

# DEVELOPMENTS ON PHOTOLYTIC DECOMPOSITION OF DIAZO COMPOUNDS

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## Abstract:

This review focus on photolytic reactions of diazo compounds, covering mainly synthetic applications such as Wolff rearrangement, 1,2-shift, X-H insertion, cyclopropanation, hydrogen abstraction and reaction with oxygen and physical organic studies, with special relevance to mechanistic considerations.

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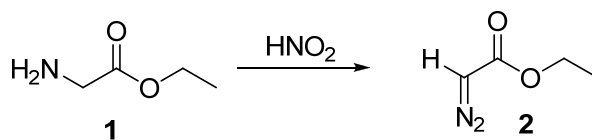
## 1. GENERAL CONSIDERATIONS

During the last two decades carbenes derived from diazo compounds have been widely used as precursors for highly valuable synthetic compounds. With the major contribution of metals like rhodium, copper or ruthenium as carbene stabilizers, diazo compound reactions have been used as an indispensable synthetic tool for any synthetic chemist.[1-4]

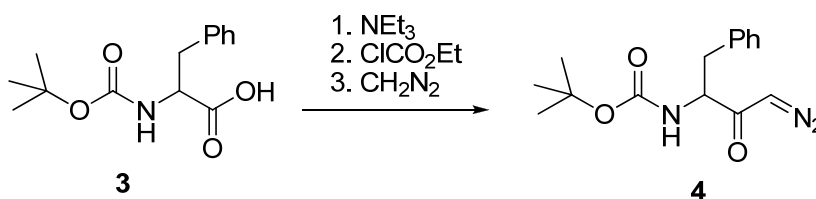
As some examples, dirhodium carbenoids have been used in C-H[5], O-H[6], N-H[7] and Si-H insertions[8], ylide chemistry[9] and additions.[10] Furthermore, extremely selective chiral catalysts have been developed and excellent results have been reported in the chiral version of such reactions.[11] Free carbene chemistry have been abandoned in detriment of the use of such stabilizers that in most cases lead to a more “controlled” chemistry, leaving free carbene chemistry forgotten and obscured at the eyes of many synthetic organic chemists. Despite the lack of use of free carbene chemistry in organic synthesis, the processes involved in this chemistry are amazingly rich regarding the mechanisms and the involved species. Probably, this is the main reason why it has been on the focus of so many physical-organic chemists.

The first aliphatic diazo compound was prepared in the 19<sup>th</sup> century by Curtius[12] when aminoacetate (**1**) was reacted with nitrous acid affording diazoacetate (**2**) (Scheme 1). This diazotization procedure can be applied in

the synthesis of a diazo compound if loss of a proton from the C( $\alpha$ )-atom of the primarily formed alkanediazonium ion is faster than the loss of dinitrogen, which makes this method almost specific for the case of aliphatic amines containing a C( $\alpha$ )-atom substituted by an acidifying group. Diazo compounds can also be prepared by acylation or cleavage of aliphatic diazo compounds containing the structural requirements. For instance, diazo carbonyl carbamate **4** can be prepared through the reaction of the carboxylate precursor with a chloroformate and further reaction of the anhydride with diazomethane (Scheme 2).[13] Making use of oxidants, diazo carbonyl compounds can be prepared by hydrazone oxidation in the presence of mercury oxide and potassium hydroxide.[14]

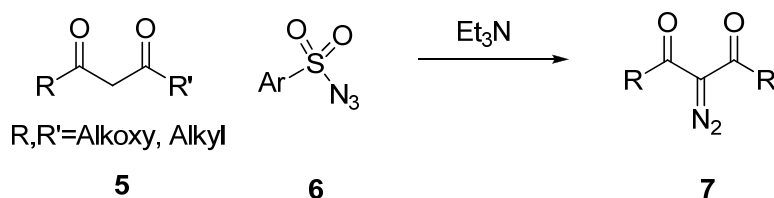


**Scheme 1**



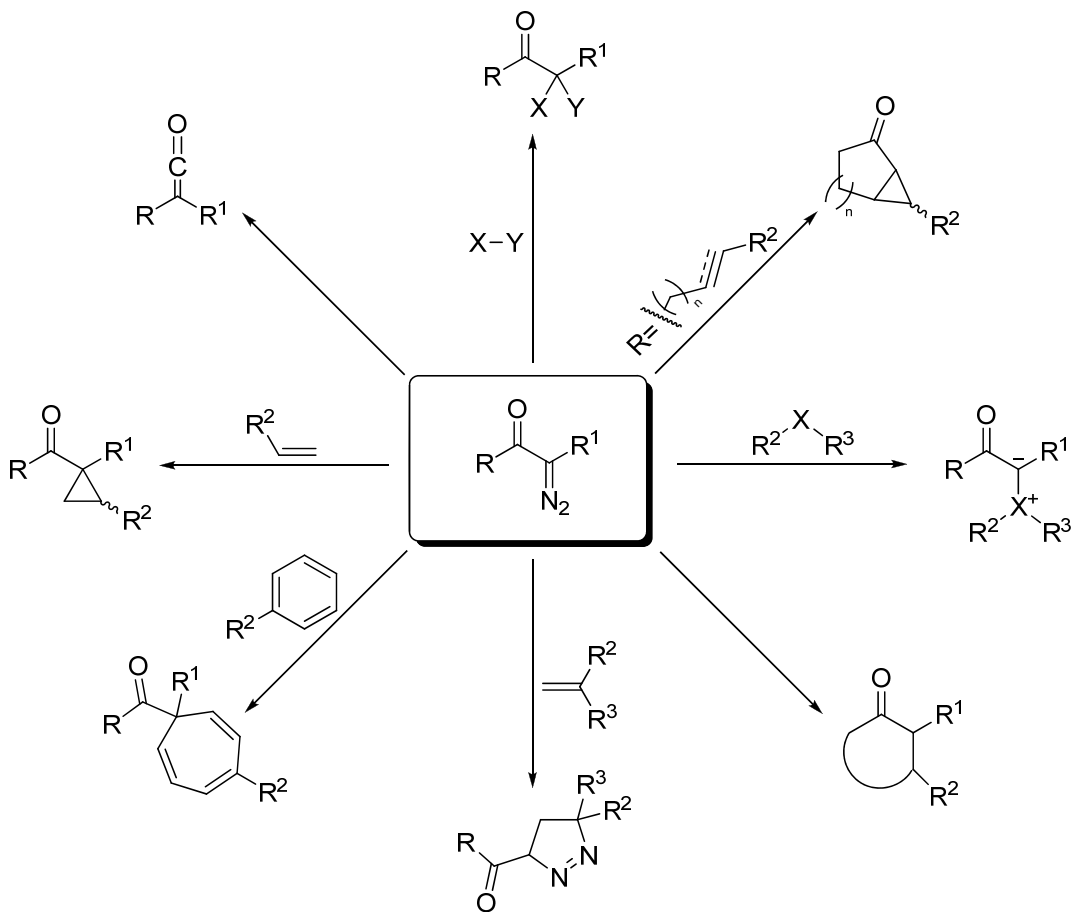
**Scheme 2**

Diazo-transfer reactions have been widely used since they are a more general method for the preparation of diazo compounds. In this reaction, the diazo moiety is transferred from the donor to an acceptor where the donor is a sulphonyl azide (**6**) and the acceptor a carbanion formed after deprotonation (Scheme 3).[3,15]



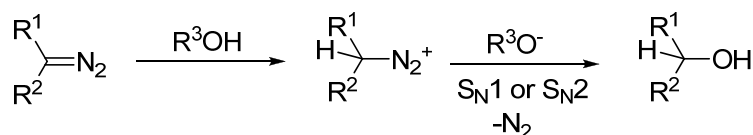
**Scheme 3**

Diazo compounds can be submitted to several reaction conditions and myriads of compounds can be obtained by the proper choice of conditions and reagents. In the absence of a metal catalyst, this decomposition can be induced by thermolysis or photolysis, generating a highly reactive intermediate species that, in most cases, affords a complex mixture of products. Depending on the diazo compound and the reaction conditions, the resulting products can be derived from C-H or X-H insertion, Wolff rearrangement, ylide formation, cyclopropanation,  $\alpha,\alpha$ -substitution reaction,  $\beta$ -hydride elimination or even other cycloaddition reactions (Scheme 4).[3]



**Scheme 4**

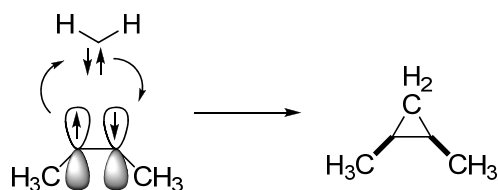
Diazo compounds can react by two very distinct pathways, while in the case of some cycloaddition reactions, dediazonation is absent and the diazo moiety is incorporated in the reaction product, the dediazonation pathway leads to a higher degree of possible reactions and hence, to a larger product variety. Despite the interesting products that can be obtained by the former pathway, this topic will not be focused in this work (see references[16-18] for recent examples on this reaction). Contrary to aromatic diazonium ions which are stabilized by  $\pi$  back-donation, aliphatic diazonium compounds can undergo dediazonation in very fast reactions. The nitrogen extrusion can occur by a bimolecular nucleophilic displacement ( $S_N2$ ), monomolecular dissociation to form a carbocation ( $S_N1$ ) or by homolytic electron transfer in a specific case.[19] Despite the use of this process in the deamination reactions, by treatment of the starting amine with nitrous acid and protonation of the generated diazo compound, this pathway is only possible if a protic and acidic media is available, as in the case of reaction with alcohols (Scheme 5).[20,21] In most cases, as a consequence of photolytic irradiation, heating or due to presence of a metal, the nitrogen extrusion of aliphatic diazo compounds leads to the formation of a carbene. Typically, in the first two cases, the non discriminatory carbene will lead to products emerging from the reaction with itself or with the solvent.



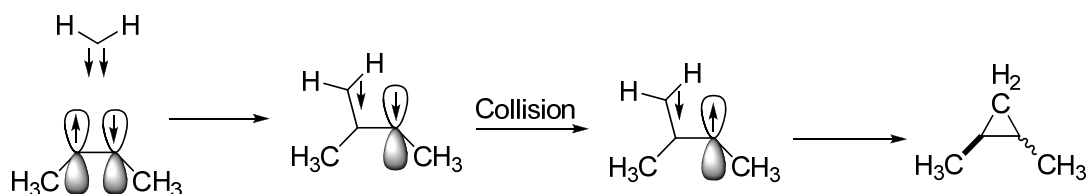
**Scheme 5**

In the absence of a metal with the ability to stabilize a carbene, the divalent carbon species can have its electrons spinpaired (singlet state carbene) or parallel spin (triplet state carbene).[22] Despite that in the former

case the species can decay to the triplet state by intersystem spin crossing (ISC), which in most cases corresponds to a lower energy state, it also can be exclusively formed if a triplet sensitizer is used (the most common sensitizer being benzophenone[23,24]). In order to determine its multiplicity, the carbene can be reacted with double bonds to generate cyclopropane derivatives. The formation of the cyclopropane ring with retention of stereochemistry (*cis* double bond leads to *cis* cyclopropane rings) should indicate the presence of a singlet species, since the movements of both pairs of electrons should occur either simultaneously or in rapid succession to the other (Scheme 6). In the case where a triplet carbene is formed, one of the unpaired electrons will form a bond with an electron of the double bond that has the opposite spin and the two remaining spin-parallel electrons will be waiting for any collision process to invert one of the spins. During this time, there is free rotation about the C-C bond and a mixture of both cyclopropane isomers is formed (Scheme 7).[20,25]



**Scheme 6**



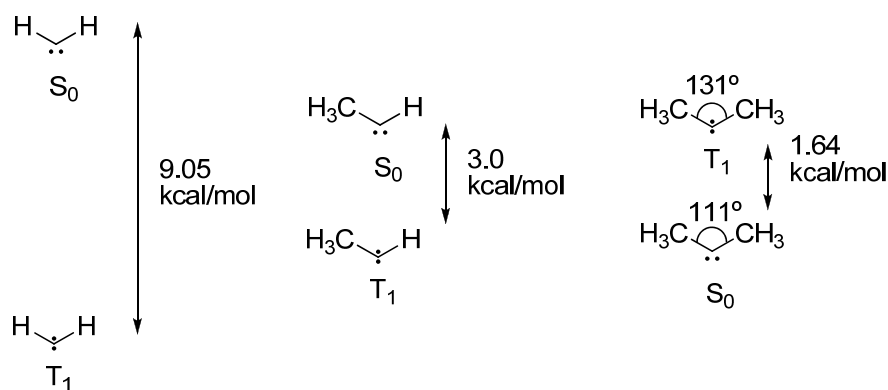
**Scheme 7**

Besides the rich chemistry inherent of diazo derived carbenes, diazo compounds can also react before dediazonation occurs in a way that leads to products very similar to the ones obtained through carbene chemistry. Through irradiation of diazo compounds with a photons source, a diazo excited state species can be generated and it could lead to the formation of free carbene species or can be quenched by reaction with another species present in the reaction medium.

## 2. SINGLET-TRIPLET GAP

In the cases where the formation of a stable free carbene is less energy demanding and/or the diazo excited state species is short lived, the  $\alpha$ -diazo carbonyl photolysis should lead to the formation of a free carbene. In these cases, the singlet-triplet energy difference (S-T gap) will be responsible for the ability of its interconversion (ISC) and consequently will dictate the product distribution. The S-T gap is strongly related to steric and electronic features of the carbene neighborhood substituents.

Since the higher triplet carbene stabilization occurs when its frontier orbitals are degenerate, a linear geometry around the carbon atom of the carbene will favour the triplet state. For instance, while the S-T gap of the simplest carbene (methylene) was reported to be 9.05 kcal/mol,[26] the introduction of a simple methyl group (ethylidene) leads to a decrease of 6 kcal/mol as calculated with *ab initio* methods[27] and in the case of dimethylcarbene the singlet state stabilization is so accentuated that this species becomes 1.64 kcal/mol more stable than the triplet state and possesses a  $111^\circ$  angle on the carbon singlet atom and  $131^\circ$  for the triplet state (Scheme 8).[28-30] Despite this energy difference, as we will see whatever its multiplicity nature, the introduction of bulky substituents lead to the carbene stabilization.



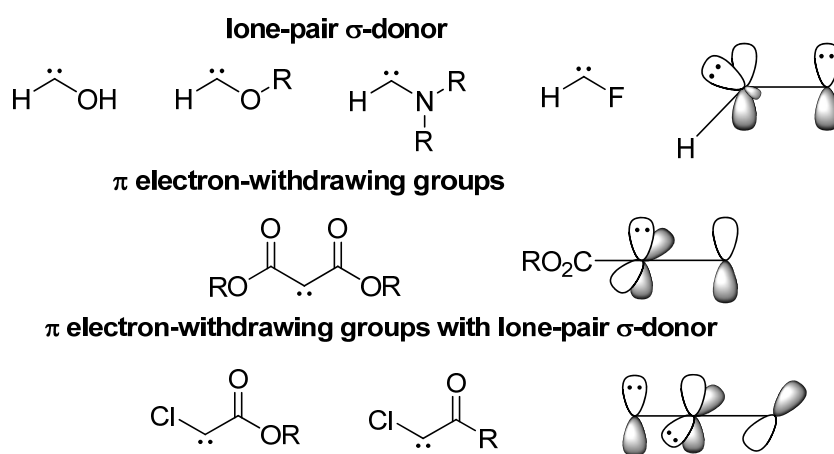
**Scheme 8**

As a representative case of the inductive effects on the S-T gap, whereas  $\sigma$ -electron-withdrawing substituents are known to be singlet stabilizers, the carbene stability goes from triplet to singlet when the substituents are changed from electropositive lithium to hydrogen and to electronegative fluorine (despite the mesomeric contribution of this atom).[31-33] In this case,  $\sigma$ -nonbonding orbital of the carbene has an increased s character while the  $p_\pi$  is left unchanged and the  $\sigma$ - $p_\pi$  gap is thus increased and the singlet state favoured.[27,34]

The nature of the carbene will be different depending on the substituents attached to the carbon atom. In the cases where lone-pair  $\pi$  donor atoms (F, OR, NR<sub>2</sub>, CR<sub>2</sub><sup>-</sup>) are directly bonded to the carbon atom, the singlet state tends to be more stable than the triplet carbene since the lone pair donation to the carbene will result in a polarized four-electron three-centre  $\pi$ -system.[35,36] This effect was also observed for the substituted phenylcarbene where strong  $\pi$ -donors like *p*-NH<sub>2</sub> lead to a S-T gap of 0.7 kcal/mol which can be compared to the 5.4 kcal/mol of simple phenylcarbene.[37]

When  $\pi$  electron-withdrawing groups are present as carbenic substituents, the vacant orbitals of the substituent tend to interact with the  $p$  orbital perpendicular to the valence plane and the  $p$  orbitals degeneracy to be undone leading to a more stable singlet carbene, despite the general linear geometry assumed by the carbene.[27,34,38-42]

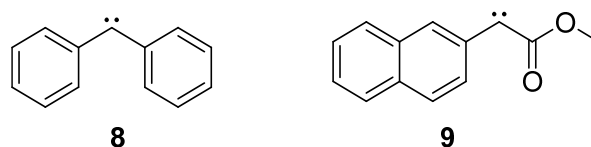
In the case where both types of substituents are present,  $\pi$  electron-withdrawing groups together with lone-pair  $\pi$  donor atoms, a mixed effect of the above are observed. The singlet carbene is strongly stabilized since the vacant  $p_y$  orbital is destabilized by the lone-pair  $\pi$  donor atom while the fully occupied  $p_x$  is stabilized by the vacant orbital of the  $\pi$  electron-withdrawing substituent.[41]



**Scheme 9**

### 3. SOLVENT INFLUENCE ON THE STABILITY AND REACTIVITY OF CARBENES

Despite all the effects on the S-T gap already mentioned, there is at least one more that is strongly related with the carbene reactivity. The solvent used in the photolytic decomposition of diazo compounds is a determining factor in the reaction selectivity, not only because of the possible reactions between the solvent and the photolytic generated species but also, because it can affect the interconversion ability of the carbene. One of the major conversion pathways is the intersystem spin crossing (ISC) between singlet and triplet states. This phenomena is strongly related with the S-T gap (smaller values of S-T gaps will lead to faster ISC) and consequently with the solvent nature. Considering that a singlet carbene state is much more polar than the triplet carbene, which in fact it can be seen as a zwitterionic species, it is expected that more polar solvents stabilize the singlet more than the triplet state. In fact, a strong relation between the solvent polarity and the  $k_{ISC}$  was observed for diphenylcarbenes (**8**), where more polar solvents like acetonitrile lead to a three-fold decrease on the  $k_{ISC}$  ( $s^{-1}$ ) when compared with isooctane.[43,44] Recently the 2-naphthyl(carbomethoxy)carbene (**9**) was analyzed through time-resolved infrared and computational methods (B3LYP calculations using polarizable continuum solvation model). In this case an inversion of populations between carbene states was observed due to the solvent stabilization of these species (approximately 1 kcal/mol). Due to the increased dipole moment in acetonitrile, when compared with heptane, a more stable singlet carbene ( $\Delta H_{ST} = -0.6$  kcal/mol) was observed. Contrarily to this, heptane led to the preferential stabilization of the triplet carbene ( $\Delta H_{ST} = 1.4$  kcal/mol).[45] This aspect was also supported by the introduction of electron donor substituents in the *ortho* and *para* positions of the aromatic ring of the phenyl(carbomethoxy)carbene.[37,46]



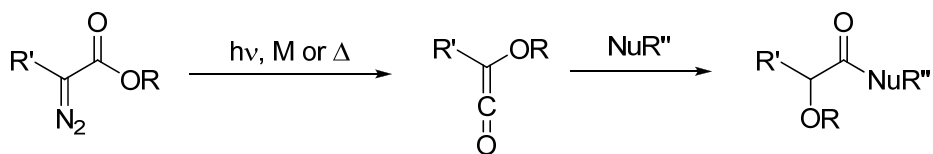
**Scheme 10**

As can be learned from any chemistry textbook, the choice of solvent is of pivotal importance for the success of a reaction and the main characteristic is to be inert towards the reaction intervenients (starting materials, products and intermediaries).[47] Despite the ability of the carbene to have its reactivity tuned by the solvent, this species can, in most cases, easily react with any protic or aprotic solvent. For instance, until the 1980's alcoholic solvents were used to quench singlet carbenes and the product distribution analyzed to determine if a singlet free carbene was being formed in the reaction which should result in the formation of the ether derived from O-H insertion reaction.[48,49] In the case of aprotic solvents, similar aspects can be found. Considering non-functionalized alkanes like isobutane or *n*-pentane, these can react with a singlet carbene *via* direct C-H insertion[50,51] or with a triplet free carbene *via* abstraction-recombination mechanism, or in some cases *via* a double hydrogen abstraction from the solvent.[52] Another aspect that strongly contributes to the carbene quenching is the presence of oxygen, since triplet oxygen can easily react with triplet carbenes to generate oxide derivatives.[53,54] Taking this aspect into consideration, the use of water which is known to have a low ability to dissolve oxygen,[55] can be a suitable solvent choice in some cases.

### 4. WOLFF REARRANGEMENT

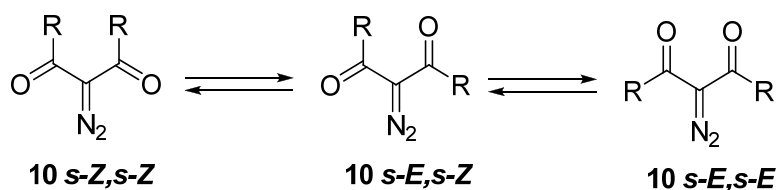
The Wolff rearrangement consists in the formation of a ketene after an  $\alpha$ -diazo carbonyl compound decomposition (photolytic, thermal or metal catalyzed). This reaction (which was first discovered by Ludwig Wolff

in 1902 [56]) has been widely used as a valuable synthetic transformation due to the controlled reactivity of the ketene with nucleophiles to yield carboxylic acids derivatives (Scheme 11) or with unsaturated systems to yield [2+2] addition products.



**Scheme 11**

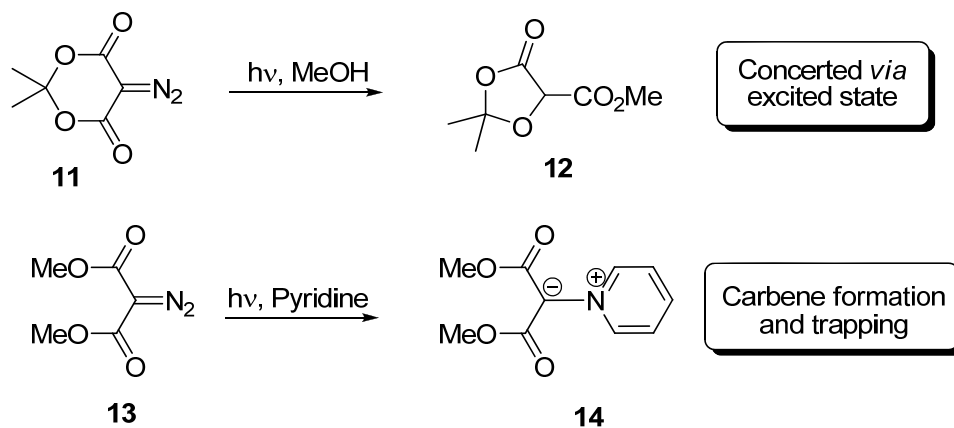
Despite the 100 years that passed since the first example described for this reaction, much remains to be known about the photolytic mechanistic features of this transformation due to two interconnected aspects. The association of this reaction with the rich chemistry of carbenes and photoexcited species, together with a very precise conformational control on the starting material that will dictate which of the substituents will suffer the 1,2-shift (adding to this the migration aptitude of such substituent) difficult the precise mechanism determination.[57] If we consider  $\alpha$ -diazo diketones, at least three planar relatively stable conformations should be considered (Scheme 12): **10** *s-Z,s-Z* where both carbonyl are oriented to the same side of  $N_2$  moiety, **10** *s-E,s-Z* with a carbonyl group on the opposite side of  $N_2$ -C-C-O and **10** *s-E,s-E* where both carbonyls are opposed to the  $N_2$  moiety. Depending on the R substituents, the population distribution can be more pronounced for one or more of the three conformations and in some cases different reactivity can arise due to some conformational constraints like the lack of resonance in extreme cases.[58]



**Scheme 12**

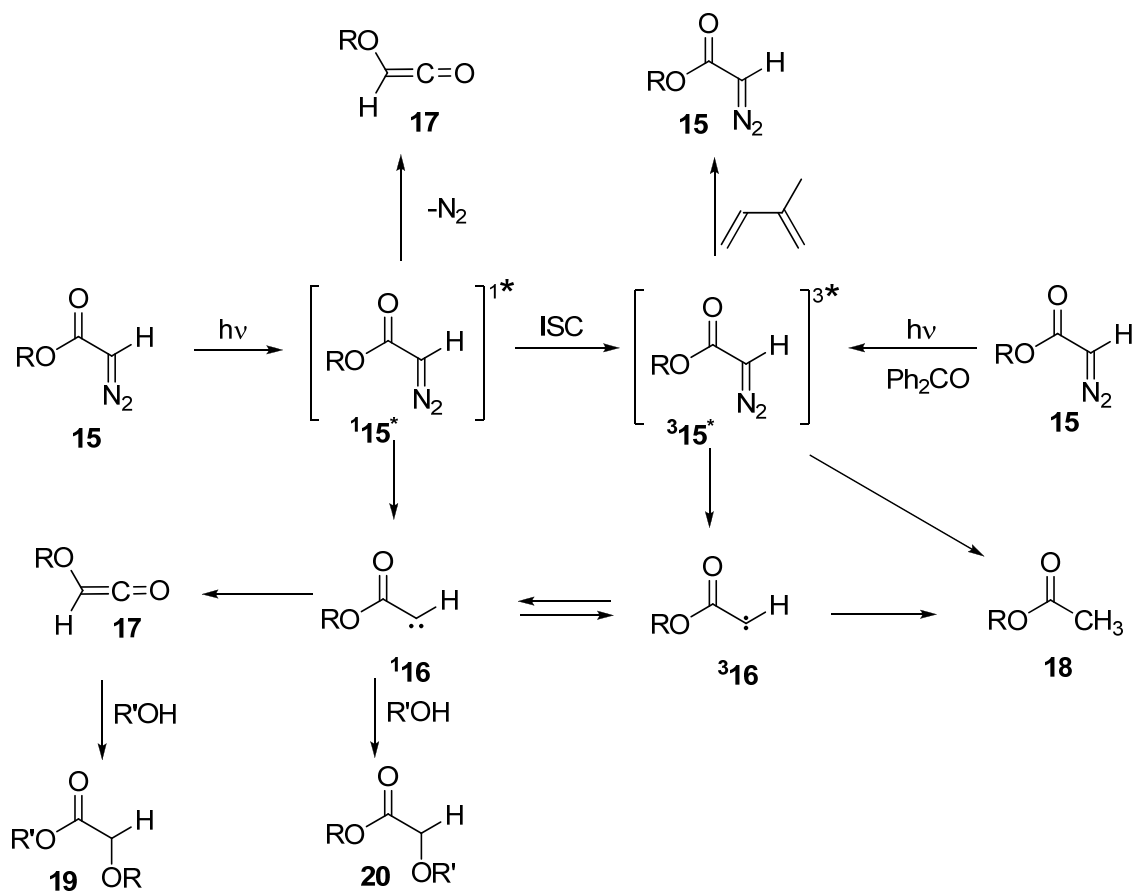
One of the most interesting aspects on the Wolff rearrangement is its mechanism. There are two hypothesis that have been widely studied and are now accepted since the mechanism should be strongly related with the substituents and the most stable conformation of the diazo compound. In a very simplified manner, the hypothesis relies in the ketene formation through a stepwise mechanism where a free carbene is present or a concerted mechanism that bypasses the presence of such species and the reaction occurrence through a ground or singlet diazo excited states.

For a concerted pathway to occur, both leaving group ( $N_2$ ) and the migrating groups have to be oriented in an antiperiplanar way. For instance, looking at diazomalonic acid esters, in the case where the diazo compound has locked *s-Z,s-Z* conformation, like Meldrum's acid diazo derivative **11**, the Wolff rearrangement product **12** is formed in 91 % [59] however, the acyclic homologue **13** decomposition leads only to the formation of carbene derived products (Scheme 13).[38] This different reactivity was explained on the basis of the assumption that the irradiation of conformationally flexible acyclic  $\alpha$ -diazoesters produces the correspondent carbenes, which do not rearrange due to the low migratory ability of oxygen, while in the case of conformationally locked Meldrum's acid the excitement of the diazo compound results in a concerted Wolff rearrangement that bypasses the carbene formation.[60]



**Scheme 13**

As observed in the case of diazomalonic acid esters where the conformational effect seems to have a strong influence on the reaction mechanism, a similar effect can be observed for simpler carboethoxycarbenes but in this case, the carbene substituents will strongly dictate the extension of ketene formation. For instance, in a remarkable work developed by Platz, it was observed that the photolytic decomposition of the simple ethyl  $\alpha$ -diaoacetate[61] **15** (R=Et), and 2-naphthyl(carbomethoxy)carbene[62] (which was also observed by Toscano[63]), lead predominantly for the formation of a carbene species that reacts indiscriminately with alcohols, ethers, and alkenes. However, in a previous work reported by Tomioka,[64] the photolysis of methyl diazoacetate **15** (R=Me) was observed to produce an excited singlet state **15\*** that could suffer Wolff rearrangement competing with singlet carbene formation or intersystem crossing to the triplet diazo compound **<sup>3</sup>15\*** (Scheme 14).

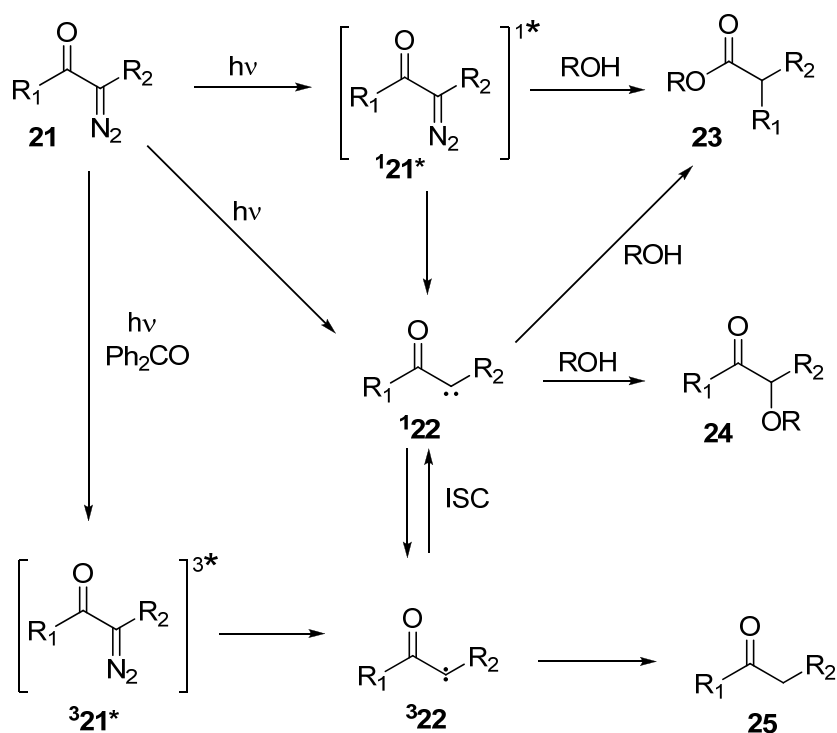


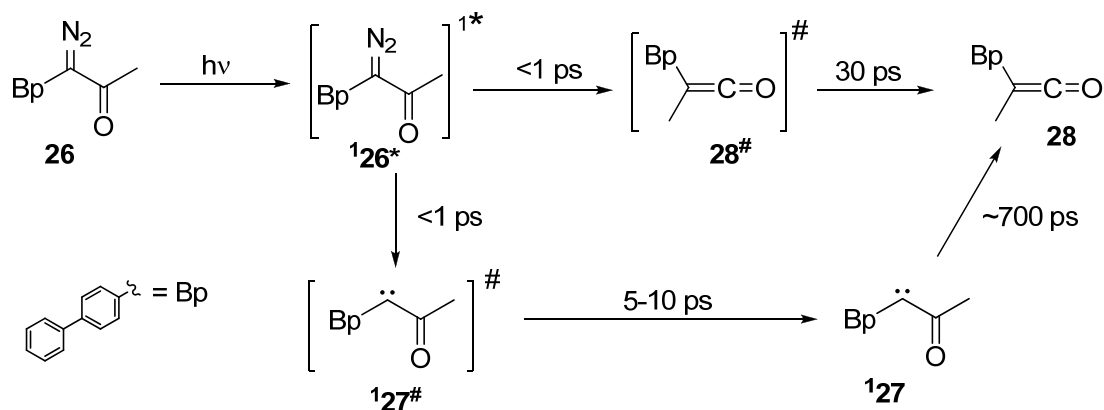
**Scheme 14**



In the case of  $\alpha$ -diazoketones, an excited diazo compound seems to be the major responsible for the formation of ketene that will undergo Wolff rearrangement. Through comparison of photosensitized and direct photolysis experiments, Tomioka observed that the use of benzophenone as a triplet sensitizer lead to suppression of the Wolff rearrangement products **23** and to upraising of double hydrogen abstraction products **25** together with some singlet-derived products **24**. However, despite the decrease of Wolff rearrangement product **23** in the sensitized experiments, it was not completely suppressed which indicates that a free singlet carbene **122** should contribute, at some extent, for the formation of such product (Scheme 15).[64] Recently, Platz observed the formation of a diazo excited state **126\*** for the BpCN<sub>2</sub>COCH<sub>3</sub> diazo ketone **26** through the use of femtosecond flash photolysis (Scheme 16). Despite the formation of a hot ketene **28\*** through the concerted extrusion of N<sub>2</sub> from the diazo excited state, this species should also decay for the ketocarbene species **127** that will also contribute for the formation of ketene (despite the slower pathway).[65] The ketene formation from 2-diazo-1,3-diphenyl-1,3-propanedione has also been assigned to the presence of a diazo excited state which in this case can decay by intersystem crossing to the triplet excited state. However, this triplet species does not participate in the ketene formation.[66]

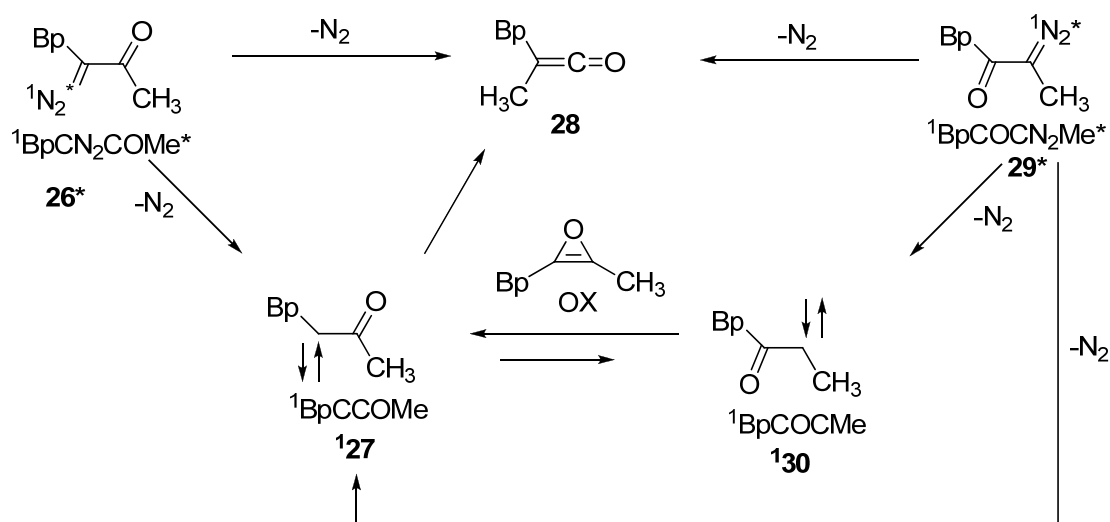
A similar case was observed for 2-diazo-1(2*H*)-acenaphthyleneone. In this case the ketene formation, which leads to a ring contracted product, was assigned to a singlet excited state after the photolysis of the ground state triplet carbene.[67]





Scheme 16

In the continuation of their work, Platz and co-workers compared the ultrafast photolysis of two isomeric diazo carbonyl compounds, BpCN<sub>2</sub>COMe and BpCOCN<sub>2</sub>Me.[68] Three possible mechanisms were advanced for the ketene formation after photolytic decomposition of BpCOCN<sub>2</sub>Me (Scheme 17). The diazo excited state <sup>1</sup>BpCOCN<sub>2</sub>Me\* can decompose to form the corresponding carbene with substantial excess vibrational energy (<sup>1</sup>BpCOCMe<sup>#</sup>) which evolves to its <sup>1</sup>BpCCOMe isomer. Another advanced mechanism consists in the migration of the oxygen atom and loss of the nitrogen molecule that could proceed in one step the diazo excited state of <sup>1</sup>BpCOCN<sub>2</sub>Me\* to form the isomeric carbene <sup>1</sup>BpCCOMe. The concerted extrusion of nitrogen and Wolff rearrangement to form the ketene was also advanced as a possible decay route.



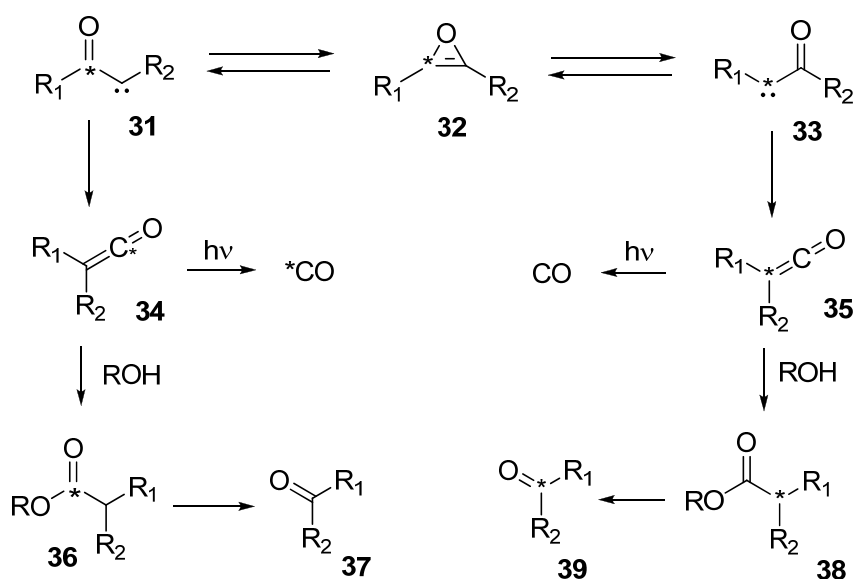
Scheme 17

Recently, Platz and co-workers reported an extensive comparison study of ester BpCN<sub>2</sub>CO<sub>2</sub>CH<sub>3</sub> and ketone BpCN<sub>2</sub>COCH<sub>3</sub> (**26**) by ultrafast photolysis [69]. The different S-T gap energy values were determined to be in the basis of the different reactivity of these two diazo compounds. The stabilization of the filled orbital by the carbonyl group diminishes the resonance of the ester moiety, while in the case of the ketocarbene, the carbonyl group can better stabilize the carbene filled orbital. This difference between both carbenes leads to a more favored singlet ketocarbene when compared with ester carbene. In fact, the triplet was determined to be the ester carbene ground state in cyclohexane, and the slow intersystem spin crossing was attributed to the difference in singlet and triplet geometries. Despite the triplet nature of the ground state,  $\Delta G_{ST}$  was stated to be within  $\pm 1$  kcal/mol [69].

The different reactivities between ester BpCN<sub>2</sub>CO<sub>2</sub>CH<sub>3</sub> and ketone BpCN<sub>2</sub>COCH<sub>3</sub>, where the ketone leads to the formation of Wolff rearrangement product in a good extent and the ester produce no appreciable amount of

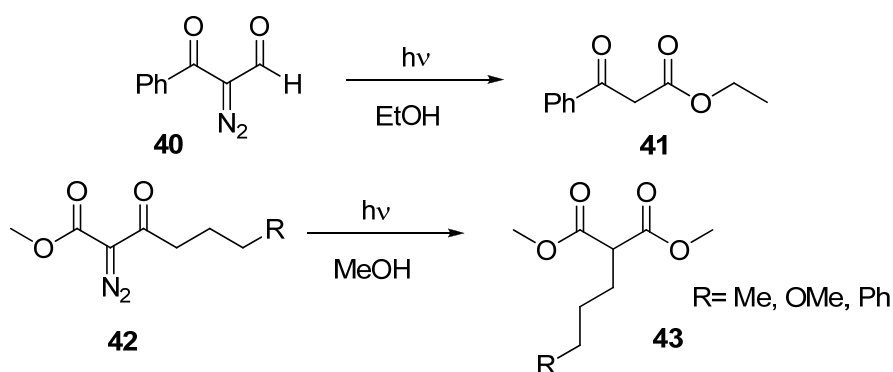
rearrangement product, were also analyzed. According to the authors, diazo excited states are the responsible species for the Wolff rearrangement to occur and the different reactivities between  $^1\text{BpCN}_2\text{CO}_2\text{CH}_3^*$  and  $^1\text{BpCN}_2\text{COCH}_3^*$  can not be only due to conformation of the diazo ground state, as previously advanced by Kaplan and Meloy [70]. The authors speculate that the loss of ester resonance energy that accompanies the Wolff rearrangement of  $^1\text{BpCN}_2\text{CO}_2\text{CH}_3$  is a key factor. The Wolff rearrangement process of the diazo ester excited state is less exothermic and slower than that of a diazo ketone homologue [69].

If a carbene species is an intervenient in the Wolff rearrangement of  $\alpha$ -diazo carbonyl compounds, an oxirene **32** might be formed and two structural different carbenes can interconvert by oxirene mediation ( $\mathbf{31} \rightleftharpoons \mathbf{32} \rightleftharpoons \mathbf{33}$ ). This topic has been reviewed in a very complete work by Zeller.[71] This interconversion is affected by carbene stability, conformational effects, and/or migratory aptitudes of the substituents and has been studied by isotopic labeling and intermolecular scavenging of carbonyl carbenes (Scheme 18).[57,71,72]



Scheme 18

Regarding the migratory aptitudes of the substituent on the photochemical induced Wolff rearrangement, it should occur in the following order H alkyl aryl SR OR  $\text{NR}_2$ . [57] For instance, while the photolytic decomposition of **40** leads to the formation of the Wolff rearrangement product **41** proceeding from hydrogen migration in a very good yield, [73] when diazo compound **42** is subjected to photolytic conditions, the Wolff rearrangement product was the alkyl migration product **43** instead of the alkoxy migration (Scheme 19). [23]



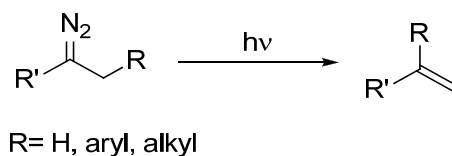
Scheme 19

Despite the good yields obtained for these two examples, the presence of substituents with less migratory aptitude usually leads towards the formation of product mixtures resulting from other kind of reactions like O-H and C-H insertion with the solvent.[74-77]

As a way to apply the  $\alpha$ -diazo carbonyl photolysis as a synthetic tool, a work by Liao and co-workers compared the  $\text{Rh}_2(\text{OAc})_4$  catalyzed decomposition of compounds possessing a free hydroxyl functional group with photolytic decomposition. While in the former the expected O-H insertion products were obtained in good yields, the photolysis led to the formation of Wolff rearrangement products, tetrahydrofurans derivatives, in reasonable yields (33-78 %).[78]

## 5. 1,2-R SHIFT

Depending on the nature and on the substituents of a  $\alpha$ -diazo compound without the presence of a stabilizing carbonyl group, its photolysis can, in most cases, lead to the formation of 1,2-R migration products. Some of the best described reactions are 1,2-H migration and 1,2-Ph migration. These reactions consist in the migration of a hydrogen atom or a phenyl substituent from the neighbour carbon to the carbon where the nitrogen moiety was present (Scheme 20).

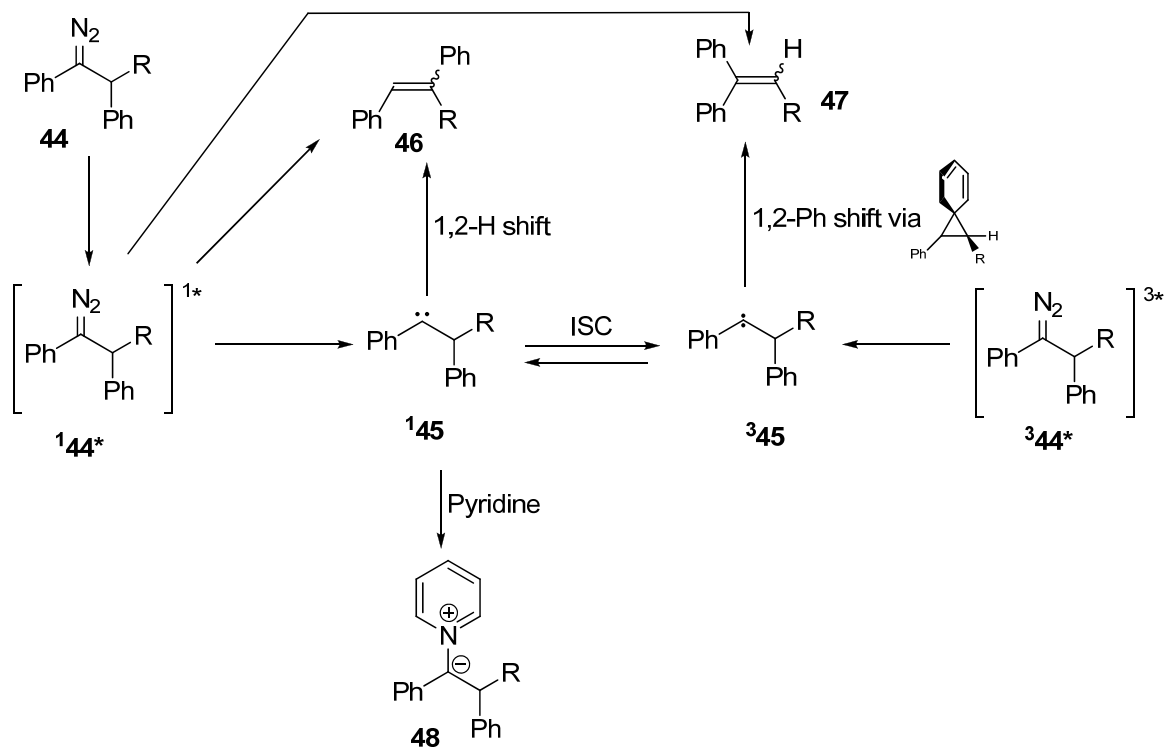


**Scheme 20**

Concerning the migration mechanism, two pathways are possible. The first bypasses the formation of carbenes while the second, a stepwise mechanism involving carbenes that can be responsible for alkene formation.

One of the first extensive works with reliable experimental evidences was advanced by Platz. While Tomioka presented some evidences that supported the carbocation formation in methanol that would eliminate to yield the corresponding alkene,[79] Platz observed that alkyl aryl diazo compounds react *via* a diazo excited state  $^1\mathbf{44}^*$  where 1,2-H migration and alkene formation are concerted. However, from ylide detection that derived from the reaction of pyridine with singlet carbenic species  $^1\mathbf{45}$ , it was possible to determine that the diazo excited species  $^1\mathbf{44}^*$  decayed towards the singlet carbene  $^1\mathbf{45}$  formation (Scheme 21).[80] About the 1,2-Ph shift migration products, they arise from triplet carbene, as observed for 1,2-diphenyl-1-diazobutane based on kinetic measurements, where a bridged spirocyclooctadienyl biradical seems to be present as indicated by Garcia.[81,82]

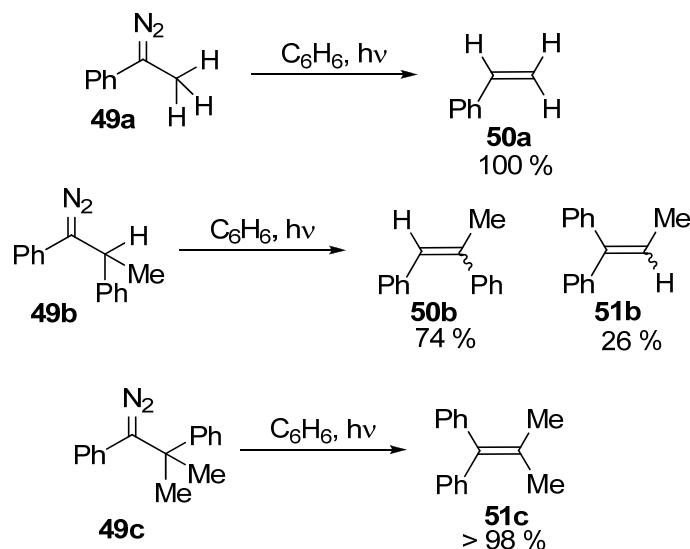
Recently, Platz studied the ultrafast photolysis of *p*-biphenyldiazomethane and *p*-biphenyldiazoethane in acetonitrile, cyclohexane and methanol. It was seen that the quantum yields for the decomposition of both compounds were the same, discarding the hypothesis where internal conversion of the diazo excited state to the ground state could be more efficient for *p*-biphenyldiazoethane than for *p*-biphenyldiazomethane. In the former case the hypothesis of a cation species responsible for 1,2-H shift was observed to be only a minor pathway and the diazo excited state contributes in ~25 % for the alkene formation.[83,84]



**Scheme 21**

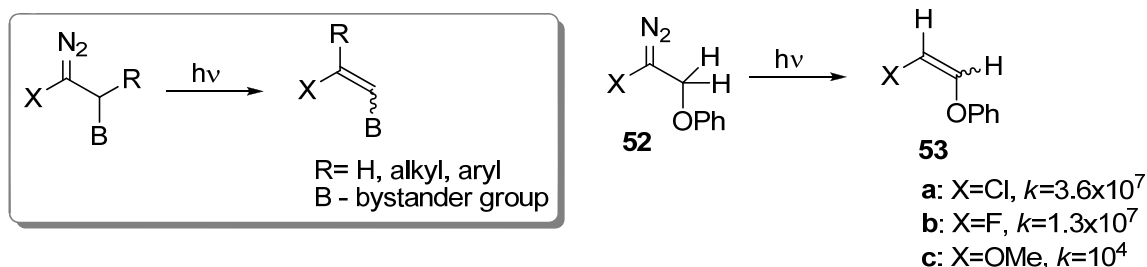
Despite the experimental evidences that demonstrate the contribution of a diazo excited state in the alkene formation from alkylphenyldiazomethanes photolysis, in the case where 1-phenylethyldiene was studied this contribution seems to be diminished, demonstrating the substituents' influence on the stabilization of a diazo excited state. In this case, where a S-T gap of 2.3 kcal/mol was determined in *n*-heptane, the free singlet carbene seems to be the responsible species for the alkene formation since it could be efficiently trapped by pyridine and the ylide detected through Laser Flash Photolysis (LFP). Furthermore, the 1,2-hydrogen shift 30-fold increase in acetonitrile is in strong accordance with a singlet carbenic species which is known to be more stable in polar solvents due to its zwitterionic nature.[85] In some cases where Wolff rearrangement can compete with 1,2-H shift, namely in the case of an  $\beta$ -oxy- $\alpha$ -ketocarbene, the use of water as solvent can even suppress the Wolff rearrangement product formation to exclusively yield 1,2-H migration product.[86,87] Recently, it was shown that the contribution from a free carbene to the alkene formation, which changes with the nature of the substituents, ranges from 60 % (R= Me) to 100 % (R=H) for the cases studied, however a dependence on the irradiation wavelength was observed.[88]

In regarding to the migratory aptitudes of the substituents, the same trend described for the Wolff rearrangement was observed, since the migratory ability of a substituent is an inherent characteristic. Hence the migratory ability can be described as H Ph Me.[89] For instance, the percent yields from steady-state photodecomposition of aryldiazo compounds **49a-c** clearly show this series (Scheme 22).[88]



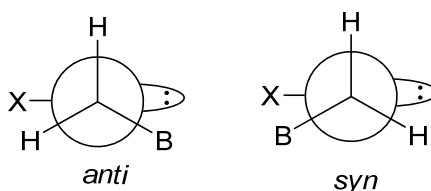
Scheme 22

Despite the importance of the migratory aptitude of each substituent, there is a strong effect raised by the substituent (X) and bystander groups (B). Concerning the nature of the substituents it was observed that electron donating substituents decreased the electrophilicity of the carbenic *p* orbital and therefore, raised the activation energy of the 1,2-R shifts and the rearrangement velocity decreased. For instance, when one of the bystander groups is OPh a strong relation between the X substituent and the  $k_{1,2-H}$  was observed for X = Cl, F (**52a, b**) and the methyl ether (**52c**, X=OMe) (Scheme 23).[90]



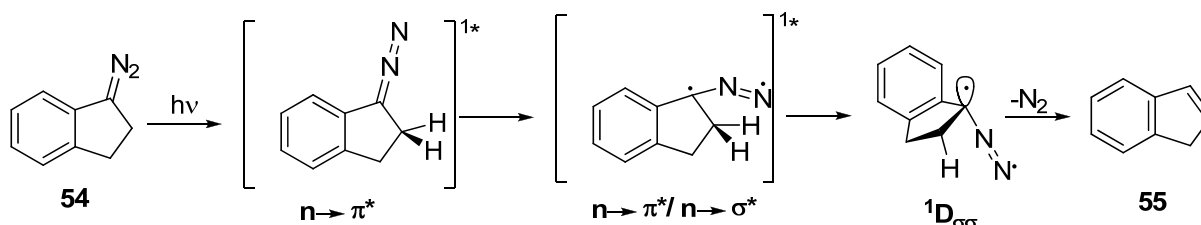
Scheme 23

The bystander assistance effect on the 1,2-R shift is better described for the thermolytic decomposition of diazo compounds,[89] where the reaction should proceed *via* a free carbene since the development of excited species is unlikely to occur. However, the same effect is expected to be present when the reaction is performed under photolytic conditions. This effect is based on the electron donor ability of the bystander substituent which "increases" the migrating C-H bond ability and facilitates the hydrogen migration. For instance, Liu reported that 1,2-H migration of benzylchlorocarbenes (X=Cl, B=X'C<sub>6</sub>H<sub>4</sub>, R=H), derived from corresponding diazirines, is accelerated by the introduction of electron donating substituents on *para* position of the aromatic ring in the following order MeO > Me > H > Cl > CF<sub>3</sub>.[91] This bystander effect, according to the described for thermolysis, is responsible for the isomer distribution since the bystander groups should benefit from an *anti* transition state where B is *anti*-like to the X substituent (Scheme 24). In this case, the *anti*-like transition state leads to the formation of the *E*-alkene while *Z* isomer comes from the *syn*-like conformation.[89,92]



Scheme 24

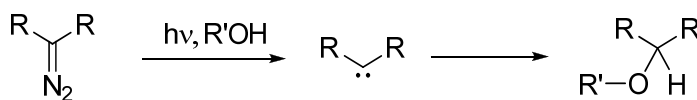
Modarelli reported another aspect concerning the conformation of the reactive species. This author reported some evidences that correlate the dihedral angle between the  $\alpha$  C-H bond and the diazo group with the 1,2-H shift ability. Based on some theoretical calculations, the authors suggest that a better overlap of migrating hydrogen with the singly filled orbital of the carbon happens in a pyramidalized geometry of the diazo excited state rather than in a planar excited state. This excited state, deriving from the lowest excited state ( $n \rightarrow \pi^*$ ), should be formed by a transition state ( $n \rightarrow \pi^*/n \rightarrow \sigma^*$ ) corresponding to a conical intersection on the energy surface and a second intersection correspondent to a diradicaloid species ( $^1D_{\sigma,\sigma}$ ) with a pyramidalized geometry at the diazo carbon which is  $\sim 42$  kcal/mol below the  $n \rightarrow \pi^*$  state (Scheme 25).[93] Furthermore, by performing photolysis of diazo compounds in the crystalline state at low temperatures, enhanced stereoselectivities can be achieved coming in part from the best alignment of the vacant orbital with the C-H bond.[81]



Scheme 25

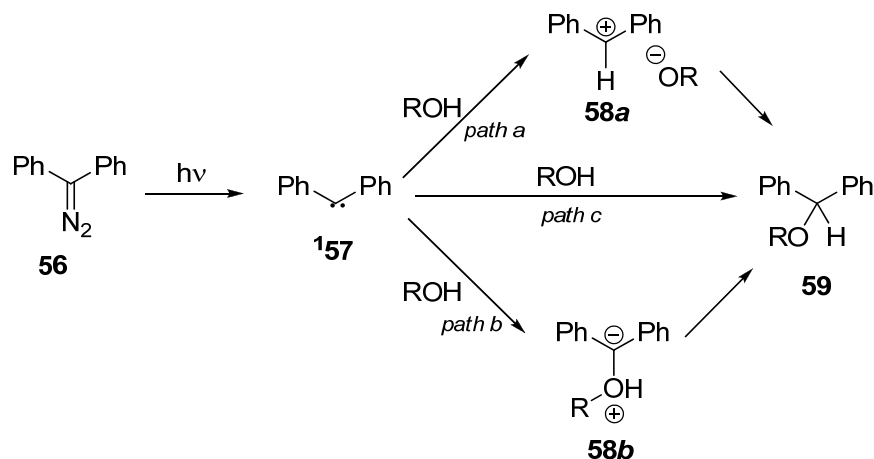
## 6. O-H INSERTION

O-H insertion reactions have been used as a powerful tool in the determination of photolytic mechanisms. Before the development of laser flash photolysis (LFP), in particular, ultrafast flash photolysis, the chemical trapping of intervenient species was one of the principal methods for the determination of a mechanism. Alcohols were thought to react selectively with singlet carbenes to generate ethers (Scheme 26).[76,94] Despite the utility of this reaction,[95] the mechanism is not yet fully clarified but recent developments have been made on this area.



Scheme 26

In a singlet carbene based mechanism, one of two things can occur (Scheme 27). The carbene **57** can abstract a proton from the alcohol to form a carbenium ion **58a** which can then be attacked by the nucleophilic alcohol, or the electrophilic carbene can attack the oxygen atom to generate an intermediate ylide **58b** followed by a 1,2-proton shift. Alternative to these two mechanisms, a third one based on a concerted step can be considered.

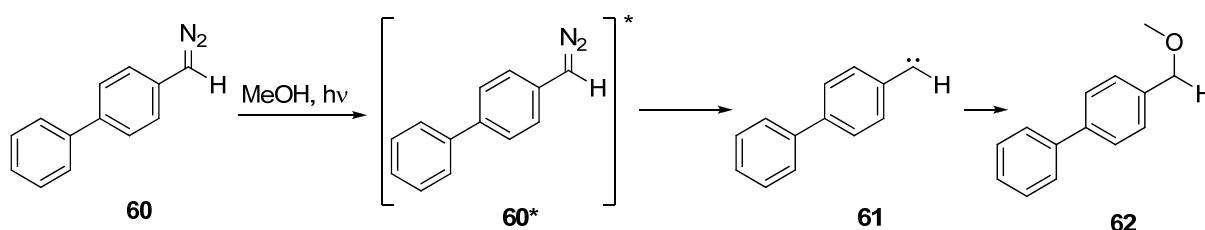


Scheme 27

The diarylcarbenes, which are represented on Scheme 27 by diphenyl carbene **157**, are very different from alkyl systems and will be considered separately. These systems have been thoroughly studied and were first reported to be protonated by Kirmse since the transient generated by LFP were virtually identical to ones obtained by  $\text{Ar}_2\text{CHX}$  photolysis in which  $\text{Ar}_2\text{CH}^+$  is obtained. In fact Kirmse claimed that this pathway would be the major one, competing with the intersystem spin crossing from singlet to triplet carbene.[96] Later, diphenyl carbenes were studied and based on the escape ability of alkoxide anion from the solvent cage together with aromatic ring electron rich substituent enhanced effect, a concerted pathway was claimed. According to the authors, the 40 fold increase in the carbene protonation when *para*-chlorines were substituted by methoxy groups could only be explained if the O-H insertion occurred *via* a concerted pathway.[97]

Recently, Kohler emphasised the mechanism where a carbocation is involved. Through femtosecond transient absorption spectroscopy and based on the isotopic effect of methanol, it was observed that the carbocation formation was extremely fast since the carbene is highly basic. Furthermore, the rate limiting step was assigned to be the nucleophilic attack of the solvent, or the alkoxide. In the case of methanol and ethanol the carbocation was observed to react with a solvent molecule by solvolysis while in the case of the worst nucleophile isopropanol the carbocation reacts with the formed alkoxide. According to the authors this pathway accounts for the ether formation only in 30 % while the predominant pathway was assigned to direct O-H insertion.[98]

The photolysis of *p*-biphenyldiazomethane **60** in methanol was studied by Platz where the formation of the methoxyether **62** was observed to occur in 89 % yield after reaction of singlet carbene **61**. For this case the formation of corresponding carbene was observed to arise from the diazo excited state **60\*** (Scheme 28).[83] *p*-Biphenyldiazoethane **63** was also studied and in this case the obtained results were seen to be very similar to the ones of diphenylcarbene. In this case a transient assigned to be *p*-biphenylmethyl cation was observed, arising from the abstraction of a proton of methanol by the singlet carbene, but due to the lack of persistence of this species it was not possible to determine its yield from the singlet carbene.[84]

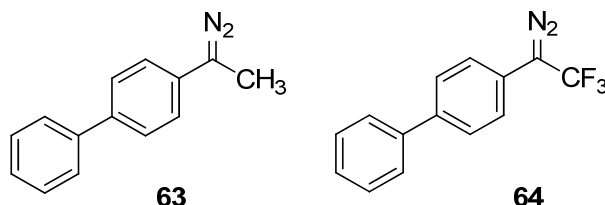


Scheme 28

The homologue *p*-biphenyltrifluoromethyl diazo **64** was also studied and interesting results were obtained. For this case, by combining the isotopic effect, where it was observed that carbene lifetime increase in MeOD, with

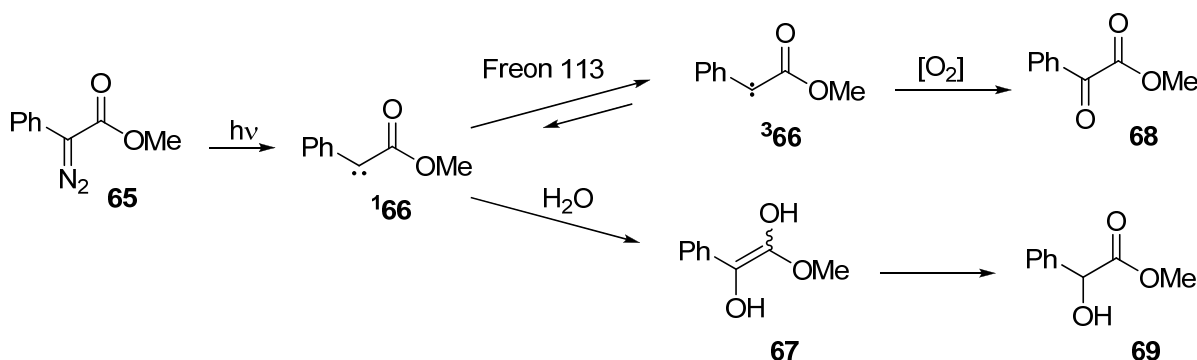


the results obtained in 2,2,2-trifluoroethanol where great enhancement of the signal assigned to the cation occurred, the principal pathway for the O-H insertion reaction was claimed to be the concerted one. The proton transfer pathway seems to be only important in the presence of strongly acidic solvents such as 2,2,2-trifluoroethanol. It should be noticed that from a series of *n*-alcohols studied (methanol to *n*-octanol), the appearance of a diazo excited state that decayed to the singlet carbene was observed and that the initial absorbance of the carbene is solvent dependent as seen on other solvents.[99]



Looking at  $\alpha$ -diazo carboalkoxy compounds, a very different mechanism for the O-H insertion was observed. The phenylcarbomethoxycarbene in the singlet state  $^1\mathbf{66}$  was determined to react with water in a way that the carbonyl group is also involved. While in the case where the reaction was performed in Freon 113 (1,1,2-trichlorotrifluoroethane) saturated air, the derived carbonyl oxide  $\mathbf{68}$  was present due to the triplet carbene  $^3\mathbf{66}$  reaction with oxygen,[54] in the case where water was used an enol intermediate  $\mathbf{67}$  is formed (Scheme 29). This difference in the product distribution was attributed to the low solubility of oxygen in water and to a shift of the carbene singlet-triplet equilibrium more to the side of the singlet carbene in water.[55,100] This enol forms were also detected for 2-diazophenylacetic acid and 4-diazo-3-isochromanone.[101]

Later, Schepp reported the formation of the cation prior to the formation of ethers when  $\alpha$ -diazo-(4-methoxyphenyl)methoxycarbonyl was submitted to photolysis. However, the carbene was not detected through LFP and the hypothesis that accounted for the direct protonation of the diazo excited state was not discarded.[102]

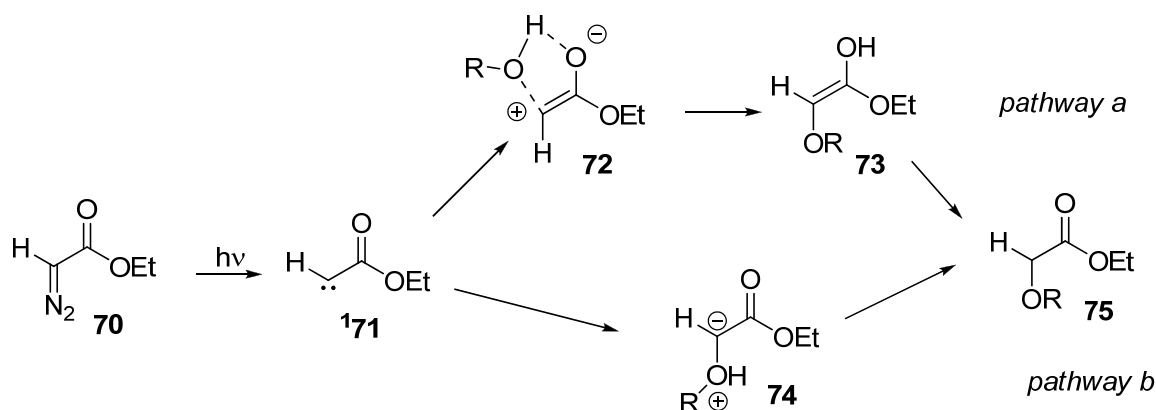


Scheme 29

About this class of compounds, an intense work has been done by Tomioka during 1980's, mainly on the neighbouring group participation. For instance, when phenylcarbomethoxycarbene was generated through its corresponding diazo compound photolysis in a mixture of 2-methyl-2-butene and methanol a mixture of cycloaddition products and O-H insertion products was obtained. However, the decomposition of 2-phenylacetate sodium salt yield almost exclusively the ether product derived from O-H insertion. According to this author, this effect can be explained by the strong interaction of the neighbouring carboxylate group with the vacant *p* orbital of the singlet carbene.[40]

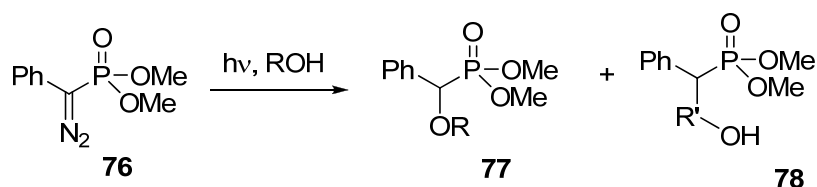
2-Diazoethyl acetate  $\mathbf{70}$  was reported to react with *iso*-propanol *via* a polar addition of the carbene, in the light of what was known in 1960's (Scheme 30, pathway a).[75,76] Recently, an ylide deriving from the singlet carbene  $^1\mathbf{71}$  was assigned to be the intermediary based on kinetic data obtained in Freon 113 photolysis (Scheme 30,

pathway b).[61] Furthermore, the methylester analogue was seen to react with *iso*-propanol to yield the corresponding ethers at room temperature while in a rigid matrix the C-H insertion products predominate due to the reaction of the triplet carbene (abstraction-recombination mechanism, *vide infra*) that becomes predominant at lower temperatures.[77]



Scheme 30

When  $\alpha$ -diazobenzylphosphonates are decomposed in alcohol, a strong temperature effect is observed. Tomioka performed an extensive work on this type of compounds after observing that the O-H insertion product formation at room temperature (71 % yield) was suppressed at 77 K, in alcohol matrices, where C-H insertion product predominates (70 % yield).[103] This reaction was further studied in other alcohols than methanol and the lack of solvation in the matrices, together with the decreased acidity of alcohols at lower temperature, were pointed as possible causes for the O-H insertion absence (Scheme 31). While O-H insertion at room temperature occurred *via* singlet carbene, the reaction in alcoholic matrices led to the formation of C-H insertion products rising from a triplet carbene where an abstraction-recombination mechanism was suggested.[104]

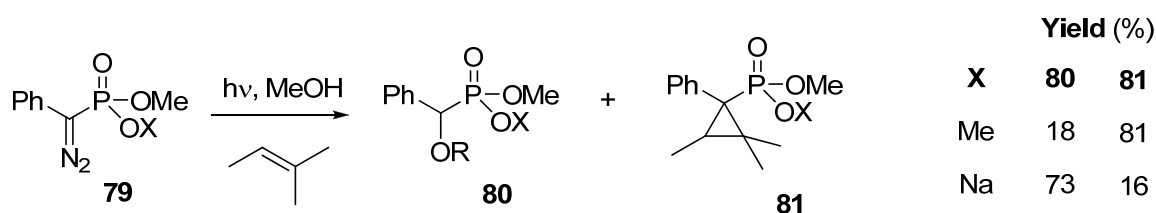


Entry	R	R'	Temperature (°C)	Yield (%)		Entry	R	R'	Temperature (°C)	Yield (%)	
				77	78					77	78
a	Me	CH <sub>2</sub>	27	98		g	Et	CH <sub>2</sub> CH <sub>2</sub>	-72	48	23
b	Me	CH <sub>2</sub>	3	95		h	Et	CH <sub>2</sub> CH <sub>2</sub>	-196	11	68
c	Me	CH <sub>2</sub>	-72	96		i	<i>i</i> -Pr	C(CH <sub>3</sub> ) <sub>2</sub>	27	61	19
d	Me	CH <sub>2</sub>	-196	18	77	j	<i>i</i> -Pr	C(CH <sub>3</sub> ) <sub>2</sub>	3	48	18
e	Et	CH <sub>2</sub> CH <sub>2</sub>	27	84	9	k	<i>i</i> -Pr	C(CH <sub>3</sub> ) <sub>2</sub>	-72	7	18
f	Et	CH <sub>2</sub> CH <sub>2</sub>	3	77	12	l	<i>i</i> -Pr	C(CH <sub>3</sub> ) <sub>2</sub>	-196	8	50

Scheme 31

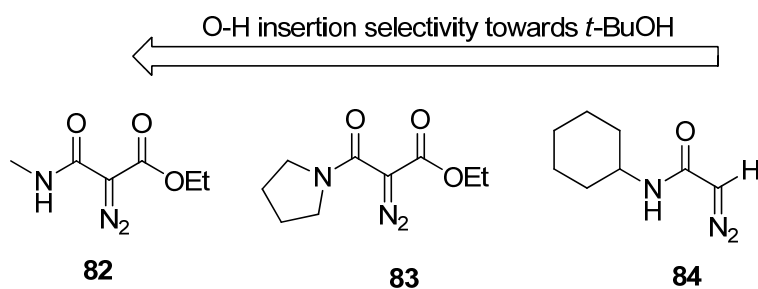
Similarly to the neighbouring effect observed for the 2-phenylacetate sodium salt where O-H insertion was favoured,[40] the same effect was observed for the phosphonate group, making the generated carbene much more nucleophilic in the case of the phosphonate anion (Scheme 32).[48] Despite the good selectivities for this case, it was later observed that the carbenic substituents also play a determinant role on the product distribution. In the case where a methoxycarbonyl moiety is present, instead of the phenyl group (with X=Na), only  $\alpha$ -

hydroxyphosphonate is observed (with X=Me), supporting a mechanism where the phosphonate moiety reacts with the carbenic centre.[105]



Scheme 32

Concerning the photolysis of  $\alpha$ -diazo acetamides, *N*-methyldiazoacetamide was reported to react with water to yield O-H insertion products together with products derived from rearrangements[74] and *N,N*-diethyldiazoacetamide to react with methanol to yield the corresponding ether in 34 %.[106] Despite the low selectivity, several  $\alpha$ -diazo amide photolysis were studied taking in account the C-H vs O-H insertion selectivities concerning the amide substituents in *tert*-butanol (Scheme 33). The influence of the amide substituent was determined to be reflected in an increased electrophilic character of the reaction intermediate leading to a more favourable O-H insertion products formation.[107]

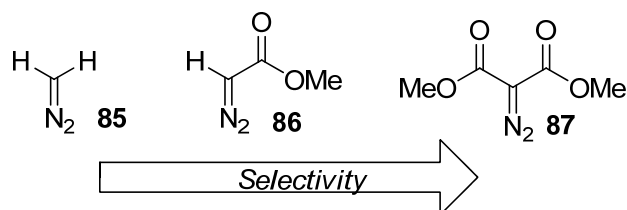


Scheme 33

## 7. C-H INSERTION

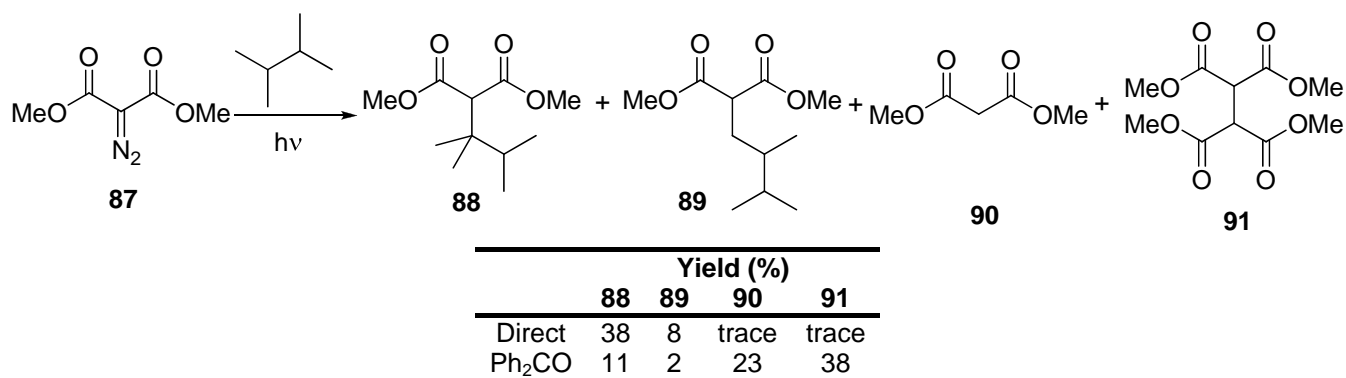
More than 60 years passed since the first report of a photochemically induced C-H insertion reaction (irradiation of diazomethane in ethyl ether),[108,109] however, the mechanistic aspects are still open for discussion. According to previous reports, C-H insertion of diazo compounds can occur through a free carbene in the singlet state,[21,39] or through the triplet carbene *via* an abstraction-recombination mechanism (typical of reaction performed in matrix at low temperatures).[110]

Starting by intermolecular C-H insertions and concerning the selectivities and reactivities of the species formed upon photolysis, Doering reported in early 1960's that between a series of carbenes, the introduction of electron withdrawing substituents led to a more selective species (Scheme 34) and that C-H bonds were more reactive as higher the degree of substitution of the carbon atom ( $3^\circ > 2^\circ > 1^\circ$ ).[42] The C-H insertion reaction of analogues of **86** on a series of alcohols (MeOH, EtOH, *i*-PrOH and *t*-BuOH) was also reported despite the low yields due to the formation of rearrangement and O-H insertion products (see above).[75,76] Analogously,  $\alpha$ -diazoamides **82-84** were seen to react rather well with the C-H bonds of *tert*-butanol, despite the better selectivities towards ether formation.[107]



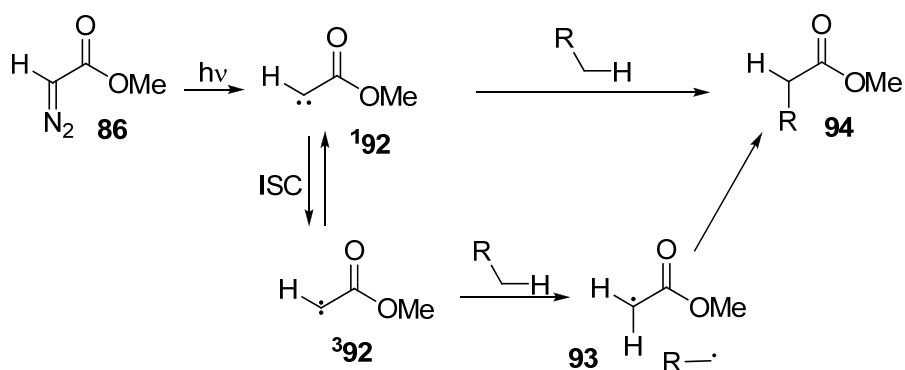
**Scheme 34**

A similar study concerning the C-H bond reactivity was also performed in the case of methyl  $\alpha$ -diazo malonate ester **87**. Through sensitized and direct irradiation of malonic ester in 2,3-dimethyl butane the authors pointed the singlet carbene as the reactive species towards C-H insertion (**88**, **89**) and the triplet carbene responsible for double hydrogen abstraction (**90**) and dimerization (**91**) products.[111]



**Scheme 35**

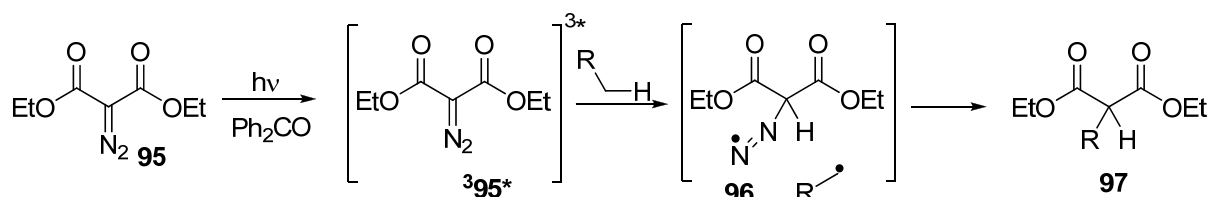
Tomioka performed a study where the structure, temperature and matrix effects on the C-H insertion were evaluated.  $\alpha$ -Diazo methyl acetate **86** and  $\alpha$ -diazo ethyl malonate were made to react in pentane and *iso*-butane and some interesting selectivities for the acetate derivative were observed. These were explained based on the presence of a mixture of carbenes (singlet and triplet). While worst C-H insertion products yields were obtained for the direct photolysis of **86**, better C-H insertion selectivities were achieved when benzophenone was used as a sensitizer, particularly at low temperatures (-196 °C). Hence, while singlet carbene **192** can react *via* direct C-H insertion, it also can be interconverted to the triplet state **392** and react through an abstraction-recombination (a-r) mechanism (*via* **93**) (Scheme 36).[52]



**Scheme 36**

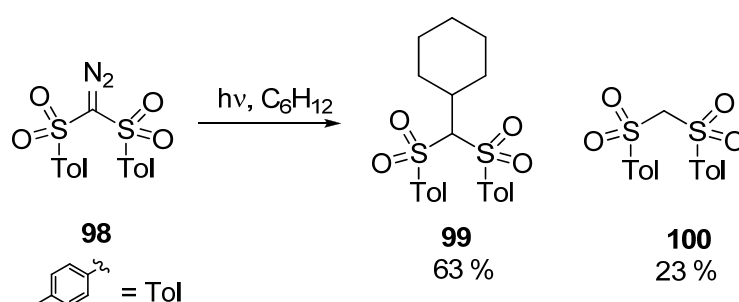
For the case of  $\alpha$ -diazo ethyl malonate a marked increase on the primary C-H insertion products was observed when going from direct to sensitized photolysis. The authors pointed that the intervenient species in this case should be the triplet diazo excited state **395\*** that would abstract a hydrogen atom from the saturated alkane and after nitrogen extrusion together with coupling of the resulting radical pairs would then lead to the product **97** (

Scheme 37).[52]



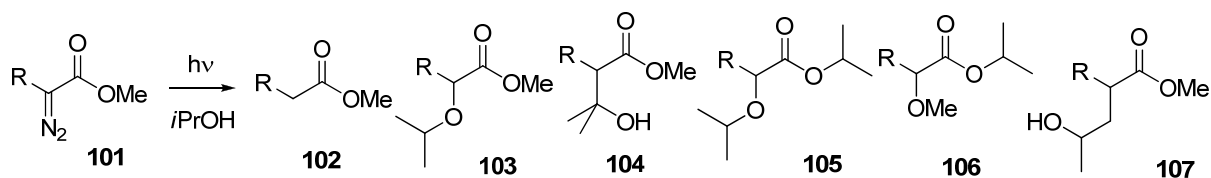
Scheme 37

The most recent example on photolytic intermolecular C-H insertion studies relates to bis(tolylsulfonyl)diazomethane **98**. This compound was described to react with cyclohexane to yield the C-H insertion product **99** in 63 % yield and the double hydrogen abstraction product **100** in 23 % yield (Scheme 38).[112]



Scheme 38

As previously referenced, the substituents directly attached to the carbene carbon atom have a strong influence on the carbene reactivity. For instance, in studies using alcoholic matrices of diazo methyl acetate **101b** and diazo methyl phenylacetate **101a** photolysis it was observed a completely different reactivity (Scheme 39). While the diazo methyl phenylacetate photolysis demonstrated an increased yield of C-H insertion products by lowering the temperature, the same was not observed for **101b**. This effect, together with sensitized irradiation results, was interpreted on the basis of fast singlet-triplet equilibrium of triplet ground-state arylcarbenes, where the C-H insertion product should be formed *via* triplet carbene by an abstraction-recombination (a-r) mechanism. Contrary to this, the C-H insertion products derived from diazo methyl acetate should arise *via* a singlet carbene (which was suggested to be the ground-state) while rearrangement products **105-106** come directly from the diazo excited state.[77]



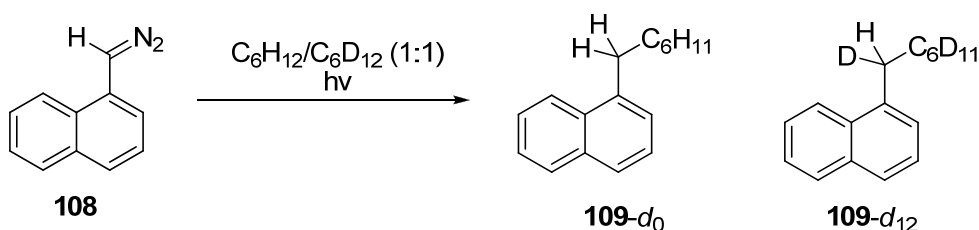
Entry	Compound	R	Temp (°C)	Yield (%)					
				102	103	104	105	106	107
1	<b>101a</b>	Ph	20	7	67	19	-	Trace	-
2	<b>101a</b>	Ph	-196	14	5	42	-	Trace	16
3	<b>101b</b>	H	20	5	35	8	11	33	-
4	<b>101b</b>	H	-196	1	28	13	Trace	11	-

Scheme 39

The photolysis of  $\text{BpCN}_2\text{CO}_2\text{CH}_3$  in cyclohexane led to the formation of C-H insertion product in 84 % yield together with the double hydrogen abstraction product in 7 %. A kinetic isotope effect of 2.5 observed in a 1:1 mixture of cyclohexane/cyclohexane- $d_{12}$  indicated the singlet free carbene as the responsible species. Though the  $^1\text{BpCCO}_2\text{CH}_3$  decay in cyclohexane and cyclohexane- $d_{12}$  indicated that the C-H insertion product should be formed from the carbene singlet-triplet equilibrium mixture.[69]

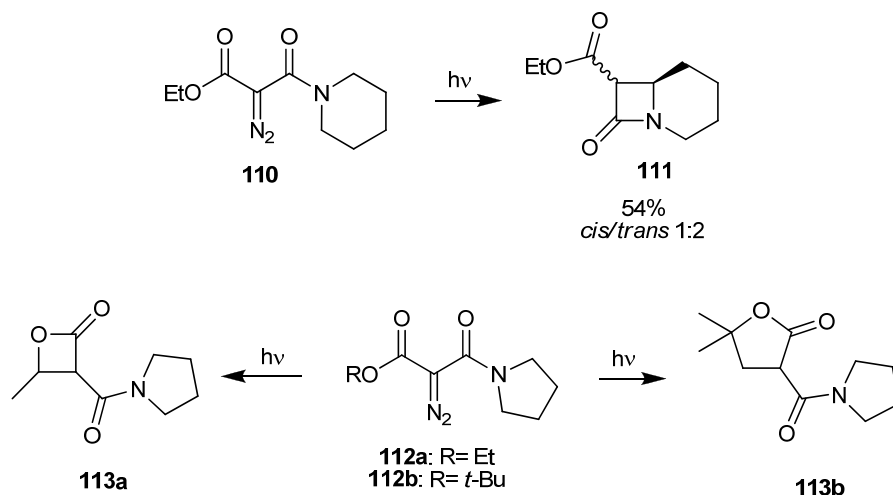
Based on the assumption that at low temperatures the triplet state of the carbene is favored, and together with several examples where increased yields of C-H insertion products were observed, a stepwise abstraction-recombination (a-r) mechanism was suggested for reactions performed in alcoholic<sup>96</sup> and alkenic<sup>97</sup> matrices for the phenyldiazomethane case and in alcoholic matrices for  $\alpha$ -diazobenzylphosphonates.[103,104] A matrix effect has been pointed as the decisive factor for the reactivity of the carbenic species. It was claimed that the singlet carbene could be formed on the matrix but, once restricted, it could decay to the triplet state at least as fast as it reacts with the matrix.[113] Latter, it was demonstrated that the increased yields of C-H insertion products on matrices were due to hydrogen atom tunneling rather than to the carbene multiplicity.[51,114] This means that in rigid matrices, triplet carbene abstracts the closest hydrogen atom without any selectivity and depending on its mobility on the matrix, O-H insertion or C-H insertion products should arise.[49,114] Based on this, Platz reported the C-H insertion of singlet phenylcarbene on cyclohexane and cyclohexene.[51]

Recently, Platz reported an ultrafast photolysis study of *p*-biphenyldiazoethane **63** (page 17) where the growth of singlet carbene was seen to accompany the decay of the diazo excited state. When the photolytic studies were performed on cyclohexane, C-H insertion products were detected and attributed to the reaction of an equilibrium mixture of singlet and triplet carbene since singlet carbenes relax faster to their lower energy triplet state than by reaction with cyclohexane.[84] This was seen to be different for the case of *p*-biphenyldiazotrifluoromethane **64** (page 17) where the highly electron withdrawing  $\text{CF}_3$  increased the electrophilicity of the singlet carbene and the C-H insertion was favored.[99] Similarly, the photolysis of 1-naphthylcarbene in cyclohexane led to the formation of C-H insertion product. The use of a 1:1 cyclohexane/cyclohexane- $d_{12}$  mixture as solvent resulted in the formation of C-H insertion products **109- $d_0$**  and **109- $d_{12}$**  while crossover products were not detected (Scheme 40). According to this, the authors claimed that a concerted mechanism was the responsible for such reaction, presumably through direct insertion of the singlet state carbene [115].



Scheme 40

The first example of a photolytic assisted intramolecular C-H insertion of  $\alpha$ -diazo amides was reported by Corey and Felix[116] in the synthesis of methyl 6-phenylpenicillanate. Later, Lowe and Parker[117] observed that photodecomposition of *N*-[(ethoxycarbonyl)diazoacetyl]piperidine **110** in carbon tetrachloride yielded the correspondent  $\beta$ -lactam **111** derived from C-H insertion in the  $\alpha$ -carbon of the piperidine unit while the use of *N*-[(ethoxycarbonyl)diazoacetyl]pyrrolidine **112a** and *N*-[(*tert*-butylcarbonyl)diazoacetyl]pyrrolidine **112b** afforded the correspondent  $\beta$ -lactone **113a**, and respectively  $\gamma$ -lactone **113b**, as a result of C-H insertion in the ester alkyl chain (Scheme 41).



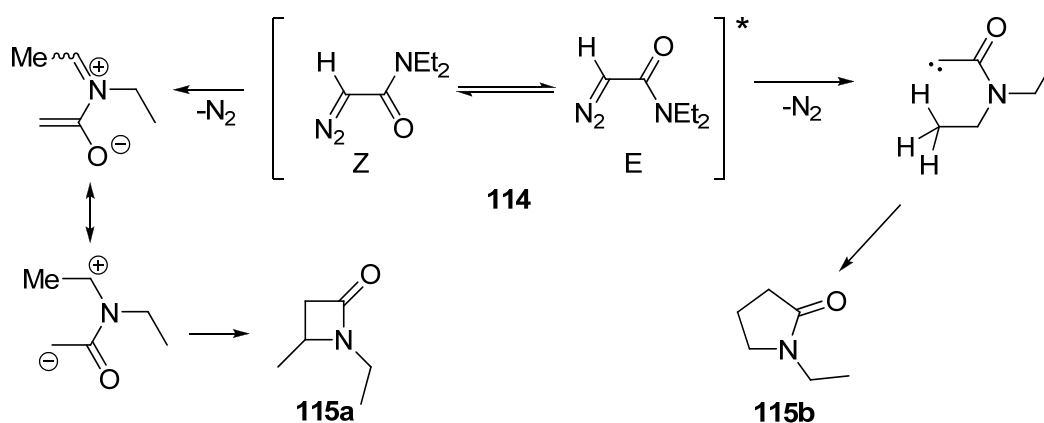
**Scheme 41**

$\alpha$ -Diazo ester decomposition was also experimentally investigated in order to obtain the correspondent lactone. However, due to the lack of proximity between the *O*-alkyl moiety and the reactive intermediate, intermolecular reactions were seen to be preferred. For instance, the decomposition of allyl diazoacetate in cyclohexane leads to the single formation of allyl cyclohexylacetate,[118] and the decomposition of *tert*-butyl diazoacetate yields *tert*-butyl cyclohexylacetate preferentially and only 9.5% of the desired lactone.[119] In contrast, Rando observed that photolytic decomposition of *N,N*-diethyldiazoacetamide in dioxane, originated the intramolecular C-H insertion products  $\beta$ - and  $\gamma$ -lactams (**115a**, **115b**) in 57% and 43% yield, respectively.[106,120] However, the use of protic solvents such as methanol had led to the formation of Wolff rearrangement and O-H insertion products and consequently a considerable decrease in the formation of  $\gamma$ -lactam. At this point, an analogy was made with the prior results on the photolysis of ethyl diazoacetate in methanol[74] and in *iso*-propanol[76] in which intermolecular C-H insertion products were suppressed. Due to these observations, it was assumed that the formation of the two lactams should arise from different pathways, in which the  $\beta$ -lactam transition state originates a greater charge separation. Based on these findings, the authors claimed that C-H insertion would be circumvented as long as there was water in the aliphatic site vicinity, and the  $\gamma$ - /  $\beta$ -lactam ratio in non-polar solvents should be governed by statistics.

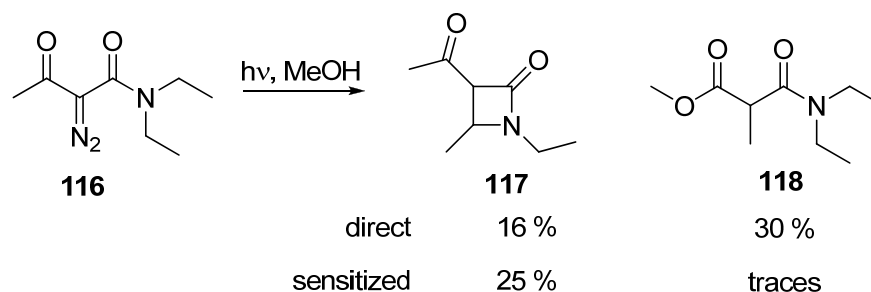
Later, Tomioka *et al.*[121,122] claimed that the intramolecular C-H insertion process in the decomposition of *N,N*-diethyldiazoacetamide could proceed through singlet carbene or singlet excited-state diazo compound. The authors suggested that the excited singlet state of *N,N*-diethyldiazoacetamide could give rise to the  $\beta$ -lactam and the Wolff rearrangement product directly or through the dissociation to nitrogen and singlet carbene. This singlet carbene could subsequently undergo C-H insertion into the C-H bonds of the methyl group to give the correspondent  $\gamma$ -lactam **115b**. Considering two possible conformational isomers of the diazoacetamide, in which the carbonyl lays *cis* (*Z*) or *trans* (*E*) to the diazo moiety, the authors reasonably assumed that there are equal populations of both forms. Taking in consideration the reported study on the rotation of internal carbon-carbon bonds of diazo-ketones,[123] the *Z* form of the singlet excited state of the diazo compound was indicated as responsible for the formation of the  $\beta$ -lactam and Wolff rearrangement product, while the *E* form was responsible for the formation of the  $\gamma$ -lactam (*via* direct "perpendicular" insertion) and the O-H insertion products (Scheme 42).[121,122] This way, the different  $\beta/\gamma$  ratios in different solvents, was attributed to the solvent influence on the *E/Z* ratio populations.

The diazo substituents were also studied and compared and a strong effect was noticed. For instance, while in the case of *N,N*-diethyldiazoacetamide (**114**) the triplet carbene was discarded as a possible intermediate, the introduction of an acetyl group as a substituent (**116**) led to the exclusive formation of  $\beta$ -lactam **117** upon

sensitised irradiation. This way, the authors suggested that such product would be formed *via* a triplet free carbene (a-r mechanism) that could be stabilized by the neighbouring carbonyl groups (Scheme 43).[122]



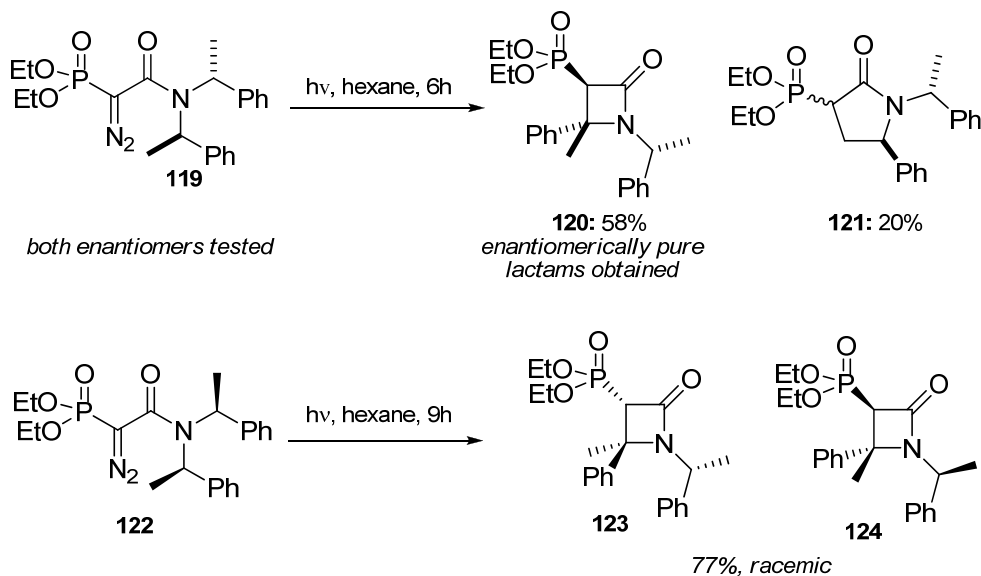
**Scheme 42**



**Scheme 43**

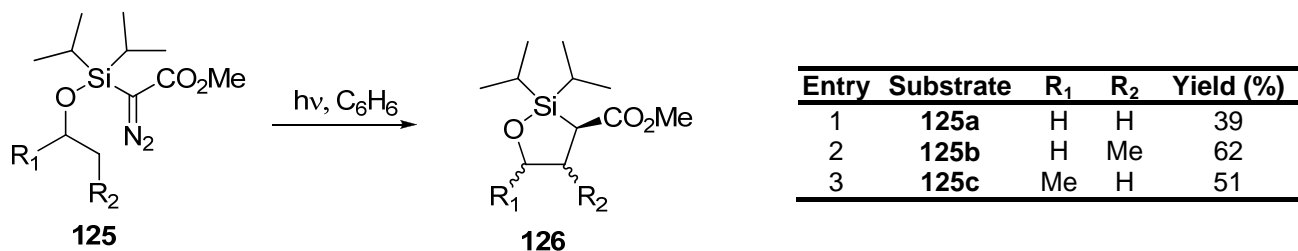
Recently, this laboratory reported the photolytic decomposition of several  $\alpha$ -diazoacetamides in hexane, water and a film. Diethoxyphosphoryl and carboethoxy as  $\alpha$ -carbonyl substituents were used and the corresponding  $\beta$ - and  $\gamma$ -lactams were obtained in reasonable yields and good diastereoselectivities in several cases. Even in water, O-H insertion products were not observed in most cases. The comparison of the photolysis obtained results with dirhodium(II) catalyzed C-H insertion was made and, in some of the cases, better regioselectivities were obtained after photolysis. A mechanism based on triplet free carbene, particularly the abstraction-recombination mechanism, was discarded based on a stereospecific C-H insertion. The two enantiomers (**119**) and *meso* compound (**122**) of a chiral  $\alpha$ -diethoxyphosphoryl- $\alpha$ -diazoacetamide were submitted to photolytic decomposition and the formation of  $\beta$ -lactams with absolute retention of configuration certified the absence of a triplet carbene (Scheme 44).[124]





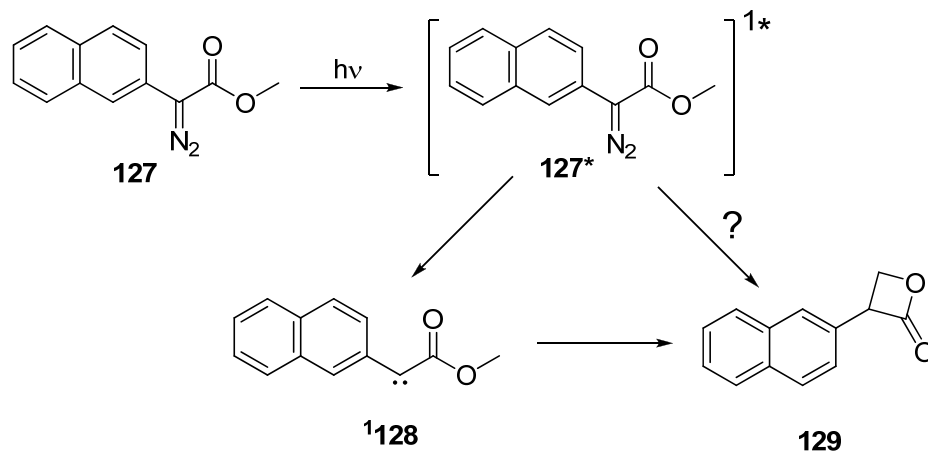
**Scheme 44**

Without any focus on the mechanistic aspects,  $\alpha$ -(alkoxysilyl)- $\alpha$ -diazoacetates **125** were reported to react under photolytic irradiation in benzene to yield tetrahydro-1,2-oxasiloles **126** by intramolecular C-H insertion. Reasonable yields were only obtained when the stationary concentration of the diazo compound was achieved and 254 nm monochromatic light used as irradiation source (Scheme 45).[125]



**Scheme 45**

Recently, an intramolecular C-H insertion mechanism based on a free carbene for the formation of  $\beta$ -lactone **129** was proposed. According to the authors, the laser flash photolysis results, where the rate of  $\beta$ -lactone **129** growth was observed to be approximately the same as the rate of carbene **128** decay, suggested that the lactone should be formed entirely from the singlet free carbene **128** with very little, if any, contribution from the diazo excited state **127\*** (Scheme 46).[63]

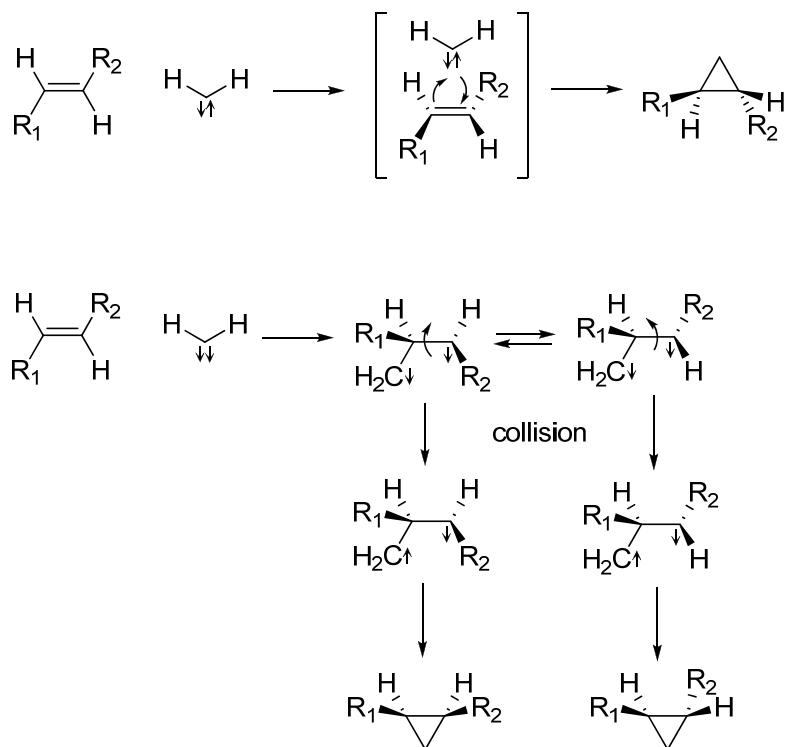


Scheme 46

In accordance with the observations of Rando,[106,120] Thornton *et al.*[126] obtained the intermolecular C-H and O-H insertion products when three examples of  $\alpha$ -diazo acetamides (**82-84**, page 19) were decomposed by photolysis. Through the decomposition of these compounds in binary mixtures of solvents (*t*-butyl alcohol/cyclohexane; *t*-butyl alcohol/water) a general preference towards O-H insertion was observed. By comparing the results of **84** with those of alkyl diazoacetates,[127] the authors claimed that the electronic influence of the carboxamide substituent increases the yield of the O-H insertion product when compared with the ester group.

## 8. CYCLOPROPANATION

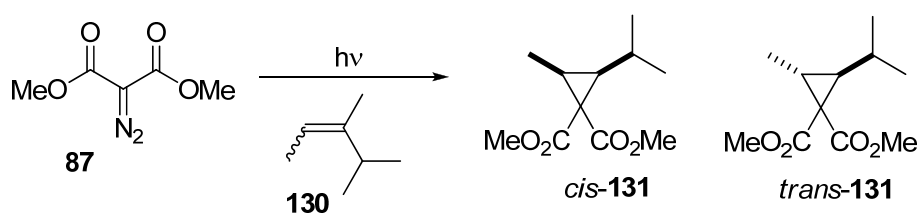
An early report on the C-C insertion reaction with carbenes was made by Doering in the mid 50's. At this time, the carbene was formed by reaction with chloroform with potassium *tert*-butoxide which was further reacted with cyclohexene to yield the fused ring product.[128] Right after, Skell and Doering observed that the addition of  $\text{CBr}_2$  and  $\text{CH}_2$  carbenes to *cis*- or *trans*-butene occurred in a *cis*-stereospecific manner, keeping the *cis* relationship of the alkene on the product.[25,129,130] This effect has been used as a synthetic valuable tool and also as a precious tool for the mechanistic considerations. It is widely known that in reactions where a carbenic species is involved its multiplicity state will be reflected on the product stereochemistry. Hence, the formation of a cyclopropane ring maintaining the same spatial arrangement of the olefinic starting material indicates the singlet carbene as the reactive species whereas the triplet carbene should lead to the indiscernible formation of both cyclopropane *cis* and *trans* isomers (Scheme 47). This phenomena can be explained by the fact that whereas  $p$ - $\pi$  and  $sp^2$ - $\pi^*$  orbitals of the singlet carbene overlap synchronously with the alkene, or one rapidly succeeds the other, in the case of the triplet carbene the same cannot happen. The two unpaired electrons cannot form a covalent bond as they have parallel spins hence, after the formation of the first C-C bond due to reaction of one electron with the double bond, one of the electrons has to invert its spin, by collision, and at this stage the biradical species can rotate itself around the C-C bond destroying the possibility of a stereospecific formation of the cyclopropane ring to occur.[20-22,131]



**Scheme 47**

Concerning  $\alpha$ -diazo carbonyl compounds reactions with alkenes, methyl diazomalonate irradiation was studied and the products stereochemistry analyzed. A very good example of what was previously described about the isomeric distribution of the cyclopropanes products can be here observed. The direct and sensitized irradiation of methyl diazomalonate **87** in the presence of *Z*-4-methyl-2-pentene **130** leads to a strong inversion of the isomeric distribution (Scheme 48). Since the *trans*-cyclopropane ring **131** is thermodynamically more stable than its *cis*-counterpart, it is expected that the free rotation around the C-C bond in the species intervenient in a triplet carbene mechanism dictates the preferential formation of such product. In fact, this has been observed for this case where the *cis* product **131** was preferentially formed in the direct irradiation and the *trans* cyclopropane ring was formed at higher extent in the photosensitized experiment. When hexafluorobenzene was used in an attempt to induce ISC, for the *Z* olefin, the authors pointed the diazo excited state as a possible intervenient species since the *cis*-cyclopropane product yield slightly increased at low concentrations of hexafluorobenzene.[111] This aspect was later referred by Platz in a LFP study, however it was not possible to reach to a solid conclusion due to the invisible character of such species.[38]

A more pronounced example that demonstrates the very different reactivity of singlet and triplet carbenes was observed for the case of diazo Meldrum's acid where no cyclopropanation products were observed upon direct irradiation but under photosensitized conditions these were the main products with an isomeric distribution very close to the expected.[111]

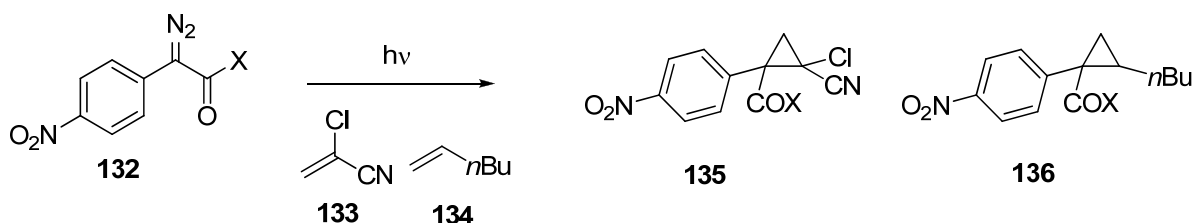


Olefin	Conditions	% <i>cis</i>	% <i>trans</i>
--------	------------	--------------	----------------

Z	direct hv	92	8
Z	hv, Ph <sub>2</sub> CO	10	90
E	direct hv	10	90
E	hv, Ph <sub>2</sub> CO	14	86

Scheme 48

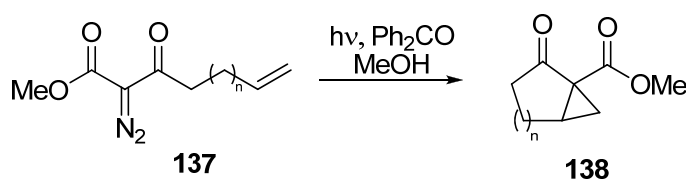
Tomioka reported on the neighboring group participation on the carbene reactivity and “philicity”, since any carbene can show both electrophilic and nucleophilic characteristics depending on the nature of reagents with which the carbene reacts.[40,132] For this, nitrophenyl  $\alpha$ -diazo esters derivatives **132a-c** were photolytic decomposed at low temperatures in a mixture of 2-methyl-but-2-ene **134** and chloroacrylonitrile **133**. A strong relation between the carbene philicity and the  $\alpha$ -substituent was demonstrated as in the carboxylate case **132c** the carbene reaction with the simple alkene **133** was totally suppressed (Scheme 49).[40]



Entry	Substrate	X	Yield (%)	
			135	136
1	<b>132a</b>	OMe	55	43
2	<b>132b</b>	OH	43	48
3	<b>132c</b>	O <sup>-</sup>	79	-

Scheme 49

An example of the conformational effects over the triplet carbene, together with the influence of substituents directly attached to the carbene was reported. It was observed that while triplet 2-alkylarylcarbenes tend to abstract hydrogen atoms from  $\delta$ - or  $\epsilon$ -C-H bonds, triplet carbonylcarbenes **137** tend to react intramolecularly with double bonds to generate five- and six-membered rings **138**, and the singlet carbene leads to the formation of the Wolff rearrangement product. According to the authors, in the majority of the cases, the lifetimes of carbonylcarbenes are controlled by the rate of spin inversion rather than by the reactivity of the triplet ground state.[23]



Entry	Substrate	n	138 Yield (%)
1	<b>137a</b>	1	88
2	<b>137b</b>	2	83
3	<b>137c</b>	3	20

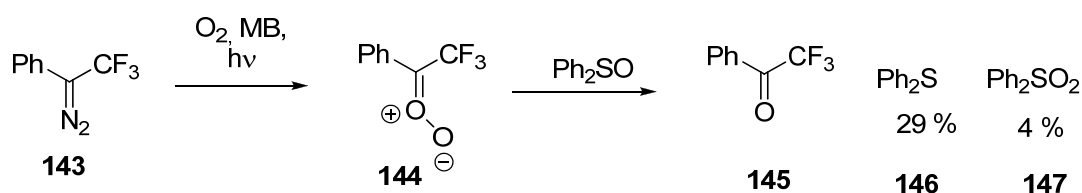
Scheme 50

This last reaction was studied as model to test the efficiency of a new triplet sensitizer.[24] 2,2',4,4'-Tetramethoxybenzophenone (TBMP-**139**) was successfully applied as triplet photocatalyst. This new sensitizer was developed as an alternative to benzophenone since triplet species can abstract hydrogens from the solvent resulting in the photosensitizer transformation into benzophenone-derived alcohols and pinacolols. Moreover the existence of diazoalkane transitions at longer wavelengths than those of benzophenone were also covered by this new triplet photosensitizer.[24]



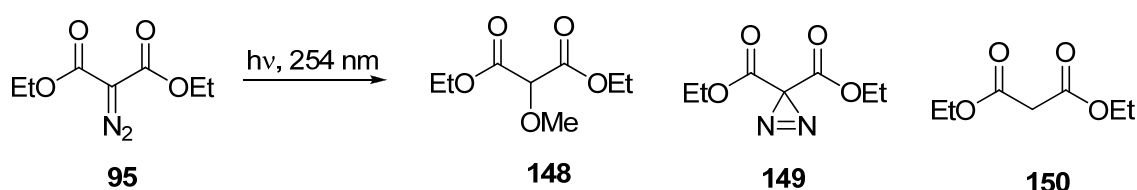
singlet oxygen oxidation of diazo compounds in which a singlet oxygen sensitizer such as methylene blue is employed. By this way, the singlet oxygen generation and its reaction with singlet carbene have been explored.

Similarly to the reaction of phenyldiazomethanes with singlet oxygen to the formation of ketones,[137]  $\alpha$ -diazo-trifluoroacetophenone **143** has been oxidized with singlet oxygen, produced by the use of methylene blue (MB) as sensitizer, where it was exemplified that the use of such sensitizer is crucial to achieve good chemoselectivities. Furthermore, the solvent choice has also observed to be of pivotal importance in the case where no sensitizers are used. While the reaction between the carbene, *via* direct irradiation of the reaction mixture containing molecular oxygen, led to the formation of a complex mixture of products in benzene or acetonitrile where carbonyl compound was not detected, when Freon-113 was used, the ketone **145** was formed in 90 % yield due to the longest carbene lifetime. The use of methylene blue allowed the formation of carbonyl oxide **144** that was further reacted with sulfoxides to yield sulfides **146** (Scheme 53), as also the formation of styrene oxide in 9 % from reaction with styrene.[138]



## 10. HYDROGEN ABSTRACTION

Due to the biradicaloid nature of triplet carbenes, double hydrogen abstraction products usually arise in diazo photolysis.[20,57] However, this process leads to the formation of non-functionalized hydrocarbons and has little or no value in synthetic chemistry. A very good example regarding the nature of the intervenient species is the photosensitized decomposition with monochromatic light of  $\alpha$ -diazo ethyl malonate **95** where only double hydrogen abstraction product **150** was formed in isopropanol while the direct monochromatic irradiation in methanol resulted mostly in the formation of corresponding ether **148** together with some diazirine **149** from isomerization of the diazo compound (Scheme 54).[60] Depending on the ground state of the carbene, these kind of products can arise also under direct irradiation as in the case of bis(toluenesulfonyl)diazomethane where in methanol the double hydrogen abstraction product can be formed in 90 % yield.[112]



Entry	Conditions	Selectivity		
		148	149	150
1	MeOH, direct	0.9	0.1	>0.01
2	<i>i</i> -PrOH, Ph <sub>2</sub> CO	0	0	1

**Scheme 54**

## 11. Conclusions

From all the photolytic decomposition of diazo compounds reported on the open literature, Wolff rearrangement reaction is the mostly used on organic synthesis. Probably this is the main reason why so many researches have been made in what concerns the reaction mechanism. However, for other reactions mechanism, in particular C-H insertion, much still needs to be done in order to clarify the nature of all intervenient species. Reactions with molecular oxygen and double hydrogen abstraction continue to be seen as undesired reactions in a synthetic point of view. However, reactions with singlet oxygen start to be very attractive as a way to introduce a new functional group in the molecule. Concerning cyclopropanation reaction and 1,2-R shifts, the reaction mechanisms are now determined for several diazo compounds, while O-H insertion mechanism seems to need further investigation.

With the recent advances of ultra flash photolysis, it is expected that these unclarified topics will attract the attention by the physical organic chemists and new developments will arise in the upcoming years.

### Acknowledgements:

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### 12. References

- [1] Wee, A. G. H. Rhodium(II)-catalyzed reaction of diazocompounds in the service of organic synthesis of natural and non-natural products. *Curr. Org. Synth.* **2006**, 3(4), 499-555.
- [2] Davies, H. M. L.; Loe, O. Intermolecular C-H insertions of donor/acceptor-substituted rhodium carbenoids: A practical solution for catalytic enantioselective C-H activation. *Synthesis* **2004**(16), 2595-2608.
- [3] Ye, T.; McKervey, M. A. Organic-Synthesis With  $\alpha$ -Diazocarbonyl Compounds. *Chem. Rev.* **1994**, 94(4), 1091-1160.
- [4] Gois, P. M. P.; Afonso, C. A. M. Stereo- and regiocontrol in the formation of lactams by rhodium-carbenoid C-H insertion of  $\alpha$ -diazacetamides. *Eur. J. Org. Chem.* **2004**(18), 3773-3788.
- [5] Davies, H. M. L.; Nikolai, J. Catalytic and enantioselective allylic C-H activation with donor-acceptor-substituted carbenoids. *Org. Biomol. Chem.* **2005**, 3(23), 4176-4187.
- [6] Im, C. Y.; Okuyama, T.; Sugimura, T. Stereoselective Formation of a Chiral Ether by Intramolecular O-H Insertion Reaction of a Metal Carbenoid Generated from Diazoacetoacetate. *Eur. J. Org. Chem.* **2008**, 2008(2), 285-294.
- [7] Davies, J. R.; Kane, P. D.; Moody, C. J. N-H insertion reactions of rhodium carbenoids. Part 5: A convenient route to 1,3-azoles. *Tetrahedron* **2004**, 60(18), 3967-3977.
- [8] Bulugahapitiya, P.; Landais, Y.; Parra-Rapado, L.; Planchenault, D.; Weber, V. A stereospecific access to allylic systems using rhodium(II)-vinyl carbenoid insertion into Si-H, O-H, and N-H bonds. *J. Org. Chem.* **1997**, 62(6), 1630-1641.
- [9] Padwa, A.; Hornbuckle, S. F. Ylide Formation From The Reaction Of Carbenes And Carbenoids With Heteroatom Lone Pairs. *Chem. Rev.* **1991**, 91(3), 263-309.
- [10] DeAngelis, A.; Panne, P.; Yap, G. P. A.; Fox, J. M. Rh-Catalyzed Formation of Dioxolanes from  $\alpha$ -Alkyl Diazoesters: Diastereoselective Cycloadditions of Carbonyl Ylides with Selectivity over  $\beta$ -Hydride Elimination. *J. Org. Chem.* **2008**, 73(4), 1435-1439.
- [11] Davies, H. M. L. Recent Advances in Catalytic Enantioselective Intermolecular C-H Functionalization. *Angew. Chem. Int. Edit.* **2006**, 45(39), 6422-6425.
- [12] Curtius, T. *Ber. Dtsch. Chem. Ges.* **1883**, 16, 2230.
- [13] Linder, M. R.; Steurer, S.; Podlech, J. (S)-3-(tert-BUTYLOXYCARBONYLAMINO)-4-PHENYLBUTANOIC ACID *Org. Syn.* **2002**, 79, 154.
- [14] Day, A. C.; Raymond, P.; Southam, R. M.; Whiting, M. C. Preparation of secondary aliphatic diazo-compounds from hydrazones. *J. Chem. Soc. C Org.* **1966**(4), 467-469.
- [15] Ferreira, V. F.; Pereira, L. O. R.; de Souza, M.; Cunha, A. C. alpha-diazo carbonyl compounds: An attractive strategy in organic synthesis. *Quim. Nova* **2001**, 24(4), 540-553.
- [16] Jin, T.; Yamamoto, Y. An efficient, facile, and general synthesis of 1H-indazoles by 1,3-dipolar cycloaddition of arynes with diazomethane derivatives. *Angew. Chem. Int. Edit.* **2007**, 46(18), 3323-3325.

- [17] Liu, Z. J.; Shi, F.; Martinez, P. D. G.; Raminelli, C.; Larock, R. C. Synthesis of indazoles by the [3+2] cycloaddition of diazo compounds with arynes and subsequent acyl migration. *J. Org. Chem.* **2008**, *73*, 219-226.
- [18] Qi, X. B.; Ready, J. M. Copper-promoted cycloaddition of diazocarbonyl compounds and acetylides. *Angew. Chem. Int. Edit.* **2007**, *46*(18), 3242-3244.
- [19] Bunse, M.; Jodicke, D.; Kirmse, W. Free radical pathways in the nitrous-acid deamination of  $\alpha$ -aminonitriles. *J. Chem. Soc. Chem. Commun.* **1992**(1), 47-49.
- [20] Smith, M. B.; March, J. *Advanced organic chemistry: reactions, mechanisms, and structure*; 5th ed.; Wiley: New York, 2001.
- [21] Zollinger, H. *Diazo chemistry II: aliphatic, inorganic, and organometallic compounds*; VCH: Weinheim ; New York, 1995.
- [22] Coyle, J. D. *Introduction to organic photochemistry*; Wiley: New York, 1986.
- [23] Fien, J.; Kirmse, W. Intramolecular reactivity of triplet carbonylcarbenes. *Angew. Chem. Int. Edit.* **1998**, *37*(16), 2232-2234.
- [24] Pastor-Perez, L.; Wiebe, C.; Perez-Prieto, J.; Stiriba, S. E. A tetramethoxybenzophenone as efficient triplet photocatalyst for the transformation of diazo compounds. *J. Org. Chem.* **2007**, *72*(4), 1541-1544.
- [25] Skell, P. S.; Woodworth, R. C. Structure of carbene, CH<sub>2</sub>. *J. Am. Chem. Soc.* **1956**, *78*(17), 4496-4497.
- [26] McKellar, A. R. W.; Bunker, P. R.; Sears, T. J.; Evenson, K. M.; Saykally, R. J.; Langhoff, S. R. Far infrared-laser magnetic-resonance of singlet methylene - singlet triplet perturbations, singlet triplet transitions, and the singlet triplet splitting. *J. Chem. Phys.* **1983**, *79*(11), 5251-5264.
- [27] Khodabandeh, S.; Carter, E. A. Methyl substitution in carbenes: lack of steric or hyperconjugative stabilization effects on the ethylidene singlet-triplet splitting. *J. Phys. Chem.* **1993**, *97*(17), 4360-4364.
- [28] Modarelli, D. A.; Morgan, S.; Platz, M. S. Carbene formation, hydrogen migration, and fluorescence in the excited states of dialkyldiazirines. *J. Am. Chem. Soc.* **1992**, *114*(18), 7034-7041.
- [29] Richards, C. A.; Kim, S.-J.; Yamaguchi, Y.; Schaefer, H. F. Dimethylcarbene: A Singlet Ground State? *J. Am. Chem. Soc.* **1995**, *117*(40), 10104-10107.
- [30] Matzinger, S.; Fulscher, M. P. Methyl substitution in carbenes - A theoretical prediction of the singlet-triplet energy separation of dimethylcarbene. *J. Phys. Chem.* **1995**, *99*(27), 10747-10751.
- [31] Irikura, K. K.; Goddard, W. A.; Beauchamp, J. L. Singlet-triplet gaps in substituted carbenes CXY (X, Y = H, fluoro, chloro, bromo, iodo, silyl). *J. Am. Chem. Soc.* **1992**, *114*(1), 48-51.
- [32] Bauschlicher, C. W.; Schaefer, H. F.; Bagus, P. S. Structure and energetics of simple carbenes methylene, fluoromethylene, chloromethylene, bromomethylene, difluoromethylene, and dichloromethylene. *J. Am. Chem. Soc.* **1977**, *99*(22), 7106-7110.
- [33] Harrison, J. F.; Liedtke, R. C.; Liebman, J. F. The multiplicity of substituted acyclic carbenes and related molecules. *J. Am. Chem. Soc.* **1979**, *101*(24), 7162-7168.
- [34] Bourissou, D.; Guerret, O.; Gabbai, F. P.; Bertrand, G. Stable Carbenes. *Chem. Rev.* **2000**, *100*(1), 39-92.
- [35] Baird, N. C.; Taylor, K. F. Multiplicity of the ground state and magnitude of the T1-S0 gap in substituted carbenes. *J. Am. Chem. Soc.* **1978**, *100*(5), 1333-1338.
- [36] Hoffmann, R.; Zeiss, G. D.; Van Dine, G. W. The electronic structure of methylenes. *J. Am. Chem. Soc.* **1968**, *90*(6), 1485-1499.
- [37] Geise, C. M.; Hadad, C. M. Computational Study of the Electronic Structure of Substituted Phenylcarbene in the Gas Phase. *J. Org. Chem.* **2000**, *65*(24), 8348-8356.
- [38] Wang, J.-L.; Toscano, J. P.; Platz, M. S.; Nikolaev, V.; Popik, V. Dicarbomethoxycarbene. A Laser Flash Photolysis Study. *J. Am. Chem. Soc.* **1995**, *117*(20), 5477-5483.
- [39] Lowry, T. H.; Richardson, K. S. *Mechanism and theory in organic chemistry*; 3rd ed.; Harper & Row: New York, 1987.
- [40] Tomioka, H.; Hirai, K.; Tabayashi, K.; Murata, S.; Izawa, Y.; Inagaki, S.; Okajima, T. Neighboring Group Participation In Carbene Chemistry - Effect Of Neighboring Carboxylate Group On Carbene Reactivities. *J. Am. Chem. Soc.* **1990**, *112*(21), 7692-7702.
- [41] Scott, A. P.; Platz, M. S.; Radom, L. Singlet-Triplet Splittings and Barriers to Wolff Rearrangement for Carbonyl Carbenes. *J. Am. Chem. Soc.* **2001**, *123*(25), 6069-6076.
- [42] Von E. Doering, W.; Knox, L. H. Comparative Reactivity of Methylene, Carbomethoxycarbene and Bis-carboethoxycarbene toward the Saturated Carbon-Hydrogen Bond. *J. Am. Chem. Soc.* **1961**, *83*(8), 1989-1992.
- [43] Langan, J. G.; Sitzmann, E. V.; Eisenthal, K. B. Picosecond laser studies on the effect of structure and environment on intersystem crossing in aromatic carbenes. *Chem. Phys. Lett.* **1984**, *110*(5), 521-527.
- [44] Sitzmann, E. V.; Langan, J.; Eisenthal, K. B. Intermolecular effects on intersystem crossing studied on the picosecond timescale: the solvent polarity effect on the rate of singlet-to-triplet intersystem crossing of diphenylcarbene. *J. Am. Chem. Soc.* **1984**, *106*(6), 1868-1869.
- [45] Wang, Y.; Hadad, C. M.; Toscano, J. P. Solvent Dependence of the 2-Naphthyl(carbomethoxy)carbene Singlet-Triplet Energy Gap. *J. Am. Chem. Soc.* **2002**, *124*(8), 1761-1767.



- [46] Geise, C. M.; Wang, Y.; Mykhaylova, O.; Frink, B. T.; Toscano, J. P.; Hadad, C. M. Computational and Experimental Studies of the Effect of Substituents on the Singlet-Triplet Energy Gap in Phenyl(carbomethoxy)carbene. *J. Org. Chem.* **2002**, *67*(9), 3079-3088.
- [47] Wypych, G. *Handbook of solvents*; ChemTec: Toronto, 2001.
- [48] Tomioka, H.; Hirai, K. Effect Of The Phosphonate Group On The Reactivity Of Carbenes - Neighboring Phosphonate Group Participation. *J. Chem. Soc. Chem. Commun.* **1989**(6), 362-364.
- [49] Wright, B. B.; Platz, M. S. Chemistry and kinetics of aryl carbenes in methanol at low temperatures. *J. Am. Chem. Soc.* **1984**, *106*(15), 4175-4180.
- [50] Bodor, N.; Dewar, M. J. S.; Wasson, J. S. Ground states of molecules. XIX. Carbene and its reactions. *J. Am. Chem. Soc.* **1972**, *94*(26), 9095-9102.
- [51] Savino, T. G.; Kanakarajan, K.; Platz, M. S. Unusual temperature-dependent isotope effects in the reactions of phenylcarbene with cyclohexene and cyclohexane. *J. Org. Chem.* **1986**, *51*(8), 1305-1309.
- [52] Tomioka, H.; Itoh, M.; Yamakawa, S.; Izawa, Y. The reactivity of carbene from photolysis of diazo-compounds towards carbon-hydrogen bonds - Effects of structure, temperature, and matrix on the insertion selectivity. *J. Chem. Soc. Perkin Trans. 2* **1980**(4), 603-609.
- [53] Ganzer, G. A.; Sheridan, R. S.; Liu, M. T. H. Reaction of phenylchlorocarbene in oxygen-doped matrices. *J. Am. Chem. Soc.* **1986**, *108*(7), 1517-1520.
- [54] Fujiwara, Y.; Tanimoto, Y.; Itoh, M.; Hirai, K.; Tomioka, H. Laser Flash-photolysis studies of methoxycarbonyl phenyl carbene and its derived carbonyl oxide at room-temperature. *J. Am. Chem. Soc.* **1987**, *109*(7), 1942-1946.
- [55] Chiang, Y.; Kresge, A. J.; Pruszyński, P.; Schepp, N. P.; Wirz, J. The Mechanism Of Acylcarbene Insertion Into O-H Bonds - Direct Observation Of The Enol Of A Carboxylic-Acid Ester In Aqueous-Solution. *Angew. Chem. Int. Edit.* **1991**, *30*(10), 1366-1368.
- [56] Wolff, L. Ueber Diazoanhydride. *Justus Liebig's Annalen der Chemie* **1902**, *325*(2), 129-195.
- [57] Kirmse, W. 100 years of the Wolff rearrangement. *Eur. J. Org. Chem.* **2002**(14), 2193-2256.
- [58] Popik, V. V.; Nikolaev, V. A. Stereochemistry and thermal-stability of diazoketones. *J. Chem. Soc. Perkin Trans. 2* **1993**(10), 1791-1793.
- [59] Bogdanova, A.; Popik, V. V. Experimental and Theoretical Investigation of Reversible Interconversion, Thermal Reactions, and Wavelength-Dependent Photochemistry of Diazo Meldrum's Acid and Its Diazirine Isomer, 6,6-Dimethyl-5,7-dioxo-1,2-diaza-spiro[2,5]oct-1-ene-4,8-dione. *J. Am. Chem. Soc.* **2003**, *125*(46), 14153-14162.
- [60] Bogdanova, A.; Popik, V. V. Experimental and theoretical analysis of the photochemistry and thermal reactivity of ethyl diazomalonate and its diazirino isomer. The role of molecular geometry in the decomposition of diazocarbonyl compounds. *J. Am. Chem. Soc.* **2004**, *126*(36), 11293-11302.
- [61] Toscano, J. P.; Platz, M. S.; Nikolaev, V.; Popic, V. Carboethoxycarbene - A Laser Flash-Photolysis Study. *J. Am. Chem. Soc.* **1994**, *116*(18), 8146-8151.
- [62] Wang, J. L.; Likhovorik, I.; Platz, M. S. A Laser Flash Photolysis Study of 2-Naphthyl(carbomethoxy)carbene. *J. Am. Chem. Soc.* **1999**, *121*(12), 2883-2890.
- [63] Wang, Y. H.; Yuzawa, T.; Hamaguchi, H. O.; Toscano, J. P. Time-resolved IR studies of 2-naphthyl(carbomethoxy)carbene: Reactivity and direct experimental estimate of the singlet/triplet energy gap. *J. Am. Chem. Soc.* **1999**, *121*(12), 2875-2882.
- [64] Tomioka, H.; Okuno, H.; Izawa, Y. Mechanism Of The Photochemical Wolff Rearrangement - The Role Of Conformation In The Photolysis Of  $\alpha$ -Diazo Carbonyl-Compounds. *J. Org. Chem.* **1980**, *45*(26), 5278-5283.
- [65] Burdzinski, G. T.; Wang, J.; Gustafson, T. L.; Platz, M. S. Study of Concerted and Sequential Photochemical Wolff Rearrangement by Femtosecond UV-vis and IR Spectroscopy. *J. Am. Chem. Soc.* **2008**, *130*(12), 3746-3747.
- [66] Ortica, F.; Pohlers, G.; Scaiano, J. C.; Cameron, J. F.; Zampini, A. Laser flash photolysis of 2-diazo-1,3-diphenyl-1,3-propanedione: An unusual long-lived triplet as a reaction intermediate. *Org. Lett.* **2000**, *2*(10), 1357-1360.
- [67] McMahon, R. J.; Chapman, O. L.; Hayes, R. A.; Hess, T. C.; Krimmer, H. P. Mechanistic studies on the Wolff rearrangement: the chemistry and spectroscopy of some  $\alpha$ -keto carbenes. *J. Am. Chem. Soc.* **1985**, *107*(25), 7597-7606.
- [68] Wang, J.; Burdzinski, G.; Kubicki, J.; Gustafson, T. L.; Platz, M. S. Ultrafast Carbene - Carbene Isomerization. *J. Am. Chem. Soc.* **2008**, *130*(16), 5418-5419.
- [69] Wang, J.; Burdzinski, G.; Kubicki, J.; Platz, M. S. Ultrafast UV-Vis and IR Studies of p-Biphenyl Acetyl and Carbomethoxy Carbenes. *J. Am. Chem. Soc.* **2008**, *130*(33), 11195-11209.
- [70] Kaplan, F.; Meloy, G. K. Structure of Diazoketones. A Study of Hindered Internal Rotation. *J. Am. Chem. Soc.* **1966**, *88*(5), 950-956.
- [71] Zeller, K. P.; Blocher, A.; Haiss, P. Oxirene participation in the photochemical Wolff rearrangement. *Mini-Rev. Org. Chem.* **2004**, *1*(3), 291-308.
- [72] Haiss, P.; Zeller, K. P. The photochemical Wolff rearrangement of 3-diazo-1,1,1-trifluoro-2-oxopropane revisited. *Org. Biomol. Chem.* **2003**, *1*(14), 2556-2558.

- [73] Zeller, K. P.; Muller, E.; Meier, H. Studies on Wolff rearrangement. 2. Migration ability of hydrogen and methyl and aryl groups. *Tetrahedron* **1972**, *28*(23), 5831-5838.
- [74] Chaimovich, H.; Vaughan, R. J.; Westheimer, F. H. Rearrangement Accompanying Photolysis of Diazoacyl Esters. *J. Am. Chem. Soc.* **1968**, *90*(15), 4088-4093.
- [75] Dominh, T.; Strausz, O. P.; Gunning, H. E. Photochemistry of Diazo Esters. 2.a Novel Reaction Path. *J. Am. Chem. Soc.* **1969**, *91*(5), 1261-1263.
- [76] Strausz, O. P.; Dominh, T.; Gunning, H. E. Rearrangement and Polar Reaction of Carboethoxymethylene in 2-Propanol. *J. Am. Chem. Soc.* **1968**, *90*(6), 1660-1661.
- [77] Tomioka, H.; Okuno, H.; Izawa, Y. Carbenes In A Rigid Matrix - Substituent Effects On The Temperature-Dependence Of  $\alpha$ -Carbonylcarbene Reactions. *J. Chem. Soc. Perkin Trans. 2* **1980**(11), 1636-1641.
- [78] Liao, M.; Dong, S.; Deng, G.; Wang, J. Synthesis of oxygen-containing heterocyclic compounds based on the intramolecular O-H insertion and Wolff rearrangement of  $\alpha$ -diazocarbonyl compounds. *Tetrahedron Lett.* **2006**, *47*(27), 4537-4540.
- [79] Tomioka, H.; Hayashi, N.; Sugiura, T.; Izawa, Y. Evidence For Protonation Of Typically Electrophilic Carbenes By Methanol. *J. Chem. Soc. Chem. Commun.* **1986**(17), 1364-1366.
- [80] Celebi, S.; Leyva, S.; Modarelli, D. A.; Platz, M. S. 1,2-Hydrogen migration and alkene formation in the photoexcited states of alkylphenyldiazomethanes. *J. Am. Chem. Soc.* **1993**, *115*(19), 8613-8620.
- [81] Shin, S. H.; Cizmeciyan, D.; Keating, A. E.; Khan, S. I.; Garcia-Garibay, M. A. Control of Carbene Reactivity by Crystals. A Highly Selective 1,2-H Shift in the Solid-to-Solid Reaction of 1-(4'-Biphenyl)-2-phenyldiazopropane to (Z)-1-(4'-Biphenyl)-2-phenylpropene. *J. Am. Chem. Soc.* **1997**, *119*(8), 1859-1868.
- [82] Garcia-Garibay, M. A. Reaction of arylcarbenes with methanol: triplet-state reactivity or spin-state equilibrium as a moving target? *J. Am. Chem. Soc.* **1993**, *115*(15), 7011-7012.
- [83] Wang, J.; Burdzinski, G.; Gustafson, T. L.; Platz, M. S. Ultrafast Study of *p*-Biphenyldiazomethane and *p*-Biphenylcarbene. *J. Org. Chem.* **2006**, *71*(16), 6221-6228.
- [84] Wang, J.; Burdzinski, G.; Gustafson, T. L.; Platz, M. S. Ultrafast Study of *p*-Biphenyldiazoethane. The Chemistry of the Diazo Excited State and the Relaxed Carbene. *J. Am. Chem. Soc.* **2007**, *129*(9), 2597-2606.
- [85] Sugiyama, M. H.; Celebi, S.; Platz, M. S. A significant barrier to 1,2-hydrogen migration in singlet 1-phenylethylidene. A laser flash photolysis study. *J. Am. Chem. Soc.* **1992**, *114*(3), 966-973.
- [86] Calvo-Losada, S.; Sordo, T. L.; Lopez-Herrera, F. J.; Quirante, J. J. The influence of protecting the hydroxyl group of  $\beta$ -oxy- $\alpha$ -diazo carbonyl compounds in the competition between Wolff rearrangement and [1,2]-hydrogen shift. Density functional theory study and topological analysis of the charge density. *Theor. Chem. Acc.* **2000**, *103*(5), 423-430.
- [87] Calvo-Losada, S.; Suarez, D.; Sordo, T. L.; Quirante, J. J. Competition between Wolff Rearrangement and 1,2-Hydrogen Shift in  $\beta$ -Oxy- $\alpha$ -ketocarbenes: Electrostatic and Specific Solvent Effects. *J. Phys. Chem. B* **1999**, *103*(34), 7145-7150.
- [88] Motschieder, K.; Gudmundsdottir, A.; Toscano, J. P.; Platz, M.; Garcia-Garibay, M. A. Excited Precursor Reactivity, Fast 1,2-H Shifts, and Diffusion-Controlled Methanol Insertion in 1,2-Diphenylalkylidenes. *J. Org. Chem.* **1999**, *64*(14), 5139-5147.
- [89] Nickon, A. New perspectives on carbene rearrangements: migratory aptitudes, bystander assistance, and geminal efficiency. *Acc. Chem. Res.* **1993**, *26*(3), 84-89.
- [90] Moss, R. A. Dynamics of intramolecular carbenic rearrangements. *Pure Appl. Chem.* **1995**, *67*(5), 741-747.
- [91] Liu, M. T. H.; Bonneau, R. Laser flash photolysis study of substituent effects on the rate of 1,2-H migration in a series of benzylchlorocarbenes. *J. Am. Chem. Soc.* **1992**, *114*(10), 3604-3607.
- [92] Evanseck, J. D.; Houk, K. N. Theoretical predictions of activation energies for 1,2-hydrogen shifts in singlet carbenes. *J. Phys. Chem.* **1990**, *94*(14), 5518-5523.
- [93] Reed, S. C.; Modarelli, D. A. Conformational effects on the excited state 1,2-hydrogen migration in alkyldiazomethanes. *Tetrahedron Lett.* **1996**, *37*(40), 7209-7212.
- [94] Moriconi, E. J.; Murray, J. J. Pyrolysis + Photolysis Of 1-Methyl-3-Diazoindole . Base Decomposition Of Isatin 2-Tosylhydrazone. *J. Org. Chem.* **1964**, *29*(12), 3577-3584.
- [95] Miller, D. J.; Moody, C. J. Synthetic Applications Of The O-H Insertion Reactions Of Carbenes And Carbenoids Derived From Diazocarbonyl And Related Diazo-Compounds. *Tetrahedron* **1995**, *51*(40), 10811-10843.
- [96] Kirmse, W.; Kilian, J.; Steenken, S. Carbenes and the oxygen-hydrogen bond: spectroscopic evidence for protonation of diarylcarbenes to give diarylcarbenium ions. *J. Am. Chem. Soc.* **1990**, *112*(17), 6399-6400.
- [97] Belt, S. T.; Bohne, C.; Charette, G.; Sugamori, S. E.; Scaiano, J. C. Carbocation formation via carbene protonation studied by the technique of stopped-flow laser-flash photolysis. *J. Am. Chem. Soc.* **1993**, *115*(6), 2200-2205.
- [98] Peon, J.; Polshakov, D.; Kohler, B. Solvent reorganization controls the rate of proton transfer from neat alcohol solvents to singlet diphenylcarbene. *J. Am. Chem. Soc.* **2002**, *124*(22), 6428-6438.
- [99] Wang, J.; Kubicki, J.; Gustafson, T. L.; Platz, M. S. The Dynamics of Carbene Solvation: An Ultrafast Study of *p*-Biphenyltrifluoromethylcarbene. *J. Am. Chem. Soc.* **2008**, *130*(7), 2304-2313.

- [100] Chiang, Y.; Kresge, A. J.; Popik, V. V.; Schepp, N. P. The mandelic acid keto-enol system in aqueous solution, generation of the enol by hydration of phenylhydroxyketene and phenylcarboxycarbene. *J. Am. Chem. Soc.* **1997**, *119*(42), 10203-10212.
- [101] Chiang, Y.; Jefferson, E. A.; Kresge, A. J.; Popik, V. V.; Xie, R. Q. Conjugate addition of water to  $\alpha$ -carbonylcarbenes. *J. Phys. Org. Chem.* **1998**, *11*(8-9), 610-613.
- [102] Schepp, N. P.; Wirz, J. Effect Of  $\alpha$ -Carbomethoxy Group On The Reactivity Of Benzyl Cations In Solution. *J. Am. Chem. Soc.* **1994**, *116*(26), 11749-11753.
- [103] Tomioka, H.; Inagaki, T.; Izawa, Y. Photolysis of  $\alpha$ -diazobenzylphosphonates in alcoholic matrices at 77K. *J. Chem. Soc. Chem. Commun.* **1976**(24), 1023-1024.
- [104] Tomioka, H.; Inagaki, T.; Nakamura, S.; Izawa, Y. Temperature-Dependence Of Product Distributions In The Photolysis Of  $\alpha$ -Diazobenzylphosphonates In Alcohols. *J. Chem. Soc. Perkin Trans. 1* **1979**(1), 130-134.
- [105] Tomioka, H.; Hirai, K. Neighboring Phosphonate Group Participation In Carbene Chemistry. *J. Chem. Soc. Chem. Commun.* **1990**(22), 1611-1612.
- [106] Rando, R. R. Conformational And Solvent Effects On Carbene Reactions. *J. Am. Chem. Soc.* **1970**, *92*(22), 6706-6707.
- [107] Wydila, J.; Thornton, E. R. Photolysis Studies Of  $\alpha$ -Diazoamides The Effect Of Carboxamide Substituents On Selectivity Ratios. *Tetrahedron Lett.* **1983**, *24*(3), 233-236.
- [108] Meerwein, H.; Rathjen, H.; Werner, H. Die Methylierung von RH-Verbindungen mittels Diazomethans unter Mitwirkung des Lichtes. *Ber. Dtsch. Chem. Ges.* **1942**, *75*(12), 1610-1622.
- [109] Doering, W. V. E.; Knox, L. H.; Jones, M. Reaction of Methylene with Diethyl Ether and Tetrahydrofuran. *J. Org. Chem.* **1959**, *24*(1), 136-137.
- [110] Tomioka, H.; Itoh, M.; Yamakawa, S.; Izawa, Y. The Reactivity of Carbenes from Photolysis of Diazo-Compounds Towards Carbon-Hydrogen Bonds - Effects of Structure, Temperature, and Matrix on the Insertion Selectivity. *J. Chem. Soc. Perkin Trans. 2* **1980**(4), 603-609.
- [111] Jones, M.; Ando, W.; Hendrick, M. E.; Kulczycki, A.; Howley, P. M.; Hummel, K. F.; Malament, D. S. Irradiation of methyl diazomalonate in solution. Reactions of singlet and triplet carbenes with carbon-carbon double bonds. *J. Am. Chem. Soc.* **1972**, *94*(21), 7469-7479.
- [112] Sander, W.; Strehl, A.; Winkler, M. Photochemistry of bis(sulfonyl)diazomethanes. *Eur. J. Org. Chem.* **2001**(20), 3771-3778.
- [113] Moss, R. A.; Dolling, U. H. Photolysis of phenyldiazomethane in olefinic matrices - chemistry of triplet phenylcarbene. *J. Am. Chem. Soc.* **1971**, *93*(4), 954-960.
- [114] Tomioka, H.; Ozaki, Y.; Izawa, Y. Mechanism of C-H insertion of carbene in rigid matrix. *Chem. Lett.* **1982**(6), 843-846.
- [115] Barcus, R. L.; Hadel, L. M.; Johnston, L. J.; Platz, M. S.; Savino, T. G.; Scaiano, J. C. 1-Naphthylcarbene: spectroscopy, kinetics, and mechanisms. *J. Am. Chem. Soc.* **1986**, *108*(14), 3928-3937.
- [116] Corey, E. J.; Felix, A. M. A New Synthetic Approach to Penicillins. *J. Am. Chem. Soc.* **1965**, *87*(11), 2518-2519.
- [117] Lowe, G.; Parker, J. Photochemical Conversion of  $\alpha$ -Diazo-Amides and  $\alpha$ -Diazo-Esters into  $\beta$ -Lactams and  $\beta$ -Lactones and  $\gamma$ -Lactones. *J. Chem. Soc. D Chem. Commun.* **1971**(11), 577-578.
- [118] Kirmse, W.; Dietrich, H. Zerfallsreaktionen des Diazoessigsäure-allylestere. *Chem. Ber.* **1965**, *98*(12), 4027-4032.
- [119] Kirmse, W.; Dietrich, H.; Bucking, H. W. Intramolekulare Reaktionen Von Alkoxy-carbonylcarbenen. *Tetrahedron Lett.* **1967**(19), 1833-1835.
- [120] Rando, R. R. Conformational and Medium Effects on Intramolecular Carbene Reactions. *J. Am. Chem. Soc.* **1972**, *94*(5), 1629-1631.
- [121] Tomioka, H.; Kitagawa, H.; Izawa, Y. Photolysis Of N,N-Diethyldiazoacetamide - Participation Of A Non-Carbenic Process In Intra-Molecular Carbon-Hydrogen Insertion. *J. Org. Chem.* **1979**, *44*(17), 3072-3075.
- [122] Tomioka, H.; Kondo, M.; Izawa, Y. Substituent effects on the product distribution in diazo amide photochemistry. Role of ground-state conformational populations. *J. Org. Chem.* **1981**, *46*(6), 1090-1094.
- [123] Kaplan, F.; Meloy, G. K. Structure of Diazoketones . a Study of Hindered Internal Rotation. *J. Am. Chem. Soc.* **1966**, *88*(5), 950-956.
- [124] Candeias, N. R.; Gois, P. M. P.; Veiros, L. F.; Afonso, C. A. M. C-H Carbene Insertion of  $\alpha$ -Diazo Acetamides by Photolysis in Non-Conventional Media. *J. Org. Chem.* **2008**, *73*(15), 5926-5932.
- [125] Maas, G.; Krebs, F.; Werle, T.; Gettwert, V.; Striegler, R. Silicon-oxygen heterocycles from thermal, photochemical, and transition-metal-catalyzed decomposition of  $\alpha$ -(alkoxysilyl and alkenyloxysilyl)- $\alpha$ -diazooacetates. *Eur. J. Org. Chem.* **1999**(8), 1939-1946.
- [126] Wydila, J.; Thornton, E. R. Photolysis Studies of Alpha-Diazoamides the Effect of Carboxamide Substituents on Selectivity Ratios. *Tetrahedron Lett.* **1983**, *24*(3), 233-236.
- [127] DoMinh, T.; Strausz, O. P.; Gunning, H. E. Photochemistry of Diazo Esters .2. a Novel Reaction Path. *J. Am. Chem. Soc.* **1969**, *91*(5), 1261-1263.

- [128] von E. Doering, W.; Hoffmann, A. K. The Addition of Dichlorocarbene to Olefins. *J. Am. Chem. Soc.* **1954**, *76*(23), 6162-6165.
- [129] Skell, P. S.; Garner, A. Y. The Stereochemistry of Carbene-Olefin Reactions. Reactions of Dibromocarbene with the cis- and trans-2-Butenes. *J. Am. Chem. Soc.* **1956**, *78*(14), 3409-3411.
- [130] von E. Doering, W.; LaFlamme, P. The cis addition of dibromocarbene and methylene to cis- and trans-butene. *J. Am. Chem. Soc.* **1956**, *78*(20), 5447-5448.
- [131] Roth, H. D. Chemically induced nuclear spin polarization in the study of carbene reaction mechanisms. *Acc. Chem. Res.* **1977**, *10*(3), 85-91.
- [132] Moss, R. A. Carbenic selectivity in cyclopropanation reactions. *Acc. Chem. Res.* **1980**, *13*(2), 58-64.
- [133] Moss, R. A.; Joyce, M. A. Reactions of methylphenylcarbene and phenylcarbene in isobutene matrices: origins of the "insertion" products. *J. Am. Chem. Soc.* **1977**, *99*(4), 1262-1264.
- [134] Moss, R. A.; Joyce, M. A. Chemistry of fluorenylidene at low temperatures. *J. Am. Chem. Soc.* **1978**, *100*(14), 4475-4480.
- [135] Tomioka, H.; Komatsu, K.; Shimizu, M. Photochemistry of matrix-isolated ( $\alpha$ -diazobenzyl)phosphonate. Observation and reactions of phosphonylphenylcarbene, phosphonyl phenyl ketone oxide, and phenylphosphonyldioxirane. *J. Org. Chem.* **1992**, *57*(23), 6216-6222.
- [136] Arnold, B. R.; Scaiano, J. C.; Bucher, G. F.; Sander, W. W. Laser flash photolysis studies on 4-oxocyclohexa-2,5-dienylidenes. *J. Org. Chem.* **1992**, *57*(24), 6469-6474.
- [137] Nojima, T.; Ishiguro, K.; Sawaki, Y. Mechanistic Study on the Reaction of Phenyl diazomethanes with Singlet Oxygen: Formation and Cycloreversion of 1,2,3,4-Dioxadiazole Intermediates. *J. Org. Chem.* **1997**, *62*(20), 6911-6917.
- [138] Nojima, T.; Hirano, Y.; Ishiguro, K.; Sawaki, Y. Dramatic Change of Carbonyl Oxide Reactivity by the Potent Electron-Withdrawing Trifluoromethyl Group. *J. Org. Chem.* **1997**, *62*(8), 2387-2395.

