Chemoselective Palladium-Catalyzed Deprotonative Arylation/[1,2]-Wittig Rearrangement of Pyridymethyl Ethers

Highlighted article by F. Gao, B.-S. Kim, P. J. Walsh
Dear Readers,

Once again catalysis has a starring role in this June issue of SYNFORM, and its presence is as chameleonic as that of Gary Oldman or Christian Bale in their filmography. In the first story X.-S. Ye (P. R. of China) takes us through a novel transformation of 2-nitro-glycals into nitro-polyols which takes advantage of an organocatalytic C=C bond cleavage promoted by pyridine. The second article zooms in on a very intriguing biocatalytic transformation developed by R. Fasan (USA) that allows for the olefination of aldehydes by α-diazo esters using the iron- and oxygen-binding protein myoglobin as catalyst. The shapeshifting continues in the third contribution, which is an account on the palladium-catalyzed arylation/[1,2]-Wittig rearrangement of pyridylmethyl ethers leading to a wide range of pyridylaryl-carbinols and derivatives thereof, that was published recently by P. J. Walsh (USA). The metamorphosis is completed and recapitulated in the final Young Career Focus interview with R. Tong (P. R. of China) who routinely makes extensive use of a wide range of catalytic methods in his total syntheses of complex natural compounds.

Enjoy your reading!

Matteo Zanda
Iminosugars, which are widely represented among natural products, possess many important biological activities, such as glycosidase inhibition, immune modulatory and chaperoning activity. However, only relatively few iminosugars are available for pharmaceutical evaluation due to difficulties connected with their separation and synthesis. Recently, Professor Xin-Shan Ye from Peking University (P. R. of China) and co-workers developed a new and convenient method for achieving the synthesis of nitro-polyls and further explored their applications in the synthesis of iminosugars.

Professor Ye’s group has studied in detail iminosugars as immunosuppressive agents or promising drugs for treating Gaucher’s disease by exploiting their capacity to act as molecular chaperones. Professor Ye said: “We have always tried to find efficient ways to synthesize various kinds of iminosugars. Carbohydrates are ideal starting materials due to their easy accessibility. What’s more, carbohydrates are considered a ‘chiral pool’ by organic chemists.” Glycals are important building blocks in synthetic carbohydrate chemistry and many ‘chiral synthons’ can be obtained via the scission of the carbon–carbon double bond in glycals. However, this conversion always took place under harsh conditions. “So, we introduced a nitro group at the C-2 position of glycals to make the cleavage of the double bond easier, leading to nitro-sugar derivatives,” explained Professor Ye, continuing: “The chain-type nitro-polyl derivatives obtained are versatile intermediates, and have the potential to provide a synthetic entry to monocyclic and bicyclic iminosugars by means of Henry, Michael and various cycloaddition reactions, and the nitro group can be reduced to the amino group as well.”

According to Professor Ye, only a handful of methods for the preparation of nitro-polyl derivatives are described; therefore, new synthetic methods are needed. “We use a Michael-type water addition–retro-Henry-type reaction to break the double bond in 2-nitroglycals,” said Professor Ye. “This is a novel, mild and efficient method for the synthesis of nitro-polyl derivatives.” After optimization of the reaction conditions, the authors found that the quantitative conversion could be accomplished at room temperature for 24 hours with pyridine as both solvent and base, and water was essential for the transformation to be efficient. “To our delight, we found that nitration of glucal and scission of the carbon–carbon double bond could be conducted in a sequential manner without significantly reduced yield,” said postgraduate student Shengbiao Tang, the first author of this paper, “and we also expanded this method to a series of glycoforms with different protecting groups.”
To verify the capacity and scope of this method, the authors applied one of the obtained nitro-polyl derivatives to the synthesis of 7a-epi-(−)-hyacinthacine A1, which is a bicyclic polyhydroxylated pyrrolidine compound. The nitro-polyl underwent a good stereoselective Michael addition reaction at first and was then transformed to 7a-epi-(−)-hyacinthacine A1 in 69% yield over four steps.

“In summary, a new and convenient transformation method for the synthesis of nitro-polyls via a pyridine-promoted scission of the carbon–carbon double bond in 2-nitroglycals has been developed. Moreover, a concise and asymmetric total synthesis of (−)-hyacinthacine A1 and 7a-epi-(−)-hyacinthacine A1 was achieved in four steps from the Michael addition products of one obtained nitro-polyl intermediate in high overall yield,” said Professor Ye, concluding: “Thus, this protocol may be widely used in the preparation of nitro-sugar intermediates of iminosugars and other bioactive natural or non-natural products.”

Dr. D.-C. Xiong

De-Cai Xiong obtained his B.S. degree in 2005 from Lanzhou University (P. R. of China) and his Ph.D. in 2010 from Peking University (P. R. of China), becoming a research assistant in Professor Xin-Shan Ye’s lab in 2010. His research involves synthetic organic chemistry, organometallic chemistry, theoretical and computational chemistry, carbohydrate chemistry, medicinal chemistry, and chemical biology.

Shengbiao Tang was born in Hunan Province (P. R. of China) in 1987. He received his B.S. degree from South-Central University for Nationalities (Wuhan, P. R. of China) in 2011 and then became a graduate student under the supervision of Professor Shende Jiang at Tianjin University (P. R. of China). Since August 2013, he has been a Ph.D. student and an exchange student in Professor Xin-Shan Ye’s lab at Peking University (P. R. of China). His main research interest is the development of synthetic methodology from glycals.
Myoglobin-Catalyzed Olefination of Aldehydes


Biocatalytic processes are widely used by pharmaceutical companies for synthesizing small-molecule drugs and intermediates. Biocatalysis is currently of enormous interest both in academia and industry for its capacity to produce a wide range of chemicals under more environmentally and economically sustainable conditions. Recently, Professor Rudi Fasan’s group at the University of Rochester (USA) reported the first example of a biocatalytic aldehyde olefination. Essentially, the authors demonstrated that engineered active-site variants of myoglobin constitute efficient catalysts for the conversion of aryl aldehydes into olefins in the presence of α-diazo esters and triphenylphosphine or triphenylarsine. This reaction is equivalent to the venerable and widely utilized Wittig reaction but it proceeds under neutral instead of basic conditions, thus eliminating incompatibility problems with basesensitive functional groups in the reactants. Professor Fasan explained: “This transformation was previously known to be catalyzed by synthetic transition-metal catalysts, but an enzymatic counterpart was not available prior to our work. Most importantly, we developed a myoglobin-based catalyst, Mb(F43V,V68F), that can promote this transformation with exquisite diastereoselectivity (95–99.9% de) while supporting one to two orders of magnitude higher catalytic turnovers (1,100–4,900 TON) than state-of-the-art transition-metal-based catalysts (Scheme 1).” In addition, the myoglobin-catalyzed reaction proceeds in aqueous solvent and at

Scheme 1 Substrate scope of Mb(F43V,V68F)-catalyzed olefination of aldehydes

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room temperature, while previously reported methods require aromatic solvents and elevated temperatures. Notably, Mb(F43V,V68F) also exhibits a remarkably broad substrate scope and could be readily applied for the transformation of a variety of aldehyde substrates, including electron-rich and electron-deficient benzaldehyde derivatives, heteroaromatic aldehydes, and benzylic aldehydes (Scheme 1).

“My group has been interested in exploring the synthetic potential of myoglobin and other heme-containing proteins as catalytic platforms for promoting nitrene- and carbene-transfer reactions,” said Professor Fasan. Having previously established that engineered variants of myoglobin can catalyze carbene-mediated reactions such as olefin cyclopropanation, N–H and S–H insertions with high efficiency and selectivity, a key insight that opened the way to the present work derived from the mechanistic studies on myoglobin-catalyzed S–H functionalization of mercaptans performed by the Fasan group, which supported the possibility of forming a myoglobin-bound sulfonium ylide catalytic intermediate.12

“We reasoned that if a phosphonium ylide could be generated upon attack of a phosphine to the electrophilic heme-carbene complex with the active site of the protein, such intermediate could then engage an aldehyde substrate in a Wittig-type olefination reaction,” said Professor Fasan. He continued: “At the planning stage, we were uncertain about whether a bulky tertiary phosphine such as PPh3 could access the active site of the protein to undergo the envisioned catalytic process. Some initial experimentation, however, showed us the feasibility of the strategy and, along with it, the plasticity of the myoglobin scaffold.” Further optimization studies indicated the superiority of triphenylarsine compared to triphenylphosphine to allow for the olefination reaction to proceed with high E-selecitivity. The reasons for this effect are not entirely clear and the group hopes that computational studies will soon provide insights into this matter.

Professor Fasan said: “Next, we screened a panel of myoglobin variants with modified active sites in order to identify one that provided the optimal combination of high catalytic activity with high chemo- and stereoselectivity. Mb(F43V,V68F) (Figure 1) emerged as the most promising catalyst in this initial study, but it is clear that there is room for improvement.” Among the objectives for the group is the development of myoglobin-based catalysts that can provide higher product conversions, for example by engineering them to be less sensitive to product inhibition. According to Professor Fasan, another challenge will be to develop myoglobin-based catalysts that can offer high levels of catalytic activity and selectivity toward aldehyde olefination in the presence of phosphine-based reagents instead of the considerably more expensive arsenic-based counterparts. “Among others, an attractive feature of the myoglobin system is that whereas it presents a well-defined active site (Figure 1), there are countless ways in which such an active site can be reshaped by mutagenesis in order to implement and fine-tune these catalytic properties,” explained Professor Fasan, continuing: “Furthermore, libraries of these genetically encoded biocatalysts can be readily produced and screened in a high-throughput manner to facilitate catalyst optimization efforts. Last but not least, we are gathering accumulating evidence from this and our previous studies that, unlike most enzymes, these myoglobin-based catalysts exhibit a remarkably broad substrate profile and predictable reactivity. So, they seem to combine the best of the two worlds, that is the exquisite selectivity characteristic of biological catalysts with the predictable reactivity and broad substrate scope typical of synthetic catalysts.”

In terms of mechanism, the authors of this study suspect that the reaction involves the formation of an electrophilic heme-bound carbeneoid intermediate that reacts with the tertiary phosphine/arsine to give rise to a phosphonium/arsonium ylide. The latter then reacts with the aldehyde to form an oxaphosphetane/oxarsetane intermediate which rearranges to yield the olefination product along with phosphine/arsine oxide as the byproduct (Scheme 2). “An intriguing, open question concerns how the protein scaffold transfers chirality onto the catalytic steps and intermediates to drive the reaction with an excellent degree of stereoselectivity,” said Professor Fasan.
Fasan. “Our experiments suggest that this must occur during the formation of the oxaphosphetane/oxarsetane intermediate but the molecular mechanisms behind this process await further elucidation.”

Professor Fasan revealed that this project was single-handedly executed by a very talented and dedicated postdoctoral fellow, Dr. Vikas Tyagi, who has been complementing his background in diversity-oriented synthesis with experience in biocatalysis, mechanistic enzymology, and chemoenzymatic synthesis.

“Biocatalysis is covering an increasingly important role in the manufacturing of fine chemicals, advanced pharmaceutical intermediates, and pharmaceuticals. However, the scope of biocatalysis in this field is currently limited to chemical transformations carried out by natural enzymes,” said Professor Fasan, who concluded: “With this and other contributions from our group, we hope to change this paradigm by making available new classes of biocatalysts for promoting synthetically valuable carbon–carbon and carbon–heteroatom bond forming reactions not found in nature.”

**REFERENCES**

About the authors

Rudi Fasan was born in Italy and received his B.Sc. from the University of Padua (Italy) in 1999. He obtained his Ph.D. in 2005 from the University of Zurich (Switzerland) working on beta-hairpin protein epitope mimetics under the supervision of Professor John Robinson. He then joined the Professor Frances Arnold’s group at the California Institute of Technology (USA) as a Swiss National Science Foundation postdoctoral fellow, working on the directed evolution of P450 enzymes for alkane oxidation. Rudi began his independent career in the Department of Chemistry at the University of Rochester (USA) in 2008 and was promoted to the rank of Associate Professor in 2014. His laboratory focuses on the synthesis and investigation of peptide-based macrocycles as inhibitors of protein–protein interactions and on the design, development, and application of metalloprotein catalysts for C(sp³)–H functionalization and asymmetric carbon–carbon and carbon–heteroatom bond formation.

Vikas Tyagi was born and raised in Uttar Pradesh (India). He obtained his M.Sc. in 2007 from C.C.S. University (Meerut, India). In 2013, he received his Ph.D. in chemistry from Central Drug Research Institute at Jawaharlal Nehru University (Delhi, India) under the supervision of Dr. Prem M. S. Chauhan, where he worked on diversity-oriented synthesis of biologically active N-heterocyclic compounds. He joined the group of Professor Rudi Fasan at the University of Rochester (USA) as a postdoctoral fellow in December of 2013. His postdoctoral research has focused on the development and investigation of engineered myoglobin catalysts for promoting ‘non-native’ carbenemediated organic transformations.
Chemoselective Palladium-Catalyzed Deprotonative Arylation/[1,2]-Wittig Rearrangement of Pyridylmethyl Ethers


Transition-metal-catalyzed cross-coupling reactions are among the most useful and versatile methods in the field of synthetic organic chemistry, especially to form key carbon–carbon bonds. A long-standing goal of this chemistry is to develop efficient methods to provide valuable compounds found in natural products and bioactive small molecules. While classical approaches use prefunctionalized nucleophiles, recent trends in the area of the cross-coupling chemistry involve direct functionalization of simple starting pronucleophiles (Scheme 1).

Recently, Professor Patrick J. Walsh’s group at the University of Pennsylvania (USA) has been interested in the functionalization of weakly acidic C(sp^3)–H bonds (pK_a > 25) through a deprotonative cross-coupling process (DCCP), wherein a weakly acidic C–H of the substrate is deprotonated by a base and functionalized in the presence of a transition-metal catalyst (Scheme 2). The scope of substrates they reported to date includes diarylmethanes, amides, sulfoxides, N-Boc-benzylalkylamines, benzyl thioethers, benzylic phosphonates, benzyl imines, and 2-aryl-1,3-dithianes, among others.

“One of the most significant outcomes of our initial investigations is that van Leeuwen’s NIXANTPHOS ligand exhibits extraordinary reactivity under basic reaction conditions (*J. Am. Chem. Soc.* 2012, 134, 13765),” said Professor Walsh. The role of bases in the reaction is essential to accomplishing this process. Professor Walsh explained: “First, the base reversibly deprotonates the pronucleophiles (R–H in Schemes 1 and 2). Likewise, NIXANTPHOS’ free N–H is deprotonated under the reaction conditions and the resulting heterobimetallic catalyst (Pd-NIXANTPHOS-M) displays exceptional reactivity when compared with other bidentate phosphine-based palladium catalysts (Scheme 2).”

Graduate student Byeong-Seon Kim envisioned a unified approach to access a series of important pyridyl-containing building blocks. Professor Walsh and co-workers considered the synthesis of a series of aryl(pyridin-2-yl)methanol cores, intrigued by the idea of using pyridylmethyl derivatives (Figure 1).
The strategy in this work (Scheme 3) entails deprotonation of the pyridylmethyl ether (A) to generate anion B, which can undergo a [1,2]-Wittig rearrangement to form C. “The anion B must be intercepted by the palladium catalyst faster than it undergoes the [1,2]-Wittig rearrangement,” explained Professor Walsh. “Interception of anion B, through transmetalation to the catalyst, enters into the cross-coupling manifold affording pyridylmethyl ether D.”

Professor Walsh remarked: “The next challenge is the control of the [1,2]-Wittig rearrangement. Compound D possesses a more acidic benzylic C–H than pyridylmethyl ether A, and deprotonation of D will lead to the [1,2]-Wittig rearrangement via E to form F.”

A number of reaction parameters were examined to either promote or inhibit the [1,2]-Wittig rearrangement, including the base, solvent, and temperature. “We found that remarkable chemoselectivity was possible by a choice of the base’s main group metal (Na vs. Li), the solvent (DME vs. CPME), and the reaction temperature (room temperature vs. > 45 °C) (Scheme 4),” explained Professor Walsh. It was found that the [1,2]-Wittig rearrangement of the arylation product D is retarded at room temperature by a coordinating solvent like DME, particularly when the sodium base is used. In contrast, operating at 45 °C with the lithium silylamide in non-coordinating solvents favors the [1,2]-Wittig rearrangement.

“The work showed that both reaction pathways are compatible with electron-deficient, -rich, -neutral, ortho-substituted, and heterocyclic aryl bromides,” said Professor Walsh. “Moreover, the arylation occurs with 2- or 4-pyridylmethyl ethers, showing that the reaction does not require a directed metatlation for deprotonation. However, the 4-pyridylmethyl derivatives were not suitable for tandem arylation/[1,2]-Wittig rearrangement under the optimized conditions,” he continued. “It is worth pointing out that the scalability of both arylation and tandem arylation/[1,2]-Wittig rearrangement reactions were illustrated with 5 mmol scale reactions to provide the product of either arylation or tandem arylation/ [1,2]-Wittig rearrangement.”
Professor Walsh concluded: "With high chemoselectivity, structural diversity can be forged from a common set of substrates. This is particularly true with tandem reactions, where several bonds are formed under nearly identical conditions without isolation of intermediates, addition of new reagents, or modification of reaction parameters." He continued: “This straightforward technique enables rapid preparation of various types of aryl(azaaryl)methyl derivatives, making it ideal for applications in the field of organic synthesis." The Walsh group has also shown that pyridylmethyl silyl ethers are good substrates for the arylation reaction (Scheme 3, $A \rightarrow D$, $R = SiR_3$, *Org. Lett.* 2016, 18, 1590).

About the authors

**Byeong-Seon Kim** was born in Andong (South Korea). He received his B.Sc. in chemistry from Korea University (South Korea) in 2003 and M.Sc. in Professor Deok-Chan Ha’s group in 2005. He was a research scientist at Korea Institute of Science and Technology (KIST, Seoul, South Korea) for one year. He is currently a Ph.D. student at the University of Pennsylvania (USA) under the supervision of Professor Patrick J. Walsh. His current research interest is in the field of homogeneous catalysis to develop fundamental bond-forming reactions and its application in new synthetic methods.

**Feng Gao** was born in Chengdu (P. R. of China). He received his B.Sc. in pharmacy science from Sichuan University (P. R. of China) in 2002 and Ph.D. in medicinal chemistry of natural products under the guidance of Professor Feng-Peng Wang in 2009. Then he moved to Sichuan Agricultural University (P. R. of China) where he was promoted to associate professor in 2010. From August 2013 to August 2014, he joined Professor Patrick J. Walsh’s group at the University of Pennsylvania (USA) as a visiting scholar. His current research focuses on homogeneous catalysis and its application in natural products chemistry.

**Patrick J. Walsh** received his B.A. from UC San Diego (USA, 1986) and Ph.D. in chemistry at UC Berkeley (USA) with Professor Robert G. Bergman (1991). He was an NSF postdoctoral fellow with Professor K. B. Sharpless at the Scripps Research Institute (La Jolla, USA). Moving across town from 1994–1999, he was an assistant professor at San Diego State University (USA) and also Professor at Centro de Graduados e Investigación, Instituto Tecnológico de Tijuana (Mexico) from 1996–1999. In 1999, he moved to the University of Pennsylvania (USA) where he was promoted to Professor in 2005, and to the Alan G. MacDiarmid Professor of Chemistry in 2008. Walsh’s interests are in asymmetric catalysis, development of new synthetic methods, reaction mechanisms, and inorganic synthesis. With Professor Marisa Kozlowski, Walsh co-authored “Fundamentals of Asymmetric Catalysis” (University Science Books, 2008).
Young Career Focus: Professor Rongbiao Tong (Hong Kong University of Science and Technology, P. R. of China)

Background and Purpose. SYNFORM regularly meets young up-and-coming researchers who are performing exceptionally well in the arena of organic chemistry and related fields of research, in order to introduce them to the readership. This Young Career Focus presents Professor Rongbiao Tong (Hong Kong University of Science and Technology, P. R. of China).

Biographical Sketch
Rongbiao Tong was born in Guangdong province, P. R. of China. He received his BS and MS degrees in chemistry from Hunan University (P. R. of China) in 2000 and 2003, respectively. He continued his graduate studies on natural product synthesis under the guidance of Professor Frank E. McDonald at Emory University (Atlanta, GA, USA) and was awarded a PhD degree in 2008. After working with Professor Amos B. Smith, III at the University of Pennsylvania (Philadelphia, PA, USA) as a postdoctoral fellow (2008–2011), he started his independent research career as a tenure-track Assistant Professor in the Department of Chemistry at the Hong Kong University of Science and Technology (P. R. of China) in July 2011. His current research interests include the development of new synthetic methods and total synthesis of natural products by strategic exploitation of oxidative dearomatization of phenols and furfuryl alcohols and biosynthetic hypothesis.

INTERVIEW
SYNFORM What is the focus of your current research activity?
Prof. R. Tong My research group and I are particularly focused on the total synthesis of natural products through development of novel synthetic technologies and strategies, which are expected to lay the groundwork for other chemistry related programs: drug discovery, new synthetic methodology, new natural product synthesis, and undergraduate/graduate student training. Strategically, oxidative dearomatization of phenols and furfuryl alcohols has been fully exploited in the early stage of our synthetic ventures, which further explore the biomimetic tactics, cascade reactions, skeletal rearrangements, non-classical chemical transformations to advance organic synthesis and the art and science of total synthesis. Our current targets include polyketides, diterpenoids, diarylheptanoids, spiroketals, and alkaloids, most of which contain novel structural motifs and/or display potent and diverse biological activities. In addition, we are also interested in the development of new synthetic protocols that would not only complement the previous methods but also offer the advantages of practicability, simple operation, high efficiency, flexibility and/or scalability.

SYNFORM When did you get interested in synthesis?
Prof. R. Tong In 1999, it was time for me to choose a program for graduate studies, because my college days were coming to an end soon (2000) and chemistry-related industrial jobs were unattractive and very limited. In the course of in-depth reviewing of Organic Chemistry for the Graduate Entrance Exam of China, I was fascinated by the mechanisms of organic reactions (carbon–carbon bond formations and functional group interconversions) and the power of organic synthesis in making molecules. This interest was further consolidated at Emory University (USA, 2003–2008) where my PhD advisor Professor Frank E. McDonald taught the unbelievably thought-provoking Advanced Organic Chemistry B and guided me to pursue the most cutting-edge research in organic synthesis. The research experience at Emory together with the exceptional and inspirational guidance by Professor McDonald transformed me into an enthusiastic and optimistic organic chemist. My postdoctoral research under the guidance of Professor Amos B. Smith, III at the University of Pennsylvania (USA) certainly inspired me to think critically about the
role of synthetic tactics in total synthesis and made me more interested in the development of practical synthetic methods.

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

**Prof. R. Tong** This is a tough question because organic synthesis has evolved tremendously over the past century and impacted nearly all aspects of our lives: clothing, foods, electronics, fuels (c.f., energy and environment), drugs, etc. Organic synthesis will continue to play these traditional roles in contemporary research as the most effective tool to make substances at the molecular level with designed physical, chemical and biological properties. In particular, recent advances in chemical and molecular biology as well as organic materials science require organic synthesis in order to understand the underlying molecular mechanism and functions, which are still in their infancy. In this regard, I believe that organic synthesis will shape the future and development of biology and materials science. As for the development of organic synthesis itself (conventionally classified into synthetic methodology and total synthesis), new synthetic methods and synthetic strategies are updated daily, revolutionizing the way of making molecules, and demonstrating the creativity and imagination of human beings. Therefore, organic synthesis is rapidly evolving to address the challenges of molecular sciences and will continue to flourish in the coming decades.

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

**Prof. R. Tong** Our research programs in the area of synthetic methods focus on the development of novel protocols to address the synthetic challenges in one or more of the following aspects: efficiency, practicability, scalability, accessibility, reproducibility, flexibility, etc. For example, (1) in situ generation of chlorine gas or its direct derivatives for diastereoselective dichlorination of alkenes was achieved by simple mixing of the nontoxic, low-cost oxone and sodium chloride; (2) substituted tetrahydropyran-4-ones could be rapidly and efficiently assembled in four steps from readily available enals, hydroxylamines, and alkenes; (3) the poorly accessible cis-fused bicyclic ethers could be forged by double cascade reactions: Achmatowicz rearrangement/bicycletaliztion and spiroketal reduction/oxa-Michael cyclization. Our total synthesis programs aim at developing novel and/or general synthetic strategies for a family of natural products. In this regard, in the past five years we have developed four general strategies to access four families of natural products, respectively: cephalosporolides and SAFLs, 6,8-DOBCOs (Scheme 1), protoberberines and aporhaeadanes, and trans-2-aryl-6-alkyltetrahydropyrans. One of the key features of these synthetic strategies is to explore the oxidative deaeromatization of phenols and furfuryl alcohols (Scheme 1). On the other hand, we are interested in biomimetic synthesis of structurally novel natural products such as tenuipyrene, penicyprone, spirooliganones A and B, ascospiroketals A and B, etc. through development of new biomimetic cascade reactions.

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

**Prof. R. Tong** Each project (synthetic method or total synthesis) addresses a synthetic challenge or problem, which has its scientific value and importance on one hand or the other, specifically or generally. For example, we reported first total syntheses of natural products that confirmed the molecular structures and provided a viable strategy and route for their chemical synthesis. If a biomimetic approach is employed in the synthesis, the corresponding biosynthesis is well supported by such synthetic studies. We are not able to evaluate which of these contributions is the most scientifically important one. However, if pressed to say something about it in my early career, I would like to recommend the exploitation of the Achmatowicz rearrangement (AchR) in total synthesis of natural products. We have made tremendous efforts to expand the synthetic utilities of the Achmatowicz rearrangement in organic synthesis, which has led to the development of concise synthetic strategies for the total syntheses of musellarins A–C in both racemic and enantioselective fashions, uprolide G acetate, uprolide F diacetate, psoracorylifol B, ent-psoracorylifol C, attenols A and B, didemniserinolipid B, diospongin B, and parvistones D and E.
Scheme 1 General synthetic strategies for the total synthesis of cephalosporolides and SAFLs and 6,8-DOBCO-containing natural products
Selective Aldol Reactions of SF₅-Acetic Acid Esters with Coupled Catalytic Cycles and Piperidines from Ynamides

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