Breakthrough in organic chemistry: Asymmetric syntheses of useful, unique chiral compounds

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Since 2002, a research team, led by Professor Osamu Kitagawa of Shibaura Institute of Technology, has developed chiral Pd-catalyzed enantioselective syntheses for N-C axially chiral compounds. Credit: Rodolfo Clix from Pexels

Atropisomers are a class of stereoisomers (chemical compounds that differ in spatial arrangement of atoms) arising from restricted rotation around a single bond and have various applications in chemistry. To date, most research on atropisomers has focused on "biaryl atropisomers" (due to the rotational restriction around a carbon-carbon bond), but it is also possible for atropisomers to arise from rotational restrictions around a nitrogen-carbon (N-C) bond. These N-C axially chiral compounds are found in various natural products and bioactive compounds and thus have promising applications in medicine and agriculture. Furthermore, these are known to be useful as chiral building blocks and chiral ligands.

Of course, before researchers can take advantage of any such applications, they need to develop a feasible method for synthesizing it. "Although a number of bioactive compounds and natural products possessing an N-C axially chiral structure have recently been found, no efficient synthetic method was known," notes Professor Osamu Kitagawa from Shibaura Institute of Technology (SIT), Japan. To address this problem, Prof. Kitagawa and his team have spent the past few decades developing efficient methods for the synthesis of N-C axially chiral compounds. In a paper recently published in *Accounts of Chemical Research*, Prof Kitagawa summarizes his team's achievements since 2002.

In 2001, Prof. Kitagawa's group started investigating a never-before-attempted catalytic asymmetric synthesis of ortho-tert-butyl anilides and other N-C axially chiral compounds. In 2005, they found that reacting achiral secondary ortho-tert-butylanilides with 4-iodonitrobenzene in the presence of a chiral palladium (Pd) catalyst (catalytic enantioselective aromatic amination) resulted in the highly enantioselective (asymmetric) synthesis of N-C axially chiral N-arylated ortho-tert-butylanilides. They next experimented with adapting this intermolecular N-arylation reaction for use in intramolecular reactions, and their efforts led to the synthesis

of compounds called "N-C axially chiral lactams" (which had high optical purities). Importantly, these reactions represented the first enantioselective syntheses of N-C axially chiral compounds with a chiral catalyst.

The investigators continued their work by using chiral Pd-catalyzed intramolecular N-arylations to achieve the enantioselective syntheses of N-C axially chiral quinoline-4-one and phenanthridin-6-one derivatives. They also used various chiral Pd-catalyzed reactions to prepare optically active N-C axially chiral compounds called N-(2-tert-butylphenyl)indoles, 3-(2-bromophenyl)quinazolin-4-ones, and N-(2-tert-butylphenyl)sulfonamides. Prof Kitagawa's research has led to the successful synthesis of potentially useful compounds, such as an N-C axially chiral mebroqualone that acts as an agonist of specific receptors present in the brain, called "GABA receptors" (and has potential therapeutic properties).

In fact, since 2005, the enantioselective synthesis of N-C axially chiral compounds has become a topic of considerable interest to chemists outside of Prof. Kitagawa's research team. For example, the literature on the synthesis of axially chiral anilides with catalytic enantioselective aromatic aminations dates back to 2005, with a research paper by Prof. Kitagawa's team, but since then, other research groups have published more than 70 original papers concerning highly enantioselective synthesis of various N-C axially chiral compounds using chiral catalysts. Further, the team's 2010 paper on the catalytic enantioselective synthesis of N-C axially chiral indoles represented an important contribution to the development of axially chiral indole chemistry, and various research groups have since developed catalytic asymmetric syntheses for various indole derivatives that include a C-C chiral axis or an N-C chiral axis. Prof. Kitagawa himself sees his laboratory's work as having important applications to "the synthesis of optically active drug compounds and natural products with N-C axial chirality."

In conclusion, Prof. Kitagawa's research team has succeeded in devising catalytic enantioselective syntheses of N-C axially chiral compounds. This work has inspired other research teams to make further contributions in the same field and has led to workable synthetic pathways for bioactive compounds with potential medicinal value. Prof Kitagawa predicts that the catalytic asymmetric synthesis of N-C axially chiral compounds will continue to draw attention, thanks to the potential uses of such compounds across a broad range of fields.

More information: Osamu Kitagawa, Chiral Pd-Catalyzed Enantioselective Syntheses of Various N–C Axially Chiral Compounds and Their Synthetic Applications, *Accounts of Chemical Research* (2021). DOI: 10.1021/acs.accounts.0c00767

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