Rhodium-Catalyzed Asymmetric Allylic Arylation of Racemic Halides with Arylboronic Acids

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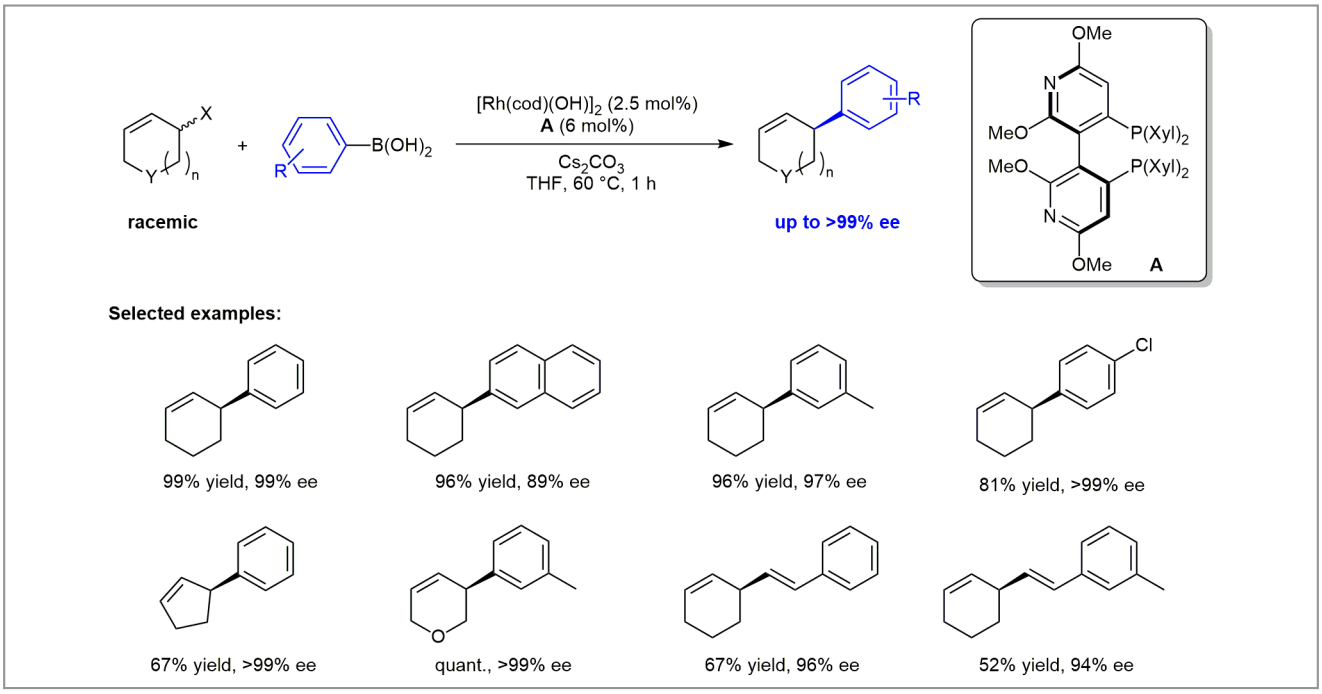
The achievement of stereocontrolled Csp^2–Csp^3 cross-coupling reactions between allylic halides and arylboronic acids continues to represent a challenging problem in organic synthesis, despite the enormous potential of this transformation.

In 2015, Professor Steve Fletcher and his group at the University of Oxford (UK) reported that non-stabilized alkyl nucleophiles generated through the hydrometalation of alkenes could be used in Cu-catalyzed asymmetric allylic alkylation (AAA) reactions with cyclic racemic allyl halides (*Nature* **2015**, *517*, 351). This reaction is complementary to the widely used Pd-catalyzed AAAs using stabilized nucleophiles in dynamic kinetic asymmetric transformations (DYKAT) initially developed by Trost et al. (*Chem. Rev.* **1996**, *96*, 395). Professor Fletcher explained: "DYKATs are attractive because they allow racemic, rather than prochiral, starting materials to be used in asymmetric catalysis. Currently, there are only very few types of reactions that can convert both enantiomers of a starting material into highly enantioenriched products in more than 50% yield, and the use of non-stabilized nucleophiles enormously broadens the scope of these transformations."

Mechanistic work suggested that the copper-catalyzed DYKATs occur because the starting materials are being racemized by the same Cu catalyst that selects one of the enantiomers of the starting material for a highly enantioselective AAA. In follow-up work, Professor Fletcher's group managed to extend these methods to sp^2-hybridized alkenylzirconium nucleophiles, but these proved much more challenging; only moderate enantioselectivities were observed and cryogenic reaction temperatures were required (*Chem. Commun.* **2015**, *51*, 5044).

Professor Fletcher said: "An elegant and efficient alternative method recently reported by our group involves arylboronic acids as the non-stabilized sp^2-hybridized nucleophile and rhodium(I) catalysts in addition to racemic cyclic allyl chlorides."



Scheme 1 Dynamic kinetic allylic alkylation using boronic acids

Professor Fletcher explained: "The new DKYAT arylation uses mild conditions (1 h at 60 °C in THF) and allows addition of a broad range of arylboronic acids. The arylation tolerates racemic 5-, 6- and 7-membered-ring electrophiles as well as addition to oxygen-containing heterocycles and the use of electron-rich styrylboronic acids." He continued: "Electron-deficient, electron-rich and sterically hindered arylboronic acids can undergo highly enantioselective addition by using a commercially available allyl bromide instead of the usual allyl chloride. Without any further optimization, the reaction was scaled up to prepare more than 600 mg of product while the catalyst loading was reduced to 1 mol% of Rh(I) with no loss of selectivity despite a slower reaction rate."

Professor Fletcher believes that this latest reaction is particularly appealing as it is effectively a catalytic asymmetric Suzuki–Miyaura coupling that forms new Csp^2–Csp^3 bonds. "Viewed in this way the method could significantly broaden the scope of normal '2D cross-coupling' that is extensively used in academic and industrial labs to provide new 3D building blocks for synthesis," he added.

Professor Fletcher said that preliminary studies on the reaction mechanism using 3,5-disubstituted cyclohexenyl chlorides show that the reaction proceeds via an overall inversion of configuration, where both enantiomers of a starting diastereomer get converted into a single enantiomer of product. He commented: "Both the new copper- and rhodium-catalyzed processes are highly robust and tolerate a wide range of functional groups. The asymmetric arylboronic acid additions may prove to be useful in the future because so many boronic acids are commercially available or easily prepared."

Perhaps the most remarkable aspect of these reactions is that they all appear to operate through completely different reaction mechanisms. Professor Fletcher concluded: "As the mechanisms haven't been previously identified, or completely characterized in the preliminary reports, further studies are necessary to fully understand these reactions. The work also suggests that a wide range of further DYKATs remain to be discovered and that these could impact the strategies that are currently used in asymmetric catalysis."

About the authors

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Stephen P. Fletcher was born in Halifax, Nova Scotia (Canada) and studied chemistry at Mount Allison University (Canada) and the University of Alberta (Canada). After postdoctoral work with Professors Ben Feringa (Groningen, The Netherlands) and Jonathan Clayden (Manchester, UK) he started a research group at the University of Oxford (UK) in 2009 as an EPSRC Career Acceleration Fellow. He is currently Associate Professor and a Fellow and Tutor in Chemistry at Keble College (Oxford, UK). Steve's research interests focus on transition-metal-mediated asymmetric catalysis, the origins of life, and dynamic stereochemistry.

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