

# Substrate Directed Enantioselective Heck Reaction of Spirooxindoles via Desymmetrization Strategy

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## Abstract

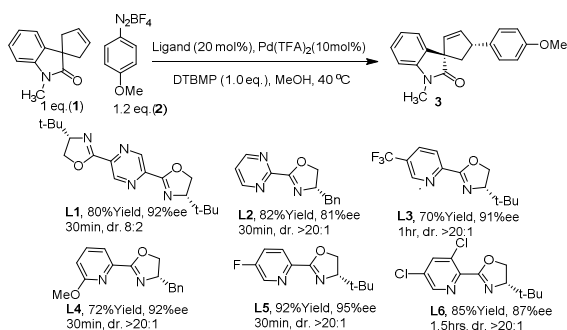
A new class of chiral spirooxindole derivatives have been synthesized in enantioselective manner under mild conditions.

## Introduction

The Pd catalyzed Heck reactions plays an important role in substrate controlled asymmetric synthesis for the construction biologically important molecules.<sup>1</sup> Isatin-based spirooxindole scaffolds have been found in several natural and non-natural products. The spirooxindoles motifs displaying versatile medicinal, pharmacological, and structural properties.<sup>2</sup> The method develop herein relies on the carbonyl directing power to achieve high enantioselectivity in the Heck arylation.

## Results and discussion

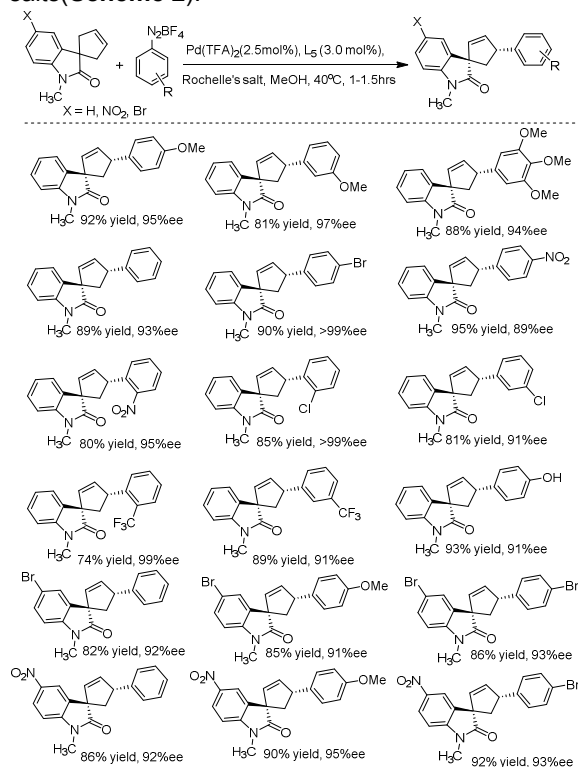
Initially we evaluated the Heck arylation with the known starting material (1) and *p*-methoxy aryl diazonium salt (2) as model reaction in methanol. Many different *N,N*, substituted oxazoline ligands were also screened (scheme 1). All the ligands provided moderate yields and selectivity but Fluorine substituted pyridine oxazole ligand L5 showed improved yield (92%) and selectivity (>20:1, 95%ee)(Scheme 1).



**Scheme 1.** Screening of Heck-Matsuda arylation with different ligands.

After the ligand screening we tested the catalyst and ligand loading. Finally, we optimized the reaction with 2.5mol% of catalyst and 3.0mol% of ligand (L5). Under these conditions the yields and the selectivity of the reaction was maintained, but reaction time increased. We further optimized the reaction condition with different bases, the cost effective

Rochelle's salt showed good results. With the new optimized reaction conditions, we explored the scope of the aryl Heck-Matsuda reaction towards several substituted aryl diazonium tetrafluoroborate salts (Scheme 2).



**Scheme 2.** Scope of the Heck-Matsuda arylation.

## Conclusion

In conclusion, we have shown that the substrate controlled Pd-catalyzed Heck arylation is a robust and versatile method to access to a variety of chiral spirooxindoles bearing two stereogenic centres. The Heck products were obtained with moderate to good yields with excellent diastereo and enantioselectivities.

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<sup>2</sup>Sing, S. G.; Desta, Y. Z. *Chem. Rev.* **2012**, *112*, 6104.