Efficient asymmetric catalytic synthesis of antidepressant escitalopram

With the support by the National Natural Science Foundation of China and the Thousand Talents Youth Program, the research team led by Prof. Tang Wenjun (**汤文军**) at the State Key Laboratory of Bio-organic and Natural Products Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, and Prof. Deng Weiping (**邓卫平**) at the School of Pharmacy, East China University of Science and Technology, reported an efficient asymmetric catalytic synthesis of antidepressant escitalopram by developing a highly enantioselective rhodium-catalyzed addition of aryl boroxines to simple aryl ketones, which was published in *Angew Chem Int Ed* (2016, 55: 4527—4531).

Construction of quaternary stereocenters remains a significant challenge in organic chemistry and often the most expensive step in drug synthesis. Chiral diaryl alkyl carbinol moieties exist in a number of therapeutic agents and natural products. Development of efficient synthesis of these chiral tertiary alcohols has gained a great deal of attention. The asymmetric addition of nontoxic, stable, and operational simple aryl boron reagents to simple unactivated ketones stands out to be most attractive, however with limited success. No efficient chiral rhodium catalysts are available that can provide both excellent enantioselectivities and satisfactory yields.

Over years, the team has focused on developing efficient chiral ligands and catalysts in tackling such problems. A structurally unique bisphosphorus ligand, WingPhos with deep chiral pockets, was developed by the group and was first published in *Angew Chem Int Ed* (2013, 52: 4235—4238), which provided excellent reactivity and enantioselectivity in asymmetric hydrogenation for the synthesis of chiral β-arylamines, key chiral building blocks for many therapeutic agents.

Using the same magic ligand, the team developed for the first time highly efficient rhodium-catalyzed additions of arylboroxines to aryl ketones that have provided a range of chiral diaryl carbinols in excellent yields and enantioselectivities with a broad substrate scope and great functional group compatibility. WingPhos proved to be crucial for the high reactivity and enantioselectivity of this transformation. This method has enabled a one-step efficient synthesis of a key chiral intermediate of antihistamine (+)-clemastine, and more excitingly, a first concise and enantioselective synthesis of antidepressant drug escitalopram. This study may greatly facilitate the syntheses of various therapeutic agents bearing chiral diaryl alkyl carbinol moieties.

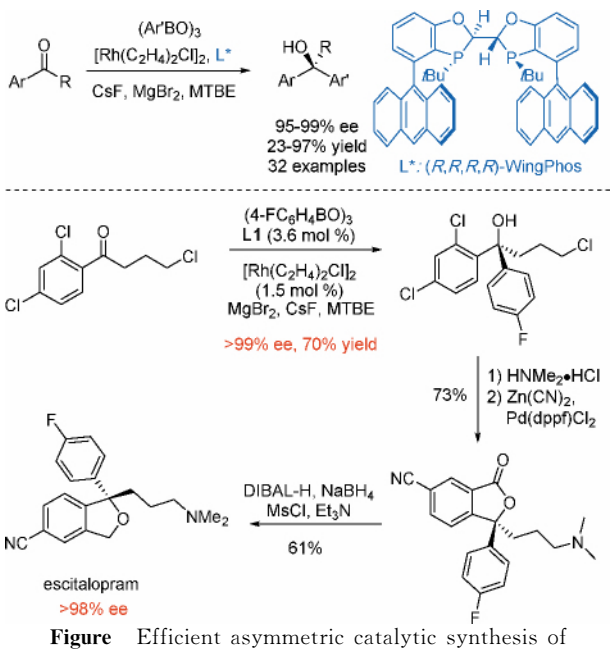

Figure Efficient asymmetric catalytic synthesis of escitalopram.