LMU LUDWIG-MAXIMILIANS-UNIVERSITÄT MÜNCHEN
insightLMU RESEARCH

Issue 03 · 2009

NATURAL SCIENCES

CHRISTINE AMRHEIN

A COMPOUND WITH MANY FACETS

Organometallic compounds are used in the production of plastics, fertilizers and even drugs. Chemists working with Professor Paul Knochel have now developed a new method that allows even highly sensitive functional groups to be combined with non-toxic metals such as magnesium. This promises wide applications in the pharmaceutical and fine chemical industries.

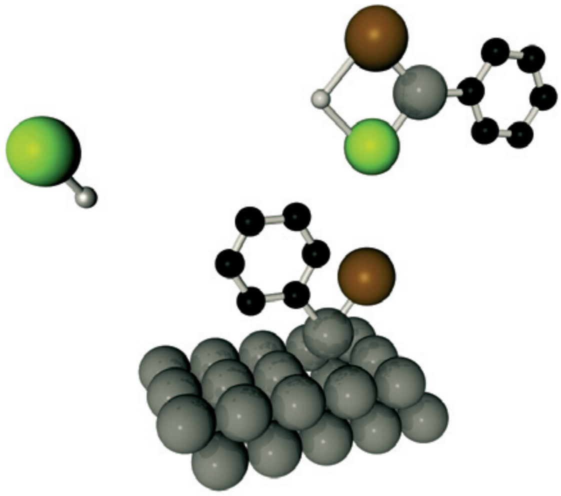
When Antoine Henri Becquerel left a photographic plate lying in his laboratory while working with uranium salts in 1896, he made a surprising discovery: The next day, the plate was blackened, even though it could not have been exposed to light. It followed that there had to be some kind of radiation present that did not come from visible light – Becquerel had discovered radioactivity. Chance often plays an important part in great discoveries, nevertheless, in most cases a researcher's expertise and creativity to realize the full implications of their surprising observations are also needed, as Professor Paul Knochel at the LMU Munich Department of Chemistry and Biochemistry found out .

As Chair of Organic Chemistry, he is currently working on the production of organometallic compounds, where a carbon-based substance and a metal atom combine into one compound. He and his team discovered an entirely novel method by which to produce a practically unlimited number of new reagents that are of enormous potential to the chemical and pharmaceutical industries. Once again, chance gave a little assistance of its own in this discovery – but only the scientist's detailed knowledge and experience made it possible to systematically investigate the newly discovered process and to grasp its full application potential.

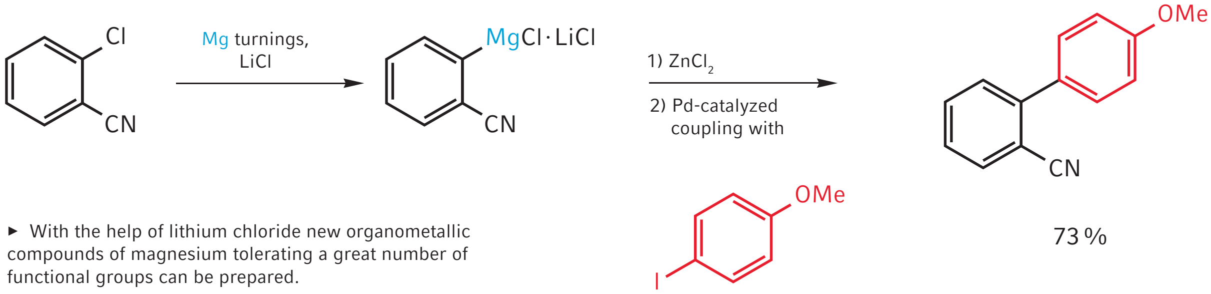
Paul Knochel's research started with the so-called Grignard reaction. This is where a carbon-halogen bond, where the halogen is either chlorine, bromine or iodine, reacts with magnesium metal in an ether as a solvent to create an organometallic compound. This reaction was discovered around 1900 by the French chemist Victor Grignard, for which he was awarded the Nobel Prize for Chemistry in 1912. Grignard reagents have a special property: They possess a strong negative charge at the carbon atom and therefore react strongly with positively charged atoms and molecules. Accordingly, they can react with a series of positively charged functional groups such as ketones, esters or nitriles to form new carbon-carbon bonds. The newly created reagents are in turn extremely important in fine chemistry and for the production of pharmaceuticals. One of the most important applications of the Grignard reaction is the synthesis of the drug tamoxifen. This is used in breast cancer therapy, and inhibits the receptors for the female hormone estrogen, which in many cases promote the growth of tumor cells. "In this application, the magnesium is required to convert the halides used into reactive intermediate products from which the end product can be made," Paul Knochel explains.

However, one significant disadvantage of Grignard reagents has always been that they only tolerate a small number of functional groups. Since the functional group determines the properties and reactivity of a chemical compound, the range of applications for organomagnesium compounds has been greatly limited, until recently. The biggest problem was the very nature of the Grignard compound itself: Their strong reactivity causes the metal atoms to remain adhered to the surface of the halides, bringing the desired reaction quickly to a halt. "Previous methods that circumvented this problem were either very expensive or too slow to be of practical use," says Paul Knochel. "Also, many synthetical methods require temperatures of 30 to 50 degrees Celsius – which destroy a majority of the sensitive functional groups." The entire process therefore only works if a very mild reaction method is employed. The chemist and his team first found the solution by accident: In 2004, together with Frankfurt-based company Chemetall, the researchers had planned to commercialize a reagent containing magnesium, lithium chloride and isopropyl chloride. They were looking for a way to speed up the reaction process. Instead of first mixing magnesium and isopropyl chloride and then adding the lithium chloride salt as usual, they simply mixed all three substances together at the same time. "We were very surprised when the reaction worked just as well in this fashion," says Paul Knochel. "But what was more astounding was that the lithium chloride actually accelerated the reaction process."

Subsequently, the scientists began systematically investigating the salt's role in the synthesis of organometallic compounds, with financial backing from the German Research Foundation (DFG). "The new method enables us to directly introduce magnesium into an already functionalized carbon-halogen bond," Paul Knochel emphasizes. All they need to do is add magnesium powder or turnings to a solution of lithium chloride and selected functionalized molecules. "It has always been unclear, exactly how the process works," says the chemist. "We assume, however, that the lithium chloride serves as a



◄ The illustration shows how the lithium chloride removes the magnesium reagent stuck to the metal surface.



► With the help of lithium chloride new organometallic compounds of magnesium tolerating a great number of functional groups can be prepared.

kind of cleaning agent, which removes the metal atoms stuck to the surface of the molecules, thus allowing a continuously ongoing reaction." This also makes organomagnesium compounds accessible to more sensitive functional groups such as nitriles, pivalates or tosylates. At the same time, the new method allows an amazing diversity of chemical variants, which the researchers have presented in highly prestigious journals. For example, different chlorides and bromides can be used in the process, and a large number of aromatic and heteroaromatic compounds are tolerated. These are molecules containing ring structures, which stand out from other organic compounds for certain special reactive properties. In another reaction step, the newly created compounds were used in so-called cross-coupling reactions. This is where new carbon frameworks are synthesized so that even larger molecules can be built. "The entire method is so simple and cheap that it is already being used widely in many different branches of the chemical industry. All reactions described can be done at moderate temperatures, and achieve yields of 75 to 97 percent – an indication that the method works very well overall." Another advantage of the new compounds is that magnesium is a non-toxic metal, so the resulting products are in general harmless to humans and nature.

But this type of reaction is by no means limited to magnesium. Knochel and his team proved in other experiments, for example, that the new synthetic method can be equally applied to a series of other metals. One of them is indium, which is also non-toxic, and which the scientists managed to introduce directly into aromatic and heteroaromatic iodides with the addition of lithium chloride. "The special thing about this reaction is that it doesn't need any complicated solvents such as ether. Instead, it is quite easily achievable in water," Paul Knochel reports. "That makes organoindium compounds doubly eco-friendly, as it were." Just like magnesium-based organometallics, the products obtained can be worked into new compounds by cross-coupling reactions, especially with functionalized iodides. "Another advantage of the indium reagents is that they tolerate particularly sensitive functional groups, such as ketones, aldehydes and ester groups. These are not suitable for reactions with most other metals, since they can be extremely easily destroyed."

DOUBLE ECO-FRIENDLY ORGANOINDIUM COMPOUNDS

In another series of tests, the chemists dealt with the production of magnesium-containing compounds under admixture of the metal zinc. "If we put magnesium, lithium chloride and zinc chloride into a solution, the zinc chloride molecules act together as a kind of peg, clamping the magnesium between them," reports Fabian Piller, who has been cooperating on the projects as a PhD student since the end of 2006. "This stabilizes the magnesium compound, which would otherwise be easily destroyed due to the methyl and ethyl esters used as functional groups." The reagents produced in this fashion can tolerate considerably more sensitive functional groups than pure organomagnesium compounds, but otherwise possess the same properties. The researchers have even achieved some promising intermediate results from aluminum compounds. "These reagents could be used in similar areas as organomagnesium compounds," says Paul Knochel. "They tolerate similar functional groups, but are even cheaper." In future, the chemists intend to investigate more novel synthetic pathways involving the metals manganese, iron, titanium and calcium. "And these metals have the advantage of having no toxic effects on humans or the environment," stresses the scientist.

Overall, the new synthetic method offers practically unlimited variability, and could be used in countless applications in the future – especially in the pharmaceutical and agrochemical industries, but also in the manufacture of electronic accessories and entirely new materials. "Compounds with nitriles, for example, play a part in the synthesis of the drug verapamil, which is used to treat coronary heart disease and cluster headache," Fabian Piller continues. "Compounds with esters, on the other hand, are used in the production of aspirin or the local anesthetic benzocaine." Such substances could be produced much more easily and affordably using the new method, and new drugs with a very broad spectrum of activity could also be synthesized this way. The development of new organometallic compounds could also be of great advantage in agrochemistry. "In this field, we hope to find new ways to produce eco-friendlier and yet more efficient pesticides and fertilizers," says Paul Knochel. Other applications could be the development of novel LEDs or screens based on harmless materials. "At the moment, it is still difficult to anticipate all of the conceivable applications, since we have not even sounded out many of the chemical possibilities yet," the chemist summarizes. "But it is great that so much is becoming feasible."

The new synthetic method is so promising in the eyes of the European Research Council (ERC) that they are generously funding Paul Knochel's future research. In August 2008, the chemist received an "advanced investigator grant" to the sum of two million euros for his project on "new organometallic compounds". The scientist has already been bestowed with many honors. In 2007, for example, he was appointed member of the French Académie des Sciences and in 2008 member of the Bavarian Akademie der Wissenschaften – both for significant scientific contributions to the field of chemistry. He was awarded the Victor Grignard Award in 2000, and at the beginning of 2009, he received the Karl Ziegler Award from the Gesellschaft deutscher Chemiker – one of the most highly endowed German awards in the field of chemistry.

Prof. Dr. Paul Knochel has been head of the Chair of Organic Chemistry at the LMU Munich Department of Chemistry and Biochemistry since 1999. In 2008, he received an Advanced Investigator Grant from the European Research Council (ERC).
www.knochel.cup.uni-muenchen.de/
knoch@cup.uni-muenchen.de