Radical Differentiation of Two Ester Groups in Unsymmetrical Diazomalonates for Highly Asymmetric Olefin Cyclopropanation

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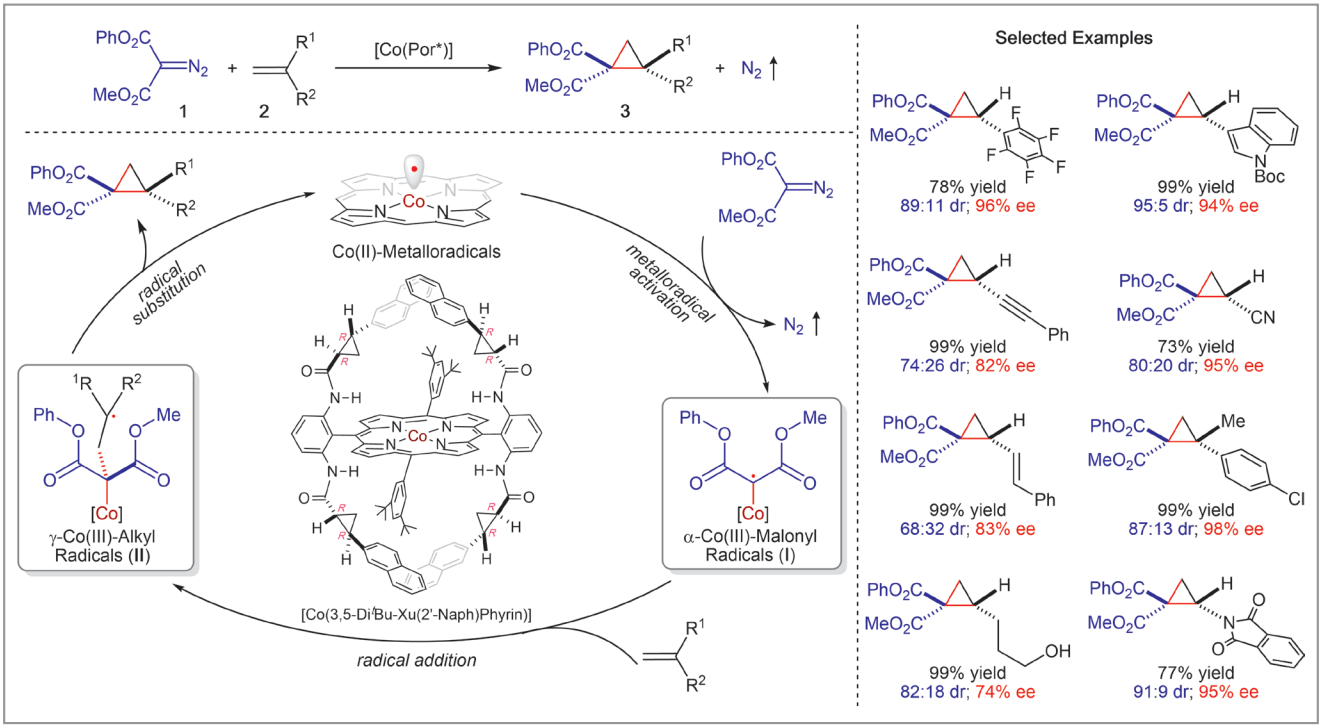
Metal-catalyzed asymmetric cyclopropanation of alkenes with diazomalonates offers a potentially attractive approach for the construction of 1,1-cyclopropane diesters – a class of valuable three-membered carbocycles that serve as important building blocks for organic synthesis – with effective control of stereoselectivity. Due to the inherent stereocontrol challenge associated with two similar electron-withdrawing ester groups, the existing catalytic systems involving electrophilic metallocarbene intermediates have shown limited substrate scope and have been hampered by low enantioselectivity.[1] One conceptually different strategy for asymmetric cyclopropanation with unsymmetrical diazomalonates has recently been reported by the research group of Professor X. Peter Zhang at Boston College (Chestnut Hill, MA, USA). Professor Zhang and co-workers have demonstrated that Co(II) complexes of porphyrins [Co(Por)], as stable 15e-metalloradicals with well-defined open-shell d^7 electronic structure, are capable of homolytic activation of diazo compounds and organic azides, generating α-Co(III)–alkyl radicals and α-Co(III)–aminyl radicals, respectively, as kinetically competent catalytic intermediates for stereoselective radical processes. "In the past two decades, Co(II)-based metalloradical catalysis (MRC) has been successfully applied for the development of various types of stereoselective radical transformations, including olefin cyclopropanation,[2] olefin aziridination,[3] C–H alkylation,[4] and C–H amination[5] as well as radical cascade[6] reactions," said Professor Zhang.

As a new synthetic application of Co(II)-MRC, Professor Zhang and co-workers have shown in this featured paper the development of Co(II)-catalyzed asymmetric cyclopropanation of alkenes with unsymmetrical diazomalonates. "Both excellent reactivity and selectivity have been achieved for this challenging cyclopropanation reaction through the fine-tuning of the D_2-symmetric chiral amidoporphyrin, to adopt



Scheme 1 Co(II)-based metalloradical catalysis for highly stereoselective olefin cyclopropanation with unsymmetrical diazomalonates

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suitable environments that can govern the stereochemical course of the catalytic process (Scheme 1)," said Professor Zhang, who continued: "We have found that [Co(3,5-Di^{t}Bu-Xu(2′-Naph)Phyrin)] is a highly effective catalyst for asymmetric cyclopropanation of various alkenes with methyl phenyl diazomalonate (MPDM). The multiple noncovalent attractive interactions between the catalyst and the substrates, both diazomalonate and alkene, help to differentiate the two similar ester groups and deliver the products in a highly stereoselective fashion." He added: "We have shown that the Co(II)-based metalloradical system can smoothly activate unsymmetrical methyl phenyl diazomalonate even at room temperature, with effective differentiation of the two ester groups to cyclopropanate wide-ranging alkenes, affording 1,1-cyclopropane diesters bearing two contiguous stereogenic centers in high yields, with excellent control of both diastereo- and enantioselectivity."

To support the hypothesis of an underlying stepwise radical pathway for the Co(II)-based catalytic process, Professor Zhang and co-workers performed combined computational and experimental studies, that provided multiple lines of convincing evidence. "The DFT calculations also revealed the existence of multiple H-bonding and π-stacking interactions in transition states involved with the cyclopropanation reaction. In addition to the rigidification of conformations, these noncovalent attractive interactions can cooperatively lower the activation barriers of the transition states, which may enhance catalytic reactivity and improve stereoselectivities of the cyclopropanation," remarked Professor Zhang. Several stereospecific transformations from the resulting enantioenriched 1,1-cyclopropane diesters were demonstrated in this work, which the authors believe will find useful synthetic applications for the construction of other chiral organic molecules. Professor Zhang concluded: "This new catalytic system, which offers a streamlined entry to chiral 1,1-cyclopropane diesters, has solved one of the long-standing challenges in the field of asymmetric cyclopropanation. It once again showcases the power and potential of MRC in addressing challenging problems in organic synthesis through a fundamentally different approach."

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X. Peter Zhang received his Ph.D. from the University of Pennsylvania (USA) in 1996 under the direction of Prof. Bradford Wayland. He then undertook postdoctoral work at the Massachusetts Institute of Technology (USA) as a National Institutes of Health (NIH, USA) Postdoctoral Fellow during the period of 1996–2001, first with Prof. Stephen Lippard and then with Prof. Stephen Buchwald. Dr. Zhang began his independent career as assistant professor of chemistry at the University of Tennessee (USA) in 2001. He moved to the University of South Florida (USA) as associate professor of chemistry in 2006 and was promoted to professor in 2010. In 2015, Dr. Zhang joined Boston College (USA) as professor of chemistry. The research program of his laboratory has been focused on the formulation of metalloradical catalysis (MRC) as a conceptually new strategy to guide the development of general approaches for effectively controlling reactivity and selectivity of radical processes.

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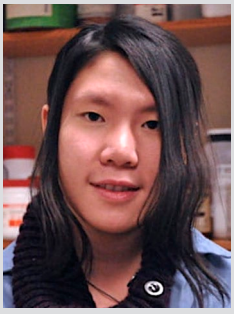

J. Xie

Jingjing Xie is currently a graduate student at Boston College (USA) in the group of Professor X. Peter Zhang, where she has carried out research work focusing on the application of 1,4-hydrogen atom abstraction as a key step for synthetic methodology development to construct biologically valuable molecules via Co(II)-based metalloradical catalysis. Before her graduate studies at Boston College, she received her M.S. degree in analytical chemistry from the University of Massachusetts Dartmouth (USA). Jingjing will join Amgen as a medicinal chemist after completing her graduate studies at Boston College.

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