

SYNFORM

People, Trends and Views in Synthetic Organic Chemistry

2008 / 06

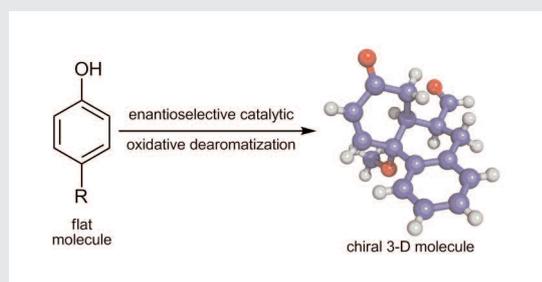
SYNSTORIES ■ ■ ■ ■

■ Making the Baeyer–Villiger (BV) Reaction Catalytic and Enantioselective with Chiral Brønsted Acid Using Aqueous H_2O_2 as the Terminal Oxidant

■ An Enantioselective Organocatalytic Oxidative Dearomatization Strategy

■ Proline-Catalyzed Mannich Reactions of Acetaldehyde

■ Synthesis and Absolute Configuration of Hormone $\alpha 1$



CONTACT ++++

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Dear readers,

Organocatalysis continues to represent a major topic and a very competitive area of research in the arena of organic chemistry. It is therefore not surprising that three out of the four **SYNSTORIES** that constitute this new issue of

SYNFORM are dedicated to new organocatalytic processes. Professor Kuiling Ding (P. R. of China) shows how to perform an old Baeyer–Villiger reaction in a brand new enantioselective manner using a chiral Brønsted acid as organocatalyst. Professor Benjamin List (Germany) describes how to use a simple yet challenging substrate like acetaldehyde as nucleophile in organocatalytic Mannich reactions. Finally, Dr. Matthew J. Gaunt (UK) reports how phenols can be oxidatively dearomatized in an enantioselective manner by means of organocatalysis. There is little doubt that organocatalysis is progressively broadening its scope, although much research remains to be done in order to see more real-life synthetic problems solved by means of this powerful technology. The fourth **SYNSTORY** covers an extremely exciting piece of bioorganic synthesis reported jointly by Dr. Arata Yajima (Japan) and Professor Yong Qin (P. R. of China) who were able to synthesize and characterize stereochemically a structurally challenging hormone of a fungus-like plant pathogen.

Enjoy your reading!

Matteo Zanda

Editor of **SYNFORM**

CONTACT ++++

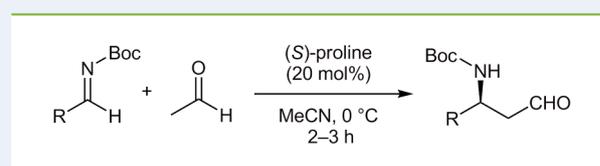
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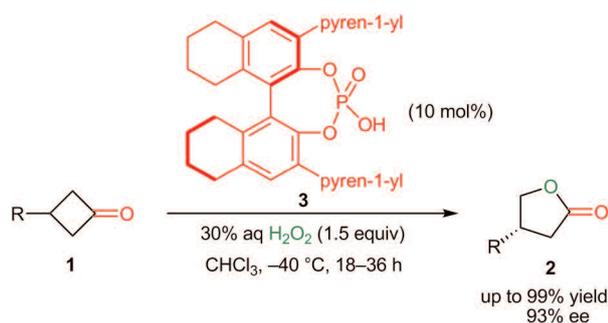
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Making the Baeyer–Villiger (BV) Reaction Catalytic and Enantioselective with Chiral Brønsted Acid Using Aqueous H₂O₂ as the Terminal Oxidant

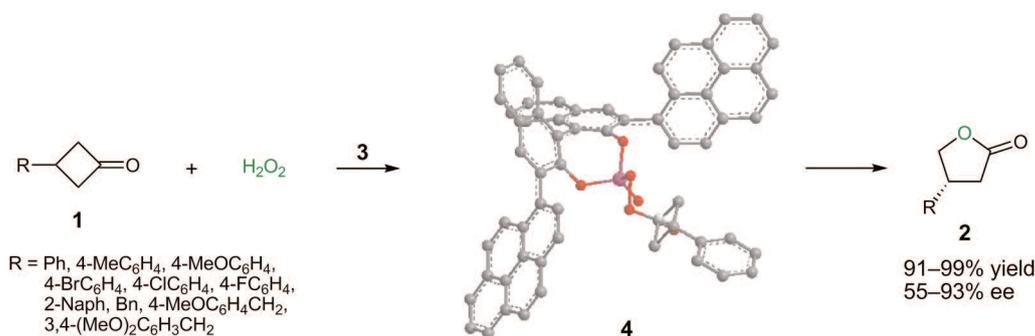
Angew. Chem. Int. Ed. **2008**, *47*, 2840–2843



The Baeyer–Villiger (BV) reaction, discovered in 1899, represents one of the most well-known and widely applied reactions in organic synthesis. Although more than a century has gone by since its discovery, the BV reaction is far from being at the end of its development. The use of stoichiometric amounts of peracid as the oxidant suffers from disadvantages – such as expensive and hazardous (because of shock-sensitivity) reagents, with the simultaneous formation of one equivalent of corresponding carboxylic acid waste – which limit their practical application. Therefore, the use of aqueous hydrogen peroxide as the stoichiometric oxidant in the presence of a promoter has been the focus of attention from the viewpoint of green chemistry. On the other hand, the area of catalytic asymmetric BV reactions is also far from fully developed even though its first enantioselective version was realized in 1994 by Strukul and Bolm independently. Since then, a variety of chiral metal complexes (or organic molecules) have been developed for application as promoters in the enantioselective BV reaction of various ketones in stoichiometric or catalytic quantity, but only very few catalyst systems are compatible with the use of the environmentally benign and economically viable aqueous hydrogen peroxide as the terminal oxidant. Another challenging issue of the catalytic asymmetric BV reaction is the difficulty associated with enantioselectivity control. The state-of-the-art of this reaction is that no chemical catalysts are able to afford products in more than 86% ee

in the catalytic BV oxidation of 3-substituted cyclobutanones, despite the fact that some enzymes demonstrate excellent enantiocontrol in the catalysis.

A new breakthrough in this area was realized very recently by Professor Kuiling Ding and his PhD student Senmiao Xu, as well as his Associate Professor Zheng Wang and Research Assistant Dr. Xue Zhang, at the Shanghai Institute of Organic Chemistry (SIOC), Chinese Academy of Sciences (P. R. of China). Senmiao Xu is also a joint PhD student with Dr. Xumu Zhang, a guest professor at SIOC, who is currently a professor at the State University of New Jersey (USA). The research was inspired by the facts that the BV reaction can be accelerated in the presence of strong Brønsted acids and that the reactivity of the peracid is dependent on the acidity of the corresponding Brønsted acid. “We envisioned,” explained Professor Ding, “that chiral peroxophosphoric acid, formed in situ from binol-derived phosphoric acid with hydrogen peroxide, might be suitable for catalyzing the BV reaction in an enantioselective manner through intermediate **4**. This concept also can be considered as an extension of our previous research on hydrogen-bond-promoted enantioselective reactions (*Chem. Eur. J.* **2004**, *10*, 5964; *J. Org. Chem.* **2006**, *71*, 2862).” The feasibility of the principle was demonstrated by the observation that a binol-derived phosphoric acid (10 mol%) can significantly accelerate the BV oxidation of 3-phenylcyclobutanone with aqueous H₂O₂ (30%), giving 3-phenyl- γ -butyrolactone in excellent yield (99%), albeit with very poor enantioselectivity (ca. 2% ee). Furthermore, no reaction occurred in the absence of phosphoric acid under otherwise identical experimental conditions. After screening a variety of binol-based phosphoric acids with diverse steric and electronic properties of the 3,3′-substituents and the backbone of the scaffold, catalyst **3**, which features bulky pyren-1-yl groups at the 3,3′-positions with a 5,5′,6,6′,7,7′,8,8′-octahydro-1,1′-binaphthyl backbone turned out to be optimal. “The BV oxidation of a variety of 3-aryl-substituted cyclobutanones **1** with aqueous hydrogen peroxide in the presence of a catalytic amount of binol-derived chiral phosphoric acids (1–10 mol%) afforded the corresponding chiral γ -lactones **2** in high yields (91–99%) and good to excellent enantioselectivities (82–93%

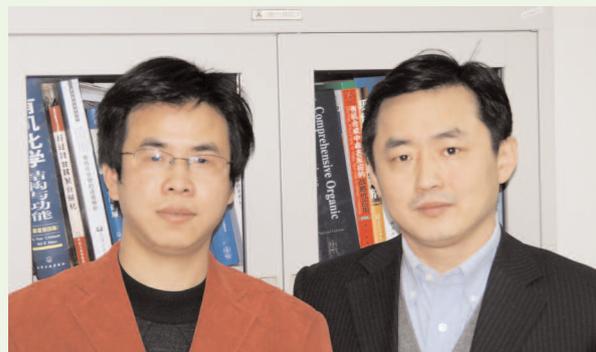


ee) under mild reaction conditions,” said Professor Ding, “although the reactions of 3-alkyl-substituted or 3,3-disubstituted cyclobutanones gave the corresponding lactones with only moderate enantioselectivities (55–61% ee).” When the catalyst loading was further reduced to 1 mol%, the oxidation of 3-(4-tolyl)cyclobutanone proceeded smoothly without any loss of enantioselectivity (93% ee).

“The present catalytic system possesses several advantageous features in terms of the following aspects,” said Professor Ding: “1) Although chiral phosphoric acids have been widely used in the catalysis of a variety of asymmetric transformations, including nucleophilic addition of aldimines, transfer hydrogenation, Diels–Alder reaction, Nazarov cyclization, multicomponent condensation and so on, this catalytic system represents the first example of a catalytic asymmetric (BV) oxidation with chiral phosphoric acid. 2) Both the activity and the enantioselectivity of the catalyst are the highest among the chemical catalysts (organometallic or organocatalysts) discovered so far for the asymmetric BV oxidation of 3-substituted cyclobutanones. 3) The use of aqueous hydrogen peroxide (30%) as the terminal oxidant merits green chemistry since water is the only byproduct formed.”

However, despite these very promising results, some challenges still remain for the further development of the procedure. “Although excellent enantioselectivities have been achieved for a broad range of 3-aryl cyclobutanones using the present procedure,” recognized Professor Ding, “further development of the catalyst is still required to extend its synthetic utility to more challenging substrates, for example, more flexible 3-alkyl cyclobutanones or more sterically demanding 3,3-disubstituted cyclobutanones.” Some of their corresponding lactones are particularly useful in the synthesis of natural products. “Detailed mechanistic studies for clarifying the substrate activation pathway and the origin of selectivity control in the cata-

lytic process are critically important for the rational design of new-generation catalysts for the target reaction,” concluded Professor Ding. ■



From left: S. Xu, Prof. K. Ding

About the corresponding author

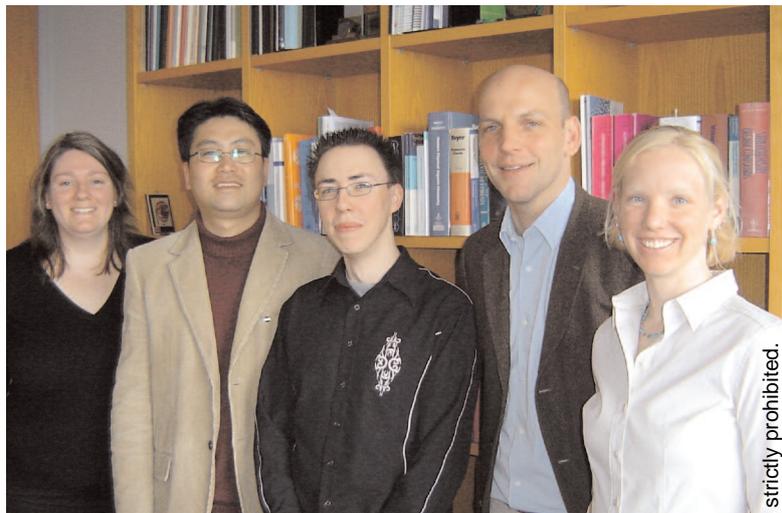
Kuilong Ding was born in 1966 in Henan Province, P. R. of China. He received his BSc degree from Zhengzhou University (1985) and his PhD from Nanjing University (1990) under the supervision of Professor Yangjie Wu. He was a faculty member of Zhengzhou University from 1990–1998, and was promoted to Full Professor in 1995. In 1993–1994 he was engaged in postdoctoral research with Professor Teruo Matsuura at Ryukoku University (Japan). In the period from 1997–1998 he was a UNESCO research fellow with Professor Koichi Mikami at the Tokyo Institute of Technology (Japan). He joined the Shanghai Institute of Organic Chemistry in 1999, where he currently is a professor of chemistry. His research interests include the development of new chiral catalysts and methodologies for asymmetric catalysis.

Inspiration and a team effort in the lab ultimately led to success, and List and co-workers obtained the products in reasonable to good yields and excellent enantioselectivities. "Moreover," Professor List said, "we were also able to develop several applications of our products, some of them offering shortcuts in the syntheses of newly approved drugs."

"Our report," said Professor List, "together with that of Hayashi and co-workers, who independently developed the corresponding cross-aldol reaction,⁴ describes the first useful applications of acetaldehyde as a nucleophile in organic synthesis. We are convinced of its enormous potential and are currently investigating several other reactions of acetaldehyde. For example, we have developed analogous organocatalytic asymmetric Michael reactions that provide the corresponding products in high enantioselectivities.⁵ The importance of our present work," he concluded, "is underlined by the fact that pharmaceutical companies have already expressed their interest in its use." ■

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From left: D. Kampen, Dr. J. W. Yang, M. Stadler, Prof. B. List, Dr. C. Chandler

An Enantioselective Organocatalytic Oxidative Dearomatization Strategy

J. Am. Chem. Soc. **2008**, *130*, 404–405

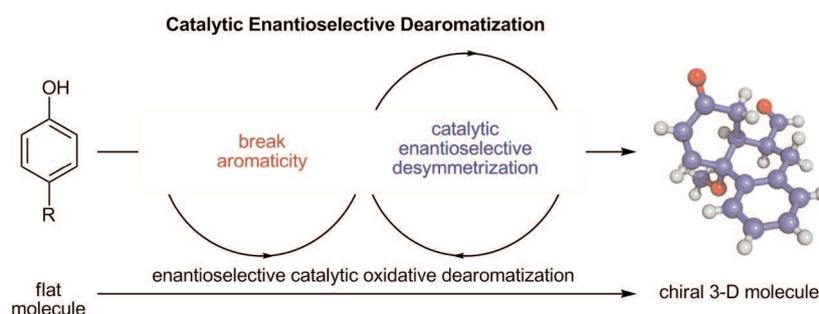
Dearomatization of substituted phenols followed by a desymmetrization reaction to form chiral intermediates represents a popular strategy for synthesizing natural product molecules. A further contribution in this area was recently reported by Dr. Matthew J. Gaunt and his group at the University of Cambridge (UK), who disclosed a catalytic enantioselective single-reaction method for direct conversion of phenols into highly functionalized chiral molecules. Gaunt and co-workers carried out fast oxidation of *para*-substituted phenols to form cyclohexadienones coupled with an amine-catalyzed intramolecular Michael addition. Oxidation of the phenol ring occurs rapidly without affecting the aldehyde side chain by using methanol as the solvent and nucleophile and a hypervalent iodine oxidizing reagent, $\text{PhI}(\text{OCOMe})_2$. Minimal contact between the iodine reagent and the chiral amine catalyst prevents side reactions and the protic solvent methanol helps to control the stereochemistry. The results are complex, non-racemic, polycyclic molecules containing three new stereogenic centers and an array of functional groups amenable to further reaction.

“The inherent reactivity and functionality stored within aromatic systems provides numerous possibilities for the synthesis of three-dimensional organic structures via dearomatization processes,” said Dr. Gaunt. “Under oxidizing conditions, the dearomatization of *ortho*- and *para*-substituted phenols forms cyclohexadienones and these products have found widespread use in the chemical synthesis of natural products.

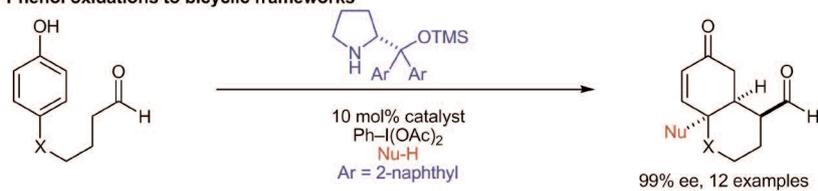
Additionally, the research groups of Feringa, Hayashi and Rovis have developed catalytic desymmetrization methods to convert the cyclohexadienone motif into useful enantioenriched molecules.”

Concerning what triggered the interest of Dr. Gaunt's group for this topic, he explained that “the elegance of these stepwise tactics led us to speculate that a catalytic asymmetric process that can directly transform an aromatic motif into the non-racemic structure would provide a powerful strategy for the rapid chemical synthesis of complex molecules. We developed a process that directly converts a *para*-substituted phenol into a highly functionalized chiral product via oxidative dearomatization and amine-catalyzed enantioselective desymmetrizing Michael reaction,” Dr. Gaunt continued. “This one-step transformation reveals a complex structure, formed with exquisite control of three new stereogenic centers and an array of exploitable orthogonal functionality, directly from a flat molecule that is devoid of architectural complexity.”

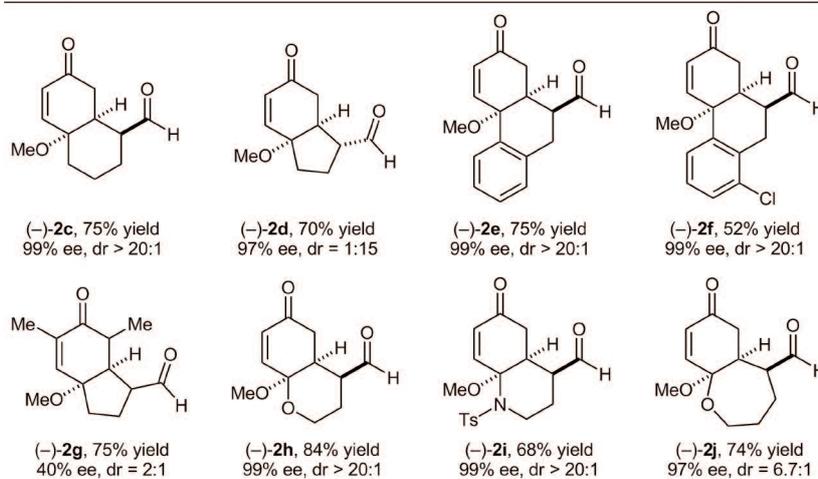
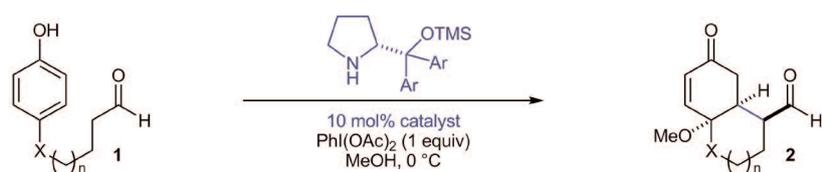
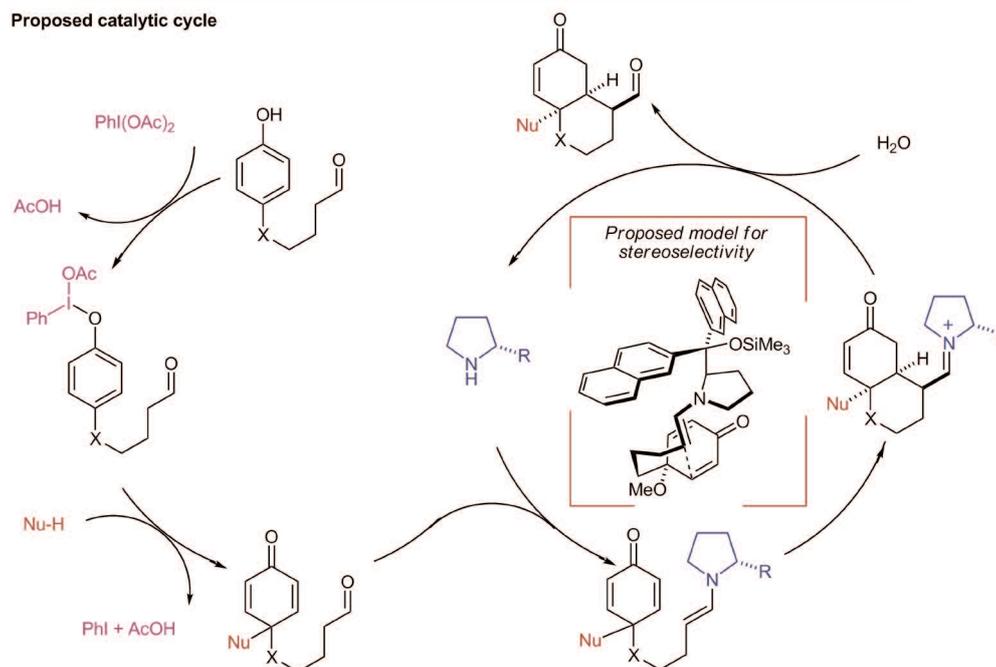
“We are currently investigating the application of this process in the synthesis of natural products, in particular alkaloid, terpene and polyketide structures,” concluded Dr. Gaunt. “We have recently uncovered some exciting leads that will enable us to generate complex non-racemic natural product structures directly from flat aromatic systems in a single step using our catalytic enantioselective dearomatization strategy.”

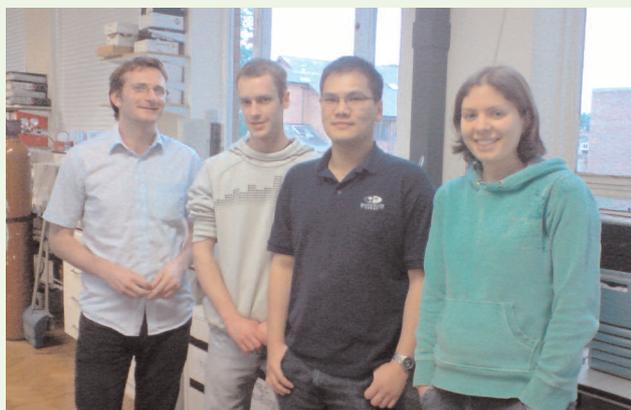
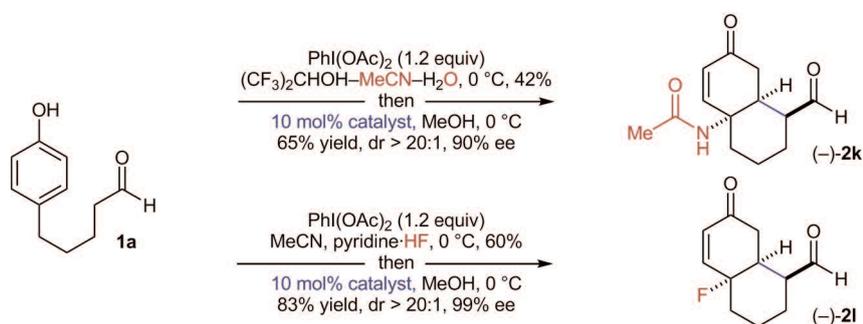


Phenol oxidations to bicyclic frameworks



Proposed catalytic cycle





From left: Prof. M. Gaunt, R. Pace, N. T. Vo, F. O'Hara

About the corresponding author

Following his BSc in Chemistry at the University of Birmingham (UK) **Matthew Gaunt** received his PhD in organic chemistry from the University of Cambridge (UK) under the guidance of Dr. Jonathan Spencer. Following postdoctoral studies with Professor Amos B. Smith III at the University of Pennsylvania (USA) he returned to Cambridge as a Research Fellow with Professor Steven Ley. He was appointed to the Faculty at Cambridge in October 2003 where he began his independent career and was recently appointed as a Royal Society University Research Fellow in October 2004. In October 2006 he was awarded tenure at Cambridge and promoted to Lecturer in Synthetic Organic Chemistry as a Philip & Patricia Brown Next Generation Fellow. Dr. Gaunt's research program is centered around the development of chemical synthesis using enantioselective catalysis, with specific interests in organocatalysis, metal-catalyzed C-H activation, cascade processes for the rapid synthesis of complex molecules and applications in chemical biology. The group's research has been acknowledged by the award of DowPharma Prize for Creativity in Chiral Chemistry in 2005.

Synthesis and Absolute Configuration of Hormone $\alpha 1$

Nat. Chem. Biol. **2008**, *4*, 235–237

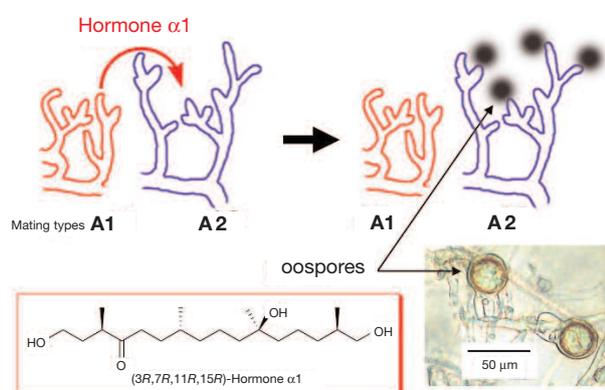
■ *Phytophthora*, whose name translates as “plant-destroyer”, is one of the most destructive pathogens in the world. In the mid-1840s, late blight, the plant disease caused by a member of this fungus-like genus, destroyed potato crops in Europe and the United States and caused the Irish potato famine. The life cycle of *Phytophthora* species features characteristic biological events, including sexual reproduction. Each individual is bisexual, capable of producing both female (oogonia) and male (antheridia). There are two mating types, A1 and A2, with sexual reproduction requiring the interaction of both.

After sexual reproduction, the oogonia develop into sexual spores called oospores, which can survive harsh conditions such as drying or freezing for months or years in the absence of a living host plant. “In 1929, Ashby proposed that sexual reproduction in *Phytophthora* was regulated by a hormone-like compound,” explained Dr. Arata Yajima from the Faculty of Applied Bio-Science, Tokyo University of Agriculture (Japan). “A factor secreted by the A1 mating type induces the formation of oospores in the A2 mating type, while a factor secreted by A2 induces the formation of oospores in A1. These factors are known as hormones $\alpha 1$ and $\alpha 2$, respectively,” he continued. “Recently, Professor Ojika from Nagoya University (Japan) and co-workers succeeded in isolating hormone $\alpha 1$ from 1830 L of culture broth of the A1 mating type

of *P. nicotianae*. Surprisingly, hormone $\alpha 1$ was found to induce oospore formation not only in *P. nicotianae* but also in *P. capsici*, *P. cambivora* and *P. infestans*.” These results indicate that hormone $\alpha 1$ is a universal mating hormone in the heterothallic species of *Phytophthora*. “We became interested in synthesizing hormone $\alpha 1$ in order to confirm its structure and to investigate its biological activity,” said Dr. Yajima.

“This work might be one of the historical works on *Phytophthora*. More than 70 years after the first proposal of the existence of $\alpha 1$ by Ashby, we have succeeded in establishing the complete structure of $\alpha 1$. It goes without saying that the greatest contribution to solve the moldy old mystery, the structure of hormone $\alpha 1$, is Professor Ojika’s isolation and elucidation of the plane structure of $\alpha 1$. The remaining last piece of the mystery was its absolute configuration, and we put it on the mysterious picture.”

According to Dr. Yajima, in the first synthesis the researchers suffered from the partial racemization of some asymmetric centers. “Because the NMR spectra of the stereoisomers of the synthetic intermediates and the final products were indistinguishable from each other, we could not realize the deterioration of stereoisomeric purity before we analyzed the corresponding MTPA esters of the final products,” he said. “In the second synthesis, we carefully chose the synthetic protocol to avoid any racemization, especially for C3 adjacent to the easily enolizable carbonyl group. Thus, we designed the second synthetic protocol to ward hormone $\alpha 1$ as simple as possible.” The bioassay, carried out by Professor Qi’s group from the School of Pharmacy, Fudan University (P. R. of China), using synthetic samples from the two countries, Japan and China, showed the same result. “Only the synthetic (3*R*,7*R*,11*R*,15*R*)-isomer shows the oospore-inducing activity, which indicates that *Phytophthora* has some stereospecific hormone receptor,” said Dr. Yajima. “Since we did not synthesize 3*S*- or 15*S*-isomers, we still don’t know whether the stereospecificity of their hormone receptor is strict or not. But, 3*S*- or 15*S*-isomers of $\alpha 1$ will be synthesized and assayed, which will bring full information of the stereospecificity of the receptor in the near future. Now our attention is focused on the hormone receptor,” he said. “We are now trying to identify the receptor by using the synthetic $\alpha 1$ and its derivatives as a chemical probe. The information about the receptor will open the way to manage *Phytophthora* injury to potato or tomato crops.”



About the authors

This work is a collaborative work of three groups from Japan and P. R. of China. Dr. Yajima's group and Professor Qin's group synthesized the four stereoisomers of $\alpha 1$, and Professor Qi's group assayed the synthetic samples. Originally, Professor Qin's group and Dr. Yajima's group were competitors. The two groups succeeded in synthesizing optically active $\alpha 1$ almost at the same time through totally different ways. The two groups became aware of each other's activity when they both asked Professor Qi to bioassay their samples. Finally, the groups followed the suggestion coming from Professor Sakagami from Nagoya University (Japan), and from an editor of *Nature Chemical Biology* and agreed to submit a collaborative paper.



Dr. A. Yajima

Arata Yajima was born in Tokyo (Japan) in 1972. He received his BSc (1995) and PhD (2000) from Tokyo University of Science under the direction of Professor Kenji Mori, where he completed the total synthesis of phytocassane D. In 2000, he was appointed as a Research Associate at Tokyo University of Agriculture, and promoted to Assistant Professor in 2003. His current research interests are focused on the total synthesis of microorganism regulators and rice phytoalexins and their chemical biology.



Prof. Y. Qin

Yong Qin was born in Yunnan (P. R. of China) in 1967. He received his BSc (1989) from Yunnan University and MSc (1992) from the Chengdu Institute of Organic Chemistry and was appointed as Assistant and Associate Professor at Chengdu Institute of Organic Chemistry (1995–1996). He received his PhD (1995) from the Institute of Chemistry under the direction of Professors Zhitang Huang and Yaozhong Jiang. He joined the group of

Professor Martin E. Kuehne at the University of Vermont (USA) as a postdoctoral fellow (1996–2000). He was appointed as research scientist at Triad Therapeutics, Inc. (USA) (2000–2003), before he moved to West China School of Pharmacy, Sichuan University, as a Professor and Vice Dean. His research interests are focused on the total synthesis of natural products, asymmetric synthesis and natural medicinal chemistry.



Prof. J. Qi

Jianhua Qi was born in Sichuan Province (P. R. of China) in 1967. He received his BSc (1987) from Sichuan Normal University (P. R. of China), his MSc (2000) and PhD (2002) from Nagoya University (Japan) under the direction of Professor Youji Sakagami. He stayed in Professor Sakagami's laboratory as a postdoctoral fellow with a Japan Society for the Promotion of Science Fellowship (2002–2007), before he moved to the School of Pharmacy,

Fudan University (P. R. of China), as a Professor. His research interests are focused on the isolation and structure determination of endogenous and exogenous bioactive substances, biological mechanisms, synthesis and biosynthesis of bioactive compounds.

There are also interesting behind-the-scenes in this highly successful example of a collaborative project. "When I found the plane structure of hormone $\alpha 1$ in Professor Ojika's paper, I was interested in it and the old story of $\alpha 1$," said Dr. Yajima. "However, $\alpha 1$ has four asymmetric carbons on its linear carbon skeleton, and it seemed to be difficult to determine its absolute configuration by analytical methods, which meant that we had to synthesize the sixteen stereoisomers of $\alpha 1$ to compare their biological activity. In our preliminary work, we found that the stereoisomeric mixture showed a five times weaker oospore inducing activity," he continued. "This indicated that some stereoisomers of $\alpha 1$ show the activity, and we could winnow the candidates down from sixteen to some extent. Thus, we started the synthesis of optically active $\alpha 1$. If the synthetic stereoisomeric mixture showed the same activity as the natural product, we might abandon the project of the asymmetric synthesis of $\alpha 1$." Fortunately, during the synthetic studies, Professor Ojika brought a piece of good news. "They succeeded in determining the absolute configuration of two asymmetric centers by MTPA method, which limited the number of possible stereoisomers to four," said Dr. Yajima. "This information encouraged us to complete the synthetic studies. We have prepared the four stereoisomers of $\alpha 1$, and only one isomer exhibited hormonal activity. How lucky we are! If the other isomers exhibited the activity, it would have been impossible to determine the absolute configuration of the natural product by this study. We owe our success to the stereospecificity of the *Phytophthora's* hormone receptor!"

COMING SOON ►► COMING SOON ►►

SYNFORM 2008/07 is available from July 23, 2008

In the next issues:

THE INSIDE STORY ►►►►

► An Interview with Sir Jack Baldwin

SYNSTORIES ■■■■

■ **A Biomimetic Enantioselective Approach to the Decahydroquinoline Class of Dendrobatid Alkaloids**
(Focus on an article from the current literature)

■ **Total Synthesis of (+)-Neopeltolide by a Prins Macrocyclization**
(Focus on an article from the current literature)

■ **Efficient, Selective, and Green: Catalyst Tuning for Highly Enantioselective Reactions of Ethylene**
(Focus on an article from the current literature)

FURTHER HIGHLIGHTS +++++

SYNTHESIS

Special Topic on "Organic Chemistry in Water"
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SYNLETT

Account on: Strategies for Constructing Diverse Chiral Environments in Multimetallic Bifunctional Asymmetric Catalysis

(by M. Shibasaki)

SYNFACTS

Synfact of the Month in category "Metal-Mediated Synthesis":
Suzuki–Miyaura Cross-Coupling of Trifluoroboratoenolates

CONTACT +++++

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