

Organocatalytic Enantio- and Diastereoselective Cycloetherification via Dynamic Kinetic Resolution of Chiral Cyanohydrins

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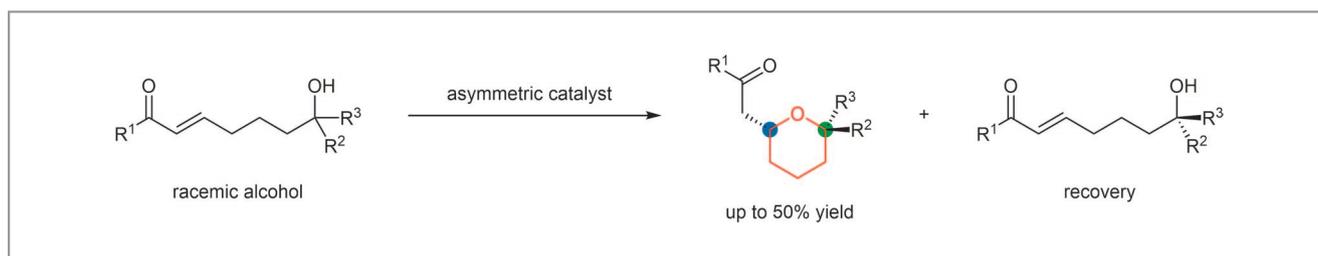
Enantioselective synthetic approaches to six-membered oxacycles are in high demand to enable the discovery of new potential therapeutic agents and bioactive molecules. However, the lack of a simple robust method for such enantioselective syntheses has limited their development. In particular, as the enantio- and diastereoselective construction of multiple stereocenters in a single operation often poses a formidable challenge, it remains desirable to develop a concise efficient method for the asymmetric installation of more than one chiral center in tetrahydropyrans. Recently, the group of Professors Sejiro Matsubara and Keisuke Asano at Kyoto University (Japan) discovered a concise organocatalytic cycloetherification for the highly enantio- and diastereoselective synthesis of tetrahydropyrans, involving simultaneous construction of two stereogenic centers, one of which is fully substituted. This method involves dynamic kinetic resolution of reversibly generated chiral cyanohydrins.

Professor Asano said: “For some time we have been interested in the synthesis of heterocyclic compounds via asymmetric intramolecular hetero-Michael addition with bifunctional organocatalysts, which selectively recognizes a specific conformation of substrates or intermediates. In particular, we have recently tackled the construction of multiple stereogenic centers in a single reaction. We previously reported an asymmetric cycloetherification of secondary or tertiary alcohols bearing an α,β -unsaturated carbonyl moiety affording tetrahydropyrans containing two stereogenic centers via kinetic resolution of the racemic alcohols (*Chem. Lett.* **2016**, *45*, 1300, [Scheme 1](#)).”

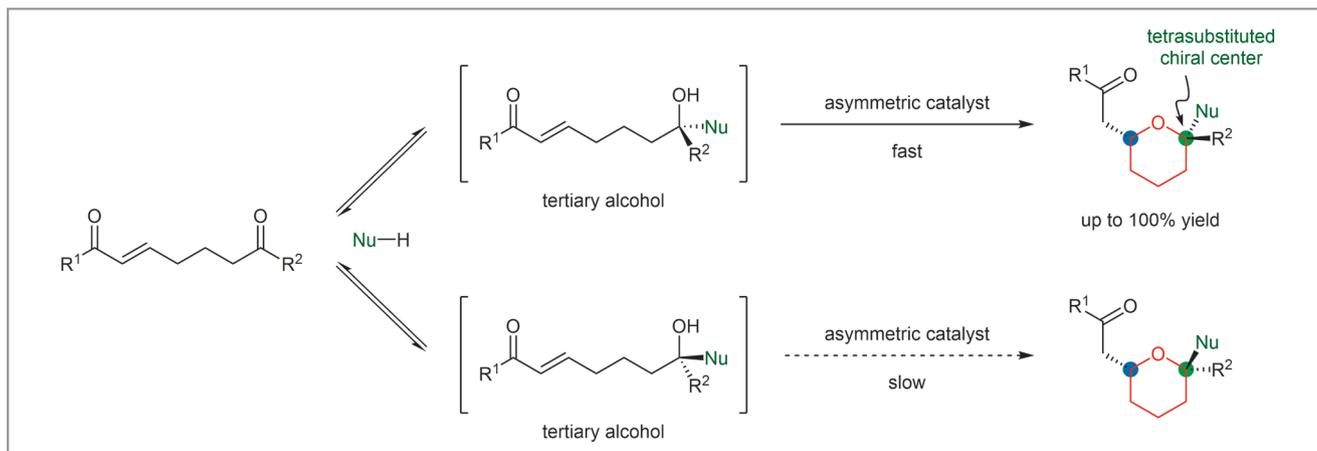
The group then wondered whether the methodology could be extended to cyclization via dynamic kinetic resolu-

tion involving racemization of chiral alcohols, thus potentially enabling quantitative yields of the desired product. “In order to construct a tetrasubstituted chiral carbon center, racemization of tertiary alcohols is necessary; however, redox processes cannot be employed in such cases and these racemizations typically require harsh reaction conditions that are not suitable for asymmetric catalysis,” explained Professor Asano. He continued: “Thus, to achieve the cyclization of chiral tertiary alcohols via dynamic kinetic resolution, I discussed with Mr. Yoneda for several hours in front of a glass board, which we often use to draw chemical structures for discussion. After an hour, we first hit on the idea that a process involving reversible addition of a carbon nucleophile to ketones may result in formal racemization of tertiary alcohols under mild conditions (Scheme 2). Actually, we previously utilized an analogous process for the asymmetric synthesis of spiroketals involving reversible generation of chiral hemiacetals from ketones with alcohols as the nucleophile (*Angew. Chem. Int. Ed.* **2015**, *54*, 15497).”

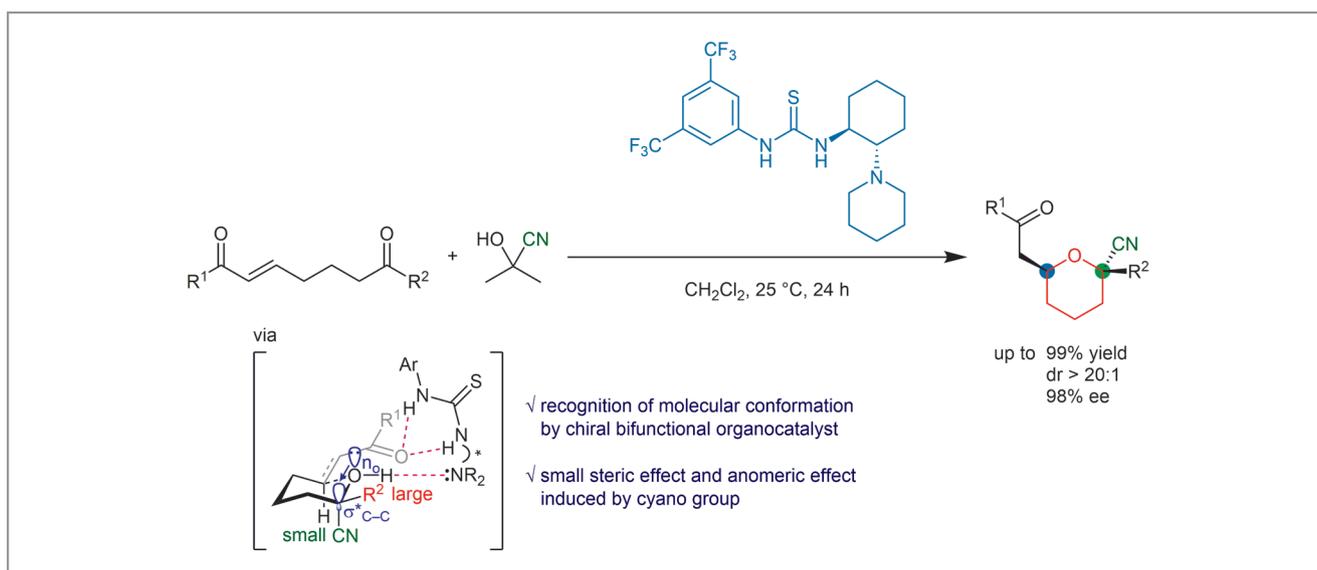
Next, the two researchers asked each other what would be suitable as the carbon nucleophile. The solution they reached after additional discussion was the use of cyanation, as it might be reversible. “Based on the discussion, Mr. Yoneda initiated the investigations for optimizing the reaction conditions including cyanide sources, catalysts, and so on,” said Professor Asano, continuing: “Although the desired product was not initially obtained at all, after dedicated efforts he identified acetone cyanohydrin as a useful cyanation reagent and managed to optimize the effective catalyst structure (Scheme 3).”



Scheme 1 Cycloetherification via kinetic resolution of racemic alcohols



Scheme 2 Cycloetherification via dynamic kinetic resolution involving reversible addition of a carbon nucleophile to ketones



Scheme 3 Organocatalytic enantio- and diastereoselective cycloetherification via dynamic kinetic resolution of chiral cyanohydrins

Regarding the excellent enantio- and diastereoselectivities, the pair had further brainstorming sessions and noticed that in this reaction the anomeric effect induced by the electronegative character of the cyano group was likely to have an important effect on the stereoselectivity with respect to the tetrasubstituted chiral carbon. “At that stage, unfortunately, Mr. Yoneda left our group to join a company, where he is currently working. Thus, further studies for the mechanistic insights and the derivatization of a reaction product were taken over by Ms. Fujii and Mr. Matsumoto. They revealed, experimentally, the importance of the cyano group for the excellent stereoselectivities as well as the synthetic useful-

ness of the cyano group, which can be further transformed to install various important functional groups on the tetrasubstituted chiral center,” said Professor Asano.

Professor Matsubara realized the importance of this transformation soon after the discovery, encouraging the group and giving numerous pieces of fruitful advice during the course of the study. “We also appreciated comments from one of the manuscript’s referees, pointing out the large impact of the small A value of the linear cyano group on weak 1,3-diaxial interactions in a six-membered chair-like conformation. Because of them, we could plausibly rationalize the stereoselectivities of the reactions,” explained Professor Asano.

“We consider that this strategy provides a platform to design efficient approaches to a wide range of optically active tetrahydropyrans, which are otherwise synthetically challenging materials,” remarked Professor Asano. He continued: “In addition, Mr. Matsumoto is currently trying to develop additional efficient synthetic reactions on the basis of this methodology. We are further aiming for the application of this catalytic system to the development of synthetic transformations involving simultaneous formation of more stereogenic centers and a versatile methodology for the construction of tetrasubstituted stereogenic carbons.”

Professor Asano concluded: “Finally, it is notable that the discussions we had with many people contributed strongly to improving this study. In particular, the initial long discussion with Mr. Yoneda opened the door to this successful research project. I thus realized that many hours spent on discussions and brainstorming sessions over research issues can then be rewarded by several years of brilliant results!”

Matthew Farnok

About the authors



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Naoki Yoneda completed his B.S. (2013) and M.S. (2015) degrees at Kyoto University (Japan) under the supervision of Professor Seiji Matsubara, and he is currently working at DKS Co., Ltd. (Japan).



Prof. K. Asano

Keisuke Asano completed his Ph.D. at Kyoto University (Japan) in 2012 under the supervision of Professor Seiji Matsubara. He was appointed as an Assistant Professor at Kyoto University in 2012 and joined the group of Professor Jun-ichi Yoshida before moving back to the group of Professor Seiji Matsubara in 2013. He received The 30th Inoue Research Award for Young Scientists (2014), the Eisai Award in Synthetic Organic Chemistry, Japan (2014), and was a Special Young Lecturer in the 95th CSJ Annual Meeting (2015).



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Prof. S. Matsubara

Seiji Matsubara was educated in chemistry at Kyoto University (Japan), completing his Ph.D. in 1986 with Professors Hitoshi Nozaki and Kimitiro Utimoto, and at the Université de Lausanne (Switzerland) where he was a Ph.D. course student with Professor Manfred Schlosser. He was appointed as an Assistant Professor at Kyoto University in 1986. After postdoctoral research with Professor Barry M. Trost at Stanford University (USA) in 1988–1989, he became an Associate Professor at Kyoto University in 1995. In 2006, he became a Full Professor at Kyoto University. He received The 3rd Inoue Research Award for Young Scientists (1987), the Incentive Award in Synthetic Organic Chemistry, Japan (1998), the Asian Core Program Lectureship Award, Korea and Malaysia (2014), and The 34th Chemical Society of Japan Award for Creative Work (2017).



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Akira Matsumoto completed his B.S. (2014) and M.S. (2016) degrees at Kyoto University (Japan) under the supervision of Professor Seiji Matsubara, and he is currently pursuing his Ph.D. studies.