

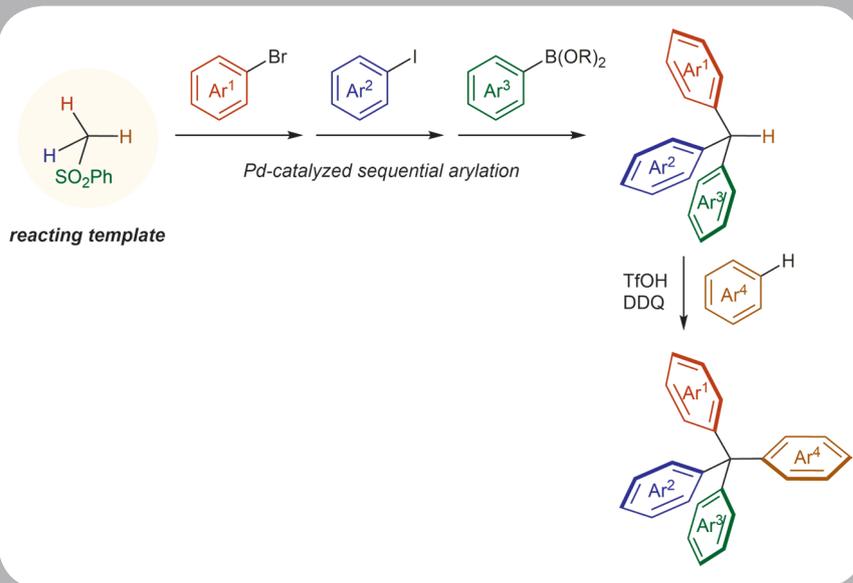
# Synform

People, Trends and Views in Chemical Synthesis

2018/07

## SYNLETT Best Paper Award 2017: Synthesis of Tetraarylmethanes by the Triflic Acid-Promoted Formal Cross-Dehydrogenative Coupling of Triarylmethanes with Arenes

Highlighted article by M. Nambo, J. C.-H. Yim, K. G. Fowler, C. M. Crudden



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## Dear Readers,

I am afraid this is going to be another brief Editorial as I am currently dealing with the preparation of an important meeting of the European Consortium PET3D, which I have the privilege to coordinate. Sadly, these research consortia funded by the European Commission might soon become a tale of the past in this country, pretty much like the dodo, the extinct flightless bird that used to live until over four centuries ago in another island: Mauritius. For this reason, I am determined to make the most of the opportunities that we still have to enjoy collaborative research with overseas colleagues before it all ends up like the dodo... I would be really curious to know whether the dodo used to bury his head in the sand, like the ostrich and some politicians too... But let's move from extinct birds to this new – and still very vital – issue of SYNFORM, which features four different types of articles for the occasion. The opening is a very interesting interview with N. Namba (Japan) and C. Crudden (Canada) who are the joint recipients of the SYNLETT Best Paper Award 2017. The follow-up article is a highly enjoyable Name Reaction Bio on three pioneers of electron-deficient nitrogen rearrangements – von Hofmann, Lossen and Curtius – by our guest author David Lewis. The third is a contribution on the Ru(II)-enabled anilide difluoromethylation recently published by Y. Zhao (P. R. of China). The closing article is a Young Career Focus interview with the up-and-coming synthetic organic chemist Sunkyu Han (South Korea).

Long live to the dodo and enjoy your reading!



### In this issue

#### — SYNLETT Highlight

**SYNLETT Best Paper Award 2017: Synthesis of Tetra-arylmethanes by the Triflic Acid-Promoted Formal Cross-Dehydrogenative Coupling of Triarylmethanes with Arenes** ..... A104

#### — Name Reaction Bio

**Rearrangement to Electron-Deficient Nitrogen: August Wilhelm von Hofmann (1818–1892), Wilhelm Lossen (1838–1906) and Theodor Curtius (1857–1928)** ..... A107

#### — Literature Coverage

**Ruthenium(II)-Enabled *para*-Selective C–H-Difluoromethylation of Anilides and their Derivatives** ..... A111

#### — Young Career Focus

**Young Career Focus: Dr. Sunkyu Han (Korea Advanced Institute of Science and Technology, South Korea)**... A114

Coming soon ..... A116

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## SYNLETT Best Paper Award 2017: Synthesis of Tetraarylmethanes by the Triflic Acid-Promoted Formal Cross-Dehydrogenative Coupling of Triarylmethanes with Arenes

*Synlett* **2017**, 28, 2936–2940

**Background.** Thieme Chemistry and the Editors of SYNTHESIS and SYNLETT present the ‘SYNTHESIS/SYNLETT Best Paper Awards’. These annual awards honor the authors of the best original research papers in each of the journals, considering their immediate impact on the field of chemical synthesis.

Cathleen Crudden, Masakazu Nambo and their co-workers are the recipients of the SYNLETT Best Paper Award 2017. The work was a collaboration between Nagoya University in Japan and Queen’s University in Canada. The authors are recognized for their work on the synthesis of tetraarylmethanes through a formal cross-dehydrogenative coupling of triarylmethanes with arenes, promoted by triflic acid. Benjamin List, Editor-in-Chief of SYNLETT, commented: “Nambo, Yim, Fowler, and Crudden have developed an elegant synthesis of tetraarylmethanes that involves an acid-catalyzed oxidative coupling of an arene with triarylmethanes, which became readily accessible in previous studies by the authors. The reaction proceeds via trityl-type cations and enables the formation of fascinating products, in which four different arenes are connected via a single stereogenic carbon atom.”

SYNFORM spoke with Masakazu Nambo and Cathleen Crudden, who were happy to share some background information regarding the prize-winning paper as well as current research activities ongoing in their groups.

### Biographical Sketches



*Prof. M. Nambo*

**Masakazu Nambo** was born in Fukui (Japan) and studied at Nagoya University (Japan). He obtained his BSc (2006), MSc (2008) and PhD (2011) degrees under the tutelage of Professors Ryoji Noyori and Susumu Saito, Professors Ryoji Noyori and Kenichiro Itami, and Professor Kenichiro Itami, respectively. In 2008, he also spent some time in Germany at the University of Münster, where he was supervised by Professor Bernhard Wünsch.

Since his PhD, Professor Nambo has worked as a Research Scientist (Asahi-Kasei E-Materials Corporation, Japan, 2011–2013) and then moved back to Nagoya University to work with Professor Cathleen Crudden, firstly as a Designated Assistant Professor (2013–2018) and now as a Designated Lecturer. His current research interests include the development of new transformations of organosulfur compounds, establishment of

new synthetic strategies for modular and straightforward synthesis, and discovery of new biological activity of multiply-arylated structures. Outside the lab, he enjoys playing outside with his two sons.



*Prof. C. M. Crudden*

**Cathleen Crudden** is Full Professor and Canada Research Chair (Tier 1) at Queen’s University (Canada), and also holds a cross appointment as a Research Professor at the Institute of Transformative Bio-Molecules (ITbM) in Nagoya (Japan). She is one of only four international faculty at ITbM, where she runs a satellite lab funded by the Japanese government. She has won numerous research awards including the 2018 Canadian Catalysis Society Award, the 2018 IPMI Carol Taylor Award, the 2017 R. U. Lemieux Award and the 2011 Clara Benson Award. She is a



fellow of the Chemical Institute of Canada (2014) and the Royal Society of Chemistry (UK, 2017). She held a Killam Research Fellowship from 2015–2016. Cathleen has been a visiting professor in the labs of Professor Ryoji Noyori, was awarded a Global Center of Excellence Professorship at Kyoto University and a Visiting Professorship in Tarragona, Spain.

Cathleen was President of the Canadian Society for Chemistry in 2012/2013 and served on the Board of Directors for two terms representing the Catalysis Division. She also served on the Editorial Advisory Board for ACCN for ten years, and has been

one of two Canadian members of the organizing committee of Pacificchem for the past 10 years. She is chair of the NSERC–Chemistry Liaison Panel. Cathleen is Associate Editor for *ACS Catalysis* and sits on the editorial advisory boards of *Chemical Record* (Japan), *Synthesis*, *Organometallics*, *ACSOmega* and *Chemical and Engineering News*. Her work in catalysis and materials has received significant acclaim, with recent work identifying a new class of carbon-based SAMs being called “game changing” and “the new gold standard” by international experts in the area.

## INTERVIEW

**SYNFORM** *Could you highlight the value of your award-winning paper with respect to the state-of-the-art, as well as the potential or actual applications?*

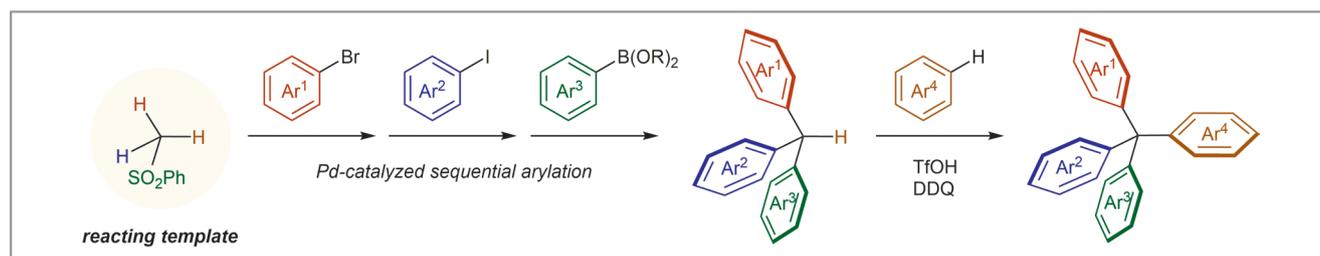
**Prof. Masakazu Nambo and Prof. Cathleen Crudden** Polyarylated methanes are valuable structures found in a variety of biologically active molecules and functional organic materials. Among arylated methanes, fully- or tetra-arylated methanes are structurally beautiful molecules that have unique chemical and physical properties and are challenging to prepare. Indeed, this rigid motif has been used as a ligand for metal–organic frameworks, *n*-type material for optoelectronic devices, and an agent for drug delivery. Very bulky tetraarylmethanes are also critical as ‘stoppers’ in rotaxane chemistry, subject of the Nobel Prize in 2016. Despite intense interest in tetraarylmethanes for these applications, most synthetic approaches rely on very classical methods, such that finding modular and straightforward syntheses of unsymmetrical tetraarylmethanes is still a challenge in synthetic organic chemistry.

In this paper, we have established a new synthetic route for the preparation of tetraarylmethanes from triarylmethanes

and arenes by a formal cross-dehydrogenative coupling. Combined with our previous studies describing cross-coupling methods for the synthesis of triarylmethanes, the method described in our SYNLETT paper permitted the preparation of structurally diverse tetraarylmethanes in four steps from readily available materials. Thus, we believe this method will provide an opportunity to explore new tetraarylmethane-based materials and pharmaceuticals.

**SYNFORM** *Can you explain the origin, motivations and strategy used for conducting the award-winning research?*

**Prof. Masakazu Nambo and Prof. Cathleen Crudden** Previously, our group has developed the modular synthesis of di- and triarylmethanes employing Pd-catalyzed sequential arylations of alkyl sulfones followed by the use of the sulfone group as an electrophile in a Suzuki–Miyaura cross-coupling. However, introducing the fourth aryl ring was challenging due to the considerable steric bulk. Therefore, we attempted the preparation of tetraarylmethanes from triarylmethanes by arylating the remaining C(sp<sup>3</sup>)–H bond. Inspired by recent progress of oxidative C–H/C–H coupling reactions, we discovered a new formal cross-dehydrogenative coupling promoted by TfOH and DDQ. This result is based on considerable efforts by



**Scheme 1** Straightforward synthesis of tetraarylmethanes (total 4 steps)

postdoctoral fellows Dr. Jacky Yim and Dr. Kevin Fowler from our groups.

The invitation to submit an article for a Special Issue dedicated to Professor Victor Snieckus was another motivation to make sure the paper was of fitting quality to recognize the monumental contributions made by my colleague and friend to the chemistry of arenes. Having it selected as the Best Paper for 2017 was yet another honor, and we were very pleased to dedicate it to Vic!

**SYNFORM** *What is the focus of your current research activity, both related to the award paper and in general?*

**Prof. Masakazu Nambo and Prof. Cathleen Crudden** One of the key research goals of our group in Canada/Japan is to establish a new synthetic strategy that permits the construction of diverse molecules in a straightforward way, from simple starting materials. Minimizing the total number of synthetic steps, including those required for substrate preparation, is very important if synthetic schemes are to be viable and useful. We are also focused on employing the power of catalysis to enable high-value transformations such as enantioselective/specific reactions and inert bond activations. A key part of this strategy is to rely upon the unique properties of different main-group elements including boron, sulfur, and phosphorus, which we believe will lead to development of versatile transformations in synthetic organic chemistry.

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

**Prof. Masakazu Nambo and Prof. Cathleen Crudden** There is no doubt that organic synthesis has made an extremely great contribution to the development of science and society and it will continue to do so in the future. In our institute in Nagoya, Japan, we have the pleasure of collaborating with some of the world's best plant and animal biologists. This collaborative relationship has made it clear that the biologically active compounds available to biologists are very limited, constituting a huge barrier to biological research. Thus, we also believe in developing simple strategies that will empower researchers outside the synthetic organic community to assemble molecules in facile, predictable ways. It is really in this way that the power of organic chemistry will be translated to other fields, and significant discoveries will result from that.



## Rearrangement to Electron-Deficient Nitrogen: August Wilhelm von Hofmann (1818–1892), Wilhelm Lossen (1838–1906) and Theodor Curtius (1857–1928)

Between 1872 and 1890, three closely related reactions that involve a stereoselective (or stereospecific) rearrangement of an alkyl group from an acyl carbon to nitrogen were reported by Wilhelm Clemens Lossen (1838–1906), who reported a base-promoted rearrangement of hydroxamic acid derivatives, by August Wilhelm von Hofmann (1818–1892), who reported the base-promoted rearrangement of *N*-haloamides, and by Julius Wilhelm Theodor Curtius (1857–1928), who reported the rearrangement of acyl azides.



Wilhelm Clemens Lossen (1838–1906) | August Wilhelm von Hofmann (1818–1892) | Julius Wilhelm Theodor Curtius (1857–1928)

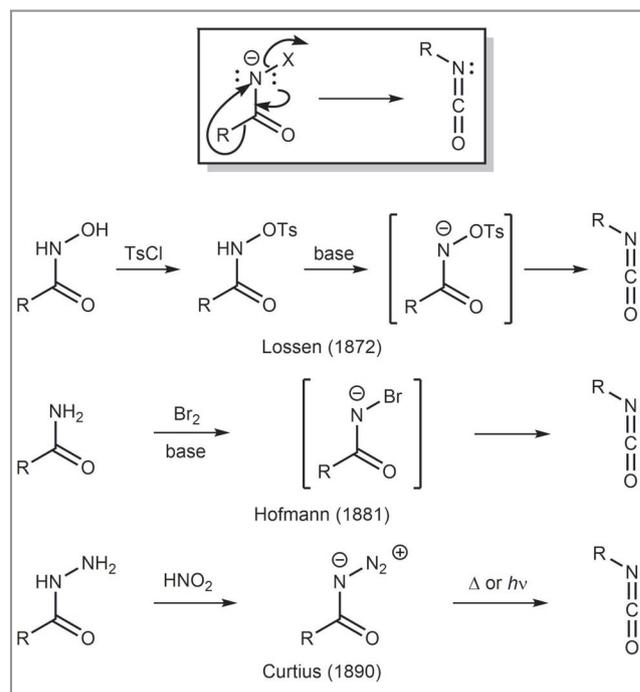
In chronological order of their publication, the reactions are the Lossen rearrangement,<sup>1</sup> the Hofmann rearrangement,<sup>2</sup> and the Curtius rearrangement<sup>3</sup> (Scheme 1). The reactions share a common mechanism, where the rearrangement occurs in the same step with the loss of a leaving group from the nitrogen, to give an isocyanate.

Lossen<sup>4</sup> was born in Kreuznach, and graduated from the Gymnasium in 1857. He then began his studies in chemistry at Giessen in 1857; two years later, he transferred to Göttingen, where he studied under Friedrich Wöhler. He graduated with his Ph.D. in 1862 for a dissertation on the structure of cocaine.<sup>5</sup> During this same period, he began his studies of atropine.<sup>6</sup> He immediately moved to Karlsruhe to work with Karl Weltzien (1813–1870), and then he moved to Halle in 1864 to study under Wilhelm Heinrich Heintz (1817–1880). Opportunities for Docents to deliver lectures were limited at Halle, so Lossen moved to Heidelberg, where he earned his *habilitation* in 1866, and promotion to Extraordinary Profes-

or in 1870. In 1877, he accepted a call to the University of Königsberg as Ordinary Professor of Chemistry. He spent the next 26 years there, until his retirement as Professor Emeritus in 1903. Following his retirement, Lossen spent the last three years at Aachen.

Lossen discovered hydroxylamine in 1855,<sup>7</sup> and spent much of the rest of his career devoted to the chemistry of hydroxylamine and its derivatives:<sup>8</sup> added to his papers on his rearrangement reaction, hydroxylamine figures in some 20% of his publications.

In contrast to the situation with Lossen, there is a vast biographical literature about Hofmann.<sup>9</sup> Arguably one of the most productive and influential organic chemists of the nineteenth century, Hofmann entered Giessen University to study philology and law. But, early in his student days, he met Justus von Liebig, who persuaded him to study chemistry instead. His life-long study of organic nitrogen compounds began with his Ph.D. project on aniline. Following his graduation in

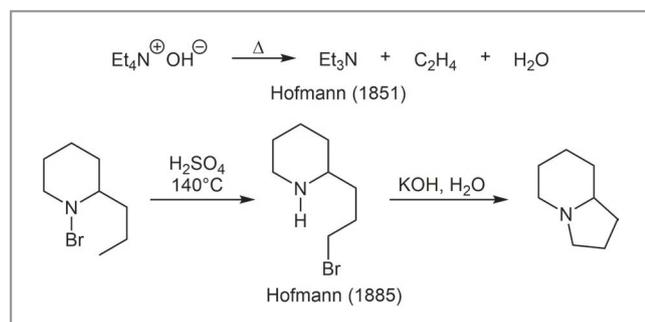


Scheme 1

1841, he became one of Liebig's assistants in 1843. In 1845, he was appointed the first director of the Royal College of Chemistry in London, which had been established by several distinguished chemists and Prince Albert, Queen Victoria's German-born husband, who was a strong advocate for science and technology in Britain. He remained there for the next two decades but, after Prince Albert's death, support for science in Britain declined. This may well have led to Hofmann returning to Bonn in 1864. In 1865 he moved to Berlin, where he remained until his death in 1892.

Hofmann was responsible for some of the most brilliant teaching and research seen in London. In his view, organic chemistry lectures without experimental demonstrations were incomplete, so he had assistants perform the demonstrations in class. After his return to Germany, Hofmann founded the German Chemical Society; his home was preserved as headquarters of that society. He was a prolific researcher, and his laboratories produced over 1,000 papers, more than 300 of them his own work. Some idea of his contributions may be gauged from the number of reactions named after him: the Hofmann elimination,<sup>10</sup> the Hofmann rearrangement, and the Hofmann-Löffler-Freytag reaction<sup>11</sup> (Scheme 2) are the most important. Hofmann was ennobled in 1888.

Curtius was born into a scholarly family at Duisburg, and entered Heidelberg University to study music and science. He studied chemistry under Robert Bunsen at Heidelberg until his required military service. Following his discharge as a first lieutenant, Curtius moved to Leipzig, where he took his Ph.D. under Kolbe in 1882 for a dissertation on hippuric acid. In 1884, he moved to Munich to study under Baeyer, and then qualified for his *habilitation* under Otto Fischer at Erlangen in 1886. On attaining this qualification, he became director of the analytical laboratories at Erlangen. In 1889, he was offered positions at Worcester Polytechnic in the U.S. and at Kiel. Curtius chose Kiel, where he was Professor of Chemistry and Director of the Chemical Institute. His career at Kiel was



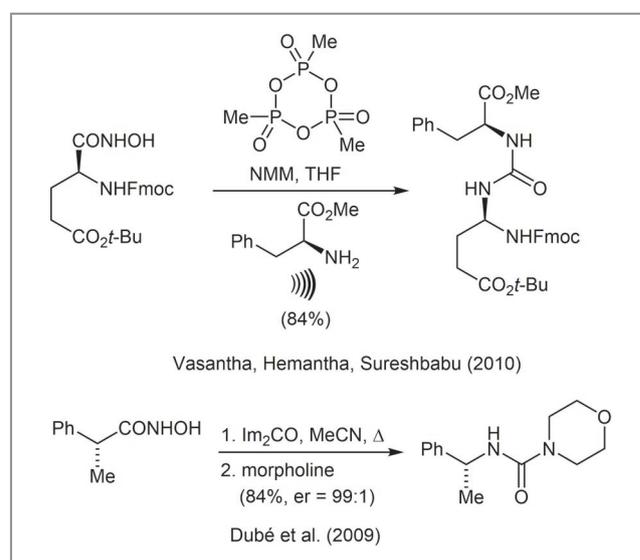
Scheme 2

very productive, and in 1895 he was appointed to the rank of *Geheimrat* (Privy Councillor).

In 1897, Curtius succeeded Kekulé at Bonn, and the next year, he returned to Heidelberg as Professor of Chemistry, succeeding Victor Meyer. Curtius spent the rest of his career there, succeeding his Ph.D. mentor, Kolbe, as editor of the *Journal für praktische Chemie*. From the beginning, much of his research concerned the reactions of nitrogen compounds, especially amides and imides. The Curtius reactions named for him were discovered in 1894 (degradation to the amine) and 1911 (formation of the isocyanate). Curtius never lost his love for music, and he entertained himself and his friends by playing the piano, singing, and composing (although he never reached the heights of another organic chemist—Borodin—as a composer). Curtius was also an avid mountain-climber.

All three rearrangements share the common feature that the reaction occurs with retention of configuration, which has made them highly useful in stereocontrolled synthesis. An idea of how these reactions have been used in synthesis, where their stereospecificity has been crucial, are gathered in Schemes 3 (Lossen), 4 (Hofmann) and 5 (Curtius).

The first entry in Scheme 3<sup>12a</sup> illustrates the use of the trimeric anhydride of methylphosphonic acid (T3P<sup>®</sup>) to form the hydroxamic acid *O*-phosphonate, *N*-methylmorpholine as the base, and heating by ultrasonic irradiation. In the same paper, the authors demonstrated that, to the limits of detection by 400 MHz <sup>1</sup>H NMR spectroscopy, the rearrangement is stereospecific. The second entry<sup>12b</sup> also shows that the rearrangement occurs with retention of configuration to the extent of



Scheme 3

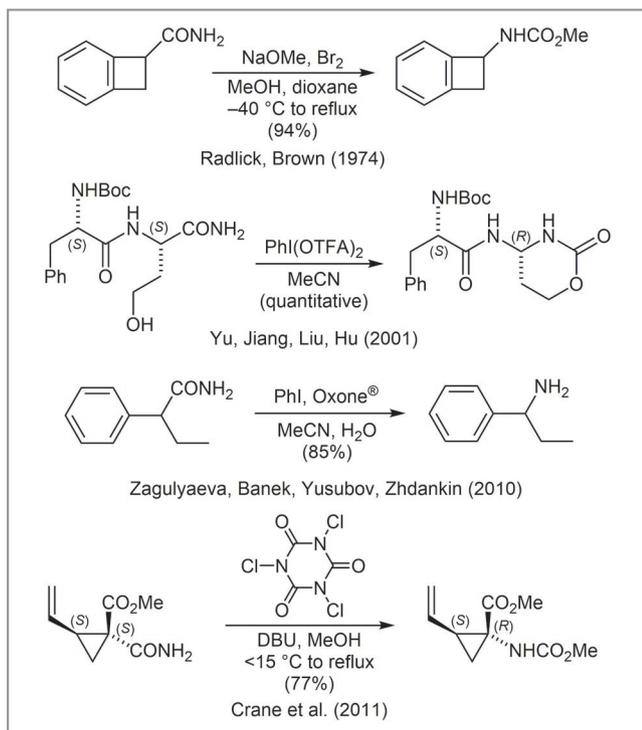
99:1. Carbonyldiimidazole was the acylating reagent, and, by releasing imidazole, it also provides the base for the reaction.

The original version of the Hofmann rearrangement often gave relatively poor yields due to over-oxidation or the poor

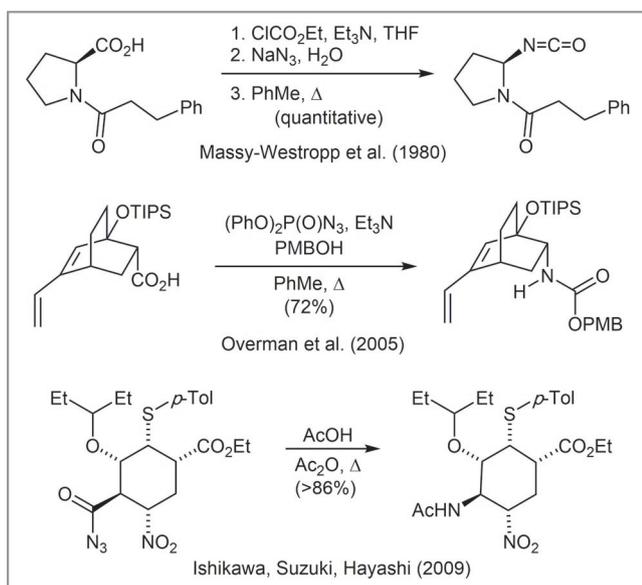
solubility of some amides in aqueous base. Developments over the last two decades, in particular, have focused on refining both of these factors affecting the reaction. Radlick and Brown<sup>13a</sup> showed that methyl hypobromite in methanol made a useful modification of the reaction, giving the urethane, which is relatively resistant to further oxidation, rather than the free amine. During the first decade of the 21<sup>st</sup> century, hypervalent iodine compounds<sup>13b,c</sup> have emerged as reagents that avoid both the strong base, and the free halogens in the reaction. The final entry in Scheme 4 contains another alternative source of the halogen oxidant: trichlorocyanuric acid.<sup>13d</sup>

Scheme 5 illustrates the usefulness of the stereospecificity of the Curtius rearrangement. In 1980, Massy-Westropp and coworkers<sup>14a</sup> used the Curtius rearrangement of an acyl azide derived from L-proline as a key step in the determination of the absolute stereochemistry of odorine. In 2005, Overman used the Curtius rearrangement as a key step in the synthesis of (±)-gelsemine.<sup>14b</sup> Hayashi's synthesis used a Curtius rearrangement of an acyl azide in acetic acid to give a key intermediate in the synthesis of (–)-oseltamivir.<sup>14c</sup>

David Lewis



Scheme 4



Scheme 5

## DEDICATION

This article is dedicated to the memory of the great pioneer of aniline chemistry, August Wilhelm von Hofmann, on the bicentenary of his birth.

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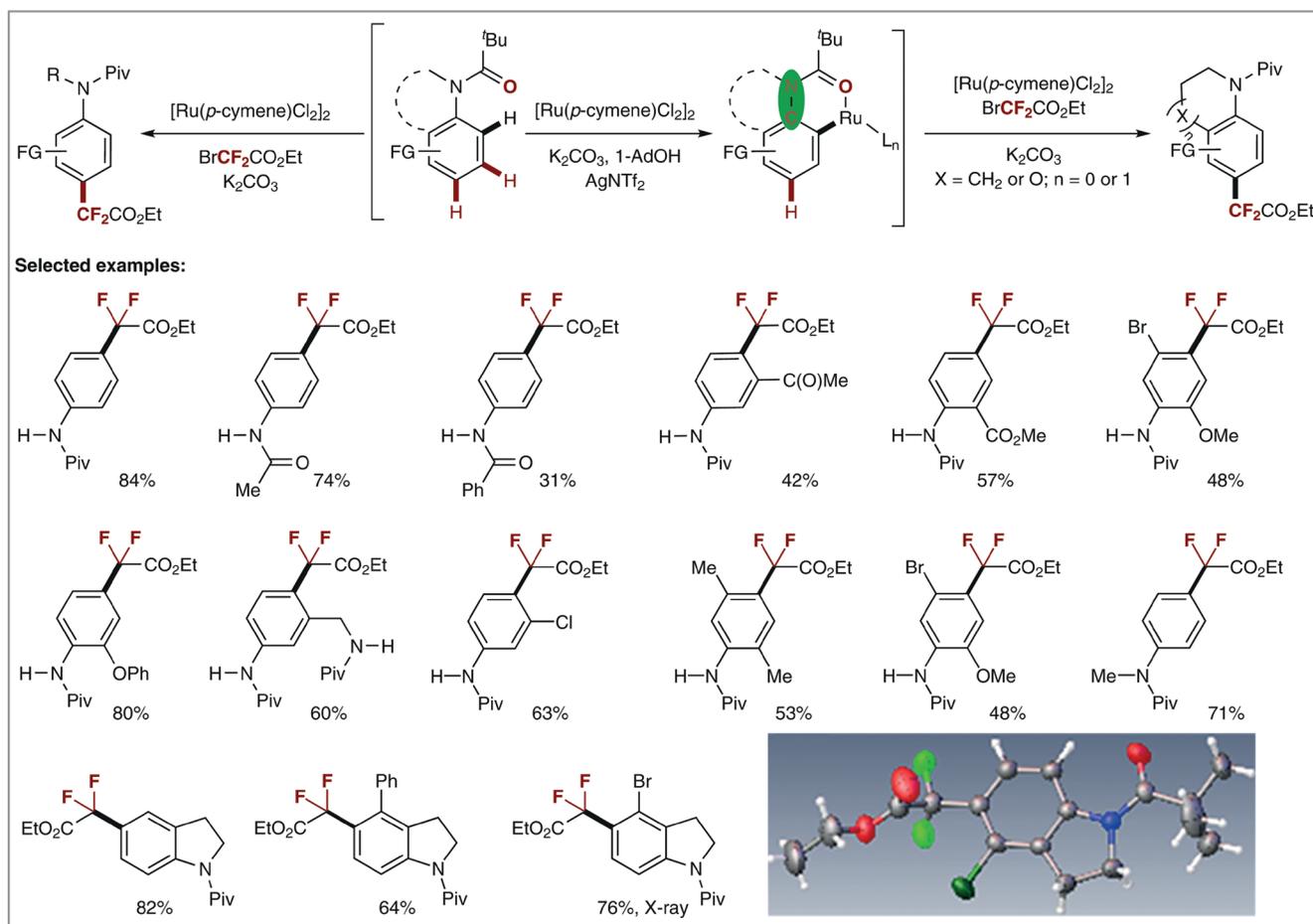
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# Ruthenium(II)-Enabled *para*-Selective C–H Difluoromethylation of Anilides and their Derivatives

*Nat. Commun.* **2018**, *9*, 1189

Highly regioselective functionalization of a C–H bond to construct complex synthetic structural units is an important and attractive process in synthetic chemistry. Especially, the highly site-selective introduction of fluorine atom(s) into aromatic rings is of particular value, because it can cause significant changes in the chemical and physical properties of biologically active compounds. However, effective strategies to achieve selective *para*-C–H functionalization of aniline derivatives are still limited in comparison with *ortho*-chelation cyclometalation processes, due to the large distance between the C–H bond and the transition-metal center. Until now, *para*-selective C–H functionalizations have been achieved by

exploiting the inherent electronic properties of substrates, sterically hindered arenes or compounds with a directing group. However, these protocols are usually limited in terms of substrate scope and selectivity ratio. Recently, the research group of Professor Yingsheng Zhao at the Key Laboratory of Organic Synthesis of Jiangsu Province College of Chemistry, Chemical Engineering, and Materials Science, Soochow University (P. R. of China) developed a general approach for accomplishing the *para*-selective C–H difluoromethylation of anilides, indolines, and quinolines by employing a ruthenium catalyst (Scheme 1).

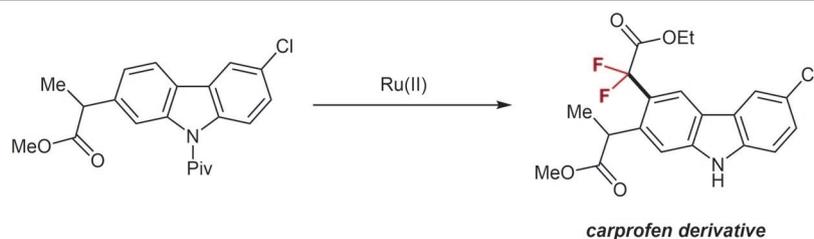


**Scheme 1** Ruthenium-enabled *para*-selective difluoromethylation

“We have focused on highly site-selective transition-metal-catalyzed C–H functionalization reactions since we set up our group in 2013,” explained Professor Zhao. He continued: “Although transition-metal-catalyzed C–H activation reactions are one of the most powerful and efficient strategies in directly installing a functional group into an organic compound, the challenge of installing fluorine functional groups, such as the highly site-selective introduction of a CF<sub>2</sub> group on aromatic rings, still remains unsolved. In this work, our major contribution to this area is the discovery that ruthenium can selectively promote *para*-selective C–H difluoromethylation

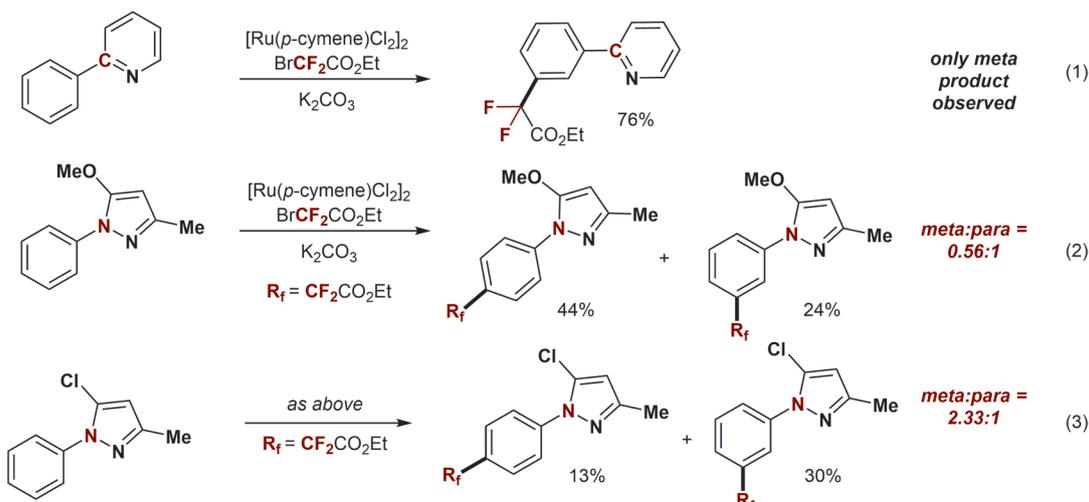
of anilides and their derivatives.” The new method developed by Professor Zhao provides a direct and efficient approach to the synthesis of *para*-difluoromethylated anilides with broad substrate scope and good functional group tolerance.

“The difluoromethyl group (CF<sub>2</sub>) is well known for improving the metabolic stability of biologically active molecules and for being a bioisosteric replacement of oxygen atoms,” said Professor Zhao, who added: “One of the most important applications of C–H functionalization is that it can be used to directly functionalize known drugs, which may lead to the discovery of new drugs. For example, a difluoromethyl-

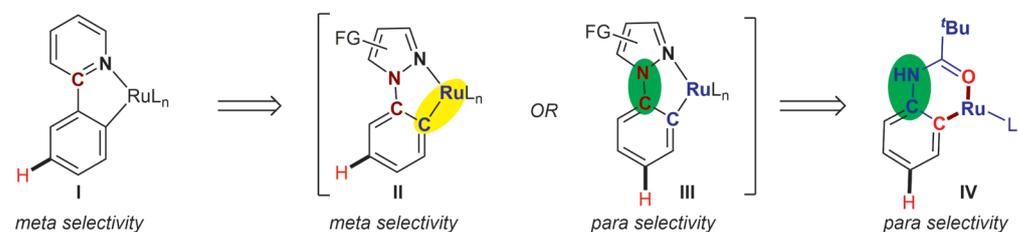


**Scheme 2** Synthesis of carprofen derivative

**a) Electronic effect on site selectivity**



**b) Electronic effect enabled site selectivity**



**Scheme 3** Preliminary mechanism studies

ated derivative of carprofen, which is a non-steroidal anti-inflammatory drug, can be easily prepared with this new method (Scheme 2)".

Professor Zhao also emphasized: "Although the exact mechanism of the ruthenium(II)-enabled *para*-selective C–H difluoromethylation of anilides and their derivatives is still uncertain, based on initial experiments (Scheme 3) we can speculate that an aryl-ruthenium species generated through directed *ortho*-metalation undergoes the reaction with radicals or electrophiles at the position *para* to the N–C center to give net *para*-functionalized products. The probable rationale for this N–C-enabled *para*-selective difluoromethylation is that the weakly coordinating nitrogen center reduces the *para*-directing ability of the Ru–C bonds. This in turn leads to a prevalence of the *para*-directing effect of anilides, indolines, and tetrahydroquinolines towards electrophiles, overriding the *para*-inducing effect of the Ru–C bonds."

Professor Zhao concluded: "An efficient approach to the synthesis of difluoromethylated anilides and its derivatives has been disclosed via a highly *para*-selective ruthenium(II)-catalyzed C–H difluoromethylation reaction. In the future, we are looking into the development of a general highly site-selective C–H activation reaction of aromatic rings. In particular, we are aiming to find a new C–H activation method which could directly introduce a fluorinated group into organic molecules, especially in pharmacologically active compounds. In the long-term, we hope our work will deliver outstanding contributions to the development of new drugs."

*Mattes Fank*

## About the authors



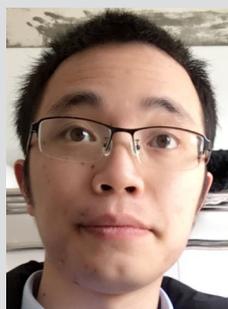
Prof. Y. Zhao

**Yingsheng Zhao** received his B.Sc. degree from Southwest University (P. R. of China) in 2003 and his Ph.D. degree under the supervision of Professor Aiwen Lei at Wuhan University (P. R. of China) in 2008. He then worked as a postdoctoral fellow in the laboratory of Professor Noyori and Professor Saito from October 2008 to September 2010 at Nagoya University (Japan). From 2010 to 2012, he worked with Professor Chen at Penn State University (USA) as a postdoctoral fellow. In November 2012, he started his independent career as an associate professor at the College of Chemistry, Chemical Engineering and Materials Science of Soochow University (P. R. of China). His research interests lie in developing highly site-selective C–H functionalization reactions.



C. Chen

**Changpeng Chen** received his B.Sc. in 2013 from Qingdao Agricultural University (P. R. of China). He then joined Professor Yingsheng Zhao's group and received his Master's Degree from Soochow University (P. R. of China) in 2016. After that, he continued working in Professor Xiaoming Zeng's group as a Ph.D. candidate at Xi'an Jiaotong University (P. R. of China). His research interests focus on Cr-catalyzed regioselective cross-coupling reactions, hydrogenations and development of novel cyclic monoamine carbenes.



C. Yuan

**Chunchen Yuan** received his B.Sc. in 2015 from Wenzheng College of Soochow University (P. R. of China). He then joined Professor Yingsheng Zhao's group at Soochow University in 2015. After that, he continued working in Professor Zhao's and Professor Xiaoguang Bao's group as a Ph.D. student at Soochow University in 2017. His research interests focus on selective functionalizations of arene C–H bonds.

## Young Career Focus: Dr. Sunkyu Han (Korea Advanced Institute of Science and Technology, South Korea)

**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. Sunkyu Han (KAIST, South Korea).

### Biographical Sketch



Dr. S. Han

**Sunkyu Han** obtained his BS degree at KAIST (South Korea) in 2006 and his Ph.D. at MIT (USA) in 2012 under the supervision of Professor Mo Movassaghi, working on the total synthesis of agelastatin and trigonolimine alkaloids. He then joined the research group of Professor Scott J. Miller at Yale University (USA), where he worked on peptide-catalyzed site-selective natural products functionalization as a postdoctoral associate. Sunkyu started his independent research career as an Assistant Professor at KAIST (South Korea) in 2014. Professor Han's laboratory is interested in total synthesis of complex natural products and natural-product-inspired development of synthetic methods. Among honors and support for his work, Sunkyu has received an Asian Core Program (ACP) Lectureship Award (2016), a POSCO TJ Park Science Fellowship (2017–2018), the Thieme Chemistry Journals Award (2018), and an EWon Assistant Professorship at KAIST (2018–2021).

### INTERVIEW

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

**Dr. S. Han** My research team is interested in the total synthesis of complex secondary metabolites and natural-product-inspired development of new synthetic methods. Current projects in my research group include the syntheses of spirocyclic PKS-NRPS-based fungal metabolites, high-order securiniga alkaloids, iboga alkaloids, piperazine alkaloids, drimanes, and epoxyquinoid natural products.

**SYNFORM** *When did you get interested in synthesis?*

**Dr. S. Han** My interest in synthesis dates back to my sophomore year at KAIST. I had conducted undergraduate research on protein crystallography under the supervision of Professor Jie-oh Lee. I became fascinated with the way microorganisms' biosynthetic machineries produce various proteins with amazing structures and functions. Subsequently, my desire to work on synthesizing molecules without the assistance of microorganisms grew, and I joined the research group of Professor Sukbok Chang as an undergraduate researcher. With the Chang group, I greatly enjoyed the process of designing reaction conditions for new molecules we envisioned, and I decided to become a synthetic organic chemist.

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

**Dr. S. Han** The rapid pace at which this world is changing makes this simple question non-trivial. I'd like to share my personal perspective on natural product total synthesis. There are three key concepts that I think researchers working on total synthesis should be reminded of: (1) Strategy, (2) New Reactivity, and (3) Extraordinary Functions.

The design of a novel synthetic strategy for a complex molecule is an intellectual luxury that only total synthesis can provide. We should put consistent, focused efforts into further streamlining the synthetic route, assuring that it is fully optimized. We should seek to form multiple desired bonds in a single transformation. And we should pursue synthetic strategies that involve drastic molecular backbone rearrangements because these often turn out to be very cool!

A complex natural product target should be regarded as a platform for the discovery of novel reactivities. We need to search for aggressive bond disconnections that require the development of unprecedented synthetic methods. And we certainly should not shy away from writing a methodology paper in which one entry happens to be a complex natural product or its key precursor.

Finally, synthetic organic chemistry must pursue a nice balance between the architectural beauty and the function of the natural product during the target selection process. When we discover a target with promising biological activities, we should devise a practical synthetic solution that can produce the natural product in sufficient quantity for further functional studies.

**SYNFORM** Your research group is active in the area of total synthesis and new synthetic methodology. Could you tell us more about your research and its aims?

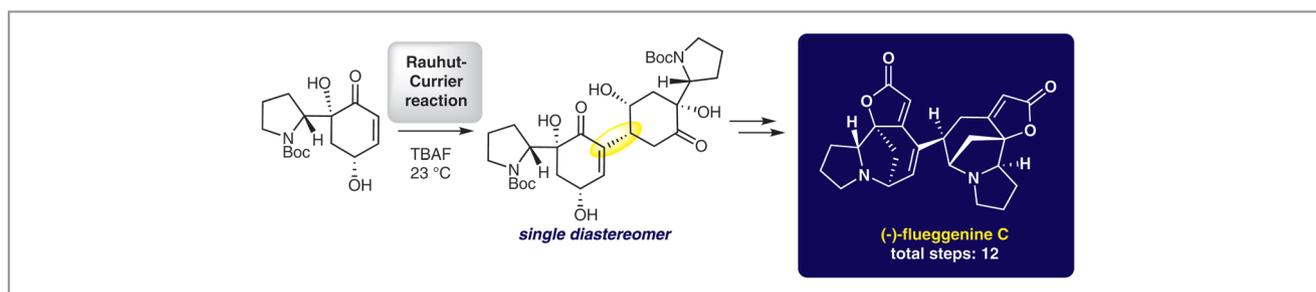
**Dr. S. Han** My research group focuses on natural product total synthesis. Biosynthetic studies or biogenetic hypotheses about the natural product guide us during both target selection and the retrosynthetic analysis process. Organisms utilize enzymes for incredible bond formations and rapid assembly of molecular complexity. We aim to achieve what Nature does by devising novel synthetic strategies and discovering new reactivities. For example, one group of targets that we are interested in is the dimeric natural product family. While the design of efficient synthetic strategies for complex natural

products is intellectually daunting, identification of the bond that connects the two monomers in dimeric natural products is easy. This ease of identification, however, does not guarantee their formation by known chemical transformations. It is for this reason that dimeric natural products provide an excellent platform for the discovery of new reactivities and have become one of the focusses for our group.

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

**Dr. S. Han** As I mentioned, our group's interest spans a broad spectrum of natural products. We have recently obtained interesting new synthetic results that I must wait to discuss until after their publication. But among published results, I am very proud of our recent paper that disclosed the first total synthesis of flueggeine C (*J. Am. Chem. Soc.* **2017**, *139*, 6302–6305, Scheme 1). In this report, we provided a fundamental solution to the long-standing problem of low reactivity and selectivity of the venerable Rauhut–Currier (RC) reaction. We discovered that an  $\alpha,\gamma$ -dihydroxy- $\alpha,\beta$ -unsaturated ketone derivative undergoes a highly efficient intermolecular RC reaction upon treatment with TBAF with complete diastereoselectivity at ambient temperature (Scheme 1). This was the first application of an intermolecular RC reaction to the total synthesis of a complex natural product. Our report also featured the first synthetic access to dimeric securinega natural product in which two monomeric units are connected by a presumed biocatalyzed RC reaction.

*Matthew Fenske*



**Scheme 1** Total synthesis of (-)-flueggeine C

## Coming soon

— Literature Coverage

### Enantioselective, Lewis Base-Catalyzed Sulfenocyclization of Polyenes

— Literature Coverage

### Superbase-Catalyzed anti-Markovnikov Alcohol Addition Reactions to Aryl Alkenes

— Literature Coverage

### Total Synthesis of Tambromycin by Combining Chemo-catalytic and Biocatalytic C–H Functionalization

## Further highlights

**Synthesis** **Review: Conjugate Alkynylation of Electrophilic Double Bonds. From Regioselectivity to Eenantioselectivity**  
(by J. R. Pedro and co-workers)

**Synlett** **Account: Tackling the Challenge of the Total Synthesis of Periploside A**  
(by X. Zhang and B. Yu)

**Synfacts** **Synfact of the Month in category “Synthesis of Heterocycles”: Dihydrobenzofuran Synthesis by Palladium/Norbornene Cooperative Catalysis**

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