# A Catalytic Enantioselective Stereodivergent Aldol Reaction

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The aldol reaction – which is the C–C bond-forming reaction at the α-carbon of a carbonyl-derived enolate with an aldehyde or ketone functionality of another molecule, under basic or acidic conditions, to afford a β-hydroxy-carbonyl derivative – is an essential transformation in organic chemistry, and in particular in polyketide synthesis. After its independent discovery by the Russian chemist/composer Alexander Borodin (1869) and the Alsatian-French chemist Charles-Adolphe Wurtz (1872), the aldol reaction has become the subject of countless studies and developments, especially concerning its stereoselective aspects and applications to the synthesis of bioactive and natural compounds. The lab of Professor Alan Healy at New York University Abu Dhabi (NYUAD, UAE) is interested in developing an efficient and general approach for polyketide synthesis, with the ultimate goal of automating this approach. “Despite the storied history of the aldol reaction, we were surprised to find a dearth of general and readily usable catalytic aldol methods,” remarked Professor Healy. He continued: “Several powerful methods exist, but these often require expensive or hard-to-access catalysts. Furthermore, different methods are often required depending on the aldehyde substrate or desired stereoisomer of the product.”

Professor Healy’s lab was specifically interested in developing a practical and synthetically useful stereodivergent aldol reaction, one in which all four possible stereoisomers of the aldol product could be obtained from the same reactants by just varying the catalyst. Professor Healy explained: “We were inspired by previous research demonstrating the utility of malonic acid half thioesters (MAHTs) in mild C–C bond-forming reactions. The very mild conditions that are required to activate the latent pronucleophilic MAHTs had been shown to be compatible with a wide range of reactive functional groups.”

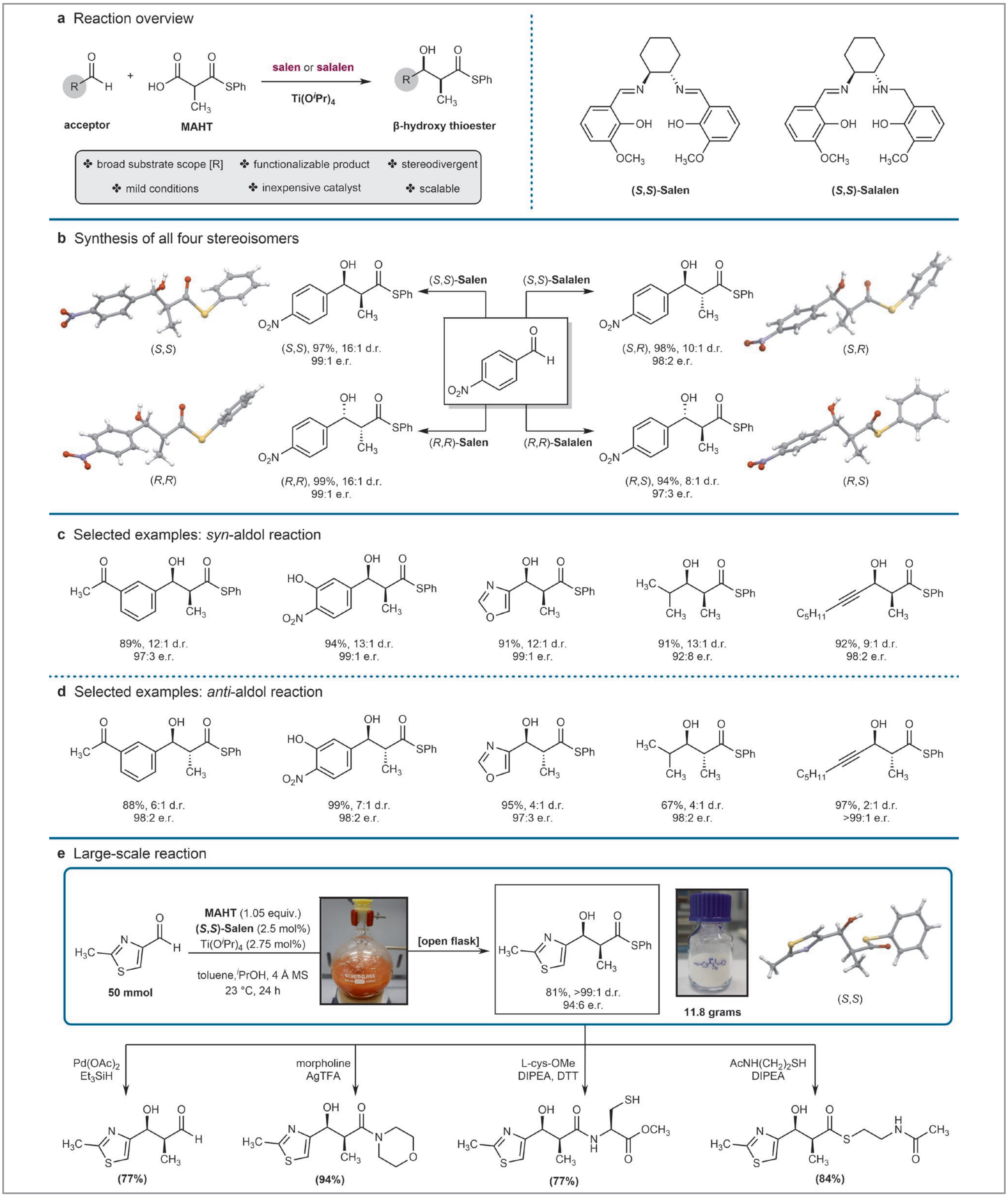
“We sought to develop a decarboxylative aldol that could be achieved using an inexpensive and easily accessible catalyst,” said Professor Healy, who continued: “We decided to focus on the salen ligands, as these are readily synthesized in one step by condensation of an inexpensive chiral diamine (~$3/gram, Ambeed) and a salicaldehyde derivative. We found that a methoxy-substituted salen ligand in the presence of titanium(IV) isopropoxide was a highly selective catalyst for the *syn*-aldol reaction. After further ligand screening, we found that the partially reduced salalen ligand provided the *anti*-aldol as the major product. As both enantiomers of the chiral diamine are commercially available, we were able to access all four stereoisomers of the aldol product from the same reactants by just varying the catalyst.”

An extensive substrate survey (35 examples in total) was conducted, including aromatic, heteroaromatic, aliphatic and unsaturated aldehydes, and it was found that the method was compatible with substrates that are not always compatible with traditional enolate-based aldol chemistry, including enolizable aldehydes, and aldehydes containing free hydroxyl, nitrile and ketone functional groups. Professor Healy pointed out: “Importantly, no side products were observed during this reaction, and as a result sluggish reactants can be pushed to completion by increasing the reaction time, concentration and/or catalyst loading.”

An abiding goal of this work was for the lab to develop a method that was very practical and would be an enabling tool for research groups around the world with varying resources. “To demonstrate its utility, we carried out the reaction on 50 mmol scale, open to air, using just 2.5 mol% catalyst, and we were able to achieve full conversion after 24 hours,” explained Professor Healy. The group found that in the majority of cases, simple filtration of the reaction mixture through celite and concentration gave the product in high purity. An additional benefit of using MAHTs as the pronucleophile was that the resulting aldol products contain a highly synthetically tractable thioester functionality. Professor Healy said: “We demonstrated that the thioester can be converted into a range of carboxylic acid derivatives under mild conditions without requiring any protecting group chemistry. Furthermore, thioesters can be converted directly into the aldehyde or ketone using Pd-mediated transformations.”

“We are very excited about the future of this approach,” said Professor Healy, who concluded: “Our goal is to develop a suite of mild, stereodivergent, carbon–carbon bond-forming reactions and apply these methods in the automated synthesis of chiral building blocks and polyketides.”




**Scheme 1** A catalytic stereodivergent aldol reaction. Selected examples illustrating the scope and application of the method.

## About the authors

*Prof. A. Healy*

**Alan Healy** was born in Co. Clare, Ireland. He completed his undergraduate studies in medicinal chemistry at Trinity College Dublin (TCD, Ireland) followed by an MSc in biomedical science from the University of Edinburgh (UK). He obtained a PhD from St Andrews University (UK) in 2014 under the guidance of Nicholas J. Westwood, and was a Charles H. Revson Senior Fellow with Seth B. Herzon and Jason M. Crawford at Yale University (USA) from 2015–2018. He began his independent career at New York University Abu Dhabi (NYUAD, UAE) in 2019 where he is currently an Assistant Professor in the chemistry program. His research group focuses on the development of novel methods to accelerate the discovery and study of dark matter metabolites.

*Dr. T. Cellnik*

**Torsten Cellnik** was born in Remscheid, Germany. He obtained his BSc in 2013 followed by his MSc in 2015 from Bergische Universität Wuppertal, Germany. Afterwards he stayed at Bergische Universität Wuppertal and received his PhD under the supervision of Professor Stefan Kirsch (2019). In 2019 he joined the Healy group at New York University Abu Dhabi (NYUAD, UAE) as a research associate. Currently his work is focused on the development of synthetic methods and their integration into automation.

*Dr. M. A. Rahman*

**Md Ataur Rahman** was born in the state of Bihar, India. He obtained a BSc and MSc degree in chemistry from Jamia Millia Islamia, New Delhi, India (2008). He received a PhD in 2015 under the supervision of Dr. J. S. Yadav (FNA, Director of IICT) at the Indian Institute of Chemical Technology, Hyderabad, India through the Academy of Scientific and Innovative Research (AcSIR). He was as a postdoctoral research fellow with Professor Andrew G. Myers at Harvard University, USA from 2016–2019. Since 2019 he has been working as a research associate in the Healy research group at New York University Abu Dhabi (NYUAD, UAE).

*Dr. B. B. Ahuja*

**Brij Bhushan Ahuja** was born in Haryana, India. He received his PhD (2015) with Dr. A. Sudalai at National Chemical Laboratory, Pune, India. After graduation, he joined Professor Arkadi Vigalok's group at Tel Aviv University (Israel), where he worked on the development of new chemo- and electrochemical sensors for the detection of nitric oxide (NO), a cell signaling molecule. In 2019, he joined the Healy group at New York University Abu Dhabi (NYUAD, UAE). His research interests include the synthesis of bioactive natural products, the development of new methodologies, drug discovery, conjugated polymer synthesis, and supramolecular chemistry.

*Prof. L. Li*

**Liang Li** is a highly accomplished researcher in the field of materials science, with a PhD from Bayreuth University in Germany. He has held research positions at King Abdullah University of Science and Technology (KAUST, Saudi Arabia) and New York University Abu Dhabi (NYUAD, UAE). In 2021, he joined Sorbonne University Abu Dhabi (SUAD, UAE) as an Assistant Professor, where he continues to pursue his research interests in quantum technology, maximum entropy method, smart materials, and crystallography. Additionally, Dr. Liang Li maintains a Visiting Professor position at NYUAD, further contributing to the advancement of the field.