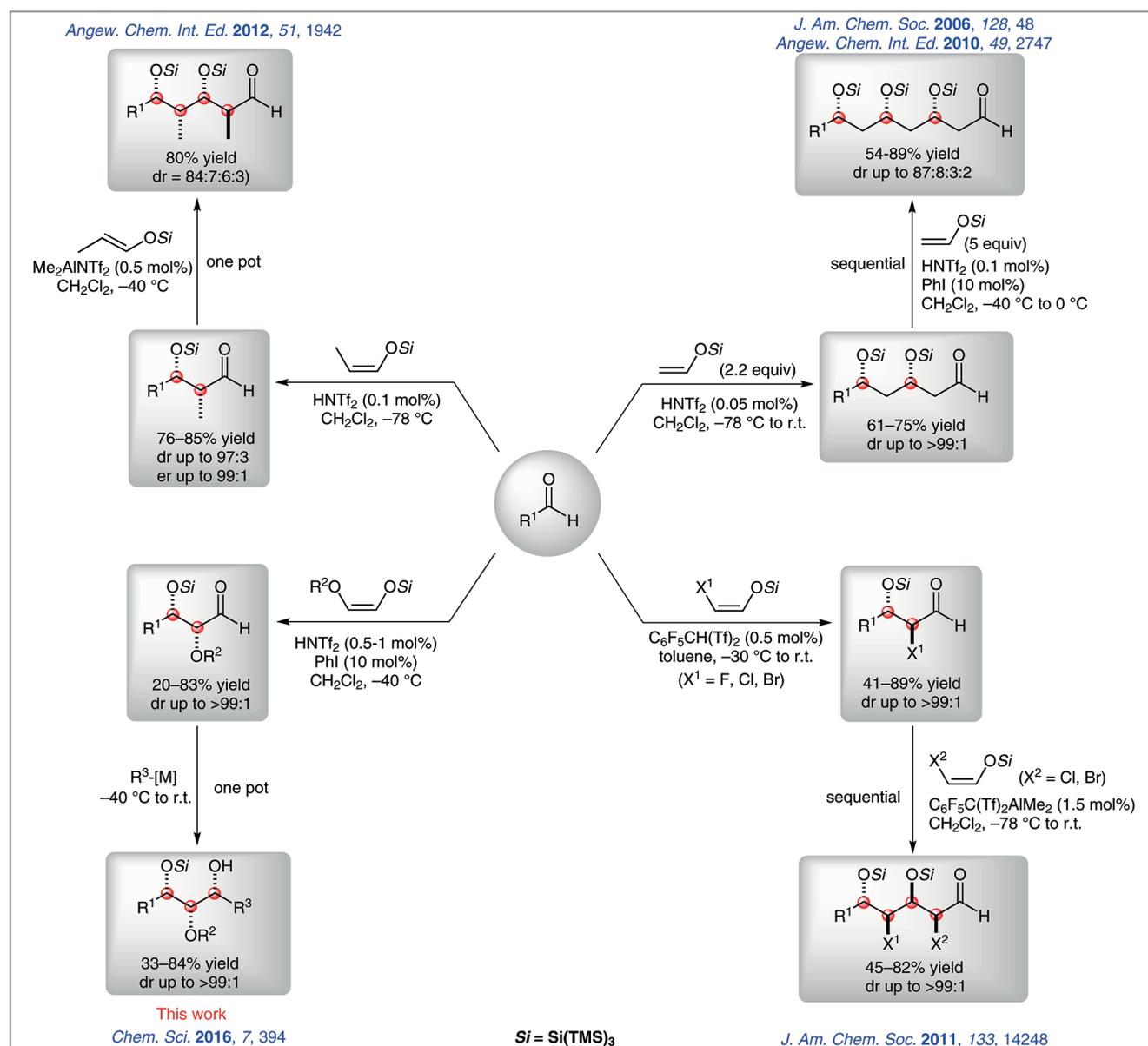


A Highly Diastereoselective 'Super Silyl' Governed Aldol Reaction: Synthesis of α,β -Dioxyaldehydes and 1,2,3-Triols

Chem. Sci. **2016**, *7*, 394–399

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-



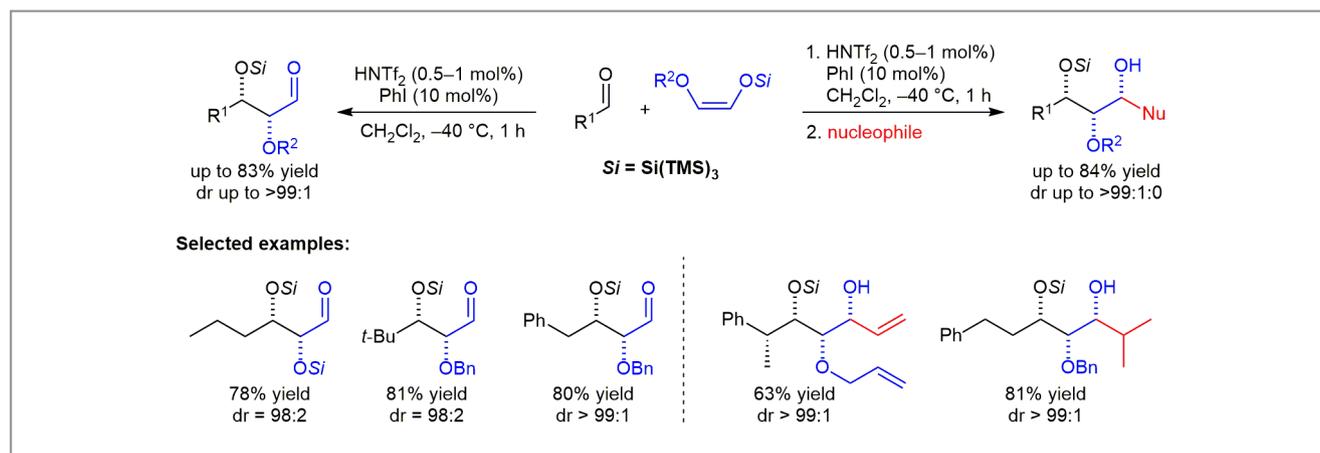
plex polyoxygenated natural products. In this context, the group of Professor Hisashi Yamamoto at the Chubu University (Japan) wanted to make a contribution towards solving these selectivity issues for the synthesis of complex polyols.

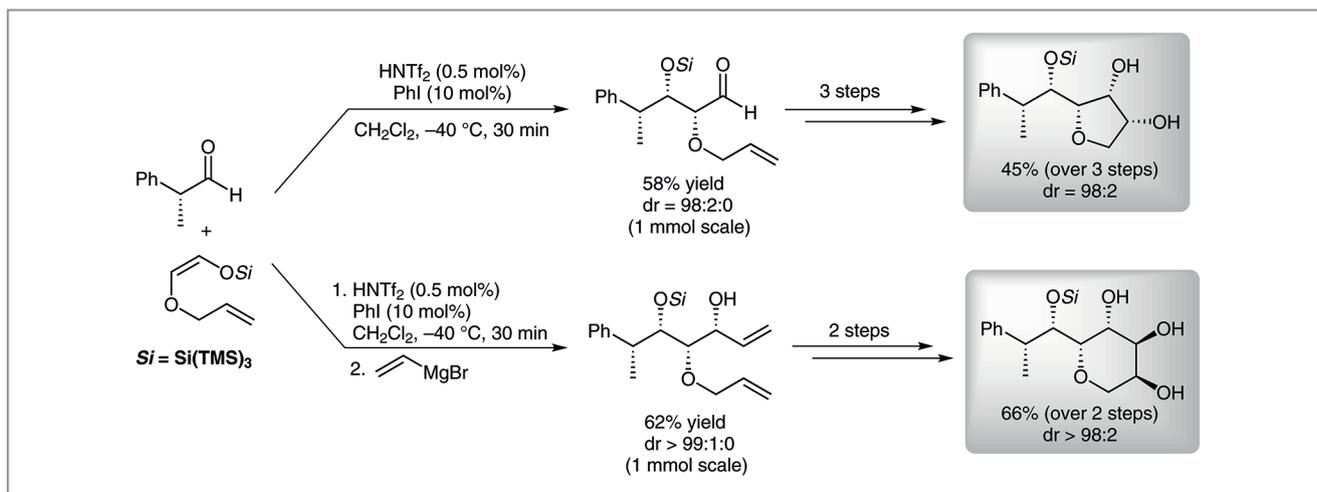
As the Mukaiyama aldol reaction witnessed a breakthrough in the last few years with the use of tris(trimethylsilyl) silyl 'super silyl' as a powerful directing group, Professor Yamamoto's group focused on the exploration of the Lewis acid and Brønsted acid catalyzed Mukaiyama aldol reaction of super 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 σ -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 $(\text{TMS})_3\text{SiNTf}_2$ 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 -dioxxygenated aldehydes, the most difficult but important challenge, that could be very useful building blocks toward the synthesis of complex natural products including sugar targets." She continued: "In-

deed, by preparing the appropriate dioxxygenated enol ether, we were delighted by the highly diastereoselective outcome of our governed super silyl Mukaiyama aldol reaction and obtained the desired α,β -dioxxygenated 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 dioxxygenated super silyl enol ethers to afford the corresponding α,β -dioxxygenated 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 ^{29}Si NMR experiments which helped us to understand that the in situ formed $[(\text{TMS})_3\text{Si-IPh}]^+$ species is the true catalyst which significantly increases the activity of $(\text{TMS})_3\text{Si-NTf}_2$."

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-





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

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 R² 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."

Mattias Fomle

About the authors



Dr. W. Gati

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 Gwilherm 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.



Prof. H. Yamamoto

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.