Highly selective catalyst developed for ring-closing olefin metathesis

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Research carried out at Boston College, in collaboration with scientists at MIT and the University of Oxford, has led to the development of an efficient and highly selective catalyst for ring-closing olefin metathesis, one of the most widely used reactions in chemical synthesis, the team reports in this week's issue of the journal *Nature*.

The team used the new catalyst, part of a large and important class of carbon-carbon double bonds, to synthesize epothilone C and nakadomarin A, both of which are molecules that have been shown to be potent anti-cancer agents. Epothilone A, an equally active agent can be prepared from epothilone C.

"Catalytic ring-closing olefin metathesis is probably the most widely used chemistry method to access biologically active molecules," said the report's principal author, Amir Hoveyda, the Joseph T. and Patricia Vanderslice Millennium Professor of Chemistry at Boston College. "The catalyst that we have identified as optimal in this study is remarkably efficient and selective. Considering the demonstrated significance of this class of reactions, even though it has thus far been largely non-selective, findings indicate that our catalysts and method will have a major influence on the future of chemical synthesis."

Carbon–carbon double bonds, also referred to as alkenes or olefins, are present in many medicinally relevant and biologically active molecules. Hoveyda and MIT Professor Richard Schrock, a co-author of the Nature report, have collaborated since 1997 in developing new and effective

catalysts for such transformations. Schrock shared the 2005 Nobel Prize in Chemistry for discovering one of the earliest types of olefin metathesis catalysts.

Alkenes exist as either the zigzag shaped trans olefin, or the E isomer, while others take the "U" shape of the cis olefin, or the higher-energy Z isomer. Z isomers require a catalyst that must be sufficiently active to be capable of promoting the chemical reaction while maintaining the cis olefin's U-shape geometry. Preserving both characteristics in a catalyst leads to reactions that deliver Z alkenes, which can be found in a large number of medicinally significant molecules and serve as starting materials for some of the most commonly used transformations in chemistry.

Ring-closing metathesis allows the formation of any ring size from readily available linear chains. However, the process is typically non-efficient or results in the formation of a significant amount of the undesired isomer, which often has less or no biological activity.

Using tungsten, the team found a catalyst that offers exceptional reactivity and selectivity while being sufficiently stable to air and moisture to make its use particularly attractive, said Hoveyda, who with Schrock co-founded the Swiss firm XiMo, which has licensed the new catalyst and its technology.

To demonstrate the utility of their catalysts, the team focused on epothilone C and nakadomarin A. Several other leading research groups in the world have previously prepared these biologically active natural products, but, in all cases, the critical ring closure step has been non-selective. This lack of selectivity badly damages the overall efficiency required to prepare these much sought after molecules, since ring formation comes at the tail end of a long sequence of reactions, sometimes as many as 20 steps.

"Losing half of your materials after you have spent so much time and energy and thought preparing it is nothing short of devastating, particularly when you cannot even separate the two isomers," Hoveyda says.

Epothilone C can be produced through fermentation, but creating various analogues by the same method would be extremely difficult. Nakadomarin A, found in marine environments, is only available in minute quantities. The highly selective process developed by the team will allow scientists to access significant quantities of these natural product as well as many of their analogs, which might prove to have more attractive therapeutic attributes.

The findings are the most recent from 14 years of collaboration between the Hoveyda and Schrock labs, work that has been supported by the National Institutes of Health since 1999. Also contributing to the study were Miao Yu and Chenbo Wang of Boston College and Andrew F. Kyle, Pavol Jakubec and Darren J. Dixon of the University of Oxford (UK).

Provided by Boston College