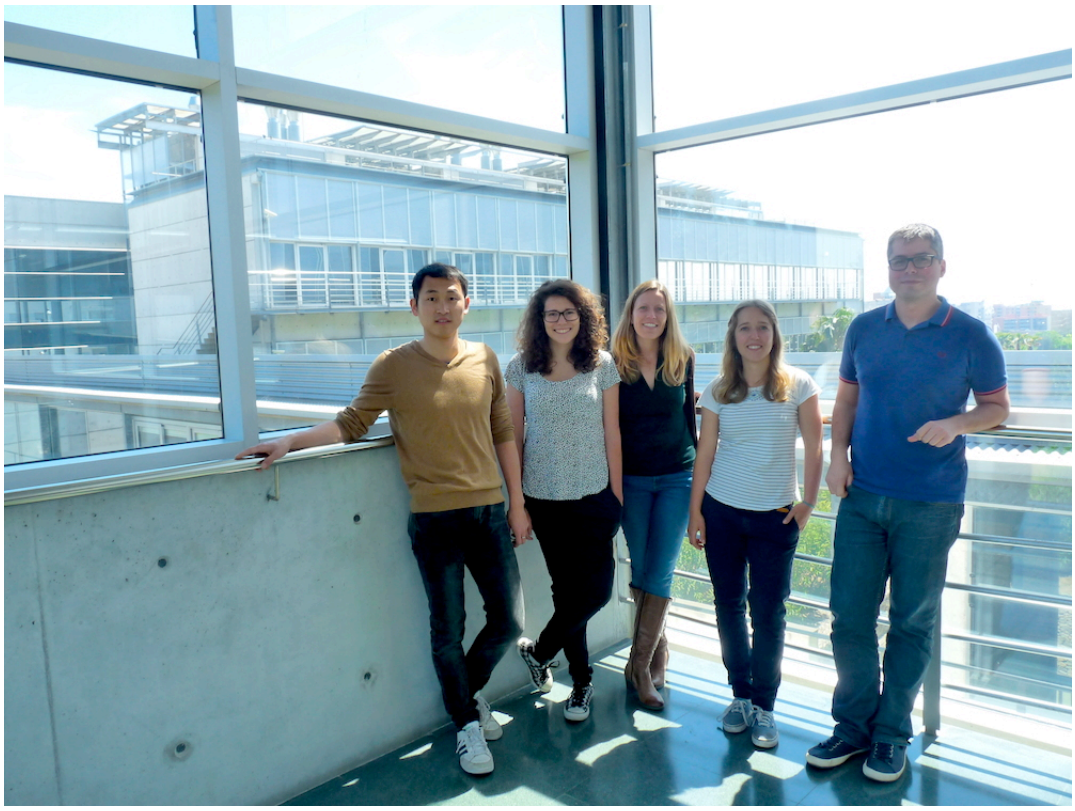
Suero Research Group



Group Leader: Marcos García Suero
Postdoctoral researchers: Ana Mª del Hoyo / Zhaofeng Wang
PhD students: Ana García
Summer fellows: Ana Andrea Escobar
Administrative support: Beatriz Martín

Abstract

The major goal of the Suero Group is to develop new small molecule asymmetric activation modes and their application in solving important synthesis problems. We are exploiting single electron transfer chemistry for the catalytic generation of unusual reactive species able to evolve through unconventional C=C and C–H bond activations. Our group aims to apply the novel reactivity concepts for streamlining the synthesis of relevant bioactive molecules in diverse areas of disease but also for the development of site-selective functionalizations of biomolecules. Currently, we are developing a novel diastereoconvergent 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 cyclopropane ring is an important cyclic motif found in many natural products, medicines or crop protection agents. The synthesis of this cycloalkane motif has inspired synthetic chemists over the last decades to develop novel technologies based on reactive methylene species able to react with alkenes through formal [2+1] cyclizations in a diastereospecific manner (Fig. 1). One important synthetic challenge has been to find alternative methylene sources to iodomethylzinc reagents (a), diazomethane (b) or sulfur/nitrogen ylides (c), able to functionalize electronically diverse alkenes in an efficient manner. It is worth to highlight that the vast majority of methodologies developed are based in the same reactivity principles involving electrophilic and nucleophilic divalent methylene sources and, it is surprising to see the scarcity of synthetic methods based on radical analogues (d).

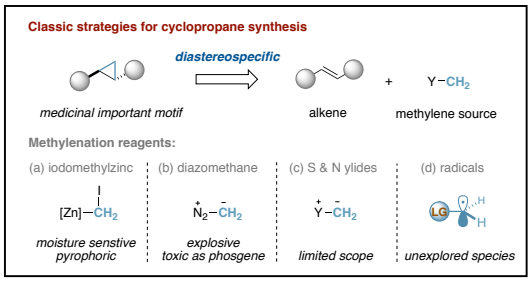


Fig. 1 – *Current alkene methylenation methodologies*

Recently, we wondered whether a single-electron transfer process on simple methylene reagents bearing two very good leaving groups could provide access to a new class of radical species with carbenoid behavior. This novel carbene equivalent could provide access to a new reactivity platform using radical species, which would complement current synthetic methodologies (Fig. 2).

A deep exploration of this concept allowed us to recently discover and develop a new alkene cyclopropanation reaction based on photoredox catalysis that uses diiodomethane as direct methylene source and mixtures of alkenes as starting materials(b). This process selectively leads to *trans*-disubstituted cyclopropanes in a fully diastereoconvergent manner – a remarkable feature of this new cyclopropanation concept. The reaction has an excellent functional group tolerance and provides access to cyclopropanes that are difficult to obtain using current methodologies. We have proved that the reaction involves the generation of a iodomethyl radical – (·)CH_2I – using different radical traps such as TEMPO. However, the origin of the diastereoconvergence is not clear yet and a light-driven isomerization mechanism seems to be unlikely based on experimental observations. The behavior of this novel methylene equivalent is opposite to the traditional reactivity observed for the corresponding counterparts, the singlet and the triplet methylene species – (:)CH_2 –. Therefore, we plan to carry out computational studies to better understand this new reactivity.

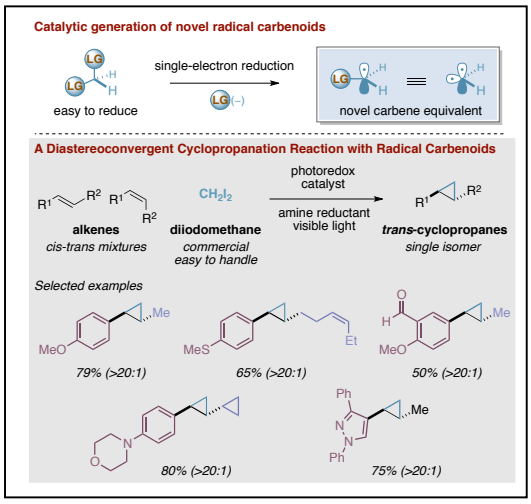


Fig. 2 - *A new cyclopropanation reaction that uses diiodomethane and E-Z alkene mixtures.*

Overall, we believe that the new cyclopropanation process, featured by its simplicity and flexibility, is useful and experimentally attractive to be used in the discovery of novel bioactive cyclopropane cores. Alkene isomeric mixtures, made from a robust Wittig olefination, are transformed in *trans*-cyclopropanes by using cheap and easy-to-handle diiodomethane. Expansion of the alkene scope, scalability studies, and the development of an asymmetric version are currently underway in our laboratory.

Articles

"A Diastereoconvergent Alkene Cyclopropanation Reaction with Radical Carbenoids"
Manuscript in preparation
Ana M. del Hoyo, Ana García-Herraiz, Marcos G. Suero.