Cyclization Shortcut

Organic Synthesis: Combined route to complex cyclic products saves steps, improves yields

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Unified Process Combined dehydrogenation/cyclization uses a palladium catalyst to convert a terminal olefin to an activated diene (not shown) that reacts with an electron-deficient olefin to form a cyclohexene product.

EWG = electron-withdrawing group

A catalytic dehydrogenation approach promises to streamline access to products of the ring-forming Diels-Alder reaction. The approach generates starting materials and enables them to be cyclized in a single process, reducing the number of steps and improving yields relative to the conventional two-stage process.

The work was carried out by grad student Erik M. Stang and chemistry professor M. Christina White of the
Until now, dehydrogenation and other C–H oxidation reactions have primarily been used to add functional groups to carbon frameworks, Stang and White point out in their paper. They instead use dehydrogenation to produce conjugated dienes and convert them into activated intermediates that participate, as they are formed, in Diels-Alder cyclization—a complexity-generating reaction that combines dienes and electron-deficient olefins into cyclohexenes.

The strategy skirts a common problem in conventional Diels-Alder chemistry: The necessary conjugated diene starting materials are often difficult to synthesize and isolate. Such dienes can be built via alkene dehydrogenations in which two adjacent C–H bonds are cleaved. But chemists rarely turn to dehydrogenation to create dienes because the reaction conditions cause dienes to oligomerize or react in other ways before they can be isolated, White says.

Stang and White’s combined dehydrogenation/Diels-Alder reaction converts terminal olefin starting materials directly into complex Diels-Alder cycloaddition products, skipping separate diene synthesis and isolation. In the combined process, the terminal olefin undergoes palladium(II) sulfoxide-catalyzed dehydrogenation and isomerization to give a reactive trans-diene intermediate, which then undergoes Diels-Alder cycloaddition with an electron-deficient olefin to form a cyclohexene.

The researchers used the dehydrogenation/Diels-Alder reaction to synthesize hydroisoindolines, cis-decalins, hydroisoquinolines, isoindoloquinolines, and other complex cyclic molecules of interest in natural product synthesis and medicinal chemistry. Their syntheses required fewer steps and produced higher yields than traditional routes do—in one case, three steps and 34% yield, compared with six steps and 17% yield for the conventional route.

Chemistry professor Paul Wender of Stanford University says Stang and White have developed a new way to make dienes for use in Diels-Alder cycloadditions, “providing in one step an impressive increase in structural complexity and thus potential value.” He notes that this type of step-count reduction is a key way to reduce the cost, generated waste, and required time of a synthesis.

Wender adds, “Achieving the combined process is notable because its reactants, reagents, intermediates, and products must be compatible and effective—a goal that can often be difficult to achieve, even with one reaction. I think the reaction has immediate practical value in both academia and industry.”
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