Asymmetric Catalysis

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Exceptional Selectivity in Cyclopropanation Reactions Catalyzed by Chiral Cobalt(II)–Porphyrin Catalysts**

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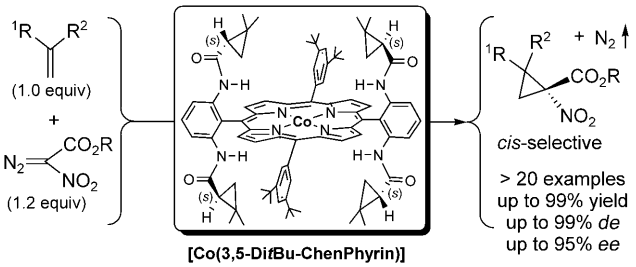
carbenes · cobalt · diazoacetates · enantioselectivity · porphyrinoids

The search for highly stereoselective olefin addition reactions has a long and continuing history, and cyclopropanation reactions of olefins using diazoacetates are core elements in this quest.[1] Catalytic methodologies, especially those built upon a platform of transition metals having chiral ligands, have stimulated developments that today offer diastereocontrol and enantioselectivities that approach the limits of stereoisomer detection.[2] Beginning with copper catalysis having chiral salen (salen = *N*,*N*′-bis(salicylidene)ethylenediamine) ligands[3] and progressing to chiral semicorrin[4] and bisoxazoline[5] ligands, rapid advances were made in enantiocontrolled intermolecular addition reactions of diazoacetates. Chiral dirhodium(II) carboxamidates fulfilled a role in intramolecular reactions[6] and, although results from many other transition metals and chiral ligands have been reported, none have surpassed the overall stereocontrol provided by copper and dirhodium catalysts until the recent emergence of cobalt(II)–porphyrin catalysts.

One of the first successes in enantioselective intermolecular cyclopropanation reactions was a report by Nakamura et al. of a chiral cobalt(II)–dioximato complex derived from camphor,[7] but difficulties in catalyst homogeneity with chiral dioximato ligands inhibited additional studies. Subsequently, Katsuki and co-workers,[8] and Yamada and co-workers[9] reported intriguing results in stereocontrolled cyclopropanation reactions using chiral cobalt(III)–salen complexes; however, at least one of the key ingredients for a breakthrough (yield, diastereoselectivity, or enantioselectivity) was missing with these catalysts. Whereas copper and dirhodium catalysts both promote additions to simple and conjugated olefins and not to unsaturated esters, nitriles, and ketones, cobalt catalysts showed activity even with unsaturated esters and nitriles. Taking cobalt catalysis one step further, Zhang and co-workers combined cobalt(II) with chiral porphyrins to produce catalysts that exhibit unique reactivities and exceptional selectivities.[10] In this recent manifestation Zhang and co-workers have reported applications using α-nitro-diazoacetates to prepare *cis*-cyclopropanes in high yield with exceptional diastereo- and enantioselectivity (Scheme 1).[11]



Scheme 1. The use of a cobalt(II)–porphyrin catalyst for the cyclopropanation of olefins. Electron-sufficient, electron-neutral, and electron-deficient olefins can be used.

Inspired by the potential of vitamin B_{12} as a catalyst, aquocobalamin and some of its derivatives were demonstrated to be effective for the cyclopropanation of styrene derivatives using ethyl diazoacetate, but with modest diastereo- and enantioselectivities.[12] As with other catalytic systems, the challenge was to enhance both the diastereocontrol and the enantioselectivity in cyclopropanation reactions using commonly accessible diazoacetates; this was first addressed by Zhang and co-workers in 2003 using modified tetraphenylporphyrins, the most successful being those with chiral cyclopropylcarboxamide attachments.[10] Prior to this undertaking, Kodadek and co-workers introduced chiral porphyrin ligands for rhodium-catalyzed cyclopropanation reactions using diazoacetates, and found low selectivities but high turnover numbers.[13] The ease of porphyrin modification has been critical to building chiral tetraphenylporphyrins as effective ligands, and Zhang and co-workers have accomplished this by using palladium-catalyzed coupling processes of chiral amides on bromoporphyrin templates (Scheme 2).

Beginning with the initial findings of exceptional diastereocontrol and enantioselectivity in the reactions using styrene and [Co(3,5-Di*t*Bu-ChenPhyrin)],[10b,d] Zhang and co-workers reported that similarly highly stereoselective cyclopropanation reactions could be achieved using *p*-tosyldiazomethane and [Co(2,6-DiMeO-ZhuPyrin)] (Scheme 3); and these carbenoid addition reactions could be performed by using the alkene as the limiting reagent rather than the

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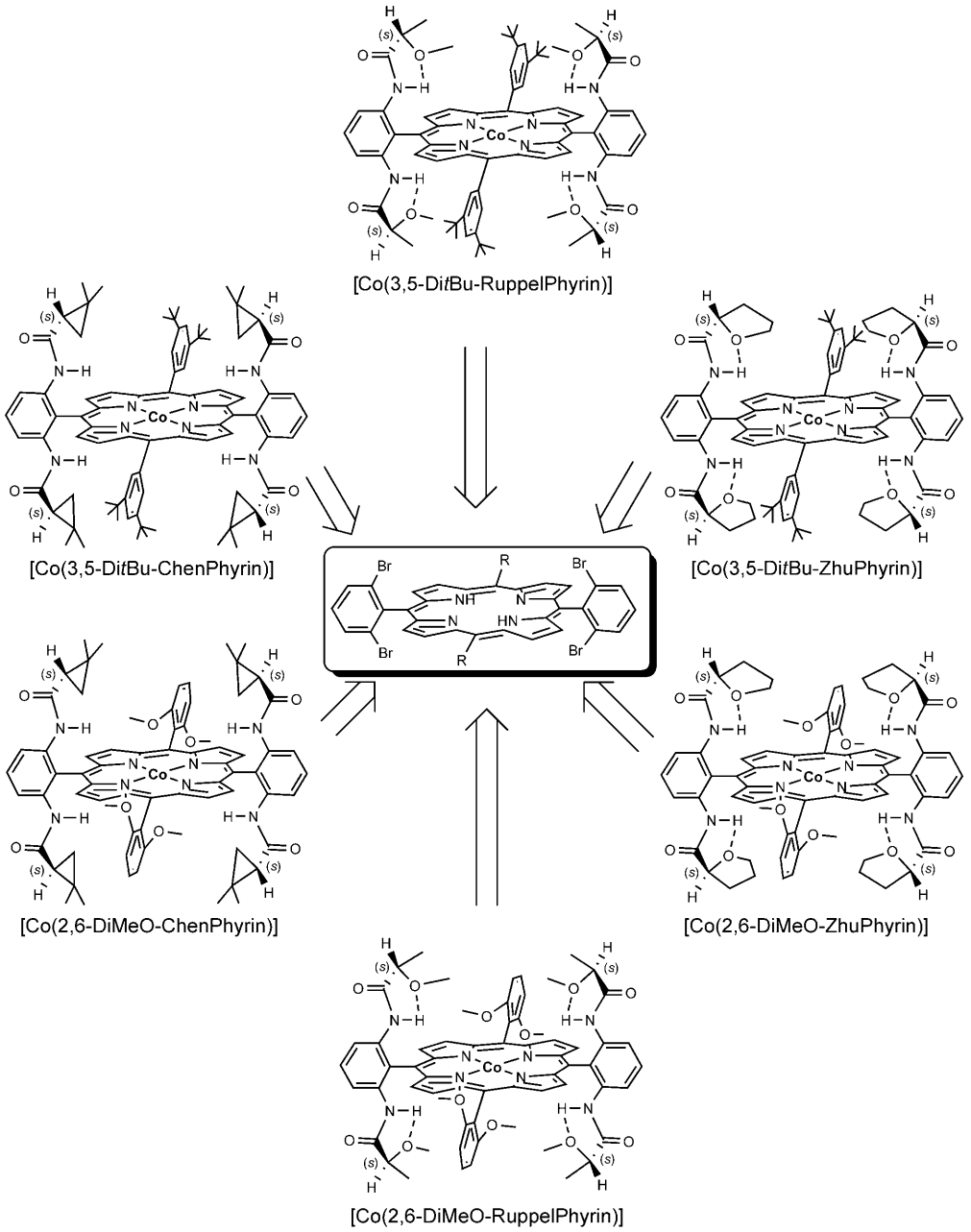
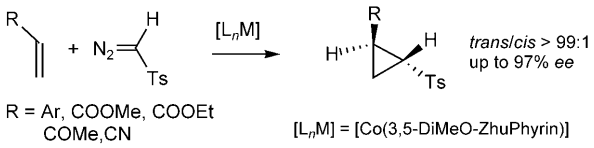
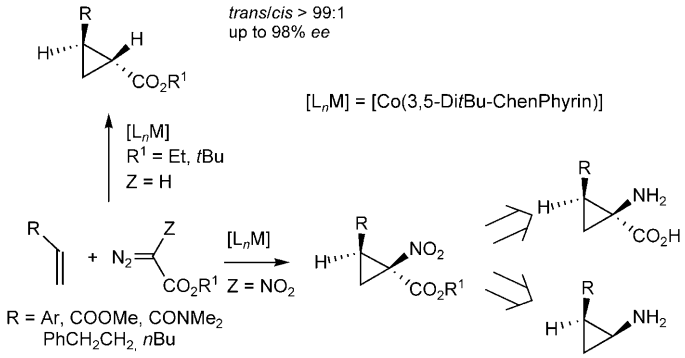


Scheme 2. A diverse array of chiral porphryins can be accessed using palladium-catalyzed coupling chemistry.

common practice of using excess alkene.[10e] Subsequent to reactions using tosyldiazomethane, the latest application, converted nitrodiazoacetates[14] into the corresponding cyclopropanes,[11] which provide convenient access to cyclopropyl amino acids and cyclopropyl amines (Scheme 4). These transformations are performed stoichiometrically without high dilution and at room temperature, and the diastereocontrol for the *trans* isomer (where R and $COOR^1$ are *trans*) is $>99{:}1$ when $R^1 = t$Bu. Relative to chiral copper and rhodium catalysts, the chiral porphyrin catalysts are unprecedented in their stereocontrol, their ability to effect cyclopropanation with stoichiometric or near stoichiometric amounts of alkenes avoiding carbene dimer formation, and their catalytic reactivity. They are also unique in their ability to undergo addition to α,β-unsaturated carbonyl compounds and nitriles,[10d] and this characteristic distinguishes them from copper and rhodium catalysts, which are generally understood to undergo electrophilic addition to alkenes and do not undergo the catalytic cyclopropanation with electron-deficient alkenes. Additionally, stereoselective applications to



Scheme 3. Cyclopropanation using tosyldiazomethane.



Scheme 4. Potential future directions for the use of cobalt(II)–porphryin catalysts for generating chiral cycloprpopanes.

other diazo compounds are anticipated, and those with which high selectivities have not yet been achieved (diazomalonates, diazoacetoacetates, for example) may be realized with chiral cobalt(II)–porphyrin catalysts. The mechanism for the addition will continue to be a topic of considerable interest.

Whereas the principal breakthroughs with these catalysts have occurred in cyclopropanation reactions, the catalytic aziridination reactions with sulfonyl and phosphoryl azides have also been reported.[15] Enantioselectivities are modest, but the application using azides rather than iodonium ylides is a promising direction. The ability of the porphyrin ring to serve as an electron sink, stabilizing transition metals in their reactions and moderating reactivities, is abundantly evident in this research with chiral cobalt(II)–porphyrin catalysts.

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