Challenging *Asymmetric* Alkene Cyclopropanation by *Unsymmetrical* Diazomalonates

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In this issue of *Chem Catalysis*, X. P. Zhang and co-authors reported the catalytic performance of D_2-symmetric chiral amidoporphyrin in promoting the synthesis of 1,1-cyclopropanediesters, during which two adjacent stereogenic centers are formed. The carbene transfer from unsymmetrical diazomalonates to a large scope of challenging alkenes occurred with high stereocontrol thanks to the efficiency of Co(II)-based metalloradical catalytic system.

The reaction between a double bond and a diazo reagent is a valuable procedure to insert into an organic scaffold a cyclopropane moiety which, thanks to the ring-strain, confers to the resulting molecule a remarkable chemical reactivity.[1] In addition, cyclopropane-containing molecules often display pharmaceutical and biological properties.[2] In order to implement high-performing, cost-effective and safe technologies for carbene transfer reactions, it is imperative to minimize risks related to the potential hazard of diazo compounds (i.e. by applying continuous-flow processes[3] and/or producing the desired diazo molecule *in situ*[4]) and/or maximize the catalytic performance of the methodology. Among the numerous synthetic protocols promoting alkene cyclopropanations, those based on the diazo reagent photolysis[5] or involving non-noble metals coordinated to ligands playing an active role in the diazo activation, have recently receiving an increasing attention because high catalytic activities are coupled with low environmental impact. In this context, the use of iron[6]- and cobalt[7] complexes of 'non-innocent'[8] and opportunely designed porphyrin ligands is an efficient strategy for taking advantage of the great potential of radical-based processes without losing stereocontrol, which is a typical drawback of reactions involving radical intermediates. In particular, cobalt(II) porphyrin-based metalloradical catalysis (MRC)[9] is demonstrating to be very competent for accomplishing the chemo- and stereoselective transfer of a carbene functionality to a large plethora of organic substrates.

In this issue of Chem Catalysis, X. P. Zhang and co-workers report[10] the catalytic efficiency of D_2-symmetric chiral amidoporphyrin cobalt(II) complex, Co(D_2-Por*), (D_2-Por* = 3,5-Di^{t}Bu-Xu(2'-Naph)Phyrin) in promoting the synthesis of chiral 1,1-cyclopropanediesters by the reaction of unsymmetrical methyl phenyl diazomalonate (MPD) with differently substituted alkenes (Figure 1). The synthetic applicability of the reported methodology was confirmed by the reactivity of a broad range of substrates. The reaction performed well by using styrene derivatives and, despite the electronic nature of the employed aromatic alkene, corresponding 1,1-cyclopropanediesters were always formed in very high yields and excellent diastereo- and enantioselectivities (up to 99% yields, 94:6 dr and 97% ee). While the increase of the steric hindrance around the double bond did not affect reaction enantioselectivities, a decrease in both reaction yields and diastereoselectivities was observed when sterically hindered styrenes were used as starting materials. A remarkable chemo- and stereoselective control was achieved in the cyclopropanation of polyaromatic and heteroaromatic alkenes as well as conjugated dienes and enynes. It should be noted that poorly reactive unsaturated substrates, such as electron-deficient and aliphatic alkenes, reacted well under applied catalytic conditions. Finally, the presence of various functional groups was tolerated and they resulted unmodified in the resulting 1,1-cyclopropanediester. Generally speaking, the efficiency of the carbene transfer reaction from the unsymmetrical MPD procedure to the double

bond allows introducing two contiguous stereogenic centers in the target molecule with high yields, diastereo- and enantioselectivities (Reaction scope, Figure 1).

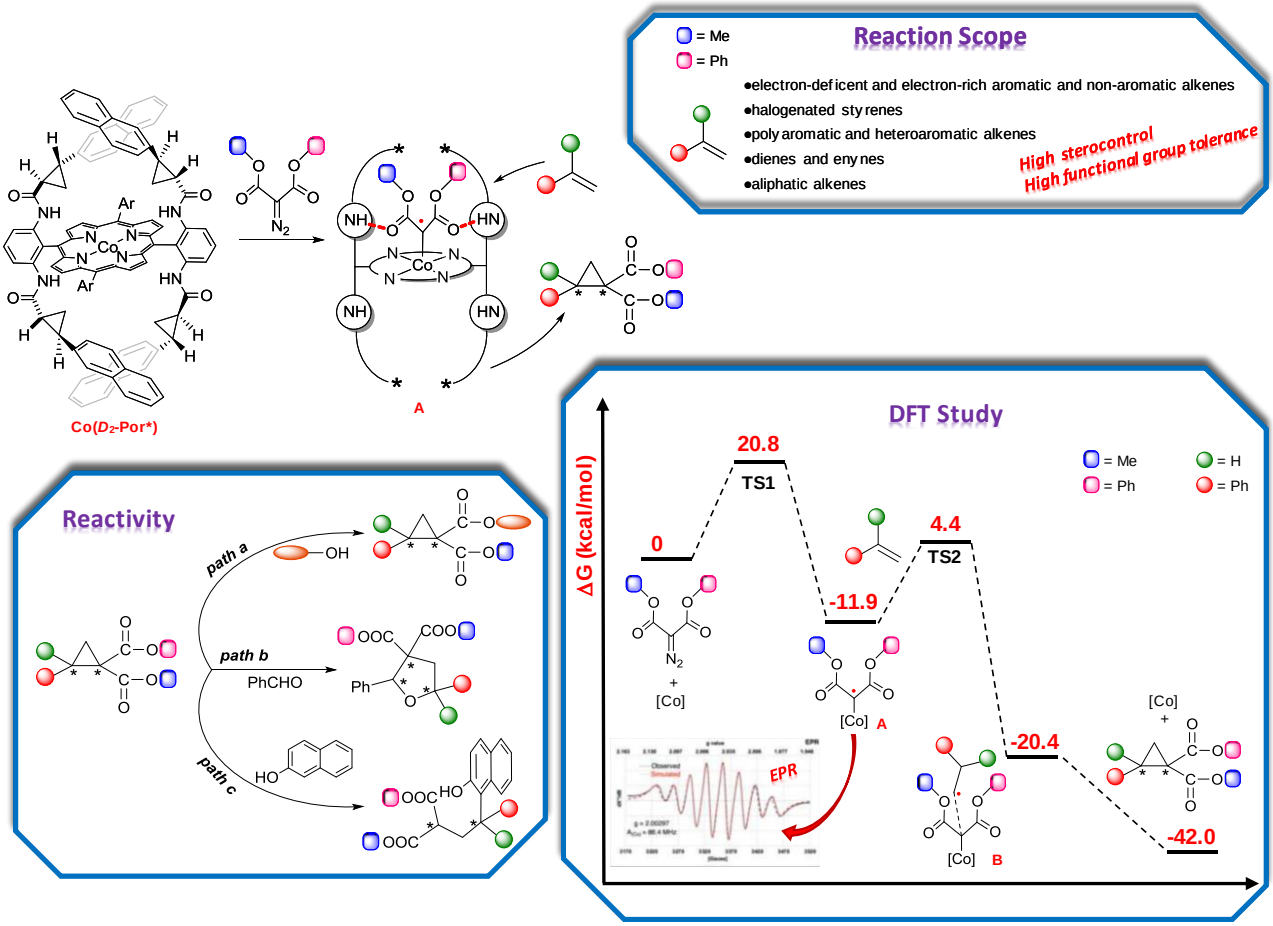

Figure 1. Alkene cyclopropanation by unsymmetrical methyl phenyl diazomalonate (MPD) catalyzed by Co(D_2-Por*) complex (D_2-Por* = 3,5-Di^{t}Bu-Xu(2'-Naph)Phyrin): reaction scope, mechanistic study and synthetic applications.

The DFT investigation, performed in order to propose a plausible mechanism, indicated that the reaction of MPD with Co(D_2-Por*) yields α-Co(III)-malonyl intermediate **A**, as the radical catalytically active species. The stability of the suggested intermediate was ascribed to the presence of a binding pocket in which multiple H-bonding and π-stacking interactions can be established between the porphyrin ligand and the coordinated carbene moiety. It was amply discussed how this structural arrangement is crucial to opportunely orientating the incoming alkene and reaching a high reaction sterocontrol (DFT study, Figure 1). The energy profile shown in Figure 1 indicates the metalloradical activation as the rate determining step of the reaction with a ΔG barrier of 20.8 kcal/mol for reaching the corresponding **TS1** transition state.

Thus, a model catalytic reaction was monitored by electron paramagnetic resonance (EPR) spectroscopy and high-resolution mass spectrometry with ESI ionization (ESI-HRMS) and, in accordance to theoretical calculations, both analyses supported the formation of the radical intermediate **A**. Finally, the lack of the reaction stereospecificity that was observed in the cyclopropanation of (*E*)- and (*Z*)-β-deuterostyrene with *tert*-butyl methyl diazomalonate, pointed out the occurrence of a stepwise radical mechanism, which explained the formation of all the four possible cyclopropane isotopomers. The ratio of the obtained diastereoisomers was dependent on the more-or-less facility of the rotation around the β-C−C bond in the γ-Co(III)-benzyl radical

species **B** (DFT study, Figure 1), which was in turn dependent on the steric hindrance of the employed cobalt catalyst.

In view of the high reaction selectivity, which permitted the formation of almost a single 1,1-cyclopropanediester, a practical utilization of the methodology can be envisage for transforming the obtained cyclopropane into other high-value fine chemicals. Some examples of the reactivity of synthesized cyclopropanes are depicted in Figure 1 (Reactivity, Figure 1). Firstly, the better leaving group capacity of phenoxy with respect to methoxy group was exploited for performing the selective transesterification of phenyl ester with several alcohols (path a, Figure 1) in a stereospecific manner. Then, considering the 1,3-dipole nature of 1,1-cyclopropanediesters, they were successfully reacted with benzaldehyde by 1,3-dipolar cycloaddition and resulting substituted tetrahydrofurans, presenting three stereocenters, were formed in high yields, diastereo- and enantioselectivities (path b, Figure 1). Finally, 1,1-cyclopropanediesters can be easily involved in ring-opening processes, as demonstrated by the very good catalytic performances of the reaction with nucleophilic agents, such as 2-naphthol, forming chiral acyclic diesters (path c, Figure 1).

In conclusion, the manuscript by X. P. Zhang and co-authors demonstrated the great synthetic versatility of cobalt(II)-based metalloradical catalysis to selectively introduce three adjacent stereocenters into an organic skeleton by reacting unsymmetrical diazo reagents with activated and non-activated alkenes. The tridimensional arrangement of the porphyrin ligand was crucial to correctly drive both the diazo activation and the transfer the so-formed carbene functionality to the incoming unsaturated molecule. The mechanism of the organic transformation was proposed on the bases of both experimental and theoretical data and it was fundamental to rationalize synthetic results. In addition, the reactivity of obtained 1,1-cyclopropanediesters was investigated and many others interesting fine-chemicals were synthesized by following very productive and selective reaction pathways.

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