

# Synthesis of *cis*-Thiiranes as Diastereoselective Access to Epoxide Congeners via $4\pi$ -Electrocyclization of Thiocarbonyl Ylides

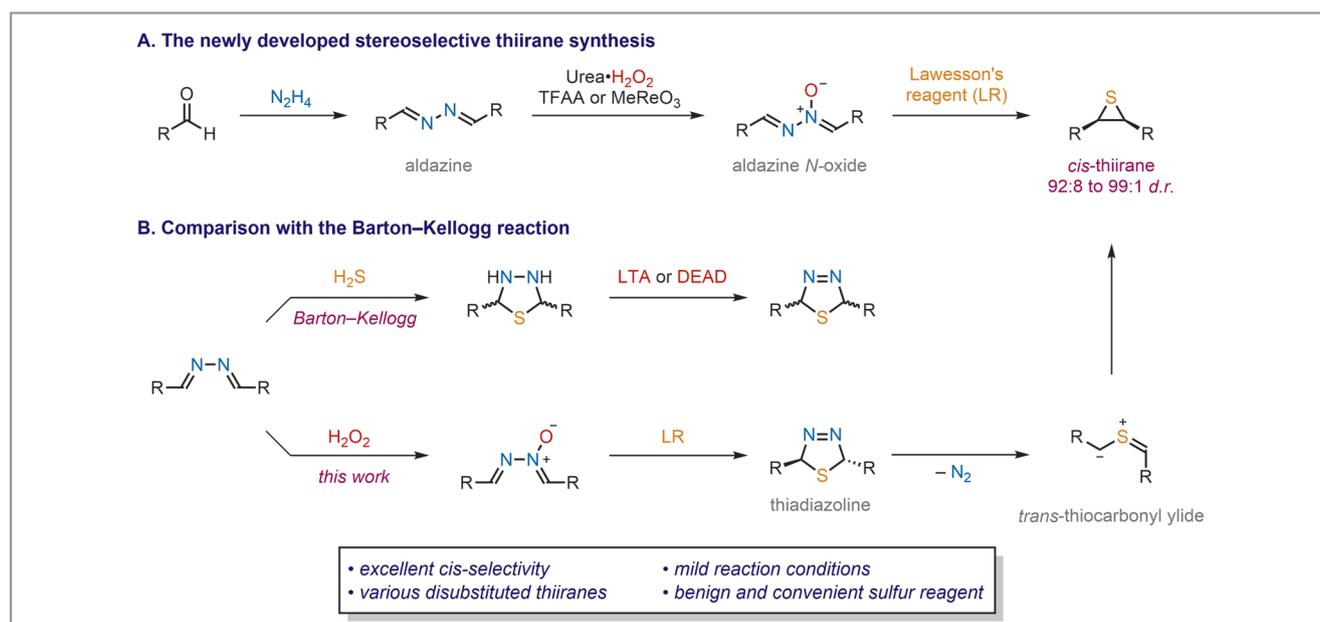
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Thiirane can be regarded as a cousin of a much more well-established congener, oxirane. However, while a myriad of synthetic methods – including enantioselective variants – have been extensively developed for oxiranes, thiirane synthesis is considerably underdeveloped, despite the structural similarity and the potential synthetic utility. “All four stereoisomers of stilbene oxide can be easily prepared and are even commercially available. In contrast, few synthetic methods are known for stilbene sulfides, and the processes typically employ stilbene oxides as the precursors,” said Professor Won-jin Chung from Gwangju Institute of Science and Technology (GIST, Republic of Korea). He continued: “In fact, thiiranes are most commonly prepared from the corresponding oxiranes via chalcogen exchange with thiocyanate or thiourea as sulfuring reagents. Stereoselective thiirane synthesis is an even more challenging task. Although a few notable examples including asymmetric catalysis have appeared recently, the reaction type and the substrate scope are still very limited.”

The group of Professor Chung has been intrigued by the unique structure-reorganizing characteristics of 1,2-diazines.

“For instance, we serendipitously discovered an unusual ring-contraction of electrophilically activated phthalazines, which are a kind of cyclic 1,2-diazine (*Synthesis* **2021**, *53*, 1760–1770),” explained Professor Chung. He added: “Then, as a continuation of our research program, acyclic 1,2-diazines such as aldazine derivatives were examined. While conducting exploratory experimentations, i.e., heuristic survey of various electrophiles, thiirane was obtained unexpectedly upon treatment of aldazine *N*-oxide with Lawesson’s reagent (Scheme 1A). We quickly realized that this kind of disubstituted thiirane is not easily accessible in a stereo-defined form, and thus we were pleased to see the outstanding *cis*-diastereoselectivities, as well as high chemical yields featured by our reactions with a wide range of diaryl substrates.”

The group hypothesized the intermediacy of *trans*-thiocarbonyl ylide which could be generated from putative *trans*-thiadiazoline. “Our newly developed process resembles the classic Barton–Kellogg reaction (Scheme 1B), in which sulfur is introduced first using hydrogen sulfide to form a fully saturated heterocyclic intermediate, and then the nitrogens are



**Scheme 1** Title reaction discovery and comparison with the precedent

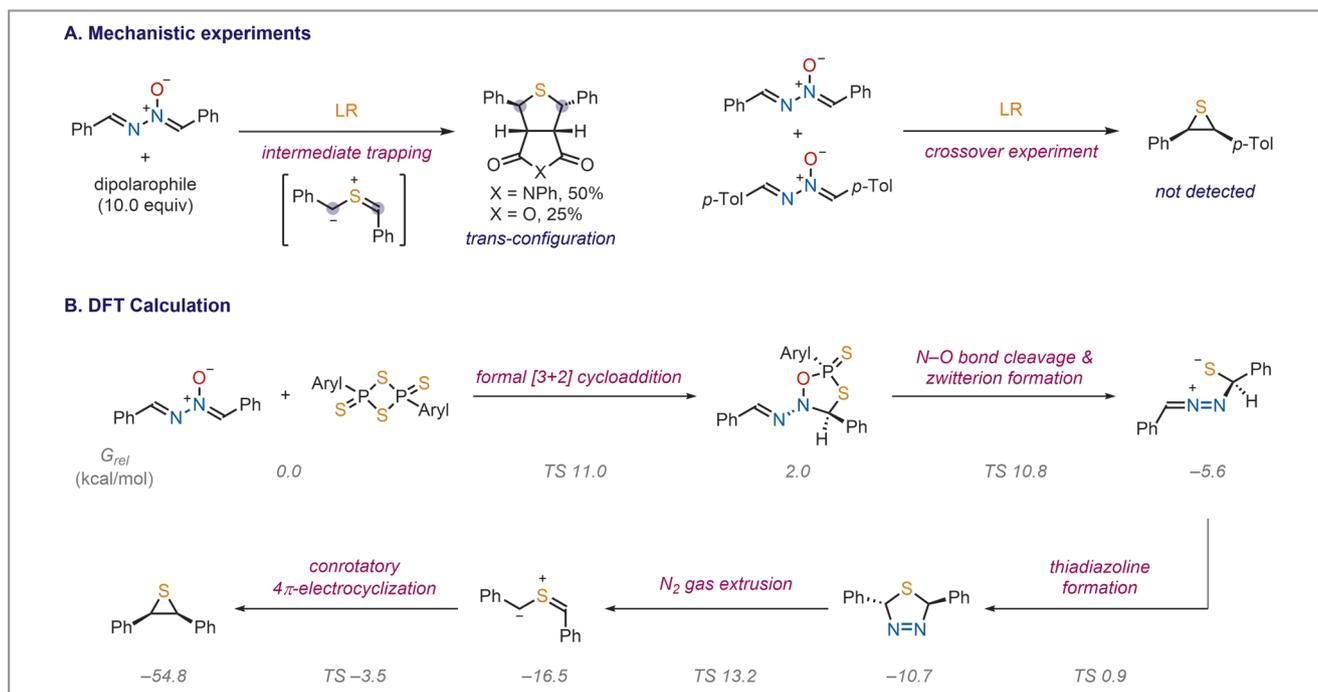
oxidized under harsh reaction conditions with toxic, and not exactly pleasant, reagents such as lead tetraacetate or DEAD,” remarked Professor Chung. He continued: “In contrast, our reaction sequence is reversed. The nitrogen part is pre-oxidized prior to the sulfuration, which – we believe – allows the use of a much more convenient, less toxic oxidant and sulfuring reagent. Furthermore, the exceptional diastereoselectivity is also a notable advantage that cannot be obtained from the Barton–Kellogg reaction.”

The key aspects of the reaction mechanism were elucidated by mechanistic experiments (Scheme 2A). “The putative thiocarbonyl ylide was successfully trapped by the dipolarophile to give the corresponding [3+2] cycloadduct, which clearly showed the *trans*-configuration around the sulfur. In addition, from a crossover experiment with a mixture of two different aldazine *N*-oxides, the aryl group scrambling was not detected at all, demonstrating the intramolecular nature of the thiirane formation,” explained Professor Chung. Then, through a collaboration with Professor Jun-Ho Choi at GIST, the DFT calculation was conducted to support the group’s proposal (Scheme 2B). Professor Chung said: “It was suggested that the processes toward the thiadiazoline formation take place on one side of the flat *E,E*-aldazine *N*-oxide, which should be responsible for the high stereospecificity. Then, the stereospecific nitrogen extrusion to *trans*-thiocarbonyl ylide

and the subsequent conrotatory 4 $\pi$ -electrocyclization furnish the observed *cis*-disubstituted thiirane product.”

“Our work constitutes a rare example of stereoselective thiirane synthesis, through which an array of thermally stable *cis*-diaryl thiiranes became available,” said Professor Chung, continuing: “Currently, we are trying to expand the reaction scope to the *trans*-diastereomers as well as unsymmetrical structures. Furthermore, we are curious to find out whether other elements such as selenium-, nitrogen-, and carbon-containing moieties could be incorporated through similar processes.” Professor Chung concluded: “Eventually, we hope to develop a general synthetic platform for three-membered heterocycles utilizing azines and azine *N*-oxides.”

*Matters female*



## About the authors



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**Su-min Song** received his MS degree from Gwangju Institute of Science and Technology (GIST, South Korea) in 2018 under the supervision of Prof. Won-jin Chung. He is continuing his PhD studies in the same research group. His research interests include the synthetic utilization of unusual reactivity of organonitrogen compounds and the development of stereoselective heterocycle synthesis.



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Prof. JH Choi

**Jun-Ho Choi** has been on the faculty of Gwangju Institute of Science and Technology (South Korea) since 2018. He received his B.S., M.S., and Ph.D. degrees in chemistry from Seoul National University (South Korea) in 1990, 1992 and 1996, and worked as a research professor at the IBS Center for Molecular Spectroscopy and Dynamics (South Korea) from 2014 to 2018. He is a computational chemist, using DFT calculation, MD simulation and graph theory to explore molecular systems. His main research interests are chemical reaction mechanism prediction, computational spectroscopy, computer-aided molecular design and water structure and dynamics in solutions.



Prof. WJ Chung

**Won-jin Chung** received his B.S. degree from Korea Advanced Institute of Science and Technology (South Korea) in 2002 and his Ph.D. from University of Illinois at Urbana-Champaign (USA) under the supervision of Prof. Scott E. Denmark in 2008. After conducting postdoctoral studies with Prof. Christopher D. Vanderwal at the University of California, Irvine (USA), Won-jin began his independent career at Gwangju Institute of Science and Technology (South Korea) in 2014. His research group has been investigating various aspects of halogenations and molecular reorganizations of 1,2-diazines.