

Doubly Stereoconvergent Crystallization Enabled by Asymmetric Catalysis

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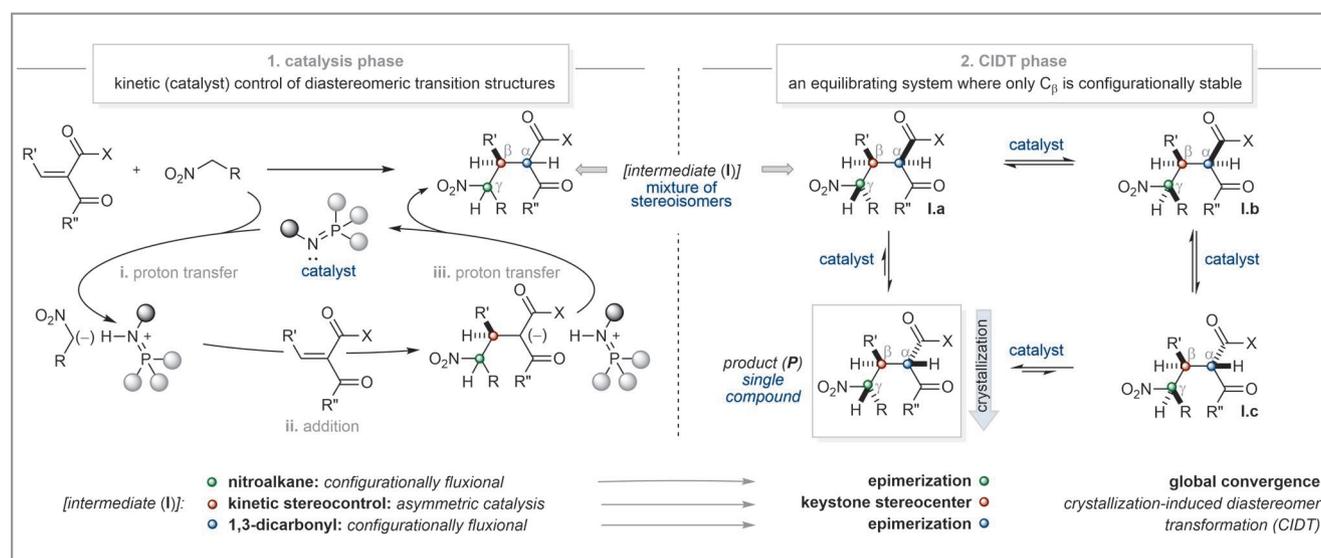
Tremendous progress continues to be made in the field of asymmetric catalysis, such as the development of new and better catalysts for the efficient construction of carbon–carbon (C–C) and carbon–heteroatom (C–X) bonds. Professor Jeffrey Johnson at the University of North Carolina at Chapel Hill (USA) pointed out to SYNFORM that reaction design tends to focus on how to maximize kinetic selectivity in the bond-forming step, while considerations around post-reaction processing (e.g. purifications) tend to receive less attention. “The result of this prioritization is that even for highly efficient reactions, significant time and resources must be spent on isolation of the desired product, which limits the potential application on large scale or in other laboratories without the appropriate equipment,” he remarked.

According to Professor Johnson, an ideal purification method is the direct crystallization or purification of the desired product from the crude reaction mixture. “When there are one or multiple stereochemically fluxional stereocenters, one can design a crystallization-induced diastereomer transformation (CIDT) in order to converge all of the equilibrating species to a single solid stereoisomer. CIDTs are highly desirable in process chemistry because they provide a means to generate dia-

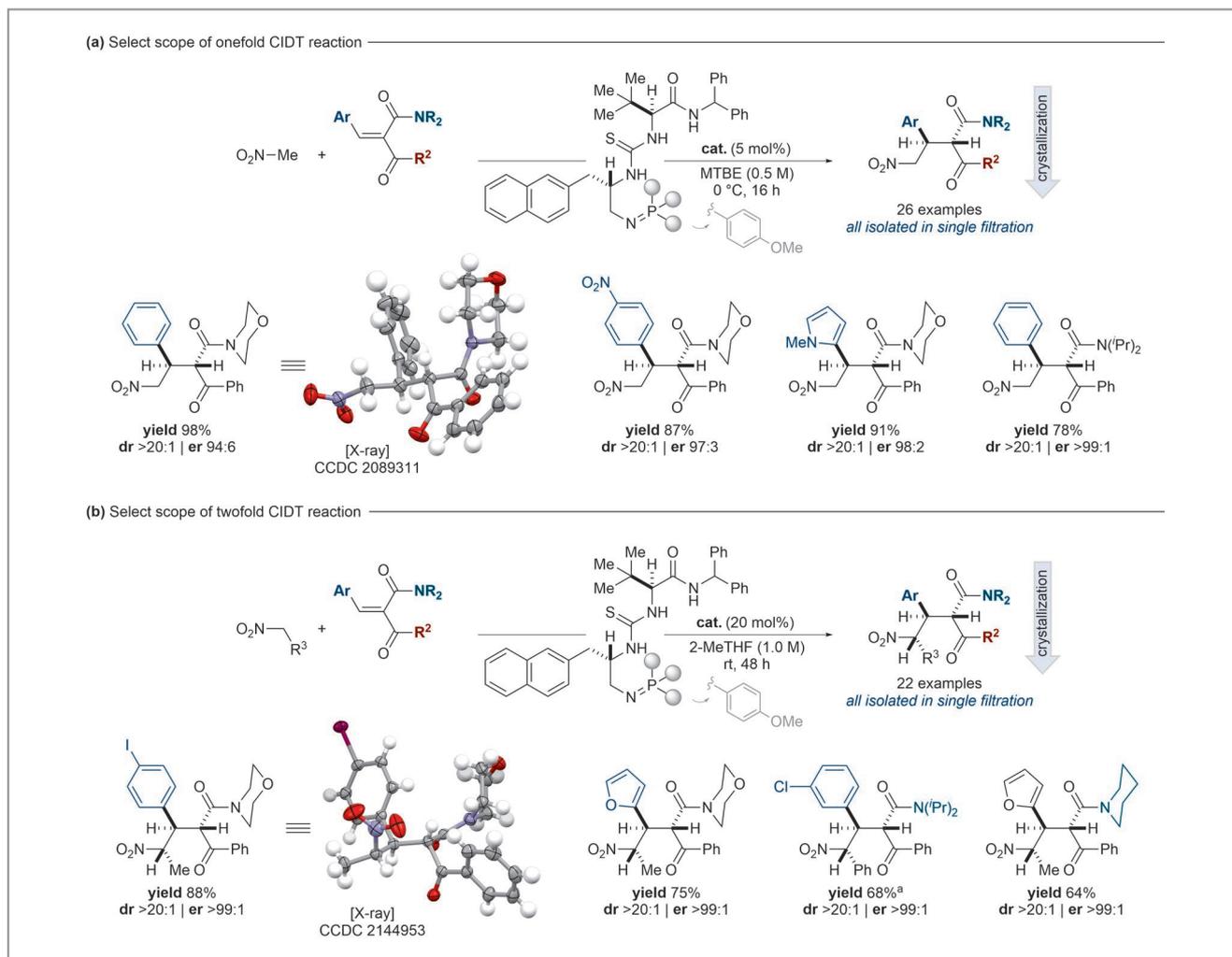
stereoenriched material without additional elaborate purification methods. There are a number of examples of discrete CIDTs populating the literature, but usually limited to a single example or an auxiliary-controlled crystallization,” said Professor Johnson.

The Johnson group was interested in developing an asymmetric Michael reaction between nitroalkanes and alkylidene β -keto amides to generate three asymmetric centers, but could not improve the diastereoselection beyond ~1:1:2:2 when the reactions were under homogeneous conditions. Professor Johnson said: “Pedro de Jesús Cruz (first author on the paper) noted that upon changing to certain ethereal solvents, the reactions become increasingly heterogeneous over time, and this change correlated to a large bump in diastereoselectivity. Perhaps most exciting was the finding that when the heterogeneous mixtures were filtered, the solid was diastereoisomerically pure product in most cases.”

The group established that these reactions were undergoing a two-phase phenomenon (Scheme 1): “The Dixon iminophosphorane catalyst initially controls the absolute kinetic enantioselectivity at C_β , but the product of this initial “catalysis phase” is then a mixture of diastereomers at C_α and C_γ ,



Scheme 1 Merger of asymmetric catalysis and crystallization-induced diastereomer transformations



Scheme 2 Select scope of CIDT reactions. ^a Reaction run in MTBE (1.0 M) as solvent.

explained Professor Johnson, continuing: “The catalyst then interconverts the four resulting diastereomers in solution. One diastereomer selectively precipitates to provide the solid single stereoisomeric product (“CIDT phase”). The catalyst functions in two roles where it initially catalyzes the C–C bond forming step with high enantioselectivity, and subsequently mediates the equilibration of the resulting four diastereomers of product.”

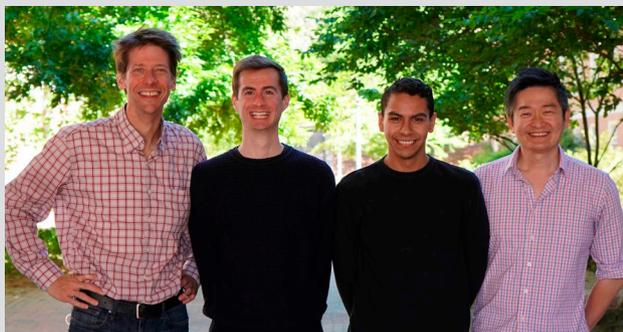
The dearth of examples of this sort of two-phase, one-pot catalysis approach provides impetus for the Johnson group and others to push this paradigm going forward. Professor Johnson said: “The one-pot approach is more efficient and greener compared to previous asymmetric catalytic methods: significant savings in time and solvent use are accrued by obviating further purification steps. Because the desired pro-

ducts crash out of the crude reaction mixture, they can all be accessed in high purity by a single filtration on a simple fritted funnel (no flash chromatography). The reactions proved to be remarkably general and user-friendly to run (Scheme 2).”

Professor Johnson concluded: “We hope that this developed merged asymmetric catalysis/CIDT strategy will be adopted and applied in future reaction design. The generality of the developed nitroalkane addition suggests the strategy holds tremendous untapped potential in future asymmetric catalytic platforms.”

Mattias Forsell

About the authors



From left: Prof. J. S. Johnson, W. R. Cassels, Dr. P. De Jesús Cruz, Dr. C. H. Chen

Pedro de Jesús Cruz received his B.S. in chemistry from the University of Puerto Rico (Puerto Rico) in 2016 with high distinction and honors in chemistry, where he conducted research under Prof. Edgardo Rivera. He completed his Ph.D. studies at the University of North Carolina at Chapel Hill (USA) in 2022, working in the laboratories of Prof. Jeffrey S. Johnson where he explored new catalytic stereoconvergent reactions. During his doctoral studies, he was also an NIH Ruth L. Kirschstein predoctoral fellow and was awarded the DOW BEST symposium and Corteva DELTA research awards. He is currently a Discovery Chemist at Merck.

William R. Cassels received his B.A. in chemistry from the College of the Holy Cross in Worcester, Massachusetts (USA), where he conducted research under Prof. Kevin J. Quinn. He began his Ph.D. studies at the University of North Carolina at Chapel Hill (USA) in 2018, working in the laboratory of Prof. Jeffrey S. Johnson. His research focuses on the development of new organocatalytic stereoconvergent reaction manifolds of β -dicarbonyls.

Chun-Hsing (Josh) Chen received his Ph.D. in physical chemistry from Brandeis University (USA) in 2010 under the supervision of Prof. Bruce Foxman. He was a postdoctoral fellow and later became a research crystallographer at the Indiana University Molecular Structure Center (USA). Josh joined the University of North Carolina at Chapel Hill Department of Chemistry (USA) as a director of the X-ray Crystallographic Core Laboratory (XCL) in September 2018.

Jeffrey S. Johnson has been a faculty member at the University of North Carolina at Chapel Hill (USA) since 2001 and has held the A. Ronald Gallant Distinguished Professorship since 2014. His research focuses on stereoselective synthesis and catalysis.