A General and Robust Method for the Preparation of (*E*)- and (*Z*)-Stereodefined Fully Substituted Enol Tosylates: Promising Cross-Coupling Partners

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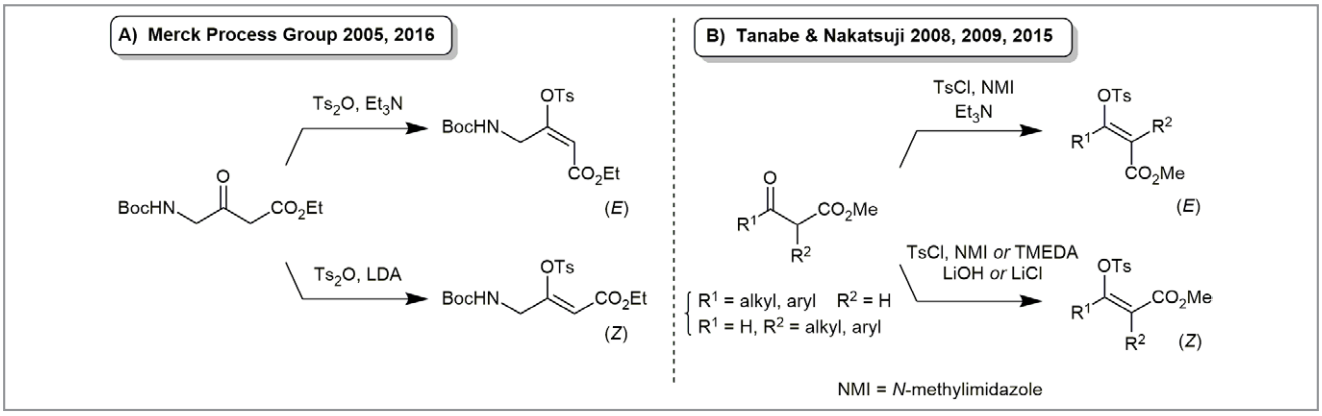
Regio- and stereocontrolled syntheses of (*E*)- and (*Z*)-stereodefined all-carbon-substituted olefins are of pivotal importance and highly challenging tasks in organic synthesis. Recent comprehensive reviews address the impressive progress in this area.[1]

Strategies based on stereoretentive cross-coupling reactions using (*E*)- and (*Z*)-stereodefined 'not fully'-substituted (R^1 *or* R^2 = H in Scheme 1) enol tosylates – which have interesting synthetic applications (see for example Figure 1) – are reliable toward this end.



Scheme 1 (*E*)- and (*Z*)-Stereocomplementary enol tosylations of 'not fully'-substituted β-keto esters

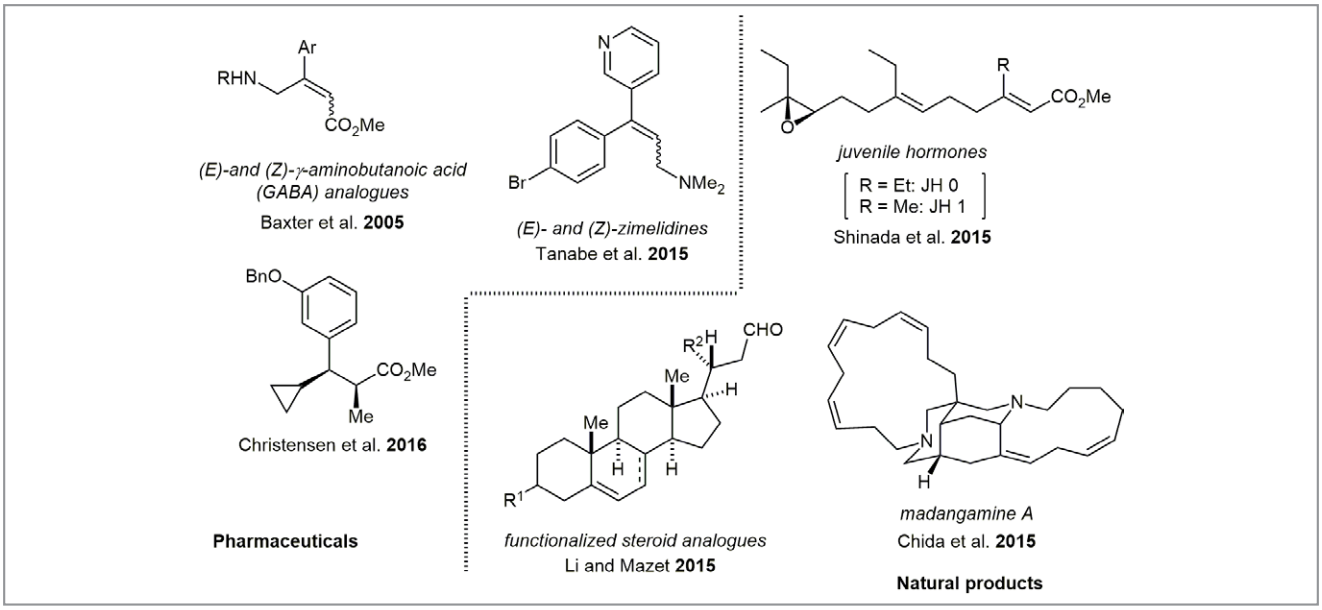
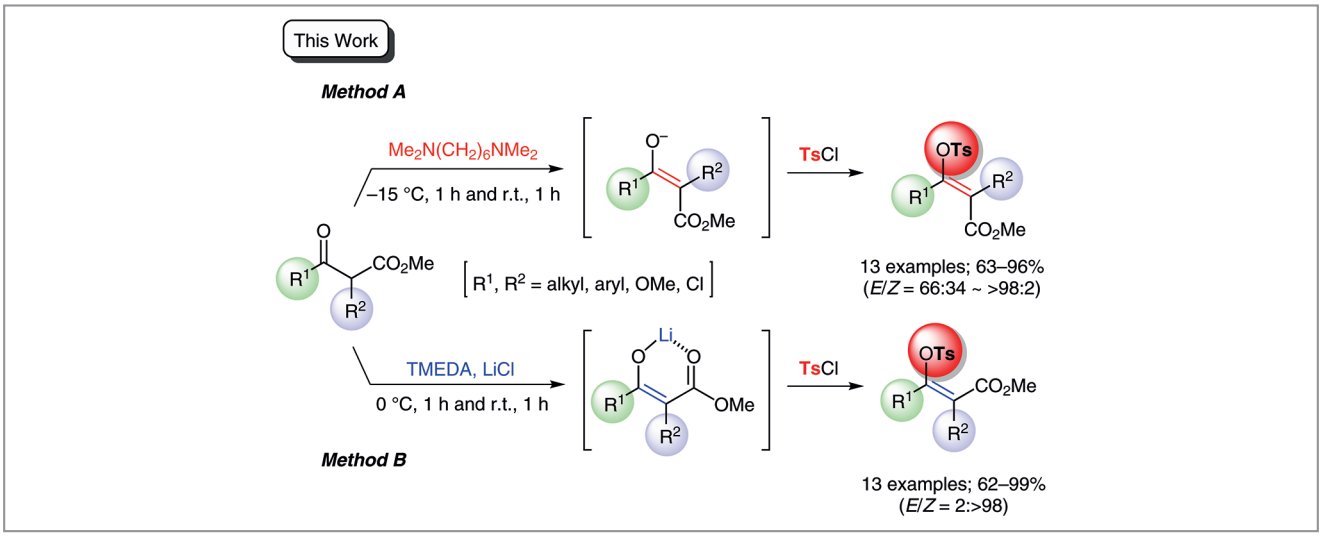
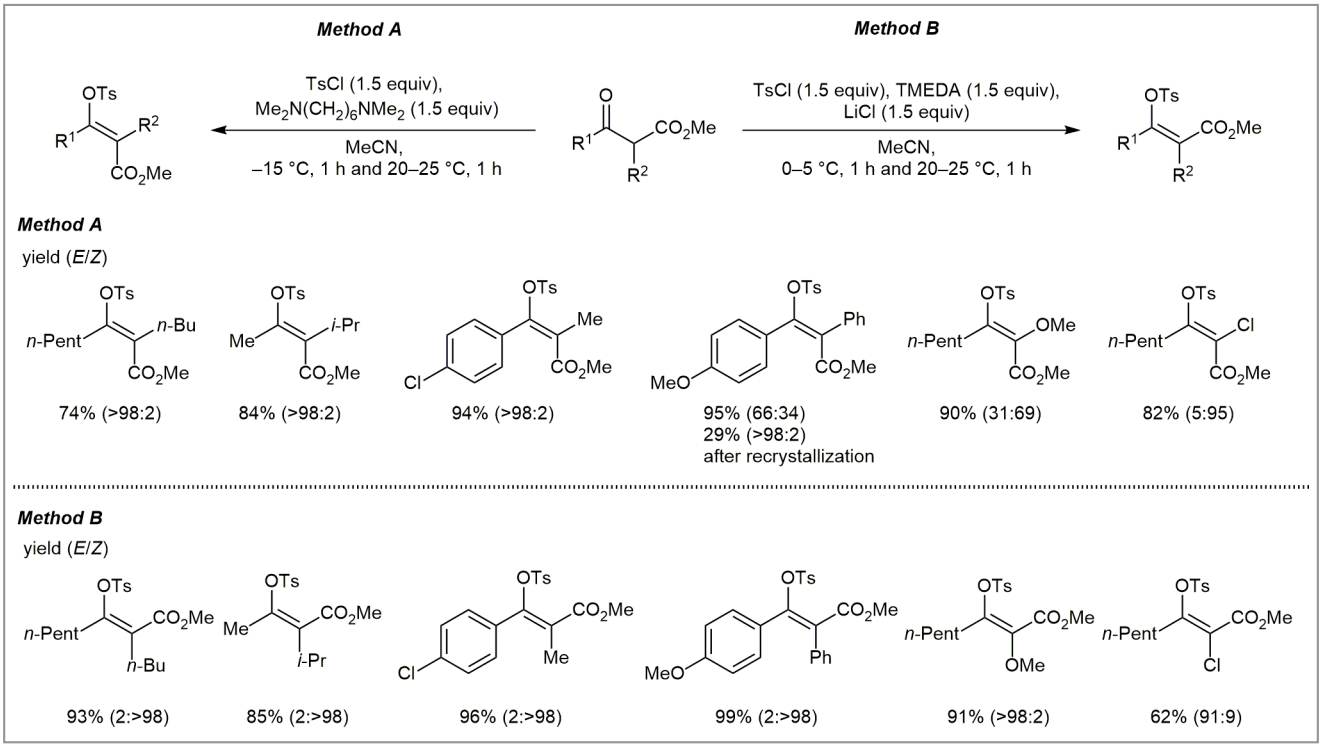


Figure 1 Synthetic applications of 'not fully'-substituted (*E*)- and (*Z*)-enol tosylates



Scheme 2 (*E*)- and (*Z*)-Stereocomplementary enol tosylations of all-carbon 'fully'-substituted β-keto esters

"For the preparation of (*E*)- and (*Z*)-enol tosylate cross-coupling partners, a group at the Merck company consistently utilizes a Ts_2O/amine system for preparing *E*-configured and Ts_2O/LiHMDS (or NaHMDS) for preparing *Z*-configured reagents (see Scheme 1),[2]" said Professor Yoo Tanabe at the Kwansei Gakuin University (Japan), "whereas in our ongoing studies we make use of the much more accessible TsCl/NMI (*N*-methylimidazole)/Et_3N (for *E*) and TsCl/NMI/LiOH (or LiCl) (for *Z*) reagents.[3]" Professor Tanabe continued: "One of our procedures will be disclosed shortly in *Organic Synthesis*



Scheme 3 Representative examples of (*E*)- and (*Z*)-stereocomplementary enol tosylations (Methods A and B)

(OS).[3d] The current privileged methodology has contributed to the successful total syntheses of some elaborated natural products and drug-related compounds, as depicted in Figure 1."

According to Professor Tanabe, the article in *Synthesis* introduces a general, cost-effective, and robust protocol for the preparation of all-carbon (fully)-substituted acyclic enol tosylate scaffolds as promising stereoretentive cross-coupling partners (R^1, R^2 = alkyl and/or aryl; Schemes 2 and 3). "Switching the reagents and conditions allows for (*E*)- and (*Z*)-stereocomplementary preparation of the corresponding enol tosylates from less reactive 'α-carbon-substituted' β-keto esters: TsCl/$Me_2N(CH_2)_6NMe_2$ was used for obtaining (*E*)-products (method A: total 13 examples; 63–96%, almost >98% *E*) and TsCl/TMEDA/LiCl for (*Z*)-products (method B: total 13 examples; 62–99%, almost >98% *Z*)," explained Professor Tanabe.

He continued: "All reactions were completed under identical optimized conditions in good to excellent yields. With regard to stereoselectivity, almost all cases produced positive and excellent results (>94:6 for method A and <2:98 for method B). Purification up to >98% de was achieved by short column chromatography or by recrystallization. As a limitation, (*E*)-selectivity using α,β-diaryl substrates is only moderate. This tendency coincides with discussions in the preceding report[3c] which ascribes it to the intrinsically more stable nature of (*Z*)-isomers. Fortuitously, these crude products could be enriched to the pure (*E*)-products (up to 98% de) by recrystallization. It should be noted that all of these stereodefined (*E*)- and (*Z*)-enol tosylates are novel compounds."

In general, these enol tosylates are relatively stable compounds that exhibit favorable reactivity for various cross-coupling reactions, thanks to recent advances in this area.

Professor Tanabe explained: "The starting α-substituted β-keto esters are readily available utilizing Ti-Claisen and base-mediated Claisen condensations between the same esters (self-type), or Ti-promoted Claisen condensations between different esters or between esters and acid chlorides (crossed-type).[4] α-Monoalkylation of parent β-keto esters is an alternative preparative method, although this is frequently accompanied by troublesome side dialkylation."

As depicted in Figure 2, a careful ^{1}H NMR monitoring experiment (–40 °C in CD_3CN) revealed that TsCl coupled with TMEDA formed a simple *N*-sulfonylammonium intermediate **IA** rather than a plausible N,N′-chelate-type intermediate **IB**. "The apparent downfield chemical shifts of the tosyl moiety in **IA** are related to the higher reactivity of the present system," remarked Professor Tanabe. He continued: "Based on the result, **IA** is likely to function as the key active species. This outcome is apparently contrary to a relevant chiral diamine-catalyzed desymmetric benzoylation of *meso*-diols with PhCOCl and related hypotheses regarding the mechanism through the corresponding N,N′-chelate-type intermediate.[5]"

A plausible mechanism for the successful emergence of (*E*)- and (*Z*)-selectivity is depicted in Scheme 4. "The (*E*)-selective reaction with highly reactive intermediate **I** proceeds via a non-chelation pathway to give (*E*)-form; $Me_2N(CH_2)_6NMe_2$ plays two different roles: that of a base reagent and also as a

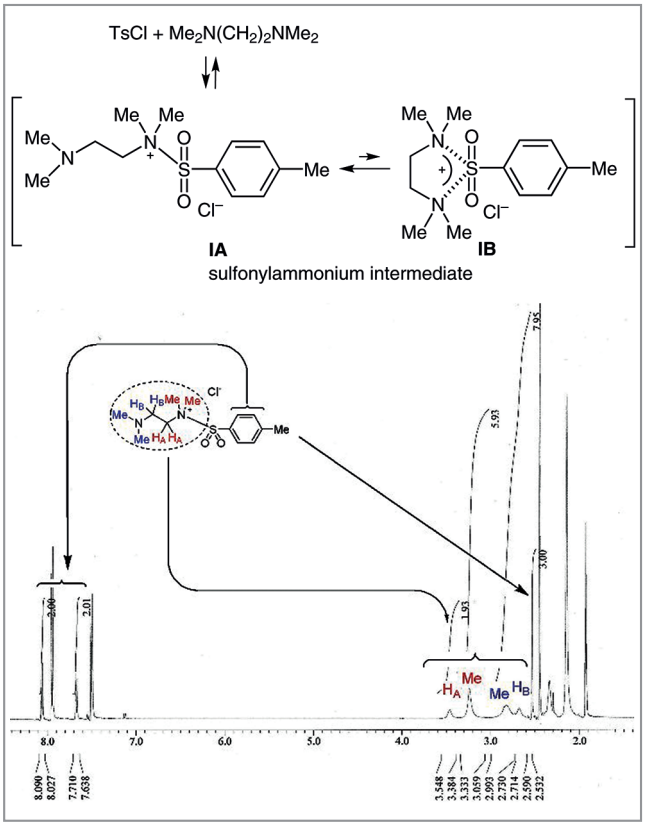
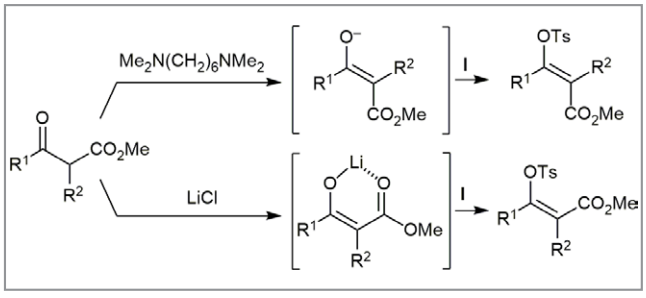


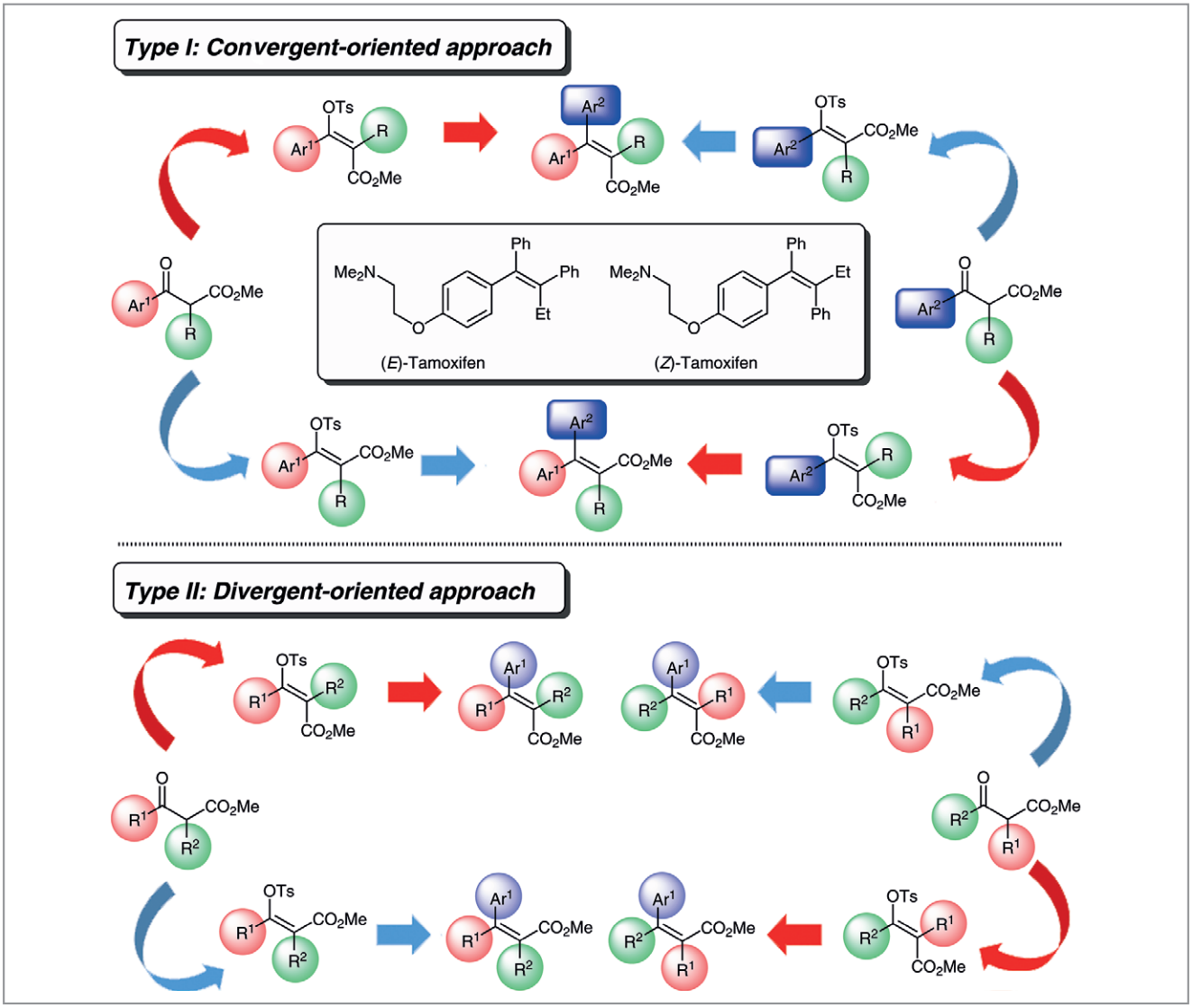
Figure 2 Formation of sulfonylammonium intermediate **IA** by ^{1}H NMR monitoring measurement at –40 °C



Scheme 4 Mechanistic investigation into the (*E*)- and (*Z*)-stereoselective enol tosylations

partner of **I** through equilibrium," explained Professor Tanabe. He continued: "$Me_2N(CH_2)_6NMe_2$ aids (*E*)-enolate formation through dipole-dipole repulsive interactions between the oxy anion and ester function. In clear contrast, the (*Z*)-selective reaction proceeds via a chelation mechanism to give (*Z*)-form; the Li cation facilitates (*Z*)-enolate formation."

Professor Tanabe and co-worker Professor Nakatsuji concluded: "The present protocol provides a useful avenue towards divergent syntheses (Type I and Type II) of various all-carbon (fully)-substituted (*E*)- and (*Z*)-stereodefined α,β-unsaturated ester scaffolds, which are distributed widely in natural products, pharmaceuticals, and supramolecules as key structural building blocks[3e] (Scheme 5). This robust and distinctive method involves stereocomplementary enol tosylations using readily available TsCl/diamine/(LiCl) reagents. High substrate generality is demonstrated in two sets (all four) of parallel and stereocomplementary synthetic pathways. Efficient parallel syntheses of zimeridine and tamoxifen were achieved utilizing subsequent highly (*E*)- and (*Z*)-stereoretentive cross-couplings (Suzuki–Miyaura, Negishi, Sonogashira, and Kochi–Fürstner)." As a final note, Professor Tanabe offered his warmest congratulations to Professor Ben L. Feringa (University of Groningen, The Netherlands) on being awarded the 2016 Nobel Prize in Chemistry.



Scheme 5 Divergent and parallel synthesis of (E)- and (Z)-α,β-unsaturated esters utilizing stereoretentive cross-couplings

About the authors

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Yuichiro Ashida was born in Fukuchiyama, Kyoto (Japan) in 1989. He received his BSc degree (2012) and MSc degree (2014) from Kwansei Gakuin University (Japan) under the direction of Professor Yoo Tanabe. Presently, he is a PhD student and engages in his doctoral studies on the development of (*E*)-, (*Z*)-stereocomplementary parallel synthesis of multi-substituted α,β-unsaturated esters utilizing (*E*)-, (*Z*)-stereodefined enol tosylates and phosphonates and subsequent cross-coupling approaches, which are directed toward process chemistry.

A. Honda

Atsushi Honda was born in Hyogo (Japan) in 1992. He received his BSc degree (2015) from Kwansei Gakuin University (Japan) under the supervision of Professor Yoo Tanabe. He is currently an MSc student in the Tanabe group. His graduate research focuses on the (*E*)-, (*Z*)-stereocomplementary parallel synthesis of multi-substituted α,β-unsaturated esters and its application to (*E*)- and (*Z*)-tamoxifens.

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Yuka Sato was born in Shizuoka (Japan) in 1988. She received her BSc and MSc degrees from Kwansei Gakuin University (Japan) in 2011 and 2013, respectively, under the supervision of Professor Yoo Tanabe. Her research focuses on (*E*)-, (*Z*)-stereocomplementary synthesis of fully substituted α,β-unsaturated esters. She is currently working at Kansai Glico Corporation Ltd.

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Hidefumi Nakatsuji received his BSc degree in 2005 and his PhD in 2010 from Kwansei Gakuin University (Japan) under the direction of Professor Yoo Tanabe. Dr. Nakatsuji then moved to Nagoya University (Japan, Professor Kazuaki Ishihara's group) and studied as a JSPS Postdoctoral Fellow and CREST project researcher until 2014. Next, he was promoted to Assistant Professor of the Tanabe group. His research interests are the development of chiral phosphine and phosphine oxide organocatalysts for MCR-type cyclizations and of condensation reactions for cost-effective reactions directed toward process chemistry.

Prof. Y. Tanabe

Yoo Tanabe received his BSc degree at Tokyo University (Japan) in the laboratory of Professor Kenji Mori. He received his PhD at the Tokyo Institute of Technology (Japan) under the direction of Professor Teruaki Mukaiyama on the development of practical acylation reactions. After leaving Sumitomo Chemical Co. Ltd, Dr. Tanabe moved to Kwansei Gakuin University (Japan) in 1991 as Associate Professor and was promoted to Full Professor in 1997. In 1996–1997, he studied at University of Groningen (The Netherlands) under the direction of Professors Richard M. Kellogg and Ben L. Feringa on chiral sulfur chemistry. His research focuses on the exploitation of useful synthetic reactions directed toward process chemistry, the concise synthesis of useful fine chemicals and the total synthesis of biologically active natural products.

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