Enantioselective Tandem Michael Addition and Cyclization Reaction Enabled by Dual Organo/Copper Catalysis: Access to Functionalized 4H-Pyrans

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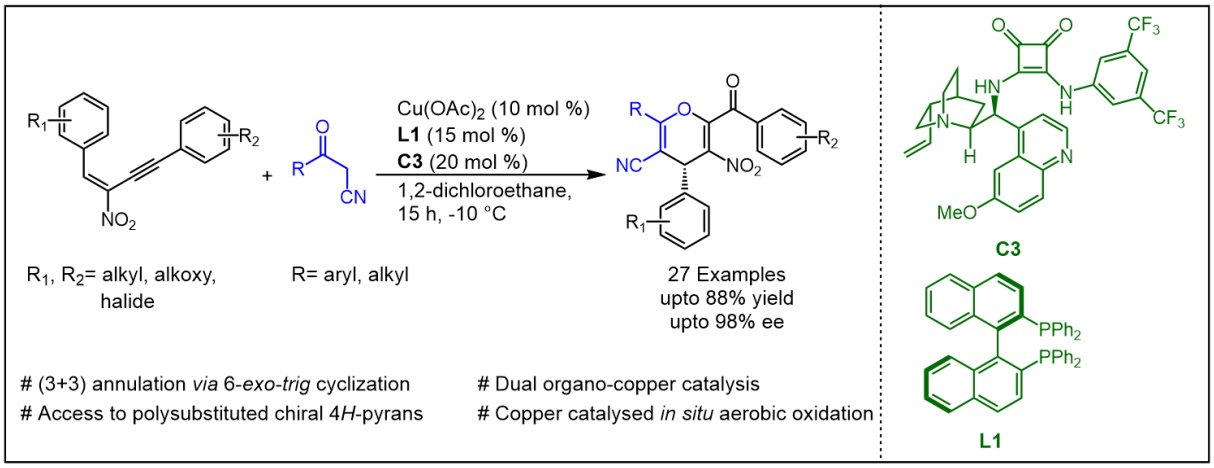
Abstract



An enantioselective (3+3) annulation for the synthesis of polysubstituted non-fused 4H-pyrans between 1,3-nitroenynes and α-cyano ketones has been developed using a cooperative organo/copper-ligand dual catalytic system. The double activation catalysis employs both the catalytic systems simultaneously to synergistically activate different substrates or reaction sites, thereby enabling complex and highly enantioselective transformations that are difficult or even impossible to achieve using a single catalytic system. The transformation proceeds through an enantioselective tandem Michael addition catalyzed by the synergistic effect of organocatalyst and metal-ligand complex, followed by Lewis acid- catalyzed annulation, furnishing pentasubstituted 4H-pyran derivatives in good yields and good to excellent enantioselectivities. This methodology highlights a unique reactivity of nitroenyne via 6-*exo-trig* cyclization followed by copper catalyzed *in situ* oxidation of benzylic protons that enables the incorporation of an oxygen atom, thereby offering a versatile handle for further structural elaboration. Mechanistic investigations were conducted to elucidate the reaction pathway, and its practical applicability was demonstrated through a scale-up reaction and versatile post-synthetic modifications.

Keywords

Enantioselective reaction, cooperative organo-copper catalysis, (3+3) annulation, 6-*exo-trig* cyclization, *in situ* aerobic oxidation.