

## Enantioselective Cu(I)-Catalyzed Borylative Cyclization of Enone-Tethered Cyclohexadienones and Mechanistic Insights

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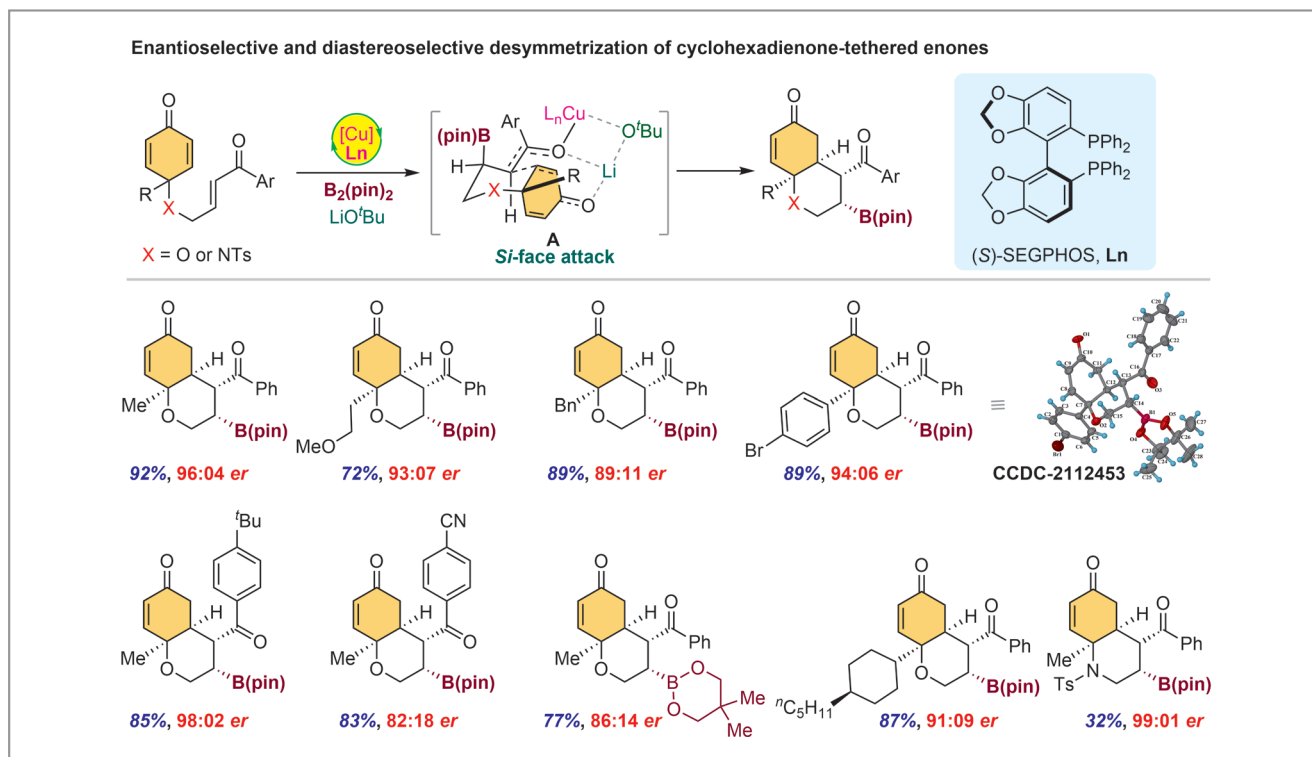
Dr. Rambabu Chegondi's research group at CSIR-Indian Institute of Chemical Technology (IICT) in Hyderabad (India) focuses on the development of new synthetic strategies with broad applications in organic synthesis. In particular, the design of new enantio- and diastereoselective desymmetrization methods for prochiral-1,3-diones, cyclohexa-2,5-dienones, and other  $C_2$ -symmetric substrates to access complex molecules with multiple stereogenic centers are major research goals in the group.

Dr. Chegondi said: "Over the last decade, the enantioselective desymmetrization of prochiral cyclohexadienones has emerged as the most powerful and convenient strategy for the rapid construction of highly functionalized bicyclic frameworks in a single operation. We have also been developing enantioselective transition-metal-catalyzed cyclizations of enone-tethered cyclohexadienones." In 2018, the Chegondi research group disclosed the Rh-catalyzed reductive cyclization of  $C_2$ -symmetric cyclohexadienones using simple (*R*)-BINAP as a chiral ligand to afford *cis*-hydrobenzofurans and *cis*-hydroindoles in high yields with up to >99% ee [*ACS Catal.* **2018**, *8*, 1440–1447]. In the following year, they disclosed a highly diastereoselective desymmetrization of enone-tethered cyclohexadienones via cascade annulation triggered by Lewis acid catalyzed Friedel–Crafts alkylation to construct bridged polycyclic indoles with highly divergent and challenging architecture [*ACS Catal.* **2019**, *9*, 10012–10019]. According to Dr. Chegondi, "Recently, copper has become a highly efficient and cost-effective catalyst for borylative addition to various functionalities using diborane reagents. Several reactions have been reported on tandem borylcupration of carbonyls, imines, alkenes, and alkynes, followed by trapping with external electrophiles. However, copper-catalyzed borylative cyclization of alkene-tethered electrophiles has been rarely studied."

The work published in the title article started when Dr. Chegondi discussed with his students the possibility of an enantioselective Cu(I)-catalyzed  $\beta$ -borylation, followed by Michael addition on prochiral enone-tethered 2,5-cyclohexadienones to form *cis*-hydrobenzopyrans. Dr. Chegondi said: "The catalytic asymmetric borylation of conjugated carbonyls followed by stereoselective intramolecular cascade cyclizations with in situ generated chiral enolates is extremely rare."

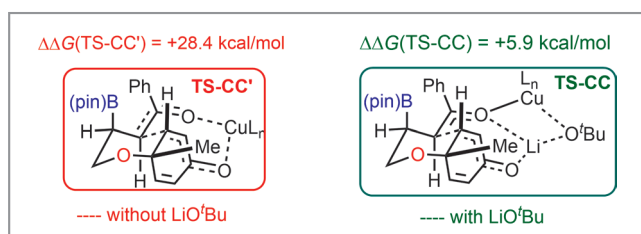
Discussing the challenges of the enantioselective Cu(I)-catalyzed  $\beta$ -borylative cyclization of enone-tethered cyclohexadienones, he added: "However, the major challenges of this reaction are the chemoselective 1,4-addition of nucleophilic boron on three different enone functionalities within the starting substrate and the diastereoselective C–C bond formation."

Dr. Chegondi recalls that the group started this investigation with an effort to conduct an elaborate optimization to enable the enantioselective Cu(I)-catalyzed  $\beta$ -borylation/Michael addition on prochiral enone-tethered 2,5-cyclohexadienones. Eventually, the  $Cu(MeCN)_4PF_6/(S)$ -SEGPLHOS catalytic system – using precisely 2.0 equiv of *t*-BuOLi at low temperature – proved to be the best conditions for this method to afford *cis*-hydrobenzopyran scaffolds in excellent stereoselectivity and yields (Scheme 1). "This enantioselective borylative cyclization is tolerated for electronically and sterically diverse substituents at the quaternary prochiral carbon center, as well as at the aryl ring of the tethered enone. This reaction is also compatible with *N*-Ts-linked cyclohexadienones, providing moderate yields and excellent enantioselectivity. The absolute stereochemistry of the four contiguous chiral centers was assigned by X-ray crystallography," said Dr. Chegondi, who added that to make the reaction even more useful, they sought to evaluate the one-pot sequential borylative cyclization/oxidation process. "The Cu-catalyzed borylation of enone under standard reaction conditions, followed by the sequential addition of the sodium perborate oxidizing agent in the same flask, afforded the  $\beta$ -alcohol product via the  $\beta$ -borylation intermediate," said Dr. Chegondi. "All reactions proceed with complete retention of stereochemistry from the C–B bond to the C–O bond in a highly enantioselective fashion, affording the corresponding products in similar yields and enantiomeric ratios." Additionally, Dr. Chegondi recalls that his group investigated the sequential borylative cyclization/oxidation in the absence of base, under standard conditions: "Interestingly, the transformation on the substrate produced the fused dioxane product via conjugate borylation/oxidation/oxa-Michael addition, instead of the C–Michael adduct, with moderate enantioselectivity. At that point, it was evident that the absence of base (*t*-BuOLi) had a significant effect on the enantioselectivity."



**Scheme 1** Enantioselective and diastereoselective desymmetrization of cyclohexadienone-tethered enones

To gain further insights into the role of *t*-BuOLi via computational studies, Dr. Rambabu contacted his friend and colleague, Dr. Kumar Vanka. After a few rounds of discussion, Dr. Vanka and his student started investigating the role of the base in the reaction. Density Functional Theory (DFT) calculations revealed that the absence of base led to a pathway for which the activation barrier needed was 22.5 kcal/mol higher with respect to the C–C cyclization step (Figure 1). Dr. Vanka acknowledged that the reviewer's suggestions were helpful to unveil the complete mechanistic pathway, as indicated in the supporting information of the title paper.



Dr. Chegondi concluded: “We have developed the enantioselective Cu(I)-catalyzed  $\beta$ -borylation/Michael addition of prochiral enone-tethered 2,5-cyclohexadienones. The reaction proceeds via 1,4-borocupration at the enone, followed by *Si*-face attack of the chiral enolate on the cyclohexadienone ring, via a chair-like transition state. DFT calculations explained the requirement of the excess base, which leads to the formation of the more favorable chiral lithium enolate, that undergoes C–C bond formation in the key desymmetrization step. One-pot sequential borylation/cyclization/oxidation afforded the corresponding alcohols without affecting the yield and enantioselectivity. This asymmetric desymmetrization strategy has broad substrate scope and generates highly functionalized bicyclic enones bearing four contiguous stereocenters with excellent yield, enantioselectivity, and diastereoselectivity, thereby offering new prospects in the rapid synthesis of highly functionalized structural motifs. The synthetic utility of this reaction has been demonstrated with a gram-scale reaction and further chemoselective transformations on the product.”

*Kumar Vanka*

## About the authors



Dr. R. Chegondi

**Rambabu Chegondi** received his M.Sc. degree from the University of Hyderabad (India) and completed his Ph.D. in organic chemistry from the Indian Institute of Chemical Technology (CSIR-IICT), Hyderabad (India) under the supervision of Dr. S. Chandrasekhar. In 2009, he joined the group of Prof. Paul R. Hanson at The University of Kansas (USA) as a postdoctoral researcher. After returning from the USA, he started his independent research career at CSIR-IICT, Hyderabad. He is currently working as a Senior Scientist and his research interests focus on the development of new catalytic enantioselective desymmetrization methods and their application towards the synthesis of biologically important complex molecules.



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**Jagadeesh Babu Nanubolu** received his integrated B.Sc. and M.Sc. degrees in chemistry from Sri Sathya Sai Institute of Higher Learning, Puttaparthi (India) in the years 1998–2003. Later, he joined the School of Chemistry, University of Hyderabad (India) for his doctoral program funded by UGC and obtained his Ph.D. under the supervision of Prof. Ashwini Nangia in 2008. He moved to University of Nottingham (UK) in 2009 for postdoctoral research funded by the EPSRC and worked with Dr. Jonathan Burley. He returned to India in 2011 and joined the CSIR-IICT. He is currently working as a Senior Scientist in the Center for X-ray Crystallography, Department of Analytical & Structural Chemistry, CSIR-IICT. His research areas of interest include crystal engineering and development of new solid forms of drugs, polymorphism, pharmaceutical co-crystallization and structure–property correlations.



Dr. K. Vanka

**Kumar Vanka** completed his undergraduate studies (B.Sc.) at the Indian Institute of Technology, Kharagpur (India), and then received his M.Sc. and Ph.D. degrees in computational chemistry under the guidance of Professor Tom Ziegler at the University of Calgary (Canada). This was followed by a postdoctoral stint at the University of Kansas (USA), under Professor Ward Thompson. He has been a scientist at the National Chemical Laboratory (CSIR-NCL), India, since December of 2007 and is currently a Principal Scientist there. His research interests include computational studies into reaction mechanisms relevant to organic, inorganic and organometallic chemistry, as well as investigations into the origins of life on earth and in the universe.

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