SYNTHESIS OF HETEROCYCLIC SYSTEMS FROM α,β-UNSATURATED DIAZOKETONES

DOI: http://dx.medra.org/10.17374/targets.2019.22.377

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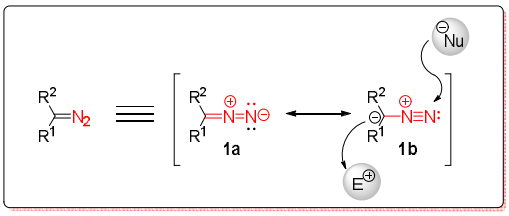
Abstract. *For over a century, since their first synthesis in 1883 by T. Curtius, diazo compounds are well-known as versatile and useful building blocks in organic synthesis, especially due to their application in numerous chemical transformations. Among the different types of diazocompounds, α,β-unsaturated diazoketones has been employed as a versatile building block. The multifunctionality presented in these compounds allows a broad range of transformation that makes the α,β-unsaturated diazoketones interesting synthetic platform. Herein we would like to present the progress in organic synthesis, shedding light on the elegant transformations already performed, employing these compounds (since the first reports by Regitz and Gupta until the new methodologies).*

Contents

1. Introduction

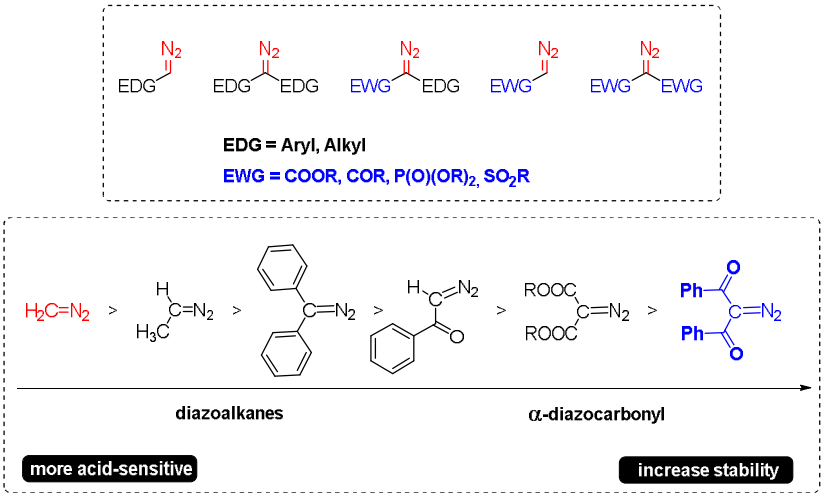
The diazo functional group has attracted the attention of many researchers due to its remarkably structural features, where a linear dinitrogen is connected to a carbon atom that can be represented by two main resonance structures contributors **1a** and **1b** (Scheme 1). The terminal nitrogen of the diazo group can be attacked by nucleophiles, while the carbon connected to the functional group presents a carbanion character and it is susceptible to perform a nucleophilic attack. These two reactive centers give to diazo compounds an ambiphilic nature, an important property that contributes to the widespread application of these compounds in organic reactions.[1,2]



Scheme 1. The structure of diazo function group.

The stability of a diazo-containing molecule strongly depends on the electronic nature of their substituents. Diazoalkanes are often considered as unstable and potentially explosive chemicals.[3-5] The main stability problem of this class of diazo compounds arises from their high acid-sensitivity, since the

protonation of the α-carbon to diazo group leads to the formation of a diazonium species, which can release dinitrogen and result in decomposition products.[6] Diazo compounds carrying an electron-withdrawing group (EWG), such as carbonyl, phosphoryl, and sulfonyl substituents are more stable and less acid-sensitive than simple diazoalkanes, since the negative charge can be delocalized from the α-carbon to these neighboring functional groups.[7-9] Staudinger and Gaule established a reactivity scale of some diazo compounds by measuring their decomposition rates in acidic conditions. It starts from the less stable diazomethane and diazo alkyl, passing to aryl substituted diazomethane derivatives until the considerably more stable α-diazocarbonyl and diazodicarbonyl compounds (Scheme 2).[10] As a consequence, the diazocarbonyl compounds are applied in numerous chemical transformations, while the use of diazoalkanes is rather limited.



Scheme 2. Classes of diazo compounds and stability.

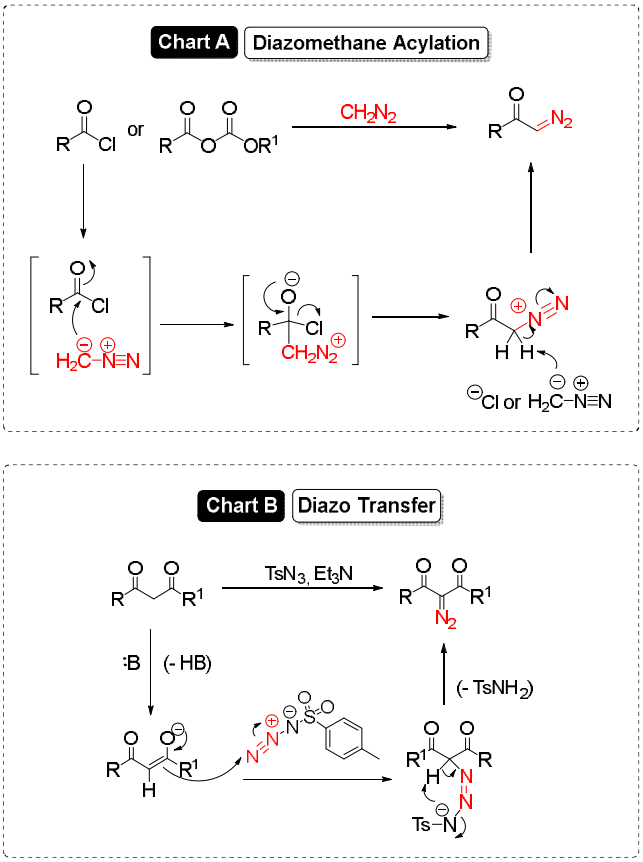
1.1. Synthesis of α-diazocarbonyl compounds

The first synthesis of a α-diazocarbonyl compound was reported by Curtius in 1883, involving the diazotization of glycine amino acid to furnish ethyl diazoacetate.[11] Some years later, Ludwig Wolff explored this compound in the well-known 'Wolff rearrangement'.[12] After that, the chemistry of diazocarbonyl compounds was reawakened only in 1927, the year that Arndt and Eistert reported an important general protocol to prepare terminal α-diazocarbonyl compounds by the acylation of diazomethane with acyl chlorides.[13] Later, this procedure was improved by Bradley and Robinson with the use of mixed anhydrides as acylating agents (Scheme 3, Chart A).[14]

Although the Arndt-Eistert reaction provides a widely protocol to α-diazocarbonyl synthesis, this approach has some limitations. Cyclic and unsaturated diazo compounds cannot be accessed by this approach. Moreover, the use of higher diazoalkanes usually are less efficient than using diazomethane.[15-17] The main drawback of working with pure diazomethane is because it is extremely toxic, highly irritating and an explosive gas. In view of these restrictions, Regitz and collaborators developed the diazo transfer technique.[18-20] This strategy consists in the transferring of diazo group from a donor to an acceptor substrate. Usually, the diazo transfer method involves carbonyl compounds with active methylene position (acceptor), such as 1,3-dicarbonyl and α-aryl-carbonyl compounds, sulfonyl azide (donor) in the presence of a base under mild conditions (do not require the use of diazomethane) (Scheme 3, Chart B).

The development of these two efficient methods to prepare diazo compounds was an important factor for the progress on new synthetic methodologies using α-diazocarbonyl compounds as substrates. The recent literature provides several examples related to preparation, properties, and applications of diazocarbonyl compounds. In summary, the typical protocols for the synthesis of diazo compounds are: (a) acylation of

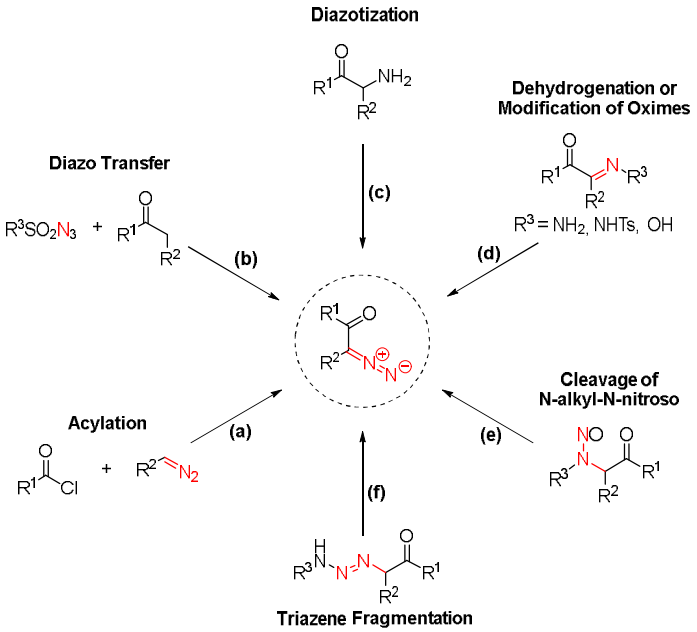
diazoalkanes; (b) diazo transfer reaction; (c) diazotization of primary amines; (d) dehydrogenation of hydrozones; tosylhydrazones and oximes; (e) alkaline cleavage of *N*-alkyl-*N*-nitroso compounds; (f) triazene fragmentation (Scheme 4).[21] Despite the fact that a carbonyl group provides more stability to diazocarbonyl compounds when compared to simple diazoalkanes, a particular caution must be taken when working with any kind of diazo compound. With respect to the more reactive diazoalkanes, several strategies are based on the use of diluted solutions of diazo compounds (prepared in special glassware for *in situ* generation of the diazo reagent) and the continuous-flow process have been developed to minimize the hazards associated with their manipulation.[22–24]



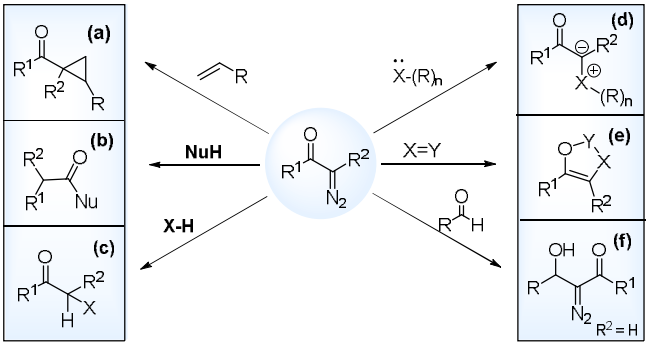
Scheme 3. Diazomethane acylation and diazo transfer methodology for the synthesis of α-diazocarbonyl compounds.

The significant applications of diazocarbonyl compounds in organic synthesis can be summarized in several current reviews.[2,25-31] These compounds can react through thermal, photochemical or transition metal catalyzed mechanisms (with extrusion of molecular nitrogen) to provide access to carbenes, for example. The carbene or metal-carbene species generated from diazo compounds can functionalize nonactivated bonds and undergo C-H or X-H insertion reactions. They can also interact with heteroatoms to favor ylide formation, react with alkenes into a cyclopropanation process or generate reactive ketene intermediates by means of the Wolff rearrangement. With the preservation of the -CN_2 moiety, diazocarbonyl compounds can also participate as 1,3-dipoles for heterocycles construction. Alternatively, because of their carbanion character at the α-carbon to the diazo group, its reactivity can be modulated and, they can act as nucleophilic

species. This strategy can be applied to form C-C bonds through nucleophilic substitution and addition reactions (Scheme 5).



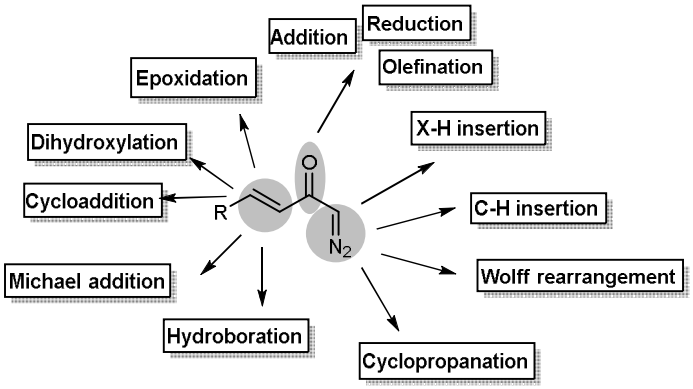
Scheme 4. General protocols for synthesis of α-diazocarbonyl compounds.



Scheme 5. Diazocarbonyl compounds as platforms in synthesis: a) cyclopropanation; b) Wolff rearrangement; c) C-H and X-H insertion reaction (X=C, O, N, P, S, Se, Si); d) Ylide formation (X=S, N, O, P); e) 1,3 dipolar cycloaddition; f) nucleophilic addition reaction to carbonyl compounds.

1.2. Synthesis of α,β-unsaturated diazoketones

Different classes of diazocarbonyl compounds are found in the literature, each one possessing an intrinsic characteristic that can be applied in different types of reactions. Among the diazocarbonyl compounds, the α,β-unsaturated diazoketones has been showing a great synthetic potential in several transformations.[32] The versatility of α,β-unsaturated diazoketones in organic synthesis is directly related to the multifunctionality that this class of compounds possess. The presence of the olefinic portion, a carbonyl and a diazo group permits a series of subsequent transformations that can be applied in the development of new methodologies (Scheme 6).



Scheme 6. Possibilities of reactions and functionalization of α,β-unsaturated diazoketone.

Since the first report in the literature for the synthesis of an α,β-unsaturated diazoketone by Grundmann[33] in 1936 (Scheme 7, Chart A), different methods have been described aiming to prepare these compounds. The bottleneck for the synthesis of α,β-unsaturated diazoketones is that the classical methods (acylation of diazomethane) leads to the formation of pyrazoline-diazoketones as the major products, due to the presence of the double bond that reacts with diazomethane *via* an intermolecular [3+2]-cycloaddition. In this fashion, the α,β-unsaturated diazoketones are usually not formed or formed in low yields.

In the pioneering work of Wotiz and Buco, the authors explored in detail the classical diazomethane acylation protocol with different types of cinammoyl chlorides.[34] However, as reported by Grundmann, the α,β-unsaturated diazoketones were not formed in most of the cases (only one example described; 24% yield) (Scheme 7, Chart B).

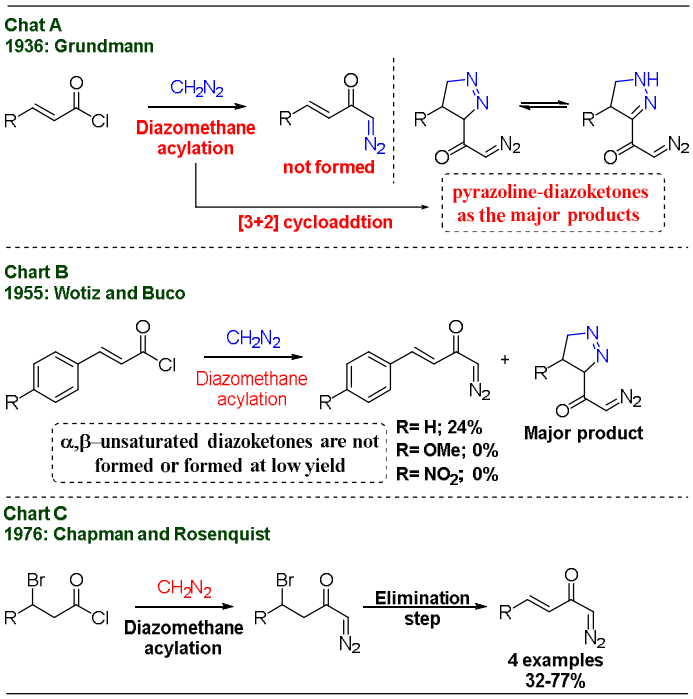
Since the pyrazoline-diazoketones formation occurs due to the reaction between the diazomethane and the olefinic portion, Chapman and Rosenquist explored a different approach for the synthesis of α,β-unsaturated diazoketones, aiming to solve the issue about the pyrazoline formation (Scheme 7, Chart C).[35] The authors chose, initially, to install the diazo portion from β-bromo acid chlorides, furnishing β-bromo diazoketones as intermediates, followed by an elimination reaction in the last step to access the olefinic portion. By this approach, Chapman and Rosenquist solved the problem of the pyrazoline-diazoketones formation and also synthesized 4 examples of α,β-unsaturated diazoketone in 32-77% yield.

Despite the great contribution of Chapman and Rosenquist, it was still necessary the development of a methodology which allowed the synthesis of α,β-unsaturated diazoketones in a greater variety and with better yields. In this way, the deformylative diazo transfer reaction was applied as an alternative method for the synthesis of these compounds. This approach was based on the synthesis of 1,3-dicarbonyl systems as intermediates from α,β-unsaturated methyl ketones, followed by the reaction with sulfonyl azides derivatives (usually tosyl azide) to furnish the α,β-unsaturated diazoketones.

The first known application of this approach for the synthesis of α,β-unsaturated diazoketones was reported by Regitz and co-workers in the sixties.[19,36] In this work the authors employed a small series of α,β-unsaturated methyl ketones, as precursors for the synthesis of 1,3-dicarbonyl compounds, *via* a Claisen condensation reaction with ethyl formate. Next, sodium enolates of these 1,3-dicarbonyl compounds were allowed to react with *p*-toluenesulfonyl azide, furnishing 8 examples of α,β-unsaturated diazoketones in 45-85% yield (Scheme 8).

A similar methodology was described years later by Gupta and co-workers, also based on the deformylative diazo transfer protocol.[37] In this work, α,β-unsaturated methyl ketones were also employed as precursors for the 1,3-dicarbonyl compounds. However, they ethyl formate was substituted by diethyloxalate in the Claisen condensation step. Changing the 1,3-dicarbonyl species, the authors were able to prepare 3 examples of the previously reported α,β-unsaturated diazoketones, though in better yields (Scheme 8).

Although the methodologies described by Regitz and Gupta have solved the problem to obtain α,β-unsaturated diazoketones in considerable yields, there are some issues related to the application of these methods. The rigorous experimental conditions employed limit the sort of substrates that could be explored in the synthesis of the unsaturated diazoketones (the use of sensitive substrates would not tolerate such harsh conditions employing metallic sodium for long reaction periods).

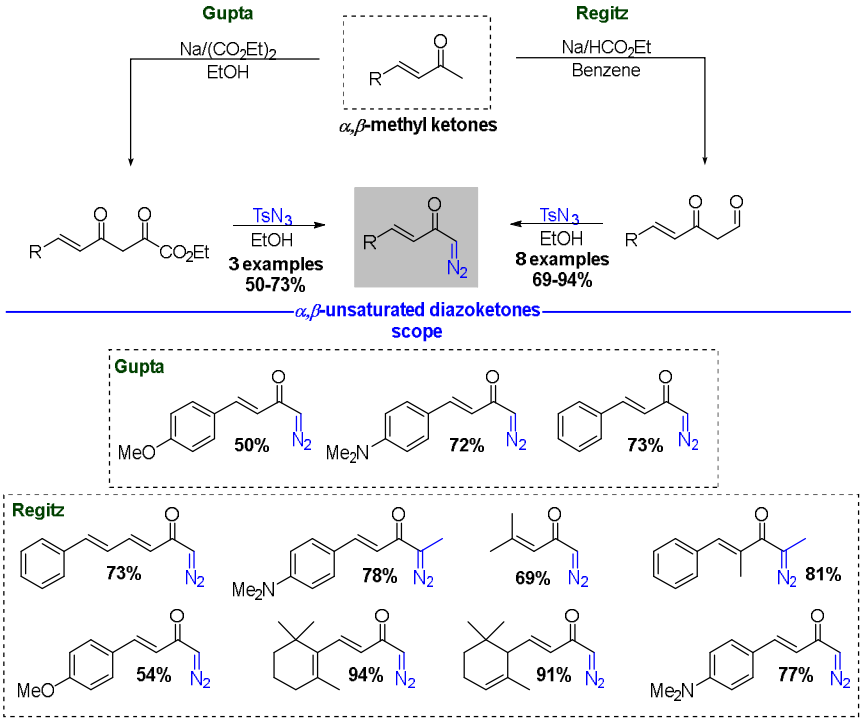


Scheme 7. Pioneering works on the synthesis of α,β-unsaturated diazoketones

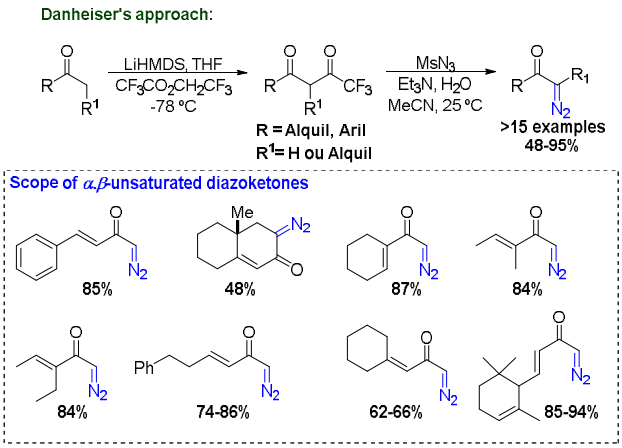
Aiming the synthesis of more complex α,β-unsaturated diazoketones, Danheiser and co-workers developed a versatile methodology built on the detrifluoroacetylative diazo transfer protocol. Despite the methodology of detrifluoroacetylative diazo transfer has already been described by Doyle and co-workers, for the synthesis of one example of a diazoketone,[38] Danheiser's approach was a breakthrough for the synthesis of α,β-unsaturated diazoketones.[39-41] Similar to the methodologies of Regitz and Gupta, Danheiser's approach was also based on the synthesis of 1,3-dicarbonyl systems as intermediates, however the authors employed kinetic conditions for the formation of the methyl ketone lithium enolate, solving the problem for the regioselectivity enolate formation in the Claisen condensation step. By the employment of the 2,2,2-trifluoroethyl trifluoroacetate (TFEA) as a powerful acetylating agent, and the subsequent reaction with mesyl azide, the synthesis of more complexes diazoketones was performed in good to excellent yields (48-95%), including 6 examples of α,β-unsaturated diazoketones (Scheme 9).

Both methodologies of Regitz, Gupta and Danheiser employs a diazo transfer on a 1,3-dicarbonyl system as a key step for the achievement of the respective α,β-unsaturated diazoketones. As for the synthesis of α-diazocarbonyl, the mechanism starts with the generation of an enolate, in this case derived from the α,β-unsaturated methyl ketones. Next, the formed enolate attacks an acetylative or formylative reagent to furnish the 1,3-dicarbonyl system as an intermediate, *via* a Claisen condensation reaction. In the presence of a base, usually a tertiary amine, a 1,3-dicarbonyl enolate is formed, which attacks sulfonyl azide with the concomitant attack of the negatively charge "NTs" to the most electrophilic carbonyl group. A triazine intermediate is formed and rapidly decompose to form the α,β-unsaturated diazoketone (Scheme 10).

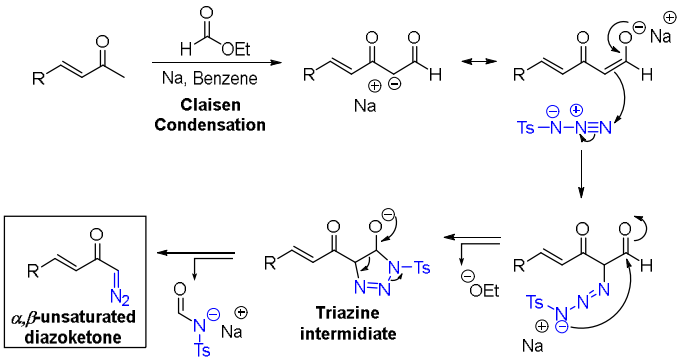
The detrifluoroacetylative diazo transfer approach developed for Danheiser is considered until nowadays one of the main methods for the synthesis of α,β-unsaturated diazoketones. Despite his approach has solved the problem for the synthesis of more complex α,β-unsaturated diazoketones, it is still limited regarding the scope of unsaturated diazoketones. The requirement of α,β-unsaturated methyl ketones as precursors might be a problem depending on the type of the desired diazoketone, since preparation of these compounds is not a trivial procedure. In this fashion the need of new methodologies for the straightforward synthesis of unsaturated diazoketones was still required.



Scheme 8. Scope of α,β-unsaturated diazoketones synthesized by Regitz and Gupta.



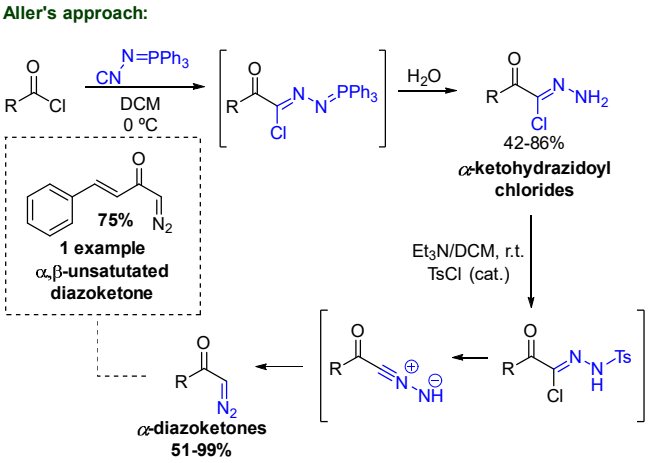
Scheme 9. Danheiser's methodology for the synthesis of diazoketones.



Scheme 10. Deformylative diazo-transfer mechanism. α,β-unsaturated methyl ketones.

2. Recent methods for the synthesis of α,β-unsaturated diazoketones

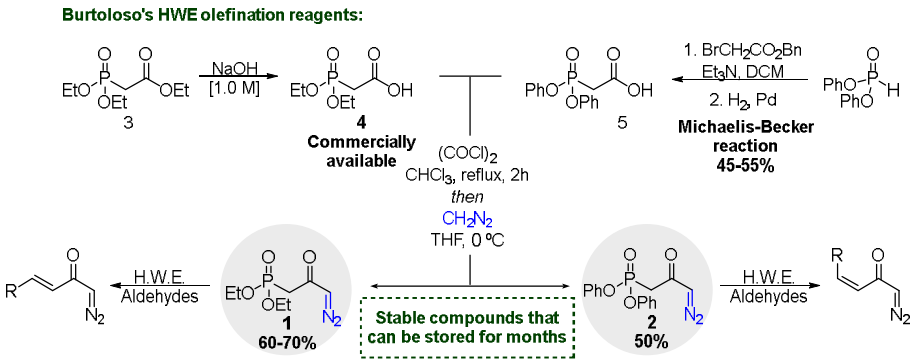
In 2000 Aller and co-workers reported an interesting methodology for the synthesis of diazoketones, based on α-ketohydrazidoyl chlorides as intermediates, followed by the treatment of these compounds with base and catalytic amounts of tosyl chloride (Scheme 11).[42] Aller's methodology draws attention due to the lack of use of diazomethane or sulfonyl azide derivatives for the diazo group installation. However, the developed methodology was most applied to furnish α-diazoketones; only one example of a α,β-unsaturated diazoketone was demonstrated.



Scheme 11. Aller's methodology for the synthesis of diazoketones.

Between 2012-2018, the synthesis of a varied scope of α,β-unsaturated diazoketones has been reported by Burtoloso's research group, based on the Horner-Wadsworth-Emmons (HWE) olefination reaction between diazophosphonates and a series of aldehydes. The Burtoloso's HWE reagents diazophosphonate **1** and diazophosphonate **2** were developed in 2012 and 2013, respectively, and were employed in the synthesis of several *E*- and *Z*-α,β-unsaturated diazoketones in the past years (Scheme 12).[43,44]

Both diazophosphonates were prepared from its respective phosphorylacetic acids **4** and **6**, *via* a carboxylic acid activation approach, followed by the diazomethane acylation reaction. The carboxylic acid activation step was performed by refluxing the corresponding phosphorylacetic acid with oxalyl chloride[$(COCl)_2$)] in chloroform ($CHCl_3$) for 2 hours. The next step consisted in the reaction between the freshly prepared acyl chloride with an ethereal solution of diazomethane, to furnish the diazophosphonate **1** and **2** in 60-70% and 50% yield, respectively.



Scheme 12. Burtoloso's HWE reagents synthesis.

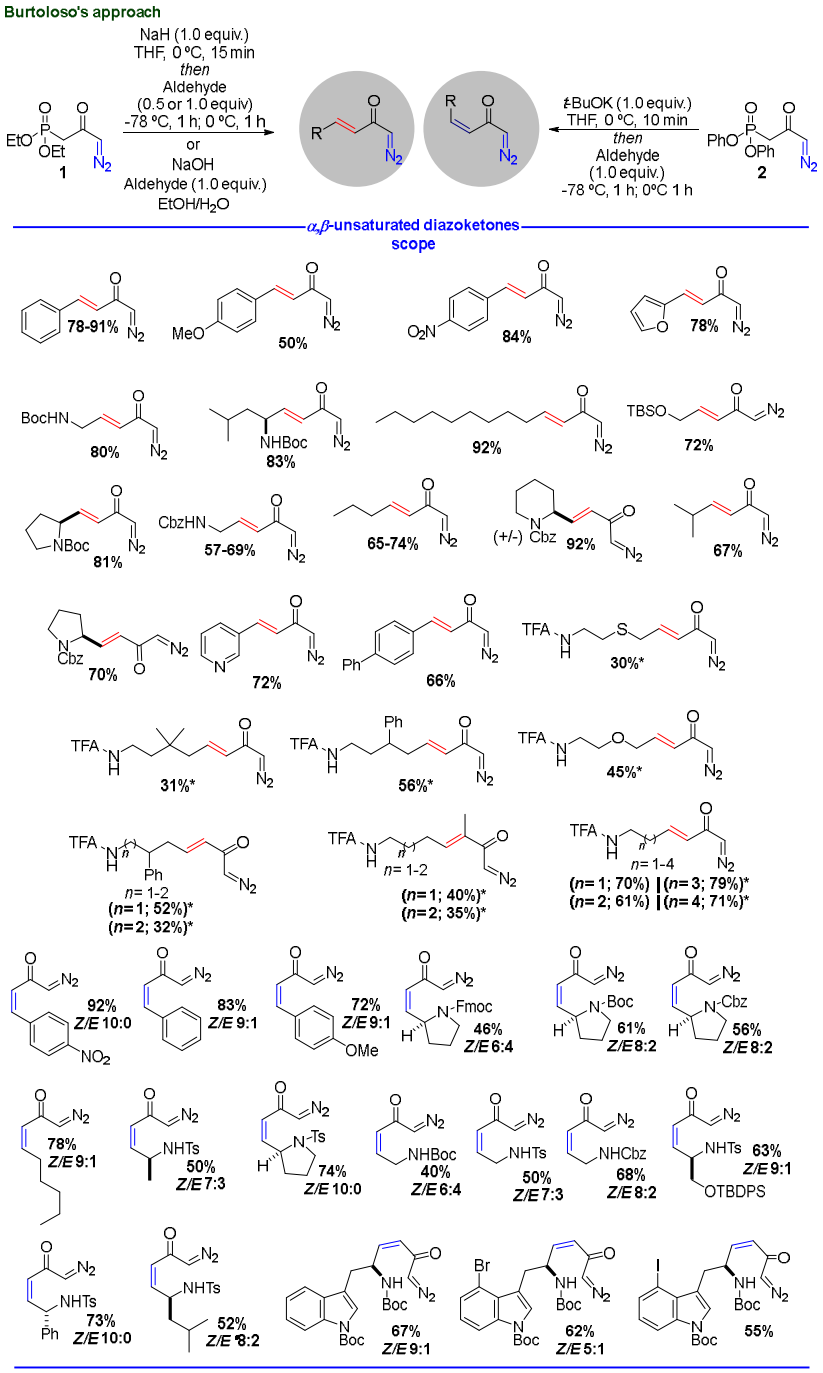
The main contribution of Burtoloso's approach was the synthesis of olefination reagents that provide the diazo group portion and allows the stereospecific formation of the double bond, depending on the class of phosphonate employed. The diazophosphonate **1** was employed in the stereospecific synthesis of *E*-α,β-unsaturated diazoketones. The optimal condition was carried out using two equivalents of the diazophosphonate, sodium hydride (NaH) as base, and tetrahydrofuran (THF) as solvent at -78 °C. The employed experimental condition furnishes only the *E*-α,β-unsaturated diazoketones (no *Z*-α,β-unsaturated diazoketone was observed).[43] Is worth mentioning that the need to use excess of the diazophosphonate **1** is to avoid the formation of coupled diazoketones as by-products and also to enforce the achievement of the desired α,β-unsaturated diazoketones as major products. Some years later, the issue about the excess of the diazophosphonate as solved, when a smoother condition was developed employing sodium hydroxide (NaOH) as base, a mixture of EtOH/water (1:1) as the solvent, and only one equivalent of the diazophosphonate. On the other hand, the diazophosphonate **2** was employed in the stereospecific synthesis of *Z*-α,β-unsaturated diazoketones. The use potassium *tert*-butoxide as the base and tetrahydrofuran (THF) as solvent at -78 °C furnishes the *Z*-α,β-unsaturated diazoketones as major stereoisomers in good yields and stereoselectivity.[44] By these approaches many α,β-unsaturated diazoketones were synthesized from simple to more complexes aldehydes, including those derived from enantiomerically pure amino aldehydes, a great improvement by Burtoloso's approach (Scheme 13).

The possibility to employ enantiomerically pure amino-aldehydes in the HWE olefination, without loss of the stereocenters, was another great improvement achieved by Burtoloso's group in the synthesis of α,β-unsaturated diazoketones. The olefination reaction with the diazophosphonate **1** was carried out without epimerization of the chiral center derived from the amino-aldehydes, as shown by HPLC studies. Even when the reactions were performed with excess of the base the diazoketones were furnished in >99 *ee*.[45] Studies for the diazophosphonate **2** in the HWE reaction with amino aldehyde has shown to be dependent on the protecting group present in the amine. The main protecting groups presented on the amino aldehydes employed in the HWE reaction was CBz, Boc or Ts. Depending on the size of the protecting group, and also the type of substituents on the α carbon to the carbonyl group, different stereoselectivities were observed (usually in good ratios).

The Burtoloso's HWE olefination reagents were an important contribution in the synthesis of α,β-unsaturated diazoketones, improving the scope and also the possibilities of application of these compounds. In the last decade, Burtoloso's group has been exploring the versatility of the α,β-unsaturated diazoketones[32] and also of the potential of the diazophosphonate in further applications.[46] The stereospecificity for the *E*- or *Z*-unsaturated diazoketone formation is a useful tool in organic synthesis, allowing the construction of stereospecific derivatives.

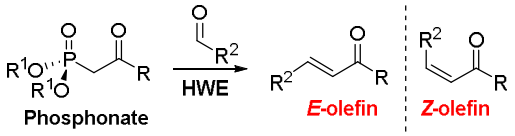
3. Mechanism for the stereospecific synthesis of *E*- or *Z*-α,β-unsaturated diazoketones

For the mechanism involved in the α,β-unsaturated diazoketones formation we must take a better look on the diazophosphonate employed in the HWE olefination reaction.



Scheme 13. Burtoloso's methodology for the synthesis of α,β-unsaturated diazoketones.

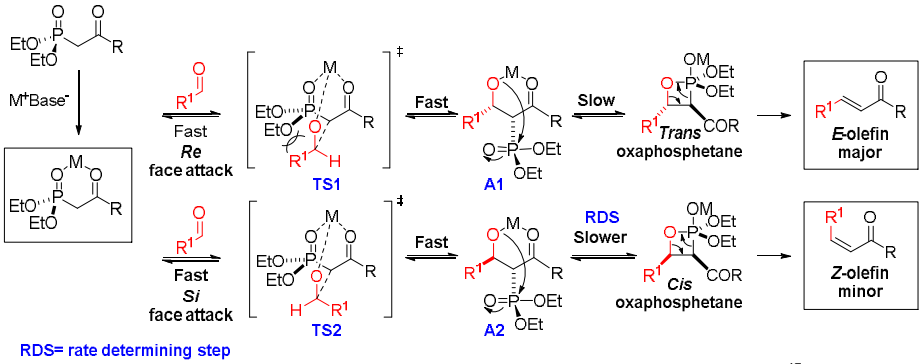
The phosphonates are a well-known class of compounds employed in organic synthesis for the major formation of *E*- or *Z*-olefins. Since the first report by Horner[47] in 1958 (and some years later by Wadsworth and Emmons),[48] the dialkyl phosphoacetate has been widely employed in the stereospecific synthesis of *E*-olefins. On the other hand, the Ando and Still-Gennari modified phosphonates have been explored in the olefination reactions to favor the formation of the *Z*-olefins as major products. The stereospecificity of the HWE reaction with phosphonates depends mainly on the groups attached to the phosphorus and the stability of oxaphosphetane intermediates (Figure 1).



Phosphonate type	Substituent	leads to
Dialkyl phosphonate	R^1= Alkyl	*E*-olefin
Ando phosphonate	R^1= Aryl	*Z*-olefin
Still-Gennari phosphonate	R^1=CH_2CF_3	*Z*-olefin

Figure 1. Some examples of phosphonate compounds.

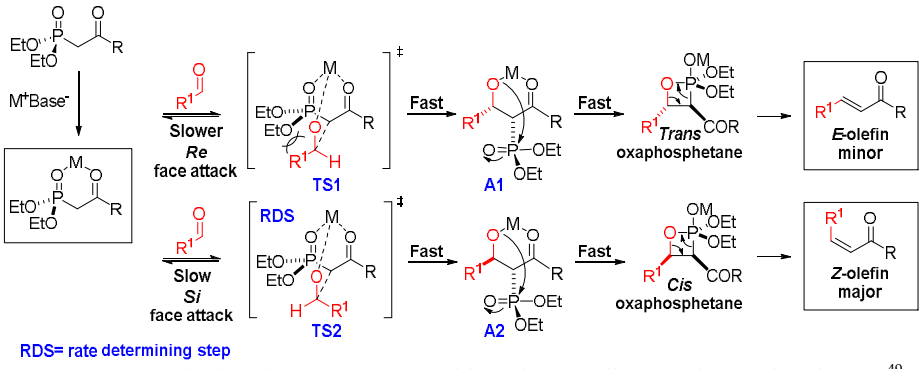
The mechanism for the HWE reaction with dialkyl phosphonates starts with the formation of phosphonate carbanion *via* the abstraction of the acidic hydrogen by a base. Once the carbanion phosphonate is formed the nucleophilic attack to aldehyde can be performed either by *Re* or *Si* face of the carbonyl group. The attack over the *Re* face is less favored due to the repulsion between the groups presented in the phosphonate carbanion and the group R^1 presented in the aldehyde in the **TS1**, leading to the formation of the intermediate **A1**. By the same criteria, the attack over the *Si* face has less steric hindrance *via* **TS2**, which favors the formation of the intermediate **A2**. The rate determining step of this reaction is the formation of the oxaphosphetane intermediates, that decomposes to form the *E* or *Z* olefin. The *trans*-oxaphosphetane formation is favored due to the less steric hindrance in its structure, promoting the formation of the *E*-olefin. Due to the reversibility of the oxaphosphetane formation for dialkyl phosphonates, the less favorable *cis*-oxaphosphetane can goes back and restore the phosphonate carbanion and aldehyde precursors. These molecules react again *via* **TS1** and **TS2** accumulating the *trans*-oxaphosphetane, which decomposes to form the *E* olefin as a thermodynamic product (Scheme 14).



Scheme 14. Mechanism for HWE reaction with dialkyl phosphonate.[47]

In the case of Ando and Still-Gennari phosphonates the HWE reaction follows similar reactional path, however diverges with the respect to the rate determining step. The presence of electron-withdrawing groups attached to the phosphorus atom in these phosphonates turns the carbon-oxygen bond on the oxaphosphetane

intermediate stronger, due to the increase of the positive character of the phosphorus atom. In this case the decomposition of the oxaphosphetane intermediate is faster compared to dialkyl phosphonates. By this way, the attack of the phosphonate carbanion to the aldehyde is now irreversible, and it becomes the slowest step of the reaction, the rate determining step. In this step the transition state **TS2** is favored due to the less steric hindrance between the groups presented in the phosphonate carbanion and the group R^1 presented in the aldehyde, which leads to the *cis*-oxaphosphetane intermediate that rapid decomposes to the *Z*-olefin (Scheme 15).



Scheme 15. Mechanism for HWE reaction with Ando- or Still-Gennari-type phosphonate.[49]

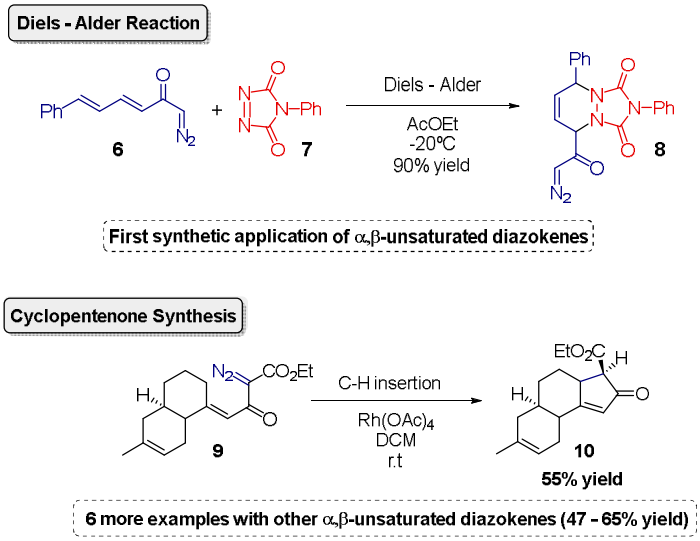
4. Synthetic application of α,β-unsaturated diazoketones

4.1. General applications

Since the firsts reports in the preparation of α,β-unsaturated diazoketones, the application of these compounds as platforms to construct more functionalized and more complexes structures has been growing. The multifunctionality that these compounds possess (presence of a diazo group, a carbonyl function and a double bond in the same molecule) has been widely explored, shedding light on versatility of the of α,β-unsaturated diazoketones as a powerful synthetic tool.[32,50]

In 1981 Regitz performed the first synthetic application of α,β-unsaturated diazoketones by studying the reactivity of these class of compounds in a Diels-Alder reaction with triazolindinones.[51] A decade later, Wenkert and co-workers described a Rh(II)-catalyzed intramolecular C-H insertion reaction of β,β-dialkylated α,β-unsaturated diazoketones to afford cyclopentenones in a range of 47-65% yield (7 examples) (Scheme 16).[52]

The diazo carbonyl group can undergo the Wolff rearrangement to provide important intermediates that can mediate several chemical transformations. As an example, Danheiser and co-workers developed an efficient protocol, involving vinylketenes and acetylenic dienophiles, leading to bezannulation products with a high degree of substitution. These methods are based on the generation of key vinylketenes intermediates from the photochemical Wolff rearrangement of unsaturated diazoketones. More stable ketenes were generated when α-silyl-α-diazo-α,β-unsaturated ketones were applied as substrates in this methodology, reacting with the double bond and acetylenic dienophiles to produce highly substituted cyclohexenones and phenols (Scheme 17, Chart A).[53,54] Brückner and co-workers used the strategy of silver benzoate-induced Wolff rearrangement of α,β-unsaturated diazoketones in MeOH on the generation of β,γ-unsaturated methyl esters. These intermediates were employed in Sharpless Asymmetric Dihydroxylation (SAD), followed by spontaneous cyclization to afforded lactones (Scheme 17, Chart B).[55] Bernardim and Burtoloso reported the synthesis of the bioprotective agent JP4-039 by using an α,β-unsaturated diazoketone as intermediate. This approach involves the direct synthesis of β,γ-unsaturated amides from the photochemical Wolff rearrangement of α,β-unsaturated diazoketones in the presence amines as nucleophiles. In the case of JP4-039, the diazoketone substrate was obtained employing diazophosphonate **1** and *N*-Boc-*L*-leucinal (Scheme 17, Chart C).[56]



Scheme 16. α,β-Unsaturated diazoketones as substrates for Diels-Alder reaction and C-H insertions reaction.

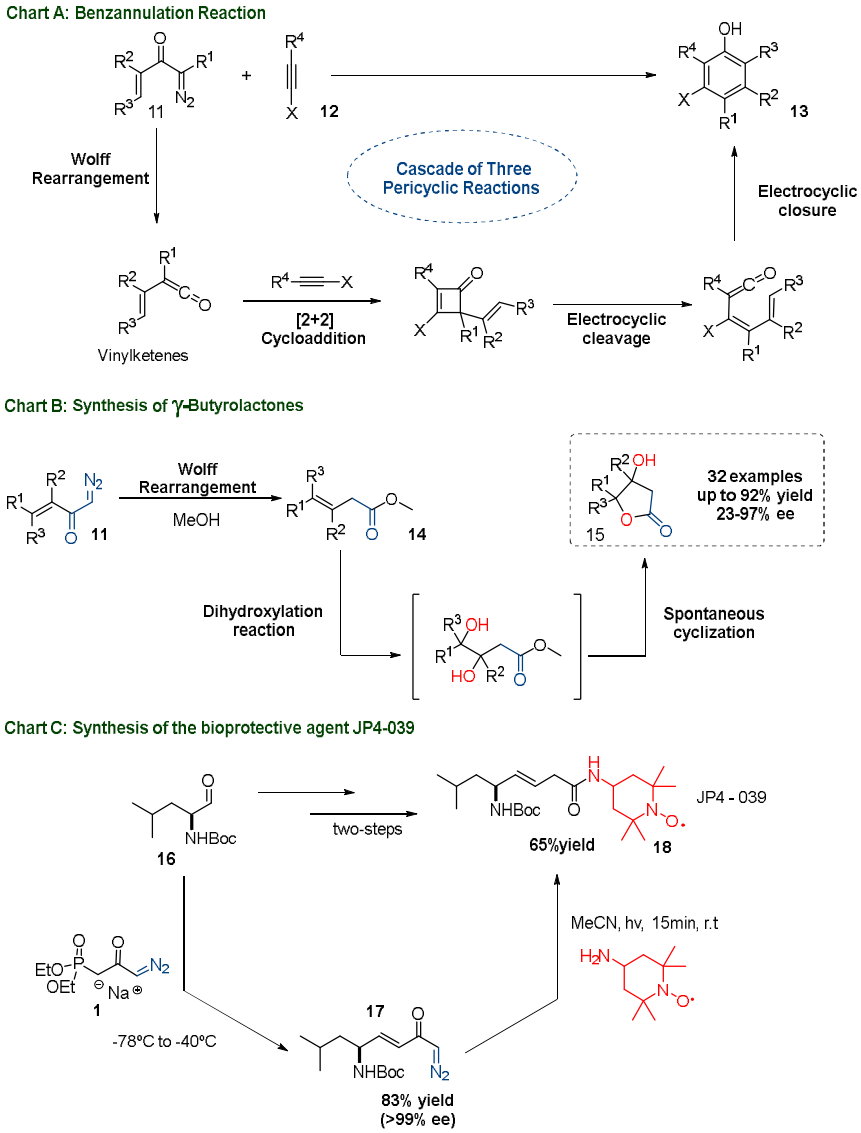
Some years later Bernardim and Burtoloso[57] improved the methodology for the Wolff rearrangement with α,β-unsaturated diazoketones *via* visible-light promoted by LED lamps, as a sustainable alternative for the classic synthetic methods employed in this transformation. Usually, the Wolff rearrangement conditions requires expensive silver salts catalysts or photolysis using an energy consuming Hg and Xe medium and high-pressure arc lamps. The alternative reported was applied in the *in situ* formation of ketenes intermediates from α,β-unsaturated diazoketones using 18Wwhite LED lamp as a light source. Next, the ketene intermediates reacted with oxygen nucleophiles to provide Arndt-Eistert homologation products in good to excellent yields. This methodology was also efficient using nitrogen nucleophiles and the scope of the reaction was expanded to alkyl-, aryl-diazoketones and diazoketones derived from α-amino acids (Scheme 18).

Ylides species can also be generated *in situ* and act as reactive intermediates to further transformations. A multistep one-pot transition metal catalyzed ylide formation/Wittig olefination/Nazarov cyclization protocol for the construction of β-methylenecyclopentenones was developed by Tang co-workers. In this transformation, diazoketones were used to provide phosphorus ylides intermediates, that in the presence of allenes led to cyclopentenones (Scheme 19, Chart A).[58] Hu and co-workers described a multicomponent reaction between diazo compounds, glyoxal and water using a bimetallic co-catalysis system Rh(II)/Zn(II) for the synthesis of unprotected diols in a single step. The key step of this transformation occurs when the oxonium ylide intermediates, generated from α-diazocarbonyl compounds and water, were trapped by Zn(II)-activated dicarbonyl compounds. In a later publication, similar strategy afforded enantiomeric enriched aminoalcohols from a $Rh_2(OAc)_4$ and chiral phosphoric acids catalyzed four component reaction with diazoketones, anilines, glyoxals, and water. This methodology was also applied with a linear alkyl vinyl diazoketone substrate to provide an important product that could act as an intermediate to access the natural product D-lyxo-phytosphingosine and its analogues (Scheme 19, Chart B).[59,60]

Recently, Liu and Hu synthesized unsymmetrical ortho-biphenols from a rhodium-catalyzed cascade C–H functionalization/aromatization coupling of *N*-aryloxyacetamides with 6-diazo-2-cyclohexenones. These transformations take place under mild and redox-neutral reaction conditions with broad substrate scope in overall good yields (Scheme 20).[61]

Despite the application of α,β-unsaturated diazoketones to the synthesis of more functionalized compounds has great importance in organic synthesis, the main application of these compounds has been focused on the synthesis of heterocyclic systems. Recently, the synthesis of heterocyclic compounds from

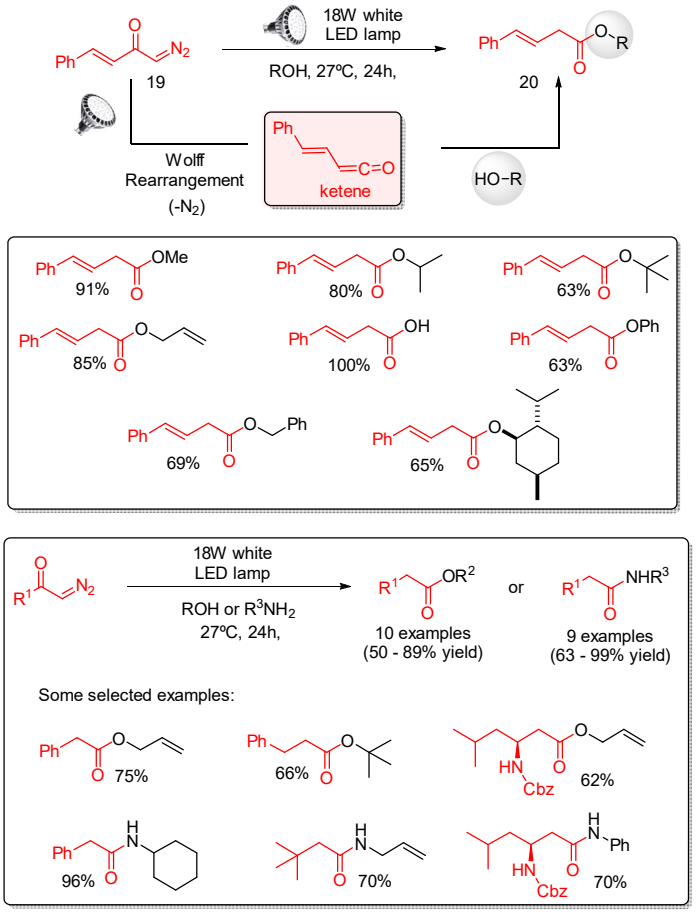
α,β-unsaturated diazoketones has grown, especially after the modern methodologies that allows the achievement of more complexes α,β-unsaturated diazoketones.



Scheme 17. Examples of Wolff rearrangement products from unsaturated diazoketones.

4.2. α,β-Unsaturated diazoketones as intermediates for the synthesis of heterocyclic systems

The synthesis of heterocyclic systems from α,β-unsaturated diazoketones is based on the multifunctionality that these compounds possess and its application as advanced intermediates. The exploration of its functionalities in different reactions has been the groundwork for the synthesis of complexes heterocycles in the past years.



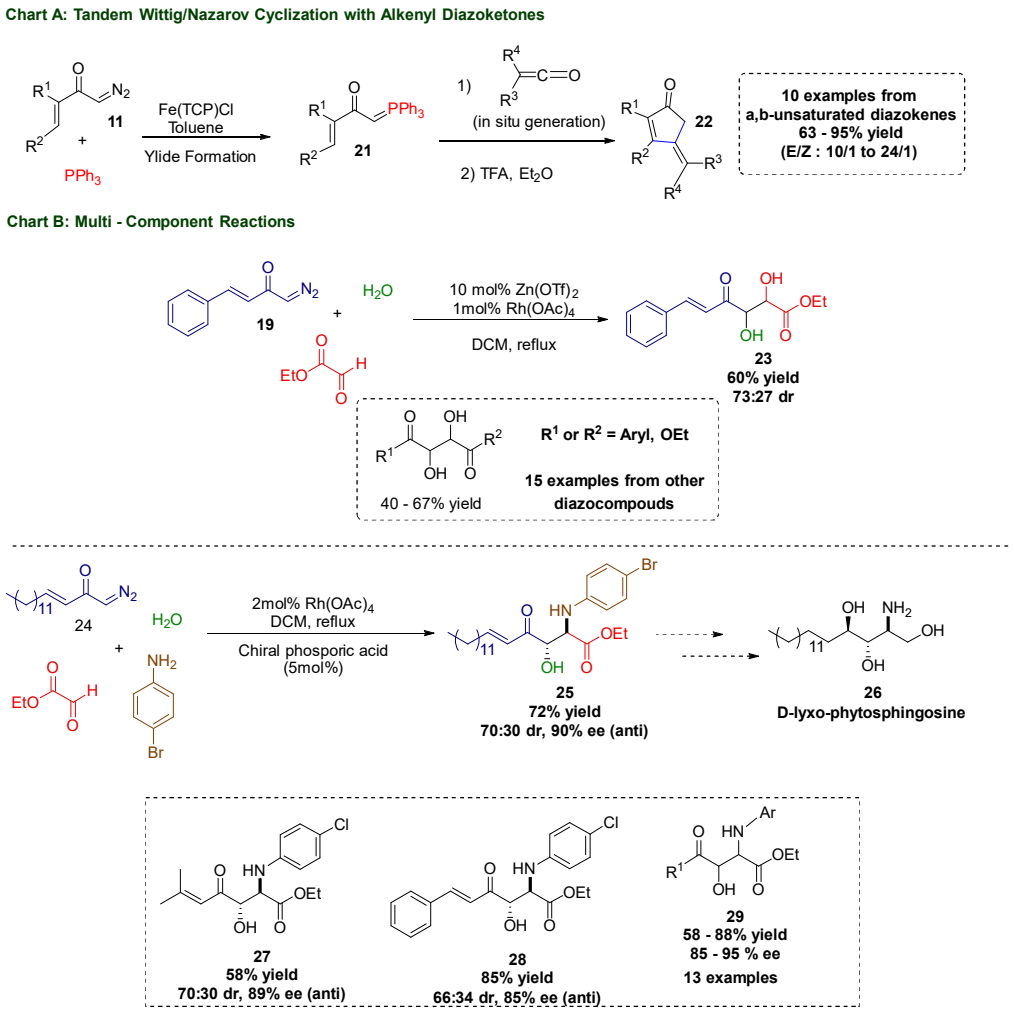
Scheme 18. Arndt-Eistert homologation reaction *via* visible-light promoted Wolff rearrangement from α,β-unsaturated diazoketones.

One of the first application of α,β-unsaturated diazoketones in the synthesis of *N*-heterocycles was reported in 1989 by the Danishefsky and coworkers.[62] The authors described an aza-Robinson annulation protocol to furnish dihydro-γ-pyridones from 1-diazobut-3-en-2-one and thiolactams. In this work, first a conjugate addition between the 1-diazobut-3-en-2-one and thiolactams was performed to generate the aza-Michael adduct in 12-95% yield. Next, this intermediate was submitted to a intramolecular thiocarbonyl reaction with a rhodium carbenoid followed by a Raney-nickel reduction to provide the dihydro-γ-pyridones in 65-73% yield. These products can be employed as building blocks to achieve functionalized indolizidines, as demonstrated for the synthesis of the compound iso-A58365A. (Scheme 21).

In 2001 cyclic amines were synthesized by Clark and co-workers *via* [2,3]-sigmatropic rearrangements of ammonium ylides.[63] Two examples of 2,5-disubstituted pyrrolidinones could be accessed from α,β-unsaturated diazoketones. This transformation involves an aza-Michael addition of the amine nucleophile to the double bond and subsequent tandem metal-catalyzed intramolecular ylide formation and rearrangement to provide the desired *N*-heterocycles in 64−85% yield. Unfortunately, the reaction proceeded with low levels of diastereocontrol (≤2:1) (Scheme 22).

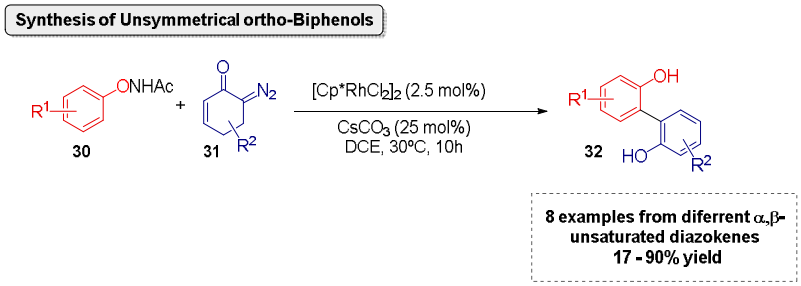
Exploring the diazo group functionality Deng and co-workers developed an asymmetric catalytic aziridination protocol to obtain vinyl aziridinyl ketones from diazomethyl vinyl ketones and imines (Scheme

23).[64] These reactions were carried out in the presence of chiral boron Lewis acids formed by triphenylborate and (S)-Vapol or (S)-Vanol ligants. *cis*-Aziridines products were obtained in good yields and in high degree of asymmetric induction (>90% ee), except when the reaction occurred in the presence of 6-diazocyclohex-2-en-1-one substrate, which gave a significative amount of the enamine byproduct.

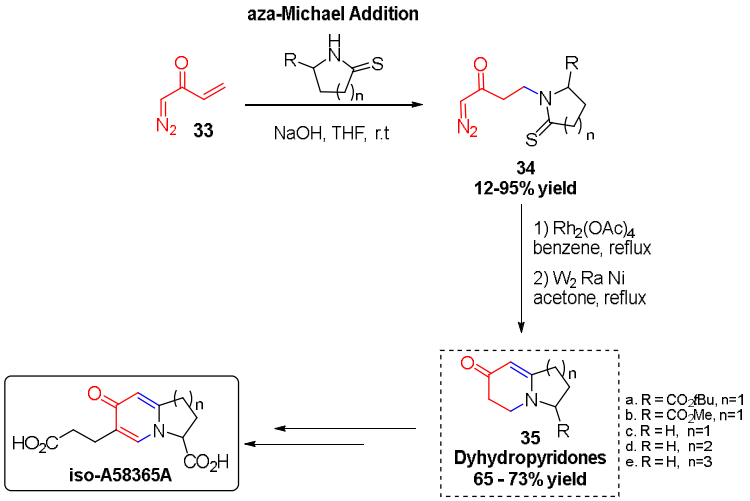


Scheme 19. Examples of α,β-unsaturated diazoketones application *via* ylide formation as intermediates in organic synthesis.

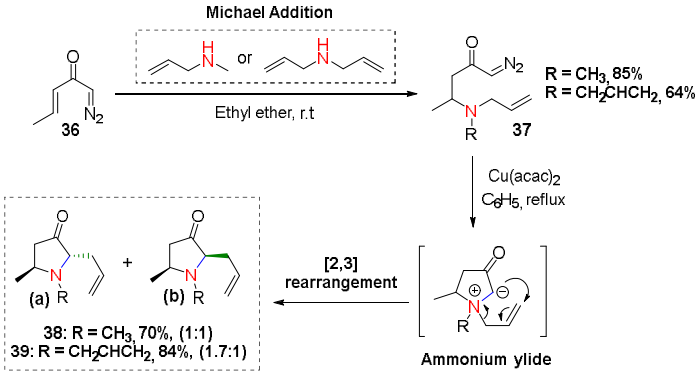
In 2013 Doyle and co-workers employed α,β-unsaturated diazoketones as building blocks for the construction of complexes bicyclic pyrazolidinones, *via* an elegant and highly diastereoselective Rh-catalyzed formal [3+2+1]-cycloaddition of azomethine imines with two molecules of a diazo ketone (Scheme 24).[65] For the optimized conditions the authors found that Rh_2(4S-MPPIM)$_4$ was the best catalyst for the formal [3+2+1]-cycloaddition, after testing different Rh-catalysts. The complex bicyclic pyrazolidinone **44a** was formed in excellent conversion (>99%) and yield (90%). The authors also changed the aryl substituent in the azomethine reagent to afford a series of complexes bicyclic pyrazolidinones in 57-90% yield and diastereomeric ratio >95:5.



Scheme 20. Synthesis of *o*-biphenols from 6-diazo-2-cyclohexenones.



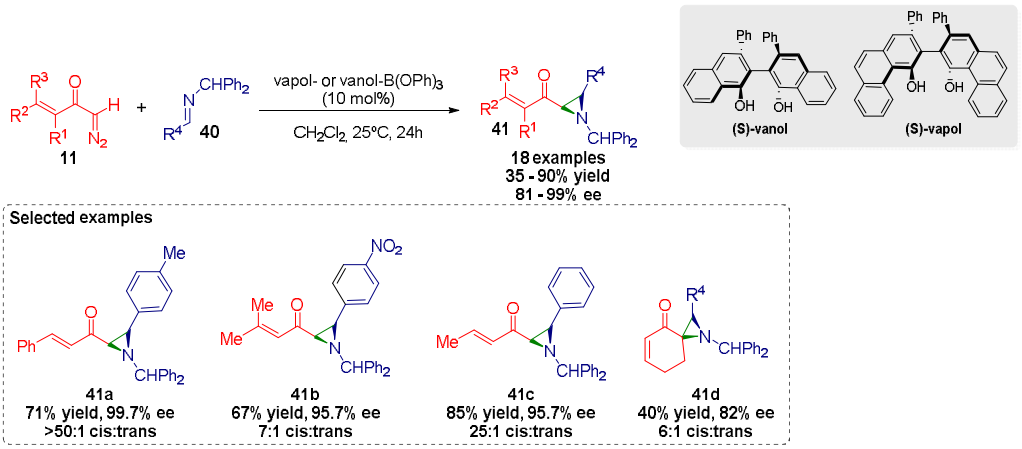
Scheme 21. Synthesis of dihydropyridones from 1-diazobut-3-en-2-one and thiolactams.



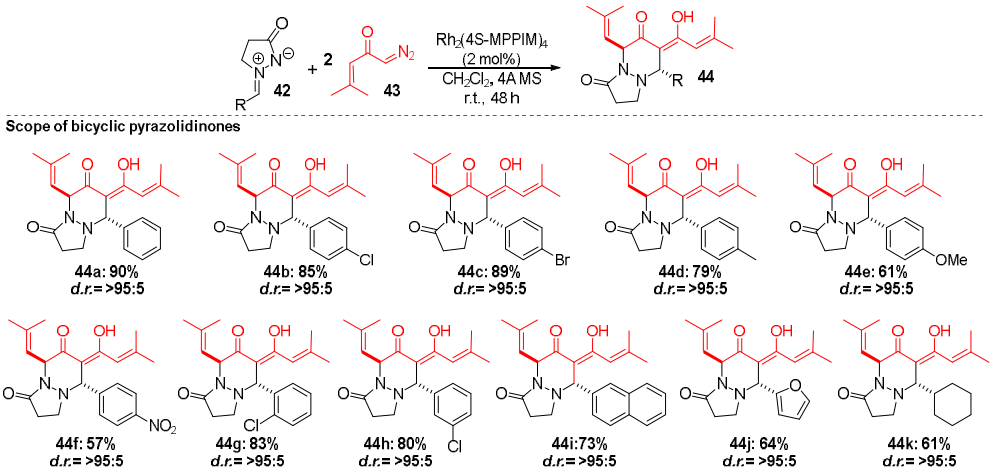
Scheme 22. Synthesis of 2,5-disubstituted pyrrolidinones from [2,3]-sigmatropic rearrangements from ammonium ylides.

In 2015 Danheiser and co-workers reported a different approach for the synthesis of substituted quinolines from α,β-unsaturated diazoketones and ynamides (Scheme 25).[66] The Danheiser' approach was based on the formation of a ketene intermediate from the α,β-unsaturated diazoketone, *via* a four-electron electrocyclic cleavage or a photochemical Wolff rearrangement. Once formed, the ketene reacts with the

ynamide *via* a [2+2]-cycloaddition to afford a cyclobutenone intermediate that, after a four-electron electrocyclic ring opening and a 6-π electrocyclic ring closure, furnishes the *N*-propargyl aniline intermediate. From this intermediate a Larock's iodocyclization can ocurrs *via* an electrophilic cyclization to furnish the quinoline core. The best condition found by the authors to the *N*-propargyl aniline intermediate was first irradiating the solution with the α,β-unsaturated diazoketones and ynamides for about 30 hours in CH_2Cl_2, then refluxing the reaction mixture in toluene for 2.5 hours. Next, the authors performed a trifluoromethylsulfonylation with triflic anhydride (Tf_2O) of the hydroxyl moiety, followed by the iodocyclization with molecular iodine. By this approach a series of substituted quinolines was synthesized in 40-84% yield. Moreover, the authors also have took advantage of the iodine presented in the structure of these quinolines to perform different transformations (cross-coupling reactions, deiodination and allylation) to furnish even more functionalized cores.



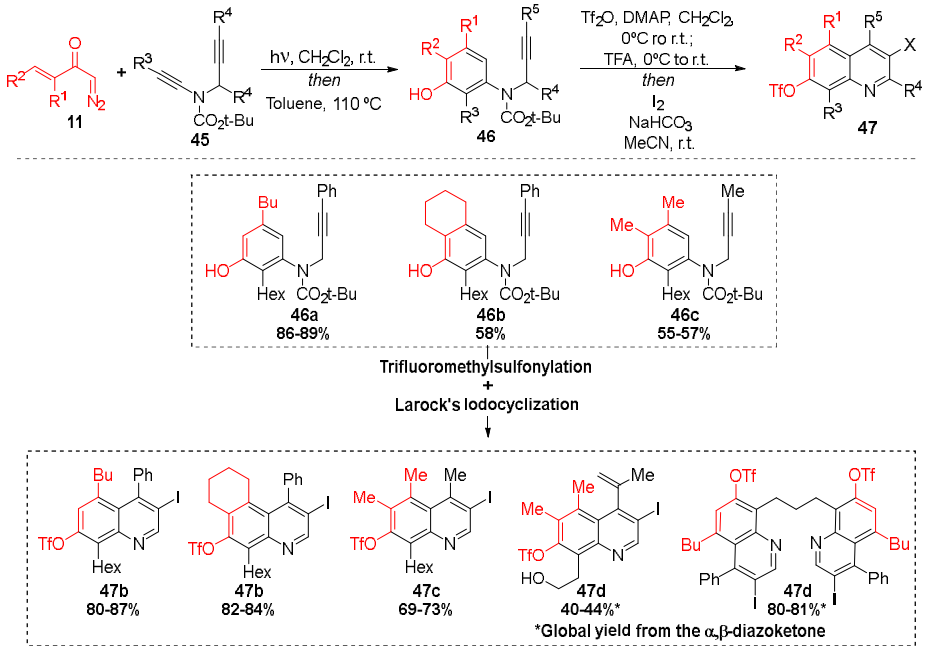
Scheme 23. Asymmetric catalytic aziridination to generate vinyl aziridinyl ketones from diazomethyl vinyl ketones and imines.



Scheme 24. Synthesis of complexes bicyclic pyrazolidinones from *α,β*-unsaturated diazoketones.

Aiming the synthesis of *O*-heterocycles, Zhai and co-workers described a versatile methodology for the construction of dibenzofurans cores employing cyclic α,β-unsaturated diazoketones as platforms.[67] This

work was based on the Pd-catalyzed cross-coupling reaction between 6-diazo-2-cyclohexenone and *o*-haloiodobenzene derivatives, followed by a Cu-catalyzed Ulmann coupling, in a *one-pot* protocol (Scheme 26). The optimal conditions employed catalytic $Pd(PPh_3)_4$ (5 mol%), with a higher loading of Cu_2O (20 mol%), to the dibenzofuran **50** in 82% yield. Once the optimized condition was secured, the authors increased the scope of dibenzofurans by exploring different substituted 6-diazo-2-cyclohexenones and *o*-haloiodobenzene derivatives. By this approach a series of substituted dibenzofurans were synthesized in 61-92%.



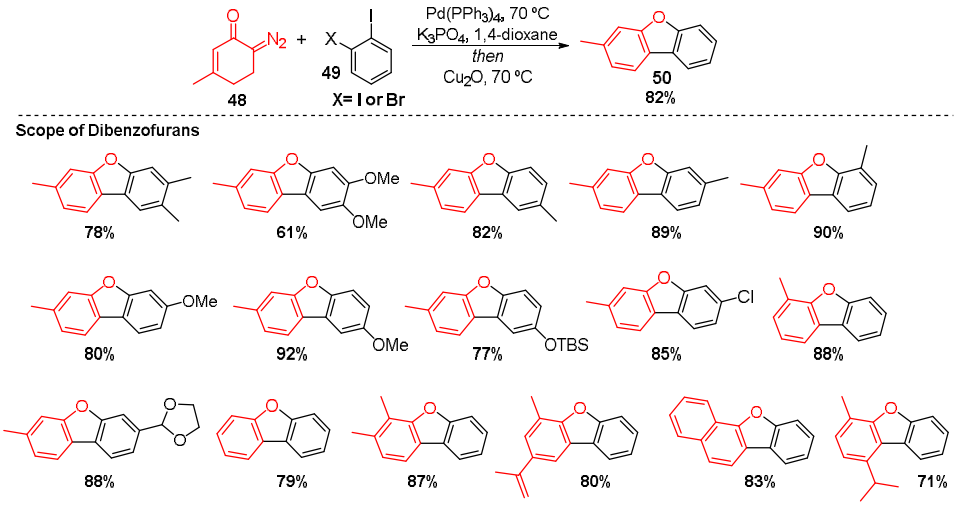
Scheme 25. Synthesis of highly substituted quinolines in two-stage benzannulation-electrophilic cyclization reactions.

Cheng and co-workers developed a mild condition protocol to provide in good yields spiro-3*H*-indazoles from 1,3-dipolar cycloaddition between 6-diazocyclohex-2-en-1-one derivatives and arynes, using *o*-(trimethylsilyl)phenyl triflate as arynes precursor (Scheme 27). An important synthetic application of these spiro-3*H*-indazoles products consisted in acid- or heat-mediated rearrangement of the acyl group to generate fused-2*H*-indazoles. This strategy was applied in a two-step manipulation of biomolecule testosterone propionate, leading to the substrate derivation in 88% yield.[68]

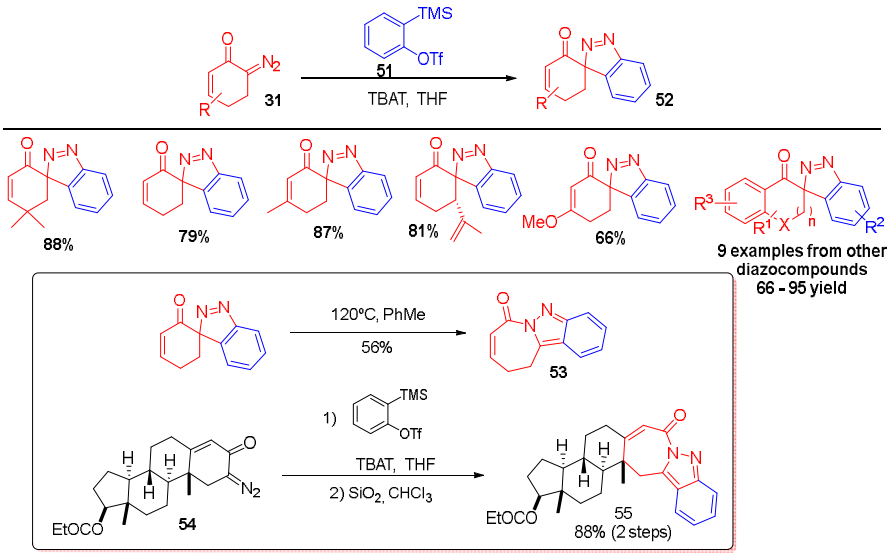
A regioselective [4+2] annulation strategy was developed by Dawande and co-workers to provide pyrido[1,2-*a*]indoles from 3-substituted indoles and diazoenals compounds (Scheme 28). The reaction occurs *via* rhodium-catalyzed formation of carbenoid specie with the diazo compound **56**, followed by a C-2 functionalization of the indol substrate to generate the enal intermediate **60a**. This intermediate is considerable unstable and readily undergoes an intramolecular cyclization to furnish a dihydropyridoindole hemiaminal **61**. Subsequent dehydration achieves the pyrido[1,2-a]indole product. In this methodology only the substrate **56** was applied as an example of α,β-unsaturated diazoketones, generating the final compound in 66% yield.[69]

An efficient strategy for the synthesis of tetrahydrocarbazoles, carbazoles, and tetrahydropyrido[1,2-*a*]indoles from α,β-unsaturated diazocarbonyl compounds and indoles was recently developed by Sakthivel and Balamurugan (Scheme 29). This transformation occurs by a tandem $Sc(OTf)_3/Rh_2(OAc)_4$ dual catalysis process involving a Michael reaction on the double bond followed by

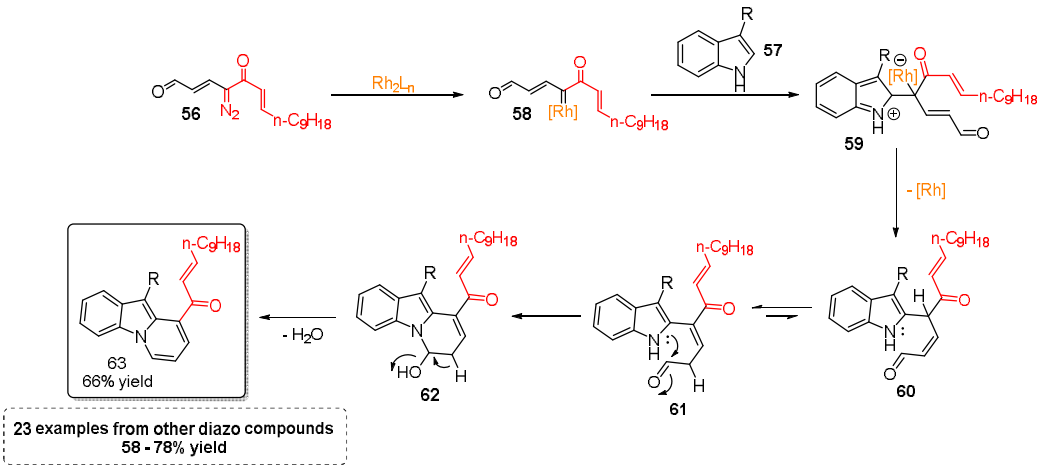
intramolecular annulation at the diazo carbon. A good regiochemistry for the Michael reaction was observed. Indole substrates without substituents in the five-membered ring added specifically through its (C3) position (otherwise for 3-substituted indoles the addition occurs through the (C2) position). The authors concluded that the $Sc(OTf)_3$ catalyst not only act in the intermolecular Michael reaction of the indole, but also has an important role in facilitating the Rh(II)-catalyzed intramolecular cyclization by interacting with the β-keto ester moiety and increasing the reactivity of the rhodium carbenoid.[70]



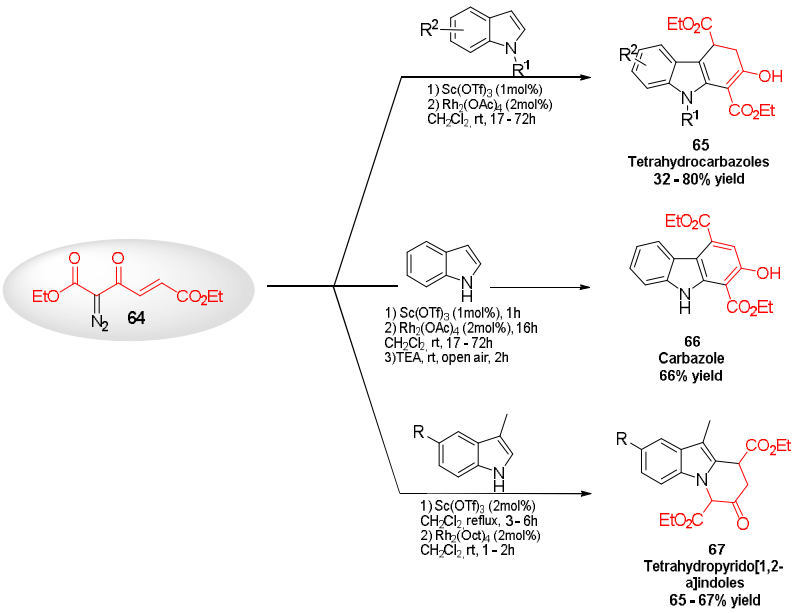
Scheme 26. Synthesis of dibenzofurans cores *via* an *one-pot* protocol for Pd-catalyzed cross-coupling and Cu-catalyzed Ulmann coupling.



Scheme 27. Spiro-3*H*-indazoles from 1,3-dipolar cycloaddition between 6-diazocyclohex-2-en-1-one derivatives and arynes.



Scheme 28. Regioselective [4 + 2]-annulation reaction to the synthesis of pyrido[1,2-*a*]indoles from indoles and diazoenals compounds.

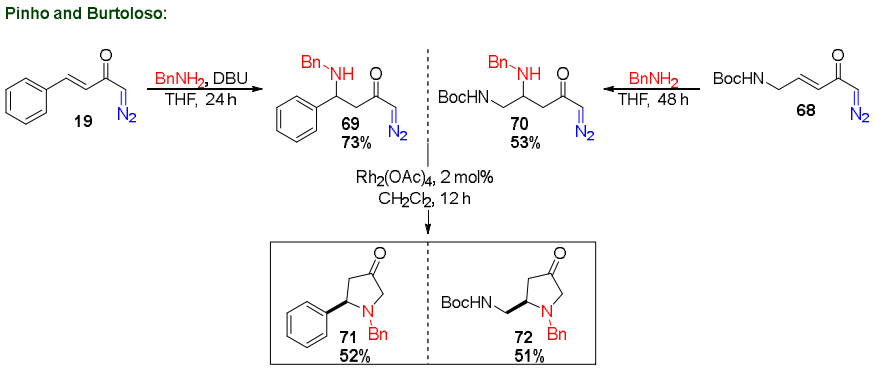


Scheme 29. Synthesis of tetrahydrocarbazoles, carbazoles, and tetrahydropyrido[1,2-*a*]indoles from α,β-unsaturated diazocarbonyl compound.

4.3. Burtoloso's research group contribution in the synthesis of heterocyclic systems *via* α,β-unsaturated diazoketones intermediates.

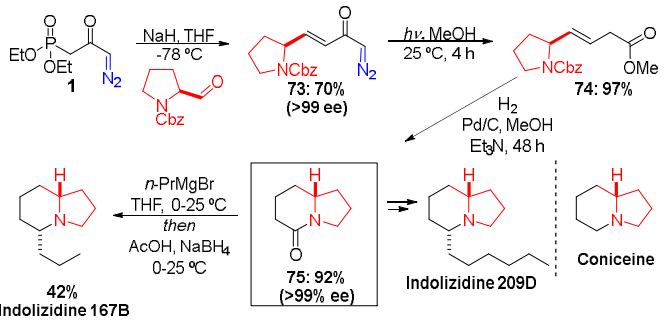
Aiming the synthesis of different types of *N*-heterocycles, Burtoloso's research group investigated the versatility of α,β-unsaturated diazoketones as building blocks for indolizidine, quinolizidine and piperidine cores synthesis. In 2011, when the preparation of Burtoloso's HWE olefination reagent diazophosphonate **1** was reported, the authors also applied the α,β-unsaturated diazoketones in the synthesis of two examples of pyrrolidines (Scheme 30).[43] The unsaturated diazoketones **23** and **69** were employed as platforms for a

aza-Michael reaction with benzylamine to fursnish the Michael adducts **68** and **70** in 73% and 53% yield, respectively. Next, a Rh-catalyzed N-H insertion was carried out to afford the 3-pyrrolidines **71** and **72** in 52% and 53% yield.



Scheme 30. Synthesis of pyrrolidines cores from α,β-unsaturated diazoketones.

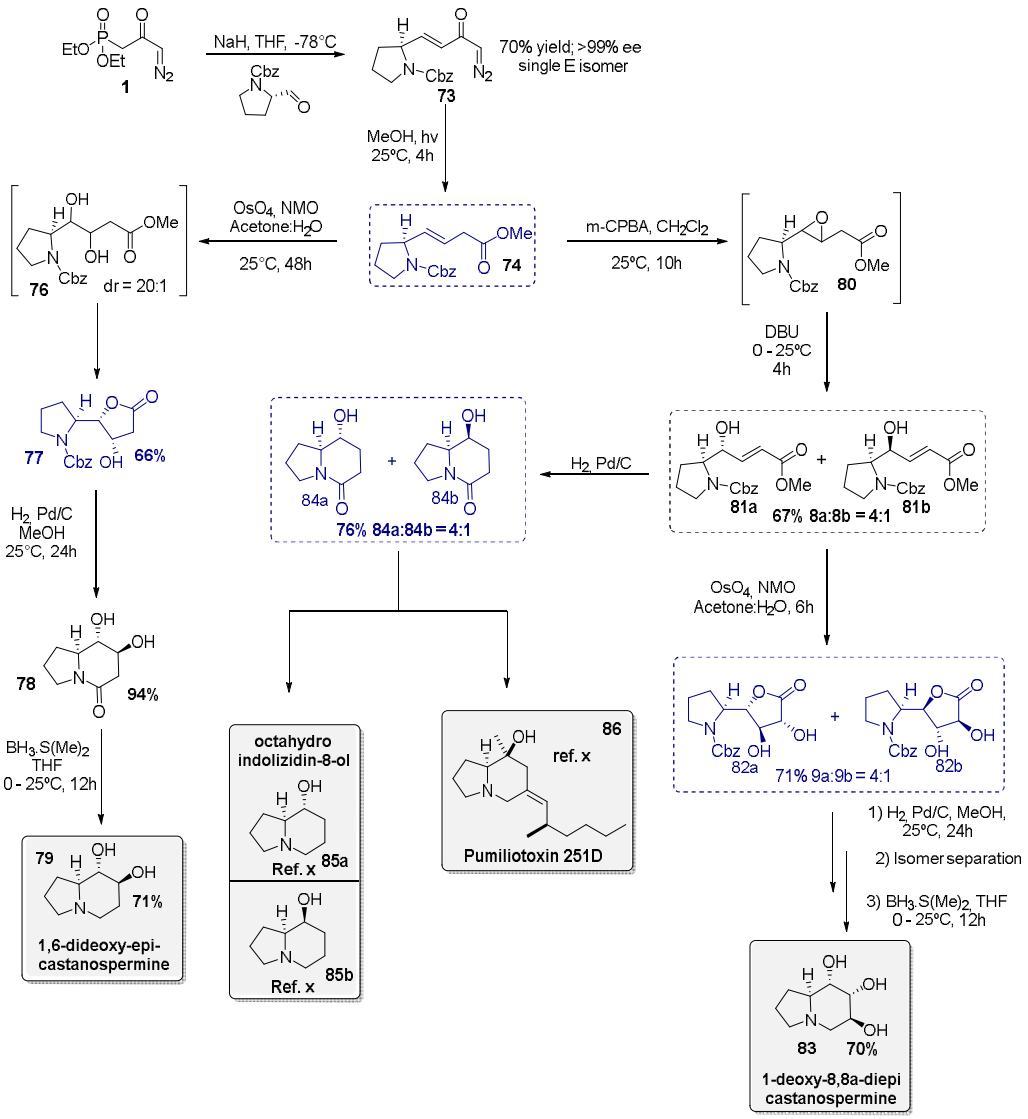
In the same year Pinho and Burtoloso applied an α,β-unsaturated diazoketone, derived from the amino acid proline, in the total synthesis of (-)-indolizidine 167B. This synthesis employed the Wolff rearrangement as the key step to construct the indolizidine core (Scheme 31).[45]



Scheme 31. Synthesis of indolizidines cores by Pinho e Burtoloso.

The work starts with the HWE reaction between diazophosphonate **1** and (*S*)-*N*-Cbz-prolinal, furnishing α,β-unsaturated diazoketone **73** in 70% yield. For the Wolff rearrangement the best condition achieved was employing a photochemical reaction with an UV light generated by an Osram 150 Xenon lamp. When the reaction was performed using methanol as the solvent, the β,γ-unsaturated amino ester **74** was prepared in 97% yield. Next, **74** was submitted to molecular hydrogen for double bond reduction, Cbz group removal and cyclization to provide the lactam **75** in 92%. From this advanced intermediate, the authors performed a propylmagnesium bromide addition, followed by a reduction with AcOH/$NaBH_4$ to furnish the indolizidine (-)-167B as a single diastereoisomer in 42% yield. It is worth mentioning that the authors also performed the formal synthesis of the (-)-indolizidine 209D and (-)-coniceine from lactam **75**. This lactam is a common intermediate previously employed in many other syntheses.

In 2012, Burtoloso's group explored the synthesis of more complex indolizidines from proline-derived amino aldehydes, aiming the stereoselective synthesis of mono-, di-, and trihydroxylated indolizidines. This approach permited the access to 1,6-dideoxy-epi-castanospermine **79**, 1-deoxy-8,8a-diepi-castanospermine **83** and octahydroindolizidin-8-ols **85a-b** from the same advanced intermediate **74**, after Wolff rearrangement, followed by stereoselective hydroxylation or epoxidation reactions (Scheme 32).[71]



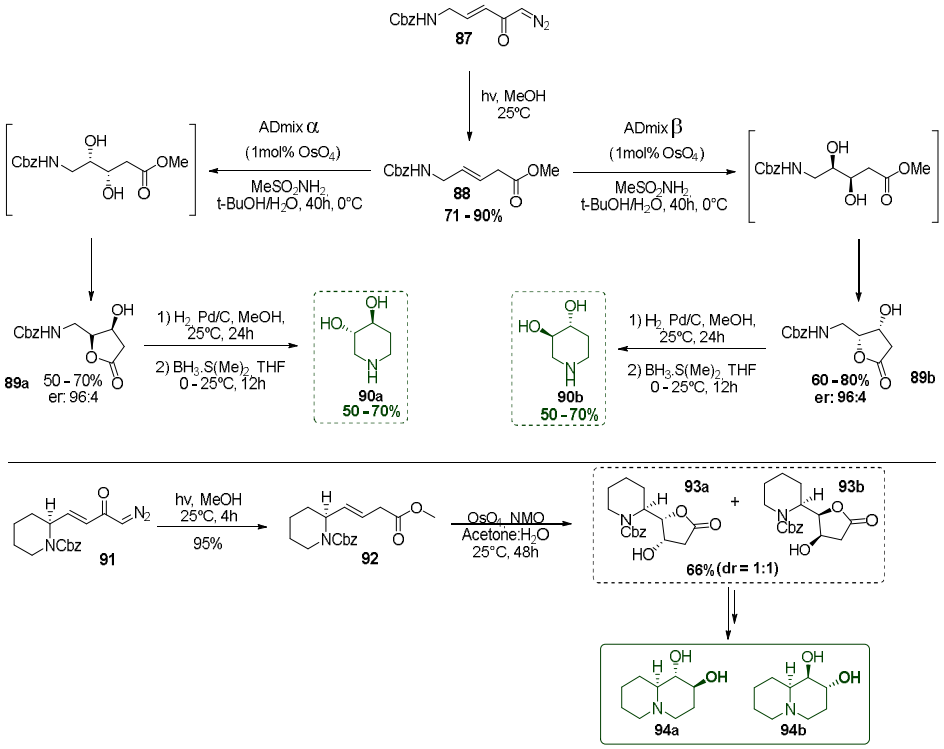
Scheme 32. α,β-Unsaturated diazoketones in asymmetric synthesis of hydroxylated indolizidines-based alkaloids.

From diazoketone **73**, a Wolff rearrangement in the presence of MeOH provided the key intermediate β,γ-unsaturated ester **74**. For the synthesis of 1,6-dideoxy-epi-castanospermine, the intermediate **74** was submitted to a stereoselective dihydroxylation reaction catalyzed by osmium tetroxide. The diol product **76** from this step was not detected because it readily suffered a lactonization process to give the lactone **77**. After that, the cyclization of the indolizidine ring was carried out in two more steps, consisting in a one-pot removal of the Cbz-protecting group/lactamization reaction and a borane-promoted reduction process to give the desired product **79** in 71% yield.

A different initial strategy was applied to obtain 1-deoxy-8,8a-diepicastanospermine **83**. This was accomplished by an one-pot epoxidation reaction/β-elimination of the β,γ-unsaturated ester **74** to provide

γ-hydroxylated α,β-unsaturated esters **81a-b**. The final steps followed the same synthetic sequence showed before (dihydroxylation, lactamization and reduction) generating the polihydroxylated indolizidine **83** in 70% yield. Finally, to accomplish the synthesis of monohydroxylated indolizidines, the advanced intermediates **81a-b** were submitted to an one-pot reduction, Cbz-deprotection, and lactamization to afford hydroxy lactams **84a-b** in 76% yield. From this mixture the formal synthesis of octahydroindolizidin-8-ols **85a-b** and pumiliotoxin 251D **86** was also accomplished.

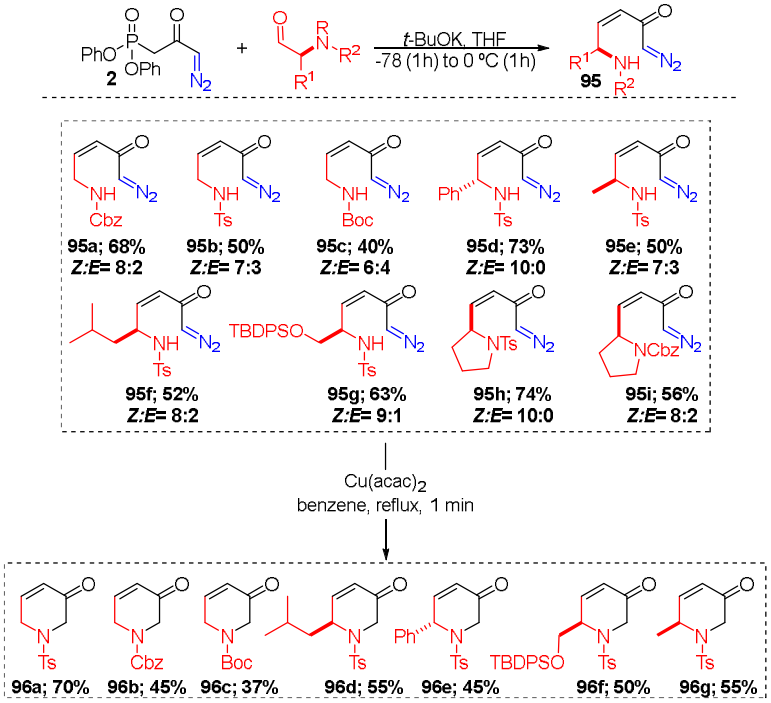
In a second moment, we decided to extend this strategy to synthesize hydroxylated quinolizidines and piperidines systems. To access a piperidine core, unsaturated diazoketone substrate **87** was first converted in the ester derivative **88** by a photochemical Wolff rearrangement in the presence of MeOH. Then, a Sharpless asymmetric dihydroxylation reaction was performed using osmium catalyst ADmix α (1 mol% of OsO4) to accomplish the chiral lactone **89a** in 70% yield (er=96:4 after HPLC analysis). Next, the reaction of **89a** with H_2/Pd resulted in the removal of the Cbz protecting group and lactone ring-opening by the free amino group to afford a lactam, which then undergoes borane-promoted reduction reaction to give piperidine **90a** in a 30-50% yield after purification. The enantiomer **90b** were also obtained from the same synthetic sequence presented above, but using Admix β instead of Admix α, for the asymmetric dihydroxylation step. Quinolizidines **94a-b** could be accessed by the same synthetic approach previously described for 1,6-dideoxy-epi-castanospermine **79** synthesis (see Scheme 32). However, for this six-membered ring analogue no selectivity was observed when the ester **92** was submitted to a OsO4/NMO promoted dihydroxylation process, providing the lactones **93a-b** as a mixture of diastereomers (dr=1:1) (Scheme 33).[72]



Scheme 33. α,β-Unsaturated diazoketones in the synthesis of hydroxylated piperidines, indolizidines and quinolizidines.

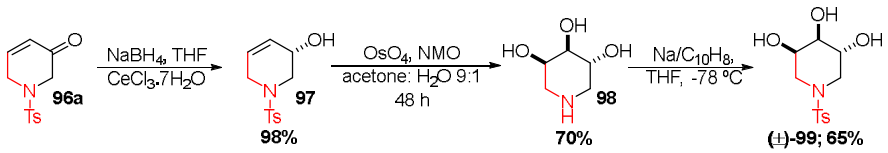
The synthesis of more complex piperidines was described by Rosset and Burtoloso in 2013.[44] In this work, initially, the authors described a method for the stereospecific synthesis of *Z*-α,β-unsaturated

diazoketones in 40-74% chemical yield. The *Z*-unsaturated diazoketones derived from amino aldehydes were employed in a Cu-catalyzed N-H insertion, affording dihydropyridin-3-one cores as advanced building blocks that could be manipulated to substituted piperidines (Scheme 34).



Scheme 34. Synthesis of dihydropyridin-3-ones from α,β-unsaturated diazoketones.

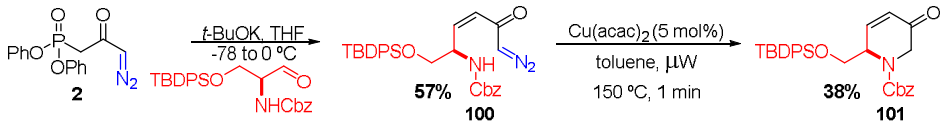
Taking advantage on the versatility of the dihydropyridin-3-ones, the authors performed a series of transformations to directly prepare a trihydroxylated natural product (Scheme 35). Reduction of the carbonyl group was performed *via* the Luche reaction, providing the protected amino alcohol **97** in 98%. Next, the authors performed a dihydroxylation of the double bond, followed by the deprotection of the tosyl group to furnish the natural piperidine **99** in 65% yield for the last step.



Scheme 35. Synthesis of a polihydroxylated piperidine from a dihydropyridin-3-ones intermediate.

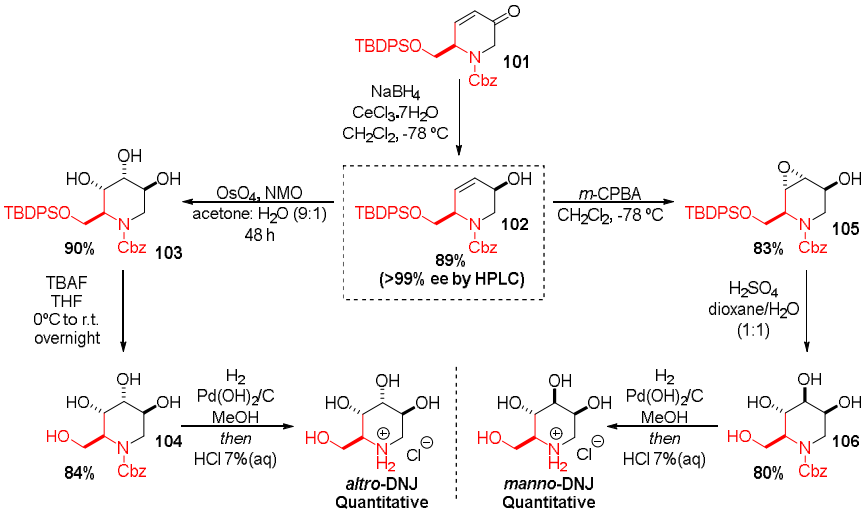
Exploring even more the versatility of the *Z*-α,β-unsaturated diazoketones, Burtoloso and co-workers performed a highly stereoselective synthesis of two Nojirimycin analogues: the (-)-1-deoxyaltronojirimycin (*altro*-DNJ) and (+)-1-deoxymannojirimycin (*manno*-DNJ) (Scheme 36).[73] The syntheses of these compounds were based on the construction of an dihydropyridin-3-one core from the *N*-Cbz-*O*-TBDPS-*L*-serinal (HWE olefination with diazophosphonate **2**, followed by a Cu-catalyzed N-H insertion reaction). The HWE olefination furnished the *Z*-α,β-unsaturated diazoketone **100** in 57% yield. After that, the authors performed a series of experimental conditions for the N-H insertion reaction

optimization. The best condition resulted in the use of $Cu(acac)_2$ (5%) in toluene with microwave heating at 100 ºC for one minute, to give **101** in 38% yield.



Scheme 36. Synthesis of the advanced intermediate **101**.

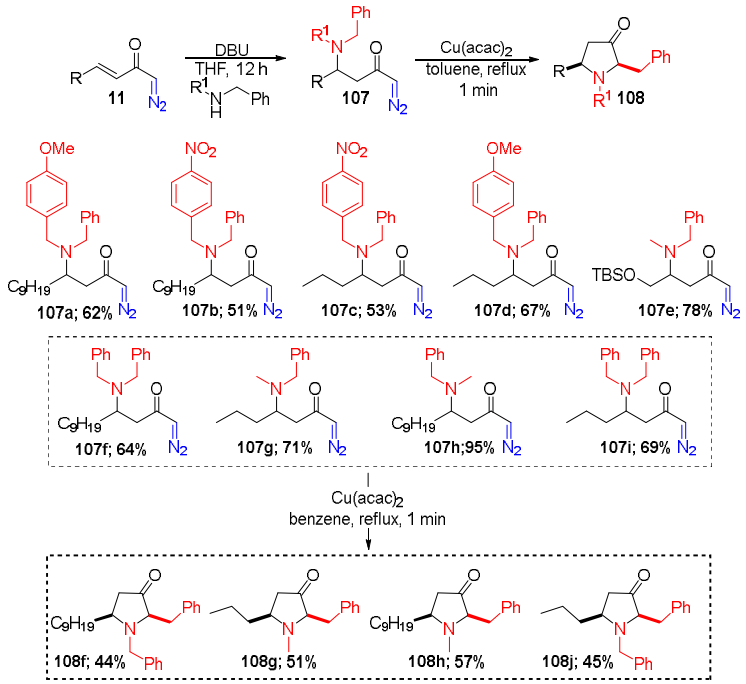
The next step consisted in the stereoselective reduction of **101** *via* the Luche reaction. The reaction was performed using $NaBH_4/CeCl_3.7H_2O$ in CH_2Cl_2 at -78 ºC to give the allylic alcohol **102** in 89% yield and 99% *ee* (without any epimerization of the stereocenters). Once the synthesis of **102** was secured, two different synthetic routes diverged from this advanced intermediate (Scheme 37). In the case of the synthesis of *altro*-DNJ the authors performed a dihydroxylation reaction over the allylic alcohol **102** to prepare the intermediate **103** in 90% yield. The dihydroxylation reaction was performed with excellent diastereoselectivity, furnishing a single isomer (the high stereoselectivity occurs due to the presence of the *O*-TBDPS group that blocks the β face of the double bond). Starting from *N*-CBz-polyhydroxylated piperidine **104**, the next steps consisted in the removal of the protecting groups TBDPS and CBz to give altro-DNJ in quantitative yield as the hydrochloride salt. The *manno*-DNJ was synthesized in a similar synthetic route. First, an epoxidation reaction over the allylic alcohol **102**, employing *m*-CPBA as the oxidizing agent, led to epoxide **105** in 83% yield. Next, an epoxide ring-opening was carried-out, with the concomitant deprotection of the TBDPS group, to provide the polyhydroxylated piperidine **106** in 80% yield. The last step consisted in the deprotection of the CBz group and hydrochloride salt formation to provide *manno*-DNJ in quantitative yield.



Scheme 37. Synthesis of the altro- and manno-DNJ from Burtoloso and co-workers.

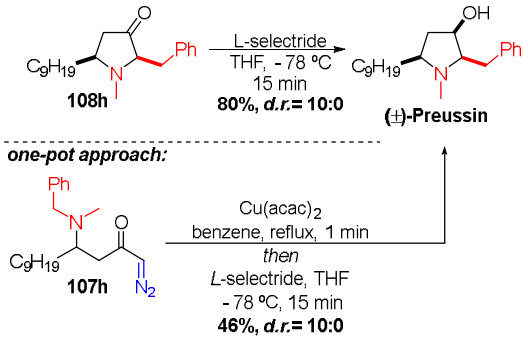
In 2014, Burtoloso's group also reported an elegant synthesis for the alkaloid (±)-Preussin in a short and straightforward sequence (three steps from the commercially available decanal) (Scheme 38).[74] This work was based on two main steps: an aza-Michael reaction between secondary amines and α,β-unsaturated diazoketones and a highly stereoselective Cu-catalyzed [1,2] Stevens rearrangement. First a series of β-amino diazoketones were synthesized *via* the aza-Michael addition, employing DBU as the base in THF, furnishing the Michael adduct in 51-95% yield. The β-amino diazoketones were submitted to the optimized

condition for the [1,2] Stevens rearrangement, which employed $Cu(acac)_2$ in toluene over reflux for only one minute. By this approach, the authors synthesized four 2,5-*cis*-disubstituted pyrrolizidines in 44-57% yield as precursors for Preussin and its analogues.



Scheme 38. Preparation of 2,5-*cis*-disubstituted pyrrolizidines *via* the aza-Michael reaction and a highly stereoselective [1,2] Stevens rearrangement.

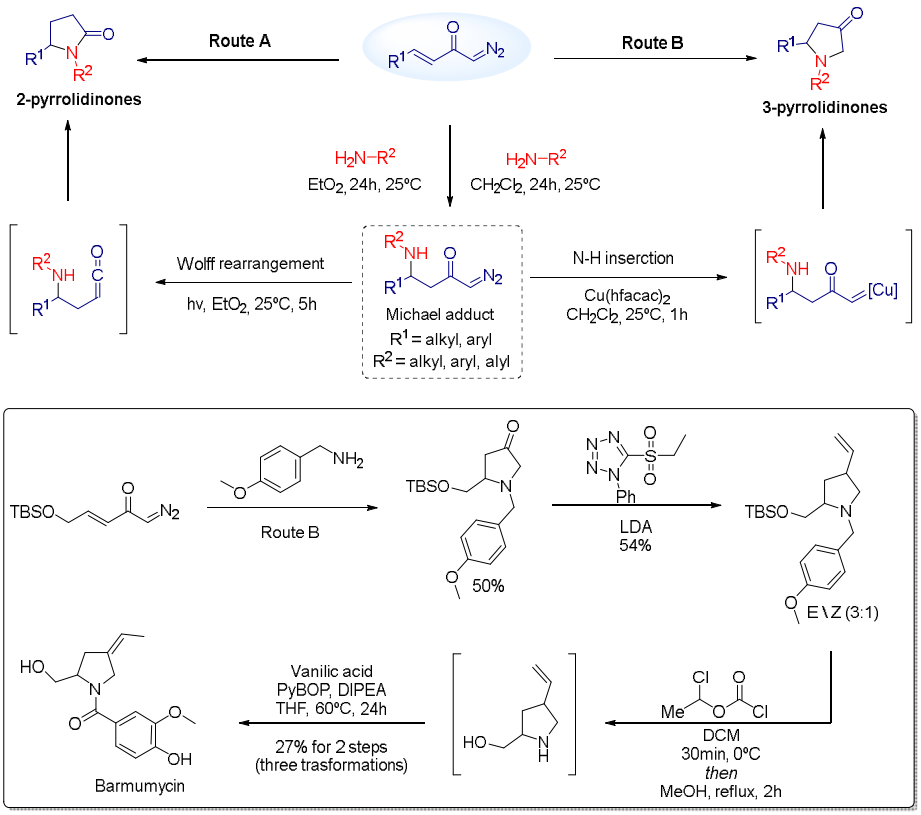
For the synthesis of the Preussin alkaloid a reduction of the pyrrolidine **108c**, employing *L*-selectride, was carried out in 80% yield (*dr*:10:0). The authors also performed the *one-pot* synthesis of Preussin from the Michael adduct intermediate in an overall yield of 46% (*dr*: 10:0) (Scheme 39).



Scheme 39. Burtoloso's approach for the synthesis of (±)-Preussin alkaloid.

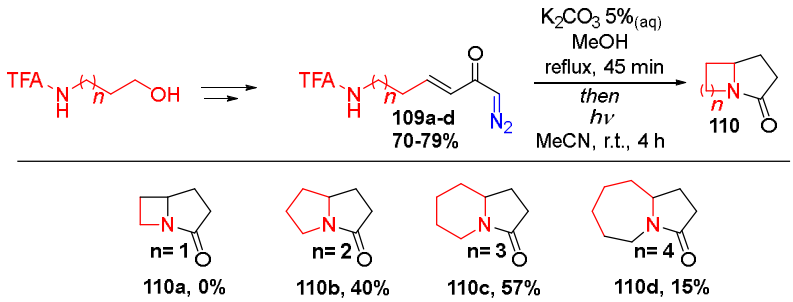
Recently, Burtoloso's group described a one-pot procedure to access 2- and 3-pyrrolidinones from unsaturated diazoketone platforms. To accomplish this transformation, a combination of aza-Michael

reaction and intramolecular cyclization were performed by two different pathways: A) in the presence of amines and light *via* Wolff rearrangement; B) in the presence of amines and copper salts as catalysts to perform an N-H insertion reaction (Scheme 40).[75] To prepare the 2-pyrrolidinones, after the formation of the aza-Michael adduct, a light-promoted Wolff rearrangement allowed the intramolecular cyclization *via* a reactive ketene intermediate (Route A, Scheme 40). Alternatively, a metal-catalyzed N-H insertion reaction pathway from the same aza-Michael adduct afforded 2-pyrrolidinones (Route A, Scheme 40). We also demonstrated an important application of this methodology in a short synthesis of the alkaloid barmumycin.



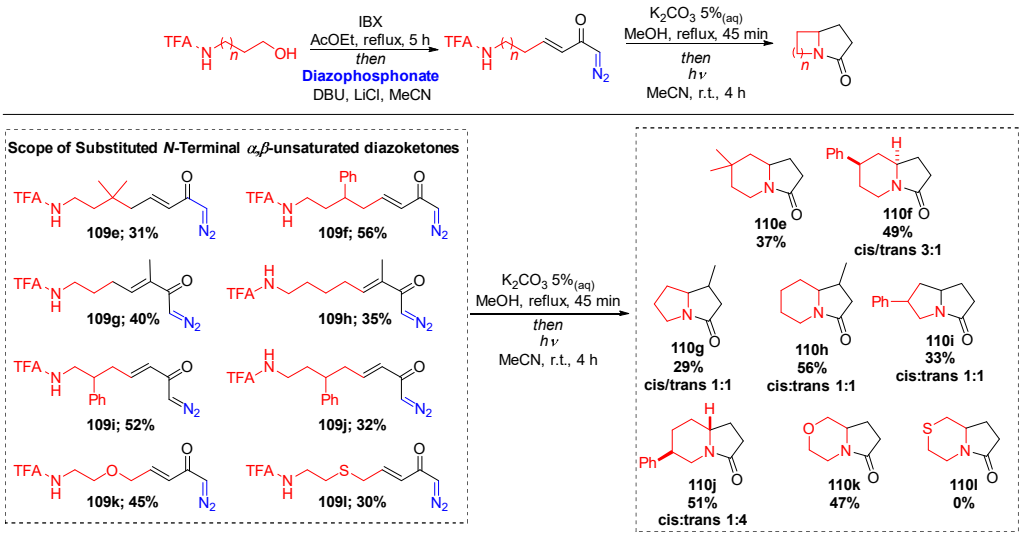
Scheme 40. Synthesis of 2-pyrrolidinones and 3-pyrrolidinones from unsaturated diazoketones and amines.

Still exploring the aza-Michael reaction on α,β-unsaturated diazoketones, though applying an intramolecular approach, Santiago and Burtoloso recently reported a straightforward protocol for the synthesis of bicyclic *N*-heterocyclic cores (especially indolizidines and pyrrolizidines) from *N*-terminal α,β-unsaturated diazoketone derivatives.[76] The work was based on performing three transformations in one reactional step (a trifluoroacetamide deprotection, an intramolecular aza-Michael addition and a photochemical Wolff rearrangement to furnish the bicyclic unit) (Scheme 41). Initially, the authors synthesized a series of *N*-terminal α,β-unsaturated diazoketones from commercially available amino alcohols *via* trifluoroacetamide protection, Parikh-Doering oxidation and HWE olefination. The α,β-unsaturated diazoketones were synthesized in 70-79% yield and submitted to the photochemical Wolff rearrangement by a an UV light (Osram 150 Xenon lamp). Although some examples of *N*-heterocyclic cores were provided, the best results were concentrated in indolizidine and pyrrolizidines cores (57% and 40% yield, respectively).



Scheme 41. Synthesis of bicyclic *N*-heterocycles *via* trifluoroacetamide deprotection/ intramolecular aza-Michael addition/photochemical Wolff rearrangement.

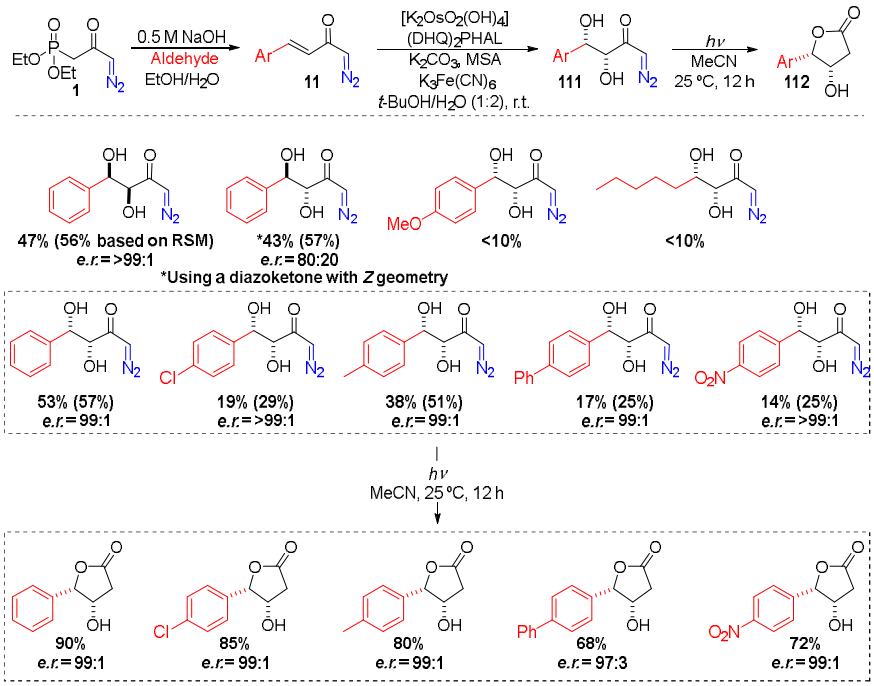
Owing to the best results for the indolizidines and pyrrolizidines, the authors expand the scope of these *N*-heterocycles by synthesizing several substituted *N*-terminal α,β-unsaturated diazoketones from different types of amino alcohols. Oxidation of the amino alcohols with IBX, followed by HWE olefination with DBU as the base, furnished the substituted *N*-terminal α,β-unsaturated diazoketones in 31-56% yield. Next, the diazoketones were submitted to the deprotection, aza-Michael addition and Wolff rearrangement protocol to give the indolizidines and pyrrolizidines in 30-56% overall yield (Scheme 42).



Scheme 42. Synthesis of substituted indolizidines and pyrrolizidines cores from α,β-unsaturated diazoketones.

Aiming the synthesis of *O*-heterocycles, Talero and Burtoloso explored the Sharpless Asymmetric Dihydroxylation (SAD) over α,β-unsaturated diazoketones for the synthesis of a series of enantiomerically pure 2-furanones in 3 steps from aldehydes.[77] The mains steps of this approach consisted in the SAD over the α,β-unsaturated diazoketones, followed by a Wolff rearrangement to construct the furanone core (Scheme 43). Initially, the authors evaluated a series of conditions to perform the dihydroxylation reaction without harming the diazo portion by exploring the amount of osmate salt, chiral ligands, bases and/or way of addition of the reagents. The best condition achieved allowed the synthesis of dihydroxylated diazoketones **111a-i** in excellent enantiomeric ratio (>99:1 *e.r.*) and in 10-53% yield (25-57% yield based on recovered starting material).

The possibility to perform dihydroxylation reaction over α,β-unsaturated diazoketones without harming the diazo portion was an important contribution, since it is well-known that the diazo group tends to decompose in the presence of certain metals. Next, the Wolff rearrangement was performed with the obtained dihydroxylated diazoketones, to produce 2-furanones by irradiating the reaction with an UV light generated by an Osram 150 Xenon lamp (12 hours). By this approach enantiomerically pure 2-furanones **112a-e** were synthesized in excellent enantiomeric ratio (>99:1 *e.r.*) and in 68-90% chemical yield.



Scheme 43. Synthesis of enantiomerically pure 2-furanones *via* (SAD) over α,β-unsaturated diazoketones.

5. Conclusions

For many years, the use of α,β-unsaturated diazoketones was stagnant due to the lack of efficient synthetic methodologies to prepare these important building blocks. With the development of efficient synthetic methodologies described by Danheiser and Burtoloso, α,β-unsaturated diazoketones became more readily available for synthetic organic chemicals and more applications could appear. Nowadays, the unquestionable importance of α,β-unsaturated diazoketones as powerful platforms in organic synthesis has been demonstrated by many applications of this class of diazo compounds as intermediates in chemical transformations. The presence of a diazo group, a ketone function and a double bond all together in a single structure is the key factor for the versatility of these compounds. It permits the creation of different pathways to provide, in few steps, functionalized-heterocycles and advanced intermediates for total synthesis of biologically active natural products.

Acknowledgment

We would thank FAPESP (Fundação de Amparo à Pesquisa do Estado de São Paulo) for financial support (2013/25504-1; 2013/18009-4; 2017/23329-9) and for the fellowship for C.A.D.C (2017/23837-4). We also thank CAPES (Coordenação de Aperfeiçoamento de Pessoal de Nível Superior-Brazil) for the fellowship for J.V.S. (PROEX-1480644).

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