

## VIP Very Important Publication

# Harnessing the Power of the De Mayo Reaction: Unveiling a Photochemical and Photocatalytic Masked [2 + 2] Methodology for Organic Synthesis

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**Abstract:** In 1962, Paul J. de Mayo initially described the photochemical reaction involving 1,3-diketones and double bonds, resulting in the formation of 1,5-diketones. Since then, this reaction has been extensively utilized for the synthesis of a wide range of fascinating natural products. Over time, this synthetic methodology has been applied to various carbonyl systems, including locked enol-tautomers of diketones,  $\beta$ -keto esters, and  $\beta$ -enaminones. Additionally, it has found application in other unsaturated systems such as allenes and alkynes. In this review article, we provide a comprehensive overview of the classical de Mayo reaction, highlighting its scope and potential. Furthermore, we focus on recent advances achieved through photocatalytic conditions. Special emphasis is placed on the regioselectivity of the process and the underlying reaction mechanism, particularly within the context of photocatalysis.

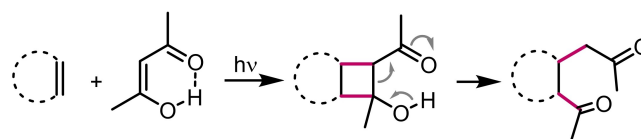
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**Keywords:** De Mayo reaction; Photochemistry; Photocatalysis; [2 + 2] photo-cycloaddition; Mechanism and regioselectivity

## 1. Introduction

The [2 + 2] photocycloaddition of two alkenes to afford cyclobutanes is one of the most employed reactions in photochemical synthesis.<sup>[1]</sup> The formation of two new carbon-carbon bonds and up to four stereogenic centers in a single step result in the rapid access to complex molecular scaffolds. Moreover, the inherent strain of the cyclobutane adducts makes them prone to undergo ring-opening reactions. In this context, Paul J. de Mayo reported in 1962 a prominent example of intermolecular [2 + 2] photocycloadditions

when 1,3-dicarbonyl compounds were employed in the reaction. In a first report, the authors observed that the UV irradiation of acetylacetone in the presence of different alkenes afforded 1,5-diketones (Scheme 1).<sup>[2]</sup>



**Scheme 1.** Initial experiments conducted by de Mayo.



Noelia Salaverri (middle) received her M.S. in Organic Chemistry from Universidad Autónoma de Madrid in 2018, working in the photocatalytic synthesis of heterocyclic compounds. Then, she continued the PhD studies in this field, conducting her research on the design of novel photocatalyzed transformations under the supervision of Prof. José Alemán and Dr. Leyre Marzo.

Prof. José Alemán (left) obtained his PhD in 2005 working on sulfur chemistry under the supervision of Prof. García Ruano. Then, he carried out his postdoctoral studies (2006–) with Prof. Karl A. Jørgensen at the Center for Catalysts in Aarhus (Denmark). He returned to Spain in 2009 as a Ramón y Cajal Researcher and in 2015 he received a Consolidator Grant awarded by the European Research Council. In 2016 he was promoted to Associate Professor and in 2023 to Full Professor in Universidad Autónoma de Madrid (UAM). Since 2022 he is the Scientific Director of the Institute for Advanced Research in Chemical Sciences in UAM (IAdChem).

Leyre Marzo (right) received her PhD in Organic Chemistry in 2015 from the Universidad Autónoma de Madrid. Then, she became a postdoctoral Alexander von Humboldt fellow with Prof. B. König at the University of Regensburg. In 2018 she returned to the Universidad Autónoma de Madrid where she is currently a Ramón y Cajal researcher. Her research interests include the development of new photocatalytic reactions and the elucidation of the reaction mechanisms behind those transformations.

The proposed mechanism for this transformation involves a stepwise  $[2+2]$  photocycloaddition reaction followed by a retro-aldol addition (Scheme 2).<sup>[3]</sup> The first step is the tautomerization of the 1,3-dicarbonyl compound into the enol form, which is strongly favoured due to the formation of an intramolecular hydrogen bond. This species reaches the singlet excited state by the absorption of UV light ( $\lambda_{\text{abs}} = 300$ –

350 nm). Intersystem crossing (ISC) efficiently produces the triplet excited state, which has a lifetime long enough to allow the intermolecular addition with an olefin to generate the most stable triplet 1,4-biradical intermediate. Then, spin inversion to the singlet biradical followed by ring closure generates a  $\beta$ -acylcyclobutanol which undergoes retro-aldol addition to afford 1,5-dicarbonyl compounds.

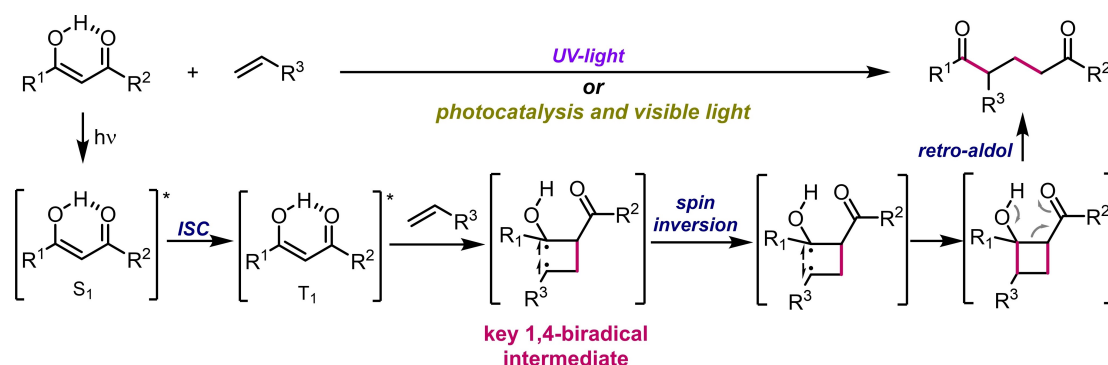
The regioselectivity for the intermolecular  $[2+2]$  cycloaddition step does not follow a simple rule, but in general non-polarized olefins are oriented to generate the most stabilized radical intermediate after the initial bond formation (key 1,4-biradical intermediate, Scheme 2). However, if the stability of the radical intermediates is similar, a mixture of regioisomers will be formed. In addition, the 1,4-biradicals not only undergo ring closure to products, but also fragmentation to the ground state precursors.<sup>[4]</sup> Weedon determined that the cyclization/fragmentation rates of biradicals can also influence the regioselectivity.<sup>[5]</sup> In polarized olefins, it is also necessary to consider the electronic interactions.<sup>[6]</sup> Moreover, in the case of disubstituted olefins, if the rotational relaxation of the 1,4-biradical is faster than ring-closure, a mixture of diastereomers will be obtained.<sup>[7]</sup> Regarding intramolecular reactions, the regioselectivity is dominated by the rapid formation of a five-membered ring (Scheme 3).<sup>[8]</sup> When the tether between the reacting olefins is only two atoms the crossed product is preferred to avoid the formation of a strained four-membered ring whereas if the tether is longer, straight adducts prevail.<sup>[9]</sup>

## 2. Photochemical de Mayo Reaction

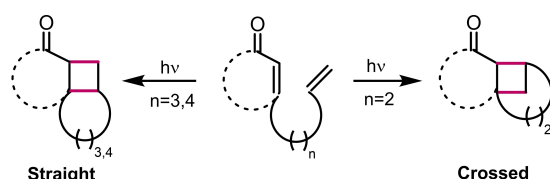
After the first intermolecular example, many groups employed this transformation for the synthesis of a wide variety of natural products,<sup>[10]</sup> including some intramolecular asymmetric approaches by starting from readily available chiral compounds. In the following sections, different examples of  $\beta$ -keto derivatives and  $\pi$ -systems that have been reported to undergo this reactivity will be described, together with an analysis of the  $[2+2]$  cycloaddition step.

### 2.1. $\beta$ -Diketones and Double Bonds

The synthesis of ( $\pm$ )-hirsutene by Weedon is one of the first synthetic applications of the intermolecular de Mayo reaction between a  $\beta$ -diketone and a non-symmetric aliphatic alkenes (Scheme 4).<sup>[11]</sup> In this case, the  $[2+2]$  cycloaddition step leads to an equal mixture of regioisomers, presumably due to the similar stability in the formation of secondary or tertiary alkyl radical intermediates. Then, silylation of the alcohol, McMurry reaction, deprotection, hydrogenation and



**Scheme 2.** Proposed mechanism for the de Mayo reaction including all the proposed reaction intermediates.



**Scheme 3.** Regioselectivity in intramolecular reactions.

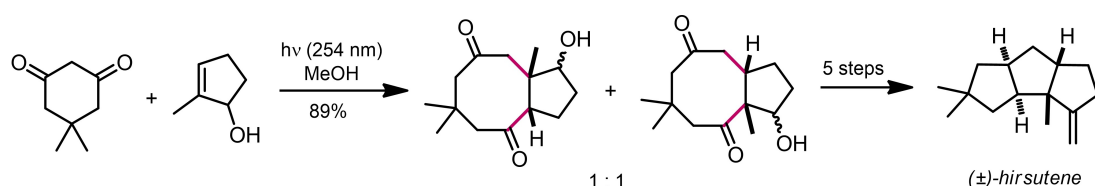
Jones oxidation afforded the tricyclic compound in a 36% overall yield.

An unusual example of the intramolecular de Mayo reaction was reported by Minter in the synthesis of the tetracyclic Galanthan system (Scheme 5).<sup>[12]</sup> Here, the [2 + 2] cycloaddition takes place between the  $\beta$ -diketone and the isocarbostyryl moiety to form a cyclobutane intermediate that evolves to the Galanthan derivative after ring closure in a 35% overall yield. The reaction proceeds with high regioselectivity for

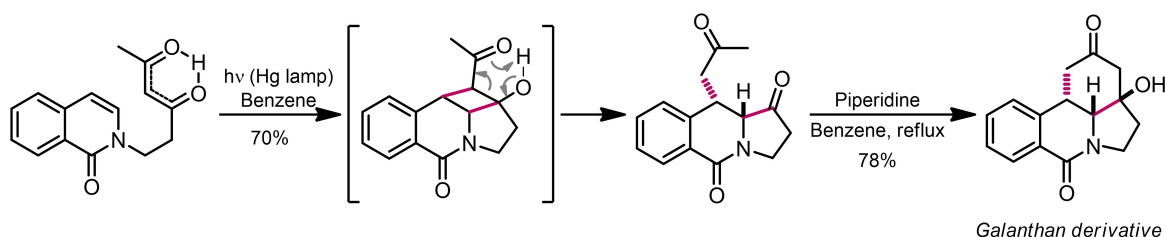
the formation of the 5-membered ring, following the rule of five.

Although the latter works illustrated the use of enolizable  $\beta$ -diketones as reactive partners in the de Mayo reaction, the vast majority of examples employ locked enol tautomers such as  $\beta$ -enol esters or vinylogous esters containing a pendant tether, which require an additional treatment to promote the ring-opening step. For instance, in the total synthesis of ( $\pm$ )- $\beta$ -bulnesene by Oppolzer, the intramolecular [2 + 2] cycloaddition takes place between the preformed enol acetate and the terminal alkene to afford regioselectively the straight adduct and 5-membered ring fused cyclobutane (Scheme 6).<sup>[13]</sup>

Further manipulations for the retro-aldol addition and Wittig reaction afford the bicyclic compound in a 24% overall yield. The formation of other fused bicyclic carbocycles from the reaction of the corresponding enol esters with pendant alkenes was also reported for the synthesis of ( $\pm$ )-daucene by Seto.<sup>[14]</sup>



**Scheme 4.** Synthesis of ( $\pm$ )-hirsutene by Weedon.

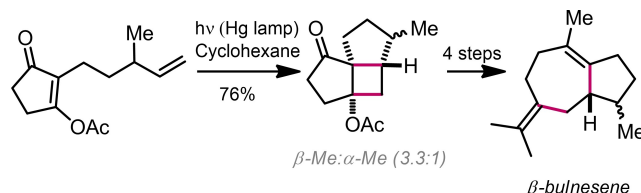


**Scheme 5.** Synthesis of a Galanthan derivative by Minter.

( $\pm$ )- $\beta$ -himachalene by de Mayo,<sup>[15]</sup> or ( $\pm$ )-epi-precapnelladiene by Pattenden.<sup>[16]</sup>

Another important example is the synthesis of the tricyclic sesquiterpene ( $\pm$ )-longifolene by Oppolzer (Scheme 7a).<sup>[17]</sup> Here, the key step to form the macrocyclic structure is a modified version of the intramolecular de Mayo reaction using the enol carbonate as masked 1,3-dicarbonyl compound. Irradiation of this substrate regioselectively forms the cyclobutane adduct which undergoes a retro-aldol cleavage after hydrogenolysis to afford the complex carbon skeleton. Then, a regioselective Wittig reaction and Simmons-Smith cyclopropanation followed by additional manipulations furnish ( $\pm$ )-longifolene in a 25% overall yield. Moreover, in this case the synthesis of enantiomerically pure (+)-longifolene was carried out by starting from (*S*)-cyclopent-2-ene-1-carboxylic acid and following the same reaction sequence (Scheme 7b).<sup>[18]</sup>

The synthesis of ( $\pm$ )-zizaene by Pattenden also exemplifies the structural diversity that can be reached using the de Mayo reaction (Scheme 8).<sup>[19]</sup> Here, the UV irradiation of a mixture of enol acetates led to the

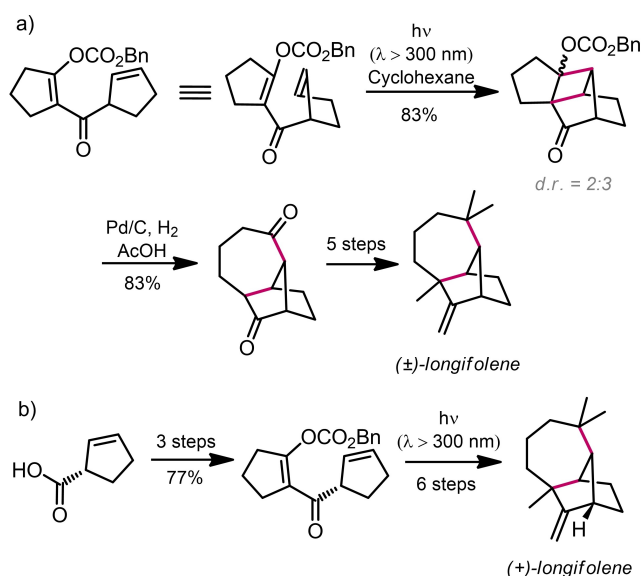


**Scheme 6.** Synthesis of ( $\pm$ )- $\beta$ -bulnesene by Oppolzer.

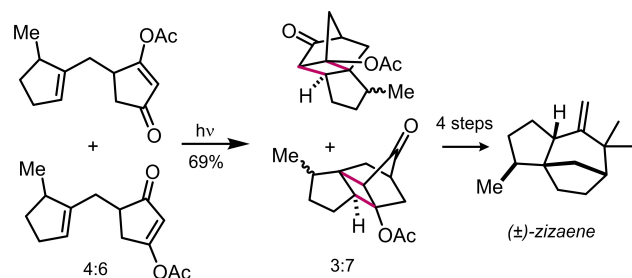
corresponding cyclobutanes. Separation of the major photoadduct followed by a four-step sequence affords the tricyclic structure of zizaene.

The key step for the synthesis of (+)-aphanamol starting from (+)-(*R*)-limonene reported by Wickberg is an diastereoselective de Mayo reaction (Scheme 9).<sup>[20]</sup> However, the photoadducts are obtained as an equal mixture of regioisomers, as commonly observed when non-polar unsymmetrical alkenes are employed in [2+2] cycloadditions.<sup>[21]</sup> Then, epoxidation followed by base treatment promotes the cyclobutane and oxirane ring-opening.

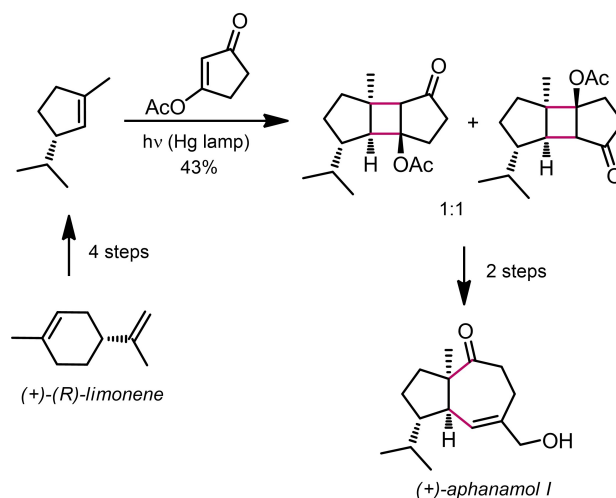
Enol ethers of 1,3-diketones (or vinylogous esters) can also undergo the de Mayo reaction, but the retro-aldol addition only takes place under appropriate conditions, such as with HI, KOH, BF<sub>3</sub>·OEt<sub>2</sub> or TMSOTf treatment. For instance, this variant of the de Mayo reaction has been employed for the construction of the BC ring system of taxane skeleton (Scheme 10).<sup>[22]</sup> Here, the tetracyclic core is formed following the rule of five to afford the straight adduct after irradiation. More recently, Lou and co-workers also employed the intramolecular reaction between enol ethers and aliphatic alkenes for the synthesis of tetracyclic terpenoids.<sup>[23]</sup>



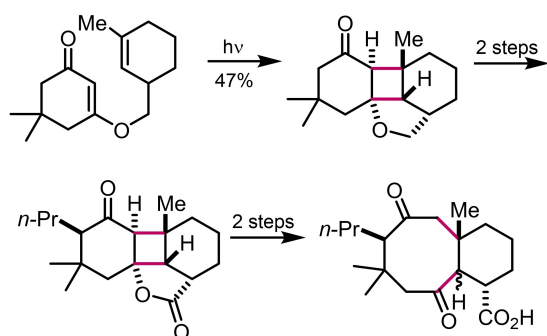
**Scheme 7.** Synthesis of ( $\pm$ )-longifolene (a) and (+)-longifolene by Oppolzer (b).



**Scheme 8.** Synthesis of ( $\pm$ )-zizaene by Pattenden.



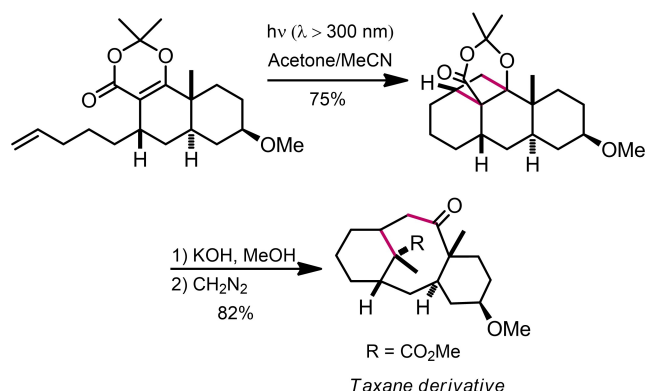
**Scheme 9.** Synthesis of (+)-aphanamol by Wickberg.



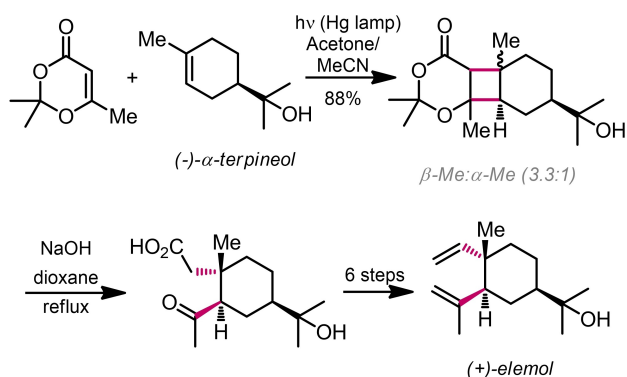
**Scheme 10.** Synthesis of the BC ring system of taxane skeleton by Kakisawa.

## 2.2. $\beta$ -Keto Esters and Double Bonds

While the latter works illustrated the utility of the de Mayo reaction with enols of  $\beta$ -diketones, the analogous transformation with  $\beta$ -keto esters can lead to the oxetane formation through a Paternò-Büchi reaction of the ketone.<sup>[24]</sup> To overcome this limitation, Baldwin introduced the use of dioxinones as locked enol tautomers of  $\beta$ -keto esters.<sup>[25]</sup> The photocycloaddi-



**Scheme 11.** Modification of the de Mayo reaction with dioxinones for the synthesis of taxane diterpenes by Winkler.



**Scheme 12.** Synthesis of (+)-elemol by Baldwin.

tion of dioxinones with alkenes as a modified procedure of the de Mayo reaction has been applied to various natural products synthesis such as the tricyclic skeleton of taxane diterpenes towards the preparation of taxol analogues by Winkler (Scheme 11).<sup>[26]</sup> In this case, the [2+2] photocycloaddition takes place to form the straight adduct and a six-membered ring. The dioxinone ring is fragmented under nucleophilic conditions to form an eight-membered ring condensed to two six-membered rings.

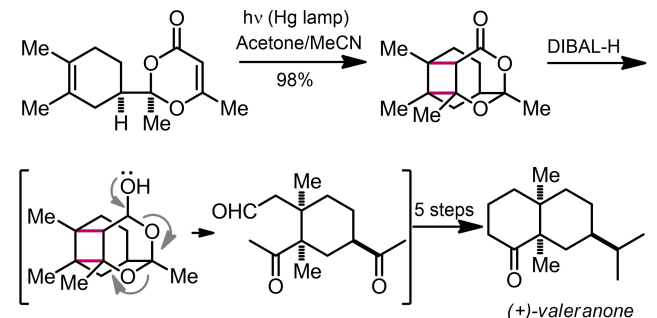
Following this strategy, Baldwin reported the total synthesis of the monocyclic terpenoid (+)-elemol starting from (-)- $\alpha$ -terpineol (Scheme 12).<sup>[27]</sup> The key step is a de Mayo reaction that proceeds with a high regioselectivity in the [2+2] photocycloaddition step to form the head-to-head adduct. Then, saponification of this intermediate leads to the 1,5-dicarbonyl compound that is transformed in (+)-elemol in 6 additional steps.

Another example of the intermolecular reaction between 2,2-dimethyl-1,3-dioxin-4-one and a cyclic aliphatic alkene is found also in the synthesis of a prostaglandin intermediate as reported by Sato.<sup>[28]</sup>

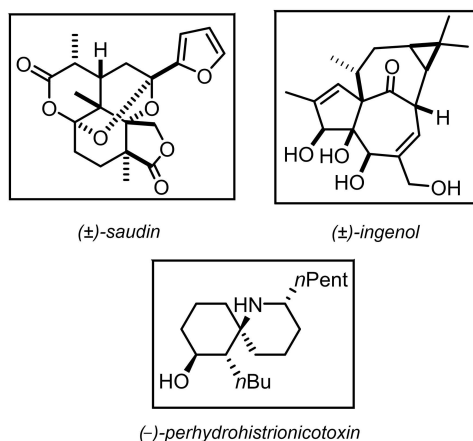
The synthesis of ( $\pm$ )-valeranone by Takeshita is based on an intramolecular de Mayo reaction between the double bond of the dioxinone and a disubstituted cyclic alkene (Scheme 13).<sup>[29]</sup> The cage adduct is formed in high yield and undergoes spontaneous retroaldol reaction after reduction of the ester moiety that is further converted into the bicyclic product after five additional steps.

Other examples based on the intramolecular reaction between dioxinones and alkenes were reported for the synthesis of the diterpenoid ( $\pm$ )-saudin<sup>[30]</sup> with a hypoglycemic effect, the diterpenoid ( $\pm$ )-ingenol<sup>[31]</sup> with diverse biological activities or the neurotoxic alkaloid (-)-perhydrohistrionicotoxin<sup>[32]</sup> (Scheme 14).

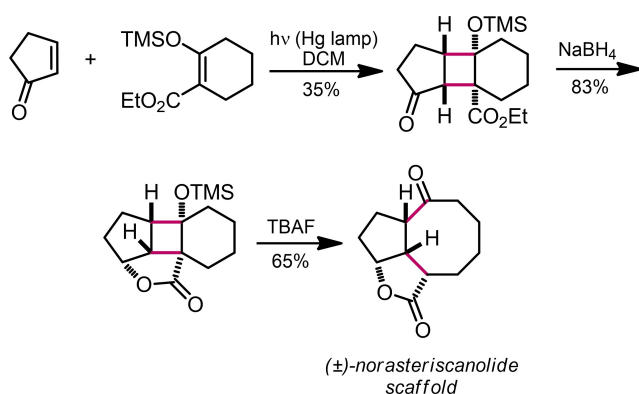
Silyl enol ethers have also been used as locked enol tautomers of  $\beta$ -keto esters in the de Mayo reaction.



**Scheme 13.** Synthesis of ( $\pm$ )-valeranone by Takeshita.



**Scheme 14.** Synthesis of natural products employing a modified version of the de Mayo reaction.



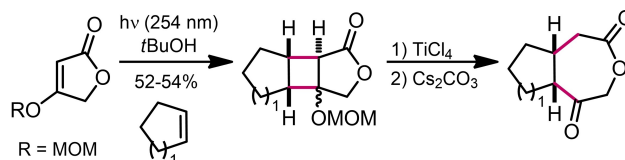
**Scheme 15.** Synthesis of (±)-norasteriscanolide structure by Langue.

dicarbonyl compound takes place with high regioselectivity to form the desired adduct. Then, reduction and deprotection promote the ring-opening to afford the five and eight-fused ring system. The same regioselectivity in the [2+2] cycloaddition step has been observed in the synthesis of bicyclic 1,3-cyclohexanediones.<sup>[34]</sup>

More recently, Bach and co-workers reported the use of protected tetronic acid in the de Mayo reaction. Interestingly, after deprotection, the retro-aldol addition results in the formation of bicyclic oxepanediones (Scheme 16).<sup>[35]</sup> Mechanistic studies support the participation of triplet excited states in the reaction.

### 2.3. Vinyllogous Amides (aza-de Mayo Reaction with Double Bonds)

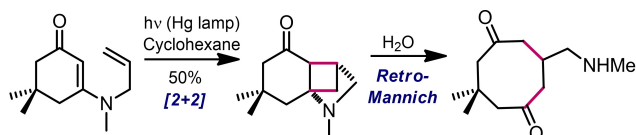
In analogy with the classical de Mayo reaction with 1,3-dicarbonyl compounds and their derivatives, vinyllogous amides follow a similar reactivity pattern. In this sense, the [2+2] photocycloaddition between a β-



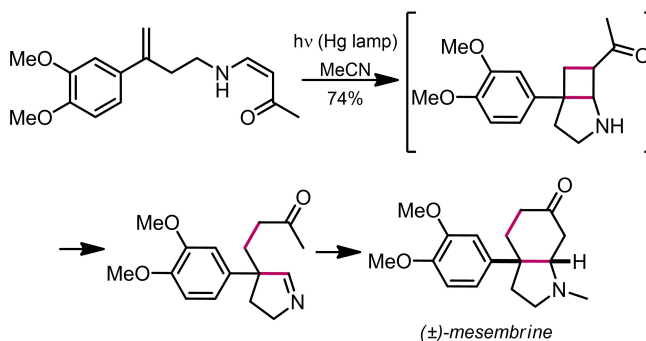
**Scheme 16.** Photochemical de Mayo reaction with β-hydroxy lactones reported by Bach.

enaminone and an alkene generates a cyclobutane that undergoes a retro-Mannich fragmentation to give a ketoimine or a ketoiminium ion which can be involved in further transformations. This [2+2] photocycloaddition/retro-Mannich sequence, known as the aza-de Mayo reaction, was observed for the first time by Tamura in 1975 (Scheme 17).<sup>[36]</sup>

After this initial observation, other groups exploited the synthetic utility of this reaction as a powerful route to construct nitrogen-containing ring systems.<sup>[37]</sup> In 1988, Winkler and co-workers reported the synthesis of the alkaloid mesembrine by using an intramolecular vinyllogous amide photocycloaddition/retro-Mannich/Mannich closure sequence (Scheme 18).<sup>[38]</sup> In this sense, the [2+2] photocycloaddition takes place between the terminal aryl-substituted alkene and the β-enaminone to form the straight and 5-membered ring adduct that finally affords the ketoimine after the retro-Mannich fragmentation. Subsequent methylation and base treatment facilitate the ring closure affording (±)-mesembrine in a 33% overall yield. This aza-de Mayo/Mannich closure sequence has also been employed in



**Scheme 17.** [2+2] Photocycloaddition/retro-Mannich fragmentation sequence observed by Tamura.



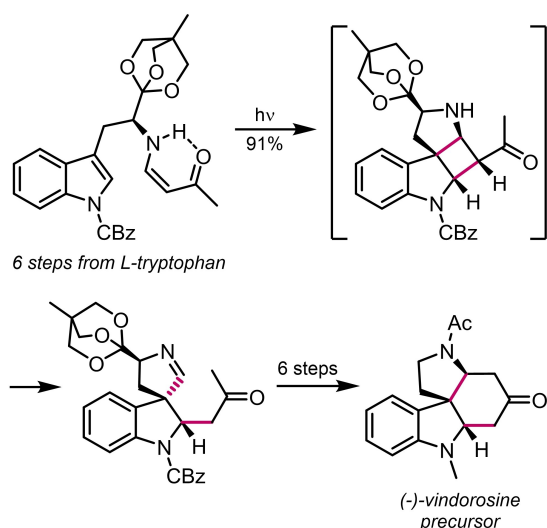
**Scheme 18.** Aza-de Mayo/Mannich closure sequence in the synthesis of (±)-mesembrine reported by Winkler.

the synthesis of hetisine alkaloids<sup>[39]</sup> and the bicyclic core of peduncularine<sup>[40]</sup> by Winkler.

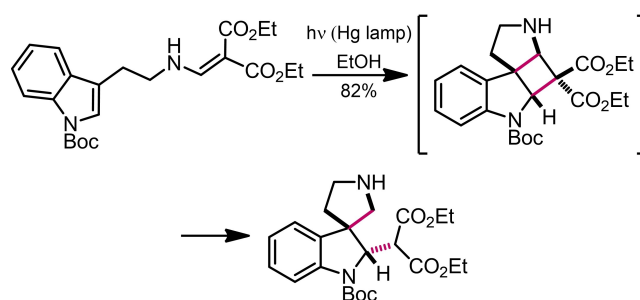
The formal synthesis of the antitumoral (–)-vindorosine starting from *L*-tryptophan by Winkler is another application of the same reaction sequence (Scheme 19).<sup>[41]</sup> Upon irradiation, the intramolecular [2 + 2] photocycloaddition of the  $\beta$ -enaminone with the indole 2,3-double bond followed by retro-Mannich fragmentation furnish the ketoimine as a single diastereomer.

The observed stereoselectivity can be explained attending to the fact that, prior to the [2 + 2] photocycloaddition, the molecule adopts the conformation in which the *ortho* ester group and the aromatic ring of the indole are as far apart as possible from each other. Then, the base-promoted ring closure affords the tetracyclic indole which is further converted to a precursor of (–)-vindorosine.<sup>[42]</sup> By using the same principle, Winkler also developed the synthesis of the complex marine alkaloids (–)-ircinol A, (+)-ircinal A, (+)-manzamine A and D.<sup>[43]</sup>

White and Ihle reported yet another distinct transformation by utilizing  $\beta$ -amino alkylidene malonates that were derived from tryptamine or aminoethyl-1,4-cyclohexadiene in the aza-de Mayo reaction (Scheme 20).<sup>[44]</sup> In this case, the intramolecular [2 + 2] photocycloaddition takes place with the indole 2,3-double bond to form a cyclobutane intermediate following the rule of five that evolves to the spiroindolopyrroline after the retro-Mannich fragmentation.



**Scheme 19.** Aza-de Mayo/Mannich closure for the synthesis of (–)-vindorosine reported by Winkler.



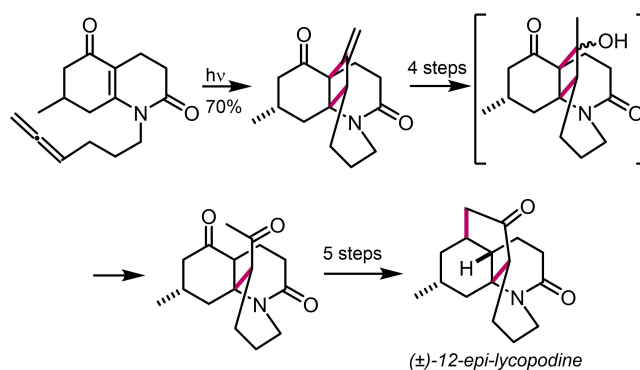
**Scheme 20.** Aza-de Mayo reaction with  $\beta$ -amino alkylidene malonates reported by White.

## 2.4. Allene and Alkyne Variants of the de Mayo Reaction

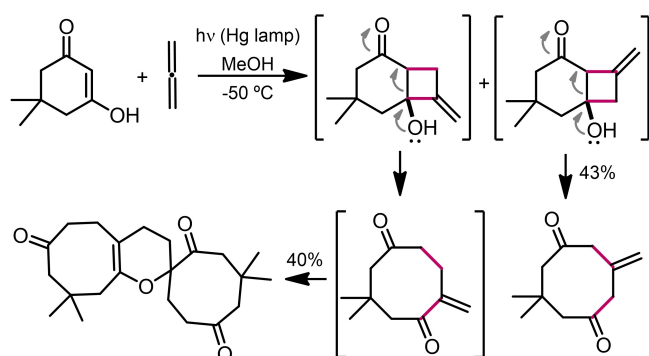
In addition to alkenes, other unsaturated systems can also undergo the de Mayo reaction. In this regard, the first intramolecular vinylogous imide-allene photocycloaddition was reported by Wiesner in 1968 in the synthesis of the natural product ( $\pm$ )-12-epi-lycophodine (Scheme 21).<sup>[45]</sup> Here, the retro-aldol fragmentation takes place after the epoxidation of the double bond and reduction. Therefore, the broken bond in this step is different from the typical de Mayo reactions.

Later, Petrzilka developed the intermolecular version of the de Mayo reaction using allenes (Scheme 22).<sup>[46]</sup> In this case, the [2 + 2] photocycloaddition results in a mixture of head-to-head and head-to-tail regioisomers that evolves to the formation of the corresponding cyclooctadienone or  $\delta$ -valerolactone respectively through spontaneous dimerization. The intermolecular reaction between a protected enol carbonate and allene has also been employed in the AB ring system of the taxane skeleton.<sup>[47]</sup>

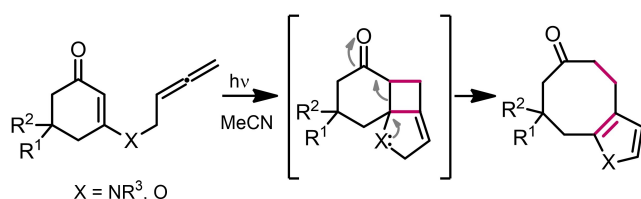
More recently, Winkler and Hiemstra reported the synthesis of bicyclic pyrrole or furan fused to eight-membered rings by the intramolecular cycloaddition of



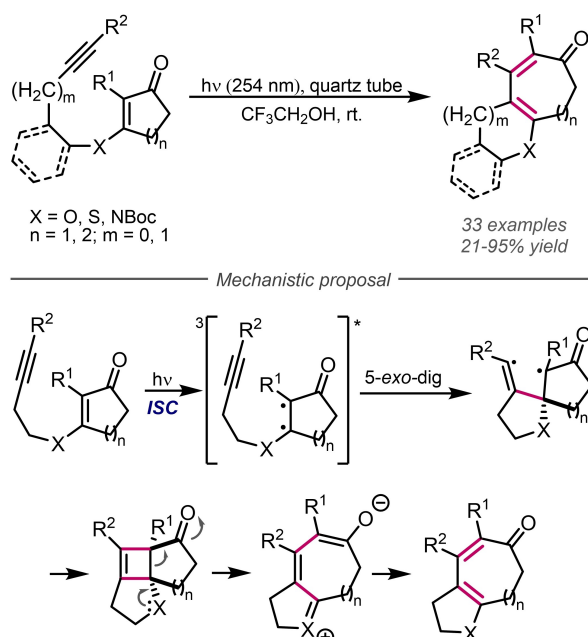
**Scheme 21.** [2 + 2] Photocycloaddition/fragmentation of allenes with vinylogous amides.



**Scheme 22.** [2 + 2] Photocycloaddition/fragmentation of allenes with 1,3-dicarbonyls.



**Scheme 23.** [2 + 2] Photocycloaddition-fragmentation of allenes with vinylogous amides or esters.



**Scheme 24.** Development of the intramolecular de Mayo reaction with alkynes by Hiersemann.

allenes with vinylogous amides or esters followed by the heteroatom-induced fragmentation (Scheme 23).<sup>[48]</sup>

In 2018, Hiersemann and co-workers reported the first intramolecular alkyne analogue of the de Mayo reaction for the synthesis of annulated seven- and

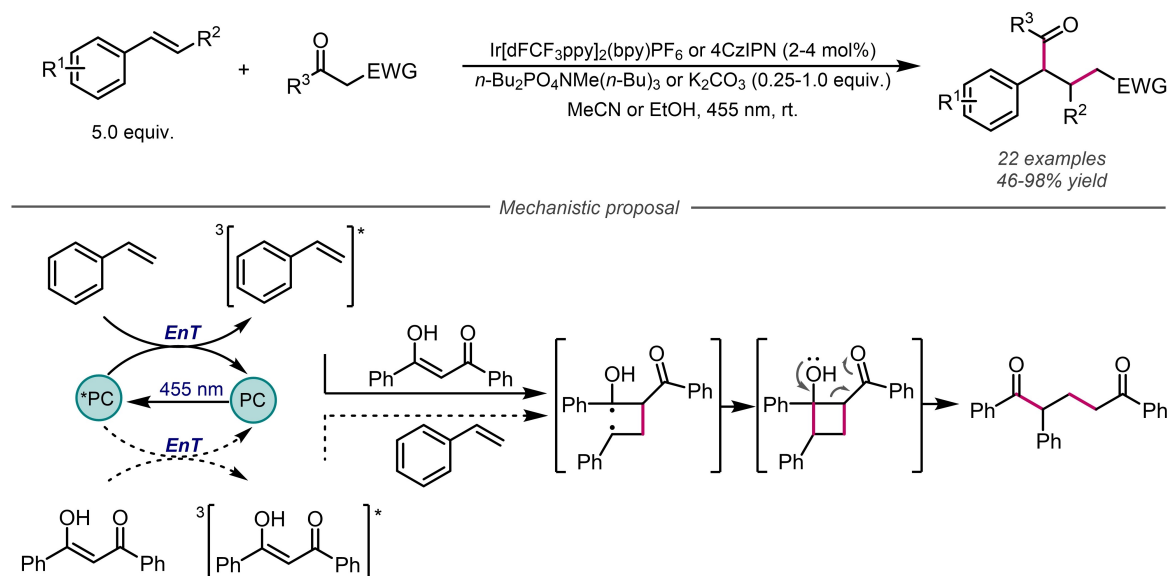
eight-membered rings and cyclohepta[*b*]indoles (Scheme 24).<sup>[49]</sup> The key to the success is the employment of a quasi-monochromatic light source that emits at 254 nm that avoids the undesired degradation processes observed with the use of 300 nm light source. Mechanistically, the substrate reaches its singlet excited state after UV irradiation. Intersystem crossing to the triplet triggers the 5- or 6-*exo*-dig cyclization to form a 1,4-biradical intermediate. Then, spin inversion and ring closure generate a cyclobutene which affords the desired product after retro-aldol or retro-Mannich fragmentation.

### 3. Photocatalytic de Mayo Reaction

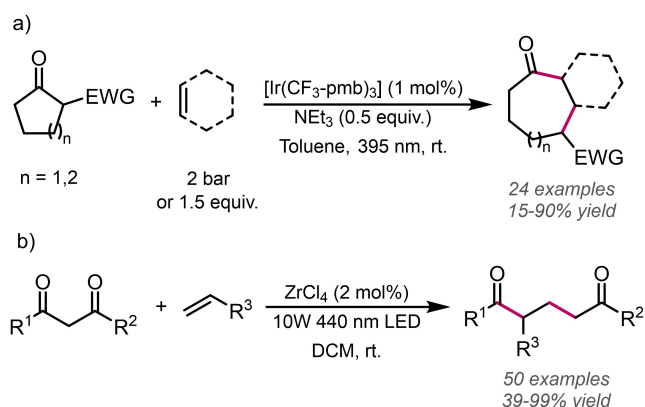
During the last decade, the appearance of visible light photocatalysis as a new mode for molecule activation has enabled the development of novel reaction pathways.<sup>[50]</sup> In this regard, Marzo and König developed the first visible light-mediated de Mayo reaction of 1,3-dicarbonyl compounds with styrene derivatives *via* energy transfer from an external photosensitizer (Scheme 25).<sup>[51]</sup> Mechanistically, according to luminescence quenching studies, the triplet excited-state iridium ( $E_T = 62$  kcal/mol) or carbazole ( $E_T = 60$  kcal/mol) photocatalysts can transfer the energy to the enol ( $E_T = 59$  kcal/mol) or the styrene ( $E_T = 60$  kcal/mol). Due to its higher concentration in the reaction media and the observation of the dimerization product, the more likely mechanism is the photosensitization of the styrene. Then, the two possible triplet excited states collapse with the other reaction partner to form a common 1,4-biradical intermediate. Spin inversion followed by ring closure generate a non-isolable  $\beta$ -acylcyclobutanol, which evolves spontaneously to form the 1,5-dicarbonyl compound. The reaction can be applied to aryl diketones, alkyl diketones and ketones bearing different EWG in the  $\beta$ -position. However, alkyl substituted alkenes are unreactive under these conditions. The authors attributed this fact to the high triplet energy of this species (80 kcal/mol). Two years later, this photocatalytic version of the de Mayo reaction was applied in the synthesis of leptosperol B by Li, Ye and Wang.<sup>[52]</sup>

In 2022, Guldi and Glorius developed the photocatalyzed de Mayo reaction of cyclic  $\beta$ -ketoesters or amides with unactivated olefins such as ethene or alkyl-substituted alkenes for the synthesis of medium-sized rings by a two-carbon homologation using the *fac*-[Ir(CF<sub>3</sub>-pmb)<sub>3</sub>] photosensitizer with a higher triplet energy ( $E_T = 73.3$  kcal/mol) (Scheme 26a).<sup>[53]</sup>

In the same year, Zhang and Luo reported the zirconium-catalyzed de Mayo reaction with styrenes and non-activated olefins under visible light conditions.<sup>[54]</sup> The complexation of the zirconium catalyst with the  $\beta$ -dicarbonyl compound forms a photoactive zirconium enolate that shows an absorp-



**Scheme 25.** Photocatalytic de Mayo reaction with 1,3-dicarbonyls reported by Marzo and König.



**Scheme 26.** a) Photocatalyzed de Mayo reaction of 1,3-dicarbonyls and unactivated olefins reported by Guldi and Glorius; b) Zirconium-catalyzed de Mayo reaction reported by Zhang and Luo.

tion band in the visible light region. Irradiation at this wavelength generates the excited-state zirconium complex that is involved in the [2 + 2] photocycloaddition followed by retro-aldol fragmentation in the presence of an olefin (Scheme 26b). 1,3-Dicarbonyls complexed as boron difluorides were also reported to undergo the de Mayo reaction in the presence of an aliphatic olefin, whereas in this case the reaction takes place from the singlet excited state.<sup>[55]</sup>

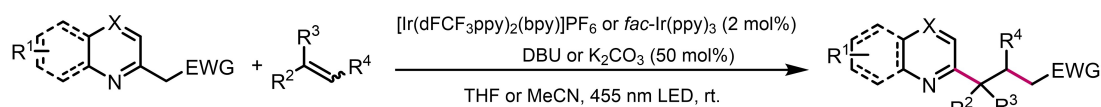
Our group also made a novel contribution to the photocatalytic de Mayo reaction. While the previous works involved the use of enols from 1,3-dicarbonyls or preformed  $\beta$ -enaminones, we discovered that  $\beta$ -electron-withdrawing substituted 2-methylene azaar-enes could also undergo this reactivity through the

formation of the enamine tautomer.<sup>[56]</sup> Therefore, the energy transfer to these species from an iridium photosensitizer triggers the [2 + 2] photocycloaddition with an olefin to generate a cyclobutane that evolves to the ring-opened product by a rearomatization process (Scheme 27). The methodology allows the functionalization of quinolines, isoquinolines, quinoxalines, pyrazines and quinolines bearing different electron withdrawing substituents in the  $\beta$ -position with a variety of styrenes as well as heteroaryl or alkyl-substituted double bonds. Moreover, its applicability has been demonstrated by the late-stage functionalization of natural products.

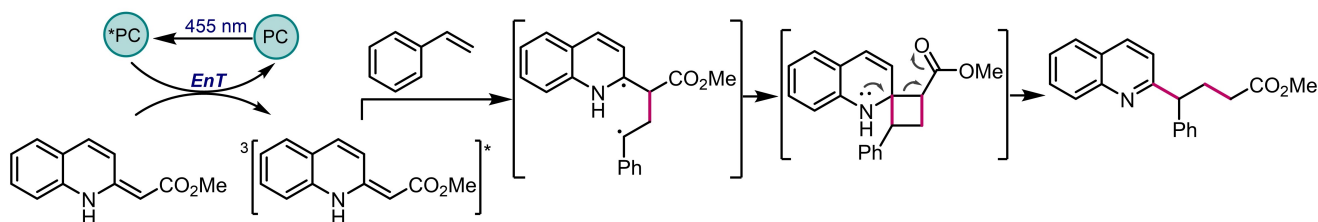
Very recently this year, Luo and co-workers developed the first visible light-mediated enantioselective de Mayo reaction through the photoexcitation of a chiral Zr-chiral phosphoric acid enolate complex (Scheme 28).<sup>[57]</sup> The enantioselectivity of the process is determined in the [2 + 2] photocycloaddition between the chiral Zr enolate and the olefin which is proposed to proceed following a triplet pathway. The reaction takes place with aryl-alkyl substituted 1,3-diketones with different styrenes and cyclic or linear aliphatic alkenes. The observed regioselectivity can be explained by the formation of the preferred aromatic enolate intermediate.

## 4. Summary and Perspective

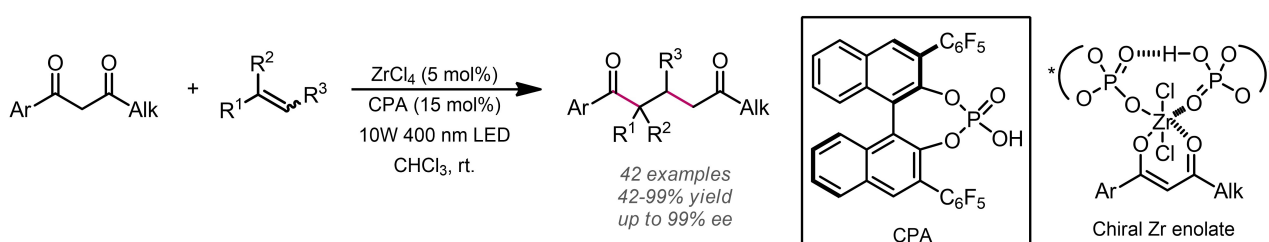
Since the discovery of the photochemical De Mayo reaction, many intramolecular variants have been applied as key steps of natural product syntheses to form different scaffolds that contain medium-sized rings. These methods involve the use of enols from 1,3-dicarbonyl compounds and preformed enols or  $\beta$ -



Mechanistic proposal



**Scheme 27.** Photocatalyzed de Mayo reaction between  $\beta$ -electron-withdrawing substituted 2-methylene azaarenes and double bonds reported by our group.



**Scheme 28.** Visible-light chiral Zr-CPA catalyzed enantioselective de Mayo reaction between 1,3-dicarbonyls and double bonds reported by Luo.

enaminones that mainly react with alkyl-substituted double bonds. Starting from chiral substrates, there are some examples that enabled the access to some enantiomerically enriched products. It is worth to mention that in the photochemical approach the examples are oriented to the preparation on natural products. Therefore, there is a lack of methodological studies, bypassing a detailed study of the reaction mechanism including the observed regioselectivity, and the scope of the reaction.

Regarding the photocatalytic version, only a few methods have been reported in the literature, mainly focussing on 1,3-dicarbonyl derivatives. In addition, only very recently an enantioselective photocatalytic approach has been described. To the date, it would be desirable the development of more versatile methodologies that gives access to a larger variety of structures, and the expansion of the asymmetric methods. Finally, an effort should be made in order to explain and predict the regioselectivity of the process.

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NMT6469) and Comunidad Autónoma de Madrid (S11/PJI/2019-00237). L. M. thanks for a Ramón y Cajal contract (Ministerio de Ciencia e Innovación) and N. S. thanks for a FPU-Spanish-Government.

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# Harnessing the Power of the De Mayo Reaction: Unveiling a Photochemical and Photocatalytic Masked [2 + 2] Methodology for Organic Synthesis

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