

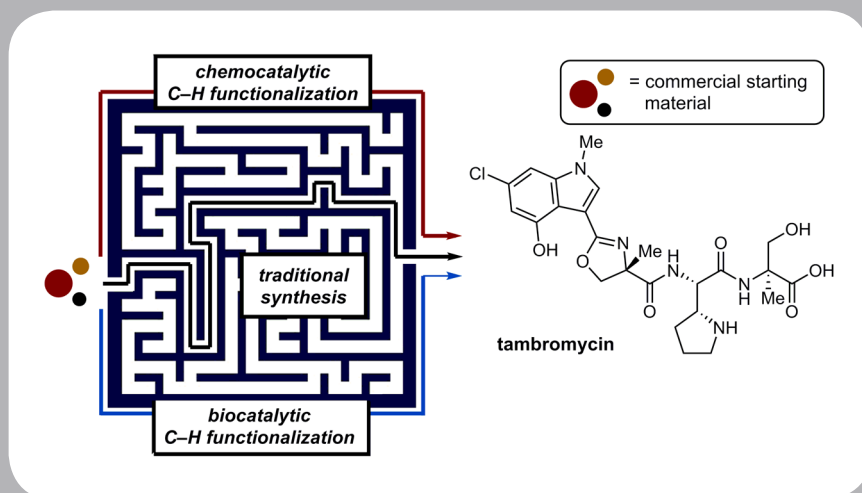
Synform

People, Trends and Views in Chemical Synthesis

2018/08

Total Synthesis of Tambromycin by Combining Chemocatalytic and Biocatalytic C–H Functionalization

Highlighted article by X. Zhang, E. King-Smith, H. Renata



Contact

Your opinion about Synform is welcome,
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marketing@thieme-chemistry.com

Dear Readers,

This is the August issue of SYNFORM, and guess what happens in this period that normally takes place on a sunny beach or a lake shore or maybe on a mountain top, if you really like physical exercise (personally I don't, and I prefer relaxing on a beach)? Yes! Holidays! Good guess! And that's exactly what I am about to do, so I am writing this editorial while I am packing my bags, as from tomorrow I am off for a well-deserved break. So, don't be surprised if this editorial is rather short, as I just can't wait to pull the plug for a couple of weeks. It's been a very long and busy year and I guess many of you will feel exactly the same. So, let's go straight to the point and have a look at what's in this issue, which is not at all in holiday mode. In fact, the first article covers the recent work of a giant of organic chemistry, Prof. Scott Denmark (USA), and his novel Lewis-base catalyzed enantioselective polyene cyclization. Another base – actually superbases – catalyzed process leading to β -phenethyl ethers is the subject of the second contribution, which stems from the research group of the up-and-coming chemist Jeff Bandar (USA). The follow-up article is a Young Career Focus interview with another emerging chemist, Adrien Quintard (France). The last article before my holiday, erm, before the end of the issue, deals with the classic topic of total synthesis of a complex target molecule, in this case tambromycin, with the added spin of combining chemical and biological catalysis to complete the synthesis. Well, I guess that's it for now, I'll see you all after the break! I'm off now, yay!

I almost forgot... 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

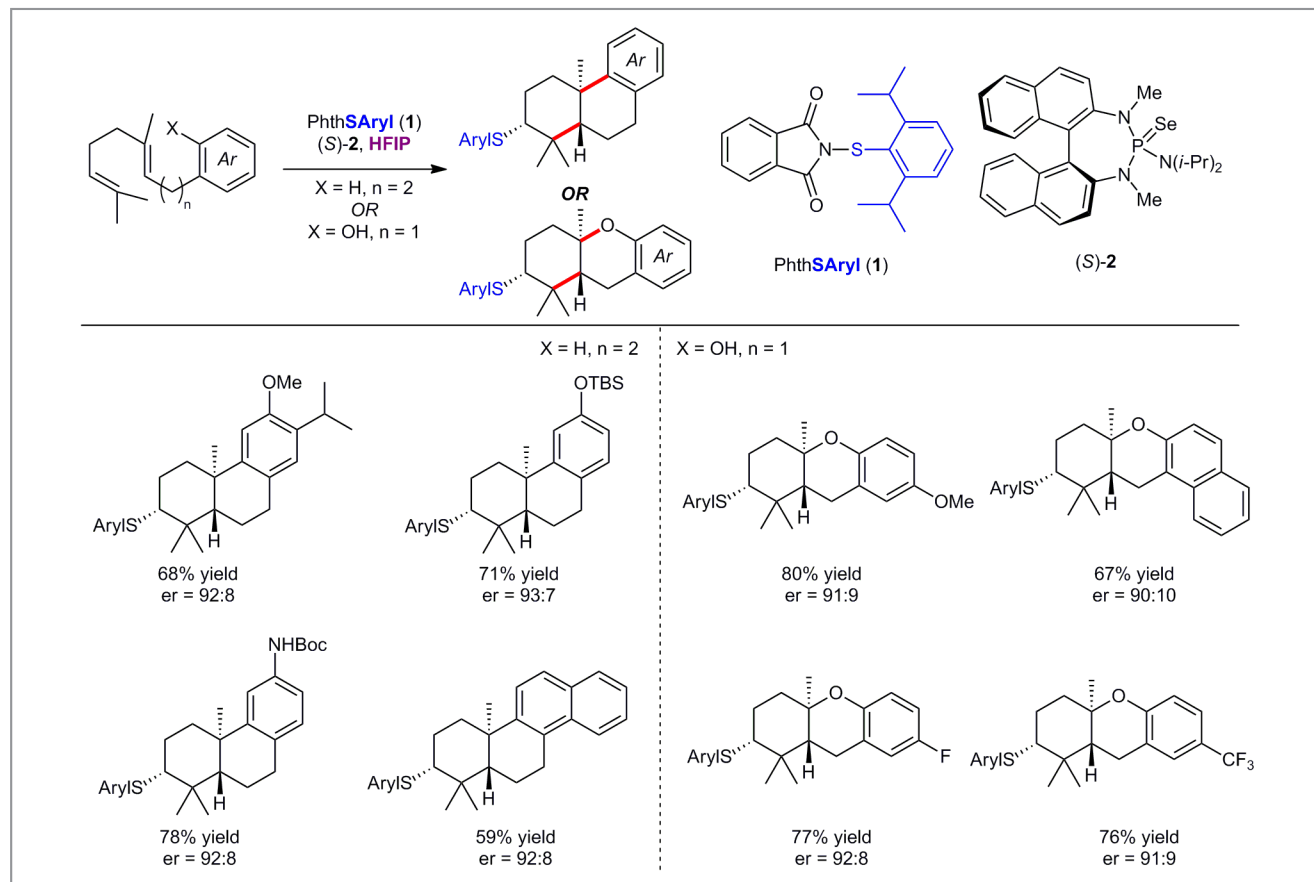
Enantioselective, Lewis Base Catalyzed Sulfenocyclization of Polyenes

J. Am. Chem. Soc. **2018**, *140*, 3569–3573

Polyene cyclization is one of the most general methods for constructing diverse polycyclic skeletons, such as those found in steroid and terpenoid natural products. The reaction, which finds its origins in the biosynthesis of polycyclic terpenes, is also attractive for synthetic chemistry, owing to its ability to form products with multiple rings and stereogenic centers in a non-stop process from simple, linear, achiral starting materials. Many methods for cyclization of polyenes have been developed that involve cationic, anionic, and radical intermediates. Despite the many advances that have been made in this area, catalytic, enantioselective polyene cyclizations are significantly less well developed. The existing catalytic processes share common drawbacks, including: (1) low func-

tional group compatibility because of the strongly acidic conditions needed, (2) incomplete cyclizations, which require further downstream steps, and (3) highly engineered substrates which deter post-cyclization modifications and limit the potential to access natural products. Thus, a high-yielding and operationally simple method for catalytic, enantioselective polyene cyclizations is still needed. Recently, the group of Professor Scott Denmark at the University of Illinois (USA) described a chiral thiiranium ion induced, polyene cyclization that proceeds in good yields with high enantioselectivities under mild conditions.

“As part of an ongoing research program to apply the concept of Lewis base activation of Lewis acids to the reactions



Scheme 1 Selected examples of enantioselective, Lewis base catalyzed polyene sulfenocyclization

of main group elements, we have focused on the activation of sulfur(II) electrophiles in recent years,” explained Professor Denmark. He continued: “Prior disclosures have demonstrated enantioselective, intramolecular oxy-, amino-, and carbosulfenylations of unactivated double bonds. To extend the utility of this concept, the application to polyene cyclization was undertaken.”

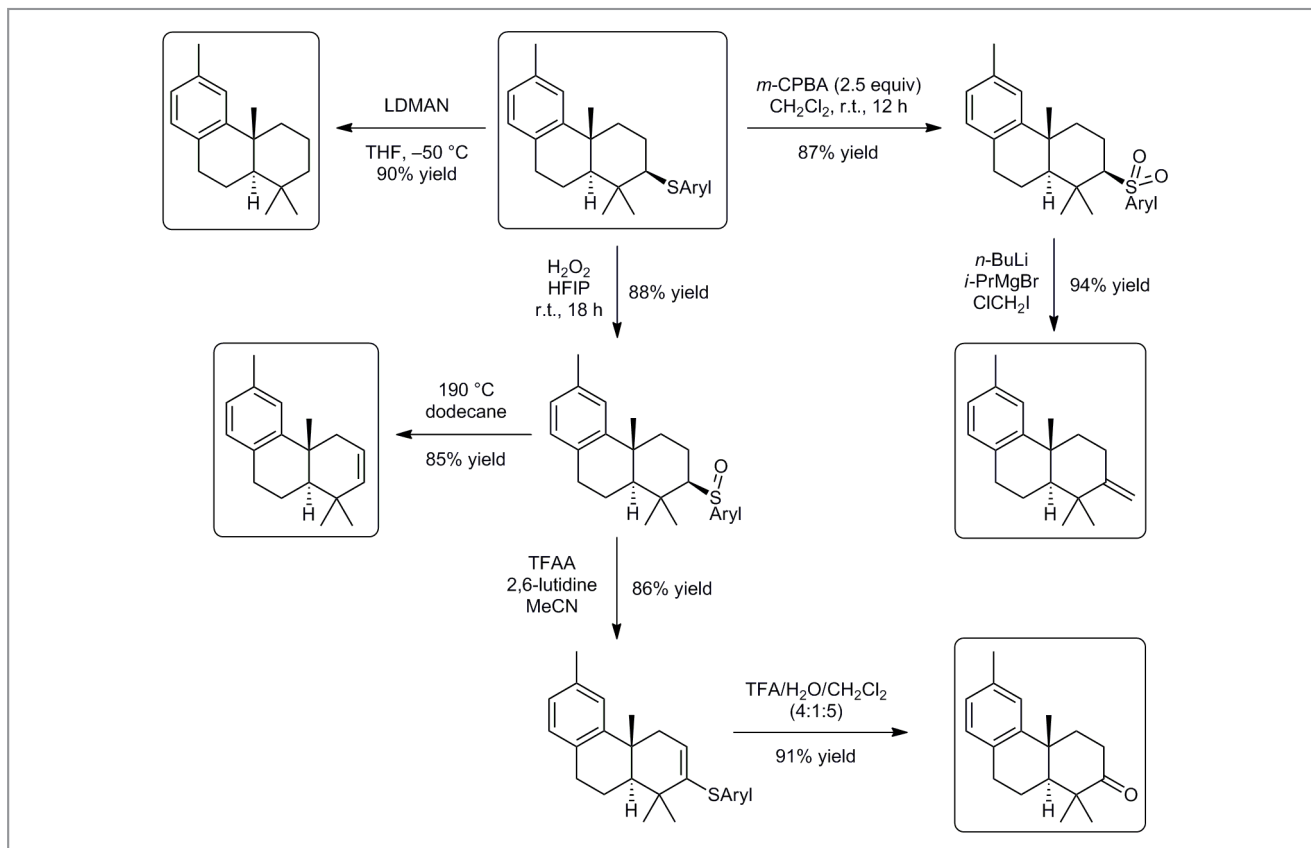
Professor Denmark revealed that initial attempts using established reaction conditions were uniformly unsuccessful owing to poor chemoselectivity. Inspired by the solvophobic effect, which assists protein folding *in vivo*, the researchers surveyed a variety of polar solvents to minimize the solvent-accessible surface area of the lipophilic polyene substrates. “We were delighted to find that hexafluoroisopropyl alcohol (HFIP) was an excellent solvent for the reaction, resulting in synthetically useful yields of the desired cyclization products,” said Professor Denmark. He speculated: “Presumably, the solvophobic effect favors a conformer of the substrate in which the distal olefin is more accessible than the internal olefin, thus improving chemoselectivity. Additionally,

Brønsted acid additives are no longer necessary because HFIP is sufficiently acidic to assist in formation of the catalytically active, cationic complex.”

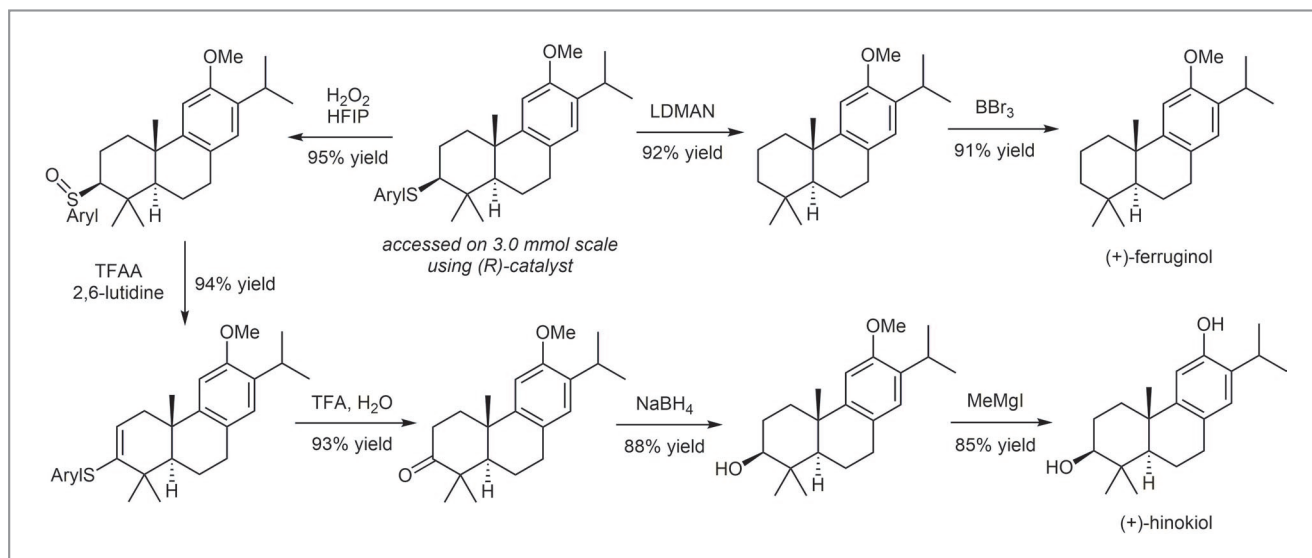
The final reaction conditions are extremely mild (Scheme 1), and the benefits include: (1) low catalyst loading (0.01 to 0.05 equiv), (2) high functional group tolerance, (3) rapid (<12 h) conversion at room temperature, (4) absence of harsh additives, and (5) no requirement for rigorous exclusion of air and water.

Professor Denmark explained: “Both homogeranylarenes and *ortho*-geranylphenols are viable substrates, delivering the cyclization products in high yields with high diastereo- and enantioselectivities. Additionally, the resulting thioether moiety in the cyclized products can be easily transformed into useful carbon and oxygen functionality (Scheme 2).”

To further demonstrate the utility of the sulfenocyclization reaction and subsequent sulfide derivatizations, two short total syntheses of (+)-ferruginol and (+)-hinokiol were easily accomplished (Scheme 3).



Scheme 2 Further derivatizations of a thioether product



Scheme 3 Total syntheses of (+)-ferruginol and (+)-hinokiol

Professor Denmark concluded: “Currently, the mechanism of the reaction is under study as is the extension of substrate scope to trienes and tetraenes, as well as the investigation of other terminating groups beyond arenes and phenols.”

Matthew Farnok

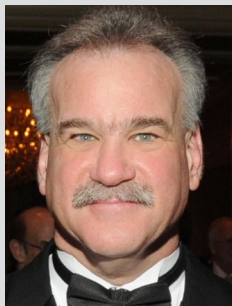
About the authors

Zhonglin Tao was born in China in 1989. He obtained his BS and PhD degrees from the University of Science and Technology of China (P. R. of China). In the last year of his undergraduate studies, he joined Professor Liu-Zhu Gong's laboratories to begin his studies in asymmetric catalysis. He completed his PhD in the same group focusing on palladium-catalyzed allylation reactions. Thereafter, he joined Professor Scott Denmark's laboratories at the University of Illinois (USA) as a postdoctoral research associate focusing on Lewis base catalyzed reactions.

Kevin A. Robb is a native of Missouri (USA). He received his BS in chemistry from Truman State University (USA) in 2013. The same year, he enrolled in graduate studies at the University of Illinois at Urbana-Champaign (USA), where he joined the research group of Professor Scott Denmark. He is currently a fifth-year PhD student.

Kuo Zhao was an undergraduate researcher in the Denmark laboratories from 2014 to 2017, and he received his BS in chemistry from the University of Illinois at Urbana-Champaign (USA) in 2017. He is currently a first-year graduate student at Princeton University in the group of Professor Rob Knowles.

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Prof. S. E. Denmark

Scott E. Denmark was born in Lynbrook, New York (USA) in 1953. He obtained an S.B. degree from MIT (USA) in 1975 (working with Richard H. Holm and Daniel S. Kemp) and his D. Sc. Tech. (under the direction of Albert Eschenmoser) from the ETH Zürich (Switzerland) in 1980. That same year, he began his career at the University of Illinois at Urbana-Champaign (USA) where since 1991 he has been the Reynold C. Fuson

Professor of Chemistry. His research interests include the invention of new synthetic reactions, exploratory organoelement chemistry, and the origin of stereocontrol in fundamental

carbon-carbon bond-forming processes. Professor Denmark is currently the Editor-in-Chief of *Organic Reactions* and edited Volume 85 of *Organic Syntheses*. He served for six years as an Associate Editor of *Organic Letters* and for nine years as Editor of *Topics in Stereochemistry*. He is a Fellow of the Royal Society of Chemistry, the American Chemical Society and the American Academy of Arts and Sciences.

Superbase-Catalyzed Anti-Markovnikov Alcohol Addition Reactions to Aryl Alkenes

J. Am. Chem. Soc. **2018**, *140*, 3547–3550

β -Phenethyl ethers are important structural features in medicinally relevant compounds, including pharmaceuticals and natural products; however, an atom-economical and straightforward synthesis of this structural unit remains a challenging endeavor for organic chemists. The group of Jeffrey S. Bandar at Colorado State University (USA) has been working on this problem. “We felt that a streamlined synthetic route to β -phenethyl ethers would be a welcome advance,” said Professor Bandar. “In particular, the direct anti-Markovnikov addition of alcohols to styrene derivatives is attractive because of the scale and diversity of the readily available starting materials.”

Professor Bandar explained that typically, in order to achieve this net transformation, chemists must perform a three-step hydroboration/oxidation/substitution sequence, all requiring stoichiometric reagents. “The value of a catalytic variant of this transformation has attracted attention from other groups; one impressive example is a photoredox-catalyzed variant developed by the Nicewicz group in 2012 (*J. Am. Chem. Soc.* **2012**, *134*, 18577),” he added.

“We were inspired by the simplicity and potential of a Brønsted base catalyzed approach for the addition of alcohols to aryl alkenes,” remarked Professor Bandar. He explained: “We expected the reaction to be highly regioselective due to the polarity of the aryl-substituted alkene. In the proposed catalytic cycle, anti-Markovnikov alkoxide attack must occur with rapid protonation of the developing benzylic carbanion, perhaps in a concerted process. There have been sporadic examples of inorganic base-promoted addition of alcohols to styrene derivatives, but these reactions typically required highly activated systems such as conjugated vinyl heterocycles.”

The group hypothesized that the identity and properties of the Brønsted base would be crucial to developing a general base-catalyzed alcohol addition protocol. “A report from Kondo in 2004 using the neutral organic superbase P_4 -*t*-Bu to catalyze the addition of alcohols to phenylacetylene sparked our interest (*Adv. Synth. Catal.* **2004**, *346*, 1090). Although that particular reaction had been known using other common inorganic bases, we thought the unique properties of the organic base might enable our reaction of interest,” said Professor Bandar, who continued: “The phosphazene superbase

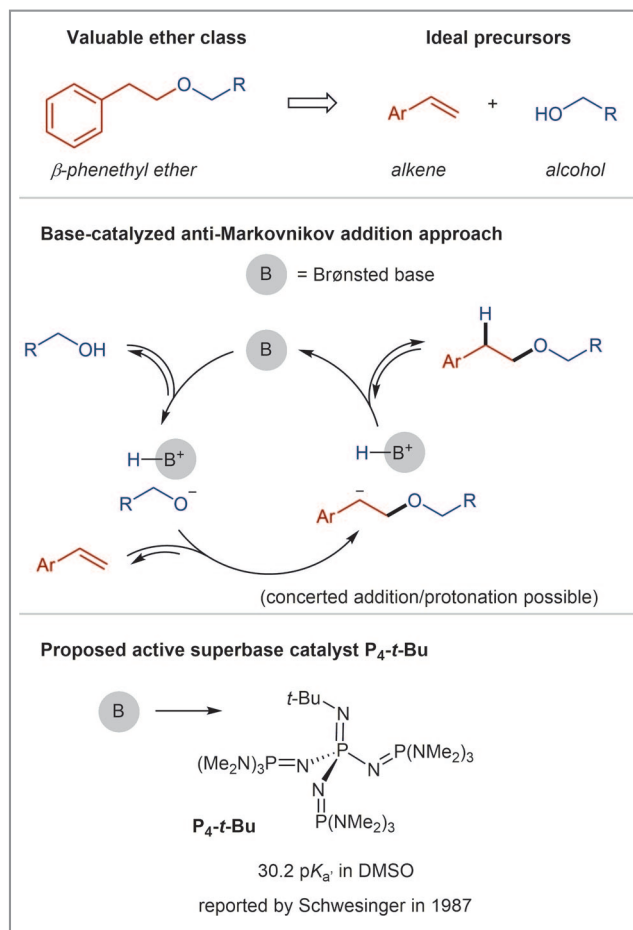


Figure 1

P_4 -*t*-Bu, first reported by Schwesinger in 1987 (*Angew. Chem. Int. Ed.* **1987**, *26*, 1167), is an incredibly strong neutral base capable of deprotonating alcohols. Compared to inorganic bases, use of P_4 -*t*-Bu leads to an alkoxide ion pair containing a proton that could enable the rapid (or concerted) protonation of the developing benzylic anion in the proposed mechanism.”

“With this proposed work, I was able to recruit Dr. Luo to join my new lab at Colorado State University where he rapidly discovered that P_4 -*t*-Bu catalyzes the addition of alcohols to styrene derivatives in aromatic solvents,” revealed Professor Bandar. He added: “We found that the reaction is reversible

and under equilibrium control. Therefore, the temperature was optimized for each substrate such that the lowest temperature at which the catalyst was active was used.”

The synthetic value of this transformation was demonstrated by its broad substrate scope, as shown by the examples in Figure 2.

Dr. Luo – a postdoctoral fellow who co-authored the article – explained: “Concerning the styrenes, diverse functional groups and substitution patterns were tolerated, such

as *meta*-nitro, -trifluoromethyl, -methoxy, and *ortho*-chloro, -bromo, -trifluoromethoxy, -iodo; many of these groups could enable further structural manipulation, if desired. Vinyl heteroareomatics (e.g. pyridine, furan, thiazole, quinoline, and isoquinoline) also worked well; in particular, 2-chloro-3-vinylpyridine delivered ether products with excellent chemoselectivity (alcohol addition over S_NAr .” He continued: “At higher temperatures, styrene provided the ether product with 22% yield. We also found that β -alkyl styrenes can participate

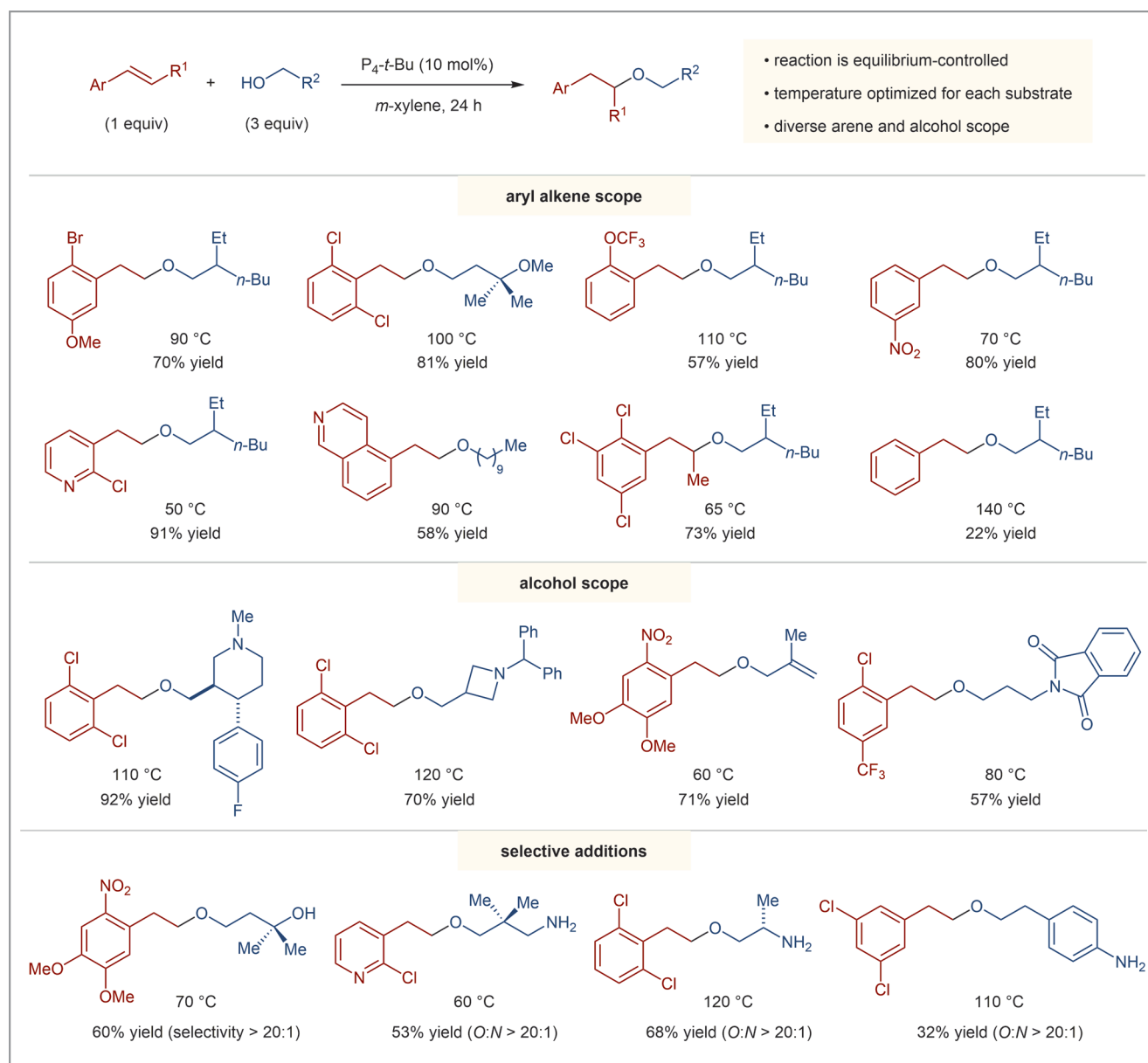


Figure 2

in this reaction, whereas α -alkyl styrenes afforded only traces of product. Electron-rich styrenes (such as 2,4,6-trimethylstyrene) did not lead to any product formation.”

A wide range of alcohols was found to react with styrenes. “A general reactivity trend showed that primary alcohols give higher yield than secondary and tertiary alcohols, for example *i*-PrOH and *t*-BuOH added to 4-trifluoromethylstyrene with 25% and 7% yield, respectively,” remarked Dr. Luo. The Colorado-based researchers also found that a range of diverse and densely functionalized primary alcohols provided ethers in high yield. Geraniol, solketal, a paroxetine derivative, and alcohols featuring olefin, azetidine, and phthalimide functional groups showed good reactivity and were well tolerated. “For primary alcohols containing a competing nucleophilic hydroxyl or amino group, our study showed that it is possible to achieve selective additions, leaving unprotected heteroatoms available for further functionalization,” added Dr. Luo.

Professor Bandar said: “For a first-generation system, we are happy with the diversity of alkenes and alcohols tolerated in this reaction. Nonetheless, we have identified several limitations that we are currently working to address. We are primarily seeking to develop more active catalysts and reaction conditions that give high yields for electron-neutral to electron-rich styrenes, as well as α -substituted styrenes. It would also be useful to achieve enantioselectivity in reactions where a stereocenter is formed (in either the α - or β -position).” He concluded: “In the long term, we hope to be able to extend our base-catalyzed approach for the addition of alcohols to other olefin classes in order to access more diverse ether structures.”

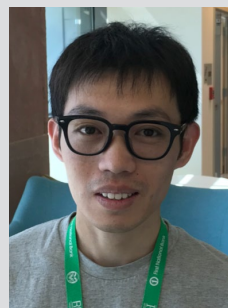
Matthew Farwell

About the authors



Prof. J. S. Bandar

Jeff Bandar received his Ph.D. from Columbia University (USA) in 2014, where he developed new synthetic applications of aromatic ions in the laboratory of Professor Tristan H. Lambert. He then advanced the understanding and application of copper hydride catalysts in asymmetric reactions as an NIH postdoctoral fellow under Professor Stephen L. Buchwald at Massachusetts Institute of Technology (USA). Jeff started his independent career in the summer of 2017 at Colorado State University (USA), where his group is developing new reactions and concepts in Brønsted base chemistry.



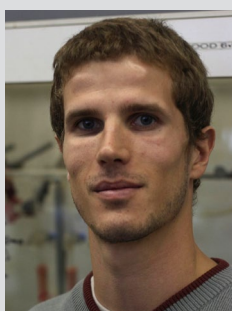
Dr. C. Luo

Chaosheng Luo received his Ph.D. from Peking University (P. R. of China) in 2015, where he worked on developing asymmetric organocatalytic methods for accessing medicinally privileged scaffolds in the laboratory of Professor Yong Huang. He then joined the research group of Professor Jeffrey van Humbeck at Massachusetts Institute of Technology (USA), where he engaged in studying the effect of an embedded electric field in asymmetric hydrogen-bonding catalysis. Following his work at MIT, Chaosheng moved to Colorado State University (USA) to continue postdoctoral studies working on superbase-catalyzed reactions under Professor Jeffrey S. Bandar.

Young Career Focus: Dr. Adrien Quintard (Aix-Marseille University, France)

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. Adrien Quintard (Aix-Marseille University, France).

Biographical Sketch



Dr. A. Quintard

Adrien Quintard studied chemistry at the University of Toulouse (IUT, France) and then at CPE-University of Lyon (France). He completed his PhD in 2011 under the supervision of Prof. A. Alexakis at the University of Geneva (Switzerland). He subsequently moved to the University of Stanford (USA) for a first post-doctoral stay working with Prof. B. M. Trost. After moving to Aix-Marseille University (France) in 2012 for a second post-doctoral position, he obtained in 2013 an ANR research grant allowing him to start his own research program on the development of multi-catalyzed transformations before becoming in 2014 CNRS researcher. Recently, he was recognized by the young researcher 'Emergence' award from the organic division of the French Chemical Society and he was a recipient of a Thieme Chemistry Journals Award.

INTERVIEW

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

Dr. A. Quintard Optimal organic synthesis is crucial for our future through providing society with access to optimized drugs or materials and also for finding solutions to the energy crisis, for example. In an attempt to find solutions to this challenge of eco-compatible synthesis, our research is centered on the development of new catalytic tools for rapidly transforming easily available molecules into elaborate molecular architectures. To obtain the best possible synthetic sequence while limiting both steps and waste generation, we do not restrict our research to the use of a single catalytic activation mode. Instead, we try to find the best possible catalysts able to selectively activate the desired chemical functions while achieving maximum efficiency. As a result, by combining several compatible catalysts, we can design innovative cascades and rapidly access complex scaffolds. With these improved synthetic tools in hand, we are able to rapidly elaborate original frameworks with designed functions that should allow us to extend our research in the future to other fields, such as the study of biological interactions, for example.

SYNFORM *When did you get interested in synthesis?*

Dr. A. Quintard To be honest, after finishing high school, I was more interested in biology than in chemistry. However, despite my poor level in chemistry, I was lucky enough to enter an excellent technical university institute (IUT of Castres in the south of France) where the teachers shared their passion for organic chemistry. At 18 years old, discovering organic synthesis is exciting because you understand that you can build up new materials and drugs while playing, to try to create them with the best possible efficiency. This passion was confirmed during my subsequent internships where I had

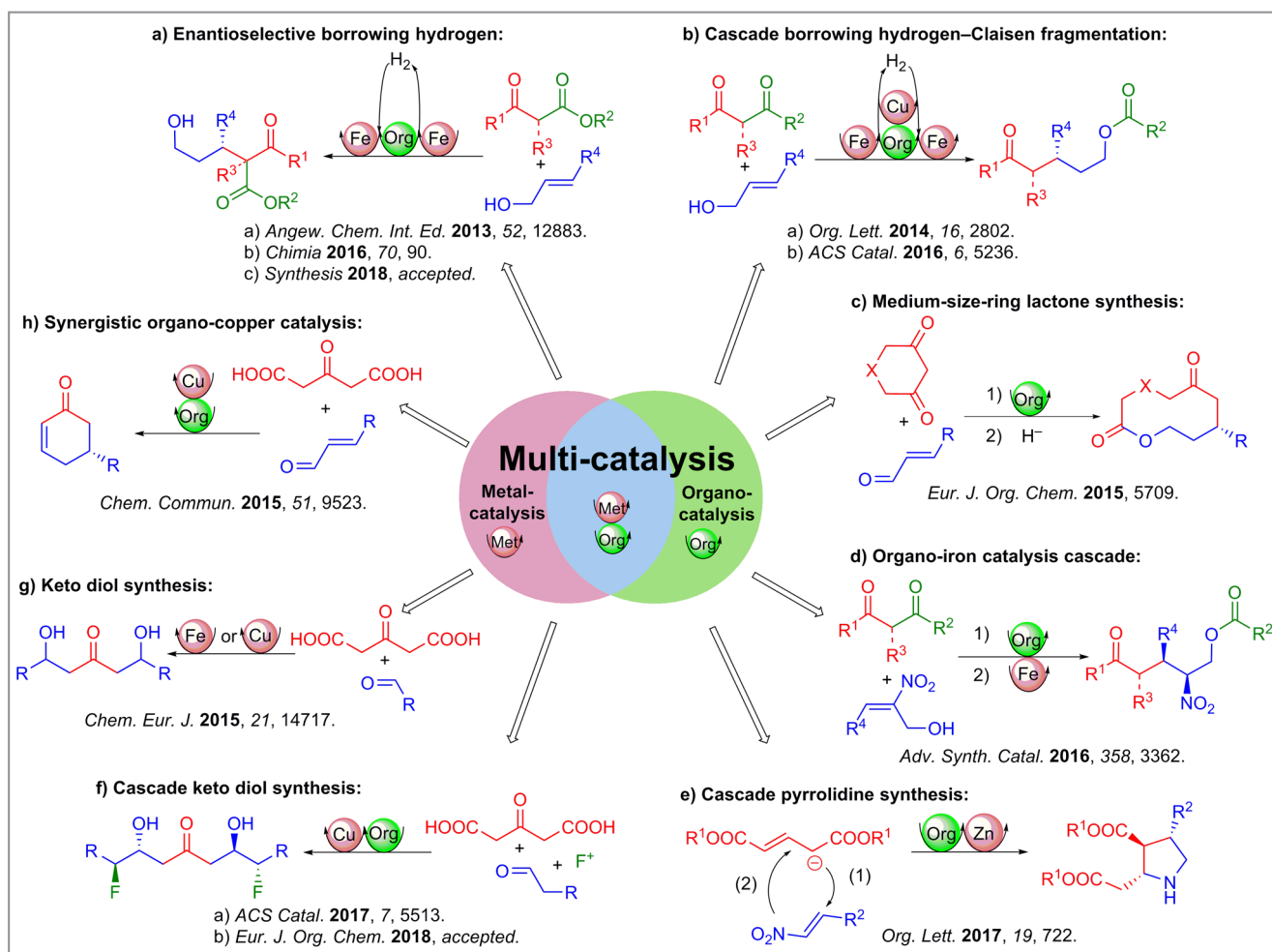
the opportunity to discover the difficult but stimulating world of research, where the term ‘playing’ is perfectly appropriate to describe this three-dimensional Lego game chemists are playing.

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

Dr. A. Quintard The current trend is to considerably diminish the role of organic synthesis. Science is full of politics and people who consider that synthesis is a mature field, only here to assist biologists or physicists; they think that it is out of date and that it will soon be replaced by synthetic biology. Synthetic biology is an excellent tool but there are no Swiss Army knives able to perform all required transformations. For now, even though organic synthesis has outstanding

potential and can create a wide range of complex structures relatively rapidly, we are still far from what can be considered as ideal synthesis, notably when looking at waste generation and time consumption. Many chemical architectures cannot be constructed on scale and cheaply because of the limitations of our current toolbox. For this purpose, we need to improve our understanding of the interactions between molecules and the way to activate and transform chemical functions, notably using catalysts with enhanced efficiency. These improvements at the fundamental level will lead to optimized eco-compatible syntheses and subsequently help physicists and biologists in their own research.

SYNFORM Your research group is active in the area of stereoselective synthesis and natural products synthesis. Could you tell us more about your research and its aims?



Scheme 1 Research overview

Dr. A. Quintard Our research is dedicated to the discovery of innovative methodologies and eco-compatible synthetic routes to access complex molecular architectures rapidly from simple building blocks. Towards this goal, we focus on the use of catalysis in a wide sense, notably using organocatalysis (aminocatalysis, chiral bases, thioureas) and metal catalysis based on abundant non-precious metals such as Fe or Cu. In order to go beyond the limitations inherent to the use of a single activation mode, a major part of our efforts focus on the development of multi-catalyzed processes allowing us to achieve the best possible reaction efficiency. Combined with cascade reactions, such an approach at the frontier between metal and organocatalysis allows the solving of key synthetic chemical problems and to considerably shorten some existing routes to crucial synthetic building blocks (Scheme 1).

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

Dr. A. Quintard Within our research program, the developments on enantioselective borrowing hydrogen is to our eyes among the most interesting. In this work, we have shown that a combination between an iron borrowing hydrogen catalyst and a chiral organocatalyst can promote the enantioselective functionalization of allylic alcohols (*Angew. Chem. Int. Ed.* **2013**, *52*, 12883–12887; *ACS Catal.* **2016**, *6*, 5236–5244). Apart from the considerable synthetic economies such a process brings to complex molecule preparation, it was also the first use of an iron catalyst in a borrowing hydrogen. Besides this hydrogen transfer processes, we have also shown more recently that we could rapidly construct valuable keto diols, key direct precursors of 1,3,5-polyols, a class of molecules of great interest. By a selective combination between an organocatalyst and a copper complex, a single cascade allowed the enantioselective fluorination of aldehydes and their in situ derivatization by the copper catalyzed aldolization, constructing up to four acyclic stereogenic centers in one single cascade (*ACS Catal.* **2017**, *7*, 5513–5517).



Total Synthesis of Tambromycin by Combining Chemocatalytic and Biocatalytic C–H Functionalization

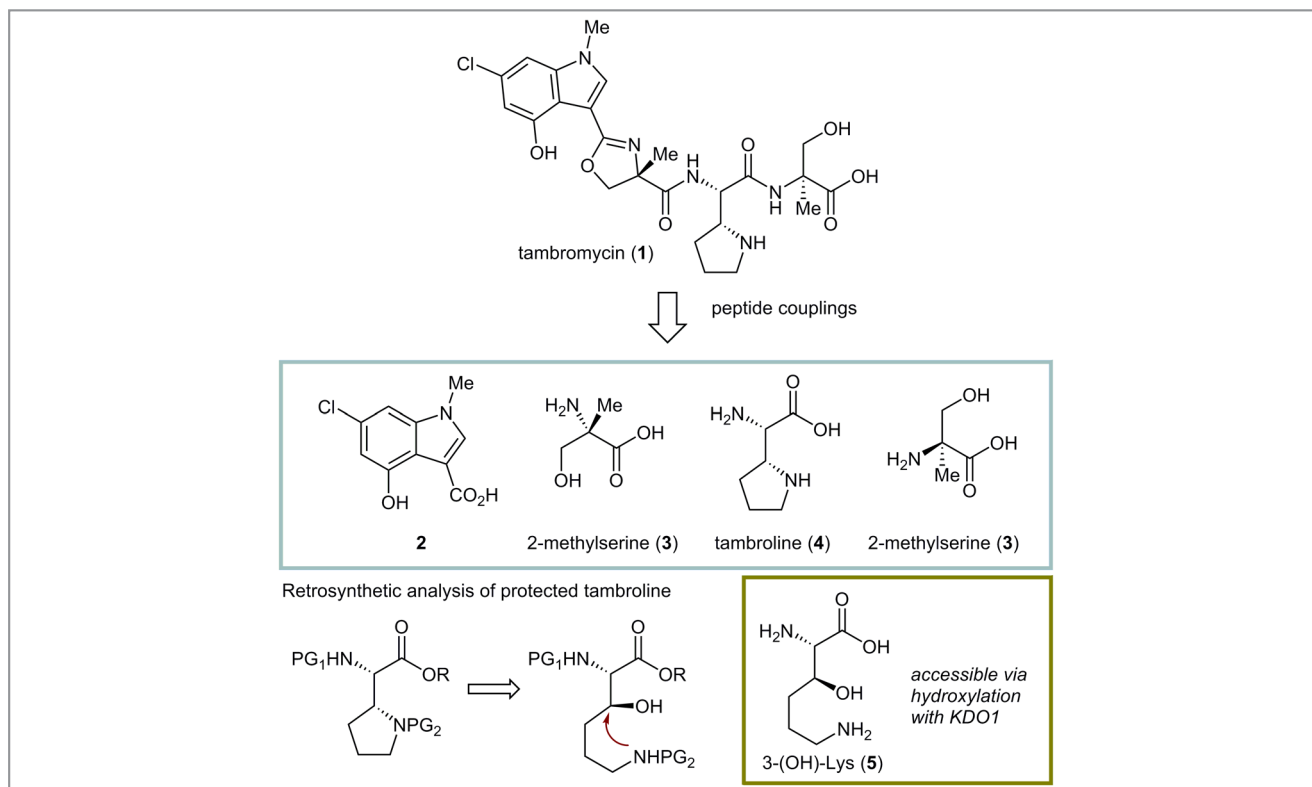
Angew. Chem. Int. Ed. **2018**, *57*, 5037–5041

Enzymes are capable of highly selective and specific synthetic transformations, but the potential of biocatalysis in total synthesis is far from being fully exploited.

The lab of Professor Hans Renata at The Scripps Research Institute (USA) is broadly interested in developing novel synthetic approaches to bioactive natural products by leveraging contemporary technology in enzyme catalysis. “We are particularly focused on the use of enzymatic hydroxylation as an enabling platform to simplify routes to complex scaffolds,” said Professor Renata. He continued: “In this regard, we chose to work with iron- and α -ketoglutarate-dependent dioxygenases (Fe/ α KGs) as their utility in organic synthesis has been relatively underexplored so far. Prior to this work, we were able to complete an efficient formal synthesis of manzacidin C by employing a selective hydroxylation of an L-leucine deriva-

tive as our key step (*J. Am. Chem. Soc.* **2018**, *140*, 1165–1169). To build on this success, we sought other synthetic targets wherein a similar synthetic logic could be applied.”

The group was first drawn to tambromycin due to its structural complexity and promising preliminary bioactivity. Notably, this natural product contains a highly unusual amino acid monomer, tambroline, which would provide a useful testbed for the use of biocatalytic retrosynthetic disconnection (Scheme 1). “In our minds, the best and most direct route to tambroline was via scission of the C3–N bond,” remarked Professor Renata. He explained: “While one could envision the use of Hofmann–Löffler–Freitag reaction on protected L-lysine to construct this bond, in our hands, the reaction failed to provide any desired product. Applying the principles of biocatalytic retrosynthesis, we realized that the pyrrolidine ring

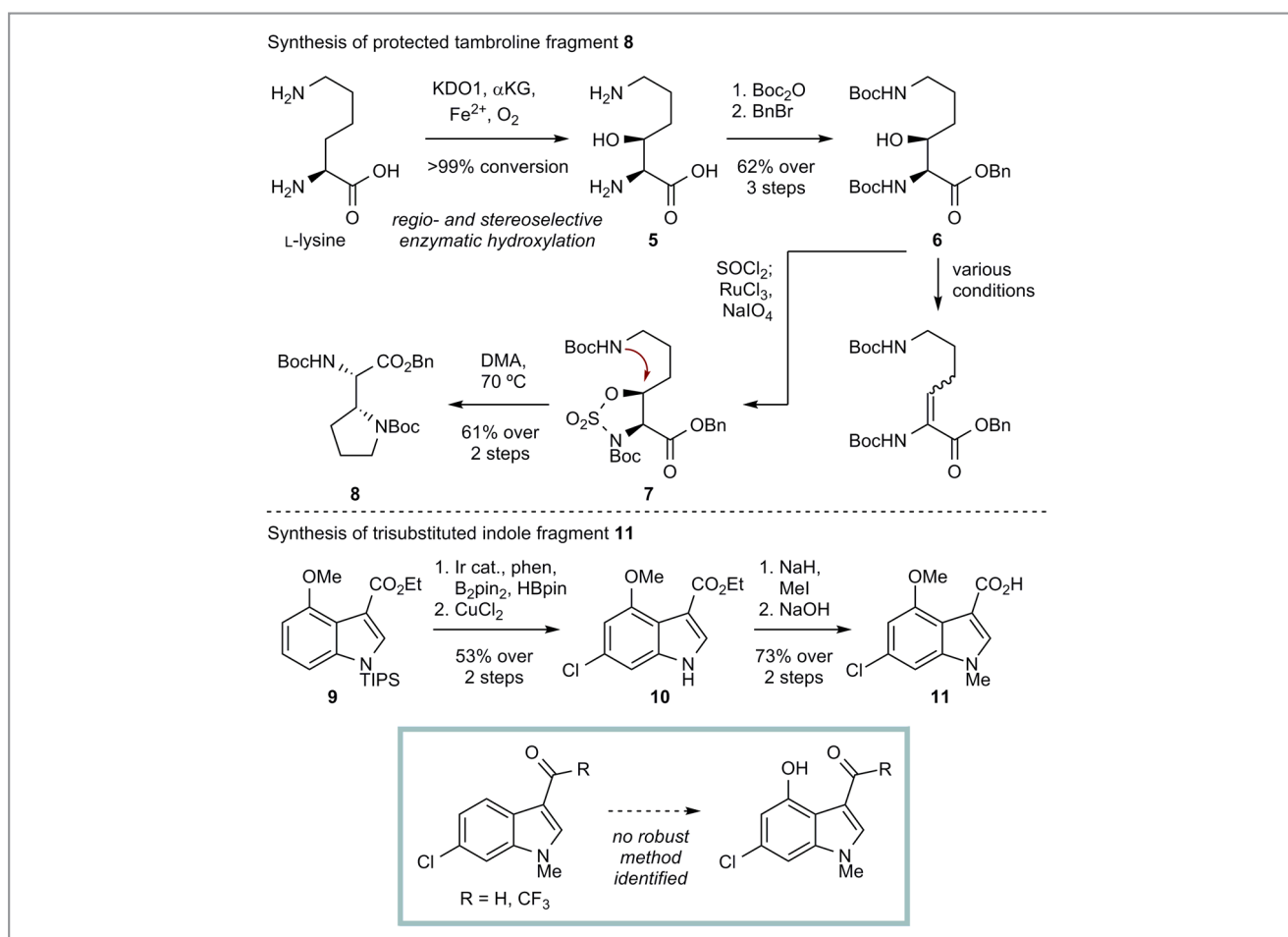


Scheme 1 Retrosynthetic analysis of tambromycin and tambroline

could be constructed via a nucleophilic substitution reaction on 3-OH-Lys, which in turn is a known product of lysine hydroxylation with an Fe/αKG, KDO1.” As the hydroxylation step would constitute the first step of their synthesis, Professor Renata and his co-workers needed to be able to conduct this transformation on multi-gram scale with good conversion and yield. At the outset, this was not a given, as prior reaction with KDO1 was only done on a scale of less than 100 mg. “We eventually found that while KDO1 has good catalytic activity, it suffers from poor soluble heterologous expression in *E. coli* even after codon optimization,” explained Professor Renata. “Fortunately, co-expression of the chaperones GroES/GroEL was able to improve the soluble expression of KDO1 significantly, and equipped with ample quantities of the enzyme, we were able to solve the initial material throughput issue in the preparation of the tambroline fragment.”

The pyrrolidine construction from **6** was the next major hurdle in the synthesis (Scheme 2, top). “The use of standard S_N2 or Mitsunobu conditions would lead to facile E1cB elimination to the dehydrolysine derivative,” explained Professor Renata. The group found that the formation of sulfamidate **7** was essential to prevent the E1cB competitive pathway. However, as revealed by Professor Renata, choice of solvent was also crucial, as the reaction kinetics of the cyclization in dimethylacetamide (DMA) were far superior to those in toluene. Indeed, conducting the reaction in the latter solvent required nearly three days of reflux to see full conversion from starting material.

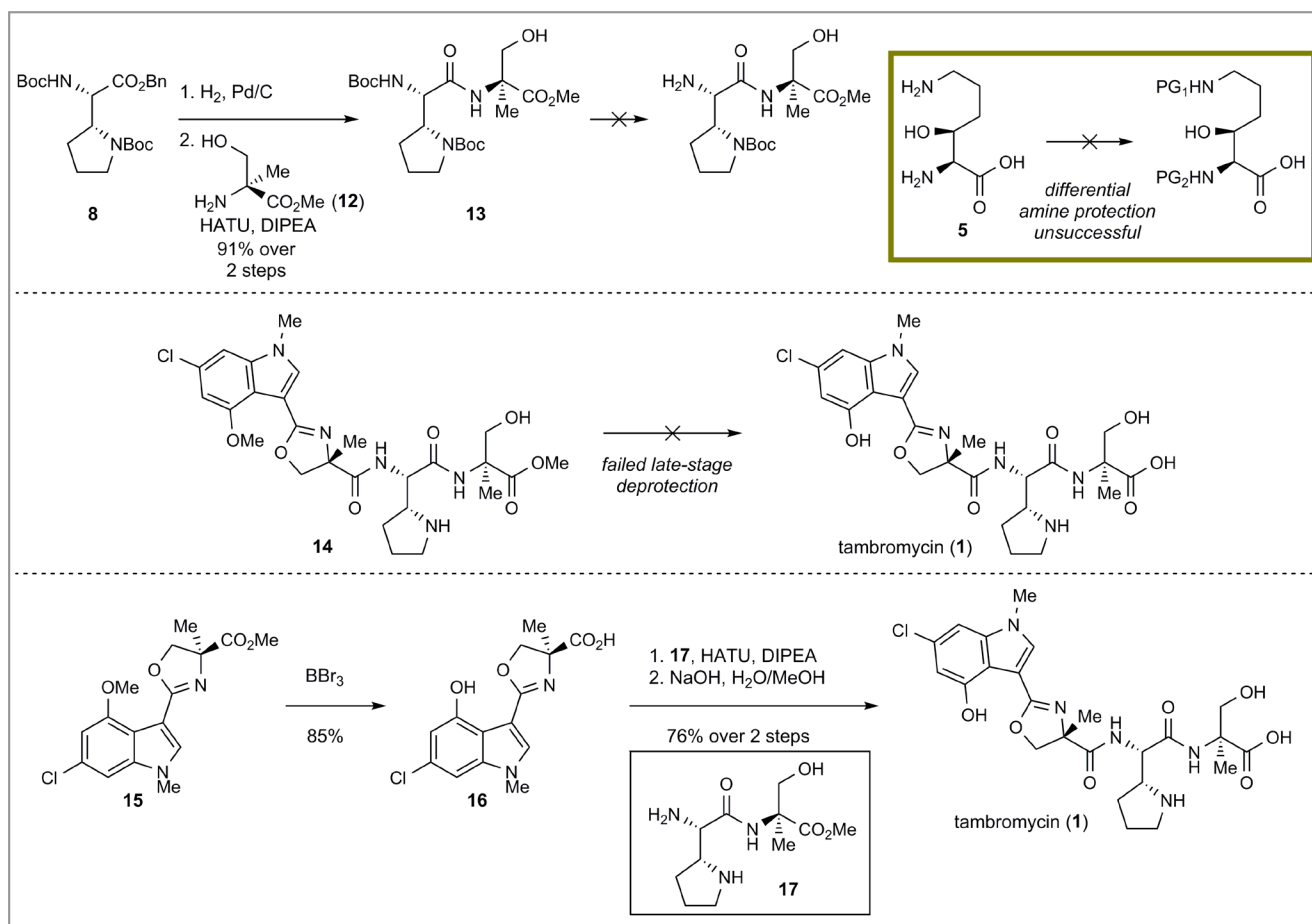
Professor Renata explained that the indole fragment was particularly interesting to tackle. “Despite the bounty of indole syntheses, the 3,4,6-trisubstituted indole motif still poses a significant synthetic challenge,” he said. “Not unlike



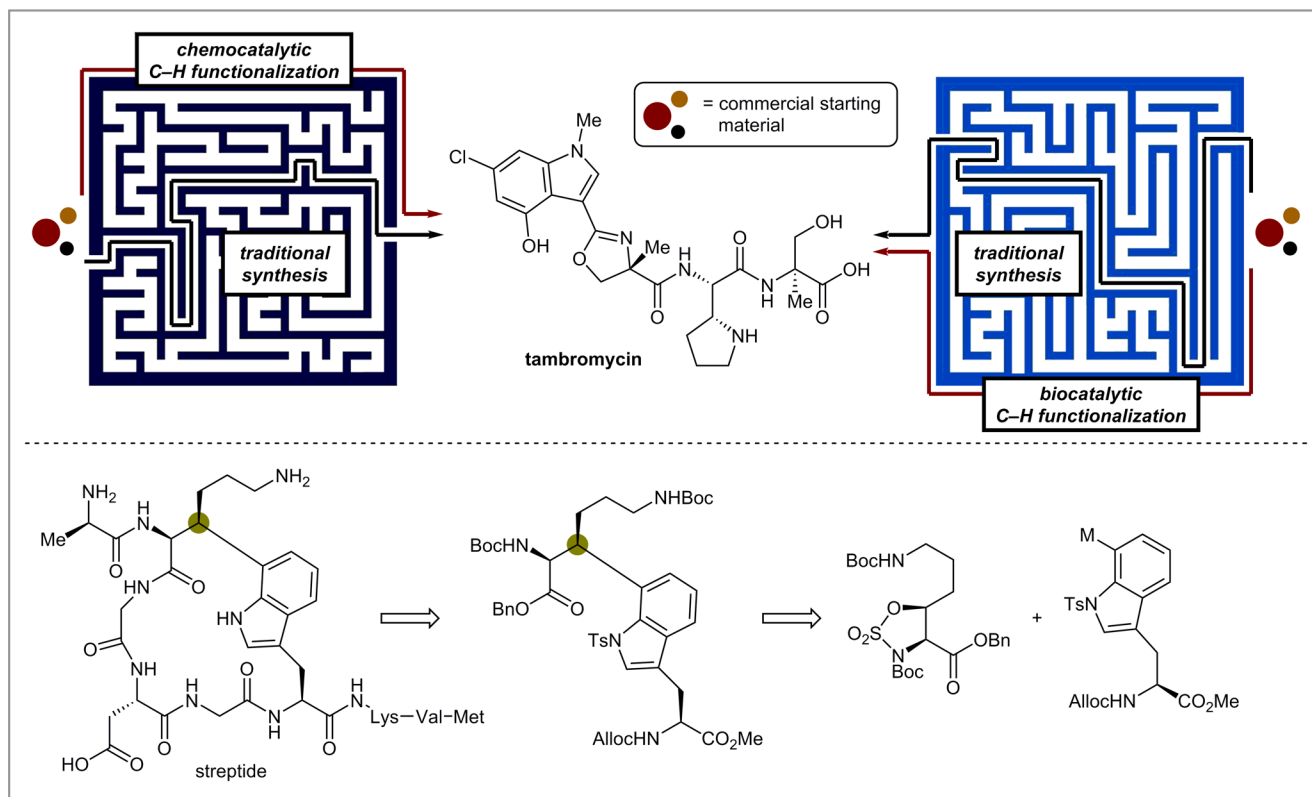
Scheme 2 Top: Preparation of protected tambroline (**8**) via enzymatic hydroxylation of L-lysine. Bottom: Preparation of key indole fragment **11** via regioselective C6 borylation of indole **9**.

the tambroline fragment, such indole is also a known structure, having previously been synthesized via Hemetsberger or Batcho–Leimgruber ring synthesis. However, none of the published routes was deemed to be particularly efficient.” Professor Renata continued: “We envisioned a ring substitution approach from a commercially available disubstituted indole would offer a more streamlined access to **11** (Scheme 2, bottom). After several failed attempts to effect C4 functionalization on various 6-chloroindole derivatives, we elected to focus on selective C6 functionalization of 3,4-disubstituted indole (e.g., **9**.” He added: “We were cognizant of recent C–H functionalization literature from Hartwig and Baran which showed that C6 borylation of indole derivatives could be effected through judicious combination of iridium catalyst, ligand and borylating reagent. To our delight, this chemistry could be performed on indole **9** on gram-scale with good yield, thereby addressing the preparation of the key indole fragment.”

At this stage, all the requisite building blocks had been prepared. However, their final assembly was not without its challenges (Scheme 3). The group had prepared the tambroline fragment as the bis-Boc derivative and initially sought methods for regioselective Boc deprotection to avoid any regioselectivity issues in subsequent coupling. However, no suitable methods could be identified. In parallel, the authors also went back to the very beginning of the synthesis to explore the possibility of effecting differential amine protections on **5** by employing an established copper-chelation method, but this also turned out to be problematic, likely due to the possibility of multiple metal chelation modes by **5**. Professor Renata explained: “Faced with these failures, we elected for a global Boc deprotection, reasoning that the local steric environments of the two free amines in the product would be different enough to allow for selective peptide coupling. Similarly, the indole fragment was prepared as the methyl ether derivative and we had hoped to keep this protecting



Scheme 3 Top: Failed attempts at effecting selective deprotection of **13** and differential protection of **5**. Middle: Unsuccessful attempt at late-stage deprotection of key intermediate **14**. Bottom: Final synthetic route to tambromycin (**1**).



Scheme 4 Top: Incorporation of biocatalytic and chemocatalytic C–H functionalization logic in the total synthesis of tambromycin. Bottom: Potential future application of biocatalytic C–H functionalization logic in the total synthesis of streptide.

group until the end of the synthesis. However, demethylation of the fully assembled tambromycin proved to be extremely difficult. Thus, we chose to remove the methyl ether group earlier in the synthesis. Of course, all of these complications made the key fragment coupling step rather daunting as both fragments **16** and **17** contained various free N–H and O–H groups. Gratifyingly, this step turned out to be highly selective as only our desired product was observed at the end of the reaction.”

“Our work highlights the use of new biocatalytic and chemocatalytic methods towards the total synthesis of a non-ribosomal peptide natural product (Scheme 4),” said Professor Renata. He concluded: “In the broader sense, we hope that this work will be the tip of the iceberg for the application of enzymatic C–H functionalization logic in total syntheses. For decades, synthetic organic chemists have developed countless methodologies for C–H functionalizations. But it is now prudent to include enzymatic transformations into our retrosynthetic designs and further applications of this strategy are being pursued very actively in our lab.”

Matteo Farab

About the authors

*Dr. X. Zhang*

working towards the chemoenzymatic total syntheses of bioactive natural products.

*E. King-Smith*

Xiao Zhang received his B.S. in chemistry from Lanzhou University (P. R. of China) in 2009. After a brief stint at Wuxi AppTec (P. R. of China), he joined the lab of Prof. Guangxin Liang at Nankai University (P. R. of China) in 2010. He obtained his Ph.D. in 2015, completing the total syntheses of (–)-isatisine A and (–)-roseophilin. In 2016, he joined the lab of Prof. Hans Renata at The Scripps Research Institute (Florida, USA) where he is now

*Prof. H. Renata*

2016. His current research focuses on the development of novel approaches to bioactive natural products through strategic application of biocatalytic methods.

Emma King-Smith earned her B.S. in chemistry in 2015 from U.C. Berkeley (USA), where she performed research under the guidance of Prof. F. Dean Toste. Following graduation, she took a gap year to work as a process chemist at Genentech. She is currently pursuing her Ph.D. at The Scripps Research Institute (Florida, USA) working under the tutelage of Prof. Hans Renata.

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C.N.R. – Istituto di Chimica del Riconoscimento Molecolare
Via Mancinelli, 7, 20131 Milano, Italy
Editorial Assistant: Alison M. Sage
synform@outlook.com; fax: +39 02 23993080

Editorial Office

— Managing Editor: Susanne Haak,
susanne.haak@thieme.de, phone: +49 711 8931 786
— Scientific Editors:
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— Senior Production Editors:
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sophia.hengst@thieme.de, phone: +49 711 8931 398
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Tobias.brenner@thieme.de, phone: +49 711 8931 769
— Editorial Assistant: Sabine Heller,
sabine.heller@thieme.de, phone: +49 711 8931 744
— Marketing Director: Julia Stötzner,
julia.stoetznern@thieme.de, phone: +49 711 8931 771
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