A Second-Generation Chemoenzymatic Total Synthesis of Platencin

Highlighted article by R. N. Muhammad, A. G. Draffan, M. G. Banwell, A. C. Willis

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Dear Readers,

It’s a rich mix of total synthesis, stereoselective reactions and heterocyclic synthesis in this April 2016 issue of SYNFORM. We kick off with a groundbreaking synthesis of pyrroles by I. A. Tonks (USA) that constructs the five-membered azole ring by assembling two equivalents of alkynes and half equivalent of a diazene by means of titanium redox catalysis. The second article offers an insight into the tandem ring-opening/alkynylation of cyclopropanols by ethynyl benziodoxolones recently published in SYNTHESIS by J.-H. Li (P. R. of China). A novel synthetic approach to the antibacterial platencin – which was isolated from a Streptomyces bacteria strain – developed by M. Banwell (Australia) and published in SYNLETT is the object of the third contribution. The issue is closed with a touch of elegance by the fourth story which reports on a spectacular example of stereocontrolled aldol reaction designed by H. Yamamoto (Japan).

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Catalytic Formal [2+2+1] Synthesis of Pyrroles from Alkynes and Diazenes via TiIII/TiIV Redox Catalysis

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Polysubstituted pyrroles are very common and important structural motifs in many biologically active compounds, drugs and materials, but the synthesis of these compounds is often very challenging. Recently, the group of Professor Ian A. Tonks at the University of Minnesota – Twin Cities (USA) has reported a groundbreaking and efficient method for accessing pyrroles having up to five substituents on the ring through a formal [2+2+1] cyclization of alkynes and diazenes promoted by a TiII/TiIV redox catalytic cycle.

“Our research in Ti-catalyzed [2+2+1] reactions,” said Professor Tonks, “has been motivated by two factors: first, by the growing interest in using ‘earth-abundant’ metals to carry out catalytic transformations; and second, from the fundamental question of whether early transition metals – which typically do not undergo facile two-electron redox processes – can be used in practical redox catalytic reactions. In general,” he continued, “the organic community has focused heavily on Fe/Co/Ni/Cu catalysts as earth-abundant replacements for many classic organometallic reactions, but Ti has several advantages over these metals: Ti is the 2nd most abundant transition metal in Earth’s crust (after Fe) and common Ti waste products (TiO2) are typically nontoxic.”

Professor Tonks explained: “The work in our Nature Chemistry paper is the coalescence of several observations. We first envisioned a potential TiIII/TiV catalytic cycle in 2013 while I was finishing my thesis with John Bercaw at Caltech. During this time a visiting student from TU Munich, Josef Meier, discovered that pyrroles and an unidentified TiIII byproduct form when reacted with a pyridine (bis)phenolate Ti imido complex, albeit in extremely low yield.1 This initial observation came about while Josef and I were characterizing the byproducts of an otherwise unremarkable alkyne hydroamination reaction – and I think highlights an important teaching moment: always characterize your byproducts; they may be more interesting than your desired reaction!”

For such a simple precatalyst, the ability for TiCl2(py)3NR complexes to facilely change between TiIII and TiIV is quite remarkable. Professor Tonks explained: “We hypothesize that diazenes (or potentially alkynes) serve a dual role in this reaction: not only do they act as the nitrene source for pyrrole synthesis, but they also may be serving as redox ‘non-innocent’ ligands – accepting electron density into the N=N π* to prevent the formation of high-energy naked TiII species.”

From the perspective of organic synthesis, the Ti-catalyzed [2+2+1] reaction also represents a new retrosynthetic disconnection for pyrrole syntheses. “The deceptively simple core of the pyrrole heterocycle belies the challenges of constructing polysubstituted (in particular tetra- and pentasubstituted) and/or electron-rich pyrroles,” said Professor Tonks. “Speaking of these challenges, Gevorgyan recently published a review article3 in which over 60 different multicomponent routes to pyrroles are presented; and a review article4 on the synthesis of Lipitor highlights the pitfalls of multicomponent strategies for pyrrole synthesis. While our [2+2+1] synthetic methodology is still in its infancy,” he continued, “the fact that we can synthesize (for the first time, in many cases) a variety of highly substituted, electron-rich pyrroles highlights it as a potentially generalizable method for pyrrole synthesis.”

According to Professor Tonks, one of the appealing characteristics of this reaction is the simplicity of the precatalyst: TiCl2(py)3NR complexes can be synthesized in one pot from TiCl4 and new undergraduate researchers in Professor Tonks’ lab synthesize it as one of their first reactions. “Ease of synthesis is an incredibly important factor when developing catalysts: it is difficult for researchers to adopt an early transition metal catalyzed protocol that involves significant inorganic synthesis. In this regard, I’ve been influenced heavily by...
Laurel Schafer’s (UBC) hydroamination catalysis that utilizes elegantly simple ligand architectures,” remarked Professor Tonks.

He continued: “Our current limitations in [2+2+1] synthesis arise mostly from issues related to regioselectivity and functional group tolerance. We are currently developing new catalyst frameworks to address these challenges. Remarkably, every Ti imido complex we have synthesized has shown at least some degree of pyrrole formation – because of this, we have high hopes that we will be able to rationally design catalysts that can exert greater regiocontrol and are more functional group tolerant than the simple system reported in our paper.”

“Extending the chemistry of the azatitanacycle intermediates towards further multicomponent reactions has been the goal for a number of researchers in this field. Aaron Odom, Philip Mountford, Tom Livinghouse and Lutz Gade have all demonstrated quite unique chemistry from these reactive intermediates,” added Professor Tonks, concluding: “With this precedent in place, we hypothesize that utilizing diazene oxidants with Ti imido catalysts will ultimately lead to broad classes of useful and practical oxidation reactions.”

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Alkynes are important structural motifs in natural products and functional materials as well as fundamental building blocks in synthetic chemistry and materials science. Among them, internal alkyl alkynes are readily prepared by the Sonogashira cross-coupling reaction of halides with terminal alkyl alkynes. However, the majority of these transformations are limited to aryl electrophiles which often require a copper co-catalyst, a base and a ligand to improve the yield, all of which complicate the procedure for organic synthesis and represent a severe disadvantage for industrial applications. “To overcome these disadvantages, the development of new electrophilic alkynylating reagents, particularly with special reaction characteristics in the formation of C(sp)–C(sp³) bonds, have gained wide interest in the past decade,” said Professor Jin-Heng Li and Dr. Ye-Xiang Xie from Hunan University (P. R. of China). “Typically, attractive electrophilic alkynylating reagents include ethynyl benziodoxolones (EBXs), which were found to be appealing alkynylating reagents for building

![Scheme 1 Silver-promoted oxidative ring-opening/alkynylation of cyclopropanols and possible mechanism](image-url)
diverse ynne molecules by the C-alkynylation with aldehydes,” they continued. “Therefore, it would be welcome to develop new strategies involving the use of new electrophilic alkynylation reagents for producing diverse alkyl alkyynes.” Professor Li’s laboratory has been particularly interested in the oxidative radical coupling methodology for the construction of carbon–carbon or carbon–heteroatom bonds. In light of these, Professor Li and co-workers reasoned that the stable alkyl carbon-centered radicals would be trapped by the electrophilic alkynyl hypervalent iodide reagents through an oxidative radical process. Recently, Professor Li’s group found a way to prove their hypothesis: a new silver-promoted oxidative radical alkynylation strategy was documented for the synthesis of alkyl alkyynes under mild conditions, in which ethynyl benziodoxolones were used as the electrophilic alkynylation reagents to react with various cyclopropanols in the presence of AgNO₃ and K₂S₂O₈ (Scheme 1).

“This method allows selective radical cleavage of the C–C bond in a wide range of cyclopropanols to form the stable alkyl carbon-centered radicals followed by coupling with various alkyynes, including aryl- and alkyl-substituted alkyynes, and represents a mild and practical route to assemble alkyl alkyynes,” said Professor Li and Dr. Xie, who added: “Although the Sonogashira cross-coupling reaction, which starts from aryl or alkenyl halides and terminal alkyynes, has been well established for incorporating alkyne moieties into organic molecules, the synthesis of aliphatic alkyynes from alkyl electrophiles still remains a formidable challenge.” Now, Professor Li and co-workers have established a new oxidative radical coupling strategy for the synthesis of aliphatic alkyynes from the reaction of electrophilic EBXs with the alkyl carbon-centered radicals, which avoid the use of alkyl electrophiles with lower reactivity.

At the beginning of this research, a series of experiments examining the catalytic systems were performed, and the ring opening/alkynylation reaction was found to occur in the presence of either silver salts or potassium persulfate. “Surprisingly, the reaction could take place without silver salts, albeit with a lower yield,” said Professor Li and Dr. Xie. “A similar yield (49%) was obtained when three equivalents of K₂S₂O₈ were used in the absence of AgNO₃. The results suggest that AgNO₃ may play two roles, as an accelerator and an oxidant.”

The control experiments support a radical process for the ring-opening/alkynylation reaction (Scheme 1). Professor Li and Dr. Xie explained: “The reaction of cyclopropanol with EBX was completely suppressed when using a stoichiometric amount of radical inhibitor (3 equiv), including TEMPO and BHT. According to the results and the proposed mechanism, while K₂S₂O₈ served as the oxidant to generate the alkyl carbon-centered radical intermediate, silver salts might play at least two roles: as the catalyst to initiate the formation of the alkyl carbon-centered radical intermediate and as Lewis acid to stabilize the radical intermediates.”

Professor Li and Dr. Xie emphasized that compared to the traditional cross-coupling reaction, there are two features worthy of note in this strategy: (1) simple operation, as the reaction does not require additives, such as copper co-catalysts, bases and ligands, and proceeds at 30 °C under neutral reaction conditions, thus providing no complicated purification steps, and (2) generality, as the broad substrate scope results in the construction of diverse aliphatic alkyynes, including dialkyl alkyynes and alkyl aryl alkyynes.

Professor Li and Dr. Xie concluded: “In this report, a great challenge was how to stabilize the alkyl carbon-centered radicals from oxidative opening of cyclopropanols, and we were lucky to find that silver salts can fill this role: they serve not only as an oxidant but also as a catalyst to improve the reaction. Inspired by these, if one discovers a catalyst which has enough activity to directly stabilize a wide range of active radical intermediates from the common chemical bonds, especially different C–H bonds in unactivated alkanes and arenes, the oxidative radical coupling between a radical and an electrophile will inarguably become the most versatile method in chemical research in the future.”

Matteo Torda
C.-Y. Wang received his B.E. degree in 2011 from Hunan Institute of Engineering (P.R. of China). Currently he is a third-year Ph.D. student at Hunan University (P.R. of China). His current research includes the C–H oxidative radical coupling and hyper-valent iodine chemistry.

Ren-Jie Song was born in 1983. He obtained his B.S. (2006) and Ph.D. degree (2011) from Hunan Normal University (P.R. of China). In 2011, he moved to Hunan University (P.R. of China) as a postdoctoral fellow with Professor Jin-Heng Li and has become a research assistant at Hunan University in 2013. Now, he focuses on the development of new synthetic methodologies and heterocycle synthesis.

Ye-Xiang Xie is a lecturer at Hunan University (P.R. of China). She graduated in 1999 from Hunan Agricultural University (P.R. of China), where she received her B.S. degree. She then moved to Hunan Normal University (P.R. of China) for the M.S. program. In 2014, she completed her Ph.D. thesis under the supervision of Professors Jian-Nan Xiang and Jin-Heng Li. Her research interest is the development of novel C–H oxidative arylation reactions.

Jin-Heng Li received his B.S. degree in 1994 from Hunan Normal University (P.R. of China) and his Ph.D. degree (2002) from University of Science and Technology of China (P.R. of China) under the supervision of Professors Huanfeng Jiang and Mingcai Chen. He then worked with Professor Dan Yang at the University of Hong Kong (P.R. of China) as a postdoctoral fellow. In 2002, he joined Hunan Normal University (P.R. of China) as a Professor. In 2011 he moved to Hunan University as a Professor. His research includes C–H oxidative couplings, cross-couplings, and cycloaddition reactions.
The identification of new antibiotics showing efficacy against the rapidly growing number of drug-resistant bacteria is becoming a worldwide priority in medicine and healthcare. Among the recently identified molecules displaying novel modes of antibacterial action, one of the most promising is platencin (Figure 1). This was isolated from the microorganism Strep tomyces platensis (see the original Synlett article for references).

The work reported in this paper from Professor Martin Banwell’s group at the Australian National University (Canberra, Australia) is an outgrowth of the group’s broader studies on the application of a class of metabolites known as the cis-1,2-dihydrocatechols to the chemical synthesis of biologically active natural products and related compounds. Professor Banwell explained that cis-1,2-dihydrocatechols of the general form 1 have been highlighted by a number of groups. Representative natural products and/or their analogues that the Banwell Group have prepared from this type of starting material are shown in Figure 3.

Immediately upon seeing the structure of the carbocyclic core of platencin (a cyclohexannulated bicyclo[2.2.2]octene) in a 2007 Chemical & Engineering News article reporting on the isolation and structural elucidation of this natural product, we thought it could be assembled via a type-1 intramolecular Diels–Alder (IMDA) reaction where an enantiomer of highly utilitarian carbocyclic frameworks can be obtained from the same enantiomer of a precursor. This concept applies to other cycloaddition processes as well.

"In our original investigations of this approach we made an appropriate triene through Negishi cross-coupling of the acetonide 3 (X = I) of diol 1 (X = I) with organozinc (Scheme 2). Remarkably, when product triene 6, which contains an unactivated dieneophile, was heated in refluxing toluene, the anticipated IMDA reaction took place to give adduct 7 (mixture of epimers at the oxygen-bearing carbon) as the major product. This adduct could be elaborated in a fairly straightforward manner to enone 8, an advanced intermediate associated with Nicolaou’s original total synthesis of the natural product."
Figure 3

Scheme 1
In a variation on the IMDA route to the platencin core, the group recently reported what Professor Banwell describes as a first-generation chemoenzymatic total synthesis of platencin (Scheme 3). The substrate involved in the key step associated with this approach was the tetra-ene where the associated side chain, now embodying a stereogenic center that had been established through the use of a chiral auxiliary, was attached to the diene core using Stille cross-coupling chemistry. Professor Banwell remarked: “Once again, the IMDA reaction served the synthesis well – it proceeded very effectively in refluxing toluene to provide adduct incorporating much more of the functionality of platencin than did the original IMDA product.” He continued: “However, the undoing of this first-generation chemoenzymatic total synthesis was a protecting group problem. The benzyl ether residue within compound could never be cleaved without accompanying removal of both C=C double bonds – we wanted to remove just the non-conjugated one and not the enone-based one. The end result is that extra steps had to be introduced into the reaction sequence so as to re-establish the enone C=C bond that we had taken so much trouble to install in the first place.”

In the work just reported in Synlett the group sought to exploit the best aspects of their two earlier syntheses by re-preparing the original and readily accessible IMDA adduct and then manipulating this in ways that had not been explored in the lead up to their original publication. “Educated by a seminal 2009 publication from the Nicolaou group, we were able to elaborate this adduct to compound shown in Scheme 4,” explained Professor Banwell, continuing: “So, conventional manipulations of this last compound got us to acetate shown in Scheme 4 but we then encountered one of our perennial problems, accessing (from overseas sources) high-quality samarium metal so as to make the corresponding iodide (as needed in the reductive deoxygenation reaction that we hoped would deliver compound ). After a desperate search through the literature we became aware of the distinctly under-appreciated studies of Torii and co-workers who showed that certain readily prepared vanadium complexes can act in the same way as SmI₂.” To the authors’ delight, the conversion proceeded smoothly using this ‘new’ reagent under ultrasonication conditions. With good quantities of compound to hand as a result of the ‘discovery’ of this vanadium-based reagent (according to Professor

Scheme 2

Scheme 3
Banwell, perhaps the most important aspect of their work reported in Synlett (Synform) the completion of the synthesis of platencin proceeded smoothly.

Professor Banwell said: “While this second-generation synthesis has some advantages over the first, when our long-time colleague Tomas Hudlicky became aware of our most recent work he immediately saw an opportunity for improvement and so we are now collaborating on the development of what we hope will be a third-generation approach and one that might be able to ‘beat’ probably the very best synthesis of platencin reported thus far by Mulzer and co-workers.”

A major motivation for the Banwell group in pursuing the sort of studies reported in the Synlett paper is the desire to identify platencin analogues that are even more effective than the natural product. The group feels that they have not yet succeeded in this regard, but some of the biological test results obtained through screening a plethora of compounds arising from their synthesis program encourage them to persist.

Going back to the IMDA aspects of their work, Professor Banwell said: “We are intrigued by the ease with which these processes work even though there is no formal activation of the dienophile. We think there is a different form of activation involved in these cases and one that involves a ‘pinching’ of the diene as a result of its annulation with the proximate acetonide residue.” He concluded: “Whether or not this seemingly unconventional mode of activation can be exploited in many other settings remains to be seen. Certainly, we have already used it in the targeted synthesis of members of the sterpurene class of natural products.”

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About the authors

Rehmani N. Muhammad was born and raised in Punjab Province of Pakistan. He completed his Masters in chemistry at The Islamia University Bahawalpur (Pakistan) then joined the Department of Collegiate Education of the Government of Pakistan. He has been working as Assistant Professor of Chemistry there since 2002. He joined the Banwell Group in 2010 as a PhD candidate and his research focus is on the synthesis of natural products of biological interest. He has interests in law, medicine and computing and secured an LLB (with distinction) in an earlier phase of his career.

Alistair G. Draffan graduated from the University of Glasgow (UK) with BSc(Hons) in chemistry before conducting PhD research under the supervision of Professor Alan Armstrong at the University of Nottingham (UK) where he developed new methodologies for selective intramolecular epoxidation. Alistair has more than 15 years of experience in medicinal chemistry and pharmaceutical R&D, particularly in the field of novel anti-infective drugs.

Martin G. Banwell gained his PhD in 1979 after studying under Professor Brian Halton at the Victoria University of Wellington (New Zealand). Following post-doctoral studies with Leo Paquette at the Ohio State University (USA) he moved to the University of Adelaide (South Australia) as a Senior Teaching Fellow. In 1981 he took up an appointment as a Lecturer in Chemistry at the University of Auckland (New Zealand) and then moved to an equivalent position at the University of Melbourne (Australia) in 1986. In 1995 he was appointed a Senior Fellow in the Research School of Chemistry at the Australian National University in Canberra (Australia) where he remains and now holds the rank of Professor.

Anthony C. Willis was born in Perth (Western Australia). He obtained his PhD from the University of Western Australia in 1977 for work performed under the direction of Professor Allan White. He then pursued post-doctoral studies at Simon Fraser University in Vancouver (Canada), with Professor Fred Einstein before returning to Australia in 1985 to a crystallography position within the Research School of Chemistry at the Australian National University in Canberra.
In the past few decades modern aldol reactions have been tackling the most common challenges in synthetic chemistry including regio-, chemo-, diastereo- and enantioselectivity. Because all these selectivity challenges can be present in the same reaction; controlling the outcome of such a process has become of imminent need, especially in the assembly of com-

**Scheme 1** Overview of the second-generation Mukaiyama aldol reaction developed in the Yamamoto group

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plex polyoxygenated natural products. In this context, the group of Professor Hisashi Yamamoto at the Chubu University (Japan) wanted to make a contribution towards solving these selectivity issues for the synthesis of complex polyols.

As the Mukaiyama aldol reaction witnessed a breakthrough in the last few years with the use of tris(trimethylsilyl) silyl 'super silyl' as a powerful directing group, Professor Yamamoto's group focused on the exploration of the Lewis and Brønsted acid catalyzed Mukaiyama aldol reaction of super silyl enol ethers. This new process is now called the second generation of Mukaiyama aldol reaction. Professor Yamamoto and his co-workers examined mono, double and triple aldol reactions with the use of the super silyl group as the key for the amazingly high diastereoselectivity obtained.

Indeed, the use of the most simple (J. Am. Chem. Soc. 2006, 128, 48 and Angew. Chem. Int. Ed. 2010, 49, 2747), halogenated (J. Am. Chem. Soc. 2011, 133, 14248) or alkylated (Angew. Chem. Int. Ed. 2012, 51, 1942) super silyl enol ethers have shown very high diastereoselectivity levels (Scheme 1). Professor Yamamoto explains the high reactivity of the super silyl enol ethers with the high homo levels of the Si–Si and Si–C α-bond, which are able to hyperconjugate to the π-orbital of the enolate in addition to high efficiency of the super silyl Lewis acid catalyst (TMS)₃SiNTf₂ generated in situ from Brønsted acid and super silyl enol ether.

Dr. Wafa Gati, the co-author of this study, said: “In a continuing work on the Lewis acid catalyzed Mukaiyama aldol reaction of super silyl enol ethers, we decided to focus our attention on the construction of α,β-dioxygenated aldehydes, the most important but challenging target, that could be very useful building blocks toward the synthesis of complex natural products including sugar targets.” She continued: “Indeed, by preparing the appropriate dioxygenated enol ether, we were delighted by the highly diastereoselective outcome of our governed super silyl Mukaiyama aldol reaction and obtained the desired α,β-dioxygenated aldehydes in moderate to good yields and with an extremely high syn selectivity.”

During the optimization of their procedure conditions, the authors discovered that their reaction proceeded quite smoothly with linear aliphatic aldehydes, although the yield was moderate. “Nevertheless, when we tested branched or aromatic aldehydes, our reaction turned out to be rather sluggish and only trace amounts of the desired compound were detected,” explained Dr. Gati. Inspired by previous work in their lab, the Japan-based researchers considered the use of an organoiodide that had previously been found to increase the rate and the reactivity of triple aldol reactions (Angew. Chem. Int. Ed. 2010, 49, 2747). Indeed, the use of a substoichiometric amount (10 mol%) of phenyl iodide confirmed the activity-enhancing effect on their reaction outcome and a very wide range of aldehydes were successfully reacted with different dioxygenated super silyl enol ethers to afford the corresponding α,β-dioxygenated aldehydes with excellent diastereoselectivities in almost all cases (Scheme 2). Dr. Gati said: “As we were intrigued by the dramatic role of the phenyl iodide, we conducted ²⁹Si NMR experiments which helped us to understand that the in situ formed [(TMS)₃Si-IPh]+ species is the true catalyst which significantly increases the activity of (TMS)₃SiNTf₂.”

Afterwards, Dr. Gati and Professor Yamamoto examined the possibility of a subsequent one-pot sequential transformation to access 1,2,3-triols which are a very common motif in natural and unnatural sugar structures. Dr. Gati recalled: “We first applied our optimal conditions to the aldol reac-
tion; then, the subsequent addition of a nucleophile such as a Grignard reagent or an organolithium allowed us to access different functionalized 1,2,3-triols with excellent control over the stereoselectivity (Scheme 2).

To explore the utility of their methodology, the two researchers considered its application in the synthesis of pentose- and hexose-like scaffolds and then designed both four- and three-step procedures for the synthesis of pentose- and hexose-like structures, respectively. Dr. Gati explained: "In both processes, our super silyl directed Mukaiyama aldol reaction was the key step toward the construction of the desired molecules with an almost perfect stereocontrol of the multiple stereocenters created during the synthetic processes (Scheme 3). It is worth highlighting that the success of this scheme is also due to the flexibility of the $R^2$ group (i.e. silyl, benzyl, allyl or methyl) which makes this process even more useful in future applications."

Dr. Gati concluded: "Our Lewis acid catalyzed Mukaiyama aldol reaction of super silyl enol ethers has enabled us to find a diastereoselective solution for a one-pot construction of up to three new adjacent stereocenters bearing hydroxy groups, and we hope that we will be able to extend it for up to five or seven consecutive stereocenters created in a one-pot double or triple aldol reaction, respectively."

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**Scheme 3** Application to the synthesis of pentose- and hexose-like scaffolds
About the authors

**Wafa Gati** graduated from the University of Monastir (Tunisia) in 2010 with an M.S. in chemistry. She then began graduate studies in chemistry under the guidance of Professor Gwillerm Evano at the University of Versailles (France) where she focused on the synthesis of nitrogen-containing heterocycles through carbometalation of ynamides. Upon completion of her Ph.D. in 2013, Dr. Gati moved to Chubu University (Japan) to undertake postdoctoral research in asymmetric Lewis acid catalysis in the Yamamoto group. Her most recent work has been centered on super silyl chemistry and Mukaiyama aldol reactions. Her interests include organometallics, asymmetric catalysis, total synthesis and exploring new places.

**Hisashi Yamamoto** received his Bachelor’s degree from Kyoto University (Japan) under the supervision of Professors H. Nozaki and R. Noyori and his Ph.D. from Harvard University (USA) under the mentorship of Professor E. J. Corey. His first academic position was as Assistant Professor and Lecturer at Kyoto University, and in 1977 he was appointed Associate Professor of Chemistry at the University of Hawaii (USA). In 1980, he moved to Nagoya University (Japan) where he became Professor in 1983. In 2002, he moved to the USA as Arthur Holly Compton Distinguished Service Professor at The University of Chicago. He moved again from Chicago to Nagoya in 2012, where he is Professor and Director of the Molecular Catalyst Research Center at Chubu University (Japan). He has been honored to receive the Prelog Medal (1993), the Chemical Society of Japan Award (1995), the Max-Tishler Prize (1998), Le Grand Prix de la Fondation Maison de la Chimie (2002), the National Prize of Purple Medal (Japan, 2002), the Yamada Prize (2004), the Tetrahedron Prize (2006), the Karl-Ziegler Professorship (2006), the Japan Academy Prize (2007), Honorary Member of the Chemical Society of Japan (2008), the ACS Award for Creative Work in Synthetic Organic Chemistry (2009), the Grand Prize of Synthetic Organic Chemistry of Japan (2009), Member of American Academy of Arts and Sciences (2011), the Noyori Prize (2011), and the Fujiwara Prize (2012). He has authored >540 original publications, >140 reviews and books, and >50 patents and is on the board of editors or on international advisory boards of more than 20 international journals. He has presented >160 plenary or invited lectures and >55 honorary lectureships.
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