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α,β-Unsaturated Diazoketones as Useful Platforms in the Synthesis of Nitrogen Heterocycles

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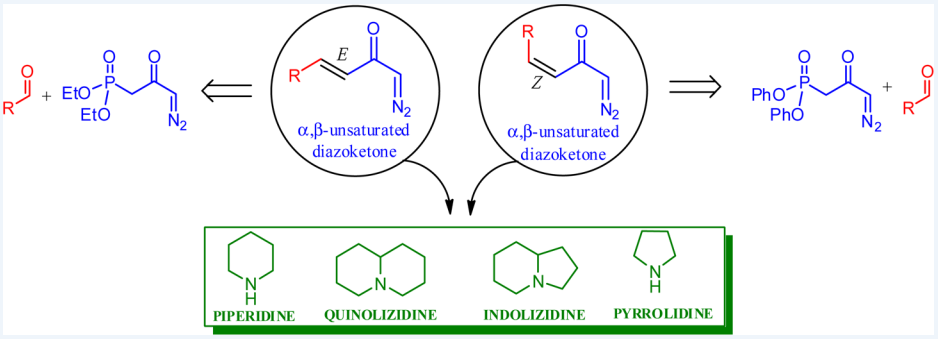

CONSPECTUS: Among the different types of diazocarbonyl substrates found in the literature to date, α,β-unsaturated diazoketones have proven to be very promising as multifunctional intermediates. Possessing a diazo group, a ketone function and a double bond all together in a single molecule, these compounds constitute versatile building blocks for synthesis. For example, double bond functionalization, followed by intramolecular insertion reactions, can be a short alternative to prepare several rings or heterocyclic compounds. Although there are many efficient methods to prepare diazoketones, very few can be extended to the synthesis of the a,β-unsaturated diazoketones; this is likely responsible for their limited application in synthesis. Unfortunately, the classical methods to prepare saturated- or aryl-diazoketones (acylation of diazomethane with acyl chlorides or mixed anhydrides) are not suitable for preparing a,β-unsaturated diazoketones, since pyrazolines (dipolar cycloaddition products from the reaction between diazomethane and the double bond) are formed. Although Danheiser's two-step detrifluoroacetylative procedure (starting from a,β-unsaturated methyl ketones) is considered the best general method, it cannot be applied to the synthesis of all types of a,β-unsaturated diazoketones. For example, the synthesis of more complex unsaturated diazoketones, as well as those with epimerizable stereocenters in the γ position, was never described before. Another point is related to the geometry of the double bond, since practically all examples described thus far refer to unsaturated diazoketones with *E* geometry. In recent years, our research group developed two new Horner−Wadsworth−Emmons reagents (containing a diazocarbonyl function) that could be easily applied in the one-step preparation of α,β-unsaturated diazoketones from aldehydes. Not only were we able to selectively synthesize *E*- and *Z*-unsaturated diazoketones, but also to employ these useful platforms in the short synthesis of several nitrogen heterocycles such as indolizidines, quinolizidines, piperidines, and pyrrolidines.

Our purpose in this Account is to introduce this class of diazoketone and provide a brief historical overview, culminating in how we developed a general methodology to prepare them. In continuation, we wish to call of the reader's attention to these important building blocks, showing how we could apply them to the synthesis of several nitrogen heterocycles, including the very short preparation of some popular alkaloids. The reader will also notice that the combination of these three important functions in the same molecule makes these compounds special as well as provides powerful platforms to access many important molecules in a direct fashion.

1. INTRODUCTION

Since the synthesis of ethyl diazoacetate (the first aliphatic substance containing a diazo group) in 1883 by Theodor Curtius,[1] more than a century has passed, and the chemistry of diazo compounds is still in progress. The recent literature still provides plenty of new examples with respect to the preparation, properties, and applications of diazo compounds, especially for the more stable diazocarbonyl compounds. Although described in 1883 and employed by Ludwig Wolff[2] in 1902 in the well-known Wolff rearrangement, diazocarbonyl compounds were unnoticed until 1927. In that year, Arndt et al.[3] developed the first general protocol to prepare a diazocarbonyl compound, involving the acylation of diazomethane with acyl chlorides. Together with the use of mixed anhydrides, this acylating protocol has become the best way to prepare a terminal α-diazocarbonyl compound from carboxylic acid derivatives (Scheme 1, Chart A). Some years later, with the need to access cyclic diazocarbonyl compounds (as well as some acyclic systems that cannot be accessed using the diazomethane acylation method), the important technique of diazo transfer was developed by Regitz et al.[4] This method,

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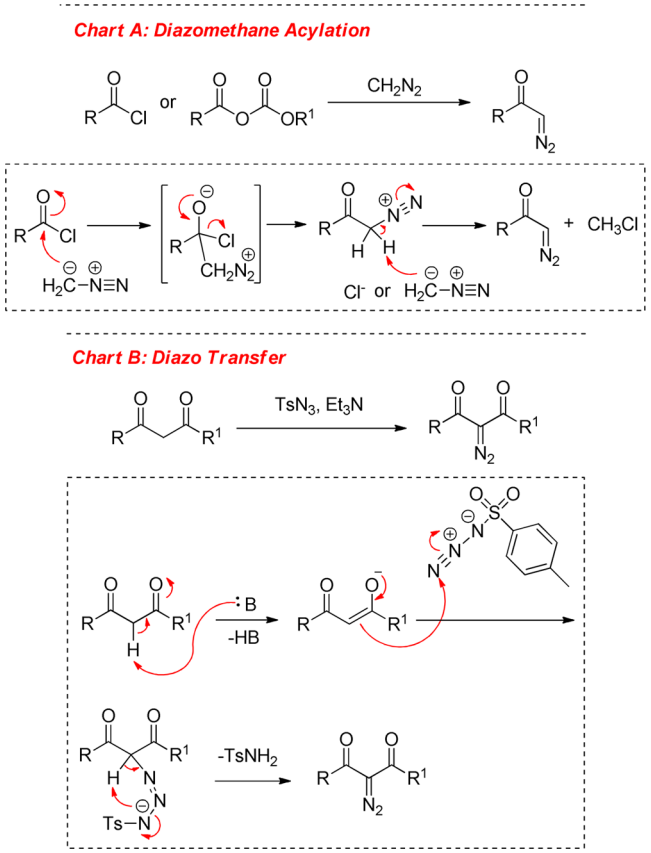
Scheme 1. Diazoketone Formation via Acylation of Diazomethane (Chart A) and Diazo Transfer (Chart B)



which involves the use of carbonyl compounds with relative acidity in the α-position (for example, 1,3-dicarbonyl and α-aryl-carbonyl compounds), a base, and a sulfonyl azide, has the advantage of being mild and not requiring the use of diazomethane (Scheme 1, Chart B).

After the development of the two main protocols to synthesize a diazocarbonyl compound (diazomethane acylation and diazo transfer), the development of the chemistry was straightforward and an exponential release of new synthetic methodologies appeared in the literature.[5−11] As depicted in Figure 1, insertion to polar (O−H, N−H, P−H, S−H, Se−H) and nonpolar (C−H, Si−H) bonds catalyzed by transition metals, chain homologation and ring contraction by the Wolff rearrangement, cyclopropanations, and dipolar cycloadditions are some of the reactions that diazocarbonyl compounds can have. In fact, there are only a few classes of compounds that perform as broad a number of different transformations.

As already mentioned, one of the key factors that permitted the advance in the appearance of new methodologies was the development of efficient methods to prepare diazo compounds. Although a vast number of structurally different diazocarbonyl compounds can now be reached using diazomethane acylation and diazo transfer protocols, a gap still exists for the more peculiar cases. One example is the α,β-unsaturated α'-diazoketones. While the literature offers thousands of examples dealing with the preparation and application of saturated or aryl-diazoketones,[5−7,12] just a few studies have been dedicated to the unsaturated ones, which is mainly due to the difficulty in their synthesis. For example, unless starting from α,β- or β,β-dialkylated unsaturated acyl chlorides or mixed anhydrides, the preparation of unsaturated diazoketones by the classical diazomethane acylation furnishes poor yields.[13,14,16] This is

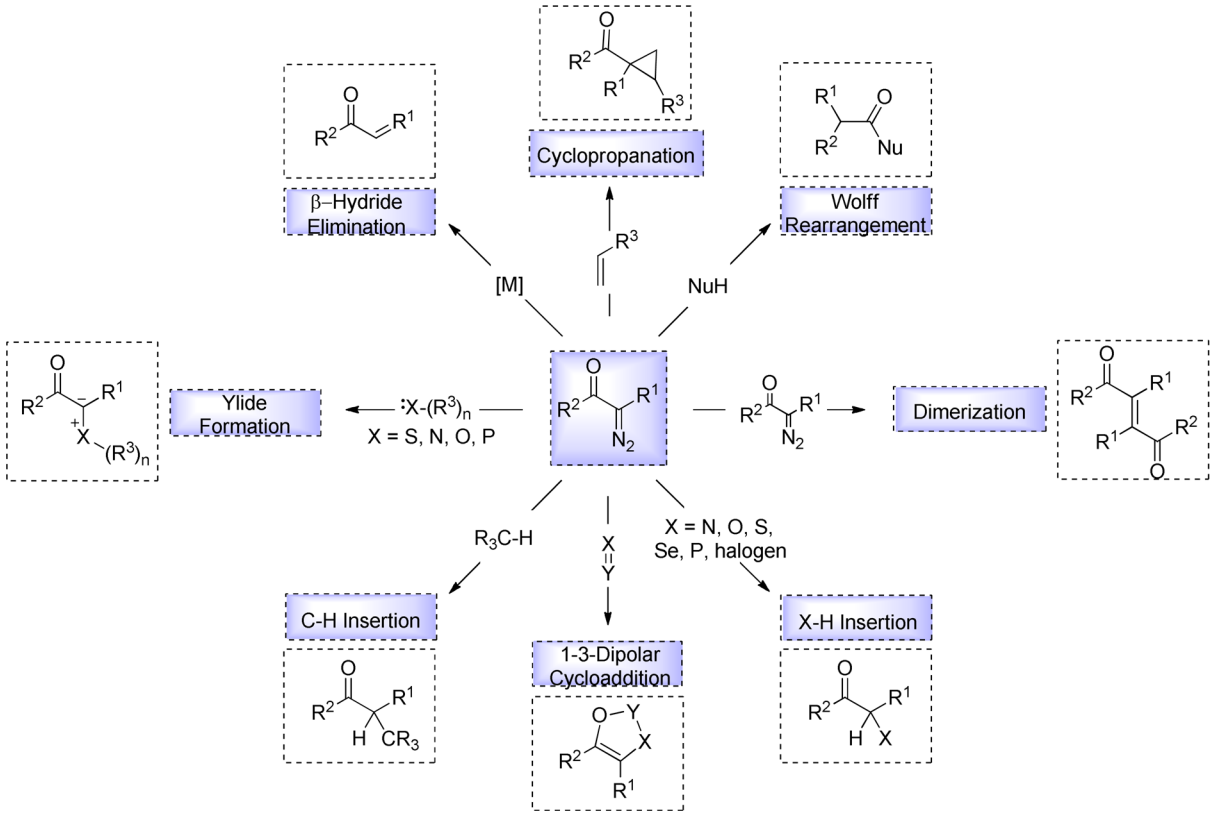


Figure 1. Some applications of diazocarbonyl compounds.

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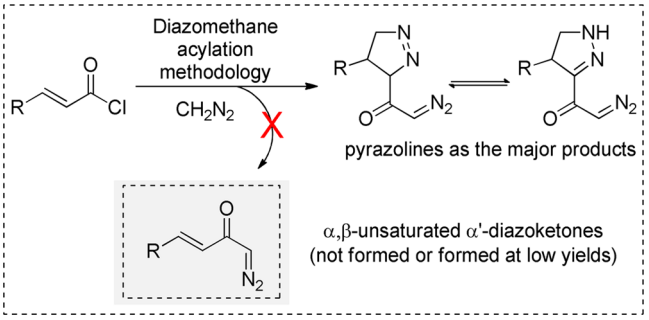
because a dipolar cycloaddition occurs between diazomethane and the conjugated double bond, which leads to the formation of pyrazolines as the main product (Scheme 2).

Scheme 2. Formation of Pyrazolines When α,β-Unsaturated Acyl Chlorides and Mixed Anhydrides Are Submitted to Diazomethane Acylation



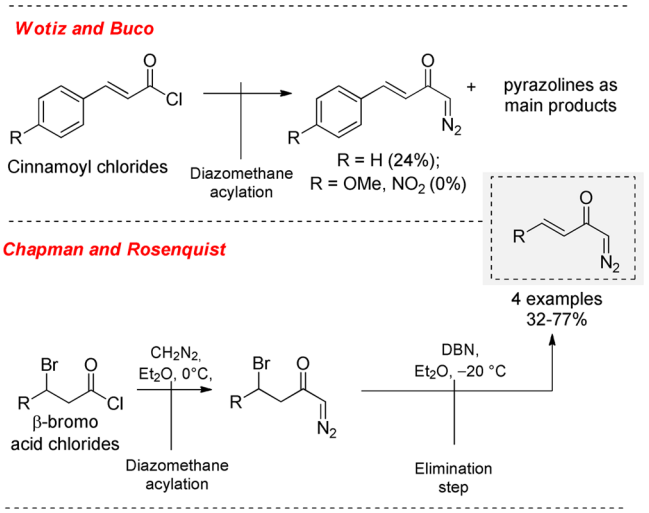
In the next section, a brief historical overview will be presented related to the synthesis of α,β-unsaturated α′-diazoketones. Although different unsaturated diazoketones such as the diazoacetoacetate enones[15] are not less important, they will not be covered in this account (diazoacetoacetate enones have different reactivities/applications and are prepared by different approaches than the ones necessary to prepare α,β-unsaturated α′-diazoketones).

2. PREPARATION OF α,β-UNSATURATED α′-DIAZOKETONES

2.1. History on the Preparation of Unsaturated Diazoketones

The first known attempt to prepare an α,β-unsaturated diazoketone was described in 1936, when Grundmann[13] mixed acid chlorides with diazomethane. Although the diazoketone functionality was formed, the double bond was completely captured by diazomethane to form the pyrazoline ring. In 1955, Wotiz and Buco[16] studied the same transformation in more detail with different cinnamoyl chlorides (*p*-H, *p*-OMe, *p*-NO_2) (Scheme 3). Once again, pyrazolines were

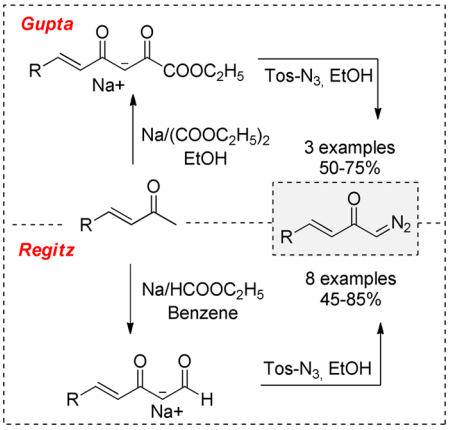
Scheme 3. Synthesis of Unsaturated Diazoketones by Buco and Chapman



formed as the main product, but a 24% yield of the unsaturated diazoketone could be obtained in one case (*p*-H) when a highly diluted solution was used. An interesting way to avoid the formation of the pyrazolines was to install the double bond after the formation of the diazoketone, as described by Chapman and Rosenquist.[17] In their work, diazomethane acylation in the presence of β-bromo acid chlorides, followed by elimination in the presence of the base DBU, furnished four examples of unsaturated diazoketones.

Regarding the synthesis of α,β-unsaturated diazoketones employing the diazo transfer method, the first known contribution was described by Regitz et al.[4] in 1970. In this work, Regitz et al. activated several α,β-unsaturated ketones in the presence of sodium and ethyl formate to provide 1,3-dicarbonyl compounds after a Claisen condensation (Scheme 4). These dicarbonyls could readily be converted to the

Scheme 4. Deformylative Diazo Transfer Employed by Regitz and Gupta for the Preparation of Unsaturated Diazoketones



respective diazoketones after diazo transfer and deformylation via a fragmentation reaction from a triazolinic intermediate (Scheme 5). This deformylative diazo transfer, initially described by Regitz in 1964 for saturated diazoketones,[18−20] was an important contribution since simple ketones do not usually react directly with sulfonyl azides. Four years later, Gupta et al.[21] suggested the use of diethyloxalate in the place of ethyl formate for the Claisen condensation and subsequent diazo transfer. This protocol furnished diazoketones in better yields. An example was the synthesis of (*E*)-1-diazo-4-phenylbut-3-en-2-one in 75%, which was not obtained in high yields by the other methods employed.

Although the method developed by Regitz and Gupta represented a great advance in the preparation of unsaturated diazoketones, it was not widespread in the chemical community. This is due to the harsh reaction conditions (Na, EtOH, or benzene, room temperature, 12−48 h), as well as the low regioselectivity in the formation of the enolates prior to the Claisen condensation. In 1990, many of the limitations mentioned above could be avoided with Danheiser's alternative method to synthesize diazoketones,[22,23] including unsaturated ones, by a different type of detrifluoroacetylative diazo transfer. This variation of Regitz's method consisted in employing kinetic conditions (LiHMDS, −78 °C, 30 min) for generating the methyl ketone enolates and the use of the very reactive trifluoroethyl trifluoroacetate as the acetylation agent (Scheme 6). In fact, the detrifluoroacetylative diazo transfer had been

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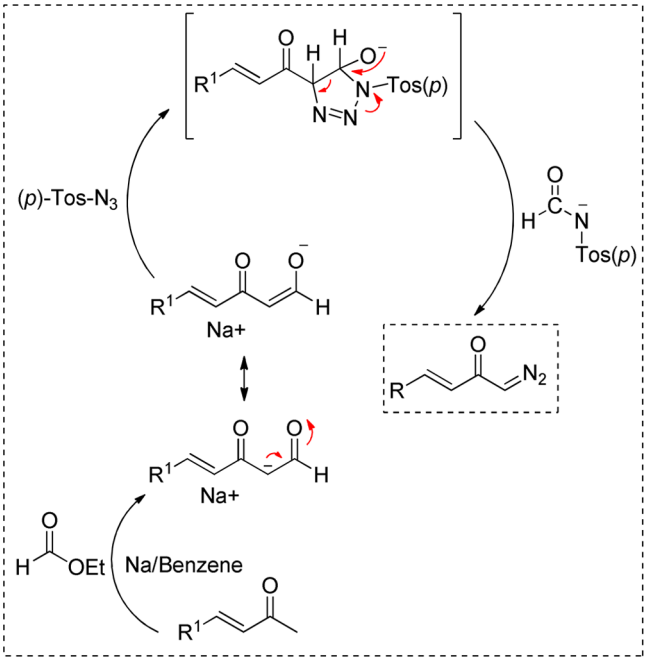
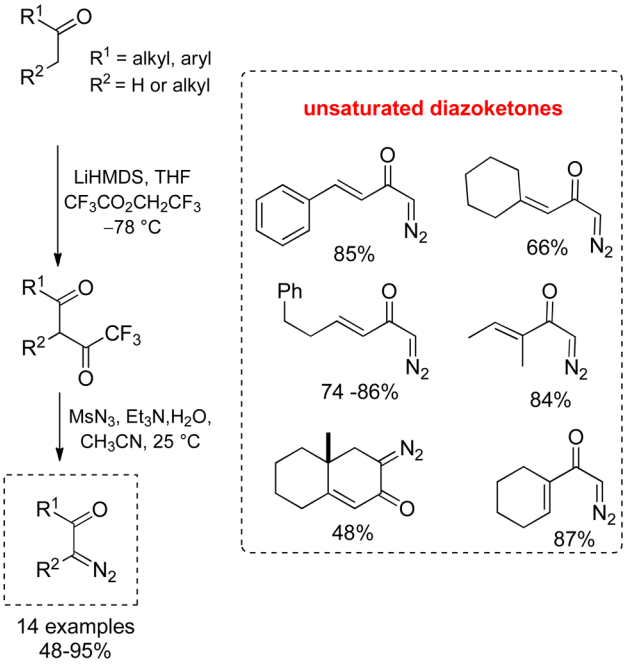
Scheme 5. General Mechanism for the Deformylative Diazo Transfer Developed by Regitz



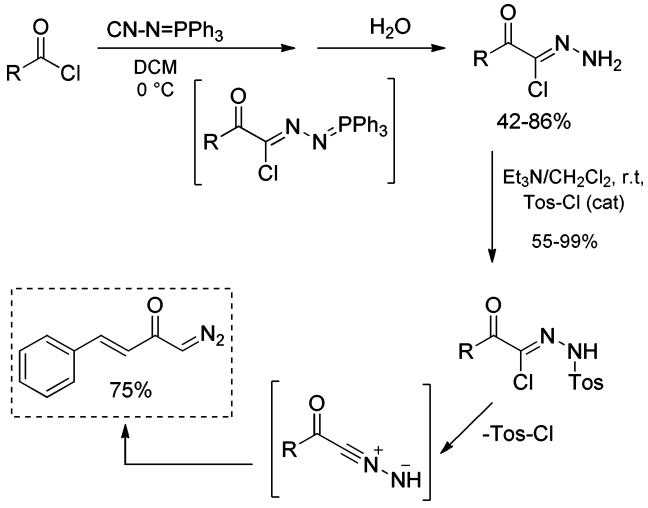
Scheme 6. Danheiser General Methodology for the Synthesis of Saturated and Unsaturated Diazoketones, Employing Methyl Ketones as Substrates



previously described by Doyle et al. in a single example,[24] but using LDA as the base and not extending to unsaturated diazoketones. Danheiser's protocol proved to be superior over the other methodologies and is considered one of the best and general methods for the preparation of α,β-unsaturated α'-diazoketones.

An interesting and different method to achieve diazoketones without the need to use diazomethane or azides was described by Aller[25] and co-workers in 2000 (Scheme 7). The method consisted of the acylation of *N*-isocyanotriphenyliminophosphorane with acid chlorides to furnish, after hydrolysis, α-ketohydrazidoyl chlorides. These chlorides were then converted to diazoketones after treatment with base and catalytic tosyl chloride. A single example was described for the synthesis of an α,β-unsaturated diazoketone in 75% yield.

Scheme 7. Aller Method for the Diazoketones Using *N*-Isocyanotriphenyliminophosphorane



2.2. Recent Advances in the Synthesis of α,β-Unsaturated α'-Diazoketones

Although the establishment of Danheiser's method permitted the access of several α,β-unsaturated diazoketones that could not be prepared efficiently by the classical methods, some advances were still necessary. For example, the synthesis of more complex unsaturated diazoketones, as well as those with epimerizable stereocenters in the γ position, was never described. Another limitation is related to the geometry of the double bond, since practically all examples described so far refer to unsaturated diazoketones with *E* geometry. The synthesis of diazoketones with *Z* geometry would require *Z*-unsaturated methyl ketones or acyl chlorides, which are not easily prepared or commercially available. Moreover, double bond isomerization to the *E*-α,β-unsaturated diazoketones could also be a problem in some of the existing protocols.

In view of the above limitations, in 2011[26] and 2013,[27] we developed two types of Horner–Wadsworth–Emmons (HWE) reagents (3-diazophosphonates **1** and **2**) that permitted the direct access of several α,β-unsaturated diazoketones with *E* and *Z* geometry from aldehydes (Scheme 8). While compound **1** was inspired in the classical triethyl phosphonoacetate (selective reagent for *E* geometries), compound **2** was inspired by the Ando phosphonate (selective for Z geometries in the HWE reaction).

Diazophosphonates **1** and **2** can be readily prepared in 50–70% yields from the corresponding phosphorylacetic acids **3** and **4**, after reaction with oxalyl chloride and diazomethane (Scheme 9). Commercially available 2-(diethoxyphosphoryl)-acetic acid **3** can also be prepared by basic hydrolysis from the cheap triethyl phosphonoacetate.[28] On the other hand, 2-(diphenoxyphosphoryl)acetic acid **4** is prepared in two steps from diphenylphosphite, following Ando's procedure[29−32] (Scheme 9). Thermogravimetric analysis also revealed very good stabilities of diazophosphonates **1** and **2**,[33] with decomposition starting only at temperatures of 120 and 150

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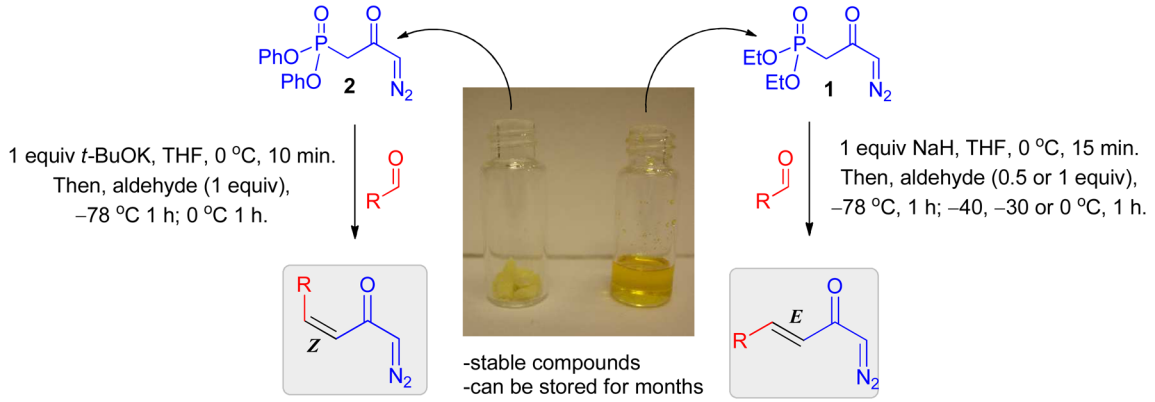
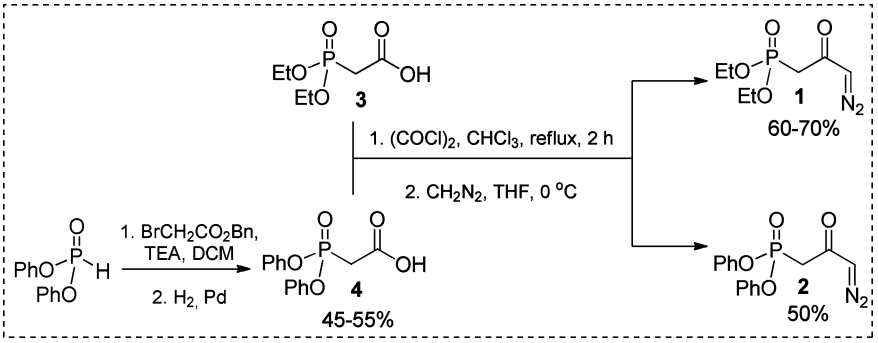
Scheme 8. Burtoloso's HWE Reagents for the Synthesis of α,β-Unsaturated Diazoketones



Scheme 9. Preparation of Diazophosphonates 1 and 2 by Burtoloso



°C, respectively. These compounds could also be prepared in a 10 g scale with safety in the laboratory.

Reagent **1** gave very good results for the HWE reaction with aldehydes, using NaH as a base. In all cases, complete *E* selectivity was obtained and no epimerization in the γ-position was detected when chiral amino-aldehydes were employed.[26] For epimerizable substrates, even when excess of the phosphonate and base is employed, no epimerization was observed, provided that reaction is quenched at −40 or −30 °C. Another point that deserves attention is that, for some types of aldehydes, excess of reagent **1** (2 equiv) is necessary to guarantee higher yields of unsaturated diazoketones and to avoid the formation of coupled diazoketones. A recent and preliminary study in our laboratory also revealed that these reactions can be performed in even milder conditions such as EtOH/water as the solvent and NaOH as the base, using only one equiv of reagent **1**.[34]

The high stereoselectivity in the HWE reaction was also observed for reagent **2**, using potassium *tert*-butoxide as the base. However, unlike the aromatic and aliphatic aldehydes, amino aldehydes showed different behaviors in the HWE reaction with reagent **2**. For example, excellent to good stereoselectivities were obtained depending on the type of nitrogen protecting group used (CBz, Boc, or Ts), as well as the size of the substituents α to the aldehyde carbonyl group. In all the cases where *Z* and *E* mixtures were obtained, the isomers could be separated by a simple column chromatography.[27] As depicted in Figure 2, several α,β-unsaturated α-diazoketones could be prepared in scales up to 1.0 g by our methodology, including complex and chiral ones.[26,27,34−39] It is worth mentioning that the method is direct and uses aldehydes, which are well-known for being easy to prepare and available from several suppliers.

This section provided to the reader an historical overview of the methods described so far to prepare α,β-unsaturated α′-diazoketones. Figure 3 summarize these advances in a timeline scale, illustrating the contribution of each author.

3. APPLICATIONS OF α,β-UNSATURATED α′-DIAZOKETONES

As previously mentioned, there are only few applications in synthesis involving α,β-unsaturated diazoketones[40−57] when compared to the saturated or aryl ones. Figure 4 illustrates the main examples using diazoketones as platforms in synthesis, where the double bond and diazo group are important for the transformation and application. Examples dealing with the construction of nitrogen heterocycles will be presented in the next section.

The first synthetic application of a,β-unsaturated diazoketones was in 1981, when Regitz employed it in the Diels−Alder reaction with triazolindiones[40] (Figure 4). Two examples, which furnished very good adduct yields, were described. Wenkert et al.[43] employed β,β-dialkylated α,β-unsaturated diazoketones in the direct preparation of cyclopentenones. Using $Rh_2(OAc)_4$, cyclopentenones were obtained in 47−65% yield after C−H insertion reactions. Danheiser employed unsaturated diazoketones to prepare vinylketenes that could be trapped by alkynes, leading to a direct benzannulation reaction.[45] This successful method permitted the preparation of several aromatic rings with a high degree of substitution. In a later publication, the problem associated with the instability of some vinylketenes was circumvented by a silylation α to the diazo group of the unsaturated diazoketones, which provided

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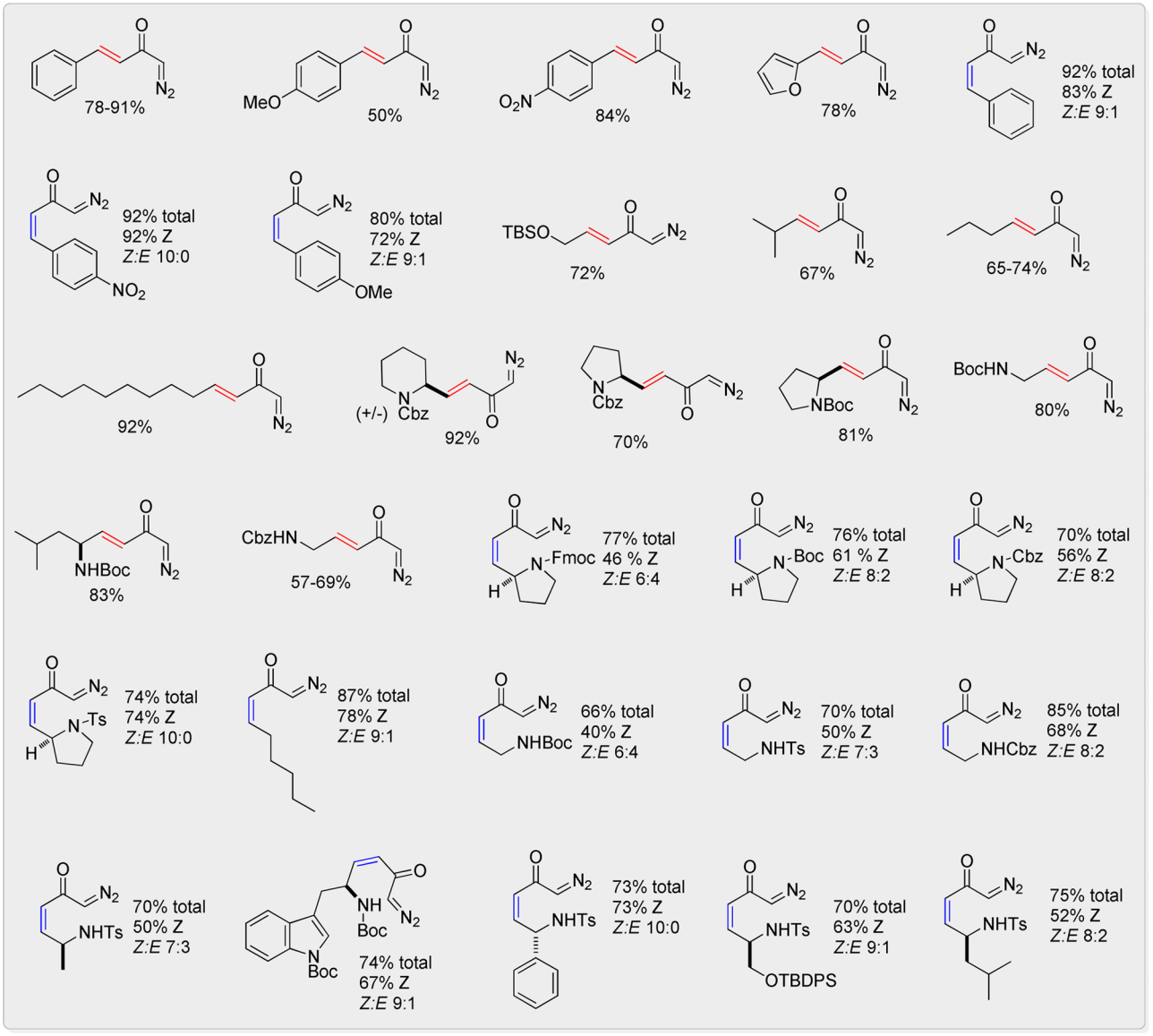

Figure 2. Examples of α,β-unsaturated diazoketones prepared by Burtoloso's methodology, employing diazophosphonates **1** and **2**, and aldehydes.

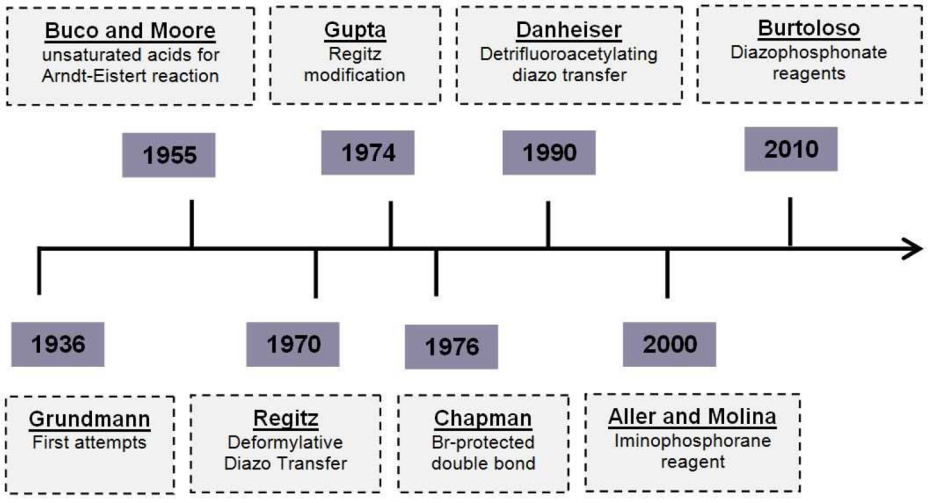

Figure 3. Timeline scale of the methods to prepare α,β-unsaturated α'-diazoketones.

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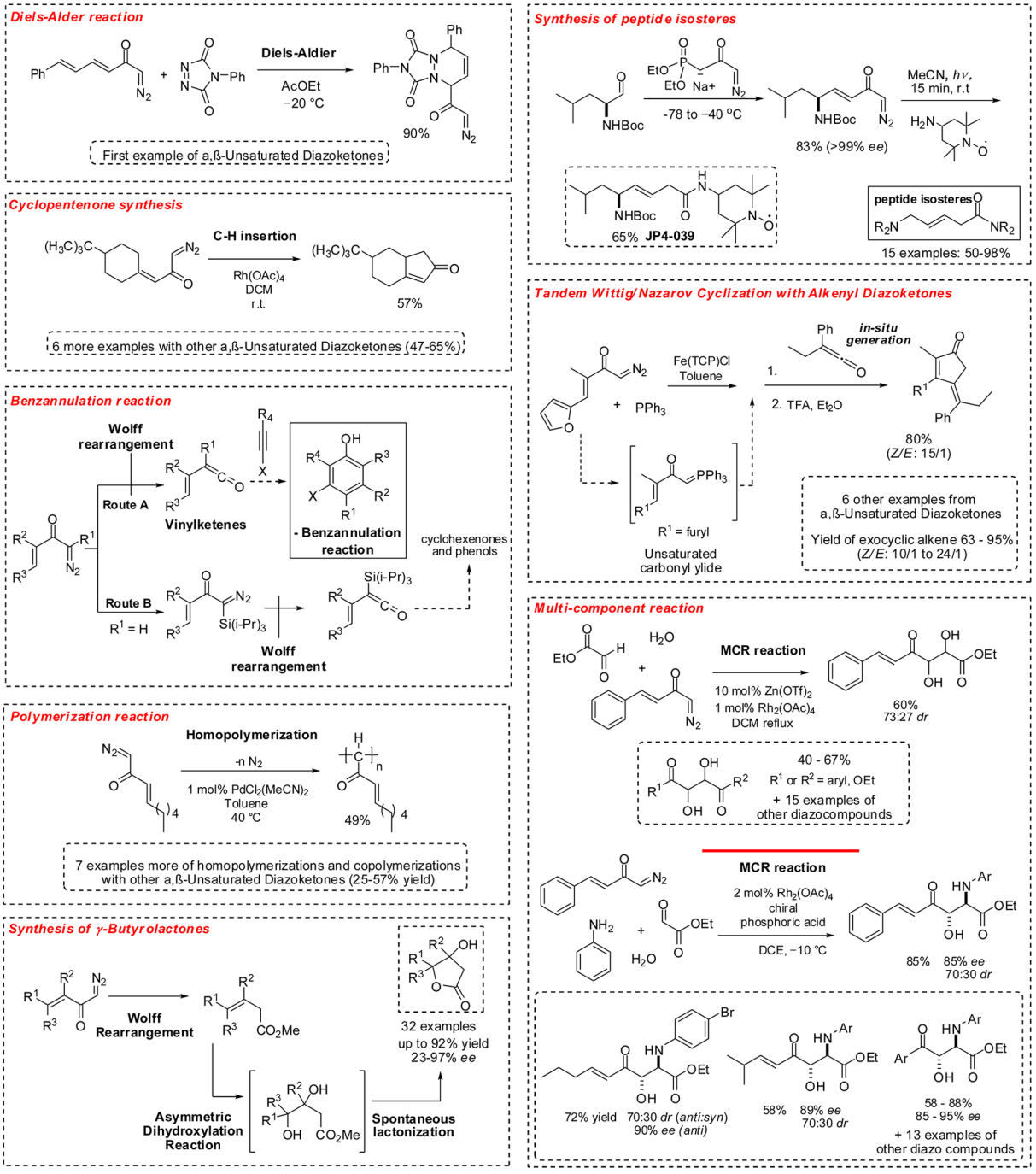

Figure 4. Examples where unsaturated diazoketones are employed as platforms in synthesis.

more stable vinylketenes.[46] Unsaturated diazoketones were also employed in polymerization reactions (polysubstituted methylene synthesis) with Pd catalysts, where the double α to the carbonyl bond is crucial for the success of the reaction. The possibility of polymerization with one carbon unit (instead of two units in the classical vinyl polymerization) makes the method interesting.[48] Brückner and co-workers described a direct approach for the construction of lactones after Wolff rearrangement, dihydroxylation and lactonization.[49] Burtoloso and Bernardim prepared several unsaturated diazoketones from chiral amino-aldehydes, using his diazophosphonate methodology. The reaction involving the delicate amino-aldehyde from (*S*)-leucine furnished the respective unsaturated diazoketone without epimerization. Photochemical Wolff rearrangement in the presence of 4-amino TEMPO provided the synthesis of the bioprotective agent JP4-039 in just two steps.[39] Tang et al. employed the diazoketones to prepare phosphorus ylides that in the presence of allenes led to cyclopentenones (in a sequence of ylide formation, Wittig olefination and Nazarov cyclization).[52] An interesting multicomponent reaction was described by Hu in the synthesis of diols.[53] The synthesis involved the use of the diazocompond, a glyoxal and water, in the presence of a double catalysis with Rh and Zn. Later, enantiomeric enriched aminoalcohols could be obtained in a four component reaction with the diazoketone, anilines, glyoxals, and water.[55] In this case, a combination of $Rh_2(OAc)_4$ and chiral phosphoric acids provided the amino-alcohols with very good diastereo and enantioselectivities. This

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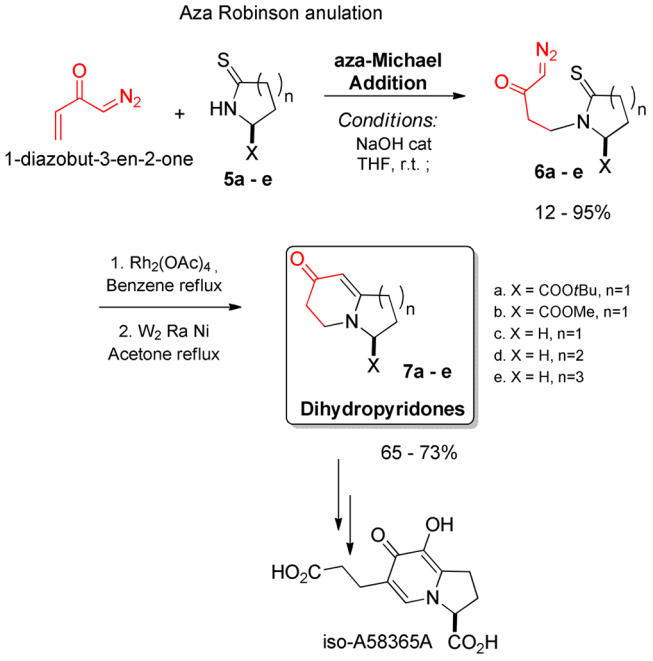
method permitted the synthesis of the natural product D-lyxo-phytosphingosine (Figure 4).

4. α,β-UNSATURATED α′-DIAZOKETONES IN THE SYNTHESIS OF NITROGEN HETEROCYCLES

Unsaturated diazoketones are special multifunctional reagents. Possessing a double bond, a ketone, and a diazo function in the same molecule, these compounds are important building blocks in synthesis. This section will describe examples from our laboratory and from others, where these three functionalities presented in unsaturated diazoketones were important and made a difference for the efficient and rapid synthesis of some nitrogen-heterocycles, when compared to existing methods. Although important, examples dealing only with ordinary manipulation of the diazoketone, where the double bond does not participate in the construction of the heterocycle will not be covered.

Following the work of Regitz et al.,[40] who described the first application of an unsaturated diazoketone to a nitrogen-heterocycle (synthesis of triazolindiones from Diels–Alder reaction; vide Figure 4), Danishefsky et al. employed these compounds in the preparation of dihydropyridones by an aza-Robinson Annulation.[41] In his work, a well-used typical reaction in the chemistry of enones, the aza-Michael addition, was applied to 1-diazobut-3-en-2-one, the simplest type of an α,β-unsaturated α′-diazoketone (Scheme 10). After conjugate addition of **5** to this unsaturated diazoketone, aza-Michael adducts **6** were formed in 12–95% yields. Next, thiocarbonyl reaction with a rhodium carbenoid, followed by Raney-nickel reduction furnished the dihydropyridones **7** in 65–73% yield. In the cases where the aza-Michael addition furnished low yields, a longer general protocol was employed: aza-Michael addition with methyl acrylate, hydrolysis, mixed anhydride activation and diazomethane addition to provide adducts **6**. These functionalized pyridines can be important building blocks for the synthesis of many indolizidines, as demonstrated by the synthesis of the compound iso-A58365A.

Scheme 10. Synthesis of Dihydropyridones from 1-Diazobut-3-en-2-one



Some years later, the synthesis of cyclic amines via [2,3]-sigmatropic rearrangements, employing ammonium salts, was described by Clark et al.[42] The chemistry also involved an aza-Michael addition from an unsaturated diazoketone in the initial steps. In the work of Clark et al., the addition of allyl amines to diazoketone **8** led to aminoketones **9** in 64–85% yield. These two examples could be applied in the direct synthesis of 2,5-disubstituted pyrrolidines, but with low diastereoselectivities (≤2:1). Although the relative stereochemistry was not determined, prolonged exposure of these mixtures to silica gel furnished better diastereoselectivities (Scheme 11). Recently, Doyle also described the synthesis of a 2,5-disubstituted pyrrolidine (2.5:1 diastereoisomeric ratio), employing diazoacetoacetate enones.[15] This could be accomplished after the aza-Michael addition in the presence of aniline and $Sc(OTf)_3$, followed by a rhodium-catalyzed intramolecular N–H insertion.

Recently, our research group studied the Stevens rearrangement for the construction of *cis*-2,5-disubstituted pyrrolidinones and its application in the total synthesis of the alkaloid preussin in three steps from decanal (Schemes 12 and 13).[38] The substrates for evaluating the Stevens rearrangement were also prepared by an aza-Michael addition from unsaturated diazoketones. This reaction proved to be very dependent on the type of α,β-unsaturated diazoketone and amine. In our case, the conditions of Clark et al. were suitable only for primary amines and β-alkyl unsaturated diazoketones. For secondary amines, 50 mol % DBU seemed to be important in order to achieve good yields of the aza-Michael adducts. After establishing the best conditions for the aza-Michael addition, several adducts could be prepared in good yields and converted to 2,5-disubstituted pyrrolidinones as single *cis* isomers, after heating them at 110 °C in the presence of 10 mol % of $Cu(acac)_2$ in toluene (Scheme 12). This method also permitted a highly stereoselective three-step synthesis of (±)-preussin from decanal with an overall yield of 40% as depicted in Scheme 13. The aza-Michael addition from diazoketone **10**, in the presence of methylbenzylamine, incorporated preussin's methyl and benzyl groups and occurred in 95% yield. Next, ylide formation in the presence of copper(II) acetylacetonate, followed by the [1,2]-Stevens rearrangement, led to the *cis*-pyrrolidinone **12**. The reduction of **12** with L-selectride from the less hindered α face completed the synthesis in a single reaction vessel from **11** and with a 40% overall yield and complete diastereoselectivity in all steps. It is interesting to note that preussin exhibits significant antifungal,[58] antiviral,[59] anticancer,[60] and antibacterial activities[61] and all its eight stereoisomers also display biological activity.

As a part of our studies employing α,β-unsaturated diazoketones for the synthesis of nitrogen heterocycles, we also decided to prepare several indolizidines, quinolizidines and piperidines, with the nitrogen atom already attached to these diazoketones (at the γ-position; Figure 5).[35−37] To accomplish that, amino-aldehydes were the reagents of choice, since they are easy to prepare and would provide the diazoketones directly from our methodology. In this sense, a diazoketone such as **13** would possess all of the carbons necessary to construct 6-membered rings (after necessary functionalizations). This would allow the preparation of piperidines, indolizidines, and quinolizidines if acyclic, proline-derived, and pipecolic acid derived amino acids were employed, respectively (Figure 5).

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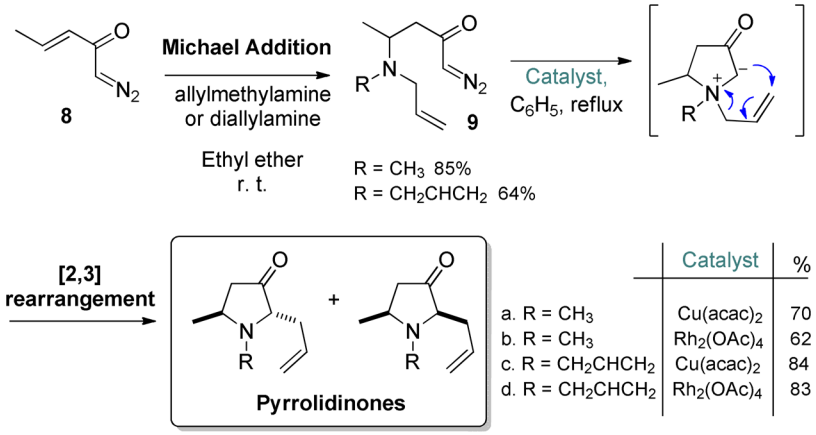
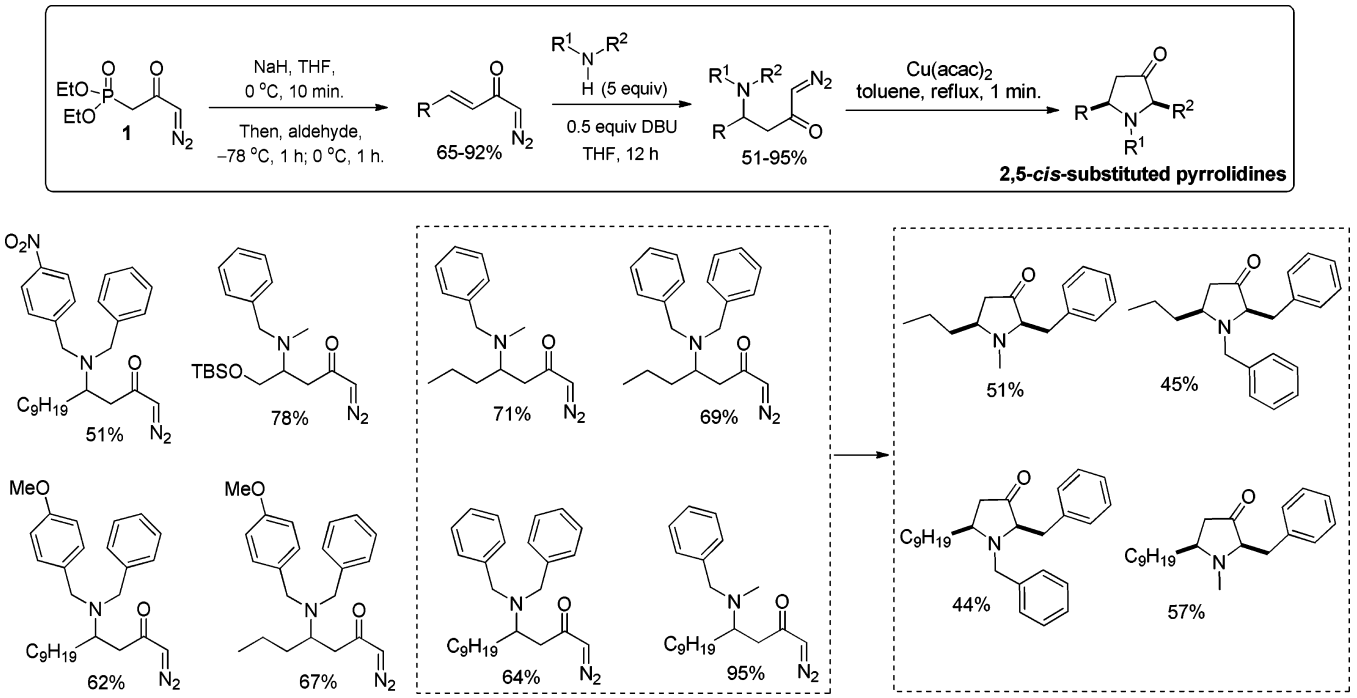
Scheme 11. Synthesis of 2,5-Disubstituted Pyrrolidinones after [2,3]-Sigmatropic Rearrangements from Ammonium Ylides



Scheme 12. Synthesis of *cis*-2,5-Disubstituted Pyrrolidinones after Stevens Rearrangements from Ammonium Ylides



We decided to evaluate this type of strategy by initially preparing the simple, but popular indolizidines 167B and 209D (Scheme 14). Starting from *N*-Cbz-(*S*)-prolinal, unsaturated diazoketone **14** was prepared in a 70% yield as a single *E* isomer. No epimerization occurred at this step according to HPLC analysis (see picture in Scheme 14). At this point, we thought that a Wolff rearrangement from **14** in methanol, followed by Cbz deprotection, would be the best way to achieve a direct cyclization to acquire the desired indolizidine skeleton. This would install a carboxyl group at the end of the chain ready for a lactamization reaction. Initial attempts to perform this Wolff rearrangement using classical conditions failed to provide ester **15**. After a careful optimization study, we found that thermal conditions using silver(I) triflate (76%) or photochemical conditions (97%) proved to be the best options. In fact, photochemical conditions were preferred considering the high yield and the fact that purification was not necessary. After the synthesis of **15**, construction of the indolizidine ring was straightforward. Hydrogenolysis of the Cbz-protecting group, with sequential double bond reduction and cyclization, furnished indolizidinone **16** in a 92% yield (>99% ee). For the synthesis of indolizidine 167B, the reaction of **16** with propylmagnesium bromide, followed by iminium formation and reduction, completed the total synthesis of indolizidine 167B.[35]

From the studies described in Scheme 14, we decided to perform the synthesis of more complex indolizidines, such as hydroxylated indolizidines and castanospermine analogues as well as quinolizidines.[36,37] Nitrogen heterocycles bearing hydroxyl groups (aza-sugars) are well-known for their ability to act as potent α- and β-glycosidase inhibitors and have been used for many years in chemical biology. One of the key points in the synthesis of compounds for biological studies is to guarantee access to many analogues from a single synthetic methodology or chemical intermediate. We thought that β,γ-unsaturated ester **15**, prepared from diazoketone **14** (vide Scheme 14), would be a good candidate to accomplish this, after hydroxylation or epoxidation reactions. To demonstrate

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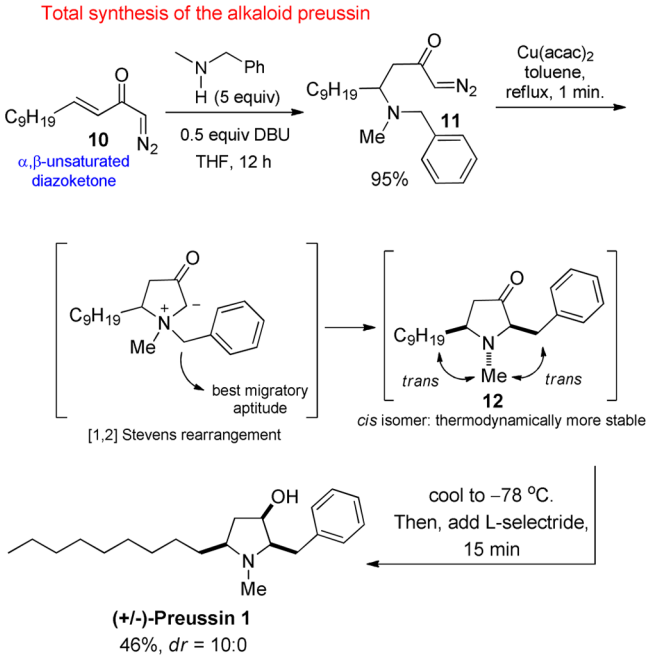
Scheme 13. Total Synthesis of Preussin



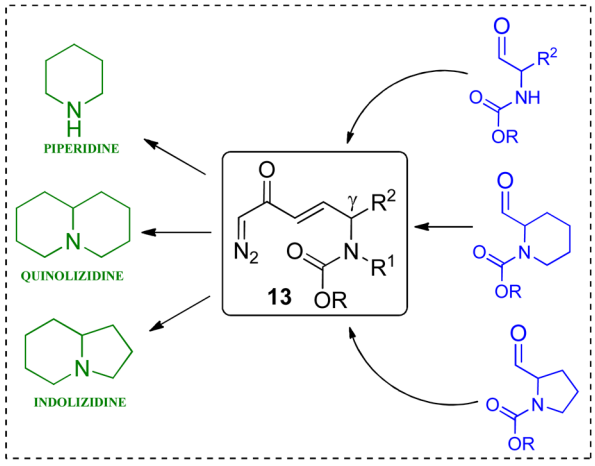


Figure 5. γ-Amino-α,β-unsaturated diazoketones as advanced intermediates to prepare piperidines, indolizidines, and quinolizidines.

this, we decided to synthesize 1,6-dideoxy-epi-castanospermine **17**, 1-deoxy-8,8a-diepi-castanospermine **18** and octahydroindolizidin-8-ols **19**, which are representative examples of two-, three-, and monohydroxylated indolizidines, respectively. We started our study by preparing compound **17** in 44% overall yield, after a highly stereoselective (20:1) dihydroxylation reaction from ester **15** (the expected diol suffered lactonization upon its formation and was not detected) in the presence of a catalytic amount of osmium tetroxide (Chart A, Scheme 15). Interestingly, no selectivity was observed when the six-membered ring analogue, prepared from pipecolal, was employed (Chart D). Cyclization to the indolizidine ring was carried out in a similar manner as previously described (vide Scheme 14), after one-pot removal of the Cbz-protecting group and lactamization. Finally, borane reduction of the lactam led to 1,6-dideoxy-epi-castanospermine **17** in a 71% yield. For the synthesis of the more complex triol **18**, a one-pot epoxidation reaction/β-elimination was carried out. Repetition of the synthetic sequence employed for **17** (dihydroxylation, lactamization, and reduction) and isomer separation, furnished 1-deoxy-8,8a-diepi-castanospermine **18** (Chart B, Scheme 15). For the same sequence employed for compound **16** (vide Scheme 14), lactamization before the dihydroxylation reaction provided monohydroxylated indolizidines **19** (Chart C, Scheme 15). The preparation of octahydroindolizidin-8-ols **19** constitutes a formal synthesis of pumiliotoxin 251D.[36]

The same synthetic sequence described above could also be applied in the synthesis of chiral dihydroxylated piperidines,[37] employing an amino-aldehyde derived from glycine or ethanolamine. In this case, Sharpless asymmetric dihydroxylation was employed, which permitted the preparation of both enantiomers in 92% enantiomeric excess. Extension of this work to other acyclic amino-aldehydes is under way (Scheme 16).

After establishing a method that allowed us a rapid access to several hydroxylated *N*-heterocycles, we wondered if γ-amino-unsaturated diazoketones with a *Z* geometry could also be employed for the direct cyclization to piperidines by means of an intramolecular N−H insertion reaction. As they would already possess the proper *Z* geometry, no manipulation of the double bond would be necessary before the cyclization. This would permit the preparation of highly functionalized piperidine systems, such as dihydropyridin-3-ones, in just two steps from amino- aldehydes (Chart A, Scheme 17). We started this work by evaluating the intramolecular N−H insertion reaction from different *Z*-unsaturated diazoketones, following our HWE protocol using diazophosphonate **2** (vide Scheme 8 and Figure 2). It is important to mention that no example of this transformation from an unsaturated diazoketone was available at the time. Different from the N−H insertion reaction from common diazoketones, the presence of the double bond (and the acidic hydrogen in the γ position) in these unsaturated diazoketones could lead to many undesired products (For example, cyclopropanation reactions, intermolecular reactions and C−H insertion at the γ position). Common catalysts and conditions usually employed for N−H insertion reactions did not provide good yields of the cyclized products. For example, rhodium catalysts furnished a complex mixture of products and copper catalysts were inactive at room temperatures. The best option proved to be heating these diazoketones in benzene or toluene in the presence of copper(II) acetylacetonate (Chart B, Scheme 17). Although dihydropyridin-3-ones were obtained in about 50% yield, the method is direct, permitting access to these compounds in only two steps from aldehydes. An application of this method in the synthesis of the natural product piperidine triol **20**, a α-glycosidase and β-galactosidase inhibitor isolated from *Eupatorium fortunei TURZ*, was also demonstrated from dihydropyridin-3-one **21**. After a sequence of three steps that involved the Luche reduction, a highly selective osmium tetroxide catalyzed dihydroxylation reaction, and tosyl group removal, (±)-(3*R*,5*R*)-piperidine-3,4,5-triol **20** was obtained in 46% overall yield[27] (Chart C, Scheme 17). The extension of this sequence to more complex dihydropyridin-3-ones and hydroxylated piperidines is under course in our laboratory.

5. CONCLUSION AND PERSPECTIVES

The chemistry of α,β-unsaturated α′-diazoketones has proven to be very promising. Unfortunately, these multifunctional platforms were not broadly investigated mainly because of the lack of methods to prepare them. With the development of the two general methodologies described by Danheiser and

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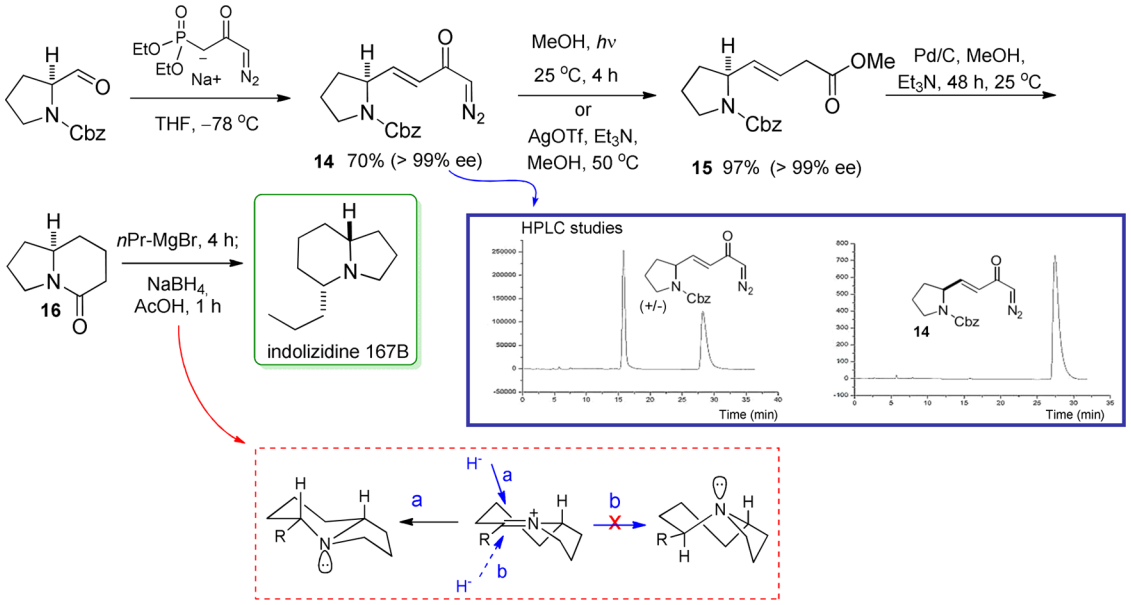
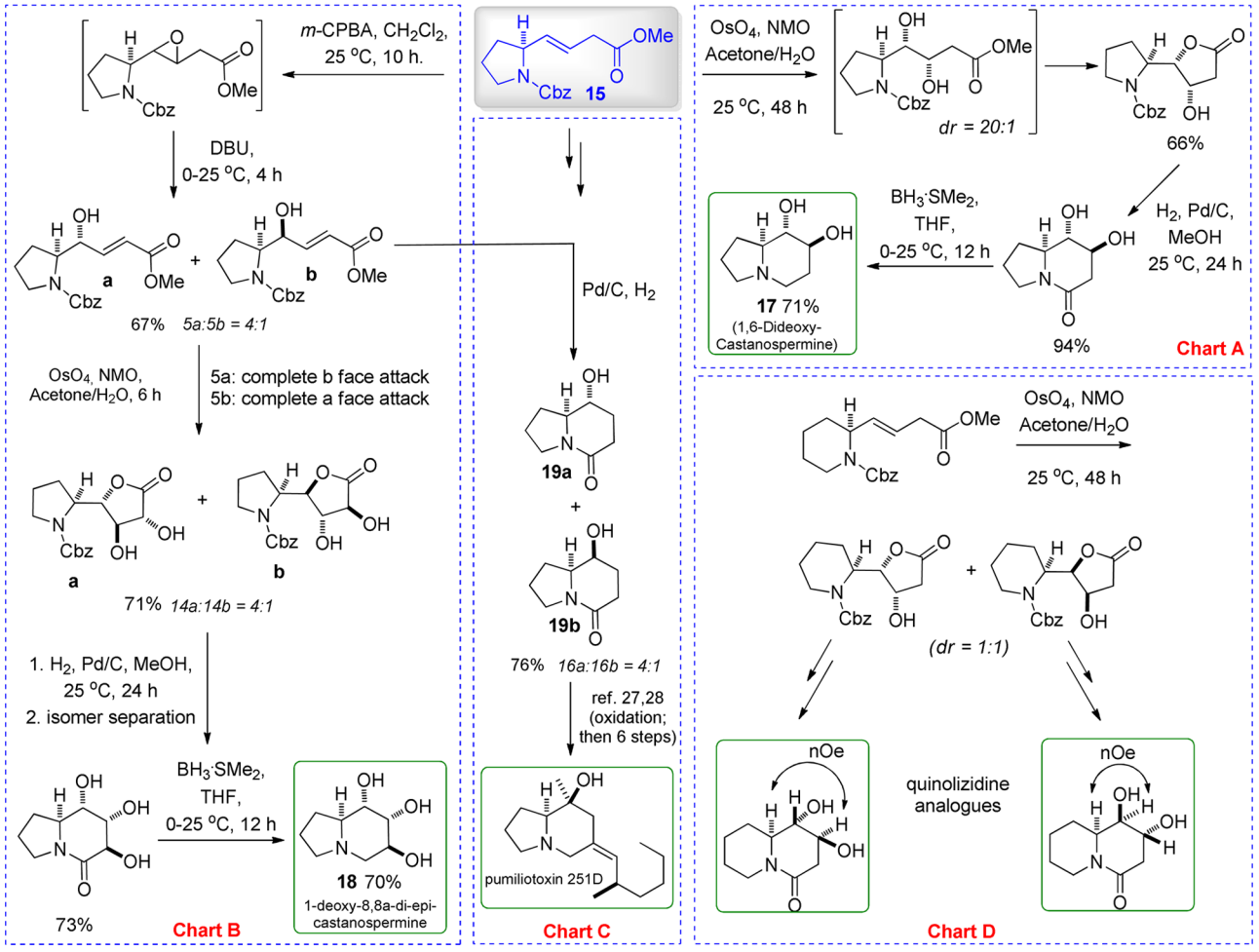
Scheme 14. Synthesis of Indolizidine 167B



Scheme 15. Synthesis of Mono-, Di-, and Trihydroxylated Indolizidines and Quinolizidines



Burtoloso, more applications could appear, demonstrating the potential of these compounds. As discussed in this Account, the combination of three important functions (a double bond, a ketone, and a diazo) in the same molecule makes these compounds powerful platforms to access many important molecules in a direct fashion. Since many gaps and a lot of space for new creative contributions exist, many transformations still deserve investigation from these substrates.

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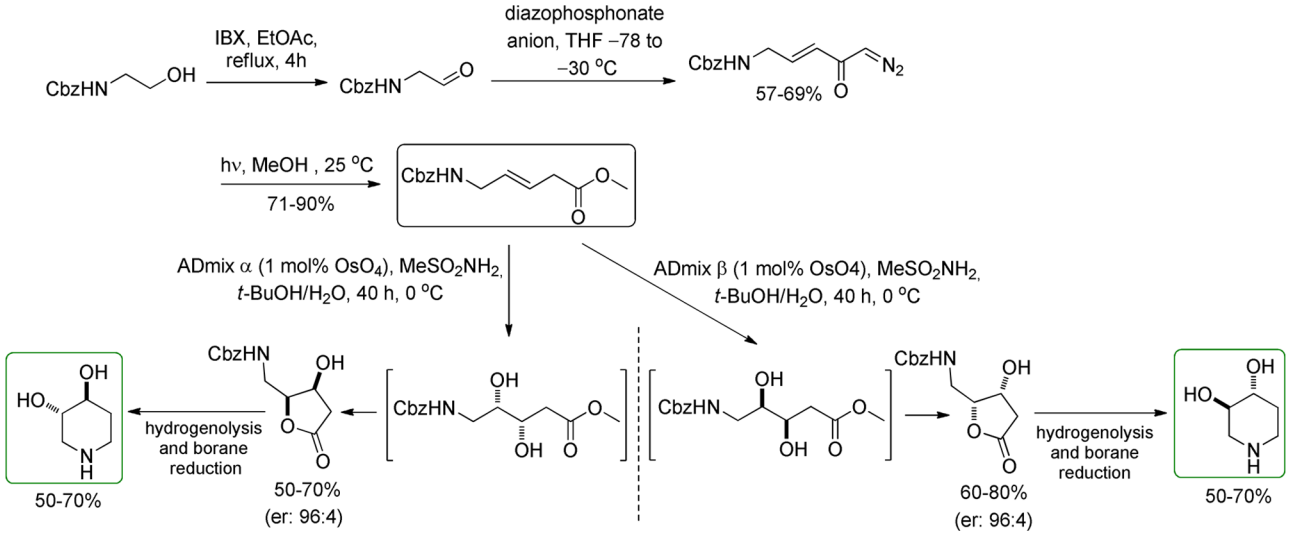
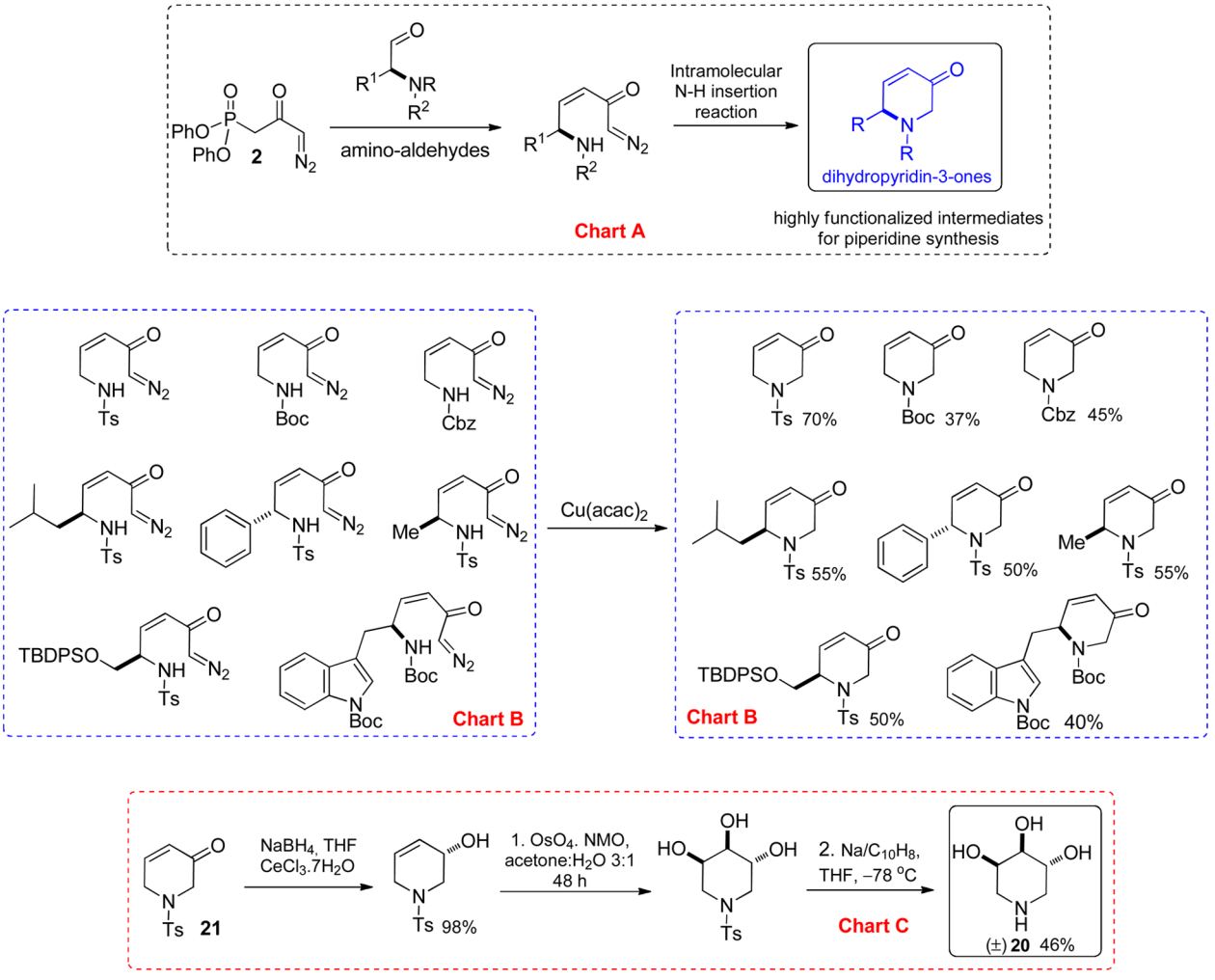
Scheme 16. Synthesis of Dihydroxylated Piperidines



Scheme 17. Synthesis of Dihydropyridin-3-ones and Their Applications in the Synthesis of Polyhydroxylated Piperidines



For example, several classical reactions for double bond functionalization are not compatible with a diazo function (especially the ones involving transition metals or Lewis acids) and cannot be applied directly to an unsaturated diazoketone. An example of this is the osmium-catalyzed dihydroxylation reaction. Asymmetric conjugated additions to these compounds as well as enantioselective functionalizations are also highly desirable.

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Notes

The authors declare no competing financial interest.

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Rafael M. P. Dias was born in Caratinga-MG, Brazil, in 1986. He received his degree in Chemistry from the Federal University of Juiz de Fora in 2009 and his M.Sc. at the same University in 2011. In the same year, he started his Ph.D. in the group of Prof. Dr. Antonio Burtoloso, where he is working on the chemistry of α,β-unsaturated diazoketones and ketosulfoxonium ylides.

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REFERENCES

(1) Curtius, T. Ueber Die Einwirkung von Salpetriger Säure Auf Salzsauren Glycocoläther. *Ber. Dtsch. Chem. Ges.* **1883**, *16*, 2230−2231.

(2) Wolff, L. Ueber Diazoanhydride. *Justus Liebigs Ann. Chem.* **1902**, *325*, 129−195.

(3) Arndt, F.; Eistert, B.; Partale, W. Diazo-Methan Und O-Nitroverbindungen, II.: N-Oxy-Isatin Aus O-Nitro-Benzoylchlorid. *Ber. Dtsch. Chem. Ges. B Ser.* **1927**, *60*, 1364−1370.

(4) Regitz, M.; Menz, F.; Liedhegener, A. Reaktionen CH-Aktiver Verbindungen Mit Aziden, XXVIII1) Synthese A.β-Ungesättigter Diazoketone Durch Entformylierende Diazogruppen-Übertragung. *Justus Liebigs Ann. Chem.* **1970**, *739*, 174−184.

(5) Ye, T.; McKervey, M. A. Organic Synthesis with α-Diazo Carbonyl Compounds. *Chem. Rev.* **1994**, *94*, 1091−1160.

(6) Regitz, M.; Maas, G. *Diazo Compounds: Properties and Synthesis*; Academic Press: Orlando, FL, 1987.

(7) Doyle, M. P.; McKervey, M. A.; Ye, T. *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds: From Cyclopropanes to Ylides*, 1st ed.; Wiley-Interscience: New York, 1998.

(8) Singh, G. S. Reactions of Organic Nitrogen Compounds with Carbenoids and Diarylketenes from Diazoalkanes and Diazocarbonyls. *Curr. Org. Synth.* **2005**, *2*, 377−391.

(9) Ferreira, V. F. Synthesis of Heterocyclic Compounds by Carbenoid Transfer Reactions. *Curr. Org. Chem.* **2007**, *11*, 177−193.

(10) Zhang, Z.; Wang, J. Recent Studies on the Reactions of α-Diazocarbonyl Compounds. *Tetrahedron* **2008**, *64*, 6577−6605.

(11) Gillingham, D.; Fei, N. Catalytic X−H Insertion Reactions Based on Carbenoids. *Chem. Soc. Rev.* **2013**, *42*, 4918−4931.

(12) Maas, G. New Syntheses of Diazo Compounds. *Angew. Chem., Int. Ed.* **2009**, *48*, 8186−8195.

(13) Grundmann, C. Ein Neues Verfahren Zur Überführung von Carbonsäuren in Aldehyde. *Justus Liebigs Ann. Chem.* **1936**, *524*, 31−48.

(14) Verma, K. A.; Wadhwa, S. Synthesis with α-Phenylcinnamoyl Chloride and Diazoalkanes. *Curr. Sci.* **1981**, *50*, 223−225.

(15) Shanahan, C. S.; Truong, P.; Mason, S. M.; Leszczynski, J. S.; Doyle, M. P. Diazoacetoacetate Enones for the Synthesis of Diverse Natural Product-like Scaffolds. *Org. Lett.* **2013**, *15*, 3642−3645.

(16) Wotiz, J. H.; Buco, S. N. The Arnt-Eistert Synthesis of Unsaturated Acids. *J. Org. Chem.* **1955**, *20*, 210−214.

(17) Rosenquist, N. R.; Chapman, O. L. A General Method for the Synthesis of Reactive α,β-Unsaturated Diazomethyl Ketones: Allenyl Diazomethyl Ketone and Vinyl Diazomethyl Ketone. *J. Org. Chem.* **1976**, *41*, 3326−3327.

(18) Regitz, M.; Heck, G. Synthesen Und Einige Umsetzungen Des 2-Diazo- Und Des 2-Hydroxy-Indandions-(1.3). *Chem. Ber.* **1964**, *97*, 1482−1501.

(19) Regitz, M. Reaktionen Aktiver Methylenverbindungen Mit Aziden, I. Eine Neue Synthese Für A-Diazo-B-Dicarbonylverbindungen Aus Benzolsulfonylaziden Und B-Diketonen. *Justus Liebigs Ann. Chem.* **1964**, *676*, 101−109.

(20) Regitz, M. New Methods of Preparative Organic Chemistry. Transfer of Diazo Groups. *Angew. Chem., Int. Ed. Engl.* **1967**, *6*, 733−749.

(21) Harmon, R. E.; Sood, V. K.; Gupta, S. K. A New Synthesis of α,β-Unsaturated Diazo-Ketones: An Improved Synthesis of 4-Diazo-3-Oxo-1-Phenyl-1-Butene (Diazomethyl Styryl Ketone). *Synthesis* **1974**, *1974*, 577−578.

(22) Danheiser, R. L.; Miller, R. F.; Brisbois, R. G.; Park, S. Z. An Improved Method for the Synthesis of α-Diazo Ketones. *J. Org. Chem.* **1990**, *55*, 1959−1964.

(23) Danheiser, R. L.; Miller, R. F.; Brisbois, R. G. Detrifluoroacetylative Diazo Group Transfer: (*E*)-1-Diazo-4-Phenyl-3-Buten-2-One. *Org. Synth.* **1996**, *73*, 134.

(24) Doyle, M. P.; Dorow, R. L.; Terpstra, J. W.; Rodenhouse, R. A. Synthesis and Catalytic Reactions of Chiral N-(diazoacetyl)-oxazolidones. *J. Org. Chem.* **1985**, *50*, 1663−1666.

(25) Aller, E.; Molina, P.; Lorenzo, Á. *N*-Isocyanotriphenyliminophosphorane; a Convenient Reagent for the Conversion of Acyl Chlorides into α-Diazoketones. *Synlett* **2000**, 526−528.

(26) Pinho, V. D.; Burtoloso, A. C. B. Preparation of α,β-Unsaturated Diazoketones Employing a Horner−Wadsworth−Emmons Reagent. *J. Org. Chem.* **2011**, *76*, 289−292.

(27) Rosset, I. G.; Burtoloso, A. C. B. Preparation of *Z*-α,β-Unsaturated Diazoketones from Aldehydes. Application in the Construction of Substituted Dihydropyridin-3-Ones. *J. Org. Chem.* **2013**, *78*, 9464−9470.

(28) Teichert, A.; Jantos, K.; Harms, K.; Studer, A. One-Pot Homolytic Aromatic Substitutions/HWE Olefinations under Microwave Conditions for the Formation of a Small Oxindole Library. *Org. Lett.* **2004**, *6*, 3477−3480.

(29) Ando, K. Practical Synthesis of Z-Unsaturated Esters by Using a New Horner-Emmons Reagent, Ethyl Diphenylphosphonoacetate. *Tetrahedron Lett.* **1995**, *36*, 4105−4108.

(30) Ando, K. Highly Selective Synthesis of Z-Unsaturated Esters by Using New Horner−Emmons Reagents, Ethyl (Diarylphosphono)-acetates. *J. Org. Chem.* **1997**, *62*, 1934−1939.

(31) Ando, K. Z-Selective Horner−Wadsworth−Emmons Reaction of α-Substituted Ethyl (Diarylphosphono)acetates with Aldehydes1. *J. Org. Chem.* **1998**, *63*, 8411−8416.

DOI: 10.1021/ar500433t
Acc. Chem. Res. 2015, 48, 921−934

(32) Ando, K. Convenient Preparations of (Diphenylphosphono)-acetic Acid Esters and the Comparison of the Z-Selectivities of Their Horner−Wadsworth−Emmons Reaction with Aldehydes Depending on the Ester Moiety. *J. Org. Chem.* **1999**, *64*, 8406−8408.
(33) Data from our laboratory. The same stabilities were observed for the α,β-unsaturated diazoketones.
(34) Bernardim, B.; Hardman-Baldwin, A. M.; Burtoloso, A. C. B. LED Lighting as a Simple, Inexpensive, and Sustainable Alternative for Wolff Rearrangements. *RSC Adv.* **2015**, *5*, 13311−13314.
(35) Pinho, V. D.; Burtoloso, A. C. B. Total Synthesis of (−)-Indolizidine 167B via an Unusual Wolff Rearrangement from an α,β -Unsaturated Diazoketone. *Tetrahedron Lett.* **2012**, *53*, 876−878.
(36) Bernardim, B.; Pinho, V. D.; Burtoloso, A. C. B. α,β-Unsaturated Diazoketones as Platforms in the Asymmetric Synthesis of Hydroxylated Alkaloids. Total Synthesis of 1-Deoxy-8,8a-Diepicastanospermine and 1,6-Dideoxyepicastanospermine and Formal Synthesis of Pumiliotoxin 251D. *J. Org. Chem.* **2012**, *77*, 9926−9931.
(37) Bernardim, B.; Lordello, L.; Burtoloso, A. C. B. α,β-Unsaturated Diazoketones as Versatile Building Blocks for the Synthesis of Hydroxylated Piperidines, Indolizidines and Quinolizidines. *Curr. Top. Med. Chem.* **2013**, *13*, 2099−2103.
(38) Rosset, I. G.; Dias, R. M. P.; Pinho, V. D.; Burtoloso, A. C. B. Three-Step Synthesis of (±)-Preussin from Decanal. *J. Org. Chem.* **2014**, *79*, 6748−6753.
(39) Bernardim, B.; Burtoloso, A. C. B. A Two-Step Synthesis of the Bioprotective Agent JP4−039 from N-Boc-L-Leucinal. *Tetrahedron* **2014**, *70*, 3291−3296.
(40) Bethluser, W.; Regitz, M.; Theis, W. DBER DIE REAKTIVITXT VON 4-PHENYL-1,2,4-TRIAZOLIN-3,5-DION MIT DIAZOVERBINDUNGEN. *Tetrahedron Lett.* **1981**, *22*, 2535−2538.
(41) Fang, F. G.; Prato, M.; Kim, G.; Danishefsky, S. J. The Aza-Robinson Annulation: An Application to the Synthesis of Iso-A58365A. *Tetrahedron Lett.* **1989**, *30*, 3625−3628.
(42) Clark, J. S.; Hodgson, P. B.; Goldsmith, M. D.; Street, L. J. Rearrangement of Ammonium Ylides Produced by Intramolecular Reaction of Catalytically Generated Metal Carbenoids. Part 1. Synthesis of Cyclic Amines. *J. Chem. Soc., Perkin Trans. 1* **2001**, 3312−3324.
(43) Ceccherelli, P.; Curini, M.; Marcotullio, M. C.; Rosati, O.; Wenkert, E. A New, General Cyclopentenone Synthesis. *J. Org. Chem.* **1990**, *55*, 311−315.
(44) Franck-Neumann, M.; Geoffroy, P.; Winling, A. Tricarbonyl Iron Complexes Bearing a Free Diazo Group II. Diene and Trimethylenemethane Diazoketone Complexes as Precursors of Highly Reactive Ketocarbenes and Diazonium Cations. *Tetrahedron Lett.* **1995**, *36*, 8213−8216.
(45) Danheiser, R. L.; Brisbois, R. G.; Kowalczyk, J. J.; Miller, R. F. An Annulation Method for the Synthesis of Highly Substituted Polycyclic Aromatic and Heteroaromatic Compounds. *J. Am. Chem. Soc.* **1990**, *112*, 3093−3100.
(46) Loebach, J. L.; Bennett, D. M.; Danheiser, R. L. (Trialkylsilyl)-vinylketenes: Synthesis and Application as Diene Components in Diels−Alder Cycloadditions. *J. Org. Chem.* **1998**, *63*, 8380−8389.
(47) Cainelli, G.; Giacomini, D.; Galletti, P.; Quintavalla, A. Synthesis of Novel 4-(2-Oxoethylidene)azetidin-2-Ones by a Lewis Acid Mediated Reaction of Acyldiazo Compounds. *Eur. J. Org. Chem.* **2003**, *2003*, 1765−1774.
(48) Ihara, E.; Fujioka, M.; Haida, N.; Itoh, T.; Inoue, K. First Synthesis of Poly(acylmethylene)s via Palladium-Mediated Polymerization of Diazoketones. *Macromolecules* **2005**, *38*, 2101−2108.
(49) Kapferer, T.; Brückner, R. Asymmetric Dihydroxylation of β,γ-Unsaturated Carboxylic Esters with Trisubstituted C═C Bonds—Enantioselective Syntheses of Trisubstituted Γ-Butyrolactones. *Eur. J. Org. Chem.* **2006**, *2006*, 2119−2133.
(50) Deng, Y.; Lee, Y. R.; Newman, C. A.; Wulff, W. D. Aziridinyl Vinyl Ketones from the Asymmetric Catalytic Aziridination Reaction. *Eur. J. Org. Chem.* **2007**, *2007*, 2068−2071.
(51) Sosa, J. R.; Tudjarian, A. A.; Minehan, T. G. Synthesis of Alkynyl Ethers and Low-Temperature Sigmatropic Rearrangement of Allyl and Benzyl Alkynyl Ethers. *Org. Lett.* **2008**, *10*, 5091−5094.
(52) Cao, P.; Sun, X.-L.; Zhu, B.-H.; Shen, Q.; Xie, Z.; Tang, Y. Multistep One-Pot Wittig/Nazarov Reaction for Construction of Cyclopentenone with Diazo Compounds and Acid Chlorides. *Org. Lett.* **2009**, *11*, 3048−3051.
(53) Zhang, X.; Guo, X.; Yang, L. P.; Hu, W. H. Rh(II) and Zn(II) Co-Catalyzed Multi-Component Reaction for the Synthesis of Vicinal Diols. *Chin. Chem. Lett.* **2009**, *20*, 1299−1302.
(54) Wang, C.-D.; Liu, R.-S. Silver-Catalyzed [3 + 2]-Cycloaddition of Benzynes with Diazocarbonyl Species via a Postulated (1H-Indazol-1-Yl)silver Intermediate. *Org. Biomol. Chem.* **2012**, *10*, 8948−8952.
(55) Qian, Y.; Jing, C.; Liu, S.; Hu, W. A Highly Enantioselective Four-Component Reaction for the Efficient Construction of Chiral β-Hydroxy-α-Amino Acid Derivatives. *Chem. Commun.* **2013**, *49*, 2700−2702.
(56) Wang, P.; Liao, S.; Wang, S. R.; Gao, R.-D.; Tang, Y. Reaction of Trisubstituted Alkenes with Iron Porphyrin Carbenes: Facile Synthesis of Tetrasubstituted Dienes and Cyclopentadienes. *Chem. Commun.* **2013**, *49*, 7436−7438.
(57) Xu, X.; Xu, X.; Zavalij, P. Y.; Doyle, M. P. Dirhodium(ii)-Catalyzed Formal [3 + 2+1]-Annulation of Azomethine Imines with Two Molecules of a Diazo Ketone. *Chem. Commun.* **2013**, *49*, 2762−2764.
(58) Schwartz, R. E.; Liesch, J.; Hensens, O.; Zitano, L.; Honeycutt, S.; Garrity, G.; Fromtling, R. A.; Onishi, J.; Monaghan, R. L-657,398, a Novel Antifungal Agent: Fermentation, Isolation, Structural Elucidation and Biological Properties. *J. Antibiot.* **1988**, *41*, 1774−1779.
(59) Goss Kinzy, T.; Harger, J. W.; Carr-Schmid, A.; Kwon, J.; Shastry, M.; Justice, M.; Dinman, J. D. New Targets for Antivirals: The Ribosomal A-Site and the Factors That Interact with It. *Virology* **2002**, *300*, 60−70.
(60) Achenbach, T. V.; Slater, E. P.; Brummerhop, H.; Bach, T.; Müller, R. Inhibition of Cyclin-Dependent Kinase Activity and Induction of Apoptosis by Preussin in Human Tumor Cells. *Antimicrob. Agents Chemother.* **2000**, *44*, 2794−2801.
(61) Okue, M.; Watanabe, H.; Kasahara, K.; Yoshida, M.; Horinouchi, S.; Kitahara, T. Short-Step Syntheses of All Stereoisomers of Preussin and Their Bioactivities. *Biosci. Biotechnol. Biochem.* **2002**, *66*, 1093−1096.

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