Switchable regioselectivity in amine-catalysed asymmetric cycloadditions

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With the support by the National Natural Science Foundation of China, a collaborative study by the research groups led by Prof. Chen Yingchun (**陈应春**) from Sichuan University and Dr. Ouyang Qin (**欧阳勤**) from the Third Military Medical University demonstrates switchable regioselective [6+2], [4+2] or [2 + 2] cycloaddition reactions with α′-alkylidene-2-cyclopentenones via aminocatalysis, producing a spectrum of chiral frameworks with high structural diversity and complexity, which was published in *Nature Chemistry* (2017, DOI: 10.1038/NCHEM.2698).

Asymmetric cycloadditions provide a straightforward strategy to produce useful chiral cyclic materials. One of the long-standing challenges in this field is the accomplishment of some uncommon cycloaddition reactions. It is also highly desirable to realize switchable regio- and chemoselective cycloaddition reactions from the same set of starting materials under readily tuned catalytic conditions, thus constructing diverse compound libraries helpful for drug discovery studies.

Our group developed a variety of cycloaddition reactions with the *in situ* formed HOMO-raised enamine species. Recently, we found that 4-aminofulvene intermediates could be generated between α′-alkylidene-2-cyclopentenones and a chiral primary amine catalyst, and underwent different regioselective cycloadditions by slightly tuning substrate combinations or reaction conditions. They could act as 6π components to accomplish γ, β′-regioselective asymmetric [6 + 2] cycloadditions with 3-olefinic (7-aza) oxindoles, furnishing fused bicycles with five contiguous stereogenic centers; the reactions completely switched to β, γ-regioselective [2+2] cycloadditions with maleimides to access fused cyclobutanes. In addition, the same set of substrates could proceed in an α, γ-regioselective [4 + 2] cycloaddition fashion by employing an unprecedented dual catalysis of amines and thiols.

This work demonstrates the power of aminocatalysis to construct chiral compound libraries with high structural diversity through switchable intermolecular cycloaddition reactions.

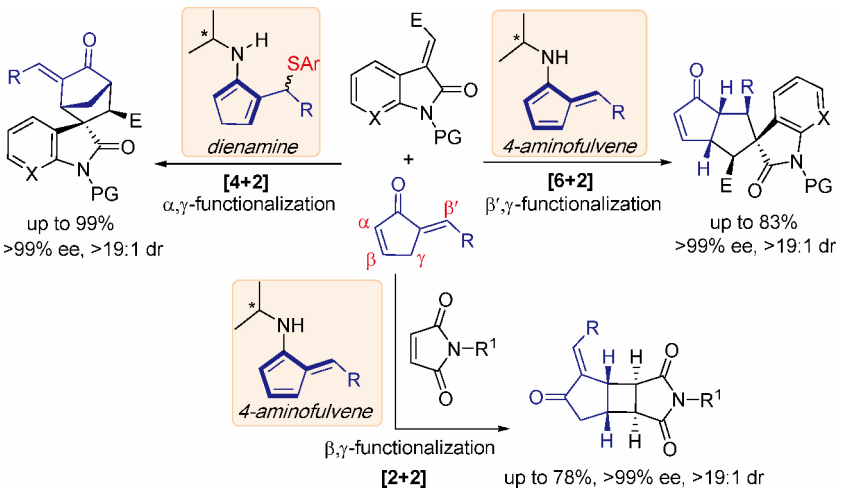

Figure Switchable regioselective cycloaddition patterns.