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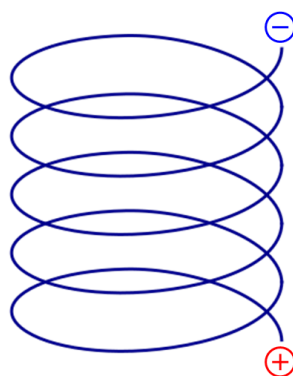
People, Trends and Views in Chemical Synthesis

2018/10

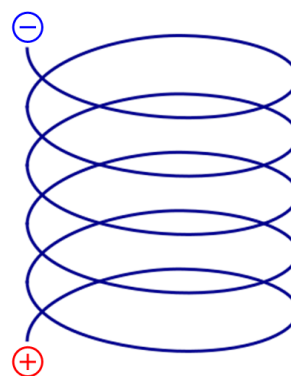
Separation of Enantiomers by Their Enantio-specific Interaction with Achiral Magnetic Substrates

Highlighted article by K. Banerjee-Ghosh, O. Ben Dor, F. Tassinari, E. Capua, S. Yochelis, A. Capua, S.-H. Yang, S. S. P. Parkin, S. Sarkar, L. Kronik, L. T. Baczewski, R. Naaman, Y. Paltiel

L-[Cya-(Ala-Aib)₅-COOH]



D-[Cya-(Ala-Aib)₅-COOH]



Thin film consisting of 50 Al/5 Ti/0.3 Co/(0.7 Ni/0.3 Co)₆/5 Au (nm), magnetized externally either normally or anti-normally to the surface

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Dear Readers,

I hope you are enjoying the new quarterly 'Biographical Name Reaction' articles dedicated to a historic overview of the life and achievements of pioneers and giants of organic chemistry and of the textbook reactions which are named after them. In July we learned about von Hofmann, Lossen and Curtius and their rearrangement reactions. In this issue we go back to the years across 19th and 20th centuries with the discovery of organomagnesium chemistry by Barbier and Grignard. Personally, I find these articles – authored by David Lewis and some of his group members – incredibly informative, enjoyable and entertaining, revealing forgotten or scarcely known aspects of the personal life of these trailblazers of organic synthesis who are best known for their scientific legacy, but whose lives and the historic context in which they operated are often much less known. This is the opening article of our October issue and I am already looking forward to reading the next 'Name Reaction Bio'! The following article covers a *Science* paper recently published by P. J. Chirik (USA) and collaborators on a single-electron reduction enabling a Co-catalyzed enantioselective hydrogenation of enamides to the corresponding α -amino acid derivatives. The next contribution reports on another *Science* paper from the groups of R. Naaman and Y. Paltiel (Israel) with their groundbreaking separation of enantiomers enabled by achiral magnetic surfaces. The issue is closed by a Young Career Focus interview with S. Thomas (UK), another up-and-coming chemist who tells us about his research and views on organic synthesis.

Enjoy your reading!!



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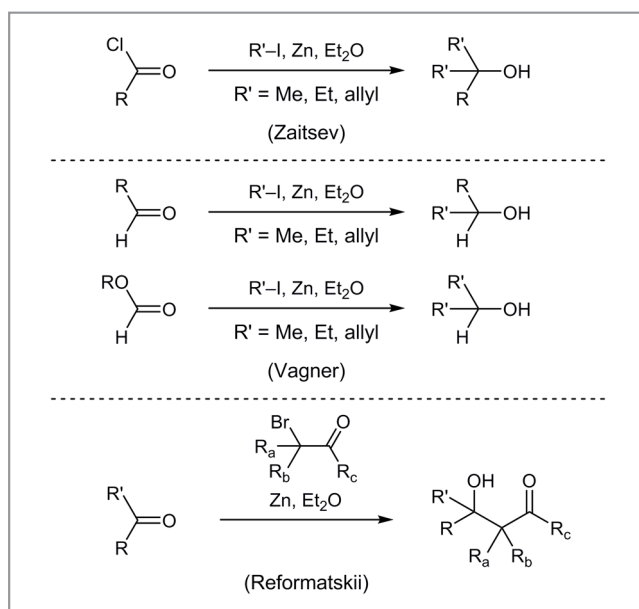
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Philippe Barbier (1848–1922) and Victor Grignard (1871–1935): Pioneers of Organomagnesium Chemistry

There are few synthetic organic chemists who have not used the Grignard synthesis of alcohols, named for Victor Grignard of the Université de Lyon, at some point in their careers.

Building on earlier work in organozinc chemistry by Russian chemists, especially Zaitsev and his students¹ (Scheme 1), Barbier and Grignard developed organomagnesium nucleophiles that were much easier to use in synthesis. Henry Gilman, who will be the subject of a later Name Reaction Bio, studied the Grignard reaction extensively, and from there expanded his work with organometallic reagents of other metals.



Scheme 1

Philippe Antoine François Barbier (1848–1922), who is considered by many to be the father of organometallic chemistry, is something of a mystery man because just prior to his death he destroyed almost all the records of his life and career.

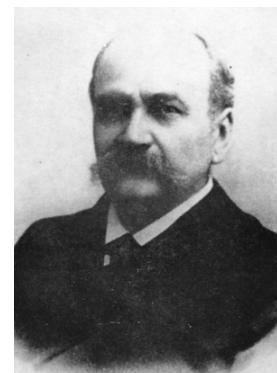
Barbier was born in Luzay (France) but little else is known about him (including his personal life) until he began his career. His death notice in the *Comptes Rendus* was reproduced in the *Journal Officielle de la République Française*;² it states that he was a student of (Pierre Eugène) Marcelin

Berthelot (1827–1907) at the Collège de France, and it was here that he published his first work, on the conversion of terpineol into cymene (Scheme 2),³ and his first work on the pyrolysis of aromatic compounds (in this case, fluorene). In his early career, he continued studying these pyrolysis reactions⁴ (Scheme 2). He earned his Dr. ès sciences from the École supérieure de Pharmacie de Paris in 1876 for a thesis on pyrolysis of aromatic hydrocarbons.⁵ He immediately became préparateur at the École before moving to Besançon as Director of the Agricultural Station, and Chargé de cours in chemistry in the faculty of sciences during the 1879–1880 academic year. In 1880, he moved to Lyon as Professor of Chemistry and became Professor of General Chemistry in 1884.

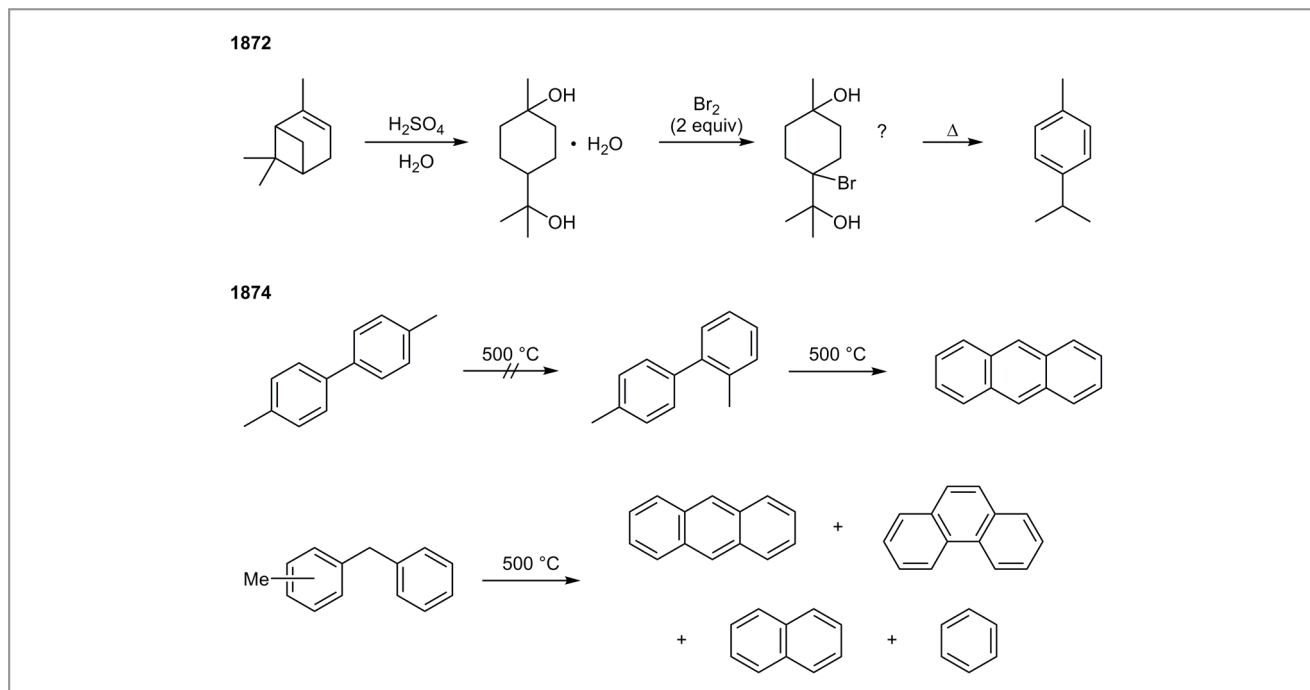
There have been no detailed obituaries or biographies of Barbier, something his student, Victor Grignard, felt was unjust. Grignard had planned to complete a biography of his mentor but was unable to find the time to hunt down the material. His son, Roger Grignard gave the most comprehensive biography of Barbier in his celebration of the centenary of the birth of his father.⁷

Barbier had the reputation of being a man of few words and was considered short, abrupt, and acerbic. He was the head of the physical science department and was known for frightening beginners away. However, once he warmed up to a person he was not shy about giving praise where appropriate.

Although his work on pyrolysis reactions was quite important in clearing up the chemistry of coal tar, he is best remembered for the Barbier reaction,⁶ which was the first study of organomagnesium nucleophiles (Scheme 3). In the single paper describing this reaction, he also indicates that he has used the reaction to make several other compounds; unfortunately, these syntheses never appeared in print. In this exothermic reaction, an alkyl halide is added to a mixture of a carbonyl compound, magnesium metal and ether. Barbier lost interest in pursuing this reaction when he found the yields to be mediocre and frequently irreproducible, and he passed it on to Victor Grignard as his doctoral problem. Barbier's pub-



Philippe Barbier



Scheme 2

lications in the 20th century concern mineralogical chemistry and the isolation and structure elucidation of new terpenoid compounds.

Victor Grignard was born in the city of Cherbourg in France, the son of a sailmaker.⁷ He attended public schools before earning a scholarship to the École Normale Spéciale at Cluny in 1889, a school that specialized in training future secondary school teachers before it closed. The closure of the École Normale gave him the opportunity to join the University of Lyon where his interest in the sciences began. He initially preferred the field of mathematics but struggled in his classes and even failed his first attempt at the final examinations. His academic career was temporarily put on hold in 1892 when, at the age of 21, he fulfilled his military service obligation, rising to the rank of corporal before being demobilized. He returned

to Lyon in 1894 to earn his Bachelor of Mathematical Sciences after passing his examinations the second time around.

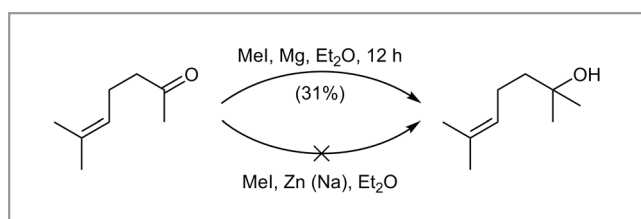
A friend persuaded Grignard to foster his interest in chemistry, encouraging him to accept a junior laboratory assistant position at the university. Chemistry was a subject in which he excelled, and he found himself liking it so much that he accepted a position as préparateur. This led him to be introduced



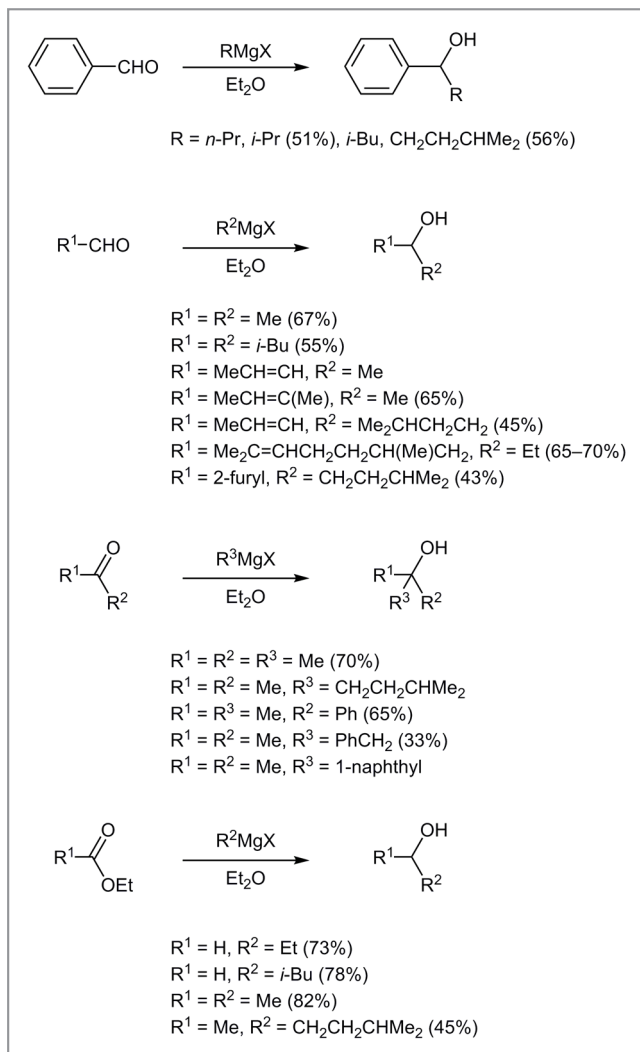
Victor Grignard

to Philippe Barbier, under whose direction he was awarded his Dr. ès Sciences degree in 1901.⁸ The alcohols synthesized by Grignard as part of his dissertation at Lyon are gathered in Scheme 4. As is evident, he explored the use of magnesium as a replacement for zinc in most of the alcohol syntheses previously reported by Zaitsev and Wagner.^{1a-1} He found that in general, his yields were superior to the older reaction. The one exception was in the formation of allyl carbinols, where the allylzinc halide was a superior nucleophile.

Grignard published his doctoral work under his name alone, which suggests that Barbier was not especially in-



Scheme 3

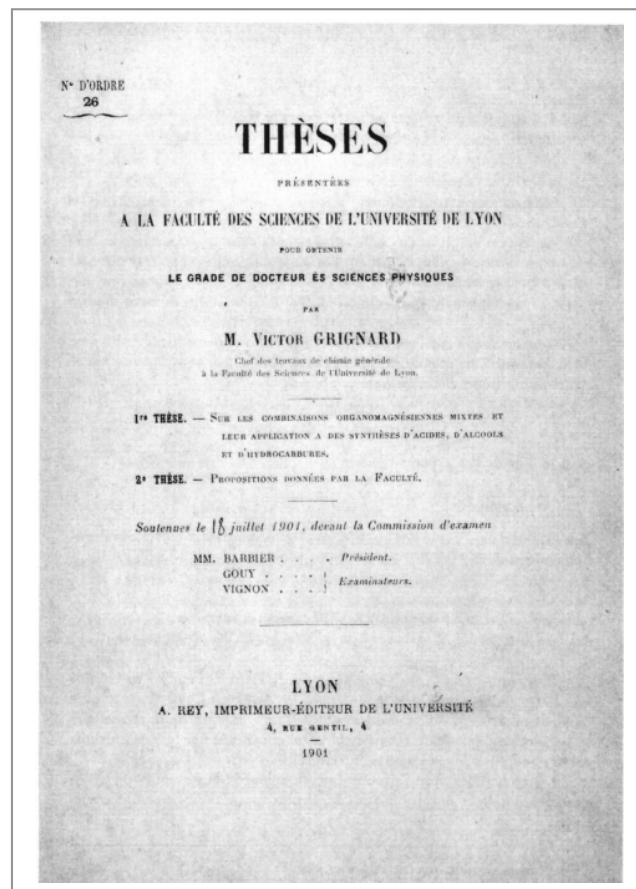


Scheme 4

terested in it at the time. Still, there is some evidence that the attention paid to his junior colleague after the early publications of his reaction⁹ gradually irked Barbier. Nevertheless, Grignard continued to work with his mentor, even after he had left Lyon.¹⁰

Grignard left Lyon for Nancy in 1909; there he became professor of organic chemistry in 1910. He married the widowed Augustine Marie Boulan that same year. In 1912, he shared the Nobel Prize in Chemistry with Paul Sabatier. He was made a Chevalier of the Légion d'honneur the same year, rising to Officier (1920) and Commandeur (1933).

Following his service in World War I, Grignard returned to his family and his academic work at the University of Nancy, but the university had been badly damaged during the war,



Title page to Grignard's doctoral work

and it was so difficult to find professors capable of teaching the courses, that it was closed until it could be rebuilt; Grignard returned to the Université de Lyon and his 'Venerable Mentor', Barbier. He spent the rest of his career there.

Being a Nobel laureate did not protect Grignard from being drafted into the French army at his former rank when World War I broke out; as a corporal, he was placed on sentry duty. After months of routine guard duty, Grignard was brought to the attention of the General Staff because he continued to wear his Médaille Légion d'Honneur medal after being ordered by his immediate superior to desist.



Corporal Victor Grignard. Note the Médaille Légion d'Honneur on his uniform.

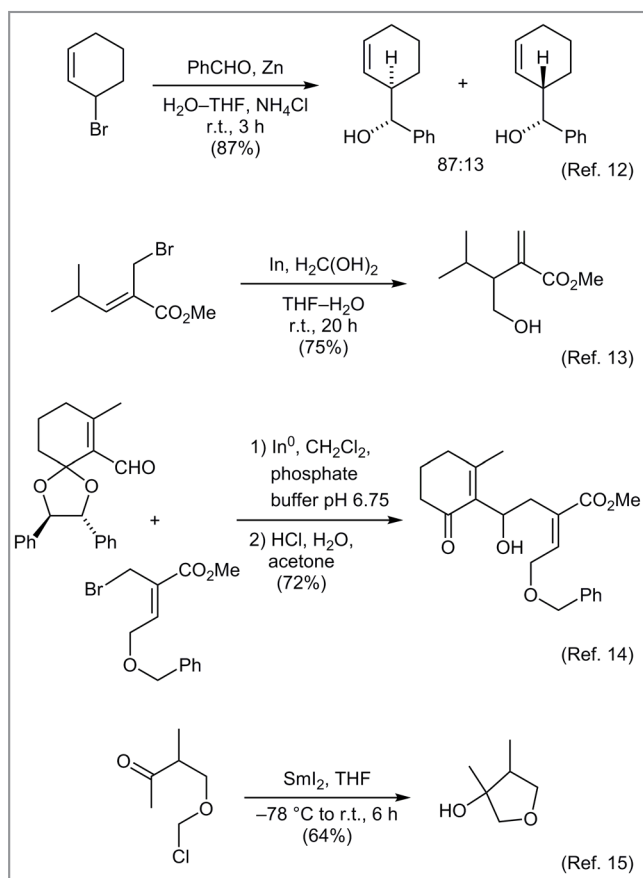
When the army looked more closely at the background of this corporal, they realized what a resource they had wasted: a world-class chemist had talents that were much better suited elsewhere. He was first assigned the task of increasing the production of explosives: when the production of TNT became inadequate, the French army turned to chemical warfare. He was seconded to the discovery and production of antidotes to chemical weapons, and then to the production of new chemical weapons.

The Nobel Prize in Chemistry for 1912 was not devoid of controversy. Neither Barbier, nor Sabatier's collaborator Jean-Baptiste Senderens, received the prize, despite their contributions being essentially of equal importance with those of the laureates. This omission was an injustice noted by Grignard himself,¹¹ who wrote to his friend Meunier on November 13, 1912 (just days after his Nobel was announced) "...to tell the truth, and between us, I would even have preferred to wait a little longer, to see the prize shared between Sabatier and Senderens and then share it myself with Barbier at a later

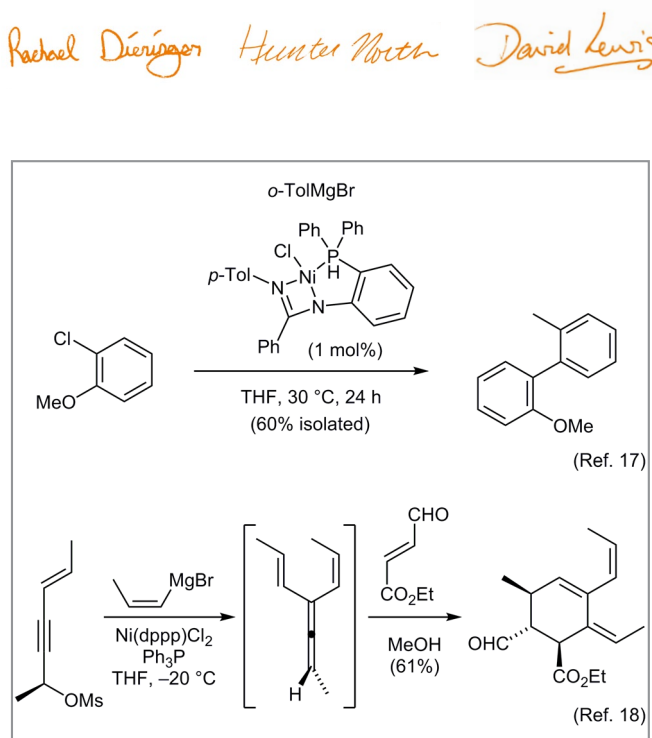
time, But what can I do against such a verdict if not congratulate myself for it! You will be very kind to give me as much information as you can on the state of health and on the state of mind of Barbier. I wonder how he will take it. But if he feels frustrated, I do not think he can blame me for it." There is evidence that the decision of the Nobel Committee may have played a major part in Barbier's decision to destroy his personal records.

The field of organomagnesium chemistry has continued to flourish and to expand to other metals since the work of these pioneering chemists. The Barbier reaction, which had been so difficult to carry out reproducibly, is still used, but the magnesium has been replaced by less reactive metals, including zinc,¹² indium^{13,14} and samarium¹⁵ that lead to organometallic intermediates that react very slowly or not at all with water, thus permitting their use in aqueous or mixed aqueous solvents (Scheme 5).

The commercial availability of solutions of Grignard reagents, including difficult-to-form allylic Grignard reagents, has made the Grignard reaction much more convenient to carry out. It has also made it possible to use the Grignard reagent as a participant in cross-coupling reactions, such as the Corriu–Kumada cross-coupling for the synthesis of diaryls.¹⁶ Recent examples^{17,18} are given in Scheme 6.



Scheme 5



Scheme 6

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Cobalt-Catalyzed Asymmetric Hydrogenation of Enamides Enabled by Single-Electron Reduction

Science **2018**, *360*, 888–893

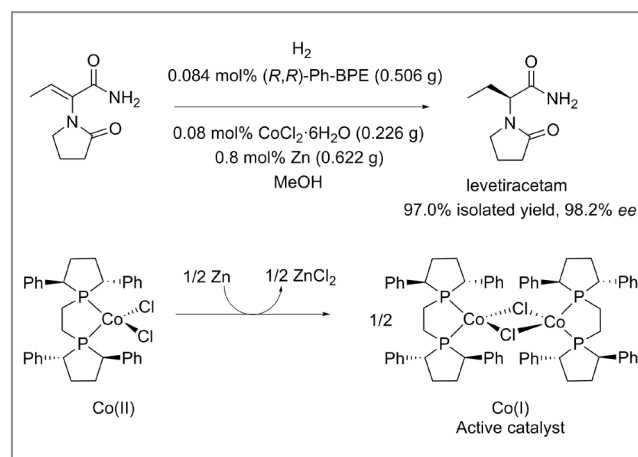
Many drug molecules, much like a pair of hands, have defined stereochemistry, meaning a specific orientation of the substituents in space. Chemists are challenged to discover methods to synthesize only one enantiomer of drug molecules rather than synthesize both and then separate. Metal catalysts, historically based on precious metals like rhodium, have been tasked with solving this challenge. Recently, a paper published in *Science* by the group of Professor Paul J. Chirik at Princeton University (USA) in collaboration with scientists from the MSD Research Laboratories (USA) demonstrated that a more Earth-abundant metal – cobalt – can be used to synthesize the epilepsy medication Keppra (levetiracetam) as just one enantiomeric form. Professor Chirik said: “The main findings of the paper are that cobalt is more active and selective than the patented rhodium route and operates in a greener solvent, methanol, than the current method. Our paper demonstrates a rare case where an Earth-abundant transition metal can surpass the performance of a precious metal in the synthesis of single-enantiomer drugs.”

One of the members of Professor Chirik’s team, Dr. Max Friedfeld, said: “In re-evaluating a catalyst system we developed in 2013, where it was demonstrated that cobalt could be used in hydrogenation to make single enantiomers of organic molecules, we identified certain criteria that limited the usefulness of the system. These detractions included relatively high catalyst loading (indicating a relatively inefficient catalyst), non-trivial catalyst synthesis steps (making wide-spread adoption less likely and lowering catalyst tunability), and the use of ultra-pure (anhydrous) non-coordinating solvents.”

The authors wanted to develop a system that was more robust and easy to use. “We wanted to accomplish a large-scale hydrogenation with cobalt to show how efficient the catalyst was,” explained Dr. Friedfeld. Professor Chirik remarked: “Our 2013 experiments were important demonstrations of principle but involved relatively simple and not medically active compounds. The solvents used in those studies were also hydrocarbons that required specialized handling. We were inspired to push our demonstration of principle into real-world examples and demonstrate that cobalt could outperform precious metals and work under more environmentally compatible conditions. Our new paper demonstrates just that and also reports that the method can be practiced on a pilot scale.”

“In the new work reported in *Science* (Scheme 1), the team used high-throughput experimentation and analysis techniques coupled with traditional organometallic synthesis to develop a catalyst system that can be used in the synthesis of levetiracetam on 200 g scale using very low catalyst loading (0.08% catalyst relative to substrate),” said Dr. Friedfeld. He continued: “This catalyst system contains three commercially available components and can be prepared simply and in situ without any purification. The catalyst components are the cobalt chloride salt, the organic supporting framework for the cobalt ion, and zinc, which serves to reduce the cobalt. The reaction takes place in methanol, a commonly used industrial solvent that can be processed and safely disposed of easily. By studying the coordination chemistry of the cobalt catalyst, we were able to determine the role of zinc and the favorable oxidation state for catalysis.”

The work used the synthesis of a generic drug as a case study to learn about how to make very efficient base metal catalysts. “In the process of optimizing this chemistry, we made important discoveries in terms of reaction conditions and catalyst activation,” remarked Mr. Michael Shevlin, one of the researchers from the MSD Research Laboratories. He continued: “We were able to show that in this case we could teach an earth-abundant metal how to do chemistry that was



Scheme 1 Cobalt-catalyzed asymmetric hydrogenation of an enamide

previously conducted with precious metals, and that we could actually get more reactivity from cobalt than was previously possible with rhodium. In the process, we showed that these new reaction conditions produced orders of magnitude more cobalt catalysts that could perform asymmetric hydrogenation, and that these conditions were generally useful across many catalysts with several different substrates.”

The collaboration between MSD and Princeton was crucial, with the authors commenting that they would not have made the same types of advances without it. The Catalysis Lab in Process Research & Development uses high-throughput experimentation tools adapted from biology and biochemistry for chemical research. “Instead of trying just a few experiments to test a hypothesis, we can quickly set up large arrays of experiments that cover orders of magnitude more chemical space,” explained Mr. Shevlin. He continued: “We’ve used these tools for years in our lab for pharmaceutical R&D, and they’re just as powerful for doing fundamental chemistry research.” Being different types of chemists that approach problems with fundamentally different perspectives also helped. “The biggest strength of the Catalysis Lab is that we have the tools to quickly discover and optimize new chemical reactions and the experience to be able to implement them as robust processes on manufacturing scale,” explained Mr. Shevlin. He continued: “The Chirik group is really good at being able to understand the fundamental behavior of catalysts, particularly base metal catalysts that are very difficult to study. The synergy is tremendous; scientists like Max Friedfeld and Aaron Zhong can conduct hundreds of experiments in our lab, and then take the most interesting results back to Princeton to study in detail. What they learn there then informs the next round of experimentation here.”

As with much research, there were a few unexpected findings along the way. “We were surprised to learn that one of the catalyst components, zinc, was so effective at generating active catalysts,” said Dr. Friedfeld. He explained further: “One challenge we had with the original system was that when we used high-throughput experimentation techniques with a harsh catalyst activator, we only generated a couple of active catalyst species. While these species were highly active and selective, it felt like we were searching for a needle in a haystack – out of hundreds and hundreds of combinations searched, only a few were good catalysts. With zinc, however, catalyst activation goes through a different mechanism and is much more effective at generating active catalysts. This is depicted in Figure 2 of the *Science* paper. Then, it was like searching for a needle in a sewing shop!”

It was also a surprise that these reactions performed best in protic solvents such as methanol. Mr. Shevlin noted: “Many

base metal catalysts in low oxidation states react with protic solvents and decompose. But our reduced cobalt catalysts not only tolerate methanol, they’re an order of magnitude more reactive in it than they were in aprotic solvents like THF or toluene.”

Professor Chirik recalled the first unexpected event during the work: “We were surprised to see that the phosphine ligand – the key source of stereochemical information – fell off the starting cobalt complex! In catalysis, this usually translates on to poor performance and most likely catalyst death. Cobalt is special; we learned that the phosphine falling off was reversible – meaning that under the activation of conditions provided by the zinc, the catalyst can heal itself. This is a special consequence of the light transition metal where changes in electronic states by one enable molecules to come and go from the cobalt, keeping it active (“alive”) in the catalytic reaction.”

The group was also surprised to learn that cobalt worked most optimally in green solvents like alcohols. For a decade, catalysts based on earth-abundant metals like iron and cobalt required very dry and pure conditions, meaning the catalysts themselves were very fragile. By operating in methanol, not only is the environmental profile of the reaction improved but the catalysts are much easier to use and handle. This means that cobalt should be able to compete or even outperform precious metals in many applications that extend beyond hydrogenation.

Turning to the significance of the work, Mr. Shevlin said: “Base metals are orders of magnitude less expensive than precious metals, but the chiral ligands we use on the metal are even more expensive than precious metals, and that cost is unlikely to change because chiral ligands are complex molecules that take many synthetic steps to make. The real motivation for base metal catalysis in my opinion is that there’s also risk involved with using precious metals in industrial processes because their availability is limited by scarcity and their prices are tied to a volatile market. In contrast, cobalt is so abundant that it’s essentially free when used in catalytic quantities. In this work, we’ve shown that cobalt has the potential for similar, maybe even better performance than rhodium.” Further, Dr. Friedfeld remarked that the work is significant because they were able to harness one-electron oxidation state changes at the metal catalyst (normally considered deleterious to reactivity) to activate the catalyst components, achieving high reactivity and enantioselectivity in a way that is operationally simple to achieve. He commented: “We hope this will inspire other chemists to use this catalyst system for alkene hydrogenation reactions they’re working on, and to consider applying toward other catalytic reactions.” Professor

Chirik agreed and highlighted an important principle in green chemistry, namely that the more environmentally friendly solution can also be the preferred one chemically. He said: “Here the catalyst is based on an earth-abundant metal but is also faster and operates in a greener solvent than rhodium. It tells the community – precious metals beware – after 50 years, cobalt and other first row metals can not only compete, but because of the way electrons flow in a unique manner, they offer new opportunities!”

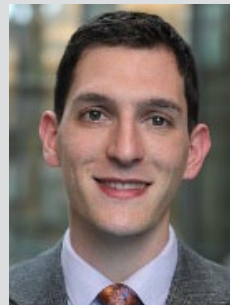
Mr. Shevlin pointed out: “Many topics in chemistry are considered “solved problems”, but chemistry that works on simple molecules on small scale in an academic lab isn’t necessarily practical to implement on an industrial scale for making complicated molecules. So much of modern catalysis was developed with precious metals because they have useful reactivity and it’s relatively easy to study their behavior. But using some of the rarest and most expensive elements on earth isn’t a great way to make complicated molecules in a cost-effective manner. Earth-abundant metals are much less studied, so there’s a wealth of new chemistry waiting to be discovered. The best way to do that is with modern techniques like high-throughput experimentation and collaborations between labs with complementary expertise.”

Professor Chirik would like readers to take away the message that chemists are continually working to improve the synthesis of important drug molecules. “We are concerned about the environment, reducing waste and learning how to discover more effective medicines in a faster more sustainable way,” he remarked, continuing: “We are also still uncovering the secrets of the periodic table and learning how to take advantage of them for the benefit of society.”

Professor Chirik concluded: “This is a great example of an academic–industrial collaboration and highlights how combination of the very fundamental – how do electrons flow differently in cobalt versus rhodium? – can inform the applied – how to make an important medicine in a more sustainable way. I think it is safe to say that we would not have discovered this breakthrough had the two groups at MSD and Princeton acted on their own.”

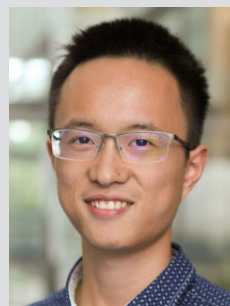
Matthew Fenske

About the authors



Dr. M. Friedfeld

Max Friedfeld obtained his B.Sc in chemistry from the University of Virginia (USA) in 2011, doing undergraduate research with Professor Brent Gunnoe and his Ph.D. in chemistry from Princeton University (USA) in 2016, under the mentorship of Paul Chirik. There he studied asymmetric catalysis with cobalt complexes. He is currently a Washington Research Foundation postdoctoral fellow at the University of Washington (USA), studying nanomaterial nucleation and growth mechanisms under the mentorship of Professor Brandi Cossairt.



H. Zhong

Hongyu “Aaron” Zhong obtained his B.S. degree in chemistry in 2016 from the University of North Carolina (USA) at Chapel Hill with highest honor. During his undergraduate studies, he worked in Professor Michael Gagne’s group on Lewis acid catalyzed diastereoselective carbohydrate de(functionalization). Fascinated by the beauty of organometallic chemistry, he joined Professor Paul Chirik’s lab at Princeton (USA) for his graduate studies. He is now working on developing cobalt-catalyzed enantioselective alkene hydrogenation in collaboration with scientists at Merck & Co., Inc. (MSD) in Kenilworth, NJ (USA).



Dr. R. T. Ruck

Rebecca T. Ruck earned her A.B. summa cum laude from Princeton University (USA) in 1998 before moving on to Harvard as an NSF fellow in the lab of Prof. Eric Jacobsen and continued her career as an NIH post-doctoral fellow at UC-Berkeley (USA) in the lab of Prof. Robert Bergman. She started in Process Research & Development at Merck & Co., Inc. (MSD) in Kenilworth, NJ (USA) in 2005, steadily assuming roles of increasing amounts of responsibility in the intervening years. She has managed a Discovery Process Chemistry team at the interface of medicinal and process chemistry,

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served as Director of Catalysis and Automation, which also involved managing efforts around reaction mechanism and flow chemistry, and is currently Executive Director of Process Chemistry. She has made contributions to programs related to hepatitis C, diabetes and antibacterials, among others. For her role in the chemistry of the beta-lactamase inhibitor, MK-7655, she was recognized as an ACS Division of Organic Chemistry Young Investigator in 2014 and, for her commitment to both scientific excellence and advancing women in chemistry, was recognized as one of the ACS Women Chemists Committee (WCC) 2016 Rising Stars. During her time at MSD, Rebecca has played a significant role in MSD's commitment to safety and is highly active in a variety of external reputation activities, including serving as the departmental recruiting lead, running a series of MSD-sponsored academic lectureships and coordinating an MSD-sponsored research award and accompanying symposium for undergraduate women in collaboration with the WCC. Rebecca was recently named the 2018 winner of the ACS Award for Encouraging Women into Careers in the Chemical Sciences.



M. Shevlin

Michael Shevlin is an Associate Principal Scientist in the Catalysis Laboratory in the Department of Process Research & Development at Merck & Co., Inc. (MSD) in Kenilworth, NJ (USA). Since joining the company in 2006, Michael has become the departmental expert in asymmetric hydrogenation through work on over 40 projects. Michael is a passionate advocate of high-throughput experimentation for reaction discovery, development, and mechanistic elucidation. He is the liaison for a collaboration with Professor Paul Chirik at Princeton University (USA) to develop base metal asymmetric hydrogenation catalysts. Michael received his M.S. degree from the University of Illinois-Chicago (USA) in 2004 and spent two years teaching at Ivy Tech State College in Lafayette, Indiana (USA).



Prof. P. Chirik

Paul Chirik was born in 1973 outside of Philadelphia, PA (USA). In 1995 he earned his Bachelor of Science in chemistry from Virginia Tech (USA). During that time, he conducted undergraduate research with Professor Joseph S. Merola studying aqueous iridium chemistry. Chirik earned his Ph.D. with Professor John Bercaw at Caltech (USA) in 2000 and was awarded the Hebert Newby McCoy award for his dissertation on metal-

locene-catalyzed olefin polymerization. After a brief postdoctoral appointment with Professor Christopher Cummins at MIT (USA), Chirik began his independent career at Cornell University (USA) in 2001. In 2006, he was promoted to Associate Professor and in 2009 was named the Peter J. W. Debye Professor of Chemistry. In 2011, Chirik and his research group moved to Princeton University (USA) where he was named the Edwards S. Sanford Professor of Chemistry. His teaching and research have been recognized with an Arthur C. Cope Scholar Award, the Blavatnik Award for Young Scientists, a Packard Fellowship in science and engineering, a Camille Dreyfus Teacher Scholar Award and an NSF CAREER Award. He is currently the Editor-in-Chief of *Organometallics* and the recipient of the 2016 Presidential Green Chemistry Challenge Award and 2017 ACS Catalysis Lectureship in Catalysis Science. He is the corresponding author on over 175 peer-reviewed manuscripts in publications including *Science*, *Nature*, *Journal of the American Chemical Society*, *Angewandte Chemie International Edition* and *ACS Catalysis*.

Separation of Enantiomers by Their Enantiospecific Interaction with Achiral Magnetic Substrates

Science **2018**, *360*, 1331–1334

The chemical building blocks of life and many biologically active materials such as drugs and pesticides are molecules that have either right- or left-handed configuration (e.g. enantiomers), a concept referred to as *chirality*. Chiral molecules having the same chemical composition but different 'handedness' may have extremely different biological effects. One infamous example is the drug thalidomide, which was marketed in racemic form, as a mixture of its two enantiomers; one had the desired therapeutic effect while the other caused severe birth defects. Other drugs, such as Ritalin and Cipramil, are also marketed in their premium enantiomerically pure forms (Focalin and Cipralex, respectively) that are more potent and have fewer side effects. Therefore, the regulatory trends in the pharmaceutical industry incentivize the marketing of enantiomerically pure materials. For example, today only 13% of chiral drugs are marketed as single stereoisomers, although FDA regulatory recommendations are to achieve separation in all drugs. Another driver for the development of enantiomerically pure materials is the extension of patent protection.

A decade of research collaboration between Professor Ron Naaman at the Weizmann Institute (Israel) and Professor Yossi

Paltiel at the Hebrew University (Israel) led to results recently published in *Science* that show chiral-selective affinity of molecules to magnetic surfaces. Professor Naaman said: "Using this technology, one enantiomer adsorbs preferentially on perpendicularly magnetized substrates when the magnetic dipole is pointing up, whereas the other adsorbs faster for the opposite alignment of the magnetization. The interaction is not controlled by the magnetic field *per se*, but rather by the electron spin orientations."

Proof-of-concept work presented in the *Science* paper showed that it is possible to achieve preferential adsorption on achiral materials, such as thin films, of a number of chiral compounds – including peptides, DNA and small molecules – by applying opposite magnetic dipoles.

Professor Naaman concluded: "This work leads to a breakthrough column and crystallization technology providing for the first time a generic technique for chiral separation. The technique is simple and cost-effective and does not have to be customized for each specific material."

An animation explaining this work is available at the link: <https://vimeo.com/257954972>

Mattes Fank

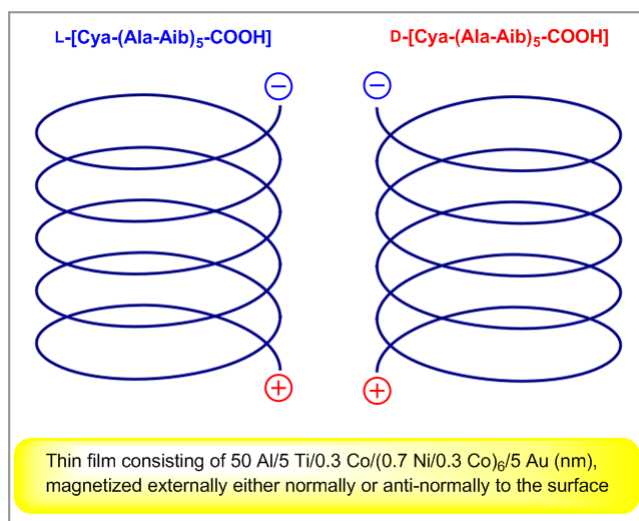


Figure 1 One of the applications of the new technology: enantioselective adsorption of peptides on the Au of a thin film coating a flow column as a result of opposite magnetizations

About the authors

*Professor Y. Paltiel*

Yossi Paltiel, born in 1968, is now in the Applied Physics Department in the Hebrew University of Jerusalem (Israel). Professor Paltiel has worked both for leading high-tech industry groups and in the academic world. He has been leading the Quantum Nano Engineering group at the Hebrew University, Israel since July 2009. The goal of Professor Paltiel's group is to establish a way to incorporate quantum mechanics into room-temperature

'classical' computation and reading schemes mimicking biological and chemical processes. Professor Paltiel has published more than 110 papers in leading journals and issued 13 patents. He has a startup company named Valentis Nanotech, founded in 2013. The company utilizes nanocellulose's unique properties to produce a biodegradable transparent sheet with additional controlled optical and gas/water barrier properties.

*Professor R. Naaman*

Ron Naaman completed his B.Sc. in chemistry at the Ben Gurion University, Beer-Sheva, Israel, and his Ph.D. at the Weizmann Institute in Israel. He then moved for a postdoctoral fellowship to Stanford, California (USA) for two years and then spent one year at the Chemistry Department at Harvard (USA). In 1980, he returned to Israel and became a faculty member at the Weizmann Institute. Since 1992 he has been a full professor in

the Department of Chemical Physics at the Institute. His research group discovered the chirality-induced spin-selectivity effect, the result of which is spin-selective electron transport through chiral molecules.

Young Career Focus: Dr. Stephen Thomas (University of Edinburgh, UK)

Background and Purpose. SYNFORM regularly meets young up-and-coming researchers who are performing exceptionally well in the arena of organic chemistry and related fields of research, in order to introduce them to the readership. This Young Career Focus presents Dr. Stephen Thomas (University of Edinburgh, UK).

Biographical Sketch



Dr. Stephen Thomas

Stephen Thomas was born in Toronto, Canada, and moved to Somerset (UK) at a young age where he completed his secondary school education at Court Fields Community School and Richard Huish College. After gaining his undergraduate degree from Cardiff University (UK), Stephen completed his PhD with Dr Stuart Warren at the University of Cambridge (UK). Following post-doctoral research with Prof. Andreas Pfaltz at the University of Basel (Switzerland), Stephen was appointed to a fixed-term lectureship at the University of Bristol (UK) associated with Prof. Varinder Aggarwal FRS, allowing him to begin his independent research career. In 2012 Stephen moved to the University of Edinburgh (UK) to take up a Chancellor's Fellowship and in 2014 was awarded a Royal Society University Research Fellowship. Stephen was awarded the 2016 RSC Hickinbottom Award, a 2017 Thieme Chemistry Award and a 2018 Pfizer Green Chemistry Research Award.

INTERVIEW

SYNFORM *What is the focus of your current research activity?*

Dr. S. Thomas We are interested in developing and understanding sustainable catalytic methods. Our focus has been on the application and use of the most abundant elements in the earth's crust as catalysts the reductive functionalisation of unsaturated groups. A key driver for us is understanding the methods we develop and how the unique reactivities of first-row transition metals and main group elements can be applied in new ways.

SYNFORM *When did you get interested in synthesis?*

Dr. S. Thomas As an undergraduate I was lucky enough to join Prof. Nick Tomkinson's lab for a summer research project at the end of my second year. Nick's enthusiasm was infectious and it led me to regularly visit the library to read the latest journal issues. It was here that I first discovered the potential for elegance in synthesis, and the limitation of synthetic methods. I can vividly recall reading Steve Ley's 'latent pseudo symmetry' approach to spongistatin and Phil Power's main group multiple bonding papers. Although my focus has shifted towards methodology and catalysis, I am still in awe of target molecule disconnections beyond the familiar.

SYNFORM *What do you think about the modern role and prospects of organic synthesis?*

Dr. S. Thomas Organic synthesis is as crucial now as it has ever been. It underpins developments in everything from medicine to materials. Synthesis can often be lost when the ultimate goal of a project is presented, seen merely as a tool. However, this hides the fundamental role synthesis has played in realising the project. In our work, ligand synthesis and the

selective variation of ligand structure is essential and often a challenge. Innovative materials require new building blocks, molecular machines require construction, biological probes require highly accurate spatial placement. Synthesis is essential for all of these.

SYNFORM *Your research group is active across the areas of methods development, catalysis and organometallic chemistry. Could you tell us more about your research and its aims?*

Dr. S. Thomas We are fundamentally interested in understanding catalyst reactivity and applying this understanding in the development of sustainable catalytic methods (Scheme 1). Therefore, we have focused on the use of first-row transition metals^{1,2} and main group elements³ as catalysts. Alongside this we are very aware that there is a barrier to using any new method, so we actively work to develop operationally simple methods which do not use reagents or techniques that necessitate specialist handling or training. This can be seen in our work on first-row transition-metal catalysis which has focused on the activation of bench-stable pre-catalysts.^{4,5} We hope that by reducing the practical barriers to trialing these reactions we will expedite the uptake and development of these methods. To understand the activation processes currently used, and those we have developed, organometallic chemistry and mechanistic analysis are key.⁶⁻⁹ This is also true of our work on main group catalysis where understanding the mechanism of catalysis has opened exciting new areas of research.^{10,11} We have been very fortunate to work with a number of exceptional academic and industrial collaborators.

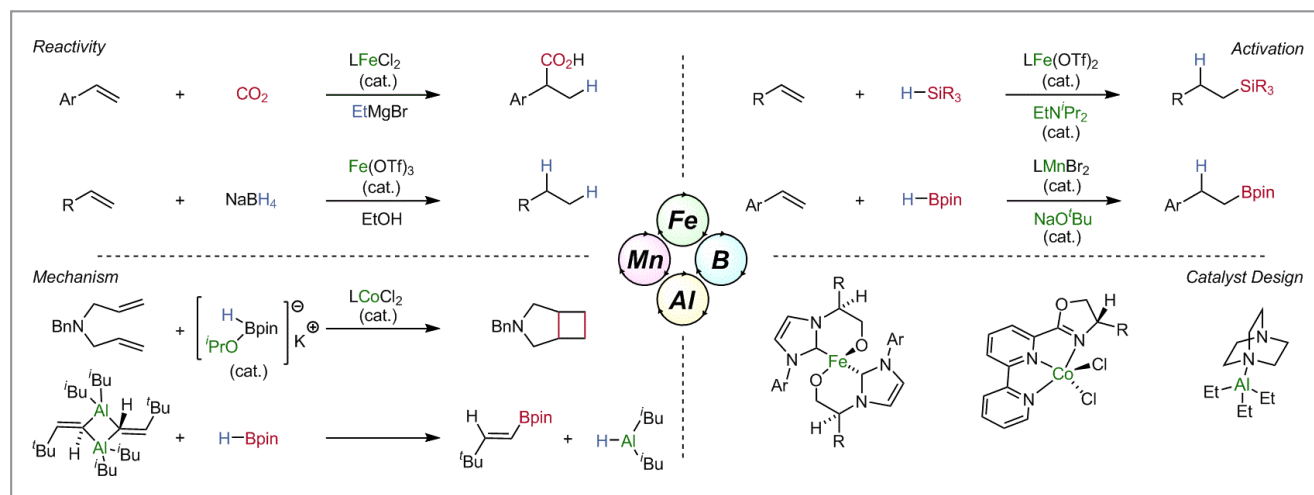
This has proved invaluable in terms of viewing a problem from different perspectives and in applying our methods to 'real-world' synthetic targets.

While we have focused on reductive catalysis to functionalise unsaturated groups, our developments have been informed by the observations of excellent coworkers of the unexpected reaction outcomes. This has taken us in directions I never would have predicted, but ones in which our key aims of developing simple, robust and sustainable catalytic methods have allowed us to contribute.

SYNFORM *What is your most important scientific achievement to date and why?*

Dr. S. Thomas That's a tough question and one to which the answer changes regularly. The people who have progressed through the group are our most important and impactful achievement. My passion for individual projects is generally dictated by the interactions with the co-worker on that project. Thankfully I have a group full of enthusiastic and excellent scientists, so one project, or achievement, is impossible to pick. If forced to answer, I would say simplicity and the ability to apply that simplicity to challenging problems.

Matthew Fenske



Scheme 1

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