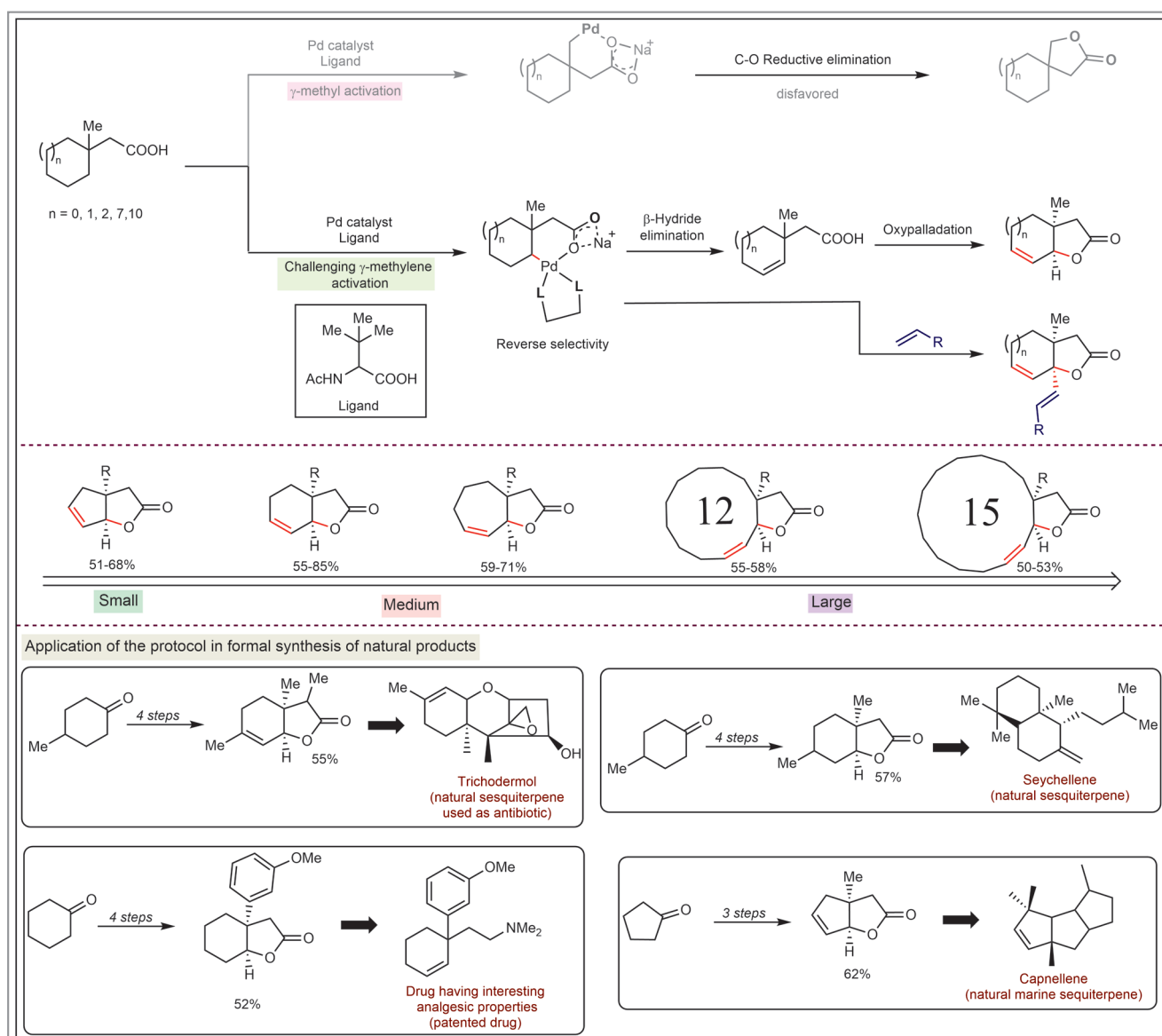


# Access to Unsaturated Bicyclic Lactones by Overriding Conventional C(sp<sup>3</sup>)-H Site Selectivity

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Bicyclic lactones are a privileged class of compounds that are ubiquitous in natural products and pharmacoactive molecules. The art of synthesizing such lactones in the most efficient ways has intrigued chemists for decades. Some of

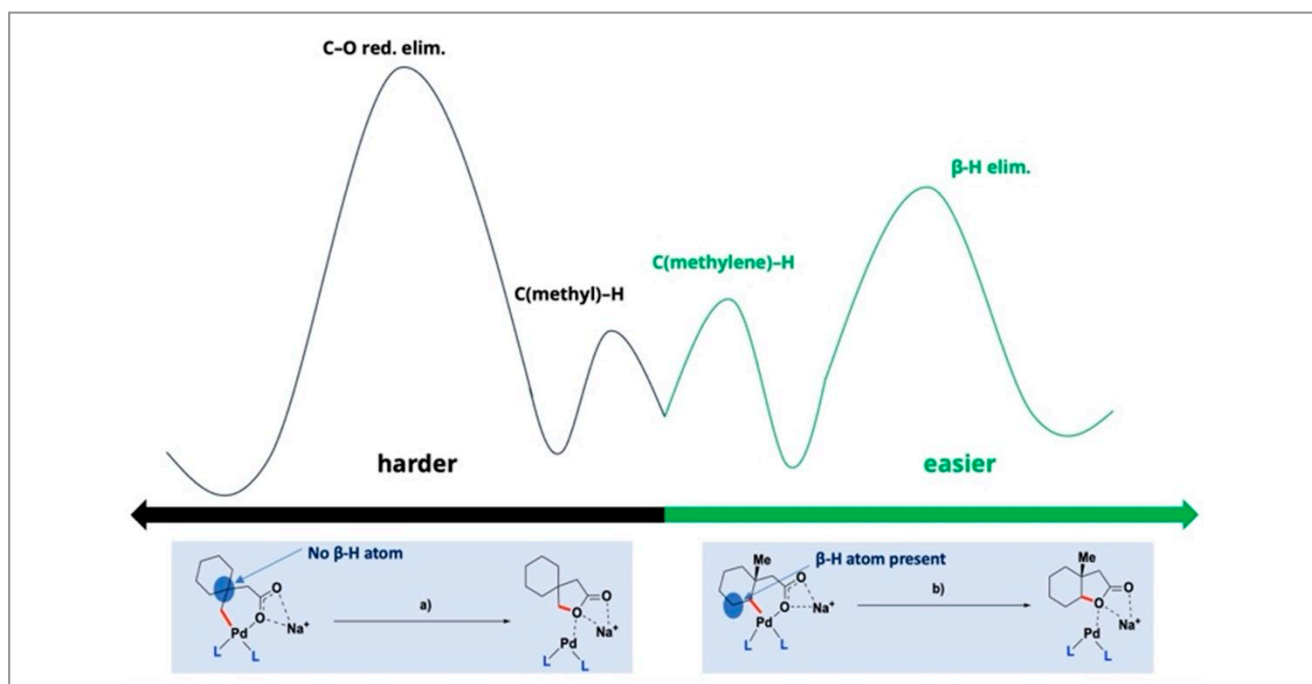
the popular methods utilized over the years are iodolactonization, intramolecular cyclization of hydroxy acids, and many more. In spite of the popularity and success of these reactions, they are perhaps not the most effective strategies



for making lactones or bicyclic lactones. “With our experience in C(sp<sup>3</sup>)-H activation, one of our long-standing goals was to simplify the synthesis of lactones or bicyclic lactones from aliphatic carboxylic acids in a single step,” stated Professor Debabrata Maiti, from the Indian Institute of Technology Bombay (India), who is also Editor-in-Chief of SYNLETT. He further elaborated: “While exploring aliphatic acids for C-H activation, we found a perfectly suitable class of substrates, namely cyclohexane-3-methyl acetic acids, that can form bicyclic lactones in a single step. However, we had to activate a methylene group in the molecule to get the fused lactone. The substrate has equally accessible methyl and methylene groups at the  $\gamma$ -positions that can be activated through carboxylate assisted C-H activation. Conventionally, methyl group activation is easier than methylene. Our challenge was to find suitable conditions that can reverse this site-selectivity.” Indeed, a bulky amino acid like *N*-acetyl-*tert*-leucine as ligand in combination with palladium acetate as catalyst and other reagents can achieve this reversed site-selectivity and form bicyclic lactones in a single step (Scheme 1). “We were quite surprised to discover the results. The activation of the methyl group in the substrate to form a spirocyclic lactone would not have been surprising. But the spirocyclic lactone did not form at all. The rationale for this was found once we started digging

out the reaction mechanism,” said Professor Maiti. A collaboration with Dr. Xinglong Zhang from the Institute of High-Performance Computing (Singapore) unraveled the reason for the reverse selectivity in this reaction. Professor Maiti further stated: “Our findings are really intriguing. Apparently, methyl activation is easier than methylene in our system, which is expected. Things become interesting after the activation. Due to the lack of  $\beta$ -hydride in the C(methyl)-H activated complex, the subsequent step must be C-O reductive elimination. However, this elementary step has an unfavorably high barrier under our conditions. DFT calculations showed a requirement of almost 45.3 kcal/mol for this step, which is unlikely to happen. So, the methyl-activated substrate goes back to the starting material. Now, although C(methylene)-H activation has a higher barrier than C(methyl)-H activation, this pathway gives the option of a  $\beta$ -hydride elimination (10.3 kcal/mol and favorable under the reaction conditions) to form an alkenoic acid, followed by cyclization to form an unsaturated bicyclic acid (Figure 1).”

At a glance the reaction looks captivating: start with a carboxylic acid and, end up with bicyclic lactone containing a double bond. “The ability to synthesize bicyclic lactones in this simpler manner provided us a great opportunity to apply our protocol in complex molecule synthesis,” explained Pro-



**Figure 1** Illustrative energy profile showing reversed selectivity for C(methylene)-H activation product over C(methyl)-H activation product

fessor Maiti. Formal synthesis of various natural products like trichodiene, seychellene, capnellene, mesembrane, and some other bioactive molecules was demonstrated in this work utilizing the novel C–H activation method. What's more, the reaction could be performed in an intermolecular fashion where an added coupling partner like an acrylate or an allyl alcohol end up adding to the  $\gamma$ -methylene site without affecting the unsaturated lactone formation. "We knew the lactone formation proceeded via a C–H activated intermediate, the idea was to explore various coupling partners that can be added to the bicyclic lactone, hence enhancing the complexity and diversity of the formed products. We found acrylates and allyl alcohols can be added, but there are many yet to be explored. The beauty of this method is the formation of a quaternary

center in the product, in a single step, from a methylene site in the starting material," said Professor Maiti, who thinks that native functional group assisted C(sp<sup>3</sup>)–H functionalization is redefining the most efficient routes for high-value aliphatic compound synthesis. "In the last 5 years, this field has grown exponentially", said Professor Maiti, concluding: "Research in this area is still in its infancy. Considering the cascade effect a simple weak coordination of carboxylate can provide, there are enormous opportunities to develop complex products from simpler starting materials via native functional group assisted C–H functionalization."

*Maiti's work*

### About the authors



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**Jayabrata Das** received his Master's degree from the University of North Bengal (India) in 2016. Then he moved to the Indian Institute of Technology Bombay (India) to pursue his Ph.D. in the group of Debabrata Maiti, where he worked on transition-metal-catalyzed remote activation of aliphatic substrates. He received his Ph.D. degree in 2022. Currently, he is a post-doctoral fellow with Prof. Timothy Cernak at the University of Michigan (USA). His work revolves around the interface of chemical synthesis and computer science.



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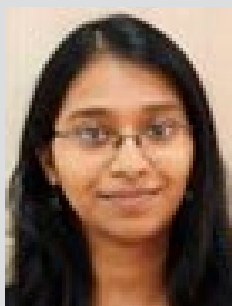
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Dr. H. Ge

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Dr. X. Zhang

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*Prof. D. Maiti*

**Debabrata Maiti** obtained his Ph.D. in 2003 from Johns Hopkins University, USA with Prof. Kenneth D. Karlin. Later he moved to Massachusetts Institute of Technology, USA to pursue post-doctoral studies with Prof. Steve Buchwald. In 2011, he joined IIT Bombay (India) as an assistant professor. He is now a full professor at IIT Bombay (India). His research area revolves around catalysis for metal-catalyzed C–H activation of arenes, heteroarenes, aliphatic compounds, photocatalysis, electrocatalysis, and artificial metalloenzymes, among others.