A synthetic drug manufacture process combining multiple components through quick, consecutive reactions

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A multi step domino reaction can improve synthesis of the breast cancer medication tamoxifen. Credit: Monkey Business Images/Monkey Business/Thinkstock

sing a simple nickel salt, A*STAR researchers have developed a mild, one-pot 'domino' reaction that can attach different hydrocarbon components to specific sites on a carbon–carbon double bond—a chemical trick essential for the production of helical molecules and anti cancer medications such as tamoxifen.

When chemists build complex organic molecules for applications such as drug synthesis, they usually perform reactions step by step to ensure good yields and minimal by-products. But having two or more bond forming transformations occur consecutively in the same beaker could save enormous amounts of time and materials. To achieve this goal, laboratories are building precursors that, once activated, undergo a series of quick chain reactions to form the final product—a process that parallels a row of tumbling dominoes.

Jin Zhao, Andy Hor, Tamio Hayashi and co-workers from the A*STAR Institute of Materials Research and Engineering and the National University of Singapore aimed to find an improved domino reaction for producing carbon–carbon double bonds known as tetra-substituted alkenes. "These types of compounds have really interesting physical, structural, and electronic properties," explains Zhao. "You can find them in biologically active natural products, while others have use as molecular switches."

To achieve their domino reaction, the researchers wanted to attach two types of hydrocarbons to a third component bearing a carbon–carbon triple bond known as an alkyne. They postulated that if the first hydrocarbon contained a special organometallic group called a Grignard reagent, it could quickly add to the alkyne through a 'carbometalation' step. Then the second hydrocarbon, in the form of an organic halide, would couple to the reactive intermediate and give a tetra-substituted alkene.

Controlling the selectivity of this multi step process was a significant challenge for the team. "The most serious problem in this reaction would be possible side reactions, where the Grignard reagent reacts with the organic halide before reaching the alkyne," explains Zhao.

To overcome this problem, Zhao and her co-workers drew on past experiences catalyzing Grignard chemistry with nickel chloride, an inexpensive salt that speeds up certain room temperature reactions. When the team mixed the three components with a pinch of nickel chloride catalyst, the results were impressive: high yields of tetra-substituted alkene targets were obtained by simply stirring for a few hours. Mechanistic studies revealed that the high selectivity of this domino process arose from an extremely fast carbometalation step.

"This work provides a simple and selective method for synthesizing tetra-substituted alkenes, notably the drug tamoxifen" adds Zhao.

More information: Fei Xue et al. Nickel-Catalyzed Three-Component Domino Reactions of Aryl Grignard Reagents, Alkynes, and Aryl Halides Producing Tetrasubstituted Alkenes, *Journal of the American Chemical Society* (2015). DOI: 10.1021/ja513166w

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