SYNSTORIES

- Total Synthesis of (−)-Haouamine B Pentaacetate and Structural Revision of Haouamine B

- Asymmetric α-Photoalkylation of β-Ketocarbonyls by Primary Amine Catalysis: Facile Access to Acyclic All-Carbon Quaternary Stereocenters

- Gold(I)-Catalyzed Polycyclization of Linear Dienediyynes to Seven-Membered-Ring-Containing Polycycles via Tandem Cyclopropanation/Cope Rearrangement/C–H Activation

- Rhodium-Catalyzed Enantioselective Hydrogenation of Tetra-substituted α-Acetoxy β-Enamido Esters

CONTACT

Your opinion about SYNFORM is welcome, please correspond if you like:
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As anticipated a few months ago, Thieme Chemistry will soon start publishing brief ‘News Articles’, highlighting some of the most important eFirst papers published in SYNLETT and SYNTHESIS. These ‘News Articles’ will further increase both visibility and impact of research articles published by Thieme Chemistry. Although ‘News Articles’ will not formally be part of SYNFORM and will only appear on the Thieme Chemistry website, it’s the SYNFORM editorial team who will identify suitable eFirst articles for this section. For this reason, I am particularly excited and pleased to welcome this new online feature that will enrich even further the content of our website. Moving to this new issue of SYNFORM, I am delighted to say that if this was poker we would be sitting on four aces here, and all of them from Asia! The first SYNSTORY describes a new protocol developd by S. Luo (P. R. of China) for synthesizing acyclic all-carbon quaternary stereocenters. The second SYNSTORY is again from the P. R. of China and specifically from Z.-X. Yu who takes us through his newly discovered gold(I)-catalyzed polycyclization reaction. And even the third SYNSTORY is from the P. R. of China, this time it’s an enantioselective hydrogenation to produce α-hydroxy-β-amino acids reported by H. Lv and X. Zhang. Still from Asia, but this time from Japan, the fourth SYNSTORY reports on the total synthesis of a fascinating natural product, haouamine B, and its structural revision resulting from the work of H. Tokuyama.

Enjoy your reading!

Matteo Zanda
Editor of SYNFORM
Asymmetric α-alkylation of carbonyl compounds is one of the fundamental C–C bond-forming reactions in forging a carbon stereogenic center, particularly for constructing acyclic all-carbon quaternary stereogenic centers, which remains a significant challenge in asymmetric catalysis and synthesis in spite of the tremendous advances in this field (see refs. 2–7 of the original manuscript). Recently, Professor Sanzhong Luo and co-workers from the Institute of Chemistry, Chinese Academy of Sciences (ICCAS) in Beijing (P. R. of China) reported the construction of acyclic all-carbon quaternary stereocenters using an open-shell radical substitution strategy by invoking the synergy of photoredox catalysis and primary amine catalysis (Scheme 1).

Professor Luo said: “For this transformation, besides the issue of stereocontrol of β-ketocarbonyls, another easily conceived pitfall is the stability and compatibility of diamine catalyst 1 under photoredox conditions. To our delight, the reaction enables the creation of all-carbon stereocenters with excellent enantioselectivities and a broad range of substrates (Scheme 1).” More intriguingly, as explained by Professor Luo, N-benzyl β-ketoamide reacted to furnish the expected C-alkylation adduct in 90% yield with 96% ee (4j). Intramolecular ketalization occurs spontaneously in the reactions involving N-aryl amides (4k–o). “The reason for high chiral induction in the ketalization step may originate from H-bonding to hydroxy-carbonyl as well as π–π interaction between the two aromatic rings,” suggested Professor Luo, who added that this class of spiro-γ-lactams has recently been found to have promising pharmaceutical profiles and their asymmetric synthesis has not been achieved so far.

“Based on the known precedence as well as our own experimental observations, we believe the current reaction proceeds via a photoredox catalysis productive pathway (Scheme 3),” continued Professor Luo. “Accordingly, a transition state TS-6 was proposed to account for the stereo-induction, wherein H-bonding between the protonated tertiary amine and the keto moiety of radical 5 would guide the approach of the radical species. This study provides an unprecedented H-bonding strategy in dictating the reactions of radical intermediates, neutral species in nature.”

The synthetic utility of the obtained 1,4-dicarbonyl compounds was also demonstrated by the authors: when treated with phenylhydrazine, adduct 4g underwent cyclocondensation to form indole derivative 7 or dihyropyridazine 8 under...
Scheme 2  Reaction scope

Scheme 3  Photoredox pathway
different acidic conditions. "Both of these compounds are privileged structural motifs in pharmaceuticals," said Professor Luo, who explained that the Norrish type II photoreaction of 4g can also proceed to furnish cyclobutane 9 bearing two non-consecutive quaternary centers with high diastereoselectivity and enantioselectivity.

Professor Luo concluded: “In summary, we have developed an enantioselective α-photoalkylation of β-ketocarbonyls by merging photoredox catalysis with chiral primary amine catalysis. The reactions enable the creation of all-carbon stereocenters with excellent enantioselectivities and a broad range of substrates including the elusive 1,3-diketones and β-ketoamides for the first time in an asymmetric alkylation reaction.”

Scheme 4 Synthetic utility of the new method

About the authors

Yunbo Zhu was born in 1987 in Shanxi province (P. R. of China). He obtained his BSc in chemistry from Northwest University (P. R. of China) in 2010. He began to pursue a PhD degree at the Institute of Chemistry, Chinese Academy of Sciences (ICCAS) under the supervision of Professor Sanzhong Luo in 2012.

Long Zhang was born in 1980 in Hebei (P. R. of China). He graduated from Nankai University (P. R. of China) in 2005 with a major in chemistry. He then spent five years pursuing a PhD degree in a joint project between Nankai University and the Institute of Chemistry, Chinese Academy of Sciences (ICCAS) under the supervision of Professors Jin-Pei Cheng and Sanzhong Luo. After obtaining his PhD, he joined Professor Luo’s group as an assistant professor in July 2010. His work focuses on the development of new asymmetric aminocatalysts as well as on DFT studies of mechanisms.
Sanzhong Luo was born in 1977 in Henan (P. R. of China). He graduated from Zhengzhou University (P. R. of China) in 1999, and then spent his graduate studies successively at Nankai University, the Chinese Academy of Sciences and the Ohio State University (USA) and received his PhD under the supervision of Professor Jin-Pei Cheng in 2005. He started his independent career in July 2005 at the Institute of Chemistry, Chinese Academy of Sciences (ICCAS) and became a full professor there in 2011. He was a visiting scholar at Stanford University (USA, with Professor B. M. Trost) in 2009. His research focuses on bio-inspired asymmetric catalysis and synthesis.
Gold(I)-Catalyzed Polycyclization of Linear Dienediynes to Seven-Membered-Ring-Containing Polycycles via Tandem Cyclopropanation/Cope Rearrangement/C–H Activation

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Daphnane and tigliane diterpenes, such as resiniferatoxin and phorbol, respectively, are widely found in natural products and many bioactive compounds. However, the synthetic efficiency for the construction of the fused 5,7,6-tricyclic skeleton of these diterpenes by traditional step-by-step strategy is usually low (for a list of references see the original paper). Recently, a research team led by Professor Zhi-Xiang Yu from Peking University (Beijing, P. R. of China) discovered and developed a gold(I)-catalyzed tricyclization for the diastereoselective synthesis of the challenging fused 5,7,6-tricyclic system of the target diterpenes from linear dienediynes. This cascade reaction occurs via a multistep sequence involving intramolecular cyclopropanation of the dienediyne substrate, Cope rearrangement of the resulting alkenylalkynylcyclopropane, C–H activation based on cyclic allene C–H insertion, and two consecutive [1,2]-shift reactions to yield the target skeletons with high diastereoselection.

“Cope rearrangement of divinylcyclopropanes is one of the most widely used reactions for the construction of seven-membered carbocycles,” said Professor Yu. “However, Cope rearrangement of alkenylalkynylcyclopropanes has rarely been used, perhaps due to the formation of a reactive seven-membered-ring allene, which may undergo rapid dimerization to give undesired products.” He added: “By using easily prepared dienediynes as substrates, we found that the seven-membered-ring allene intermediate, which was generated in situ by the Cope rearrangement of an alkenylalkynylcyclopropane, undergoes C(sp)–H activation of the side chain, instead of the undesired dimerization, to furnish the fused 5,7,6-tricyclic system. The present polycyclization reaction is a good example for step-economic construction of complex and challenging skeletons of important molecules from simple starting materials.”

“The present reaction is the second unexpected C–H activation reaction reported by our group,” said Professor Yu. “Previously we have developed a process for the rhodium-catalyzed allylic C–H activation/addition to alkene and used it for the synthesis of multi-substituted tetrahydropyrroles, tetrahydrofurans, and cyclopentanes bearing quaternary carbon centers (*J. Am. Chem. Soc.* **2010**, *132*, 4542; *Angew. Chem. Int. Ed.* **2011**, *50*, 2144).” Professor Yu explained: “Developing new C(sp)–H activation reactions under mild conditions is a challenge.”
conditions to streamline organic synthesis is pursued by many leading synthetic chemists throughout the world. Although my group is not directly involved in this ‘hot’ field, we always keep an eye on its development. Our present reaction suggests that many other ‘unexpected’ C–H activation reactions are waiting for further exploration by synthetic chemists.”

One of the research interests of Professor Yu’s group is to develop new ring-formation reactions and apply these reactions to the synthesis of natural products (for a review, see: J. Org. Chem. 2013, 78, 6842). “The present polycyclization can be regarded as a formal [4+3]/C–H activation reaction,” said Professor Yu, who concluded: “In addition to developing more powerful ring-formation reactions, we are going to do more investigations on the present polycyclization. We are currently studying the detailed reaction mechanism using DFT calculations. Our next goal is to explore other chemistry of cyclic allenes.”

**About the authors**

**Zhi-Xiang Yu** obtained his PhD from the Hong Kong University of Science & Technology (P. R. of China) in 2001. After a three-year postdoctoral study at University of California, Los Angeles (USA), he joined the faculty of Peking University (P. R. of China) as an associate professor in 2004 and was promoted to full professor in 2008. With a research philosophy of “chem-is-try, computationally and experimentally”, his laboratory focuses on the application of computational and synthetic organic chemistry to study reaction mechanisms, develop new reactions and catalysts, and apply the new reactions discovered from his group to synthesize natural and non-natural products.

**Pei-Jun Cai** obtained his BSc degree from Wuhan University (P. R. of China) in 2011 and is currently a fourth-year graduate student in Professor Zhi-Xiang Yu’s group.

**Yi Wang** received his BSc degree from Peking University (P. R. of China) in 2012 and is currently a third-year graduate student in Professor Zhi-Xiang Yu’s group.

**Cheng-Hang Liu** obtained his BSc degree from Peking University (P. R. of China) in 2014 and is currently a first-year graduate student in Professor Zhi-Xiang Yu’s group.
Asymmetric hydrogenation of polysubstituted enamides has become one of the most powerful strategies for the stereo-controlled synthesis of non-racemic chiral amines, amino acids and their derivatives, and has important practical applications in the pharmaceutical industry. However, due to the strong steric hindrance, the hydrogenation of tetrasubstituted enamides is very challenging and only a few special tetrasubstituted enamides have been effectively obtained in an enantioselective manner (for references see ref. 18 in the original article). Therefore, development of an efficient method for synthesizing multifunctionalized chiral amines via hydrogenation of tetrasubstituted enamides is highly desirable.

The group of Professor Xumu Zhang at Wuhan University (P. R. of China) has a strong ongoing interest in developing economic and environmentally friendly routes to synthesize chiral non-racemic molecules with strong biological activities. Recently, as a result of a research effort directed by Professors Hui Lv and Xumu Zhang, the group successfully developed a very effective catalytic enantioselective hydrogenation of tetrasubstituted enamides to biologically important α-hydroxy-β-amino acids. Professor Zhang said: “The synthesis of enantiomerically pure chiral α-hydroxy-β-amino acid moieties drew our interest because of the unique properties of these compounds. 1 Although there are many approaches to the synthesis of α-hydroxy-β-amino acid derivatives, a straightforward synthesis of chiral α-hydroxy-β-amino acid derivatives through asymmetric hydrogenation of α-acetoxy β-enamido esters had not been reported prior to this work.”

“By employing the Rh-DuanPhos catalytic system developed in our lab, we have achieved asymmetric hydrogenation of tetrasubstituted α-acetoxy β-enamido esters under mild conditions,” explained Professor Zhang, who added: “This new methodology has several advantages over existing methodologies: (1) the reaction allows the synthesis of structurally diverse α-hydroxy-β-amino acid derivatives with excellent yields and excellent enantioselectivities, which is more atom-economic and more practical than previous synthetic routes. (2) The reaction has a broad substrate scope and potential applications in total synthesis or drug synthesis. Moreover,” concluded Professor Zhang, “the methodology can be used for a very direct synthesis of the C13 side chain of paclitaxel.”

REFERENCES

About the authors

Qingli Wang was born in Heilongjiang Province (P. R. of China) in 1985. She received her Bachelor’s degree (2009) and Master’s degree (2012) from the Wuhan Institute of Technology (P. R. of China). In 2012 she joined Professor Xumu Zhang’s research group and is currently a PhD student in the College of Chemistry and Molecular Sciences, Wuhan University. Her research interests focus on asymmetric hydrogenation.

Hui Lv obtained his BSc degree in 2003 from Xiangtan University (P. R. of China) and PhD in 2010 from the Institute of Chemistry, Chinese Academy of Sciences (ICCAS, Beijing, P. R. of China). He continued his research as a postdoctoral associate at Nanyang Technological University (Singapore) from 2010 to 2012. He began his academic career at Wuhan University in 2013 in Professor Xumu Zhang’s group. His research focuses on asymmetric hydrogenation and the application of transition-metal complexes of N-heterocyclic carbenes.

Xumu Zhang received his BS degree in chemistry (1982) from Wuhan University and MS in chemistry (1985) from the Chinese Science Academy, Fuzhou (P. R. of China), under the supervision of Professor Jiaxi Lu. After a short stay at UC San Diego (USA), he received his PhD in chemistry in 1992 from Stanford University (USA) under the guidance of Professor James P. Collman. He then carried out postdoctoral work at Stanford University for two years. In 1994, he joined the Department of Chemistry at The Pennsylvania State University (USA) as an assistant professor of chemistry. In 2003, he was promoted to Full Professor. In 2007, he moved to The State University of New Jersey (USA) and was appointed as Distinguished Professor. In 2011, he joined Wuhan University as the winner of the “Thousand Talent Program.” His research interests include the development of chiral phosphine ligands for asymmetric catalysis, the investigation of asymmetric hydrogenation and carbon–carbon bond-forming reactions, the synthesis of biologically active compounds, and the discovery of new synthetic methods.
Total Synthesis of (–)-Haouamine B Pentaacetate and Structural Revision of Haouamine B


In the last few decades, developments in NMR techniques have significantly advanced the structure elucidation of organic compounds, even for samples in sub-milligram quantities. NMR techniques are indispensable in current organic chemistry, especially for the identification of scarce complex natural products. However, analysis of NMR spectra of a natural product with similar structural subunits might cause mis-assignment of overlapping or close signals, leading to an incorrect structural determination.

Haouamines A and B (Scheme 1, i), isolated from a marine tunicate by Zubia and co-workers, are structurally unique alkaloids possessing strong cytotoxicity against the HT-29 human colon carcinoma cell line (haouamine A; IC₅₀ = 200 nM). Although haouamine A (1) was synthesized by Baran in 2006, no total synthesis of haouamine B (2) has been reported. In 2012, Trauner and Zubía reported that the initially proposed haouamine B (2) should be revised to 3 based on careful analysis of the ¹H NMR spectra of natural haouamine B pentaacetate. However, this was not the end of the ‘haouamine saga’.

In fact, the group of Professor Hidetoshi Tokuyama at Tohoku University (Japan) just recently settled the matter by means of the first total synthesis of (–)-haouamine B pentaacetate.

In 2011, Tokuyama’s group reported the synthesis of indeno-dihydropyridone 4, as a partial structure of the initially proposed haouamine B (2) (Scheme 1, ii). Professor Tokuyama said: “This was the first project undertaken since I moved to Tohoku University. We were excited that a quite unusual intramolecular Friedel–Crafts reaction via an azetidinium carbocation 5 was promoted by TiOH, which facilitated smooth construction of the quaternary carbon center.” According to Professor Tokuyama, of interest was the observation that the stereochemistry of the key intermediate 6 was opposite to that predicted by Ellman’s report for the stereo-controlled synthesis of β-lactam 7.

Professor Tokuyama and co-workers focused on the synthesis of the 1,2,3,4-tetrasubstituted benzene ring in the revised haouamine B (3) (Scheme 1, iii). However, treatment of compound 8 under the established conditions did not give the desired compound 9. Instead, the unexpected indeno-β-lactam 10 in 37% yield (in dichloromethane), or the de brominated compound 11 in 34% yield (in acetonitrile) were obtained. “The unexpected reaction outcomes would be caused by the additional methoxy group, reducing nucleophilicity of C2b carbon by the steric repulsion and the electron-withdrawing effect (meta to the C2b position) of the methoxy group,” explained Professor Tokuyama.

The Japanese researchers then switched the bromine atom to a benzyloxy group to suppress the ipso substitution (Scheme 2); however, reaction of 12 provided the undesired chromane 13 in 44% yield, presumably via oxonium ion 14 by nucleophilic addition of the ethereal oxygen atom to the carbocation. Finally, Professor Tokuyama and co-workers found that the trisopropylsilyl (TIPS) group was effective for promoting the desired conversion. In this case, the authors established very mild conditions [Sc(Otf)₃] and 2,6-di-tert-butylpyridine to avoid the undesired formation of chromane 13 through acidic removal of the TIPS group. After palladium-catalyzed removal of the TIPSO group, the indane-fused β-lactam 15 was converted into indeno-dihydropyridone 16.

While facing the problem of constructing the paracyclophane skeleton in 2011, the Tokuyama group members were among those in Japan who suffered from the Great Earthquake in Sendai. Professor Tokuyama said: “Our research facilities were severely damaged, and I realized we had to stop our research for several months. Fortunately, Professors Dirk Trauner (University of Munich) and Oliver Reiser (University of Regensburg) offered us an opportunity to send my graduate student Mr. Yuichi Momoi to Professor Trauner’s laboratories at the University of Munich for three months to learn the detailed protocol for the paracyclophane skeleton. Finally, we synthesized the revised structure of haouamine B pentaacetate (17) and confirmed its absolute configuration.”

Professor Tokuyama said: “We greatly appreciate their warm support and kind cooperation. We also received invaluable information on the formation of aza-paracyclophane from Professor Trauner and Dr. Maria Matveenko. We appreciate financial support from the Alexander von Humboldt Foundation, the German Chemical Society, for Mr. Momoi’s stay,” concluded Professor Tokuyama.
(i) Structural revision of haouamine B (Trauner and Zubia, J. Am. Chem. Soc. 2012, 134, 9291.)

\[ \text{(-)-haouamine A (1)} \]

\[ \text{initially proposed structure of haouamine B (2)} \]

\[ \text{revised structure of haouamine B (3)} \]

(ii) Previous work (Tokuyama, Synlett 2011, 73.)

\[ \text{MeO} \]
\[ \text{MeO} \]
\[ \text{Boc} \text{O} \text{CO}_2\text{Me} \]
\[ \text{LHMDS} \]
\[ \text{THF} \]
\[ -78 \degree \text{C} \]
\[ 86\% \]

\[ \text{MeO} \]
\[ \text{MeO} \]
\[ \text{MeO} \]
\[ \text{MeO} \]
\[ \text{Bn} \]

\[ \text{TIOH} \]
\[ \text{MeCN} \]
\[ -45 \degree \text{C to r.t.} \]
\[ 74\% \text{ (2 steps)} \]

\[ \text{MeO} \]
\[ \text{MeO} \]
\[ \text{OMe} \]
\[ \text{Bn} \]

(iii) Unexpected cyclization (this work)

\[ \text{MeO} \]
\[ \text{MeO} \]
\[ \text{MeO} \]
\[ \text{Bn} \]
\[ 2b \]

\[ \text{TIOH} \]
\[ -45 \degree \text{C to r.t.} \]

\[ \text{MeO} \]
\[ \text{MeO} \]
\[ \text{OMe} \]
\[ \text{Bn} \]

\[ \text{not detected} \]

\[ \text{10} \]
\[ 37\% \text{ (in CH}_2\text{Cl}_2) \]

\[ \text{11} \]
\[ 34\% \text{ (in MeCN)} \]
REFERENCES


About the authors

Hidetoshi Tokuyama was born in Yokohama (Japan) in 1967. He received his PhD in 1994 from the Tokyo Institute of Technology (Japan) under the direction of Professor Ei-ichi Nakamura. He spent one year (1994–1995) at the University of Pennsylvania (USA) as a JSPS postdoctoral fellow with Professor Amos B. Smith, III. He joined the group of Professor Tohru Fukuyama at the University of Tokyo in 1995 and was appointed associate professor in 2003. In 2006, he moved to Tohoku University (Japan), where he is currently a professor of pharmaceutical sciences. His research interests include the development of synthetic methodologies and the total synthesis of natural products.

Kentaro Okano was born in Tokyo (Japan) in 1979. He received his BS degree in 2003 from Kyoto University (Japan) under the supervision of Professor Tamejiro Hiyama. He then moved to the laboratories of Professor Tohru Fukuyama at The University of Tokyo (Japan) and started his PhD research on synthetic studies toward the antitumor antibiotic yatakemycin using a copper-mediated aryl amination strategy. In 2007, he joined the faculty at Tohoku University (Japan), where he is currently an assistant professor in Professor Hidetoshi Tokuyama's group. In 2014, he visited Professor Amir Hoveyda's laboratories at Boston College (USA) as a visiting researcher. His current research interest focuses on natural product synthesis based on the development of new synthetic methodologies.

Kenji Sugimoto completed his PhD in 2005 under the guidance of Professor Masataka Ihara at Tohoku University (Japan) and spent a year in the same group as a research assistant. He then joined the research group of Professor Hidetoshi Tokuyama at Tohoku University as an assistant professor. In 2010, he moved to University of Toyama (Japan) as an assistant professor in the research group of Professor Yuji Matsuya and was promoted to the position of associate professor in 2012. His research interests are the development of novel domino reactions, their applications in total synthesis, and the synthesis of biologically active compounds.

Yuichi Momoi completed his undergraduate studies in the research group of Professor Hidetoshi Tokuyama (Tohoku University, Japan) in 2010. He then continued on in the same laboratory to pursue his PhD studies. He stayed at the research group of Professor Dirk Trauner (Ludwig Maximilians University Munich, Germany) for three months in 2011.

Keiichiro Okuyama received his BS degree in 2006 from Tohoku Pharmaceutical University (Japan), where he carried out undergraduate research under the supervision of Professor Tadashi Kato. He then moved to the laboratories of Professor Hidetoshi Tokuyama, Tohoku University and began his PhD research on synthetic studies toward haouamine B. In 2011, he received his PhD, and is currently working for Astellas Pharma Inc. as a drug discovery researcher.

Hiroki Toya received his PhD in 2012 under the guidance of Professor Hidetoshi Tokuyama at Tohoku University (Japan). Now, he works for Astellas Pharma Inc. (Japan) as a medicinal chemist.
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In the next issues:

SYNSTORIES ■ ■ ■ ■

- Highly Enantioselective Synthesis of 3,4-Dihydropriyns through a Phosphine-Catalyzed [4+2] Annulation of Allenones and β,γ-Unsaturated α-Keto Esters (Focus on an article from the current literature)

- Total Syntheses of Linear Polythiazole/Oxazole Plantazolicin A and Its Biosynthetic Precursor Plantazolicin B (Focus on an article from the current literature)

- Chemoselective Activation of sp³ vs sp² C–H Bonds with Palladium(II) (Focus on an article from the current literature)

FURTHER HIGHLIGHTS ******

SYNTHESIS
Review on: Recent Developments in the Synthesis of Imidazo[1,2-a]pyridines (by A. Kumar et al.)

SYNLETT
Account on: Synthesis of Unnatural Steroids Using the Bistro Strategy (by M. Santelli et al.)

SYNFLACS
Synfact of the Month in category “Synthesis of Materials and Unnatural Products”: A Rapid Route to Core Nitrogen Containing Polycyclic Aromatics

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