A Novel Asymmetric Synthesis Strategy for Enantioselective Cyclopropane Used as Pharmacophore Motifs in Medications

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Chiral cyclopropanes are privileged structural motifs in pharmaceutical chemistry, essential for enhancing the potency and metabolic stability of therapeutics, including next generation antivirals, anticancer agents, and cardiovascular inhibitors. However, conventional synthesis remains a sustainability bottleneck, using explosive diazo precursors and transition metals like Rhodium. This research introduces an unprecedented, metal free enantioselective cyclopropanation strategy. For the first time, benzyl halides are utilized as radical precursors under mild conditions by integrating visible light photoredox activation with chiral iminium organocatalysis. Under blue LED irradiation, benzyl halides undergo homolytic cleavage to generate benzyl radicals that engage alpha,beta-unsaturated aldehydes activated by a chiral secondary amine catalyst. Through a radical polar crossover mechanism, the system closes to form enantioenriched cyclopropane rings. Optimized reaction conditions yielded a 78 percent isolated yield with a 90 percent enantiomeric excess, as confirmed by Chiral HPLC and 1H NMR spectroscopy. Comparative analysis showed that reactions performed in air dropped to a 42 percent yield, validating the oxygen-sensitive radical pathway and the necessity of an inert argon atmosphere. This methodology operates at room temperature using photons as energy input, achieving high atom economy while eliminating toxic metallic residues. By replacing rare earth metals with organic molecules and light, this study transforms a long-standing synthetic challenge into a safe, scalable, and environmentally responsible solution. It represents a conceptual leap in radical organocatalysis, pioneering a new class of light-driven asymmetric transformations for sustainable drug discovery.

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