Docket #: S22-298

A method for the construction of aminocyclobutanes from copper-catalyzed aqueous [2+2] cycloadditions of unactivated olefins

Researchers in the Burns group at Stanford designed a reaction methodology that allows for a green and inexpensive cycloaddition of amine or amide-containing unactivated olefins for the synthesis of biologically relevant cyclobutanes. Traditional [2+2] cycloadditions rely on electronically activated olefins to drive the reaction, which limits the scope of the products and requires additional chemistry to remove undesired activating functional group. Copper (I)-catalyzed photochemical cycloaddition can engage unactivated olefins but is air-sensitive and suffer from compatibility and reactivity problems.

The Burns group devised a new aqueous copper (II)- catalyzed reaction that allows for cycloadditions of olefins containing basic functional groups such as amines and amide, which are chemically important structures in many biologically active molecules. The reaction is environmentally friendly, water-tolerant, inexpensive and easily scalable, and can be done in any organic synthesis labs. This method is easily applicable to large-scale production of strained cyclobutanes scaffold in many pharmaceutical compounds, including but not limited to piperidine and pyrrolidine.

Applications

- Large-scale production of strained building blocks in pharmaceutical industries
- Research tools for synthesis of novel cyclobutane-containing compounds

Advantages

- Environmentally friendly, scalable and user friendly
- Reaction run in water, and utilize inexpensive copper (II) salts and low-intensity UV light irradiation
- Tolerant of biologically relevant amide or amine-containing unactivated olefin
- Readily incorporated into small molecule synthesis and pharmaceutical synthesis

Publications

- Mansson, Carl MF, and Noah Z. Burns. "Aqueous Amine-Tolerant [2+ 2] Photocycloadditions of Unactivated Olefins." *Journal of the American Chemical Society* 144.43 (2022): 19689-19694.

Patents

- Published Application: WO2024030363
- Published Application: 20260337163

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