

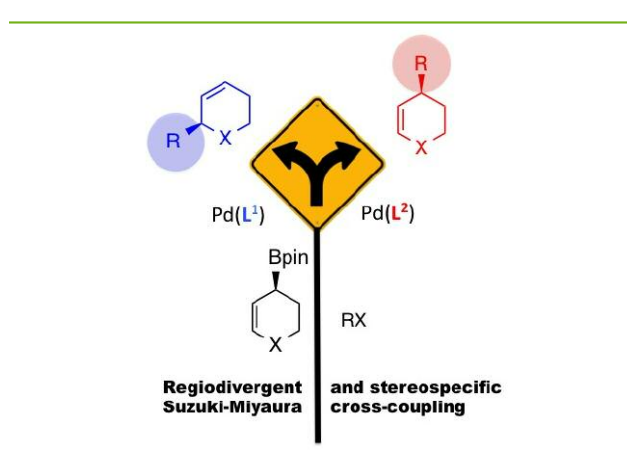
# Synthesis of Chiral Heterocycles by Ligand-Controlled Regiodivergent and Enantiospecific Suzuki–Miyaura Cross-Coupling

*Nat. Commun.* **2014**, *5*, 5474

Controlling the regioselectivity of an organic reaction at one's discretion while also maintaining full control of the stereochemistry of the process is a luxury in organic synthesis and not many methods are known for achieving such an outstanding level of control in the generation of stereogenic allylic systems. Recently, Professor Dennis Hall and co-workers at the University of Alberta (Canada) described the first example of a Suzuki–Miyaura cross-coupling with allylic boronates where both the configuration of an  $sp^3$  carbon (stereoselectivity) and the regioselectivity of the coupling process are fully controlled by the catalyst and especially the nature of the ligand (Figure 1).

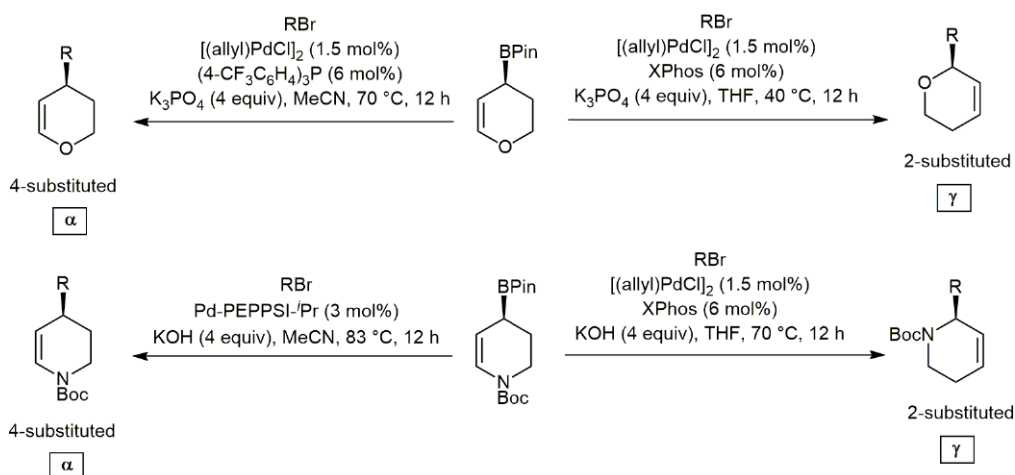
What distinguishes this work from prior contributions is not only the merging of stereo- and regiocontrol, but also the ability to achieve this feat with functionalized allylic boronates. Professor Hall explained: “The heterocyclic allylic boronates employed as substrates contain a conjugated heteroatom and as such are more complex than a majority of chiral secondary allylboronates reported in the literature.”

“These chiral heterocyclic allylic boronates are precursors of important varieties of substituted pyran and piperidine

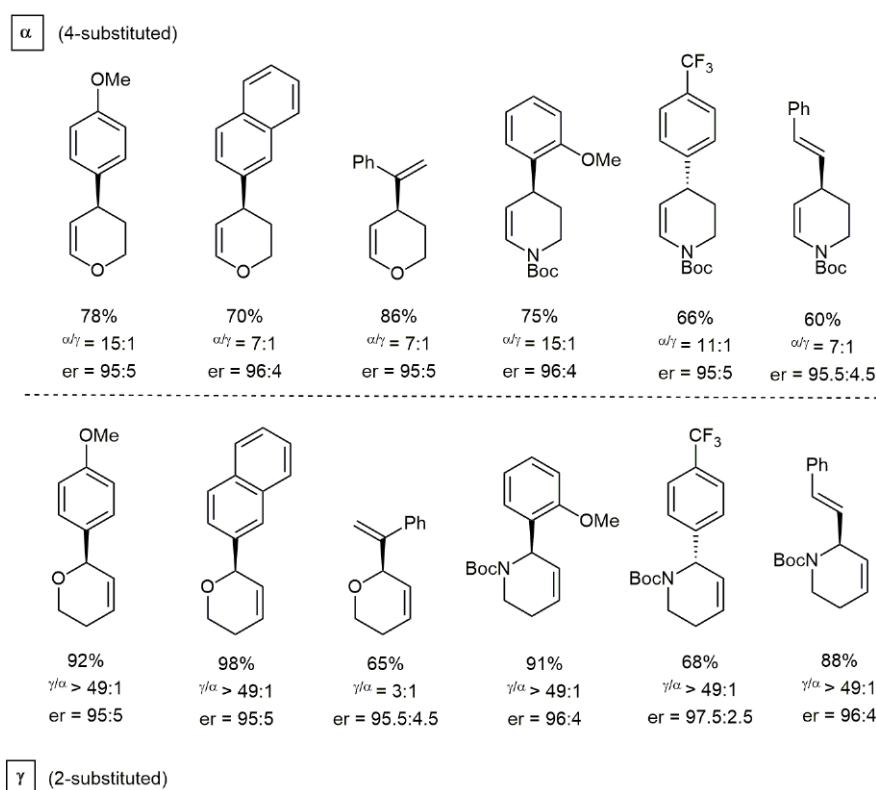


**Figure 1** The regiochemical direction of a stereospecific allylic Suzuki–Miyaura cross-coupling is controlled by a judicious choice of ligand on the palladium catalyst.

units present in a vast number of natural products and drugs,” said Professor Hall, continuing: “These key precursors highlight the usefulness (or utility) of the catalytic enantioselective



**Scheme 1** Hall's methodology



**Figure 2** Some of the compounds synthesized using Hall's methodology

tive borylative isomerization that we previously reported and that we also employed in carbonyl allylboration.”

According to Professor Hall, this work also highlights the power and complementarity of state-of-the-art ligand systems for cross-coupling reactions, such as the biaryldialkylphosphines (Stephen Buchwald) and the NHC carbene catalysts (Michael Organ).

“All of the experimental work was performed in the skilled hands of 5<sup>th</sup> year graduate student Jinyue Ding and 4<sup>th</sup> year graduate student Taras Rybak,” acknowledged Professor Hall. “Shortly after completing this work, Ding defended his PhD thesis and has now taken up a position as a Research Scientist in medicinal chemistry at Inception Sciences in Vancouver.”

“Ironically, the most difficult part of the project often was not the actual reaction, but the development of chiral HPLC conditions to measure the enantioselectivity of the reaction,” continued Professor Hall. “In some cases, the preparation of derivatives of the products was necessary. On the other hand, these derivatization reactions and the synthetic application to anabasine and paroxetine further exhibit the versatility of the cross-coupling products.”

The group is now investigating the application of their methodology on other heterocyclic allylboronates and fine-tuning the regioselectivity with other unexplored ligands. “We would like to further demonstrate the value of this methodology towards the synthesis of other natural products and valuable drug targets that are currently difficult to access,” said Professor Hall, concluding: “Future work will also include the mechanistic study of stereoselective and regioselective Suzuki–Miyaura reactions. Based on the mechanistic understanding, more novel and practical reactions could be developed.”

**Matteo Zanda**

### About the authors



From left: T. Rybak, Dr. J. Ding, Prof. D. Hall

**Dennis Hall** was born in Baie-Comeau, Province of Québec (Canada) in 1968. In 1991, he enrolled in graduate studies under the guidance of Professor Pierre Deslongchamps at Université de Sherbrooke (Canada). His graduate research project involved new synthetic methods and strategies applicable to natural product synthesis. His work culminated on the development of a new tandem transannular [4+2]/aldol approach to diterpenes such as Aphidicolin, and on new findings on the mechanism of the Diels–Alder reaction. After obtaining his PhD degree in 1995, Hall moved on to explore new areas of investi-

gation such as bioorganic chemistry and combinatorial chemistry, working as an NSERC Postdoctoral Fellow in the laboratory of Professor Peter G. Schultz, then at the Department of Chemistry at UC Berkeley (USA). In his postdoctoral stay from 1995–1997, he was involved in various projects and learned to apply his knowledge of organic synthesis to problems in bioorganic chemistry. In August 1997, he returned to Canada to take an academic position at the Department of Chemistry, University of Alberta. He was promoted to Professor of Chemistry level in July 2005.

**Jinyue Ding** was born in Henan (P. R. of China). He obtained his BSc at Zhengzhou University in 2008 in the same province. He moved to Canada in 2009 and obtained his PhD at the University of Alberta in 2014 under the supervision of Professor Dennis Hall. He is currently living in Vancouver and employed as a Senior Scientist I at Inception Sciences Canada.

**Taras Rybak** was born in Hamilton (Canada) in 1985. He received his BSc degree in Honours Chemistry at the University of Waterloo (Canada). He is currently a PhD student at the University of Alberta under the supervision of Professor Dennis Hall. His research focuses on the development of new methods for preparing and functionalizing pyran compounds towards the synthesis of medicinally relevant natural products.