

University of Louisville
Department of Chemistry
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Literature Seminar

When: January 26, 2023

Time: **12:00 p.m.**

Location: CBL-16

Novel Catalytic Access to Challenging Atropisomers

Abstract: Atropisomers are conformational stereoisomers. Their existence occurs because of the restricted rotation of a σ -bond, primarily constrained by the electronic or steric effects of flanking substituents, causing a rotational energy barrier¹. The magnitude of the rotational energy barrier determines the half-life or rate of racemization. Literature precedents indicate that a half-life of at least 1000 seconds is required for the separation of individual conformers². Nonetheless, atropisomers exhibit vast applications, including natural products,³ pharmaceuticals,⁴ organocatalysts,⁵ and ligands.⁶ Among different classes of atropisomers, (hetero)biaryls are also considered as extremely valuable atropisomers.⁷ Their most exciting catalytic synthetic methods involve transition metal-catalyzed enantioselective cross-couplings of aryl halide and organometallic species, including organomagnesium⁸, organozinc,⁹ and organoboron¹⁰ reagents. The Suzuki-Miyaura coupling is one of the common approaches to accessing valuable atropisomers. The π -conjugated substrates have been explored lately, including aryl-naphthyl and binaphthyl systems.¹¹ However, catalytic access to enantioenriched biaryls is always challenging. The ligand attached to the metal catalyst plays a crucial role in enantioselectivity. In 2022, Phipps and co-workers developed a chiral sulfonated version of the SPhos ligand (also called sSPhos) for exploiting secondary interactions in the catalytic cycle. With this approach, the authors have achieved a variety of biaryls in excellent enantioselectivities.¹² Mechanistic investigation supported the role of H-bonding in dictating the stereoselectivity in transmetalation and reductive elimination steps of the catalytic cycle. However, this method requires high palladium loading. Thus, the methodology generates toxic metal waste and is not sustainable. Later, Mei and co-workers merged transition metal catalysis with electrochemistry to access similar molecules and to enable enantioselective nickel-catalyzed electrochemical reductive homocoupling of aryl bromides under mild conditions using electricity as a reductant¹³. Notably, nickel is a more sustainable metal than palladium. Besides, electricity as a reductant is superior and sustainable, compared to commonly used metallic reductants, such as Li, Mn, and Zn. However, this method is limited to access homo-coupled products only. Later, Smith and coworkers reported a more sustainable and atom-economic method of direct oxidative coupling between aryl and heteroaryl partners using an earth-abundant and non-toxic iron catalyst.¹⁴ This methodology enables the synthesis of challenging heteroaryl atropisomers in good yields with exceptional enantioselectivities. The presence of a special ortho substituent in the substrate is not required. These recent methodologies still have numerous limitations, and greener catalytic alternatives are still absent in the literature.

References:

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