

ASYMMETRIC CYCLOPROPANATION OF OLEFINS BY METAL CARBENOIDS

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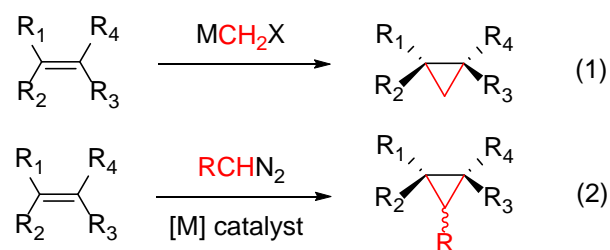
BACKGROUND

The highly strained cyclopropane unit, present in many in natural and bioactive compounds, is of special interest to both theoreticians and synthetic chemists.¹ Starting in the 1950s, the search for efficient ways to construct this moiety has resulted in tremendous progress.² Among the methods studied, cyclopropanation mediated by metal carbenoids is arguably the most important.

Since most of the cyclopropane containing intermediates and targets in organic synthesis are chiral, it is highly desirable to generate this unit in a stereoselective manner. The cyclopropanation of olefins by metal carbenoids, capable of generating up to three contiguous stereocenters, faces the challenges of both diastereoselectivity and enantioselectivity. The use of directing groups, chiral auxiliaries and chiral ligands have been utilized for the asymmetric synthesis of cyclopropanes.

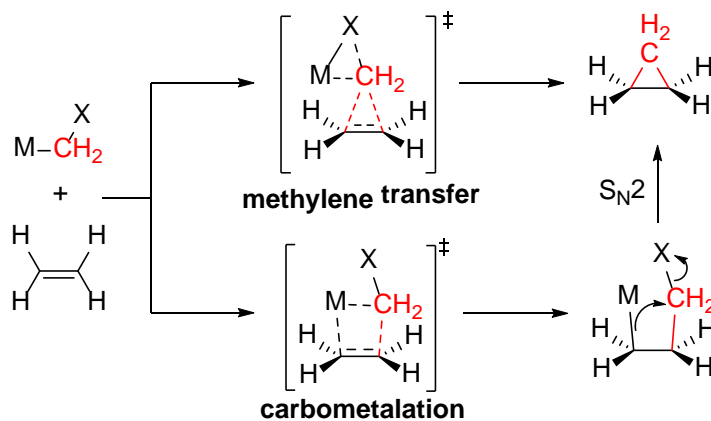
METAL CARBENOIDS IN OLEFIN CYCLOPROPANATION

Olefin cyclopropanation mediated by metal carbenoids is divided into two classes: halomethylmetal-mediated cyclopropanation (eq. 1) and transition metal-catalyzed decomposition of diazo compounds (eq. 2). In both cases the configuration of the olefin is retained in the cyclopropane product.²



Cyclopropanation by Halomethylmetals

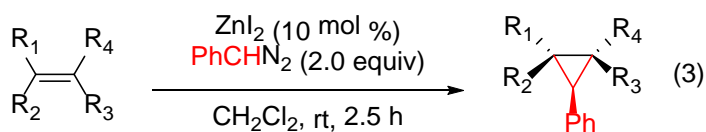
Since the first report by Simmons and Smith, various reagents have been used in halomethylmetal-mediated cyclopropanation (eq. 1; M = Zn, Sm, Al, Li). Despite the common usages and historical importance of the Simmons-Smith (SS) and related reactions, their mechanism is still a subject of debate. Experimental and computational



Scheme 1. Two pathways of Simmons-Smith reaction

studies support a concerted methylene transfer over a stepwise carbometalation mechanism (Scheme 1).³

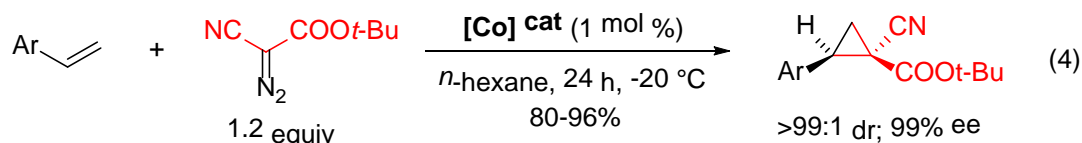
The SS and related reactions proceed in a highly stereoselective fashion with chiral substrates. However, with olefins void of stereocenters in proximity, progress in asymmetric cyclopropanation has been slow. Recently, the catalytic, enantioselective SS reactions of certain substrate classes have been reported by several research groups. Charette reported the use of chiral phosphoric acids⁴ and later, zinc salts⁵ (eq. 3) as catalysts in the SS reaction. Reactions using substoichiometric amounts of chiral ligands, including amino alcohols and diamines have also been reported.⁶



Various transition metals catalyze the decomposition of diazo compounds to generate metallo-carbenes, and in the presence of olefins this process often leads to effective cyclopropanation (eq. 2). The stereochemical outcome of the reaction is controlled by chiral ligands, as shown in seminal studies on copper-catalyzed cyclopropanation using semicorrin⁷ and bisoxazoline⁸ ligands. Significant advances have been made in the last ten years with a variety of diazo reagents bearing one or two electron withdrawing groups (eq. 4),^{9,10} and “push-pull” diazo compounds.¹¹

Transition Metal-catalyzed Decomposition of Diazo Compounds

Future directions in the field include the development of diastereoselective and enantioselective catalysts applicable to unfunctionalized alkenes of different substitution patterns and more effective reaction conditions to utilize diazomethane in cyclopropanation.



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Future Directions

Substrate generalization remains a challenge in asymmetric, metal-mediated cyclopropanation. Future directions in the field include the development of diastereoselective and enantioselective catalysts applicable to unfunctionalized alkenes of different substitution patterns and more effective reaction conditions to utilize diazomethane in cyclopropanation.

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