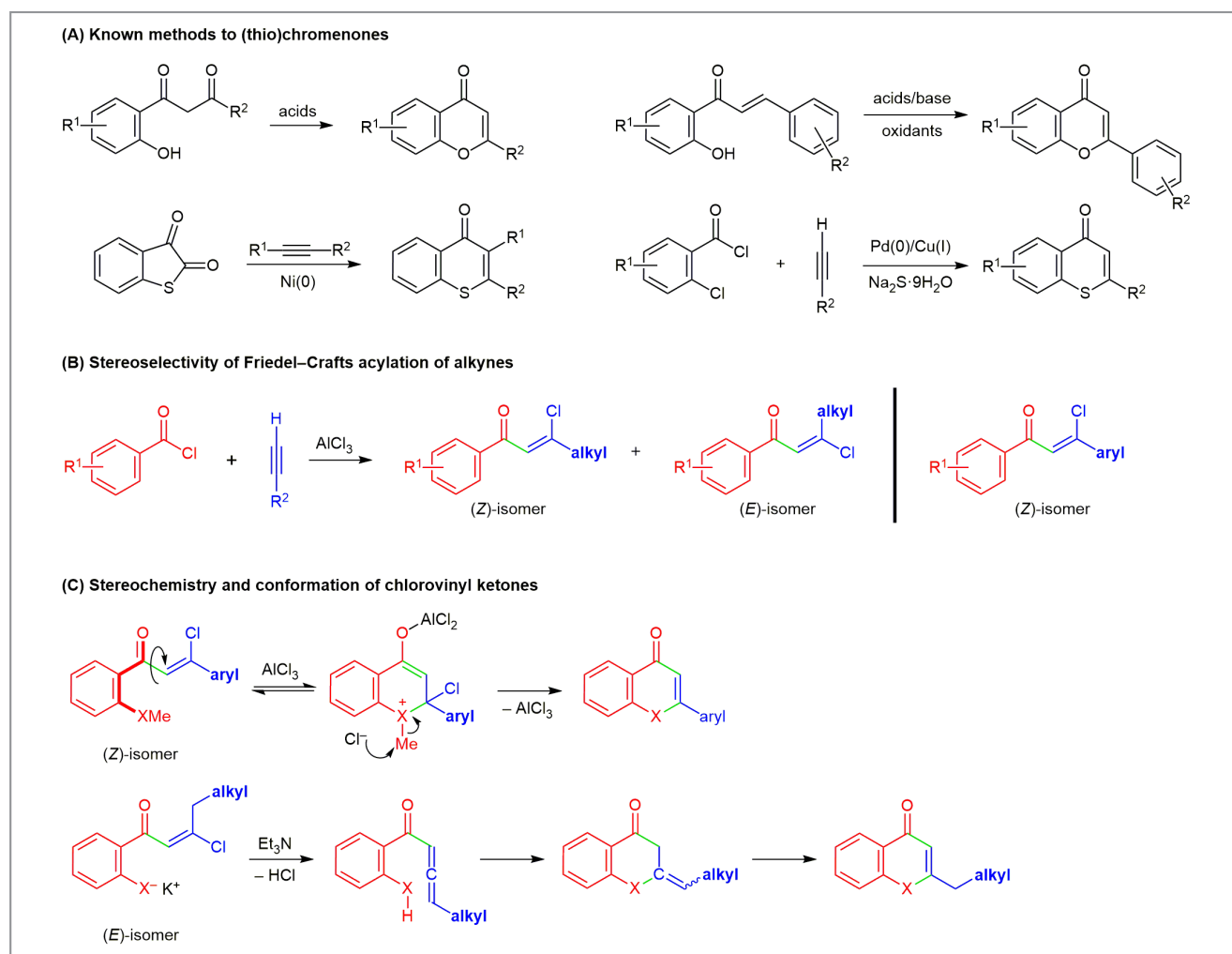


β -Chlorovinyl Ketones to (Thio)chromenones: A Substrate-Controlled Mechanistic Dichotomy

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Chromenones and thiochromenones are widely represented among natural products and their synthetic derivatives typically display a wide array of biological activities. The growing interest in the pharmaceutical properties of (thio)chromenones has spurred the development of novel synthetic methods to (thio)chromenone derivatives. The typical synthetic approaches to chromenones rely on the intramolecular condensation of *o*-hydroxy 1,3-diones and the intermolecular conjugate addition of *o*-hydroxy chalcones under oxidation

conditions (Scheme 1, A). In contrast, the synthetic approaches to (thio)chromenones are limited to a handful of Ni-catalyzed and Pd-catalyzed reactions of thio-substituted substrates. With the aim of developing a facile and efficient synthesis of (thio)chromenones without using elaborated substrates or expensive reagents, the group of Professor Kyungsoo Oh at Chung-Ang University (Seoul, South Korea) proposed a reaction sequence of Friedel–Crafts acylation of alkynes and intramolecular cyclization of in situ generated β -chlorovinyl ketones.



Scheme 1

"The Friedel–Crafts acylation of alkynes can result in the formation of stereoisomeric β -chlorovinyl ketones. Our previous studies suggested that the stereoselectivities for reactions involving alkyl- and aryl-substituted alkynes is substrate-dictated (Scheme 1, B)," explained Professor Oh. He continued: "Thus, the use of alkyl alkynes can lead to the kinetically favored (*Z*)- β -chlorovinyl ketones and the thermodynamically favored (*E*)- β -chlorovinyl ketones. While the (*E*)/(*Z*)-selectivity of reactions utilizing alkyl alkynes could be controlled by the reaction temperature and the amount of AlCl_3 , the aryl alkynes exclusively produced (*Z*)- β -chlorovinyl ketones regardless of the reaction conditions used. The reaction pathways of such distinctive stereochemistry of β -chlorovinyl ketones has been the focal point in the synthesis of (thio)chromenones."

The stereochemistry of β -chlorovinyl ketones afforded mechanistic insights into the formation of (thio)chromenones. Professor Oh explained that utilizing the methoxy- and thiomethoxy-substituted aryl acid chlorides, the Friedel–Crafts acylation of aryl alkynes led to the formation of (*Z*)- β -chlorovinyl ketones with an intact (thio)methoxy group (Scheme 1, C). In contrast, the formation of (*E*)- β -chlorovinyl ketones with a hydroxy (or thiol) group was observed from alkyl alkynes. "The most probable conformation of (*Z*)- β -chlorovinyl ketones with an intact (thio)methoxy group would initiate a conjugate addition reaction in the presence of a Lewis acid, such as AlCl_3 , through the activation of the carbonyl group," remarked Professor Oh. After the demethylation of the oxonium (or thionium) ion and elimination of chloride, the (thio)chromenones were obtained. For (*E*)- β -chlorovinyl

ketones with a hydroxy (or thiol) group, the most probable conformation would prefer the intramolecularly H-bonded conformation. Thus, the use of base was required to break the H-bonding network. "To this end, instead of employing strong bases, we turned to the use of KOt-Bu and a mild base, Et_3N , to prompt a mild α -vinyl enolization of (*E*)- β -chlorovinyl ketones to allenes that in turn undergo a rapid cyclization to (thio)chromenones," said Professor Oh, continuing: "This mild in situ allene formation avoids the functional group compatibility issues present under strongly basic conditions. The substrate scope of the current method was broadly applicable to aryl and alkyl alkynes with suitably substituted acid chlorides, providing a facile one-pot access to pharmaceutically important heterocycles, (thio)chromenones (Figure 1)."

Professor Oh concluded: "From our studies on the divergent reaction pathway of stereoisomeric β -chlorovinyl ketones, we were strongly reminded of the stereochemical and conformational significance of compounds involved in the subsequent reaction pathways."

Professor Oh

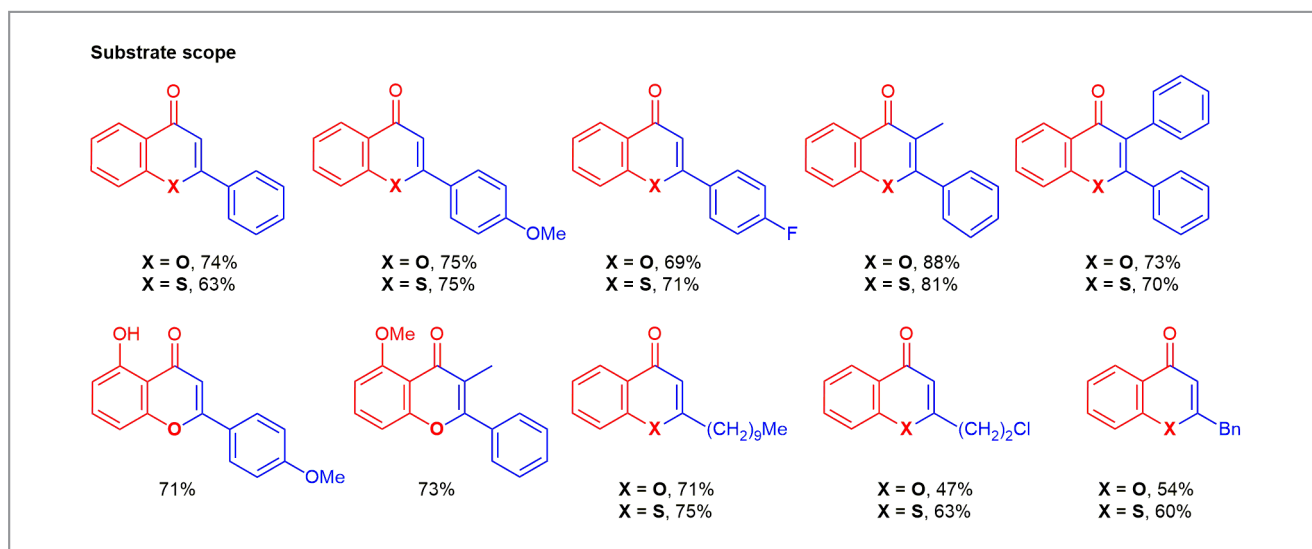


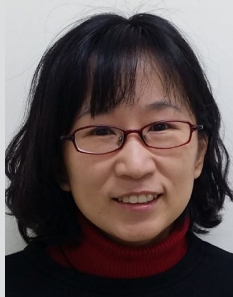
Figure 1

About the authors

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encompass synthetic methodology, catalysis, and medicinal chemistry.

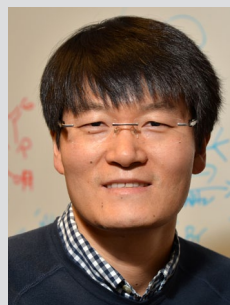
Eunsun Song was born in Daejeon (South Korea). She received her B.S. in chemistry from the Chungnam National University (South Korea) in 2015, and then joined the Professor Kyungsoo Oh's group at the College of Pharmacy, Chung-Ang University (South Korea). For her Master's degree, Eunsun is currently working on the synthesis of heterocyclic compounds with a strong emphasis on furan synthesis. Her research interests

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2003 for her doctoral studies. While at Penn, she worked on the stereoselective synthesis of cyclopropyl derivatives under the guidance of Professor Patrick J. Walsh. In late 2008, she joined the Department of Chemistry & Chemical Biology at Indiana University–Purdue University Indianapolis (IUPUI, USA), where she worked as a research scientist in collaboration with Professor Kyungsoo Oh. In 2014, she was appointed as an Assistant

Hun Young Kim was born in Seoul (South Korea). She attended the Ewha Woman's University (South Korea) and received her B.S. in chemistry in 1997. Continuing her research training at Ewha, she obtained her M.S. degree in 1999 under the guidance of Professors B. T. Ahn and M. Y. Lee. After five years at the Samsung R&D Center in Suwon (South Korea) as a research chemist, she moved to the University of Pennsylvania (USA) in

Professor in the College of Pharmacy at Chung-Ang University (South Korea). Her current research interest lies in the field of asymmetric catalysis with strong focus on the development of conceptually new asymmetric strategies.

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an immunosuppressant drug. At the end of 2002, he joined the laboratory of Professor Jeffrey D. Winkler as a postdoctoral fellow at the University of Pennsylvania (USA). At Penn, he investigated the Diels–Alder reactions of electron-rich dienes and the synthesis of neokaualamine, a dimeric manzamine. In 2005, he was appointed as an Assistant Professor at the Indiana University–Purdue University Indianapolis (IUPUI, USA) and promoted to Associate Professor with tenure in 2011. After a brief sabbatical of seven months at Imperial College London (UK), he was appointed Associate Professor in the College of Pharmacy at Chung-Ang University (South Korea) in 2014. In 2015, he attained the Science Research Center (SRC), a key national research laboratory, in the College of Pharmacy at Chung-Ang University, focusing on cancer metastasis research. His current research interest is centered on the development of novel synthetic strategies for pharmaceutically important chemical entities, in particular anticancer agents.

Kyungsoo Oh was born in Incheon (South Korea). After early education in Korea and Japan, he read chemistry at Queen Mary College, University of London (UK), obtaining a B.Sc. (First Class) in 1999. Under the auspices of AstraZeneca he studied for his Ph.D. in the laboratory of Professor Philip J. Parsons at the University of Sussex (UK). While at Sussex, he worked on the silicon-mediated fragmentation and the total synthesis of rapamycin,