

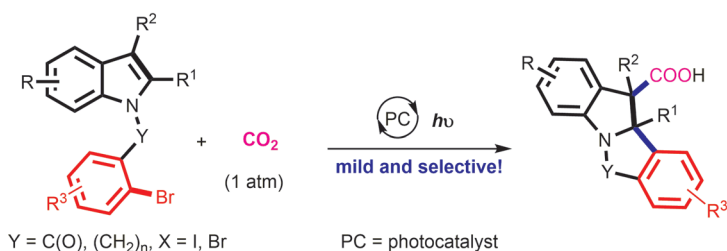
# Synform

People, Trends and Views in Chemical Synthesis

2020/11

## Reductive Dearomative Arylcarboxylation of Indoles with CO<sub>2</sub> via Visible-Light Photoredox Catalysis

Highlighted article by W.-J. Zhou, Z.-H. Wang, L.-L. Liao, Y.-X. Jiang, K.-G. Cao, T. Ju, Y. Li, G.-M. Cao, D.-G. Yu



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Thieme

## Dear Readers,

During the last 6 months, working from home has become the norm for many, including myself. I have to confess that I quite like it, it is very handy to stay at home all day in a comfortable tracksuit – or even in a pyjamas, for those who wear them – without wasting hours commuting to the office. No nerve-wracking drive in the traffic. No need to look for parking. All the comforts of your home available 24/7, without the need of venturing outside. Less risk of getting a cold or worse... Not to mention the economic side of things; one can save quite a lot of money working from home. It is amazing how efficient videoconferencing has become, at least if you have a good internet connection. It is not perfect, I agree; you cannot do all the things you would do in a physical meeting or lecture, but still there are at least as many pros as cons. But there is one aspect that is really worrying me: the lack of interaction with the real world. In the short term, it did not bother me too much, as I am not a crowd-loving extrovert and I am not constantly looking for physical contact either. Quite the opposite, to be frank. In the medium term, which is pretty much now, I am starting to miss the coffee with friends and colleagues in the morning, and after lunch. The occasional chats and the random meetings in the corridor. Or on the train, why not. But it is the long term that is really starting to worry me: Will I become a sort of bear in a cave? A post-modern Neanderthal man, perhaps? Will I lose the capacity of socially interacting with humans in flesh-and-bone? At the end of the day, life is so predictable and – yes – boring, when you spend the whole day staring at your laptop's screen, rather than going out and living your life in full, in the real world, outside the virtual bubble. So, yes, I really enjoyed working from home, I still sort of do, but after 6 months of hermit lifestyle I am now ready to go back to my old way of living, and

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I am actually pretty desperate to do so!! Almost as desperate as I am to read this new issue of SYNFORM, which starts with the ground-breaking reductive dearomative arylcarboxylation of indoles with CO<sub>2</sub> – using visible photoredox catalysis – reported by D.-G. Yu (P. R. China). A duo of papers published in *Nat. Chem.* follow: the pyrotechnic total synthesis of brevianamide A by A. L. Lawrence (UK) and the ingenious synthesis of  $\alpha$ -aryl-ketones and nitriles via *para*-C–H functionalization/decarboxylative coupling discovered by P. H.-Y. Cheong and R. A. Altman (USA). Finally, the intriguing boron chemistry developed by C. Martin (USA) is covered in a Young Career Focus interview.

Enjoy your reading!



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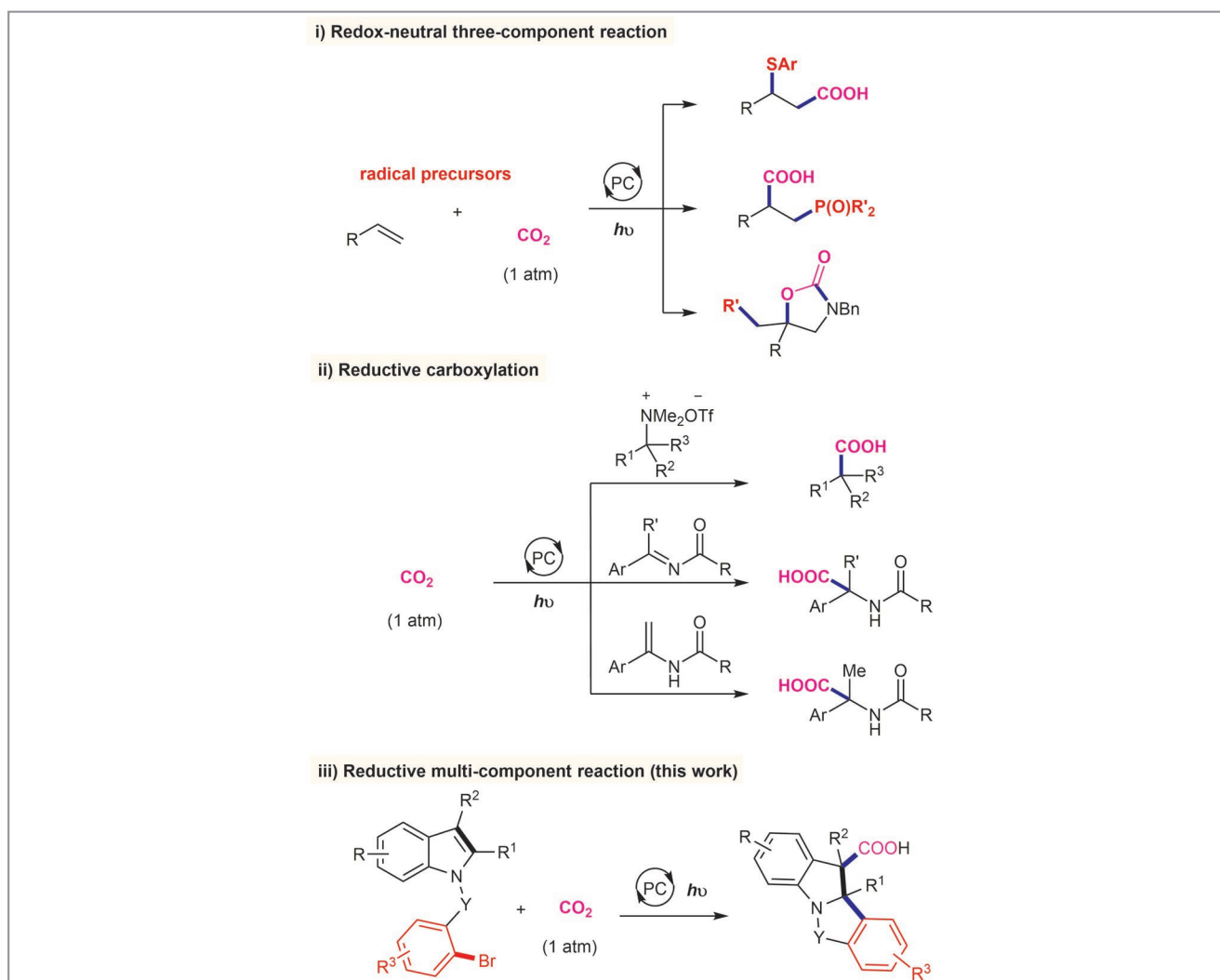
If you have any questions or wish to send feedback, please write to Matteo Zanda at: [synform@outlook.com](mailto:synform@outlook.com)

# Reductive Dearomative Arylcarboxylation of Indoles with CO<sub>2</sub> via Visible-Light Photoredox Catalysis

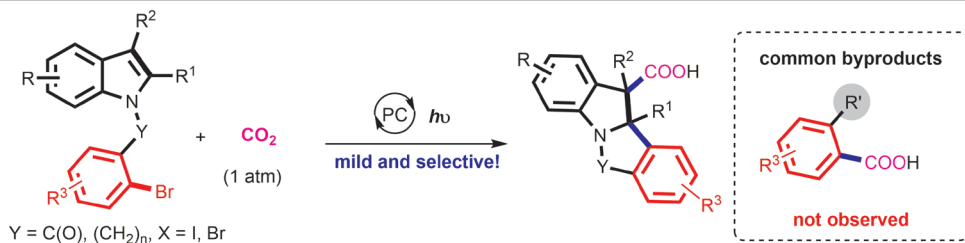
*Nat. Commun.* **2020**, DOI: 10.1038/s41467-020-17085-9

The catalytic reductive coupling of two electrophiles with one unsaturated bond represents an economic and efficient way to construct complex molecular skeletons, and is commonly achieved by transition-metal-catalyzed two-electron-transfer reactions. However, the latter almost invariably suffer from chemoselectivity issues, which are caused by side reactions of the in situ generated organometallic reagents, including  $\beta$ -H

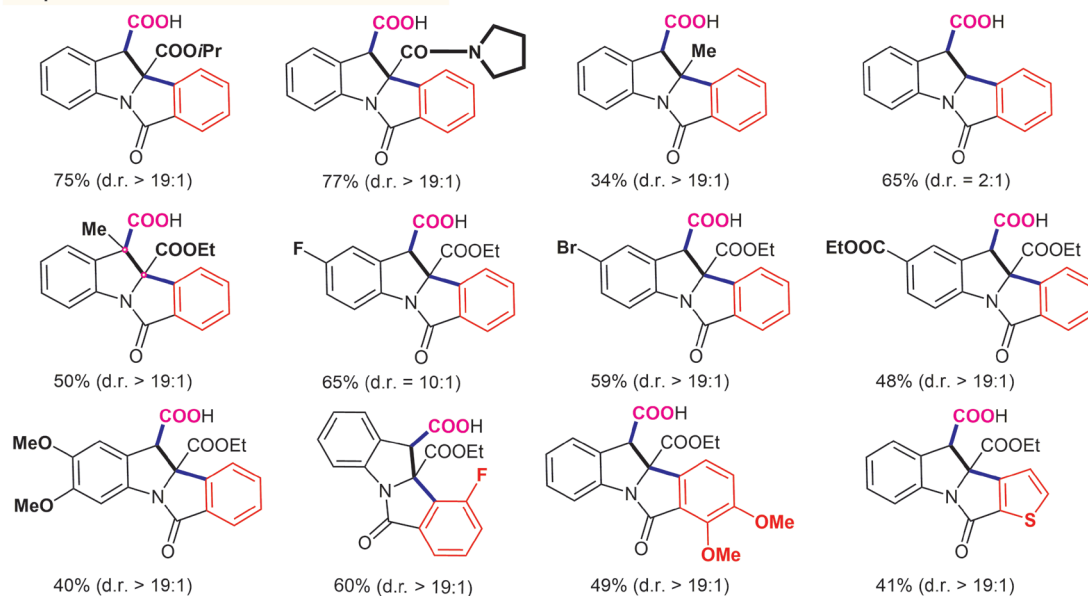
elimination and ipso direct coupling. Inspired by the merits of visible-light photoredox catalysis, the group of Professor Da-Gang Yu, from Sichuan University (Chengdu, P. R. China), has recently reported a novel strategy relying on visible-light photoredox-catalyzed successive single electron transfer (SSET), thus accomplishing the first example of dearomative arylcarboxylation of indoles with CO<sub>2</sub>.



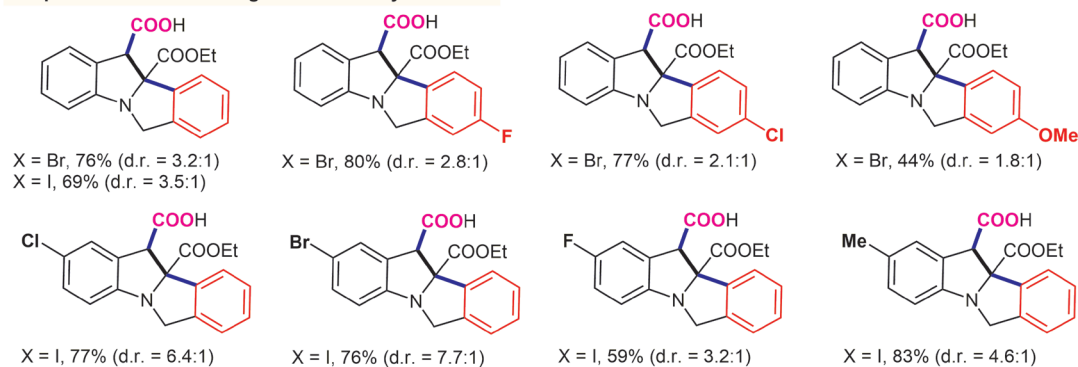
**Scheme 1** Visible-light-driven CO<sub>2</sub> utilization in Yu's group; PC = photocatalyst.



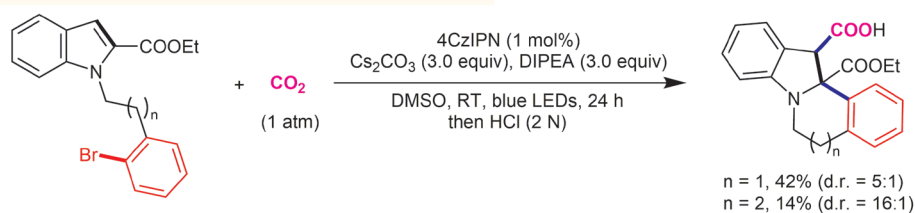
## Scope of substrates with substituents on indoles



## Scope of substrates bearing unactivated aryl bromides



## Synthesis of six- or seven-membered-ring-containing product



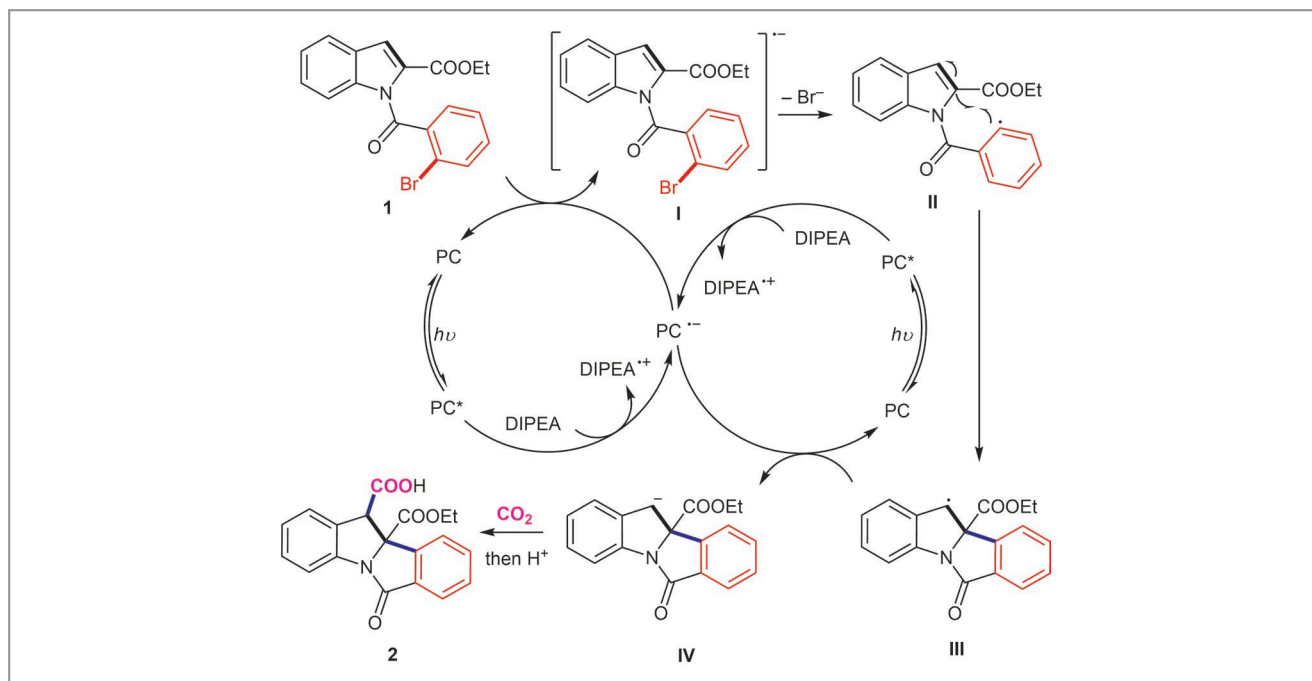
Scheme 2 Selected examples of the reductive dearomative arylcarboxylation

The focus of Professor Yu's group has been on searching for new strategies and useful chemistry in the field of CO<sub>2</sub> utilization and visible-light photoredox catalysis (Scheme 1). "By studying the intersection of these two areas, we wish to mimic nature to realize efficient visible-light-driven CO<sub>2</sub> utilization," explained Professor Yu. He continued: "Along with other great chemists in this field (for the full list of references see the original paper), in the last few years we designed and developed redox-neutral and regioselective three-component thiocarboxylation (*Angew. Chem. Int. Ed.* **2017**, *56*, 15416–15420), phosphonocarboxylation (*Nat. Commun.* **2019**, DOI: 10.1038/s41467-019-11528-8) and oxy-alkylation (*Org. Lett.* **2018**, *20*, 190–193; *Org. Lett.* **2018**, *20*, 3049–3052) of alkenes." Moreover, the group also discovered the reductive carboxylation with CO<sub>2</sub> of enamides/imines (*Angew. Chem. Int. Ed.* **2018**, *57*, 13897–13901) and C–N bonds in tetraalkyl ammonium salts (*J. Am. Chem. Soc.* **2018**, *140*, 17338–17342), in which the SSET strategy was successfully developed. Based on these two strands of work, Professor Yu's group further challenged themselves with the task of developing the multi-component reductive carboxylation with unsaturated bonds, especially those in aromatic rings (*ACS Catal.* **2017**, *7*, 8324–8330).

In their latest account, Professor Yu and his group have developed a novel reductive dearomative arylcarboxylation of indoles with CO<sub>2</sub> via visible-light photoredox catalysis, realiz-

ing the synthesis of valuable but difficult-to-access 3D cyclic skeletons of indoline-3-carboxylic acids. "This SSET process avoids possible side reactions via transition-metal catalysis, including ipso carboxylation of aryl halides and  $\beta$ -hydride elimination," explained Professor Yu. He continued: "These reactions feature mild reaction conditions (room temperature, 1 atm CO<sub>2</sub>), good functional group tolerance, high chemoselectivity and low loading of photocatalyst. Besides the activated aryl halides bearing electron-withdrawing groups, unactivated aryl halides, which are more electron-rich and thus more challenging to engage in single-electron reduction via photocatalysis, are also reactive in these conditions (Scheme 2). Furthermore, the corresponding products bearing six- and seven-membered rings can also be obtained. With the benzylic anions as the possible intermediates (Scheme 3), D<sub>2</sub>O and aldehyde could be used as alternative electrophiles – besides CO<sub>2</sub> – in such a process."

The authors believe that this SSET strategy might provide a new dimension for CO<sub>2</sub> utilization, visible-light photoredox catalysis and multi-component reductive couplings. "Other designs with different kinds of electrophiles and unsaturated bonds would be successful by using this strategy," noted Professor Yu, who concluded: "We would like to acknowledge that an elegant intermolecular arylcarboxylation of alkenes with CO<sub>2</sub> (*J. Am. Chem. Soc.* **2020**, *142*, 8122–8129)



**Scheme 3** Possible mechanism of the reductive dearomative arylcarboxylation. PC = photocatalyst, i.e. 3,5-tetrakis(carbazol-9-yl)-4,6-dicyanobenzene (4CzIPN).

was achieved independently by Professor Gang Li from Fujian Institute of Research on the Structure of Matter (Fuzhou, P. R. China) at almost the same time.”

*Mattias Fendler*

## About the authors



Prof. W.-J. Zhou

**Wen-Jun Zhou** was born in Sichuan province, P. R. of China, in 1984. He obtained his bachelor's degree in 2006 at Northwest Normal University (P. R. of China) and Ph.D. under the guidance of Prof. Jin-Xian Wang in the same university, in 2011. He then worked independently at Neijiang Normal University (P. R. of China). Since 2015, Dr. Zhou has been carrying out his postdoctoral research in the group of Prof. Dr. Da-Gang Yu, Sichuan University (P. R. of China). His research focuses mainly on synthetic organometallic chemistry, photoredox chemistry and radical chemistry.



Z.-H. Wang

**Zhe-Hao Wang** received his M.S. degree from Lanzhou University (P. R. of China) in 2018. He then moved to Sichuan University (P. R. of China) for his doctoral studies where he worked on the development of CO<sub>2</sub> transformation via visible-light photoredox catalysis under the supervision of Prof. Da-Gang Yu and Prof. Yiwen Li.



L.-L. Liao

**Li-Li Liao** obtained her B.S. degree in 2016 at Sichuan University (P. R. of China) under the supervision of Prof. Da-Gang Yu. She is currently a PhD student in the same research group. Her research interests include photoredox catalysis and CO<sub>2</sub> utilization.



Y.-X. Jiang

**Yuan-Xu Jiang** received his B.S. degree in applied chemistry from Huaqiao University (P. R. of China) in 2018. He is currently pursuing his Ph.D. at Sichuan University (P. R. of China) under the guidance of Prof. Da-Gang Yu. His research projects focus on the activation and utilization of CO<sub>2</sub>.



K.-G. Cao

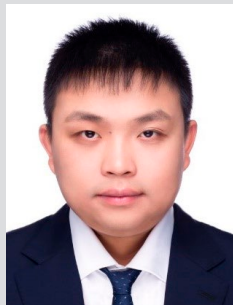
**Ke-Gong Cao** received his B.A. from College of Chemistry, Sichuan University (P. R. of China) in 2020. In the same year, he will continue his research in the group of Prof. Da-Gang Yu as a Master's student in Sichuan University. His research interests focus on CO<sub>2</sub> utilization via photoredox catalysis.



T. Ju

**Tao Ju** received his B.A. degree in 2012 from Jinling College of Nanjing University (P. R. of China) and his M.A. degree in 2015 from Yangzhou University (P. R. of China). In the same year, he joined the research group of Prof. Da-Gang Yu and in 2019 received his Ph.D. at Sichuan University (P. R. of China). His research interests focus on visible-light-driven carboxylation with CO<sub>2</sub>.

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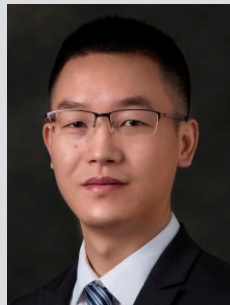
K. Prof. Y. Li

**Yiwen Li** received his B.S. in chemistry from University of Science and Technology of China (P. R. of China, 2008) and Ph.D. in polymer science from the University of Akron (USA, 2013). After two years' postdoctoral training at University of California, San Diego (USA), Yiwen began his independent career at Sichuan University (P. R. of China) in 2016, where he is currently a professor at College of Polymer Science and Engineering (P. R. of China) and State Key Laboratory of Polymer Materials Engineering (P. R. of China). His current research interests focus on the bio-inspired polymers including synthetic melanin and polyphenolic materials. He has published 100+ peer-reviewed articles, and served as the associate editor for *Materials Express* (ASP) and editorial board member for *Giant* (Elsevier) and *Molecules* (MDPI).



G.-M. Cao

**Guang-Mei Cao** received her B.Sc. in chemistry at Sichuan University (P. R. of China) in 2017. She is currently a PhD student in Prof. Dr. Da-Gang Yu's group at Sichuan University. Her research interests focus on chemical utilization of CO<sub>2</sub>.



Prof. D.-G. Yu

**Da-Gang Yu** was born in Jiangxi province, P. R. of China, in 1986. He received his Ph.D. with Prof. Dr Zhang-Jie Shi from Peking University (P. R. of China) in 2012. He carried out postdoctoral research under a Humboldt fellowship in the group of Prof. Dr. Frank Glorius, Muenster University (Germany). Since 2015, he has been working independently at Sichuan University (P. R. of China) with support from "The Thousand Young Talents Plan" and National Natural Science Foundation of China–Outstanding Young Scholars. His research interests focus mainly on novel transformations of CO<sub>2</sub>, radical chemistry and novel transition-metal catalysis. He has received many honors, including "Organic Chemistry Frontiers" Emerging Investigators in 2016, Thieme Chemistry Journals Award in 2017, Chinese Chemical Society Youth Award in 2018, "Science China Chemistry" Emerging Investigators and "Chemical Communications" Emerging Investigators in 2020.

## Total Synthesis of Brevianamide A

*Nat. Chem.* **2020**, *12*, 615–619

“Brevianamide A, the prototypical member of the remarkable bicyclo[2.2.2]diazaoctane family of alkaloids, was isolated by Birch and Wright in 1969 and has eluded chemical synthesis ever since,” said Professor Andrew L. Lawrence, University of Edinburgh (UK), introducing his group’s recent major achievement: the first chemical synthesis of brevianamide A, using a biomimetic strategy. “All previous attempts to synthesise brevianamide A have only provided access to brevianamide B, a minor coisolated diastereomer (isolated d.r. of A:B in *Penicillium brevicompactum* is  $\approx 90:10$ ).”

Professor Lawrence’s group have long been interested in developing biomimetic synthetic strategies towards complex natural products. “This bio-inspired approach facilitates the design of short, efficient syntheses that provide opportunities to test the chemical feasibility of proposed biosynthetic pathways,” added Professor Lawrence, who went on to explain: “Brevianamide A could not be accessed previously because all other approaches featured a common ‘end-game’ strategy of indoleoxidation and semipinacol rearrangement (Scheme 1a). Unfortunately, late-stage oxidation of the polycyclic indole intermediate exhibits exclusive selectivity for the convex face of the indole, which following stereospecific semi-pinacol rearrangement leads to brevianamide B. Thus, it was clear that a fundamentally different approach was required if we wanted to access brevianamide A.”

Dr. Robert Godfrey, a PhD student in the Lawrence group at the time, had prepared the natural product dehydro-deoxy-brevianamide E on large scale during attempts to access some related natural products. “After studying the reactivity of this versatile intermediate in great detail, we began to suspect that its oxidation product, ‘dehydro-brevianamide E’ might be a key (bio)synthetic precursor to brevianamide A,” explained Dr. Godfrey (Scheme 1b).

The authors were delighted to observe that simply treating ‘dehydro-brevianamide E’ with aqueous base gave direct conversion into brevianamides A and B (Scheme 1c), presumably via their proposed biomimetic domino retro-5-*exo-trig*/semi-pinacol/tautomerization/Diels–Alder reaction sequence (Scheme 1b). Remarkably, the diastereomeric ratio observed from the reaction in the laboratory (d.r. 93:7) matched closely with the ratio obtained when these alkaloids are isolated from the fungus. EPSRC-funded Postdoctoral Research Associate, Dr. Nicholas Green explained: “Although *Diels–Alderase* enzymes are known to be involved in the biosynthesis of related

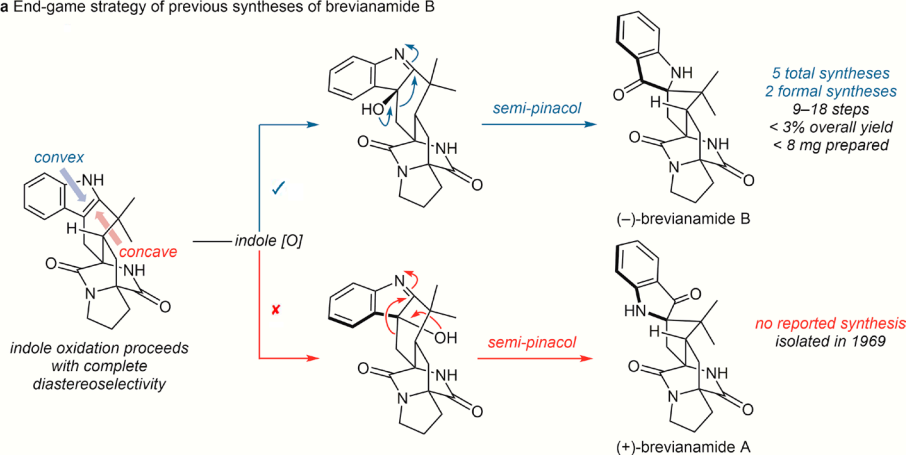
bicyclo[2.2.2]diazaoctane alkaloids, our results suggest that a *Diels–Alderase* enzyme is not required to explain the stereochemical outcome in the biosynthesis of the brevianamides.” Dr. Robert Godfrey added: “It was particularly rewarding to see our proposal of a *Diels–Alderase*-free biosynthesis was later supported by a beautifully detailed biosynthetic study reported by Williams, Sherman, Li and co-workers (*Nat. Catal.* **2020**, *3*, 497–506).”

When asked about the future of the field, Professor Lawrence responded, “There has been a tremendous amount of progress on studying the structure, synthesis, origins, and function of these amazing alkaloids, most notably by the group of Professor Robert M. Williams at Colorado State University. There are, however, many important questions and synthetic challenges that remain to be answered, which should continue to attract new researchers to the field. I wrote to Professor Williams last year to inform him of our work. I was a little apprehensive about reaching out; we chemists can sometimes be rather territorial. I needn’t have worried, in his response he very kindly and warmly wrote “*Congratulations on a really outstanding and brilliant synthesis of Brevianamides A and B! This is very exciting*”. Without his great body of work on these fascinating natural products our total synthesis would have never happened.”

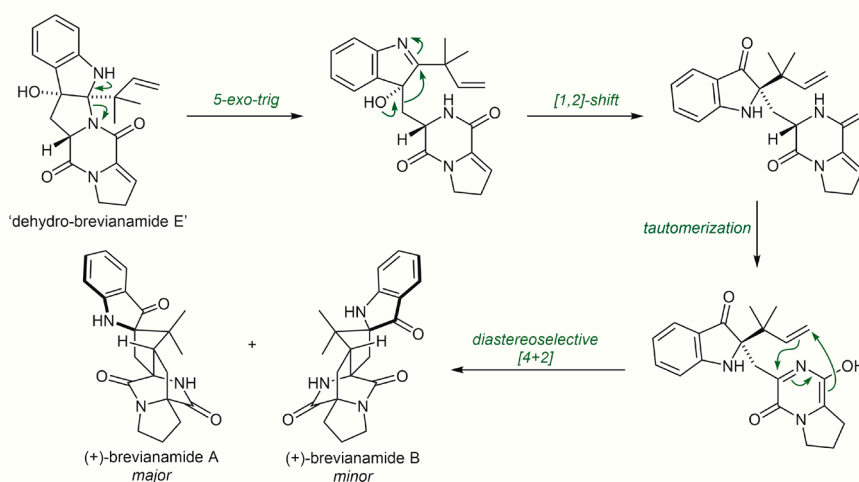
Professor Lawrence concluded: “We were shocked and very sad to hear of Professor Williams’ death on 13<sup>th</sup> May 2020, and we dedicate this work to his memory.”

*Andrew Lawrence*

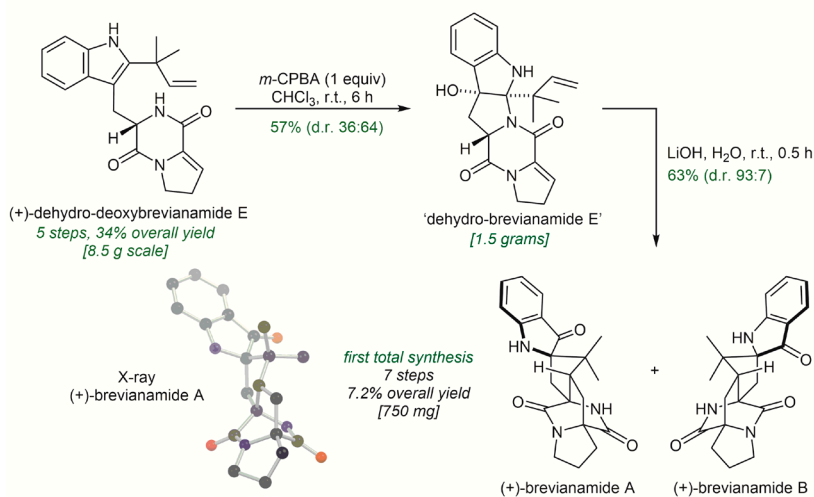
## a End-game strategy of previous syntheses of brevianamide B



## b Biosynthetic speculation (building on the earlier proposals of Birch, Sammes and Williams)



## c Biomimetic conversion of dehydro-deoxybrevianamide E into brevianamide A and B



Scheme 1

## About the authors



Dr. R. C. Godfrey

**Robert C. Godfrey** was born in Sweden and received his BSc degree from University of Cambridge (UK) in 2014. He completed his PhD in 2019 under the supervision of Professor Andrew L. Lawrence at the University of Edinburgh (UK) and rejoined the group as a Postdoctoral Research Associate in the same year. His research is focused on the biomimetic synthesis of the brevianamides and related prenylated indole alkaloids.



Dr. N. J. Green

**Nicholas J. Green** completed his PhD studies as a Rod Rickards Scholar with Professor Michael S. Sherburn at the Australian National University (Australia) before undertaking postdoctoral research with Professor Andrew L. Lawrence at University of Edinburgh (UK), and is now working with Dr. John Sutherland at the MRC Laboratory of Molecular Biology in Cambridge (UK). Nick's background is in organic synthesis spanning transition-metal and organic catalysis, total synthesis, and biomimetic chemistry, and he is now investigating the origins of life.



Professor A. L. Lawrence

**Andrew L. Lawrence** completed his undergraduate studies at the University of Oxford (UK) in 2006 (MChem, Hons 1st Class) and subsequently obtained a DPhil degree in 2010 under the supervision of Professor Sir Jack E. Baldwin FRS and Dr. Robert M. Adlington. He then spent two years (2010–2011) as a Postdoctoral Research Associate with Professor Michael S. Sherburn at the Australian National University (ANU) in Canberra (Australia). In 2012, he began an Australian Research Council DECRA Fellowship at the ANU before moving back to the UK in late 2013 for a Lectureship position at the University of Edinburgh (UK). He was promoted to Senior Lecturer in 2017 and Full Professor in 2020.

# Connecting Remote C–H Bond Functionalization and Decarboxylative Coupling Using Simple Amines

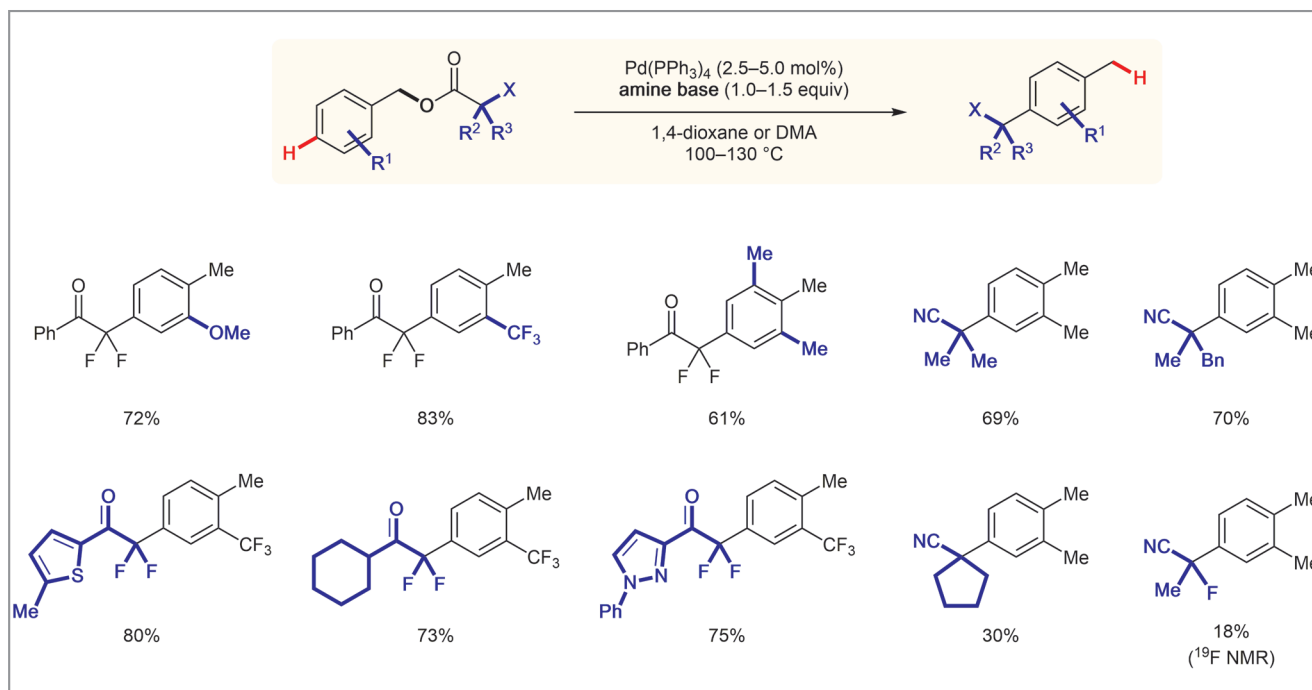
Nat. Chem. 2020, 12, 489–496

Regiocontrolled rearrangements taking place in high yields using experimentally simple conditions are key assets in the organic chemistry toolbox, especially if such processes result in the selective functionalization of unactivated C–H bonds. Recently, the groups of Professor Ryan A. Altman at The University of Kansas (USA) and Professor Paul Ha-Yeon Cheong at Oregon State University (USA) joined forces to investigate a novel methodology for achieving the decarboxylative *para*-functionalization of benzyl ester derivatives promoted by palladium catalysts and simple amine bases.

“This was a fortuitous finding from the get-go,” remarked Professor Altman. He continued: “At the outset of the project we were optimizing a decarboxylative benzylation reaction (Angew. Chem. Int. Ed. 2016, 55, 9080–9083), and one astute PhD student recognized an intriguing and unexpected minor side product that occasionally popped up in reactions. Her for-

titude to first optimize and then characterize the minor side product revealed a *para*-selective functionalized arene, which was produced from a benzyl-substituted substrate. Though such products had been seen in analogous reactions, previous research teams could not control the chemoselectivity for benzylation vs. *para*-selective functionalization. However, we discovered that one could control the chemoselectivity using simple amine bases. Though there were initial concerns that the reaction would only work on fluorinated ketone-derived nucleophiles, later researchers expanded the scope of compatible substrates to include non-fluorinated and nitrile-based nucleophiles (Scheme 1).”

Professor Altman explained that rigorous mechanistic experiments and thorough computational studies by Professor Cheong’s group supported a catalytic cycle involving an intriguing reversible dearomatization/irreversible base-

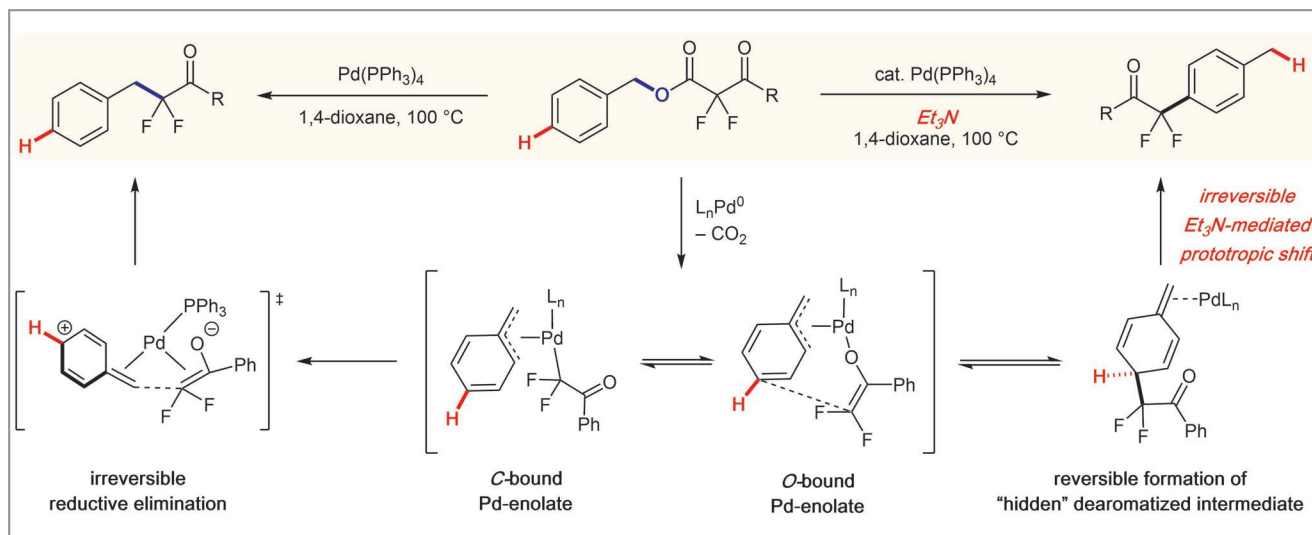


mediated rearomatization sequence that provided the *para*-substituted arene products (Scheme 2). Notably, the group's computational efforts revealed that the reaction proceeded through a "hidden" dearomatized intermediate that likely transiently exists in other catalytic processes and might be exploited in to-be-developed reactions. "This unusual finding will hopefully spark new insight and opportunities to access unique products as yet inaccessible by current means," said Professor Altman. He continued: "We hope to exploit this dearomatization/rearomatization sequence to expand the scope of the reaction to include a broad spectrum of alternate nucleophiles."

Also notably, the project connected two significant reaction paradigms in organic chemistry, namely decarboxylative coupling and C–H functionalization reactions. Professor Altman told us: "Although these two reaction paradigms typically require orthogonal substrates and proceed under complementary reaction conditions [e.g. Pd(0/II) vs. Pd(II/IV) cycles, basic vs. acidic additives, reductive vs. oxidative conditions], in our hands, simple amine bases linked the complementary mechanisms. Notably, this reaction did not require chelation or template assistance and functioned on a diverse array of electron-donating and electron-withdrawing arenes, which contrasts many C–H functionalization reactions of arenes."

"Overall, this was a complete team effort from start to finish with both the Kansas and Oregon State teams completely turning over personnel," said Professor Altman, who concluded: "Thus, the project really transcended two different generations of researchers in each laboratory, and is a testament to the scientific insight, grit, teamwork, and communication from both groups."

*Matthew Fenske*



**Scheme 2** The use of amine bases converted a decarboxylative benzylation reaction into a *para*-selective C–H functionalization. Both reactions proceed through  $\text{L}_n\text{Pd}(\text{benzyl})(\text{enolate})$  complexes that exist as an equilibrium of O- and C-bound enolates. From the C-bound enolate, classical reductive elimination provides the benzylation product, while the O-bound enolate can undergo a reversible sigmatropic reductive elimination to generate a hidden dearomatized intermediate. This intermediate bears an acidic proton that, in the presence of an appropriate weak base, will undergo a 1,5-prototropic shift to deliver the product of *para*-selective functionalization.

## About the authors



Dr. F. de Azambuja

Francisco de Azambuja was born and raised in Brazil. He obtained his Ph.D. in chemistry from the State University of Campinas (Brazil) in 2015 and from there moved to WWU Münster (Germany) before joining Professor Altman's group at The University of Kansas (KU, USA) for an intense postdoctoral period, mostly dedicated to metal-catalyzed fluoroalkylation reactions. In 2018, he moved from KU Lawrence to KU Leuven (Belgium) to indulge his interest in catalytic materials. Since then, he has been developing novel reactions and metal-oxide based catalysts as alternatives to sensitive conventional transition-metal catalysts.



Dr. M. S. Yang

Ming-Hsiu Yang joined Professor Altman's group as a graduate student (2011–2017), focusing on the development of Pd-catalyzed fluoroalkylation reactions and metal-free transformations for accessing fluoroalkenes as peptidomimetics. She is currently a postdoctoral research associate in Professor Boger's lab at The Scripps Research Institute (USA). Her current research is focused on developing TLR agonists as immune modulators and their bioconjugates with immunogenic peptides.



T. Feoktistova

Taisiia Feoktistova obtained her B.S. (2017) at Whitworth University (USA) before starting her current studies under the supervision of Prof. Paul Ha-Yeon Cheong at Oregon State University (USA). Her current research interests are focused on utilizing DFT to elucidate reaction mechanisms.



Dr. M. Selvaraju

Manikandan Selvaraju received his B.Sc. (2004) and M.Sc. (2006) degrees from Bharathidasan University, Tiruchirappalli (India), and then worked as a Research Associate at GVK Biosciences, Hyderabad (India) from 2006–2009. He continued his education, earning his Ph.D. (2014) from National Chiao-Tung University (Taiwan), where he also worked as a postdoctoral research associate (2014–2017) under the supervision of Professor Chung-Ming Sun. Since 2017, he has worked as a postdoctoral research associate in Professor Altman's group at The University of Kansas (USA). Currently, his research interests include cross-coupling and C–H functionalization reactions.



Dr. A. Brueckner

Alex Brueckner obtained his B.A. in chemistry from Hanover College (USA) in 2015. He then joined the PHYC laboratory at Oregon State University (USA), where he completed his Ph.D. in 2019. In his Ph.D. work, he used cutting-edge computational chemistry techniques to study complex chemical systems. Since graduating, he has been a postdoctoral research fellow at Merck & Co., Inc., Kenilworth, NJ (USA). His current research efforts aim to understand the complex conformational landscape of macrocyclic peptides in the context of drug discovery.



M. Grove

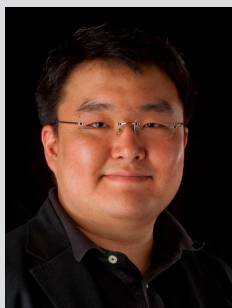
Markas Grove is a PhD candidate in the Cheong group at Oregon State University (OSU, USA). He received his B.S. in biochemistry from the University of Washington (USA) in 2012 and his M.Ed. from the University of Washington – Tacoma (USA) in 2014. After working at a public school from 2013–2016, he joined the Cheong group at OSU and received an M.S. in chemistry in 2019. Currently his research interests include group additivity methods for metal-oxo clusters, the application of metal-oxo clusters as thin-film precursors, and modeling kinetic effects in organic synthesis.

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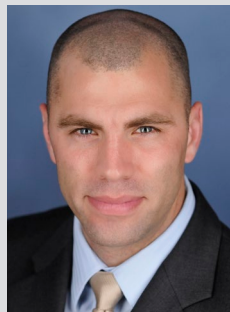
Dr. S. Koley

**Suvajit Koley** is a postdoctoral research associate in Professor Altman's group at The University of Kansas (USA). He received his B.Sc. degree from the University of Calcutta (India) in 2009. After obtaining his M.Sc. (2011) and Ph.D. (2017) degrees in organic chemistry with Prof. Maya Shankar Singh from Banaras Hindu University (India), he joined Prof. Ganesh Pandey's research group as a National Post-doctoral Fellow in the Center of Biomedical Research (India) from 2017–2018. His current research interests include cross-coupling reactions, C–H functionalization reactions, and reactions of fluorinated alkenes.



Prof. P. H. Y. Cheong

**Paul Ha-Yeon Cheong** is the Bert and Emelyn Christensen Associate Professor of Chemistry at the Department of Chemistry, Oregon State University (USA). Paul spent most of his youth in Indonesia and Thailand, before coming to the US for his post-secondary education. He was originally an English major in his undergraduate institution of Bowdoin College (Brunswick, ME, USA), before he switched to chemistry to receive his AB in 2001. He received his Ph.D. in organic chemistry from University of California Los Angeles (USA) in 2007 under the tutelage of Professor K. N. Houk. After a brief stint as postdoc in the same lab, he started his independent career at Oregon State in 2009. His research group's scientific passion is in exploring scientific mysteries by discovering and explaining hypotheses and principles that underlie chemistry and nature. Towards this goal, his group applies state-of-the-art computational chemistry techniques and tools to a wide array of scientific mysteries, ranging from synthetic organic chemistry to inorganic semiconductors.



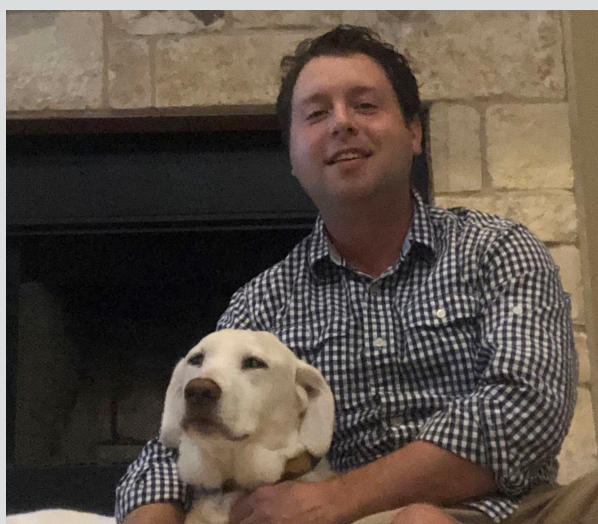
Prof. R. A. Altman

**Ryan A. Altman** received a B.S. Chem. from Creighton University (USA) in 2003 and a PhD in organic chemistry from the Massachusetts Institute of Technology (USA) in 2008, studying as a Pfizer and National Institutes of Health predoctoral fellow in the laboratory of Professor Stephen L. Buchwald. He subsequently trained as an NIH postdoctoral fellow under the guidance of Professor Larry E. Overman at the University of California, Irvine (USA, 2008–2011), after which he joined the Department of Medicinal Chemistry at The University of Kansas (KU, USA) as an Assistant Professor. After his promotion to Associate Professor (2017), his group moved to Purdue University (USA) to join the Department of Medicinal Chemistry and Molecular Pharmacology and the Department of Chemistry (2020). The Altman group works at the interface of synthetic organic and medicinal chemistries, with synthetic emphases in the areas of organometallic and organofluorine transformations and unique chemical reactivities enabled by fluorinated substructures. The group's collaborative medicinal interests span a range of disease states, including pain, anxiety and mood disorders, and aging.

## Young Career Focus: Dr. Caleb Martin (Baylor University, USA)

**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. Caleb Martin (Baylor University, USA).

### Biographical Sketch



Dr. C. Martin

**Caleb Martin** grew up in Waweig, New Brunswick, Canada. He began his studies in chemistry at Mount Allison University (Canada) where he obtained his BSc in 2007 working with Glen Briand and Steve Westcott on indium and palladium chemistry, respectively. He completed his PhD on group 16 cations at Western University (Canada) in 2012 with Paul Raggona. Upon completion of post-doctoral studies on carbene chemistry at UC Riverside and UC San Diego (USA) with Guy Bertrand, he began his independent career at Baylor University in Waco, TX (USA) in the Department of Chemistry and Biochemistry in 2013. His group's research interests are focused on the synthesis, reactivity, and properties of unusual tricoordinate boron species.

### INTERVIEW

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

**Dr. C. Martin** My group's research is centered on investigating conjugated boron heterocycles, spanning synthesis, reactivity, metal complexation, and molecular properties. Our targets typically have unusual bonding arrangements or electronic structures that have an effect on their reactivity and properties.

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

**Dr. C. Martin** I started research as a second-year undergraduate student at Mount Allison University and had the opportunity to pursue synthetic inorganic projects, working with Glen Briand and Steve Westcott on indium and palladium chemistry, respectively. I quickly realized making unique molecules was fascinating. Being the first person or team to make a particular molecule is a thrilling experience that I now share with my own students. It is exciting to think about the potential impact that a single synthetic discovery can have, whether it is a particular property of that species, unusual reaction that initiates a new direction, or how it will impact or motivate other studies in the chemistry community in the future.

I have always enjoyed cooking and find my interest in synthesis can be related to their similarities. In cooking and synthesis, we commonly follow recipes but there are aspects of art and skill that are integrated in developing new products. In both, we do not always know the outcome when attempting something and that is the motivation to conduct the experiment.

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

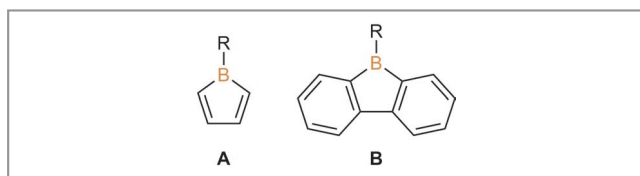
**Dr. C. Martin** It is clear that synthesis is evolving and has a critical role in modern society. Whether it be in pharmaceuticals, fertilizers, electronics, or other ubiquitous substances,

we are becoming reliant on synthesis to both sustain and improve our quality of life. There is always the potential for a more efficient compound, a more economical route, or a new compound that could revolutionize a field. Accordingly, I think that there is a necessity for synthesis, and more importantly, as an academic, a need to train the next generation of synthetic chemists.

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

**Dr. C. Martin** Our program is focused on the synthesis of boron heterocycles. Within this field, our interests are broad and directions are primarily guided by the reactivity and interests of the group members. Below I have summarized the major projects in the group.

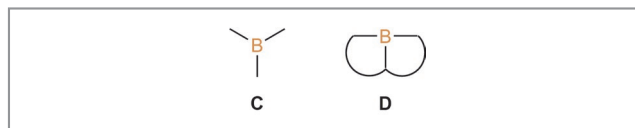
Investigating the reactivity of anti-aromatic boroles (Figure 1): Boroles are  $BC_4$  heterocycles with four  $\pi$ -electrons making them antiaromatic (**A**). This electronic state makes them high in energy and reactions are driven by thermodynamics.<sup>1</sup> Accordingly, the ring can undergo insertions,<sup>2–10</sup> ring opening,<sup>11</sup> Diels–Alder type reactivity,<sup>12,13</sup> and addition reactions.<sup>14–16</sup> We have been taking advantage of the diverse reactivity to access boron frameworks and examine their properties. This chemistry has been extended beyond monocyclic boroles to derivatives with fused aromatics to the  $BC_4$  ring (i.e. **B**) to access unsaturated molecules with extended conjugation.<sup>17–22</sup>



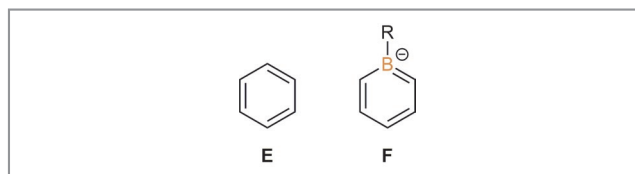
**Figure 1** Borole (**A**) and borafluorene (**B**)

The synthesis of pseudo T-shaped boranes (Figure 2): Boranes are effective Lewis acids for a variety of stoichiometric and catalytic transformations. VSEPR rightfully predicts a trigonal planar geometry as the ground state for boranes (**C**). Our efforts have focused on using pincer ligands as a method to perturb the geometry at boron to access pseudo T-shaped Lewis acidic boranes (**D**).<sup>23,24</sup>

The coordination chemistry of unsaturated boracycles (Figure 3): Since the discovery of ferrocene, organometallic chemists have been using unsaturated cyclic  $\pi$ -systems as ligands. Efforts have primarily focused on carbon-based systems, particularly cyclopentadienide and benzene (**E**). Our



**Figure 2** Typical trigonal planar boranes (**C**) and target pseudo T-shaped boranes (**D**)

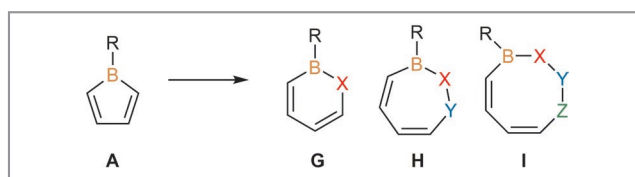


**Figure 3** Benzene (**E**) and anionic boratabenzene (**F**) as a ligand for metals.

group is studying in the coordination chemistry of boron-containing analogues of these species (**F**) and examining the properties of their metal complexes.

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

**Dr. C. Martin** Our group's most significant achievement to date has been ring insertion reactions into antiaromatic  $BC_4$  ring systems.<sup>1</sup> Although these species have been known for over 50 years, their reactivity had not been investigated. This was the subject of our group's first publication and has been developed in many another manuscripts. We have been able to prepare six-, seven-, and eight-membered-ring boracycles via the reactions of boroles with small molecules (**G–I** in Scheme 1). In the six-membered rings where a heteroatom with a lone pair is introduced, the products are six  $\pi$ -electron aromatic ring systems.<sup>25</sup> We are still using this foundational route to target ring systems with desirable properties for electronic materials or biologically active molecules.



**Scheme 1** Synthesis of six-, seven-, and eight-membered boracycles from boroles

*Martin Farber*

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## Coming soon

## Literature Coverage

Continuous-Flow C(sp<sup>3</sup>)-H Functionalizations of Volatile Alkanes Using Decatungstate Photocatalysis

## Literature Coverage

## Total Synthesis of (+)-Caldaphnidine J

## Literature Coverage

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

## Further highlights

**Synthesis** Review: Synthetic Advances in the C-H Activation of Rigid Scaffold Molecules

(by N. Grover and M. O. Senge)

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**Synfacts** Synfact of the Month in category "Chemistry in Medicine and Biology": A PROTAC for KRAS G12C Degradation

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