

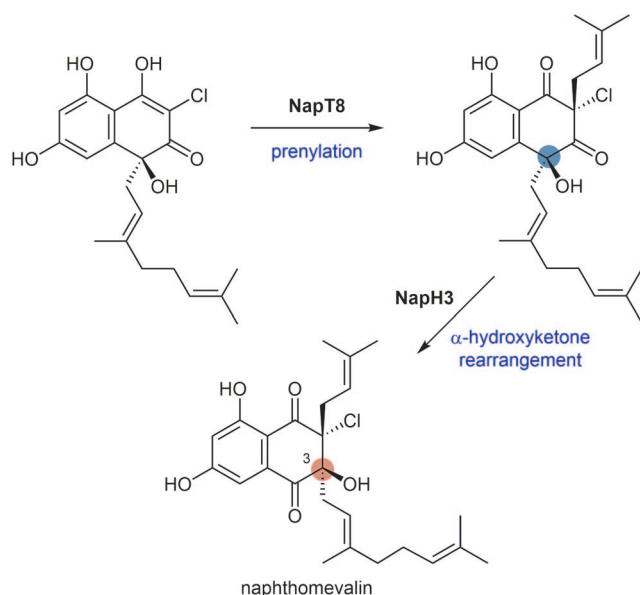
Synform

People, Trends and Views in Chemical Synthesis

2018/04

A Unifying Paradigm for Naphthoquinone-Based Meroterpenoid (Bio)synthesis

Highlighted article by Z. D. Miles, S. Diethelm,
H. P. Pepper, D. M. Huang, J. H. George, B. S. Moore



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Dear Readers,

Today is a typical Scottish day, damp with drizzle, breezy, dark. Your mood won't be great if you are affected by the weather, but luckily, I am not meteoropathic so my only issue on a day like this is to stay dry and try not to catch a cold... But last week we had the 'beast from the east' in this country, with temperatures which plummeted to $-10\text{ }^{\circ}\text{C}$ and snow and ice. Trains stuck in the snow, airports paralyzed and travelers stranded wherever they got 'surprised' by the storm (even though the weather forecast had very reliably predicted this exact situation well in advance). It was pretty grim for many, including myself, as I got stranded for days in a big city in England, and I only managed to get home after countless flight cancellations and last-minute hotel bookings. In a situation like that you realize how fragile our transports system is and how our lifestyle is actually quite precarious, as twenty centimeters of snow and a few days of unseasonal weather are more than enough to bring massive disruptions to our schedules and routines. Luckily, there are still rock-solid certainties in our lives and I am glad that SYNFORM is one of these! No matter how the storm howls, every month you will find it online, keeping you up to date with some of the most exciting news and developments in organic synthesis. For example, this issue starts with a new, entertaining and highly informative Biographical Name Reaction authored by David Lewis, that will take us back in time to the life and work of Friedel and Crafts and their discovery of the alkylation and acylation reactions which are named after them. The follow-up article is a Young Career Focus interview with Norman Metanis (Israel) who talks about his research and ideas. The next contribution covers a *Nat. Chem.* paper on the biosynthesis of meroterpenoids stemming from an 'antipodal' collaboration between J. H. George (Australia) and B. S. Moore (USA). And last but not least, the issue

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is closed by an article on the Ru(II)-catalyzed olefination developed by C.-J. Li (Canada). Because SYNFORM is reliable in any weather and season!

Enjoy your reading!



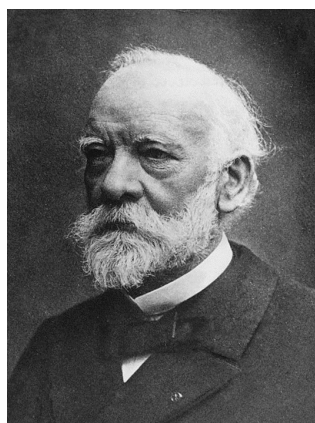
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Charles Friedel (1832–1899) and James Mason Crafts (1839–1917): The Friedel–Crafts Alkylation and Acylation Reactions

In 1877, the first two papers of a series of nine appearing over the following four years,¹ were published by French chemist Charles Friedel,² and his American collaborator James Mason Crafts.³ The reaction between a carbon electrophile and an aromatic hydrocarbon now bears the name of both chemists, and has become one of the foundational electrophilic aromatic substitution reactions.

Charles Friedel was born in Strasbourg (France), to a banker. On graduation from the Protestant Gymnasium, he enrolled in the Science Faculty at the University of Strasbourg, where Pasteur was a member of the faculty. Pasteur assigned him work in chemistry and crystallography, thus setting him on his career course: Friedel would make major contributions in both organic chemistry and mineralogy.



Charles Friedel (1832–1899) | Louise Jeanne Salomé Combes [Friedel] (1838–1908)

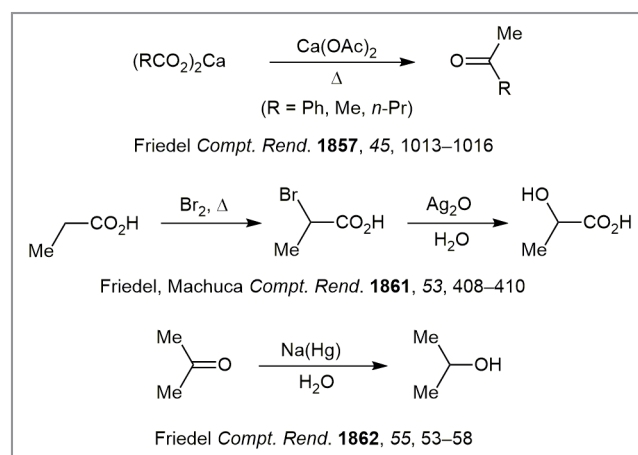
Friedel graduated with the baccalauréat de lettres in 1849 and the baccalauréat en sciences physique, with distinction, in 1850. He spent the year after his graduation working in his father's banking house, but it soon became apparent that he did not have the temperament to work in finance. So, at 20 years old, he was sent to Paris to live with his grandfather, the zoologist Georges Louis Duvernoy (1777–1855). On his arrival in Paris he entered the Lycée Saint-Louis to study for the baccalauréat de mathématique. In 1854, he obtained the licence mathématique. In 1855, he received the licence physique.

In 1856, Friedel was chosen to be Conservator of Collections at the École de Mines, a position he held for the next

20 years. The same year, he married Émilie Salomé Koechlin (1837–1871), who became mother of his four daughters and his first son. When she was a young girl near Nîmes, Émilie had lived in a house where the coffins of her ancestors were held – as Protestants, they had been denied Christian burial. At the beginning of the Franco-Prussian War, in 1870, Friedel sent Émilie and the children to Switzerland for their safety while he worked for the defense of the city of Paris. He did not learn of his young wife's death from pneumonia until after the capitulation.

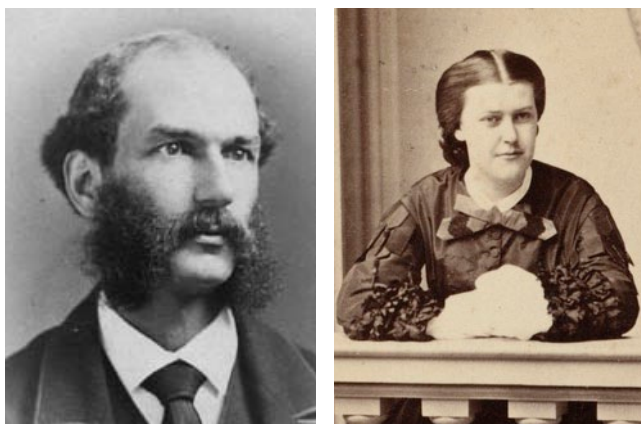
In 1854, Friedel entered the laboratory of Charles Adolphe Wurtz (1817–1884), another Strasbourg native with whom he became a lifelong friend. During his work with Wurtz, Friedel synthesized lactic acid, and established the chemistry of the two hydroxy groups in α -hydroxy acids. His studies of aldehydes and ketones led to him becoming the first to prepare isopropyl alcohol, by reduction of acetone with sodium amalgam, and thus establishing the existence of secondary alcohols as a class (Scheme 1).

In 1873, Friedel married Louise Jeanne Salomé Combes (1838–1908), who became the mother of his youngest son. The Friedel family produced several important French scientists. His son Georges (1865–1933) became an important crystallographer (Friedel's law is named for him) and his second son, Jean (1874–1941), became a biologist in Nancy. Georges' grandson (Friedel's great-grandson), Jacques (1921–2014), was an important physicist and materials scientist.



Scheme 1

The other partner in the discovery and development of this reaction, James Mason Crafts, was born in Boston (USA), and studied at the Lowell Academy; he graduated S.B. from the Lawrence Scientific School of Harvard University in 1858. Despite his long career and number of research publications, he never earned a doctoral degree. After his graduation, he spent a short time studying with E. N. Horsford (1818–1893) at Harvard, and then moved to Germany. There, he spent much of his first four years at Heidelberg, studying with Robert Bunsen (1811–1899). In 1862, he moved to France, where he spent another four years in the laboratory of Charles Adolphe Wurtz at the Sorbonne.



James Mason Crafts (1839–1917) | Clemence Haggerty Crafts (1841–1912)

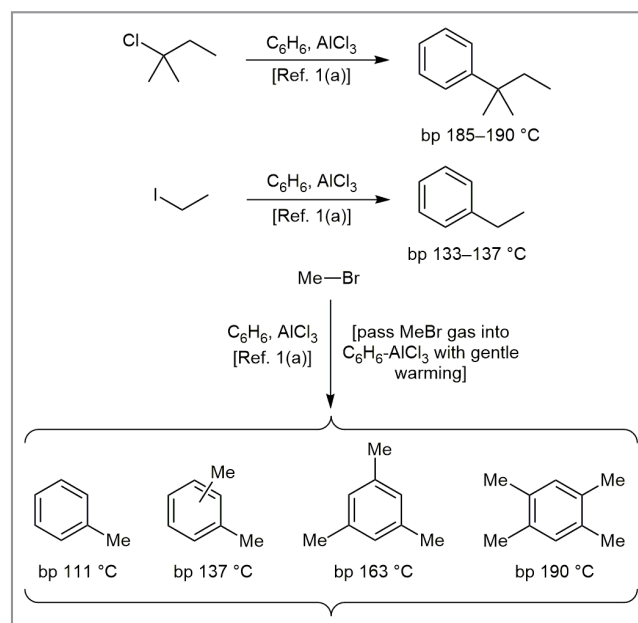
During Crafts' period in Heidelberg, Bunsen was heavily engaged in his systematic spectroscopic studies of the elements with Gustav Robert Kirchhoff (1824–1887), and Crafts had the good fortune to become Bunsen's assistant during his time in Heidelberg. Despite this opportunity, Crafts published no papers during his time in Bunsen's laboratory.

In Wurtz' laboratory, Crafts was initially assigned to a problem on ethylene sulfide, and Crafts' first papers were in the area of organosulfur chemistry. Four years later, in 1865, he returned to the United States, and in 1866 he became mine examiner in Mexico – a perilous position at that time because of the physically difficult terrain and the dangers posed by bandits. Although very modest, Crafts occasionally told friends of his adventures in Mexico. In 1867, he took up a position as Professor of Chemistry and Dean of the Chemical Faculty at Cornell University, which had been founded just two years earlier. The next year, he married Clemence Haggerty (1841–1912); the couple had four children.

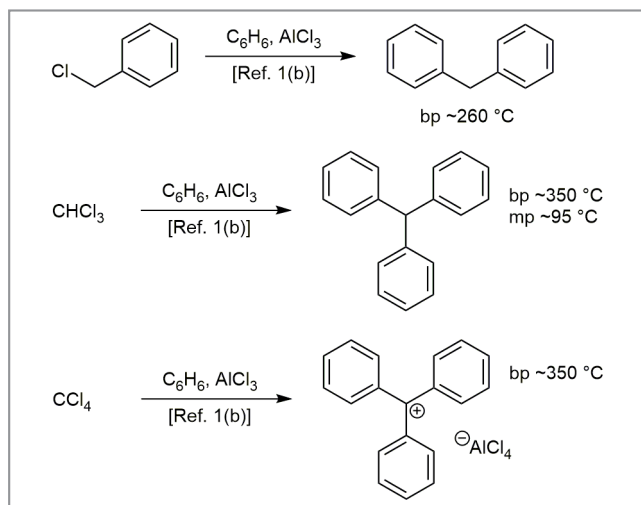
In 1870, Crafts moved to the Massachusetts Institute of Technology (MIT) as Professor. His work here was so demanding that his health suffered; in 1874, he changed his title to non-resident professor, and returned to France. It was during this sojourn in France that he began his incredibly fruitful collaboration with Friedel. In 1880, he resigned his non-resident professorship at MIT. He remained in France for another decade – possibly the most productive years of his scientific career. It was not until 1891 that he returned permanently to the United States, and MIT. From 1892–1897 he served as Professor of Chemistry, and then in 1897 he became Acting President, and then President of MIT. In 1900, he resigned his position, and returned to his research work.

Crafts' accomplishments were honored by his election to the National Academy of Sciences in 1872. Until the end of the nineteenth century, Crafts was a frequent visitor to the Sorbonne, where he became a close personal friend of his co-worker, Charles Friedel. In 1885, he received the Prix Jecker of the Académie des Sciences de Paris, and became a Chevalier de la Légion d'Honneur. He was awarded an honorary LL.D. from Harvard University in 1898, and the Rumford Medal of the American Academy of Sciences in 1911. His last years were rendered difficult by his health, but he remained mentally vigorous to his death in 1917.

Friedel and Crafts first met in 1861, when Crafts entered Wurtz' laboratory after his time in Heidelberg. The two men quickly became firm friends and close collaborators. In their first joint paper,^{1a} which was based on their joint research after



Scheme 2



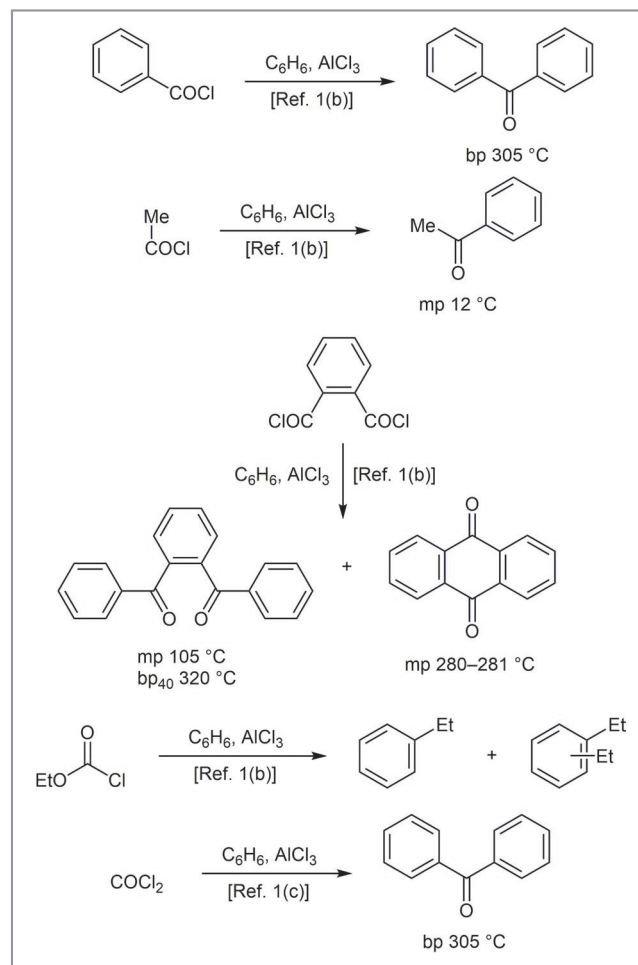
Scheme 3

Crafts had returned to France, Friedel and Crafts described what is now known as the Friedel–Crafts alkylation (Scheme 2). In the next two,^{1b,c} they extended their study of alkylation into polyarylmethanes, described the acylation reaction (Scheme 3), and identified which metal halides would catalyze the reaction.^{1d} Much more detailed accounts of their joint research appeared in the *Annales de chimie et de physique*.⁴

Their initial observations that *tert*-amyl chloride [which they called *amyl* chloride in the original paper] reacted with aluminum foil to give a wide range of saturated and unsaturated hydrocarbons, along with hydrogen chloride, led the two investigators to test if it was the metal or the metal halide that promoted the reaction; it proved to be the aluminum halide. They concluded that the alkyl halides might react with highly unsaturated compounds such as benzene in the presence of the aluminum halide. They were right (Scheme 2). They also showed how polymethylation could be easily accomplished, and the polymethylbenzenes separated on the basis of boiling point.

In their second paper, Friedel and Crafts extended their results to the formation of polyarylmethanes (Scheme 3; they did, however, misidentify the product with carbon tetrachloride as tetraphenylmethane). In the same paper, they introduced the acylation reaction (Scheme 4) with benzoyl chloride, acetyl chloride, and phthaloyl chloride. In a subsequent paper,^{1c} they showed that phosgene produces benzophenone.

The thorough early work of Friedel and Crafts established their reaction as a premier method for the formation of carbon–carbon bonds to aromatic rings, and the reaction has been a staple in the synthetic organic chemist's toolbox. Like other venerable synthetic reactions, the Friedel–Crafts reac-

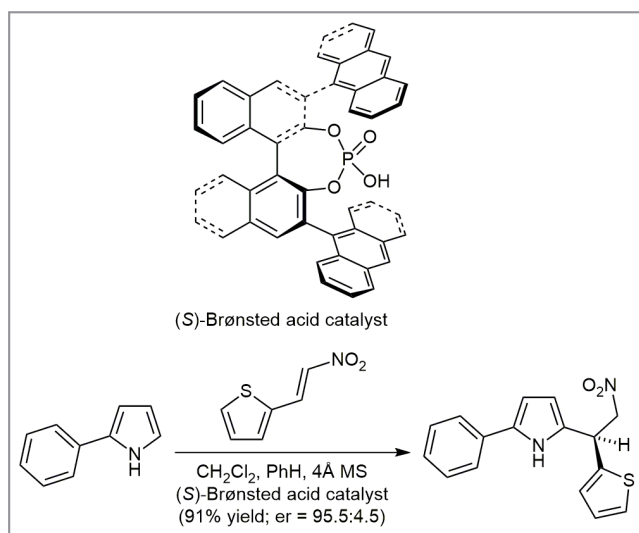


Scheme 4

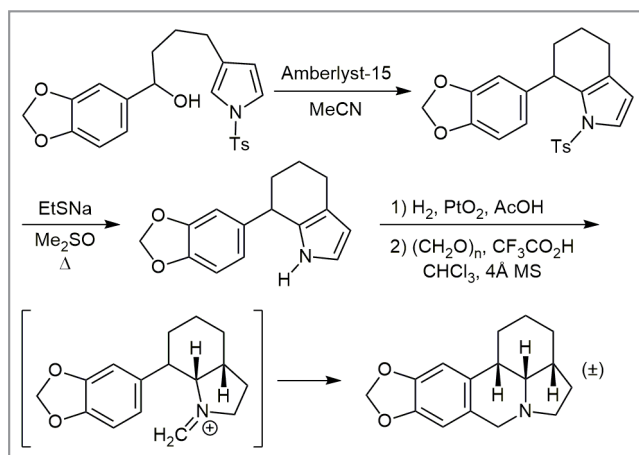
tion has become the basis for any number of improvements and unforeseen applications. During the 1970s and 1980s, titanium tetrachloride became popular as a Lewis acid, and with the development of enol silyl ethers as surrogates for enolate anions, reactions such as the tertiary alkylation of the enol trimethylsilyl ethers⁵ were developed.

The 21st century has seen the focus of research on this reaction move to the asymmetric Friedel–Crafts alkylation of electron-rich aromatic heterocycles by means of chiral organocatalysts and chiral Lowry–Brønsted acids,⁶ such as the *C*₂-symmetric phosphoric acid derivative⁷ in Scheme 5, which catalyzes the substitution of 2-phenylpyrrole by nitroalkenes.⁸ This phosphoric acid can serve alone as a chiral catalyst, or as a chiral adjuvant with a Lewis acid catalyst.

The reaction has recently been applied to the synthesis of γ -lycorane by two sequential intramolecular Friedel–Crafts reactions (Scheme 6).⁹



Scheme 5



Scheme 6

David Lewis

REFERENCES

- (1) (a) C. Friedel, J.-M. Crafts *Compt. Rend.* **1877**, 84, 1392–1395; (b) C. Friedel, J.-M. Crafts *Compt. Rend.* **1877**, 84, 1450–1454; (c) C. Friedel, J.-M. Crafts *Compt. Rend.* **1877**, 85, 673–676; (d) C. Friedel, J.-M. Crafts *Compt. Rend.* **1877**, 85, 74–77; (e) C. Friedel, J.-M. Crafts *Compt. Rend.* **1878**, 86, 884–887; (f) C. Friedel, J.-M. Crafts *Compt. Rend.* **1878**, 86, 1368–1371; (g) C. Friedel, J.-M. Crafts *Compt. Rend.* **1880**, 91, 257–260; (h) C. Friedel, J.-M. Crafts *Compt. Rend.* **1881**, 92, 833–837; (i) C. Friedel, J.-M. Crafts, E. Ador *Compt. Rend.* **1879**, 88, 880–885.
- (2) For biographies of Friedel, see: (a) J. M. Crafts *J. Chem. Soc.* **1900**, 77, 993–1019; (b) G. Lemoine *Compt. Rend.* **1900**, 131, 205–210; (c) A. Willemart *J. Chem. Educ.* **1949**, 26, 3–9.
- (3) For biographies of Crafts, see: (a) C. R. Cross *Biogr. Mem. Nat. Acad. Sci., U.S.A.* **1919**, 9, 159–177; (b) T. W. Richards *Proc. Nat. Acad. Arts Sci.* **1918**, 53, 801–804; (c) A. A. Ashdown *J. Chem. Educ.* **1928**, 5, 911–921; (d) H. P. Talbot *Proc. Am. Chem. Soc.* **1917**, 171–173 [this is referred to by Ashdown in ref. 3c].
- (4) (a) C. Friedel, J.-M. Crafts *Ann. Chim. Phys. [vi]* **1884**, 1, 449–532; (b) C. Friedel, J.-M. Crafts *Ann. Chim. Phys. [vi]* **1887**, 10, 411–424; (c) C. Friedel, J.-M. Crafts *Ann. Chim. Phys. [vi]* **1887**, 11, 263–277; (d) C. Friedel, J.-M. Crafts *Ann. Chim. Phys. [vi]* **1888**, 14, 433–472.
- (5) (a) J. K. Rasmussen *Synthesis* **1977**, 91–110; (b) P. Brownbridge *Synthesis* **1983**, 1–28; (c) P. Brownbridge *Synthesis* **1983**, 85–104.
- (6) For reviews, see: (a) P. R. Schreiner *Chem. Soc. Rev.* **2003**, 32, 289–296; (b) J. Seayad, B. List *Org. Biomol. Chem.* **2005**, 3, 719–724; (c) P. M. Pihko *Angew. Chem. Int. Ed.* **2004**, 43, 2062–2064; (d) M. S. Taylor, E. N. Jacobsen *Angew. Chem. Int. Ed.* **2006**, 45, 1520–1543; (e) S.-L. You, Q. Cai, M. Zeng *Chem. Soc. Rev.* **2009**, 38, 2190–2201; (f) V. Terrasson, R. M. de Figueiredo, J. M. Campagne *Eur. J. Org. Chem.* **2010**, 2635–2655; (g) D. Parmar, E. Sugiono, S. Raja, M. Rueping *Chem. Rev.* **2014**, 114, 9047–9153; (h) D. Parmar, E. Sugiono, S. Raja, M. Rueping *Chem. Rev.* **2014**, 114, 10608–10620.
- (7) (a) T. Akiyama, J. Itoh, K. Yokota, K. Fuchibe *Angew. Chem. Int. Ed.* **2004**, 43, 1566–1568; (b) T. Akiyama, J. Itoh, K. Fuchibe *Adv. Synth. Catal.* **2006**, 348, 999–1010; (c) T. Akiyama *Chem. Rev.* **2007**, 107, 5744–5758; (d) A. G. Doyle, E. N. Jacobsen *Chem. Rev.* **2007**, 107, 5713–5743; (e) M. Terada *Chem. Commun.* **2008**, 4097–4112; (f) D. Kampen, C. M. Reisinger, B. List *Top. Curr. Chem.* **2010**, 291, 395–432; (g) Q. Cai, Z.-A. Zhao, S.-L. You *Angew. Chem. Int. Ed.* **2009**, 48, 7428–7431; (h) Y.-F. Sheng, Q. Gu, A.-J. Zhang, S.-L. You *J. Org. Chem.* **2009**, 74, 6899–6901; (i) S. Schenker, A. Zamfir, M. Freund, S. B. Tsogoeva *Eur. J. Org. Chem.* **2011**, 2209–2222.
- (8) J. Itoh, K. Fuchibe, T. Akiyama *Angew. Chem. Int. Ed.* **2008**, 47, 4016–4018.
- (9) B. N. D. Doan, X. Y. Tan, C. M. Ang, R. W. Bates *Synthesis* **2017**, 49, 4711–4716.

Young Career Focus: Dr. Norman Metanis (Hebrew University of Jerusalem, Israel)

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. Norman Metanis (Hebrew University of Jerusalem, Israel).

Biographical Sketch



Dr. N. Metanis

Norman Metanis earned his B.A. degree in Chemistry in 2000 (*Cum Laude*) from the Technion – Israel Institute of Technology, Haifa (Israel). He then moved to The Scripps Research Institute (TSRI), La Jolla (USA) as a visiting student and spent one year in the laboratories of Professors Ehud Keinan and Philip Dawson. Upon returning to the Technion, he completed his M.Sc. degree in 2004 (*Cum Laude*).

Then he moved back to TSRI where he again worked with Professors Ehud Keinan and Philip Dawson on a joint program between the Technion and TSRI. Upon the completion of his Ph.D. in 2008, Dr. Metanis joined the group of Professor Donald Hilvert at ETH Zurich (Switzerland) until 2013. Then he moved to the Institute of Chemistry at the Hebrew University of Jerusalem (Israel) as a Senior Lecturer (Assistant Professor). Among the awards that Dr. Metanis has received in the last five years are the Ma'of Award for Outstanding Arab Assistant Professor (2013), the Thieme Chemistry Journals Award (2017), and he was selected as outstanding lecturer for "Organic Chemistry for Medical Students" (2017).

INTERVIEW

SYNFORM What is the focus of your current research activity?

Dr. N. Metanis My research group is involved in multiple projects at the interface of chemistry and biology. Generally, we study the chemistry of proteins: protein folding, protein design, structural–activity relationships, posttranslational modifications, and therapeutic proteins. In particular, we focus on human selenoproteins,¹ a group of 25 proteins,² roughly half of which are still poorly characterized (Figure 1).

SYNFORM When did you get interested in synthesis?

Dr. N. Metanis I got interested in synthesis in my first year as an undergraduate when I attended organic chemistry cour-

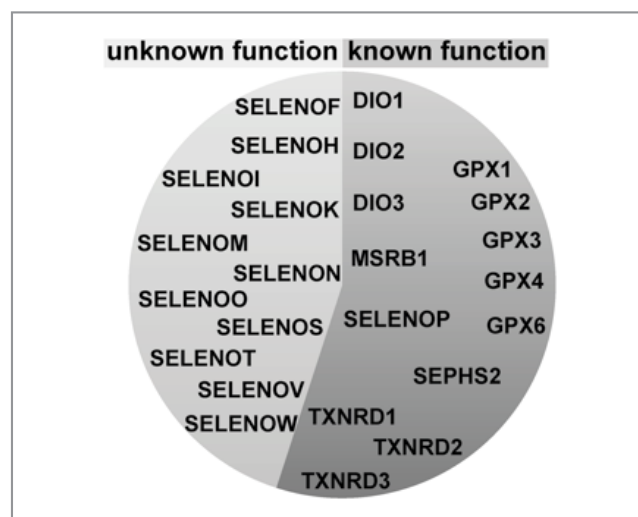


Figure 1 The human selenoproteins (roughly half of them still functionally uncharacterized or poorly studied)

ses at the Technion – Israel Institute of Technology. I started reading papers involving synthesis in the library of the chemistry department. I remember the pile of journals: *Tetrahedron*, *J. Am. Chem. Soc.* and *Angew. Chem.* among others, in hard copies, not electronically available at that time.

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

Dr. N. Metanis Organic synthesis keeps changing; it is hard to keep up with the new methodologies being developed by leading scientists. In addition, many young scientists play a role in these developments and are making leading discoveries in this field. New strong bond activation and functionalization methods will certainly have a significant impact on natural product synthesis, drug development, and other synthetic goals. Another field that is being pursued and developed in recent years is the application of chemoselective modifications to macromolecules such as nucleic acids and proteins. These modifications open new horizons in the field of chemical biology.

SYNFORM Your research group is active in the areas of protein and peptide chemistry. Could you tell us more about your research and its aims?

Dr. N. Metanis Indeed, my research group is active in the chemistry of peptides and proteins, from the development of new synthetic methodologies and chemoselective reactions applied to proteins, to the manipulation of protein structure in order to shed light on its function at the molecular level. Our current focus has been on elucidating the function of human selenoproteins (Figure 1). Generally, these are poorly studied proteins, since it is quite challenging to prepare them in sufficient quantities using biological methods. Along these lines, we recently succeeded in obtaining two human selenoproteins,³ SELENOM and SELENOW through chemical protein synthesis. This poorly studied family of proteins is now within reach and these syntheses should allow us to study them in detail in the future.

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

Dr. N. Metanis My hope is that my most important scientific achievement is yet to come. Nonetheless, I have made some important contributions in the fields of protein folding and chemical protein synthesis. Specifically, through substitution of cysteine with selenocysteine (just a single atom change:

sulfur to selenium), we found that it is possible to steer folding in a predictive and more productive path that avoids the predominant formation of trapped intermediates that normally appear during folding of the wildtype protein.^{4–7} Furthermore, during our early work on selenoproteins, we found, by serendipity, that selenocysteine can be converted selectively into alanine (referred to as deselenization) in the presence of unprotected cysteine residues using a common reductant [tris(2-carboxyethyl phosphine, TCEP)].⁸ We have developed this reaction as a way to expand the native chemical ligation (NCL), which is one of the most applied reactions in chemical protein synthesis, but was originally limited to ligations at cysteine, to ligation sites of alanine and serine (Figure 2),^{9,10} both being among the most common residues in proteins.

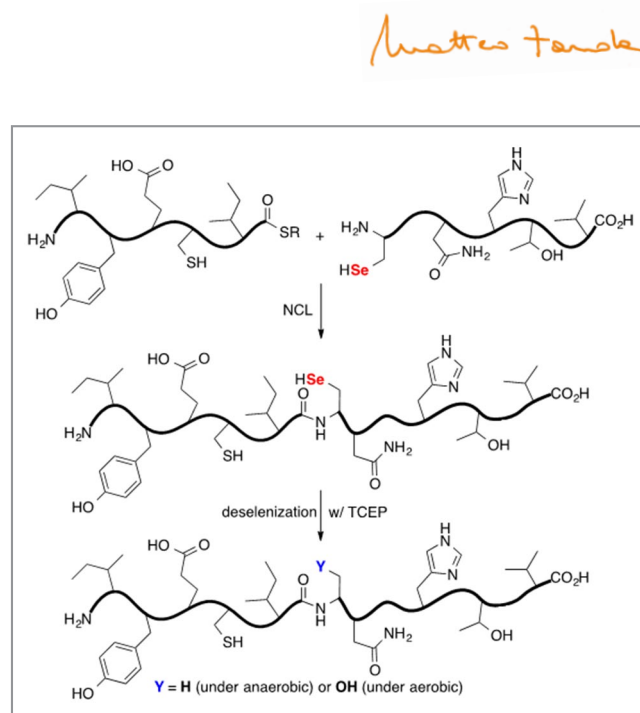


Figure 2 Native chemical ligation at selenocysteine followed by deselenization to provide Ala or Ser (depending on the conditions)

REFERENCES

- (1) R. Mousa, R. N. Dardashti, N. Metanis *Angew. Chem. Int. Ed.* **2017**, *56*, 15818.
- (2) G. V. Kryukov, S. Castellano, S. V. Novoselov, A. V. Lobanov, O. Zehtab, R. Guigo, V. N. Gladyshev *Science* **2003**, *300*, 1439.

- (3) L. Dery, P. S. Reddy, S. Dery, R. Mousa, O. Ktorza, A. Talhami, N. Metanis *Chem. Sci.* **2017**, *8*, 1922.
- (4) N. Metanis, D. Hilvert *Chem. Sci.* **2015**, *6*, 322.
- (5) N. Metanis, D. Hilvert *Curr. Opin. Chem. Biol.* **2014**, *22*, 27.
- (6) N. Metanis, D. Hilvert *Angew. Chem. Int. Ed.* **2012**, *51*, 5585.
- (7) N. Metanis, C. Foletti, J. Beld, D. Hilvert *Isr. J. Chem.* **2011**, *51*, 953.
- (8) N. Metanis, E. Keinan, P. E. Dawson *Angew. Chem. Int. Ed.* **2010**, *49*, 7049.
- (9) P. S. Reddy, S. Dery, N. Metanis *Angew. Chem. Int. Ed.* **2016**, *55*, 992.
- (10) S. Dery, P. S. Reddy, L. Dery, R. Mousa, R. Notis Dardashti, N. Metanis *Chem. Sci.* **2015**, *6*, 6207.

A Unifying Paradigm for Naphthoquinone-Based Meroterpenoid (Bio)synthesis

Nat. Chem. **2017**, *9*, 1235–1242

Over the past 30 years a large number of diverse and fascinating meroterpenoid natural products have been isolated from marine bacteria, including the merochlorins, the napyradiomycins (of which naphthomevalin is the simplest example), and the marinones (Figure 1). Professor Jonathan H. George, from the University of Adelaide (Australia), said: “These families of natural products are biosynthesized and derived from 1,3,6,8-tetrahydroxynaphthalene (THN), but the mechanisms of these biosynthetic pathways were unclear before our collaborative work with Professor Bradley S. Moore’s group at the University of California San Diego (USA).”

The George research group is broadly interested in the development of biomimetic cascade reactions for the rapid synthesis of complex meroterpenoid natural products. “In addition to synthetic efficiency, we firmly believe that this approach can give insight into biosynthetic pathways, as well as highlight possible structure revisions of biosynthetically dubious natural product assignments,” explained Professor George.

Professor Moore revealed: “This paper was a special treat. I’ve been fascinated with the chemical structures of the naphthoquinone-based meroterpenoid natural products for many years and have marveled on how microbes assemble these antimicrobial molecules by combining polyketide and terpenoid chemistry.” Little did he know then that half way around the world, Professor George’s lab was similarly intrigued with these molecules, yet from a synthetic point of view.

Professor George confirmed: “Our synthetic interest in THN-derived meroterpenoids began with merochlorin A,

which possesses four contiguous stereocenters in a bicyclo[3.2.1]octanone core. The key step of our synthesis of merochlorin A was a cycloaddition triggered by oxidative dearomatization of the THN ring system.” The Moore group also completed their own biomimetic synthesis and biosynthetic studies of merochlorin A (and merochlorin B) in which they showed that a single multi-tasking vanadium-dependent haloperoxidase enzyme (VHPO) called Mcl24 controlled the chlorination, oxidative dearomatization and cycloaddition steps.

“Our two worlds collided in 2015 when Jonathan reached out to me after we had published the discovery and biosynthesis of the merochlorin antibiotics (*J. Am. Chem. Soc.* **2012**, *134*, 11988; *Angew. Chem. Int. Ed.* **2014**, *53*, 11019; *Angew. Chem. Int. Ed.* **2014**, *53*, 11023) and his lab had published an elegant biomimetic synthesis of merochlorin A (*Angew. Chem. Int. Ed.* **2013**, *52*, 12170),” explained Professor Moore, continuing: “In 2015 Jonathan’s lab shifted focus to another meroterpenoid compound, naphthomevalin, and in their biomimetic synthesis approach, they developed a key reaction involving the α -hydroxyketone rearrangement of a protected 4-prenylated tetrahydroxynaphthalene intermediate in which the isoprene chain shifted from C-4 to C-3.”

The Moore group’s original characterization of the Mcl24 VHPO enzyme revealed that it was singularly responsible for converting pre-merochlorin into merochlorins A and B. In those Cl⁺-induced cascade reactions, a site-selective naphthol chlorination is followed by an oxidative dearomatization/terpene cyclization sequence to construct the complex carbon

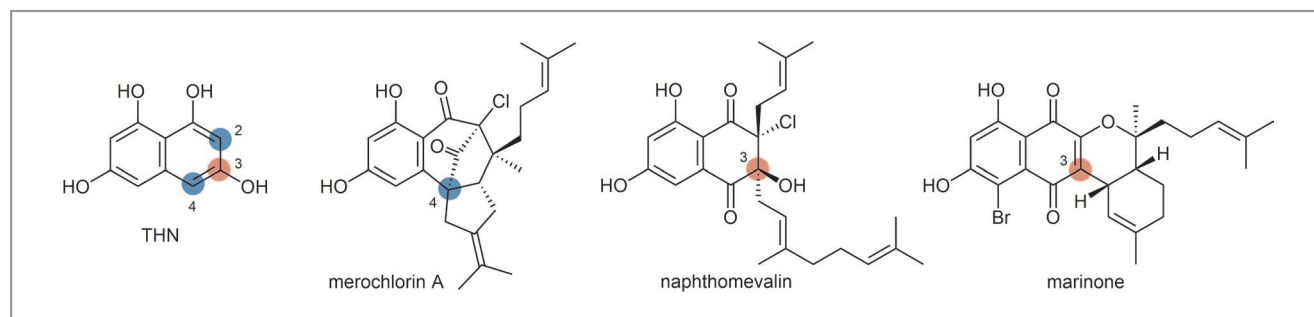


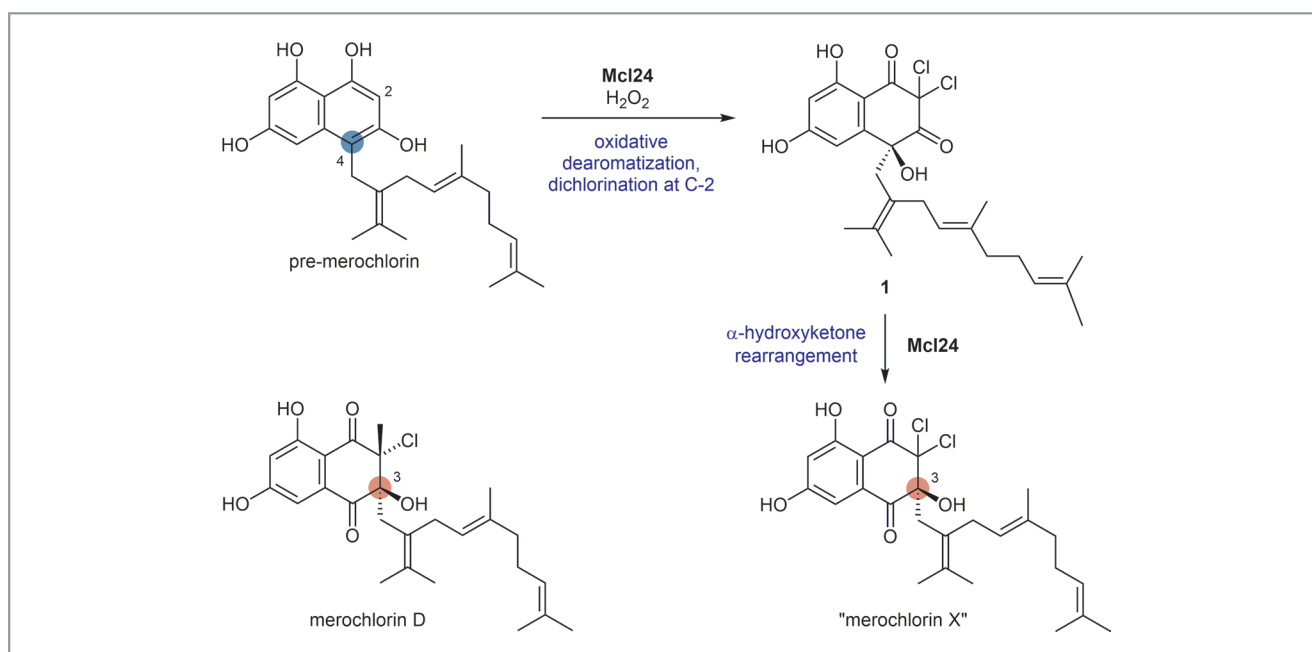
Figure 1 Bacterial meroterpenoids derived from THN

framework of the merochlorins in a single step. “My postdoc Stefan Diethelm, who was classically trained as a synthetic organic chemist turned biochemist, noticed that Mcl24 could do more and explain the origin of merochlorin D in which the terpene chain was attached to C-3 instead of C-4,” remarked Professor Moore (Scheme 1). He continued: “When he assayed the Mcl24 enzyme at an elevated pH, a previously unrecognized minor product was produced in greatest abundance. Upon solving the structure of the dichlorinated ‘merochlorin X’, we were all surprised that the terpene chain had migrated to the C-3 position, just like that in the merochlorin D natural product. This result revealed a novel reaction in nature involving a halogen-mediated α -hydroxyketone rearrangement reaction and impressively showed that a single enzyme was responsible for constructing the diverse molecular diversity in the merochlorin series.”

At the same time as the Moore group's discovery of the Mcl24-mediated dichlorination, oxidative dearomatization and α -hydroxyketone rearrangement of pre-merochlorin, the George lab completed their own biomimetic total synthesis of naphthomevalin using remarkably similar key steps (Scheme 2). “In our biomimetic synthetic design, we deliberately minimize the use of protecting groups. As well as cutting the step count of the overall route, this also allows us to explore the pre-disposed, innate reactivity of our proposed biosynthetic intermediates on route to the final natural product,” explained

Professor George. He continued: “However, in the case of our naphthomevalin synthesis we found that protection of the C-5 and C-7 phenols on the left-hand ring of the THN derivatives (e.g. compound **2**) was necessary for selective oxidative dearomatization and chlorination steps. In our first-generation strategy (as yet unpublished) we used aryl methyl ethers to protect the C-5 and C-7 phenols – which worked perfectly until the final deprotection step!” After several false starts Professor George and co-workers were eventually forced to re-design the strategy to allow the use of more labile MOM-protecting groups instead. “The re-design and execution of the synthesis took almost a whole year of hard work from my very talented PhD student, Henry Pepper,” he acknowledged.

The first key step of the successful synthesis was a one-pot oxidative dearomatization at C-4 of the THN derivative using $\text{Pb}(\text{OAc})_4$ followed by dichlorination at C-2 using NCS to give **3**. “This step is remarkably similar to the Mcl24-mediated reaction of pre-merochlorin shown previously in Scheme 1. We then removed one of the C-2 chlorine substituents using a highly selective LDA-mediated dechlorination, and we cleaved the acetate group using KOH to give **4**,” said Professor George. He continued: “Diastereoselective prenylation of **4** using prenyl bromide and NaH gave **5**, which was deprotected to give **6** using mild acidic conditions to remove the MOM-protecting groups. A final α -hydroxyketone rearrangement then shifted the geranyl group from C-4 to C-3 under thermal conditions,



Scheme 1 Mcl24-mediated reaction of pre-merochlorin

thus rationalizing the C-3 geranyl substitution pattern of naphthomevalin. We were not surprised by the success of the final 1,2-shift, as at that point we had conducted extensive studies of this reaction on model systems. We generally found that heating the α -hydroxyketone substrates overnight at reflux in toluene was required for 100% conversion, but the reaction is very clean with no by-products. However, the fact that the reaction did not occur appreciably at lower temperatures led us to speculate that it must be enzyme-catalyzed in nature.”

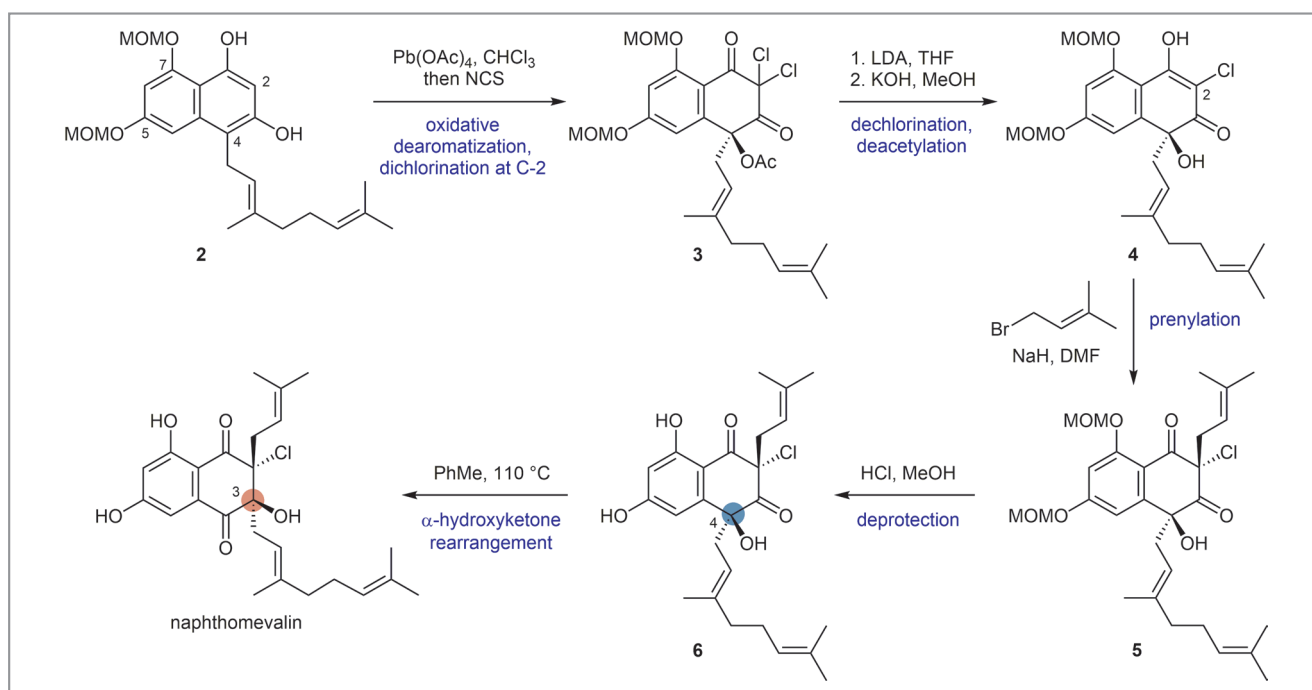
It was at this point that the Adelaide-based researchers contacted the Moore group, knowing they were interested (and had published previously) on merochlorin and napyradiomycin biosynthesis. “We both realized that our synthesis could give access to several possible biosynthetic intermediates via MOM deprotection at any point. These (racemic) substrates could be used to reveal the biosynthetic function of VHPOs (and other enzymes) discovered by the Moore group,” said Professor George.

This novel synthetic insight simplified beautifully the biogenesis of many of the naphthoquinone-based meroterpenoid natural products that had isoprene groups attached at both carbon centers.

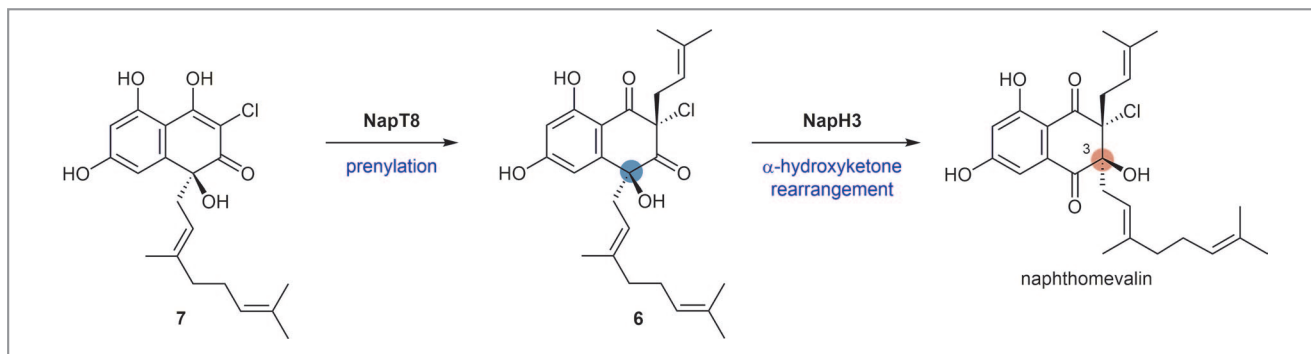
“Remarkably, Stefan Diethelm in my lab had just identified the Mcl24 enzyme that catalyzed the tandem oxidative

chlorination and α -hydroxyketone rearrangement reaction much like that accomplished by Henry Pepper in a fume hood in Australia,” said Professor Moore. “We had both independently discovered the same reaction, one by an enzyme and the other by a chemical reagent. Another postdoc in my lab, Zachary Miles, went on to show that this new enzymatic reaction was evident in both the napyradiomycin and merochlorin series and was also likely responsible for the construction of many more meroterpenoids in *Streptomyces* bacteria. It was this discovery that led to our *Nat. Chem.* article where we introduced a new, simplified paradigm for the assembly of naphthoquinone-based meroterpenoid natural products using enzymes and/or chemical reagents.”

Both labs found their collaboration enjoyable, as it brought many fresh ideas and complementary expertise to the table. Professor Moore remarked: “For us, our biosynthetic enzymology work on the merochlorins and napyradiomycins uncovered a number of novel biosynthetic transformations relating to asymmetric alkene and arene halofunctionalization reactions catalyzed by a rare class of vanadium-dependent chloroperoxidases in bacteria. These reactions have no precedence in the biochemical literature and at the time of their discovery were quite unexpected.” The George lab was able to provide synthetic material that allowed the Moore lab to rigorously interrogate some of their biosynthetic hypotheses.



Scheme 2 Biomimetic total synthesis of naphthomevalin



Scheme 3 New enzyme reactivity of NapT8 and NapH3 discovered in this work

At the same time, they were able to use enzymes, such as the prenyltransferase NapT8 and the chloroperoxidases NapH3 and NapH1, to catalyze chiral resolving transformations on racemic synthetic material to ultimately give enantiopure naphthomevalin and napyradiomycin A1 (Scheme 3).

“One reviewer of our submitted manuscript asked for CD spectra of all enzymatic products,” said Professor George. “These CD spectra conclusively showed that when the NapT8 prenylation and the NapH3 α -hydroxyketone rearrangement were conducted on fully synthetic, racemic substrates **7** and **6**, kinetic resolutions were observed. This shows that the prenylation and α -hydroxyketone rearrangement steps are both stereospecific and enzyme-catalyzed in napyradiomycin biosynthesis.”

Since completing the work that led to the *Nat. Chem.* publication, the two labs have continued their collaborative project. For three months at the end of 2017, graduate student Lauren Murray from the George lab in Adelaide visited the Moore lab at UC San Diego to pursue two related meroterpenoid target molecules called naphterpin and marinone. Lauren is a synthetic chemist who recently completed the synthesis of naphterpin via a route that she predicted was biomimetic. She then joined postdoc Shaun McKinnie from the Moore lab to interrogate the biosynthesis of marinone and they were able to quickly elucidate most of the pathway with the help of an assortment of synthetic materials. “That work is nearing completion and again shows the power and beauty of collaborative science between synthetic and biosynthetic laboratories,” said Professor Moore. “I think that our work also highlights the future of synthetic chemistry in which biosynthetic enzymes are added to the toolkit of synthetic chemists as they ponder the fastest and most efficient way to construct complex organic molecules.” He concluded: “I recently wrote a *Synlett* Account article entitled “Asymmetric Alkene and Arene Halofunctionalization Reactions in Meroterpenoid Biosynthesis”

(*Synlett* **2018**, 29, DOI: [10.1055/s-0036-1590919](https://doi.org/10.1055/s-0036-1590919)), which includes a short overview of this *Nat. Chem.* article in section 4. That article may provide the readers with some good additional backstory to this joint paper with the George lab.”

Matthew Fensholt

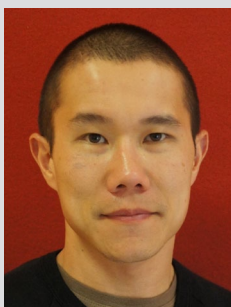
About the authors

The George lab



Dr. H. P. Pepper

Henry Pepper graduated with a BSc (First Class Honors) from the University of Adelaide (Australia) in 2011. He then earned his PhD in Chemistry in 2016 from the University of Adelaide, working under the supervision of Professor Jonathan George. His research interests focus on dearomatization strategies in the biomimetic synthesis of natural products. He was the recipient of the RACI Best PhD Thesis in Organic Chemistry Award in 2017 and was a Reaxys PhD Prize finalist in 2015.



Prof. D. M. Huang

David Huang received his BSc degree with First Class Honors and the University Medal from the University of Sydney (Australia) in 1998. He earned his PhD in Chemistry in 2002 from the University of California, Berkeley (USA), where he worked under the direction of Professor David Chandler as a Fulbright Scholar. After a stint as a scientific copyeditor for Springer-Verlag, he carried out postdoctoral research at the University of Lyon (France), then at the University of California, Davis (USA). He joined the Department of Chemistry at The University of Adelaide (Australia) in 2010, where he is now an Associate Professor. His research is broadly concerned with theory and computation of soft condensed matter, with a focus on applications in renewable energy and functional materials.



Prof. J. H. George

Jonathan George received an MChem degree from the University of Oxford (UK) in 2001, followed by a PhD in 2006 from University College London (UK), where he worked under the supervision of Professor Karl Hale. He then returned to Oxford to work as a postdoctoral researcher with Professor Sir Jack Baldwin and Dr. Robert Adlington. In May 2010, he joined the Department of Chemistry at the University of Adelaide (Australia), where he is now an Associate Professor. His research interests include the biomimetic synthesis of natural products, the development of cascade reactions, and biosynthesis.

The Moore Lab



Dr. Z. D. Miles

Zachary Miles was born in Madison, WI (USA) and received his BS in biochemistry from the University of Wisconsin-Madison (USA) in 2009. He obtained a PhD under the guidance of Professor Vahe Bandarian at the University of Arizona (USA) in 2014, with his dissertation research entailing the enzymology in the biosynthesis of the modified nucleoside queuosine. He then undertook a position as a postdoctoral researcher in the laboratory of Professor Bradley Moore, wherein his research focused around the biosynthesis of marine natural products. Since 2017 he is applying his experience towards enzyme engineering for industrial purposes as a research scientist at BASF Enzymes in La Jolla, CA (USA).



Dr. S. Diethelm

Stefan Diethelm received his MSc in Biology from ETH Zürich (Switzerland) in 2009. He then joined the group of Professor Erick M. Carreira for PhD studies working on alkaloid natural product total synthesis. In 2014, he moved to the USA where he conducted postdoctoral research on natural product biosynthetic enzymology in the group of Professor Bradley S. Moore at the Scripps Institution of Oceanography in San Diego (USA). Since 2015 he is working as a medicinal chemist at Idorsia Pharmaceuticals in Switzerland.



Prof. B. S. Moore

Bradley Moore is Professor of Marine Chemical Biology at the Scripps Institution of Oceanography (USA) and Chair and Professor of Pharmaceutical Chemistry at the Skaggs School of Pharmacy and Pharmaceutical Sciences at UC San Diego (USA). He holds degrees in chemistry from the University of Hawaii (USA; BS 1988) and Washington (USA; PhD 1994), was a postdoctoral researcher at the University of Zurich (Switzerland; 1994–1995), and held prior faculty appointments at the Universities of Washington (1996–1999) and Arizona (USA; 1999–2005). Professor Moore has published over 180 papers on the chemistry, biochemistry, and genetics of natural product drug leads and toxins from (primarily) marine microbes.

Ruthenium(II)-Catalyzed Olefination via Carbonyl Reductive Cross-Coupling

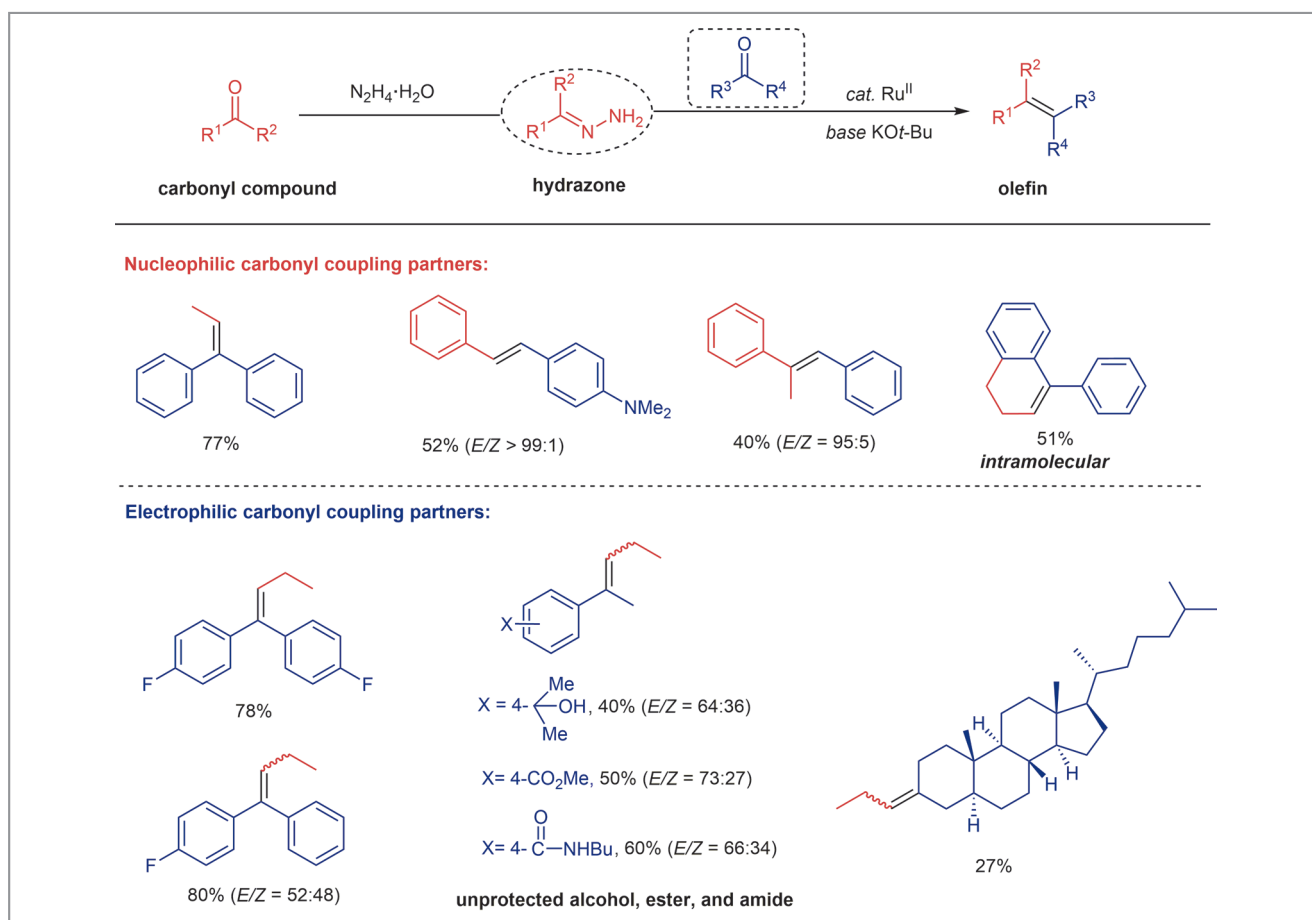
Chem. Sci. **2017**, *8*, 8193–8197

Efficient construction of carbon–carbon double bonds is a central subject in synthetic chemistry. The direct reductive coupling of naturally ubiquitous carbonyl compounds offers a tremendous synthetic potential for the synthesis of olefins, yet the catalytic carbonyl cross-coupling reaction remains largely elusive.

Recently, a new paper describing an innovative ruthenium(II)-catalyzed, hydrazine-mediated olefination reaction via direct carbonyl reductive cross-coupling was published by the group of Professor Chao-Jun Li at McGill University (Montreal, Canada). Professor Li explained: “From

the sustainability point of view, carbonyl cross-coupling represents an ideal strategy to access olefins because naturally widespread carbonyl functional groups are generally regarded as renewable feedstocks. As a proof of principle, we have developed a new and efficient catalytic method for olefin synthesis, which possesses a distinct mechanistic profile and highlights the use of abundant carbonyl functional groups.”

“Considering the state-of-the-art in this field, the well-known McMurry reaction enables direct reductive homocouplings of carbonyl compounds to access olefins by employing stoichiometric amounts of low-valent titanium reagents



Scheme 1 Ruthenium(II)-catalyzed olefination via carbonyl reductive cross-coupling

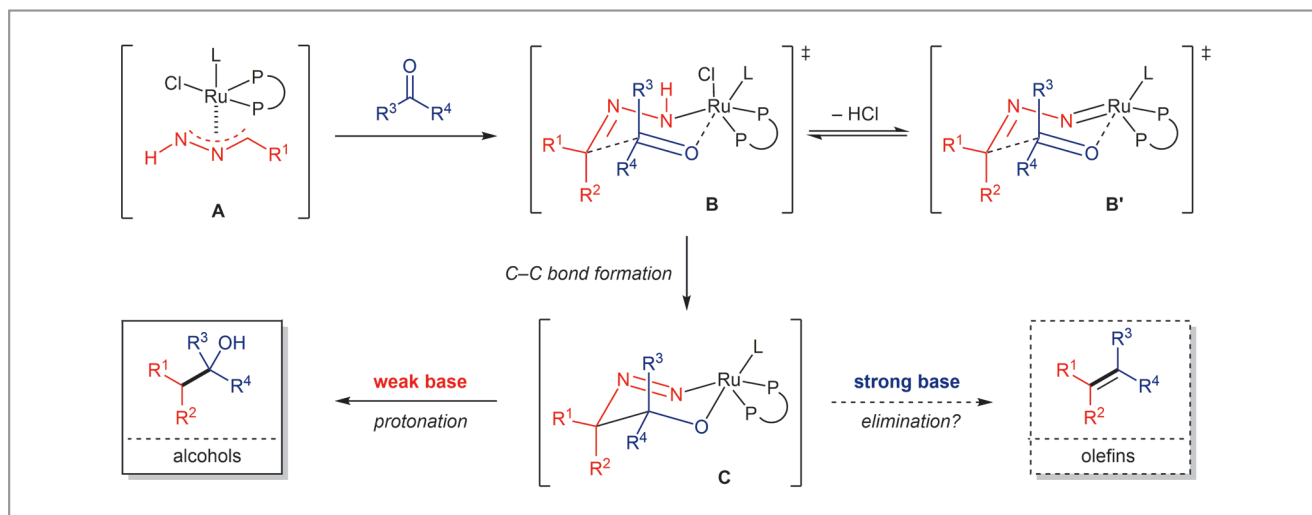
and strong metal reductants (e.g. LiAlH_4 and alkali metals),” said Professor Li (for references, see the original *Chem. Sci.* article). He added: “Although the issue of selective cross-couplings of two unsymmetrical carbonyl compounds has been addressed, three challenges still remain: (1) the use of stoichiometric quantities of metal wastes accompanied by excessive amounts of metal-based reagents, (2) poor chemoselectivity and (3) unsatisfactory functional group tolerance.”

“Our catalytic method not only enables facile and selective cross-couplings of two unsymmetrical carbonyl compounds in either an intermolecular or intramolecular fashion but also features good functional group tolerance. Furthermore, the reaction generates nitrogen and water as the only environmentally benign stoichiometric by-products,” explained Professor Li. He continued: “This new ruthenium(II)-catalyzed chemistry accommodates a variety of substrates and proceeds under mild reaction conditions. Specifically, this chemistry covers a broad spectrum of nucleophilic or electrophilic carbonyl coupling partners, regardless of their electronic nature. The intramolecular olefination also proceeds smoothly in the present reaction system. Notably, functional groups that are commonly incompatible with traditional carbonyl olefination approaches, such as unprotected alcohols, esters, and amides, are well tolerated in this chemistry and potentially amenable to further functionalization.”

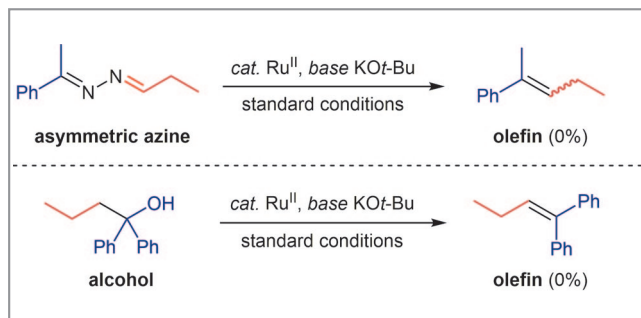
“Very recently, we have disclosed a novel ruthenium-catalyzed deoxygenation chemistry for the highly selective and efficient cleavage of aliphatic primary C–O bonds in complex organic molecules (*J. Am. Chem. Soc.* **2016**, *138*, 5433; also Ir-catalyzed, see: *Eur. J. Org. Chem.* **2013**, 6496). Capitalizing on

the proposed intermediate **A**, its coupling with another carbonyl molecule was conceived for C–C bond formation via a six-membered chair-like cyclic transition state **B** (alternatively, **B'** with the loss of HCl). Upon its further rearrangement, a wide range of *sec*- and *tert*-alcohols were readily obtained by the protonation of **C** (*Nat. Chem.* **2016**, *9*, 374). Diverging from **C**, we conjectured that the olefin production might also be feasible through an elimination pathway. In fact, this hypothesis gained further support from a few literature precedents of metalloazines in the late 80's. In these papers, Schwartz and co-workers reported the use of metalloazines as stoichiometric reagents for carbon–carbon double bond formation (for references, see the original *Chem. Sci.* article),” said Professor Li. He continued: “The base plays an important role in a series of hydrazone-based processes developed recently in our lab. While a weak base (e.g. K_3PO_4) generally works better for carbonyl addition, imine addition and Michael reactions employing aromatic carbonyl substrates (for references, see the original *Chem. Sci.* article), a strong base (e.g. KOt-Bu) is required to trigger olefination reactions when aliphatic carbonyl counterparts are involved as hydrazone precursors.”

The group performed further experiments to shed light on the mechanistic details of this reaction, which turned out to be an E1cB-type process. “Our control experiments indicated that metal-assisted decomposition of the corresponding asymmetric azine and base-mediated elimination of the corresponding alcohol should not be involved in the present reaction system, because none of the olefin products was detected in either case,” said Professor Li.



Scheme 2 Design principle for olefination via catalytic carbonyl reductive cross-coupling

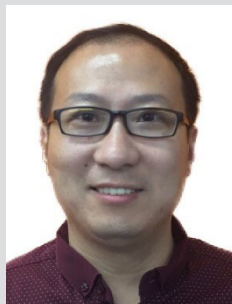


Scheme 3 Control experiments for the olefin formation

He concluded: "Olefins are ubiquitous chemicals in areas such as materials science, as well as vitally important substrates for the chemical and pharmaceutical industry; therefore, we hope that both academia and industry will take advantage of this new catalytic approach to synthesize olefins directly from simple and naturally abundant carbonyl compounds. This chemistry possesses a distinct mechanistic profile and has the advantages of cross-coupling capability, mild reaction conditions, good functional group tolerance and stoichiometric benign by-products. Taken together, our findings are expected to spur more interest in developing catalytic methods in this field."

Matthew Farnick

About the authors



Dr. W. Wei

Wei Wei earned his B.Sc. with honors (2005) and M.Sc. (2008) in Chemistry at Liaocheng University and Sichuan University (P. R. of China), respectively. He pursued his Ph.D. at Chengdu Institute of Biology, Chinese Academy of Sciences (P. R. of China). His Ph.D. research mainly focused on the development of efficient synthetic methodologies based on aerobic oxidation and dioxygen activation. Then, he moved to Qufu Normal Uni-

versity (P. R. of China) as an Associate Professor in 2012. During 2016–2017, he worked as a postdoctoral researcher at McGill University (Canada) where he studied the carbonyl reductive olefination reaction with Professor Chao-Jun Li. His recent research focuses on the development of green approaches to construct sulfur- or phosphorus-containing compounds.



Dr. X.-J. Dai

Xi-Jie Dai was born and raised in the Southeastern coast of China, where he earned his B.Sc. with honors (2009) and M.Sc. (2012) in Chemistry at Donghua University and Xiamen University (P. R. of China), respectively. He then travelled to the Western hemisphere, pursuing his Ph.D. with Professor Chao-Jun Li at McGill University (Canada). His Ph.D. studies were initially focused on the development of direct and selective alcohol

deoxygenation strategies using late transition metals. Later, he and other colleagues pioneered new synthetic routes to forge carbon–carbon single and double bonds between unsubstituted hydrazones and various electrophiles (e.g. aldehydes, ketones, imines, activated alkenes) with a catalytic amount of metal. After graduating from McGill this year, he decided to cross the Canada–USA border to work with Professor Stephen L. Buchwald at Massachusetts Institute of Technology (USA) as a NSERC Postdoctoral Fellow. He is currently working on the copper-hydride project at MIT. He strongly advocates making new benchtop synthetic discovery more practical and approachable for a wide spectrum of audiences. His interests also include in-depth exploration of a larger chemical space and beyond by leveraging the advancement of robotic technology in the pharmaceutical industry.



Dr. H. Wang

Haining Wang received his B.S. degree in July 2005 from Hefei University of Technology (HFUT, P. R. of China) and earned his Ph.D. degree in organic chemistry from the Institute of Chemistry, Chinese Academy of Sciences (ICCAS, P. R. of China) in 2011. In 2011, he moved to Nanjing University (P. R. of China) as an associate researcher, working with Professor Yian Shi. During 2014–2017, he worked as a postdoctoral researcher

at the McGill University (Canada) where he studied umpolung Grignard-type reactions with Professor Chao-Jun Li. Since 2017 he has held the position of R&D Scientist in 1-Material Inc. (Canada). His recent research focuses on the design, synthesis, and application of organic photovoltaic materials.



Prof. C.-J. Li

Chao-Jun Li received his Ph.D. (with honor) with Professors T. H. Chan and D. N. Harpp at McGill University (Canada) in 1992 and spent 1992–1994 as a NSERC Postdoctoral Fellow with Professor Barry M. Trost at Stanford University (USA). He was an Assistant (1994), Associate (1998) and Full Professor (2000) at Tulane University (USA). Since 2003, he has been a Canada Research Chair (Tier I) and E. B. Eddy Chair Professor (since 2009)

at McGill University (Canada). Currently, he serves as the Co-Director of the FQRNT Center for Green Chemistry and Catalysis and the Associate Editor for *Green Chemistry* (RSC) (since 2005). He received a number of prestigious awards including the US NSF's CAREER Award (1997), a US Presidential Green Chemistry Challenge Award (2001), the Canadian Green Chemistry and Engineering Award (2010), and the R. U. Lemieux Award of the Canadian Society for Chemistry (2015). Professor Li was elected as a Fellow of the RSC (UK, 2007), the Royal Society of Canada (2012), the AAAS (2012), the CIC (2013), the ACS (2015), and TWAS (2016). His current research efforts are to develop green chemistry for organic synthesis. Representative well-known researches include Grignard-type reactions in water, alkyne–aldehyde–amine coupling (A^3 -coupling), and cross-dehydrogenative-coupling (CDC) reactions among others. He was listed among the World's Most Cited Scientists by Thomson Reuters/Clarivate Analytics (2014, 2015, 2016, and 2017).

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and
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Via Mancinelli, 7, 20131 Milano, Italy
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Editorial Office

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