Dual Activation Strategy to Achieve C–C Cleavage of Cyclobutanes: Development and Mechanism of Rh and Zn Co-catalyzed [4+2] Cycloaddition of Yne-Vinylcyclobutanones

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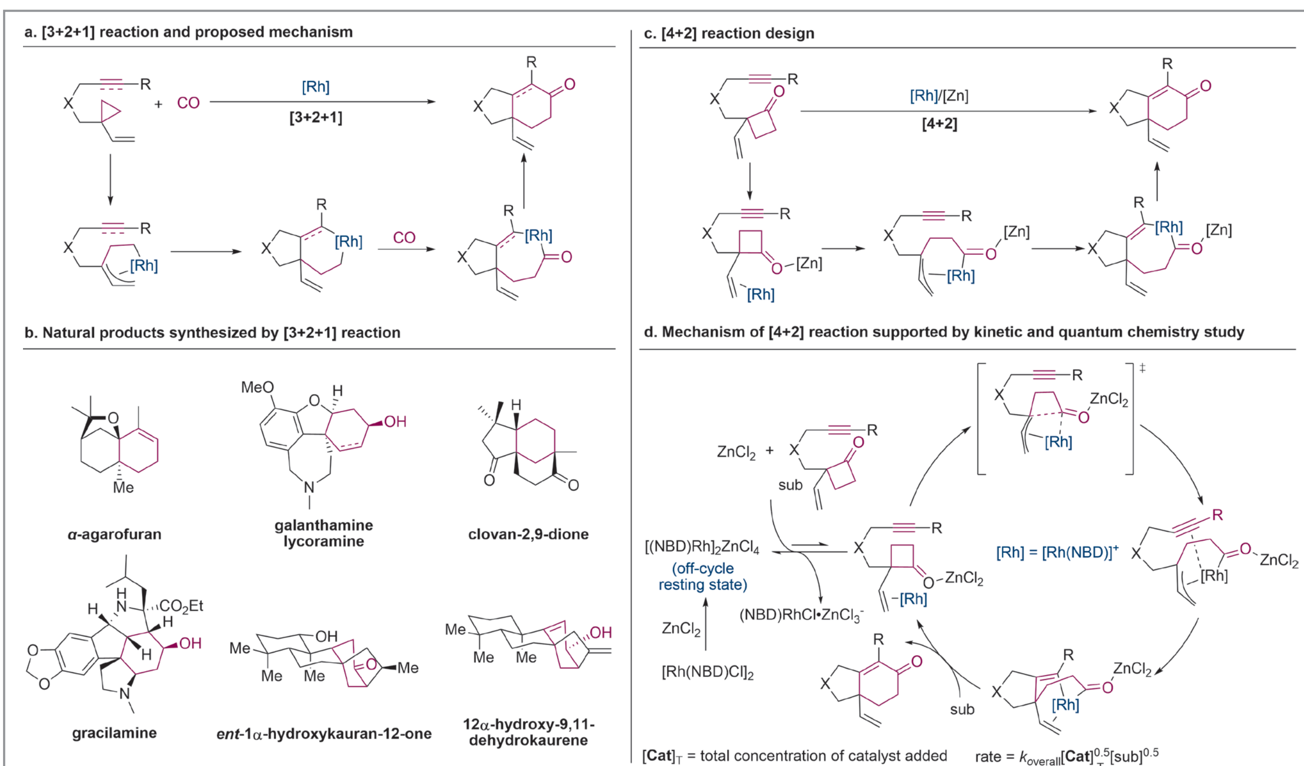
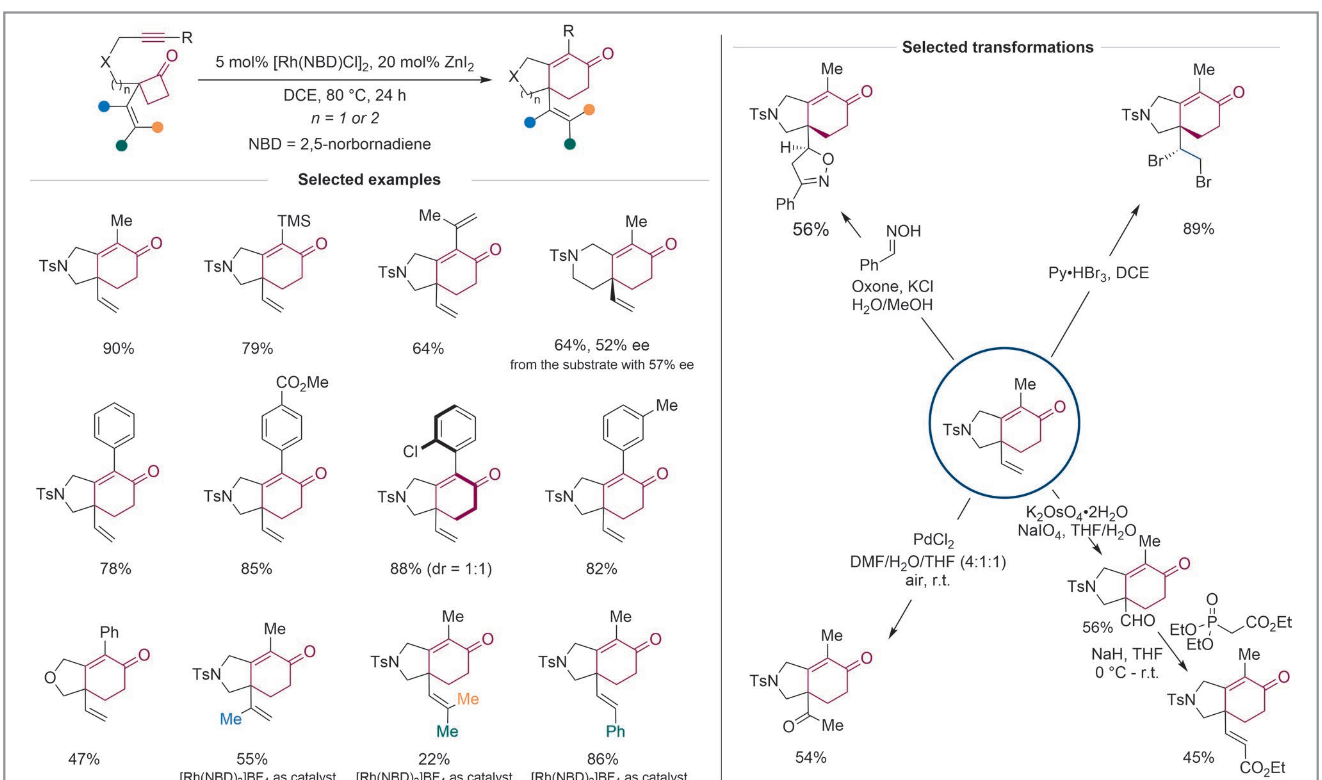
Prof. Zhi-Xiang Yu and his students from the College of Chemistry, Peking University (P. R. of China) are interested in inventing ring formation reactions, also taking advantage of quantum chemistry calculations and experiments to study the mechanisms of these novel reactions. In addition, the Yu group has been endeavoring to apply these reactions in the synthesis of natural products and pharmaceuticals. "So far, a dozen ring formation reactions, such as four types of [3+2], [3+2+1], [5+1], [4+2], [5+2], three types of [4+2+1], [5+2+1], [7+1], benzo-[7+1] cycloaddition reactions, ene-diene cycloisomerization, and diene-diyne cycloisomerization reactions, have been developed in the group," said Professor Yu. "Among these, the [5+2+1], [3+2+1], and [5+1] cycloaddition reactions, and ene-diene cycloisomerization, have been used in the synthesis of natural products both by us, and by other groups as well." As an example, the Rh-catalyzed [3+2+1] reaction of ene/yne-vinylcyclopropanes and carbon monoxide (Scheme 1), can build 5/6, 6/6 bicycles and other multicycles with a vinyl group at the bridgehead position. Professor Yu said: "We have applied this reaction to synthesize natural products of α-agarofuran, galanthamine, lycoramine, clovan-2,9-dione and gracilamine (Scheme 1b). Prof. Xiaoguang Lei, also from Peking University, elegantly applied this reaction to synthesize *ent*-kaurane diterpenoids in a highly step-economic approach (Scheme 1b)."



Scheme 1 The [3+2+1] reaction and its application in total synthesis of natural products (a, b), [4+2] reaction design (c) and mechanism (d)

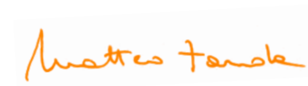
Professor Yu explained that the vinylcyclopropyl group in the substrates of the [3+2+1] reaction acts as a three-carbon synthon. “We also discovered this in two other [3+2] reactions using vinylcyclopropane derivatives as substrates,” he added, continuing: “The vinyl group is critical in helping the ring opening of cyclopropane, as that shown in the proposed mechanism of the [3+2+1] reaction in Scheme 1a. Based on these discoveries, we then hypothesized this C–C bond activation mode could also be used to activate four-membered rings.” He explained further: “Cyclobutanones have been widely used in cycloaddition chemistry. For example, Prof. Dong Guangbin at the University of Chicago (USA) developed an intramolecular [4+2] reaction of ene/yne-cyclobutanones, which provides a powerful method for synthesizing 5/6 and 6/6 rings. But they did not try to see whether they could apply this to the synthesis of bicyclic molecules with a bridgehead quaternary all-carbon center, which is a challenge in syntheses. We then envisioned a new strategy, introducing a vinyl group to cyclobutanone to help the C–C cleavage, as indicated by the proposed mechanism shown in Scheme 1c, and then this could realize a new [4+2] reaction. We can also introduce a Lewis acid to activate the carbonyl group in the cyclobutanone, so that a metal and Lewis acid co-catalyzed [4+2] reaction can be achieved.” To their excitement, the researchers in Professor Yu’s group found that the newly designed yne-vinylcyclobutanones underwent [4+2] cycloaddition smoothly using both Rh and Zn as catalysts, and 5/6 or 6/6 bicyclic products with an all-carbon quaternary bridgehead center could be generated (Scheme 2). “The reaction has a broad scope and many examples have been shown in this study,” said Professor Yu, adding: “The vinyl group in the [4+2] cycloadduct can be converted into other useful groups, further demonstrating that six-membered carbocycle-embedded bicycles with an all-quaternary carbon in the bridgehead position can be effectively produced by this new cycloaddition reaction. In addition, we found that a chiral substrate can give an enantioenriched product, suggesting this [4+2] reaction can achieve the asymmetric synthesis of cycloadducts, if enantioenriched substrates are used. This can complement our previous [3+2+1] reaction, because an asymmetric version of this reaction has not been realized.” Professor Yu and his students also showed that, upon replacement of the vinyl group in the substrate by an ethyl group, the resulting substrate cannot undergo the [4+2] reaction, further supporting the key role of the vinyl group in facilitating the C–C cleavage of the cyclobutanones.



Scheme 2 The [4+2] reaction of yne-vinylcyclobutanones catalyzed by Rh and Zn and further transformations of a [4+2] cycloadduct

"To gain a deeper understanding of the reaction mechanism, we performed visual kinetic analysis and computational studies. Based on the evidence gathered in these experiments, we proposed that the active catalytic species is cationic Rh, generated via dissociation of dimeric off-cycle species in the resting state, which is possibly formed between the dimeric catalyst and the substrate," added Professor Yu. He continued: "The rate-determining step is the C–C cleavage in the cyclobutanone, assisted by both Rh and Zn. We also measured the rate law of the [4+2] reaction. The other two roles of Zn, in helping the in situ generation of cationic Rh catalyst to occur slowly and preventing catalyst deactivation, were also evidenced by our mechanistic investigation. This information is shown in Scheme 1d and related insights will be helpful for the future design of new reactions and catalysts."

"The present [4+2] reaction can be regarded as an equivalent of our previous [3+2+1] reaction, which has proven its broad utility in the synthesis of several natural products with a bridgehead quaternary carbon center," said Professor Yu, who concluded: "Therefore, we can envision that this new [4+2] reaction of yne-vinylcyclobutanones will also become a powerful tool for synthetic chemists. We also believe that such a new strategy of using a vinyl group to activate four-membered rings will inspire the development of more reactions via C–C cleavage chemistry."



About the authors

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Zhi-Xiang Yu was trained as a chemist at Wuhan University, P. R. of China (1987–1991), Peking University, P. R. of China (1994–1997), and the Hong Kong University of Science & Technology, P. R. of China (1997–2001) for his Bachelor's, Master's and Doctoral degrees, respectively. He completed his postdoctoral studies from 2001–2004 at UCLA (USA). In 2004, he started his independent career at Peking University, rising from associate professor to full professor and is now a Changjiang Professor. He is interested in studying reaction mechanisms, developing ring-formation reactions, and applying these reactions in natural product synthesis and drug discovery.

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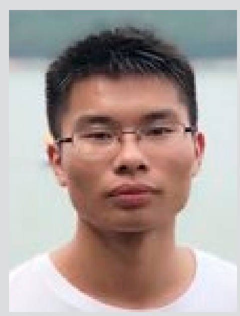

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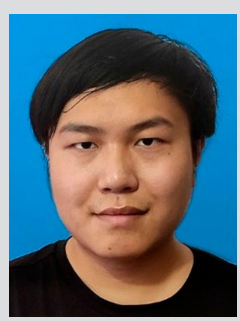

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