

## Suero Research Group



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### Abstract

The major goal of the Suero Group is to develop new activation modes and their application in solving important synthesis problems. We are exploiting single electron transfer chemistry for the catalytic generation of elusive species able to activate C=C and C–H bond in an unprecedented manner. Our group aims to apply the novel reactivity concepts for streamlining the synthesis of natural products and late-stage

functionalization of therapeutic agents. Moreover, we believe that our program will find applications in PET imaging and site-selective functionalizations of biomolecules.

Currently, we are developing a novel stereoconvergent alkene cyclopropanation reaction based on the catalytic generation of novel radical carbenoids. This process employs a reactivity principle that differs from classical cyclopropanation reactions.

The catalytic transfer of a methylene group to alkene molecules for the synthesis of cyclopropane cores is a long-standing challenge in chemical synthesis.<sup>[1]</sup> At present, classical protocols rely on the use of iodomethylzinc reagents, diazomethane or sulfur ylides, which possess problems with efficiency, availability, and safety.<sup>[4]</sup> Although reliable control of the stereochemistry is achieved, these processes remained confined to the utilization of isomeric pure alkenes. Taking into consideration the inherent difficulties for accessing stereodefined substituted alkenes, the means to design a stereoconvergent cyclopropanation using *E,Z*-alkene mixtures with easy to handle and commercially available methylene source would be highly appreciated. Despite the advantages realized, it is rather surprising that such strategy remains largely underdeveloped, probably due to the need for designing a new reactivity principle by using less-conventional carbene precursors.

Recently, our group has introduced a novel reactivity concept based on the catalytic generation of radical carbenoid species by means of photoredox catalysis (Fig. 1). These radicals are substituted with an excellent leaving group, and their reactivity is reminiscent of that of carbene species.

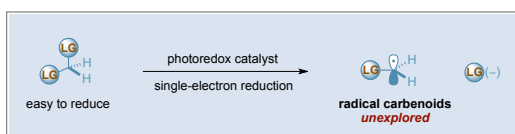


Fig. 1 – Photocatalytic generation of radical carbenoids

By exploiting this concept, we reported the first stereoconvergent cyclopropanation reaction by means of photoredox catalysis using diiodomethane as the methylene source. This transformation exhibits broader functional group tolerance and it is characterized by an excellent stereocontrol *en route* to *trans*-cyclopropanes regardless of whether *E*- or *Z*-styrene substrates were utilized. It is worth to highlight that the reaction works with isomeric mixtures of tri-substituted olefins and we have provided compelling evidence of the involvement of the carbenoid iodomethyl radical by using classic trapping reagents (1,1-diphenylethene; TEMPO) or radical clocks.

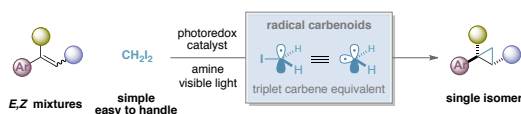


Fig. 2 – Catalytic cyclopropanation with  $\text{CH}_2\text{I}_2$

This new cyclopropanation reaction was published as a communication in *Angewandte Chemie*, was one of the most accessed articles in December 2016, and selected as Front Cover (Fig. 3)

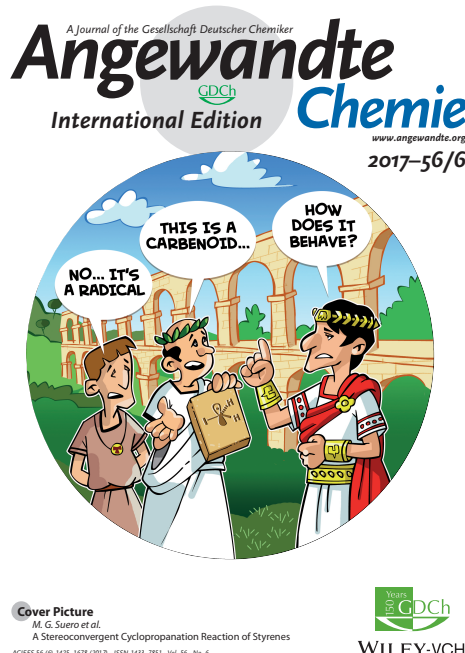


Fig. 3 – Three romans discuss the ambiguity nature of our carbenoid at the Pont del Diable (Tarragona).

After this, we discovered that our radical carbenoid was amenable for the cyclopropanation of Michael acceptors (Fig. 4). This process presents a broader functional group tolerance when compared with the classic Corey–Chaykovsky cyclopropanation.

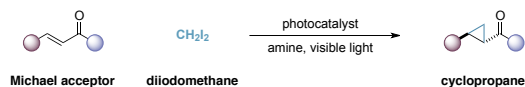


Fig. 4 – Catalytic cyclopropanation of Michael acceptor.

To sum up, we have developed a new alkene cyclopropanation reaction with simple  $\text{CH}_2\text{I}_2$ , which is based in reactivity principles that are opposite to the conventional ones. The radical carbenoid intermediate reacts with alkenes in a chemoselective manner and provides the cyclopropane ring in molecules with functionalities that are not tolerated in Simmons–Smith or Corey–Chaykovsky reactions. Preliminary results show that this new reaction can be extended to non-activated olefins and substituted 1,1-diodoalkane can generate new radical carbenoids.

## Articles

“A Stereoconvergent Cyclopropanation Reaction of Styrenes”

*Angew. Chem. Int. Ed.* (2017) 56 -1610-1613.

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“Photoredox-Catalyzed Cyclopropanation of Michael Acceptors”

*Eur. J. Org. Chem* (2017) DOI: 10.1002/ejoc.201601604

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