

RECENT ADVANCES IN SELECTIVE [2+2] CYCLOBUTANE FORMATION

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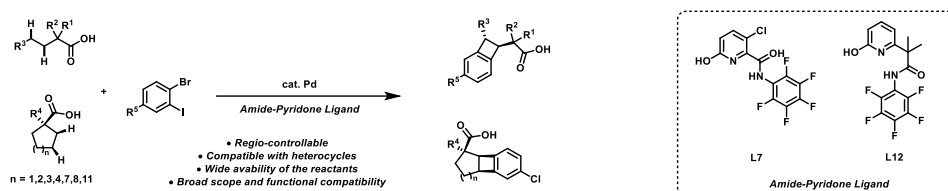
Introduction

Cyclobutanes have always been ideal targets for synthetic chemists due to their abundance in various useful natural products and their ability to form larger rings. One of the best ways to form cyclobutanes is [2+2] reactions, which can generate the desired targets in one single step. In the past decades, enormous [2+2] reactions that are regio- or stereoselective were published.³ However, the problem is still obvious, each reaction requires a specific set of substrates which limits their usage. In this report, we will be discussing the most up-to-date solutions to these issues.

Metal catalysis

Metal catalysts are known for their broad applicability. Particularly, complexes based on palladium have seen utility, ranging from coupling to C-H activation. In 2023, Ji-min Yang and colleagues discovered a regio-controllable [2+2] benzannulation which is catalyzed by palladium.⁴ This method can form a cyclobutane directly from adjacent C(sp³)–H bonds. Despite several requirements for the substrate, this alkane-based [2+2] is highly enabling and impactful.

Scheme 1. Regio-controllable [2+2] Benzannulation with Palladium



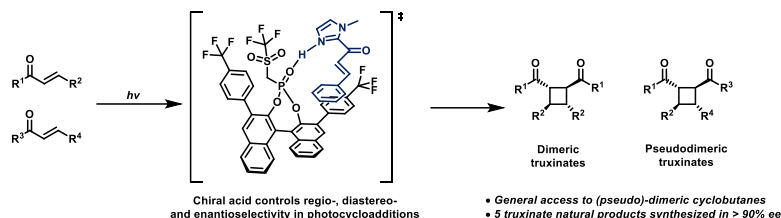
Allenes are also interesting starting materials for cyclobutane formation. Wanlong Xiao and coworkers developed an enantioselective [2+2] cycloaddition of allenyl imide with substituted alkenes in 2022.⁵ They chose chiral *N, N'*-dioxide-magnesium (II) complex as their catalyst. In the same year, Wenxuan Xu et al. achieved regio- and diastereoselectivity in similar substrates using rare-earth catalysts.⁶

Organic catalysis

Non-metal catalysts can also be utilized in generating cyclobutanes with good selectivity. One good example is a Tehshik P. Yoon lab's paper published in 2023.⁷ They developed a chiral

phosphorus acid catalyst that promotes highly selective visible-light photocycloadditions. This method requires an imidazole directing group; however, it can be removed in one step, and products can be quickly transformed into natural products.

Scheme 2. Enantioselective Photocycloadditions with Chiral Phosphorus Acid



Enzyme catalysis

When it comes to selectivity problems, directly holding the substrates and keeping them in the right direction sounds like the most straightforward solution. While these structures must be highly complicated, Nature has given us some inspiration. In 2022, two papers reported enantioselective [2+2]-cycloadditions with triplet photoenzymes, achieving good selectivity.⁸⁻⁹ The main drawbacks were narrow and highly tailored substrate scope and availability of these enzymes to broader synthetic community.

Outlook

[2+2] reactions have kept on attracting people's interest over centuries. Generating regio-, stereo-, and enantioselective cyclobutanes can be of great importance in synthesis. In the future, further expanding the substrate scope will most probably remain a major focus.

References

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