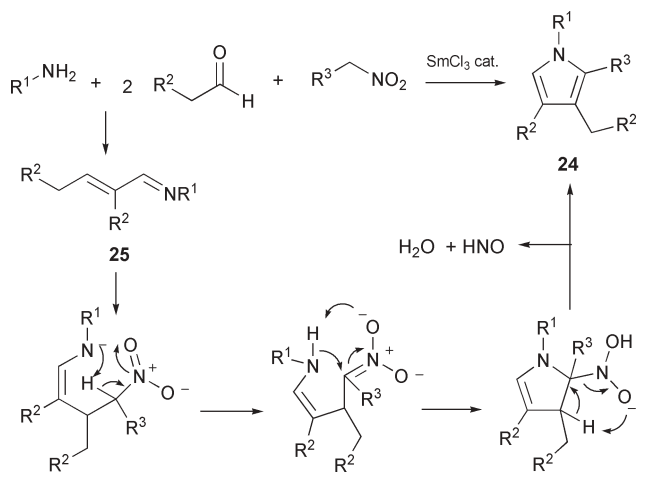


Scheme 9 ABB′C 4C coupling of amides, aldehydes and dienophiles.

alkynoates.[29] In general, α-ketoesters bearing α-hydrogens are more reactive and acidic than simple aldehydes and ketones. Since they are even more acidic than terminal alkynoates, their combined reaction catalysed by a nucleophile (tertiary amine) triggers a cascade of reactions that starts with a self-condensation of the α−ketoester, followed by a lactonisation and Michael addition to afford isotetronic acids **26** (Scheme 11). It is remarkable that one of the α-ketoester units acts twice as the nucleophile (*via* the α-carbon in the aldol condensation and *via* the oxygen in the lactonisation) and the other α-ketoester unit twice as the electrophile (the ketone group in the aldol condensation and the ester group in the lactonisation). The role of triethylamine is to indirectly trigger the aldol reaction. As previously seen in Scheme 3, Et_3N adds to an alkyl propiolate to generate a much stronger base **7** which is the species that deprotonates the first α-ketoester in the self-condensation.



Scheme 11 Homoaldol-based ABB′ 3CRs.



Scheme 10 $SmCl_3$-catalysed ABB′C 4CR of amines, aldehydes and nitroalkanes.

Cyclic enol ethers or enamines

3,4-Dihydro-2*H*-pyran, 2,3-dihydro-2*H*-furan, N-protected 2,3-dihydropyrroles, and N-protected 1,2,3,4-tetrahydropyridines (Fig. 4) have all been used as privileged building blocks in ABB′ type MCRs when combined with aryl primary amines.

These substrates can act as the aldehyde component in the *in situ* formation of the corresponding imines and as

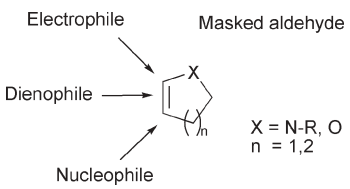
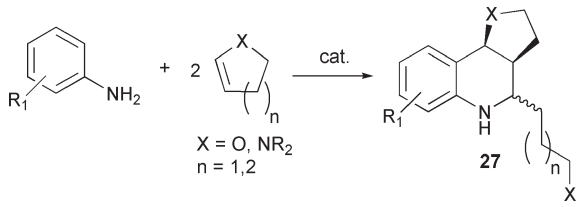


Fig. 4 Reactivity profile of cyclic enol ethers or enamines.



Scheme 12 ABB′ 3C synthesis of the tetrahydroquinoline core.

electron-rich dienophiles in a subsequent aza-Diels–Alder reaction (Scheme 12). In consequence, a tricyclic product **27** with a tetrahydroquinoline core is efficiently obtained.

Although Povarov and Michailov published in 1964 the first MCR of a substituted aniline with an enol ether,[30] it was Batey *et al.* in 1999[31] who realized the full scope of this reaction and the dual role played by one of the components. Numerous studies have since appeared regarding the reaction medium, the substrates, the nature of the catalyst and the diastereoselectivity of the process.[32–36]

The use of cyclic enol ethers has been more common than their nitrogen counterparts. Batey *et al.* first reported the $Dy(OTf)_3$-catalysed reaction of 2,3-dihydro-2H-furan with various substituted anilines to form the corresponding 2-(hydroxyalkyl)tetrahydroquinoline derivatives **27** (X = O, n = 1).[10] More recently, further research has shown that the reaction can be performed with KSF clay, $InCl_3$ in H_2O, $Sc(OTf)_3$ in [bmim]PF6, In in aqueous HCl, and without catalyst in hexafluoroisopropanol. Although more scarce, the use of endocyclic enamines has found a relevant application because the reaction of methyl 4-aminobenzoate with N-protected 2,3-dihydropyrrole provides direct access to the core structure of the Martinella alkaloids (Fig. 5).

Martinelline and martinellic acid are natural products found in root extracts of the Amazonian *Martinella iquitosensis* vine which has been used by the indigenous population to treat various eye ailments. This MCR allows the rapid construction of the tricyclic core of these guanidine alkaloids with the correct diastereoselectivity in only two synthetic steps and good overall yield, and Batey and Powell have already accomplished its total synthesis using this MCR as the key step.[34] Essential to their success was the search for the catalyst that would favour the desired *endo* adduct during the hetero Diels–Alder reaction. Ultimately, camphorsulfonic acid in THF was chosen to predominately form the correct diastereomer.

Summary and outlook

We have shown how the chemo-differentiated incorporation of identical building blocks into the final product can transform a bimolecular reaction into a MCR. These reagents can be considered to be privileged building blocks because they have the ability to transform one chemical functionality in the starting material into a broader set of functionalities or structural motifs in the product. This ensures that the MCRs in which they participate maintain the ability to generate molecular complexity and diversity.

The ABB′ notation[10] is proposed to designate the chemo-differentiating 3C MCR that introduces into the final product one molecule of component A and two molecules of component B. Most importantly, this notation highlights the dual role played by component B and it stresses that it is incorporated in two different manners. Although ABB′ 3C MCRs are the most common among this type of transformations, we have also shown more complex multicomponent reactions such as ABBB′ 4C, ABB′C 4C and AABBB′ 5C reactions.

Among the reduced set of compounds that fulfil the needed requirements, we have highlighted the use of ketenes, terminal conjugated alkynoates, enolisable aldehydes or ketones, and cyclic enol ethers or enamines. Although these building blocks have appeared in the literature more frequently in this type of reaction, these are not the only reagents that meet the needed requirements and it is anticipated that in the future we will see a larger and broader set of such chemo-differentiating multicomponent reactions that will possibly lead to novel molecular frameworks in a single reaction step.

Finally, we hope that in the future, when new reactions of this type appear in the literature, they will be categorized as chemo-differentiating reactions in order that they can enter the pool of MCRs available to organic chemists.

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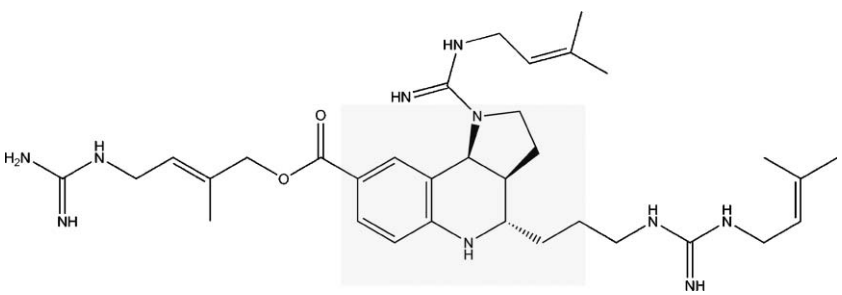

Fig. 5 (±)-Martinelline.

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