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Catalytic enantioselective synthesis of cyclobutenes from alkynes and alkenyl derivatives

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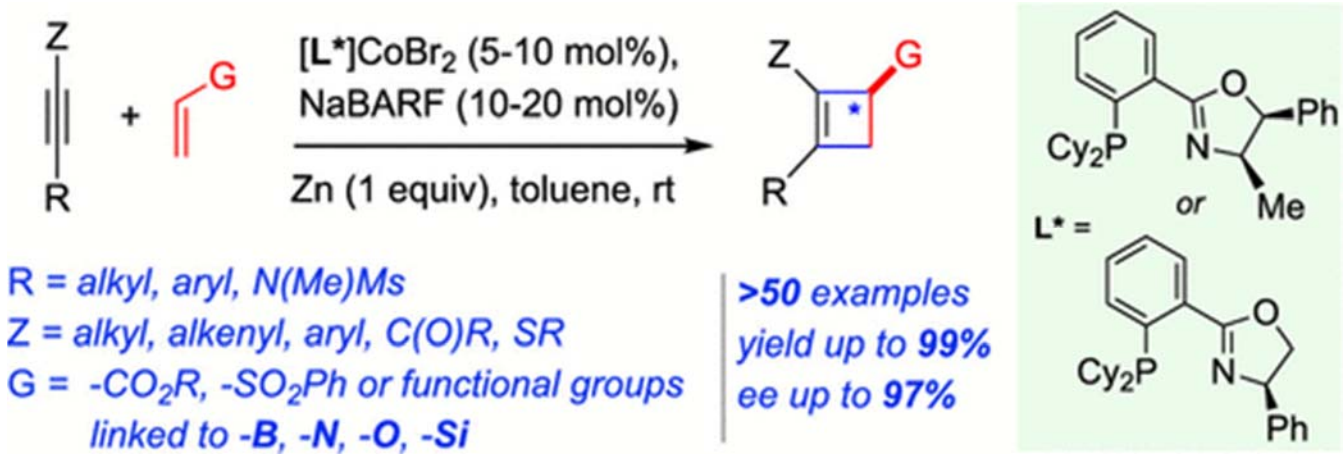
Discovery of enantioselective catalytic reactions for the preparation of chiral compounds from readily available precursors, using scalable and environmentally benign chemistry, can greatly impact their design, synthesis, and eventually manufacture on the scale. Functionalized cyclobutanes and cyclobutenes are important structural motifs seen in many bioactive natural products and pharmaceutically relevant small molecules. The simplest approach to make cyclobutenes is through an enantioselective [2 + 2]-cycloaddition between an alkyne and an alkenyl derivative. Known reactions of this class that give acceptable enantioselectivities are of very narrow scope and are strictly limited to activated alkynes and highly reactive alkenes. Here, we disclose a broadly applicable enantioselective [2 + 2]-cycloaddition between a wide variety of alkynes and alkenyl derivatives, two of the most abundant classes of organic precursors. The key cycloaddition reaction employs catalysts derived from readily synthesized ligands and an earth-abundant metal, cobalt. Over 50 different functionalized cyclobutenes with enantioselectivities in the range of 86–97% ee are documented. In addition to this development, some of the novel observations made during these studies including a key role of a cationic Co (I)-intermediate, ligand and counter ion effects on the reactions, will be discussed.



Co-catalyzed enantioselective [2 + 2] cycloaddition