Catalytic Enantioselective Alkylation of Sulfenate Anions to Chiral Heterocyclic Sulfoxides Using Halogenated Pentanidium Salts

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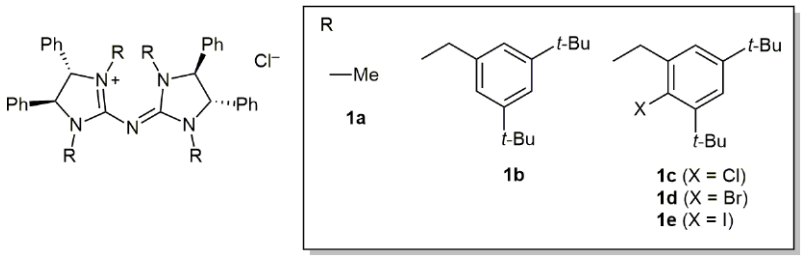
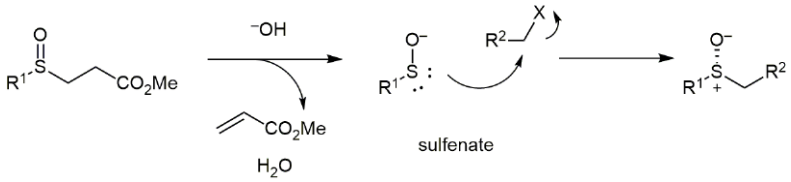


Figure 1

Sulfoxides of high stereochemical purity are widely used in organic synthesis as organocatalysts, ligands, and chiral auxiliaries. Molecules incorporating a sulfinyl group are also important in medicinal chemistry, as witnessed by the presence on the market of important drugs such as esomeprazole, armodafinil, and sulindac, which belong to the sulfoxide family.

The group of Professor C.-H. Tan at the Nanyang Technological University (Singapore) has been interested in Brønsted base catalyzed enantioselective reactions for many years. Professor Tan explained: "We have utilized bicyclic guanidine to demonstrate the wide applicability of this class of catalysts (*Synlett* **2010**, 1589). Building on this work, we became interested in creating a 'super-guanidine' and found that such moieties are efficient phase-transfer catalysts when fully alkylated (Figure 1)." The catalyst is highly amenable to variation by changing its R groups, and the term 'pentanidium' was coined to describe this new catalyst structure in the initial report (*J. Am. Chem. Soc.* **2011**, *133*, 2828). "We were so excited when we found that this catalyst can work at low catalyst loading of 0.02 mol%! This is the most efficient catalytic system that we have found in our laboratory," said Professor C.-H. Tan.

From a synthetic perspective, explained Professor C.-H. Tan, this work represents a breakthrough in exploiting nucleophilic sulfenate (Scheme 1) as a viable methodology in the asymmetric synthesis of sulfoxide in high optical purity. "This should be complementary to current methodologies based on an electrophilic sulfur center (Andersen method and its variants) and oxidation of sulfide," he said. "In particular, sulfoxides with hetereocycles that are sensitive to oxidation and organo-magnesium reagents could be synthesized."



Scheme 1

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The reaction optimization was performed solely by Dr. Lili Zong. "Initially, I used pentanidium **1b** (Scheme 1) for development, but the desired sulfoxide was formed with only a moderate level of enantioselectivity. It was frustrating and discouraging because extensive variation of reaction parameters could not increase the ee value," said Lili. "Based on recent work by the groups of Professors Huber and Bolm, I was motivated to synthesize the halogenated analogue of **1b** and, to my delight, much better results in terms of yield and ee value were obtained with **1d** and **1e**." The additional halogen-bonding non-covalent interaction was preliminarily postulated, and the synergistic effect within the halogenated pentanidium provided an enhanced asymmetric induction in the reaction processes.

Dr. Choon Wee Kee performed the computational work. "After listening to Lili when she reported her work during our group meeting and together with my experience with halogen bonds from my time with Professor Wong at the National University of Singapore, I was immediately convinced that halogen bonds could be important in the transition states (TS). This motivated me to study the reaction computationally," said Dr. Choon Wee Kee.

From the calculations, a halogen bond between the iodine of the catalyst and the leaving bromide in the TS is indeed evident (Figure 2). The halogen bond was estimated to provide 6.6 kcal/mol of stabilization. In addition, multiple non-classical hydrogen bonds are also found to provide stabilizing non-covalent interactions in the TS.

"Halogen bonds are often regarded as similar to hydrogen bonds in terms of directionality and interaction energies and have found widespread applications in supramolecular chemistry and medicinal chemistry," said Professor C.-H. Tan. "However, in contrast to the ubiquitous application of hydrogen bonds in organocatalysis, the use of halogen bonds is relatively less common; thus, this work provides a rare example in which there is theoretical evidence that a halogen bond is involved in the TS of an enantioselective reaction."

"In conclusion, we have found a novel methodology to synthesize valuable sulfoxides of high optical purity and demonstrated the feasibility of halogen bonding in asymmetric organocatalysis via theoretical calculations," said Professor Tan. "It is satisfying to know that sulfenate, an active intermediate, can be stabilized using halogen bonding and be directed towards a productive reaction," added Dr. Choon Wee Kee.

Matteo Zanda

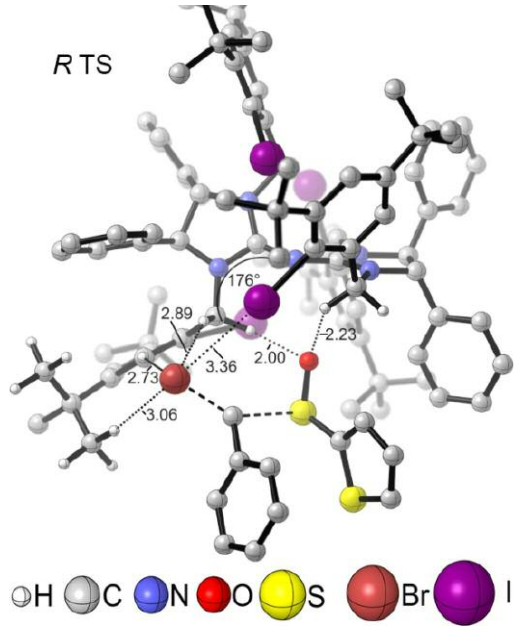

Figure 2

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About the authors

From left to right: Dr. C. W. Kee, Prof. C.-H. Tan, Dr. L. Zong

Lili Zong obtained her Bachelor's degree from Harbin Institute of Technology (P. R. of China) in 2006 and then her Master's degree in organic chemistry from Nanjing University (P. R. of China) in 2009. She received her PhD from National University of Singapore (Singapore) in 2014 and will join Professor Choon-Hong Tan's group as a research follow.

Choon Wee Kee was born in 1984 in Singapore. He received his BSc (1st class honours in chemistry) from the National University of Singapore in 2009 and performed research under the guidance of Dr. Zhao Jin as an undergraduate and also a research assistant. He was the valedictorian for the chemistry class of 2009. He performed both experimental and computational research as a graduate student under the supervision of Professors Choon-Hong Tan and Ming Wah Wong. He received his PhD in 2014.

Choon-Hong Tan graduated with a PhD from the University of Cambridge (UK) in 1999 under the supervision of Professor Andrew Holmes. Following that, he carried out postdoctoral training at Harvard University (USA). Subsequently, he worked as a Research Associate at Harvard Medical School (USA) before joining the National University of Singapore as Assistant Professor. He moved to Nanyang Technological University (Singapore) in 2012.

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