Chemists achieve major milestone of synthesis: Remote chiral induction

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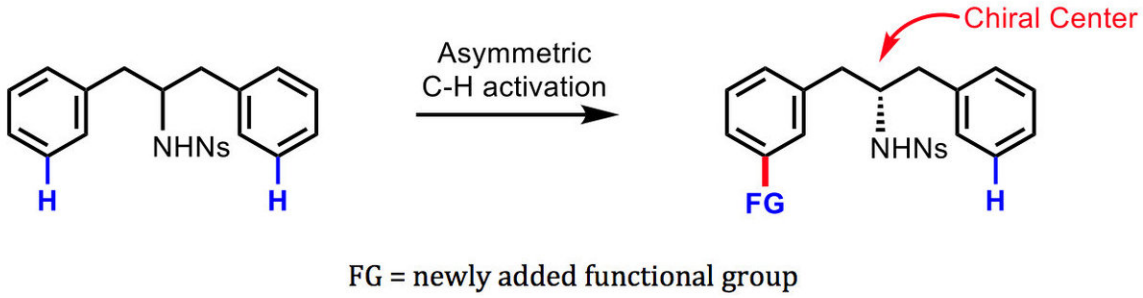

The new method developed by Yu and colleagues. Credit: Jin-Quan Yu/Scripps Research

Chemists at Scripps Research have addressed one of the most formidable challenges in synthetic chemistry by inventing a method for "enantioselective remote meta-CH activation," which enables the making of chiral molecules that were previously difficult or impossible to synthesize.

The method, reported today in *Nature*, is likely to be adopted widely for the making of prospective drugs and other chemical products.

"This new method should allow us to explore a large 'chemical space' that had been essentially off-limits," says Jin-Quan Yu, Ph.D., senior

investigator and Frank and Bertha Hupp Professor of Chemistry at Scripps Research.

Chiral molecules are asymmetric, with "right hand" and "left hand" forms. Often only one of these forms (called enantiomers) has the desired biological or chemical activity, while the other is inert or even has unwanted side effects—and most ordinary reactions yield an impure, 50:50 mix of both.

There are methods for turning a symmetric molecule into a chiral one and obtaining pure quantities of one enantiomer rather than the other. However, these methods typically involve the attachment of a reactive cluster of atoms called a functional group to the starting molecule at the point that becomes the center of asymmetry: the so-called chiral center. The new method attaches a new functional group relatively far from the chiral center—a feat previously achievable only by enzymes in living cells. Since the chiral center typically contains another functional group, the resulting chiral molecule ends up with two widely spaced functional groups, potentially conferring unique and potent bioactivity.

"The chiral molecules we can make with this method can be designed to interact with widely spaced binding sites on a target protein, for example," Yu says.

Key to the new method is a specially designed helper molecule, a "transient chiral mediator," based on the organic compound norbornene. It enables the crucial step of attaching the new functional group asymmetrically to an initially symmetric starting compound—far from the chiral center on the molecular backbone but, even so, yielding nearly 100 percent pure quantities of the desired enantiomer.

Yu's team demonstrated the technique by using it for the "remote chiral induction" of benzylamines and phenylethyl amines, broad classes of

molecules that form the bases for many modern drugs as well as many biologically active compounds in plant and animal cells. The resulting chiral molecules typically comprised more than 95 percent of the desired enantiomer and less than 5 percent of the unwanted enantiomer.

Yu and his group currently are exploring ways to widen the scope of this strategy to other classes of starting molecule. They are also using their new method to create large libraries of previously inaccessible compounds, which can be screened to discover potential new drugs.

More information: "Enantioselective Remote Meta-C-H Arylation and Alkylation via a Chiral Transient Mediator,"*Nature* (2018). DOI: 10.1038/s41586-018-0220-1 , www.nature.com/articles/s41586-018-0220-1

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