Duke chemist has new way to tell right from left

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A Duke University chemist has apparently solved a long-standing frustration in creating certain synthetic molecules that make up drugs, which could lead to better drugs with fewer side effects.

Like human hands, many molecules that make up drugs come in two shapes, right and left. But usually only one of the two versions has the desired effect; the other is at best useless and sometimes even harmful. For example, side effects from the morning sickness drug Thalidomide resulted in profound birth defects because one shape of the molecule was therapeutic and the other was dangerous.

Don Coltart, an assistant professor of chemistry at Duke, appears to have found a way to make synthetic ketone molecules in just one version or the other using a process that is faster, cheaper and less wasteful than the best techniques now available.

And unlike previous attempts to make just one shape of these molecules, a process called asymmetric synthesis, the new method should be able to scaling up to industrial manufacturing quantities.

"Asymmetric synthesis of ketones is not new, but we can do it more practically and easily," said Coltart, who developed the new technique with graduate student Daniel Lim."

Though well-known to the pharmaceutical industry, this problem of molecular handedness in ketones has been difficult to solve. Academic

labs have succeeded at asymmetric synthesis over the last two decades, but only by using extreme conditions (e.g. temperatures of -100 degrees Celsius), and costly and time-consuming steps.

Conducted at zero C to -40 C, the new process uses a small molecule called a "chiral auxiliary" to attach pieces to a molecule being built, which causes the new pieces to have the correct handedness. The process is up to 98 percent accurate, Coltart said, and the auxiliary molecules can be easily released and recycled after they've done their work.

"He did something very different," said Samuel Danishefsky of Columbia University and the Memorial Sloan-Kettering Cancer Center, who is Coltart's former post-doctoral mentor. "You could have had a hundred people look at this problem and not see it the way he did. It's a very nice idea."

Coltart said there is a huge need for drug companies to be more selective to make better drugs with fewer side effects, which this new process might help achieve. Pharmaceutical companies might also use the new technique to turn existing formulations of drugs sold as mixtures into a pure form having only the active form of the drug, giving them another seven years of patent protection.

The work, which was funded internally by Duke, appears online in the international edition of the European journal *Angewandte Chemie*. (dx.doi.org/10.1002/anie.200800848)

Source: Duke University