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Synthesis

Amination Advance

New reaction is first to catalytically convert allylic C-H to C-N

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MAKING CERTAIN antibiotics and other nitrogen-containing compounds has just gotten easier with the solution to a long-standing problem in organic synthesis.



White Research Group/ University of Illinois, Urbana-Champaign
Fraunhofer (left) and White.

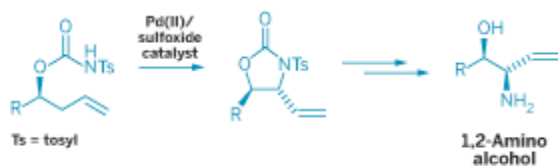
Chemists have sought a direct catalytic way to replace hydrogen with nitrogen at an allylic carbon, the sp^3 -hybridized carbon atom adjacent to a $C=C$ group, a common target of modification in organic compounds. So far, the primary means for putting nitrogen at that carbon requires going through oxygen. Typically, a hydroxyl group replaces the hydrogen first and is then replaced by a nitrogen-containing group. This route can lengthen and complicate syntheses, because the oxygenated materials require additional manipulations.

Now, the oxygen-involving step can be sidestepped. Chemistry professor M. Christina White and grad student Kenneth J. Fraunhofer at the University of Illinois, Urbana-Champaign, have devised the first method that catalytically converts an allylic C-H directly to C-N (*J. Am. Chem. Soc.* **2007**, *129*, 7274).

"This discovery redefines the state of the art for making certain types of molecules," White says. The reaction makes it possible to more rapidly synthesize stereochemically defined oxazolidinones, which form the skeletons of a class of antibiotics that includes linezolid. Oxazolidinones also can be further transformed into medicinally important amino alcohols.

White and Fraunhofer used the reaction to create a key chiral oxazolidinone intermediate in the

synthesis of acosamine, an amino sugar found in the cancer drug epirubicin. They needed only half the number of steps required by the conventional synthetic route, which goes through oxygen.



Skipping Oxygen An allyl group with a tethered carbamate (left) is converted to an allylic 1,2-amino alcohol without an oxygen-requiring step.

The reaction uses a Pd(II)/sulfoxide catalyst to transfer nitrogen in an N-tosyl carbamate group directly to an allylic carbon atom.

For now, White's group has demonstrated only an intramolecular version of the reaction, in which the carbamate is tethered to the allyl group. Tethering, White says, increases the reactivity of the process and promotes diastereoselectivity. But tethering isn't a necessary condition for the reaction, and White's group is currently working on a more versatile intermolecular version.

The main challenge in developing the reaction "was to avoid a competing reaction of nitrogen directly with the olefin," White says. The Pd(II)/sulfoxide catalyst system they used avoids this pitfall, because it preferentially activates the allylic C-H bond for cleavage (thereby making this carbon accessible to nitrogen attack), whereas other catalysts of this type tend to make the olefin receptive to nucleophilic attack by nitrogen.

White notes that the new reaction complements a set of rhodium nitrene-based aliphatic C-H aminations developed recently by Justin Du Bois' synthetic chemistry group at Stanford University. Together, the two types of reactions "begin to create a toolbox of C-H-to-C-N bond-forming reactions that have significant potential for streamlining the process of small-molecule synthesis," White says.

Her technique "is significant, as the novel functionalization of allylic C-H bonds allows access to 1,2-amino alcohols, which are key components of nonnatural amino acids and amino sugars," comments synthetic chemist Reinhard W. Hoffmann of Philipps University, in Marburg, Germany. It also makes it possible to introduce "functionality late in a synthesis on elaborate molecular skeletons, and it is likely, while not yet demonstrated, that it does not require protection of bystander functional groups. Hence, there is the clear potential of streamlining overall syntheses of complex target structures."

Synthetic chemist Phil Baran of Scripps Research Institute says the new reaction "is a breakthrough" that "will find widespread use in total synthesis. It compels us to look at the allylic C-H bond in an entirely new way and will have a dramatic impact in the way we think about making molecules."

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