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Continuous-Flow C(sp³)-H Functionalizations of Volatile Alkanes Using Decatungstate Photocatalysis

Highlighted article by G. Laudadio, Y. Deng, K. van der Wal, D. Ravelli, M. Nuño, M. Fagnoni, D. Guthrie, Y. Sun, T. Noël

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Thieme

Dear Readers,

When I opened the window this morning I saw an amazingly bright and blue sky, it could not be any better. Then I suddenly remembered that a few hours earlier a new President and Vice-President of the United States of America had been announced, and I realized that – for the first time this year – there was light at the end of the tunnel. This editorial is not about politics, but I believe that the world is a much better place now: better for science, better for the environment, better for us and – most of all – better for our children. This is going to be a very strange and different Christmas for many, but it is a Christmas of hope, as there are signs that better times are ahead of us. But let's have a look at the last SYNFORM issue of 2020 – a year that will not be missed. We start with a new, extraordinary Name Reaction Bio article by David Lewis on the Baeyer–Villiger reaction, followed by Timothy Noël's (The Netherlands) *Science* paper on the C(sp³)–H functionalizations of light hydrocarbons. The third article is another Literature Coverage piece: it covers the elegant total synthesis of the Daphni-phyllum alkaloid (+)-caldaphnidine by Jing Xu (P. R. of China). The article that closes the issue and the year for SYNFORM is a Young Career Focus interview with Denis Chusov (Russian Federation): look at the picture – besides reading the interesting article – because I think it beautifully represents the sense of hope for the future.

Goodbye 2020...

Enjoy your reading!

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If you have any questions or wish to send feedback, please write to Matteo Zanda at: synform@outlook.com

Johann Wilhelm Friedrich Adolf von Baeyer (1835–1917) and Victor Villiger (1868–1934): Peracid Oxidation of Ketones

The reaction between ketones and peracids, now known as the Baeyer–Villiger reaction, was first reported by Adolf von Baeyer (1835–1917) and his student and collaborator, Victor Villiger (1868–1934) in 1899.¹ Of the two men, von Baeyer is by far the better known, having won the Nobel Prize in Chemistry in 1905.

von Baeyer (left) and Villiger (right). Image of von Baeyer courtesy of Science History Institute. The image of Villiger ©2019, Matthew A. Bergs; all rights reserved. Reproduced by permission of the artist.

Johann Friedrich Wilhelm von Baeyer² was born to Lieutenant-General Jakob Baeyer and Eugenie, née Hitzig, on October 31, 1835. From a young age, he demonstrated his interest in science by his exploration of chemistry. When just 9 years old, he was conducting plant nutrition experiments, and just three years later³ he isolated a new double salt of copper, whose formula was established as $\text{CuCO}_3 \cdot \text{Na}_2\text{CO}_3 \cdot 3\text{H}_2\text{O}$ by Struve in 1851.⁴

At age 17, Baeyer entered the University of Berlin, where he began his study of physics and mathematics. In his two years there, however, neither physics nor mathematics excited him as much as chemistry. Both physics and chemistry were taught as complete sciences, looking backwards. Chemistry, on the other hand, was taught as a new, vibrant science, and it was this that changed Baeyer's mind.

In 1855, Baeyer left the University for a year of military service, and after he had satisfied his obligation he returned to his studies, this time in chemistry at the University of Hei-

delberg, where Robert Bunsen (1811–1899) was one of the most important chemists in Germany working in one of the most modern laboratories. While with Bunsen, he published two papers, one on idiochemical induction,⁵ and a second on methyl chloride.⁶

In 1840, Bunsen had begun research on cacodyl compounds,⁷ and Baeyer continued that research in Bunsen's laboratory. However, the relationship between student and mentor deteriorated, and an argument between the two men led to Baeyer leaving Bunsen's research group and joining that of August Kekulé (1829–1896). The two men became life-long friends.

Bunsen (left) and Kekulé (right). Image of Bunsen courtesy of Universitätsbibliothek Heidelberg. Public domain image of Kekulé downloaded June 2020 from <https://commons.wikimedia.org/wiki/File:Frkekulé.jpg>.

Despite his break with Bunsen, Baeyer continued his research on organic arsenic compounds of the cacodyl (Me_2As) series.⁸ In 1858, he submitted his work on cacodylic acid, $\text{Me}_2\text{As}(\text{O})\text{OH}$, done in Kekulé's laboratory, to Berlin University, where he was awarded his Ph.D. in 1858. This dissertation⁹ was written in Latin. During this time, Kekulé had become Professor at Ghent, and as soon as he held the Ph.D., Baeyer followed him there.

In 1860, Baeyer presented his *habilitation* lecture (again, in Latin), then returned to Berlin as a Privatdozent in the Berlin Gewerbeinstitut (The Royal Trade Institute, later the Königliche Technische Hochschule Charlottenburg). There he

began his work with coloring matters, including indigo and alizarin, the red dye from madder root. In 1871, the Alsace-Lorraine region was ceded to France as a result of Prussia's victory in the Franco-Prussian War of 1870–1871. This event was accompanied by the University of Strasbourg becoming the Kaiser-Wilhelm-Universität, and an influx of new, young German-speaking staff members. One of these was 36-year-old Adolf von Baeyer, who became Professor in 1871. Four years later, Baeyer became the successor to Justus von Liebig at the University of Munich, where he spent the rest of his career.

Baeyer's research made a huge impact on the field of organic chemistry. His major contributions to organic chemistry include the Baeyer strain theory (Figure 1),¹⁰ and a series of papers on indoles, indoxyl, and isatin,¹¹ culminating in the synthesis of indigo (1; Scheme 1).¹²

Figure 1 Baeyer's strain theory (image taken from *Ber. Dtsch. Chem. Ges.* **1885**, *18*, 2269–2281)

Scheme 1

In his degradation studies of uric acid (3), he obtained the dimeric pyrimidinetrione, hydriluric acid (4), as well as monomeric pyrimidinetrione derivatives 5 (violuric acid), 6 (alloxan), and 7 (barbituric acid) (Scheme 2), along with several other pyrimidine derivatives.¹³ In 1871, he reported the discovery and synthesis of the phthalein dyes (Scheme 3);¹⁴ in 1900, he published a paper that proposed a system of nomenclature for polycyclic and spirocyclic compounds.¹⁵

Later he brought his chemical knowledge to the University of Munich, where the true synthesis of indigo developed alongside some of his other projects, such as his work with acetylene and polyacetylene which later developed into the Baeyer strains theory of carbon rings. More specifically, he

Scheme 2

Scheme 3

proposed that the stability of carbocyclic compounds was dependent on the angles' deviation from the commonly accepted 109° standard. In 1905, he received the Nobel Prize in Chemistry, further distinguishing himself in his field.

The other member of the team was Swiss chemist Victor Villiger (1868–1934), the son of a lawyer and later City Administrator of Lenzburg, and grandson of the Swiss Aarau po-

litician and reformer, Augustin Kweller (1805–1883). He was born in the small village of Cham am Zuger See and educated at the Aarau Canton School. In 1888, he entered the University of Geneva, where he studied chemistry for a year and a half under Carl Graebe (1841–1927) before completing his compulsory year of military service.

Carl Graebe ca. 1860 (left) and Heinrich Caro ca. 1900 (right). Public domain images retrieved from https://commons.wikimedia.org/wiki/File:Carl_Graebe_1860-07-13.jpg (accessed July 10, 2020) and https://commons.wikimedia.org/wiki/File:Heinrich_Caro_ca1900.jpg (accessed July 10, 2020).

After completing his military service, Villiger volunteered for several months in the laboratory of the Research Chemist of the City of Zürich. Then, in the spring of 1890, he moved to Munich, where he entered Baeyer's laboratory. He began his Ph.D. studies there in 1893, focusing on the structure of the benzenoid and hydrobenzenoid compounds that had led to Baeyer's 1888 paper¹⁶ on the structure of benzene, where he had first reported his centric formulas (Figure 2). Villiger received his Ph.D. in 1893 for his studies on hexahydroisophthalic acid.¹⁷

Figure 2 Baeyer's centric formulas for the structures of (l–r) hydroquinone, phloroglucinol and terephthalic acid (images taken from *Justus Liebigs Ann. Chem.* **1888**, 245, 103–190)

Baeyer was very much impressed by the young Villiger, and therefore retained him as an assistant for another eleven years after his graduation. Initially, Villiger worked with Baeyer on the 'hot topic' at the time – the structure of terpenoid compounds.¹⁸ During this work, the β -lactam **14** and stereoisomeric lactones **16** and **17** from camphoronic acid (**15**) were prepared.¹⁹

Literature searches using any search engine and the names Baeyer or Villiger, separately, return more hits on the Baeyer–Villiger reaction than on anything else. This important reaction was first described in the last two years of the nineteenth century,¹ and has remained an important synthetic organic

Scheme 4

Scheme 5

method.²⁰ The first examples of the Baeyer–Villiger oxidation of cyclic ketones were carried out using menthone (**18**), tetrahydrocarvone (**20**), and camphor (**22**); they are collected in Scheme 5.

The first reagent used in the reaction was Caro's acid (monopersulfuric acid), developed by the pioneering dye chemist, Heinrich Caro (1834–1910), who had worked with Baeyer on the synthesis of indole.²¹

Scheme 6

Three distinct mechanisms for the reaction were proposed (Scheme 6). The first, by Baeyer and Villiger themselves,^{1a} passes through a dioxirane (**25**), the second, proposed by Wittig and Pieper,²² passes through a carbonyl oxide (**26**), and the third, proposed by Criegee,²³ involves an α -hydroxyalkyl perester (the Criegee intermediate, **27**).

Evidence confirming the Criegee mechanism was obtained by Doering and Dorfman,²⁴ who used ^{18}O -labeled benzophenone (marked in red in Scheme 6) as the substrate for the reaction. The carbonyl- ^{18}O -labeled ester (**29**) was obtained as the exclusive product, which is consistent with the Criegee mechanism, but neither of the others. A series of studies²⁵ established the migratory aptitudes of alkyl substituents as shown in Figure 3. The relative reactivities of commonly used peracids are summarized in Figure 4.

The Baeyer–Villiger oxidation of C-20 steroidal ketones was shown quite early on to give a single diastereoisomer of the product;²⁶ shortly thereafter, the rearrangement was shown to occur with retention of configuration.²⁷ This was effected by Turner as shown in Scheme 7. Thus, catalytic hydrogenation of 1-acetyl-2-methylcyclohexene (**30**) gave *cis*-1-acetyl-2-methylcyclohexane (**31**); this ketone was readily epimerized by base to the *trans* isomer (**32**). The treatment

of these two ketones with perbenzoic acid in chloroform gave the diastereoisomeric acetates **33** and **34**, showing clearly that the rearrangement had occurred with retention of configuration.

Figure 3 The migratory aptitudes, in the Baeyer–Villiger oxidation, of groups attached to the carbonyl carbon

Figure 4 The relative reactivities of peracids in the Baeyer–Villiger reaction

Scheme 7

The Baeyer–Villiger reaction has been a valuable synthetic method for nearly a century and a quarter, and it should come as no surprise that the reaction has come under intense research directed at ‘greening’ the reaction.²⁸ Under the standard conditions, the reaction poses several problems that need

to be addressed if it is to be carried out under green conditions: 1) Organic peracids are shock-sensitive, and oxidation hazards, covered by special regulations in their transportation and disposal. 2) The stoichiometric reaction generates one mole of the carboxylic acid per mole of peracid; this must be recycled or disposed of as hazardous waste. 3) The reaction involves the use of solvents that are not generally environmentally benign.

To address these problems, considerable effort has gone into identifying catalytic methods for the reaction. These include the catalytic generation of the peracid from aldehydes and molecular oxygen, a reaction known under the general name of the Mukaiyama oxidation (Scheme 8).^{29a} The Mukaiyama oxidation was quickly expanded by the use of catalysts^{29b–d} and forms the basis for an industrial synthesis of ϵ -caprolactone (Scheme 8),^{30a} which was still under investigation nearly two decades later.^{30b}

Scheme 8 The Mukaiyama oxidation of cyclohexanone to ϵ -caprolactone

Hydrogen peroxide also remains one of the most favored terminal oxidants for the greening of the Baeyer–Villiger oxidation. A search of Google Scholar for 2020 using the keywords ‘Baeyer–Villiger’ and ‘hydrogen peroxide’ returned 303 results as of October 20. One recent report³¹ details the *in situ* generation of hydrogen peroxide and coupled Baeyer–Villiger oxidation in the presence of molecular oxygen under catalysis by cerium(IV) ammonium nitrate and *N*-hydroxypyridine (Scheme 9).

Other researchers have studied methods for reducing the shock sensitivity of the oxidant. A representative example of recent work in this area³² has identified perdecanoic acid as a non-toxic, shock-resistant replacement for the more sensitive and toxic lower-molecular-weight peracids.

The most recent research aimed at making the reaction enantioselective is being addressed by examining biocatalysis. Baeyer–Villiger monooxygenases (BVMO) are flavoprotein monooxygenases that have been widely exploited for carrying out the asymmetric Baeyer–Villiger oxidation (a Google Scholar search, in July 2020, for the period 2016–2020 returns

Scheme 9 Coupled catalytic alcohol oxidation and Mukaiyama oxidation with oxygen as the terminal oxidant

over 460 hits). The enzyme structure and sequence have both been determined, and the enzyme has become a popular target for modification.³³ Several reviews³⁴ of the uses of these enzymes for asymmetric Baeyer–Villiger oxidations have been published since 2011.

REFERENCES

- (1) (a) A. Baeyer, V. Villiger *Ber. Dtsch. Chem. Ges.* **1899**, *32*, 3625–3633. (b) A. Baeyer, V. Villiger *Ber. Dtsch. Chem. Ges.* **1900**, *33*, 124–126. (c) A. Baeyer, V. Villiger *Ber. Dtsch. Chem. Ges.* **1900**, *33*, 858–864.
- (2) For biographies of Baeyer, see: (a) R. Huisgen *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 297–311.
- (b) A. de Meijere *Angew. Chem. Int. Ed.* **2005**, *44*, 7836–7840.
- (c) G. Nagendrappa *Resonance* **2014**, *19*, 489–522.
- (3) W. H. Perkin *J. Chem. Soc., Trans.* **1923**, *123*, 1520–1546.
- (4) Abstract (Referate) *Ann. Chem. Pharm.* **1851**, *80*, 253–255.
- (5) A. Baeyer *Ann. Chem. Pharm.* **1857**, *103*, 178–181.
- (6) A. Baeyer *Ann. Chem. Pharm.* **1857**, *103*, 181–184.
- (7) (a) R. Bunsen *Ann. Chem. Pharm.* **1839**, *31*, 175–180.
- (b) R. Bunsen *Ann. Chem. Pharm.* **1841**, *37*, 1–57.
- (c) R. Bunsen *Ann. Chem. Pharm.* **1842**, *42*, 14–46.
- (d) R. Bunsen *Ann. Chem. Pharm.* **1843**, *46*, 1–48.
- (8) A. Baeyer *Ann. Chem. Pharm.* **1858**, *105*, 265–276.
- (9) A. Baeyer *Inaugural-Dissertation*, University of Berlin, Germany, **1858**.
- (10) A. Baeyer *Ber. Dtsch. Chem. Ges.* **1885**, *18*, 2269–2281.
- (11) For a history of Baeyer’s work that culminated in the synthesis of indigo, see: A. v. Baeyer, In *Adolf von Baeyer’s gesammelte Werke*, Vol. 1; A. v. Baeyer, V. Villiger,

- V. Hottenroth, R. Hallensleben, Eds.; Friedrich Vieweg u. Sohn: Braunschweig, **1905**; XXXVIII–LV.
- (12) A. Baeyer, V. Drewson *Ber. Dtsch. Chem. Ges.* **1882**, *15*, 2856–2864.
- (13) (a) A. Baeyer *Ann. Chem. Pharm.* **1863**, *127*, 199–236. (b) A. Baeyer *Ann. Chem. Pharm.* **1864**, *130*, 129–175.
- (14) (a) A. Baeyer *Ber. Dtsch. Chem. Ges.* **1871**, *4*, 555–558. (b) A. Baeyer *Ber. Dtsch. Chem. Ges.* **1871**, *4*, 658–665. (c) A. Baeyer *Polytech. J.* **1871**, *201*, 358–362.
- (15) A. Baeyer *Ber. Dtsch. Chem. Ges.* **1900**, *33*, 3771–3775.
- (16) A. Baeyer *Justus Liebigs Ann. Chem.* **1888**, *245*, 103–190.
- (17) (a) V. Villiger *Inaugural-Dissertation*, University of Munich: Germany, **1893**. (b) A. Baeyer, V. Villiger *Justus Liebigs Ann. Chem.* **1893**, *276*, 255–265.
- (18) (a) A. Baeyer, V. Villiger *Ber. Dtsch. Chem. Ges.* **1896**, *29*, 1923–1929. (b) A. Baeyer, V. Villiger *Ber. Dtsch. Chem. Ges.* **1898**, *31*, 2067–2079. (c) A. Baeyer, V. Villiger *Ber. Dtsch. Chem. Ges.* **1899**, *32*, 2429–2447.
- (19) A. Baeyer, V. Villiger *Ber. Dtsch. Chem. Ges.* **1897**, *30*, 1954–1958.
- (20) (a) C. H. Hassall *Org. React.* **1957**, *9*, 73–106. (b) P. A. S. Smith, In *Molecular Rearrangements*, Vol. 1; P. DeMayo, Ed.; Interscience Publishers, Inc.: New York, **1963**; 577–591. (c) J. B. Lee, B. C. Uff *Q. Rev. Chem. Soc.* **1967**, *21*, 429–457. (d) G. R. Krow *Comprehensive Organic Synthesis* **1991**, *7*, 671–688. (e) G. R. Krow *Org. React.* **1993**, *43*, 251–798. (f) M. Renz, B. Meunier *Eur. J. Org. Chem.* **1999**, 737–750.
- (21) (a) A. Baeyer, H. Caro *Ber. Dtsch. Chem. Ges.* **1877**, *10*, 692–693. (b) A. Baeyer, H. Caro *Ber. Dtsch. Chem. Ges.* **1877**, *10*, 1262–1265.
- (22) G. Wittig, G. Pieper *Chem. Ber.* **1940**, *73*, 295–297.
- (23) R. Criegee *Justus Liebigs Ann. Chem.* **1948**, *560*, 127–135.
- (24) W. v. E. Doering, E. Dorfman *J. Am. Chem. Soc.* **1953**, *75*, 5595–5598.
- (25) (a) S. L. Friess *J. Am. Chem. Soc.* **1949**, *71*, 14–15. (b) W. v. E. Doering, L. Speers *J. Am. Chem. Soc.* **1950**, *72*, 5515–5518. (c) S. L. Friess, N. Farnham *J. Am. Chem. Soc.* **1950**, *72*, 5518–5521. (d) S. L. Friess, A. H. Soloway *J. Am. Chem. Soc.* **1951**, *73*, 3968–3972. (e) R. R. Sauers, R. W. Ubersax *J. Org. Chem.* **1965**, *30*, 3939–3941.
- (26) (a) R. E. Marker *J. Am. Chem. Soc.* **1940**, *62*, 2543–2547. (b) V. Burckhardt, T. Reichstein *Helv. Chim. Acta* **1942**, *25*, 821–832. (c) V. Burckhardt, T. Reichstein *Helv. Chim. Acta* **1942**, *25*, 1434–1443. (d) L. H. Sarett *J. Am. Chem. Soc.* **1947**, *69*, 2899–2901.
- (27) (a) R. B. Turner *J. Am. Chem. Soc.* **1950**, *72*, 878–882. (b) T. F. Gallagher, T. H. Kritchevsky *J. Am. Chem. Soc.* **1950**, *72*, 882–885.
- (28) (a) Y. Zhou, X. Chen, X. Ling, W. Rao *Green Chem.* **2019**, *21*, 5611–5615. (b) M. Uyanik, K. Ishihara *ACS Catal.* **2013**, *3*, 513–520. (c) C. Jiménez-Sanchidrián, J. R. Ruiz *Tetrahedron* **2008**, *64*, 2011–2026. (d) G.-J. ten Brink, I. W. C. E. Arends, R. A. Sheldon *Chem. Rev.* **2004**, *104*, 4105–4124.
- (29) (a) T. Yamada, K. Takahashi, K. Kato, T. Takai, S. Inoki, T. Mukaiyama *Chem. Lett.* **1991**, *20*, 641–644. (b) S.-I. Murahashi, Y. Oda, T. Naota *Tetrahedron Lett.* **1992**, *33*, 7557–7560. (c) M. Hamamoto, K. Nakayama, Y. Nishiyama, Y. Ishii *J. Org. Chem.* **1993**, *58*, 6421–6425. (d) K. Kaneda, S. Ueno, T. Imanaka, E. Shimotsuma, Y. Nishiyama, Y. Ishii *J. Org. Chem.* **1994**, *59*, 2915–2917.
- (30) (a) H. A. Wittcoff, B. G. Reuben *Industrial Organic Chemicals*; John Wiley & Sons: New York, **1996**; 254. (b) J. Zang, Y. Ding, Y. Pei, J. Liu, R. Lin, L. Yan, T. Liu, Y. Lu *React. Kinet. Mech. Catal.* **2014**, *112*, 159–171.
- (31) R. Du, H. Yuan, C. Zhao, Y. Wang, J. Yao, H. Li *Mol. Catal.* **2020**, *490*, 110947.
- (32) M. Sitko, A. Szelwicka, A. Wojewódka, A. Skwarek, D. Tadasiewicz, L. Schimmelpfennig, K. Dziuba, M. Morawiec-Witczak, A. Chrobok *RSC Adv.* **2019**, *9*, 30012–30018.
- (33) For a recent example, see: R. D. Ceccoli, D. A. Bianchi, M. A. Carabajal, D. V. Rial *Mol. Catal.* **2020**, *486*, 110875.
- (34) (a) H. Leisch, K. Morley, P. C. K. Lau *Chem. Rev.* **2011**, *111*, 4165–4222. (b) R. Wohlgemuth *Comprehensive Organic Synthesis II* **2014**, *7*, 121–144. (c) M. J. L. J. Fürst, A. Gran-Scheuch, F. S. Aalbers, M. W. Fraaije *ACS Catal.* **2019**, *9*, 11207–11241. (d) E. Romero, J. R. G. Castellanos, G. Gadda, M. W. Fraaije, A. Mattevi *Chem. Rev.* **2018**, *118*, 1742–1769.

Continuous-Flow C(sp³)-H Functionalizations of Volatile Alkanes Using Decatungstate Photocatalysis

Science 2020, 369, 92–96

C(sp³)-H functionalization of alkanes in the absence of proximal directing groups is considered one of the most challenging and important reactions in contemporary synthetic organic chemistry. In particular, the incorporation of light alkanes, such as methane, ethane, propane and butane, into organic molecules is extremely attractive because it would move the perception of these chemicals essentially as fuel materials to potentially valuable synthetic building blocks.¹

Building on their experience in decatungstate-photocatalyzed C–H oxidations,² the group of Prof. Dr. Timothy Noël at the Eindhoven University of Technology (The Netherlands) focused their attention on this valuable – yet absent in organic synthesis – chemical conversion of gaseous alkanes, which could benefit from continuous-flow microreactor technology. First author of the paper, Dr. Gabriele Laudadio, remarked: “At the onset of the project, we wondered if we could engage these inert and insoluble gasses into synthetically valuable transformations using cheap decatungstate as a photocatalyst. Decatungstate had shown its value for activating larger alkane scaffolds, often with remarkably high selectivity which can be ascribed to the large size of the catalyst and its electronic properties. If successful, this catalyst would show significant scope, allowing for a diverse set of synthetic applications using Hydrogen Atom Transfer (HAT) photocatalysis.” Furthermore, as noted by Prof. Dr. Timothy Noël: “Flow chemistry would be

key in our reaction design: not only to make sure that the reaction medium is well irradiated, but also to bring the gasses into close contact with the photocatalyst³ (Figure 1).”

Preliminary trapping experiments with TEMPO afforded the corresponding TEMPO-propane adducts and gave the group confidence for potentially interesting and useful reactivity. In particular, the authors were intrigued by the excellent selectivity provided by decatungstate for the most substituted carbon of propane (86:14 ratio of secondary vs primary derivative).

Prof. Dr. Noël recalls that he immediately realized the importance of this seminal result, knowing how difficult it is to obtain good selectivity without the presence of directing groups. He said: “I still remember the meeting when this result was presented; I became really excited. We decided to investigate further to see if we could obtain more synthetically useful results.” At that point, Prof. Dr. Noël asked Yuchao Deng, who was a visiting Chinese PhD student in the lab, to join the team.

Yuchao and Gabriele carried out the propane optimization and identified the substrate scope. Gabriele remarked: “The decision to employ a Vapourtec setup was crucial, because we could move from stop flow to continuous flow, accelerating our reaction dramatically (Scheme 1). Importantly, a high-intensity light source was needed to provide much-reduced reaction times.”

Figure 1 Decatungstate photocatalysis in flow enables the activation of light alkanes

Scheme 1 Importance of photon flux and catalyst loading for the effectiveness of the decatungstate C(sp³)-H functionalization of propane

Next, Gabriele and Yuchao set out to explore different gaseous substrates (Scheme 2). Yuchao said: “Activation of isobutane led to a novel methodology to install *tert*-butyl groups in a very easy and scalable way, with high selectivity (96:4 *tert*-butyl versus isobutyl). Also, activation of ethane was successfully achieved just by cranking up the pressure, which was needed to get ethane into solution, and requiring only minor adjustments to the reaction protocol.”

When the ethane transformation was also wrapped up, the group was ready to take on the final challenge of methane. “Methane possesses the strongest C(sp³)-H bonds known in Nature and we were not sure whether decatungstate would be able to cleave those efficiently,” said Prof. Dr. Noël. He continued: “Methane has been a daunting challenge for many decades, occupying many researchers without much success so far. Typically, cleaving methane’s C(sp³)-H bonds requires extremely high temperatures (> 500 °C) and is only industrially done for a few processes. We reckoned that if methane would work, it would be a big deal.” However, in their first attempts, the group realized that HAT on acetonitrile was prominent, with only traces of the desired methylated product observed.

“We did not expect this outcome, because activation of C-H bonds on acetonitrile should be prevented due to a polarity mismatch,” observed Gabriele, continuing: “We realized that this solvent effect could only be observed when the reactivity of tetrabutylammonium decatungstate (TBADT) is pushed to its limits.”

The presence of this byproduct was suppressed simply by using acetonitrile-*d*₃ as solvent. “In this way the corresponding methylated products could be isolated,” confirmed Prof. Dr. Noël, who concluded: “This method represents an important strategy to convert light alkanes into value-added molecules. Via decatungstate photocatalysis, we could break strong C(sp³)-H bonds at room temperature, avoiding harsh reaction conditions. In addition, it is important to notice that similar transformations typically require organometallic reagents to yield these compounds. Hence, decatungstate photocatalysis literally allowed us to take the clutter out of synthesis. Our laboratory is already working on scaling up this process and improving some minor limitations of our method (e.g. deuterated solvents for methane functionalization).”

Matthew Farnock

Scheme 2 Selection of the scope obtained with the decatungstate C(sp³)-H functionalization of light hydrocarbons. Standard conditions for the decatungstate C(sp³)-H functionalization of isobutane: olefin (1 equiv, 0.1 M), isobutane (4.3 equiv), TBADT (1.0 mol%), CH₃CN/H₂O (7:1), 10 bar pressure, 60 W of 365 nm LEDs, 4 h reaction time, room temperature. Reported selectivity reflects the *tert*-butyl/*isobutyl* ratio. Standard conditions for the decatungstate C(sp³)-H functionalizations of propane: olefin (1 equiv, 0.1 M), propane (4.1 equiv), TBADT (1.0 mol%), CH₃CN/H₂O (7:1), 10 bar pressure, 60 W of 365 nm LEDs, 4 h reaction time, room temperature. Reported selectivity reflects the *isopropyl*/*n*-propyl ratio. Standard conditions for the decatungstate C(sp³)-H functionalizations of ethane: olefin (1 equiv, 0.1 M), ethane (8 equiv), TBADT (2.0 mol%), CH₃CN/H₂O (7:1), 25 bar pressure, 60 W of 365 nm LEDs, 8 h reaction time, room temperature. Standard conditions for the decatungstate C(sp³)-H functionalizations of methane: olefin (1 equiv, 0.02 M), methane (20 equiv), TBADT (5.0 mol%), CD₃CN/H₂O (7:1), 45 bar pressure, 150 W of 365 nm LEDs, 6 h reaction time, room temperature.

REFERENCES

- (1) J. F. Hartwig, M. A. Larsen *ACS Cent. Sci.* **2016**, 2, 281–292.
- (2) G. Laudadio, S. Govaerts, Y. Wang, D. Ravelli, H. F. Koolman, M. Fagnoni, S. W. Djuric, T. Noël *Angew. Chem. Int. Ed.* **2018**, 57, 4078–4082.
- (3) C. Sambiasi, T. Noël *Trends Chem.* **2020**, 2, 92–106.

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His research interests focus on novel synthetic methodologies combining continuous-flow microreactor technology with electrochemistry and photochemistry.

Prof. Dr. T. Noël

most recently the VIDI award (2015), the Thieme Chemistry Journals Award (2016), the DECHEMA prize (2017) and the Hoogewerff Jongerenprijs 2019. He is the editor in chief of *Journal of Flow Chemistry*.

Gabriele Laudadio was born in 1991 near Pescara, Italy. In 2016 he received his M.Sc. degree in organic chemistry at the University of Pisa (Italy). His Master's thesis was conducted under the supervision of Professor A. Carpita. He recently obtained his Ph.D. in chemistry with *Cum Laude* at the Eindhoven University of Technology (The Netherlands) in the group of Prof. Dr. Timothy Noël. His research inter-

Timothy Noël was recently promoted to Full Professor at the University of Amsterdam (The Netherlands) where he is the Chair of Flow Chemistry. His research interests range from organic chemistry to chemical engineering and encompass more specifically flow chemistry, organic synthesis and synthetic catalytic methodology development. His work has received several awards, including

Total Synthesis of (+)-Caldaphnidine J

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"What makes a natural product attractive to synthetic chemists?" asks Professor Jing Xu from SUSTech, Shenzhen (P. R. of China): "The answer is usually the biological activity, or the pharmaceutical potential, or the structural complexity that represents an intriguing synthetic challenge." It is Professor Xu's opinion that the daphniphyllum alkaloids – isolated from plants of the genus *Daphniphyllum* – clearly belong to this category of compounds, since there is no doubt that they have long attracted a lot of attention from the synthetic community. "Since the milestone synthetic achievements by Professor Clayton H. Heathcock three decades ago, the synthesis of various members of daphniphyllum alkaloids has bloomed in this decade, too," added Professor Xu, who went on to explain that there are more than 300 daphniphyllum alkaloids known to date, making up a structurally remarkably diversified and fascinating natural product family. As shown in Figure 1, daphniphyllum alkaloids from nine subfamilies have been synthetically accessed so far. "Our group has a research focus on the total synthesis of daphniphyllum alkaloids with highly diversified structures, including calyciphylline A-type (*Angew. Chem. Int. Ed.* **2019**, *58*, 7390–7394), daphnezomine A-type (*J. Am. Chem. Soc.* **2019**, *141*, 11713–11720), bukittinggine-type (*J. Am. Chem. Soc.* **2019**, *141*, 13043–13048), yuzu-

rimine-type (*Nat. Commun.* **2020**, DOI: 10.1038/s41467-020-17350-x), daphniglaucin C-type (*Org. Lett.* **2019**, *21*, 4309–4312) and daphnilactone B-type alkaloids (*Chin. J. Org. Chem.* **2019**, *39*, 1079–1084)," said Professor Xu.

Since Hirata's isolation of yuzurimine in 1966, nearly 50 yuzurimine-type alkaloids have been isolated, which account for about one-sixth of all known daphniphyllum alkaloids. "Despite extensive synthetic studies, no total synthesis of any member from this largest subfamily of daphniphyllum alkaloids has been achieved. Caldaphnidine J was isolated by the Yue group in 2008. It possesses a hexacyclic ring system, six contiguous stereogenic centers, two quaternary centers, and an $\alpha,\beta,\gamma,\delta$ -unsaturated carboxylic ester. This formidable synthetic challenge prompted us to initiate a research program toward its synthesis," explained Professor Xu. He continued: "It was a long, extremely difficult but finally successful journey. As depicted in Scheme 1, the highlights of our approach include 1) a facile six- $\rightarrow$ seven-membered ring expansion strategy; 2) Shi's Pd-catalyzed regioselective hydroformylation; 3) a Sm(II)-mediated pinacol coupling; 4) a novel, one-pot Swern oxidation/ketene dithioacetal Prins reaction; 5) a regioselective elimination; and 6) a regio- and diastereoselective hydrogenation." The group's work resulted in the first synthesis of a

Figure 1 Daphniphyllum alkaloids from nine subfamilies have been synthetically accessed

Scheme 1 Total synthesis of (+)-caldaphnidine J

member of the largest subfamily of daphniphyllum alkaloids. Professor Xu remarked: "We believe that the strategies and methods applied in our work should inspire further advances in the synthesis of daphniphyllum alkaloids and much more."

Professor Xu commented that one of the most interesting findings in the group's approach to the title compound was probably the one-pot Swern oxidation/ketene dithioacetal Prins reaction. "As we mentioned in our manuscript, the oxidation of the secondary hydroxyl group in compound **6** gave decomposition or messy results under various conditions," he explained, continuing: "However, the TFAA/DMSO conditions gave a relatively 'clean' reaction that produced a major, yet unknown, product." He concluded: "To our great pleasure, thorough characterizations of this unknown compound finally disclosed a novel one-pot Swern oxidation/ketene dithioacetal Prins reaction."

Matthew Farah

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Lian-Dong Guo obtained his PhD in 2016 from Xiamen University (P. R. of China) under the direction of Professor Pei-Qiang Huang. He joined Professor Jing Xu's group at SUSTech as a postdoctoral researcher from 2016–2020. His research focuses on the total synthesis of natural products, in particular, the synthesis of alkaloids.

H. Fu

Heyifei Fu obtained his BSc in chemistry from SUSTech (P. R. of China) in 2019 under the supervision of Prof. Jing Xu, where he participated in the total synthesis of daphniphyllum alkaloids. He then moved to Dartmouth College (USA) to pursue his PhD studies under the supervision of Prof. Ivan Aprahamian.

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Young Career Focus: Professor Denis Chusov (Nesmeyanov Institute, Russian Federation)

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 Professor Denis Chusov (Nesmeyanov Institute, Russian Federation).

Biographical Sketch

Prof. D. Chusov

Denis Chusov graduated from the Moscow Chemical Lyceum (Russian Federation) and obtained his undergraduate degree from the Higher Chemical College of the Russian Academy of Sciences (Russian Federation). He defended his Ph.D. thesis under the supervision of Prof. Yuri N. Belokon at the Nesmeyanov Institute of Organoelement Compounds in Moscow (Russian Federation). He then worked as a visiting researcher at Newcastle University (UK) with Prof. Michael North and at Université Paris-Sud 11 (France) with Prof. Henri Kagan. His postdoctoral studies were conducted at Max-Planck-Institut für Kohlenforschung (Germany) with Prof. Benjamin List. He is currently an Associate Professor at the Nesmeyanov Institute (Russian Federation).

INTERVIEW

SYNFORM What is the focus of your current research activity?

Prof. D. Chusov The development of highly effective catalytic systems is equally important for core academic research and industrial applications. However, nowadays the progress is typically achieved by the preparation of more structurally complex and expensive catalysts. The finding of application of simple catalysts for new reactions is one of the goals that we are focused on. Other areas of our research involve the search for new ways of activation of simple catalysts to gain higher activity in known reactions. Currently research in our group focuses on developing new selective reductive addition reactions.

SYNFORM When did you get interested in synthesis?

Prof. D. Chusov I believe that mathematics is the first subject which requires thinking. I have always been interested in mathematics. Once I went to a municipal mathematics olympiad and won a prize. After that, I received some invitations to various mathematics schools. My friend suggested I attend evening classes at the Moscow Chemical Lyceum; I went there and decided to enroll at the Lyceum for a full-time study. To do this, I needed to pass the entrance exams and although I got a good grade in mathematics, I failed the chemistry exam. Therefore, I needed to study chemistry over the summer to pass the exam resit in autumn.

At the Chemical Lyceum I studied many subjects including mathematics, chemistry, and human sciences. At that time, I figured out that I am very interested in organic chemistry. Fortunately, a unique situation was created in the Chemical Lyceum: students were able to carry out research in the real research institutes, so I was given an opportunity to participate in the work of a research laboratory and carry out a project in organic synthesis when I was only 16 years old.

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

Prof. D. Chusov Seems like organic chemistry still has a special place amongst the interests of students in chemical universities and schools. In this area the connection between science and art becomes more visible. It is shown in the beauty of certain syntheses, in the elegance of obtaining certain compounds, in the uniqueness of many reactions. It can be said that in organic synthesis, some kind of design at the smallest size of the objects is possible. Unfortunately, we cannot create the desired new objects with a certain consistency at the sub-molecular level. As for the prospect of organic synthesis, it is hard to imagine that in the future, medicinal chemistry or materials science can be developed without an organic or organoelement compound.

SYNFORM Could you tell us more about your group's areas of research and your aims?

Prof. D. Chusov The main research area of our group focuses on reductive additions without an external hydrogen source. Let's look at this idea on the example of reductive amination reaction. I like this reaction very much, as the majority of medicinal chemists do, because it is a very convenient method of amine synthesis. It is a reliable method which can be applied to a wide variety of substrates. The starting materials are aldehydes or ketones and ammonia or amines. In industry, aldehydes are easily obtained from hydrocarbons, though even simple alcohols, like propanol, butanol and other terminal alcohols with higher molecular weight, are obtained from the corresponding aldehydes. On the other hand, aldehydes can be easily converted into various classes of chemical compounds.

The classical version of reductive amination involves the interaction of an aldehyde with an amine. After that we get a Schiff base and water (Scheme 1). Then molecular hydrogen with a catalyst is added to the Schiff base to obtain the target amine. Precise analysis shows that at the first step we take two hydrogen atoms from the molecules, and at the second step we add them again. That does not look like a very efficient idea, and it means that we can avoid using an external hydrogen source. Ideally, we can mix ammonia or an amine with a carbonyl compound and get a more substituted amine and oxygen (Scheme 2). However, in a reduction process it is not realistic to get an oxidizing agent such as oxygen in the end; therefore we need a reagent which is able to scavenge the oxygen atom and does not contain hydrogen atoms in it. For this purpose, we use carbon monoxide, a waste product of steel manufacturing (Scheme 3).

Scheme 1 Classical way of reductive amination

Scheme 2 Ideal way of reductive amination

Scheme 3 Reductive amination using carbon monoxide as a reducing agent

As a result, we developed even more than reductive amination protocols without an external hydrogen source (*Angew. Chem. Int. Ed.* **2014**, *53*, 5199–5201; *Org. Lett.* **2015**, *17*, 173–175; *Org. Biomol. Chem.* **2017**, *15*, 6384–6387). Interaction of any carbonyl compound with any hydrogen-containing nucleophile is in line with this concept (*Mendeleev Commun.* **2018**, *28*, 113–122). We showed that CH-acids and other CH-nucleophiles (like ketones with an α -hydrogen atom), amides, carboxylic acids can be applied in this protocol (Scheme 4). It is interesting that the method appeared to be very selective. Hydrogen and hydride agents can reduce not only various functional groups in target compounds (Table 1) (*ACS Catal.* **2016**, *6*, 2043–2046) but even the starting aldehydes and ketones, which then leads to a complete failure of the reaction (*Synthesis* **2019**, *51*, 2667–2677).

Moreover, using CO allowed us to synthesize tertiary sterically hindered amines via reductive amination (*Chem. Commun.* **2016**, *52*, 1397–1400). The classical approach with molecular hydrogen does not lead to the target amines since even reduction of an aromatic ring with hydrogen is easier than obtaining such hindered amines (Scheme 5). Even direct reductive amination of sterically hindered ketones like camphor is

Scheme 4 Reductive addition of different hydrogen-containing nucleophiles without an external hydrogen source

	H ₂ /Ni	H ₂ /Rh	LiAlH ₄	NaBH ₄	Rh/CO
R ₂ N-Cbz	✗	✗	✗	✓	✓
R ₂ N-COCF ₃	✗	✓	✗	✗	✓
R ₂ N-Bn	✗	✗	✓	✓	✓
RO-Bn	✗	✓	✓	✓	✓
Ar-NO ₂	✗	✗	✗	±	✓
Ar-CN	✗	✗	✗	±	✓
Ar-Br	✗	✓	±	✓	✓

Table 1 Functional group tolerance in the reductive amination reaction using different reducing agents

very challenging using classical reductive agents (*Org. Biomol. Chem.* **2017**, *15*, 10164–10166).

Notably, it is written in organic chemistry textbooks that for reductive amination reactions, special reducing agents exist. For example, sodium cyanoborohydride and triacetoxyborohydride selectively conduct this reaction since they do not reduce the C=O bond in an initial aldehyde (Scheme 6).

However, when we read a scientific article, including the original article about sodium triacetoxyborohydride, we can see that even there the researchers show that these hydrides do reduce aldehydes.

That is the reason I like our approach. It is very convenient since the reaction can be carried out without any solvent at low catalyst loadings if needed, and even at such conditions we can get nothing but the target compound in the reaction mixture at the end. Moreover, if you do not have access to carbon monoxide gas you can replace it with other non-hydrogen non-gaseous reducing agents such as metal carbonyls [e.g. iron carbonyl (*Org. Biomol. Chem.* **2017**, *15*, 10164–10166; *Eur. J. Org. Chem.* **2019**, 32–35)]. We used this approach for the total synthesis of different compounds (Scheme 7) (*J. Org. Chem.* **2020**, *85*, 9347–9360). For example, we designed the total synthesis of luotonin A from two simple compounds like nitrobenzaldehyde and hydroxyproline (Scheme 8).

Scheme 5 Synthesis of tertiary sterically hindered amines using CO vs. H₂

Scheme 6 Advantages vs. challenge of reductive amination with sodium cyanoborohydride and sodium triacetoxyborohydride

Scheme 7 Total synthesis of vasicinone, isaindigotone, luotonin, and rutaecarpine based on reductive addition of amines to nitrobenzaldehydes without an external hydrogen source

Scheme 8 Retrosynthetic scheme of luotonin A

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

Prof. D. Chusov My most significant achievement is that I chose science, and it means that now I do not have a limit in evolution at my work. And my most important scientific achievement in my opinion is the development of reduction protocols without an external hydrogen source. When we have enough hydrogen atoms in the starting compounds and all we need is to combine these compounds and reduce the

resulting molecule, we can use a reducing agent which does not contain hydrogen atoms and obtain the target compounds with tolerance to all the functional groups and even to obtain such compounds which totally could not have been obtained before.

Coming soon

— Literature Coverage

Boron-Enabled Geometric Isomerization of Alkenes via Selective Energy-Transfer Catalysis

— Literature Coverage

Asymmetric Remote C–H Borylation of Aliphatic Amides and Esters with a Modular Iridium Catalyst

— Literature Coverage

Regio- and Enantioselective Allylic Alkylation of Terminal Alkynes by Synergistic Rh/Cu Catalysis

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Synthesis Review: Recent Applications of Continuous Flow in Homogeneous Palladium Catalysis

(by P. Koř and co-workers)

Synlett Account: Taming Nitrene Reactivity with Silver Catalysts

(by J. M. Schomaker and co-workers)

Synfacts Synfact of the Month in category “Synthesis of Natural Products and Potential Drugs”: Total Synthesis of (±)-Tronocarpine

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