

# Rhodium-Catalyzed Tandem Reaction for the Synthesis of $\alpha,\beta$ -Disubstituted Amides and Esters

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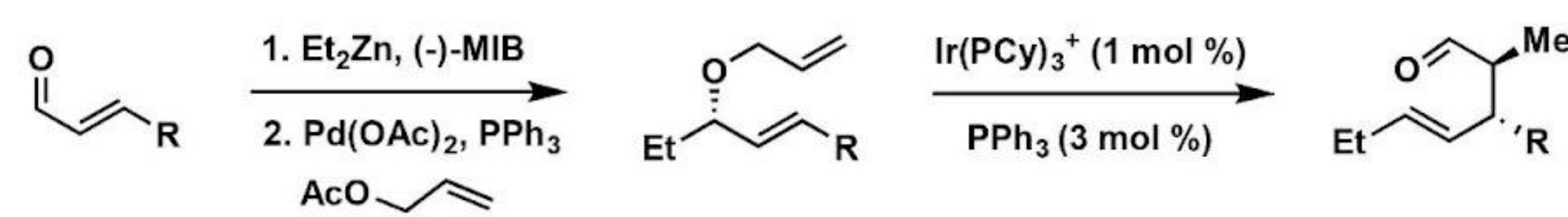
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## Introduction

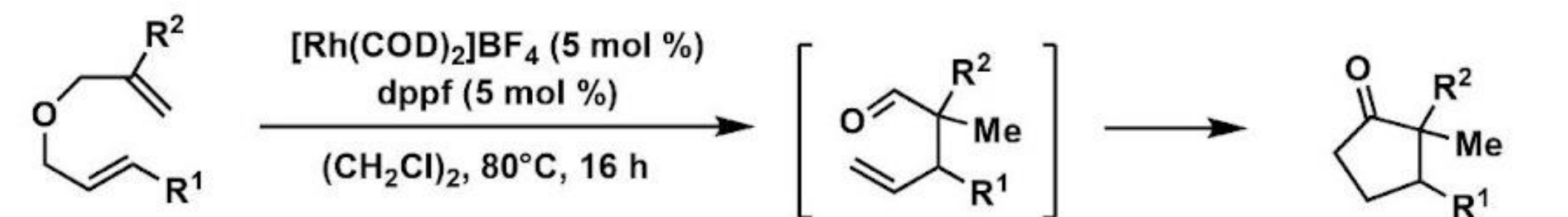
Dr. Trang Nguyen in the Hull Group aimed to develop a tandem process for the synthesis of  $\alpha,\beta$ -disubstituted amides and esters via the isomerization – Claisen rearrangement reaction of diallyl ethers.<sup>1</sup> In previous work, Nelson, et. al used a cationic iridium catalyst to achieve the desired rearrangement<sup>2,3</sup> (Fig. 1a), while a more recent study by Tanaka, et al. employed a cationic rhodium catalyst similar to the catalyst chosen for this work's amidation reactions.<sup>4</sup> (Fig. 1b) Initial attempts to achieve this transformation using tetrasubstituted substrates proved challenging, with low yields and diastereoselectivity. Consequently, she explored the isomerization – Claisen rearrangement approach as the first step in the tandem process, leveraging readily accessible starting materials.

The Claisen rearrangement is initiated using the diallyl ether as the starting material, employing the rhodium catalyst  $[\text{Rh}(\text{COD})_2]\text{BF}_4$  and the dcePhos ligand to modify metal center reactivity. The additive sodium tetrafluoroborate ( $\text{NaBF}_4$ ) significantly increased yields, likely acts as a co-catalyst, assisting in bond-breaking and bond-forming processes. Tetrahydrofuran (THF) serves as the solvent. In the next step, 2.5 equivalents of an amine or alcohol nucleophile react by utilizing the rhodium catalyst, supplemented for nucleophilic addition. Cesium carbonate ( $\text{Cs}_2\text{CO}_3$ ) acts as a base for nucleophilic deprotonation, while chalcone acts as a hydrogen acceptor. Water in a 1/20 volume ratio to enhance solubility, and potentially plays a role in the catalytic cycle.

A: Nelson, et al. iridium-catalyzed olefin isomerization - Claisen rearrangement



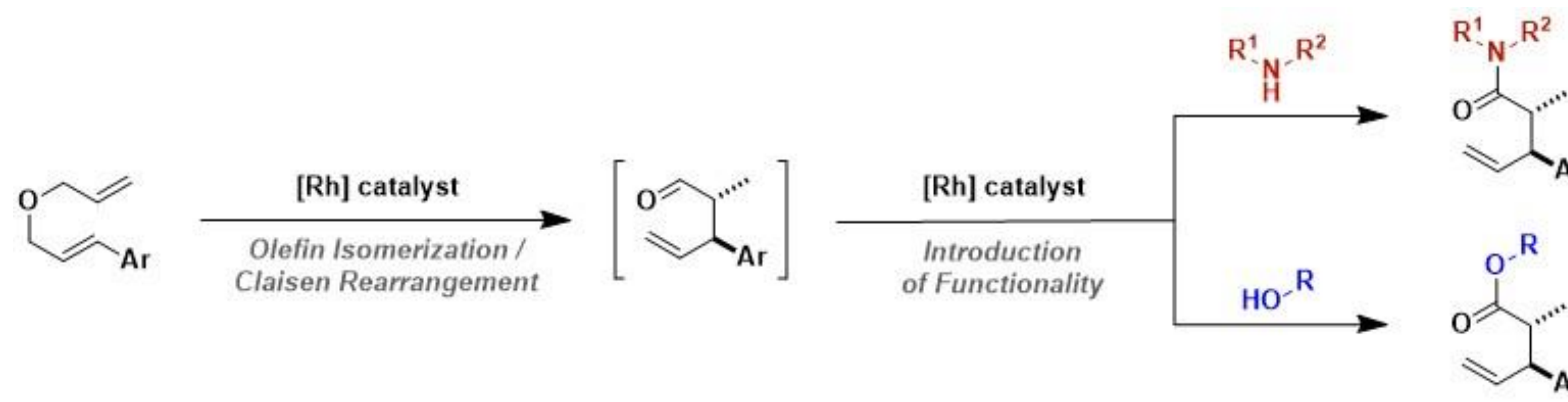
B: Tanaka, et al. rhodium-catalyzed olefin isomerization - Claisen rearrangement



## Research Goal

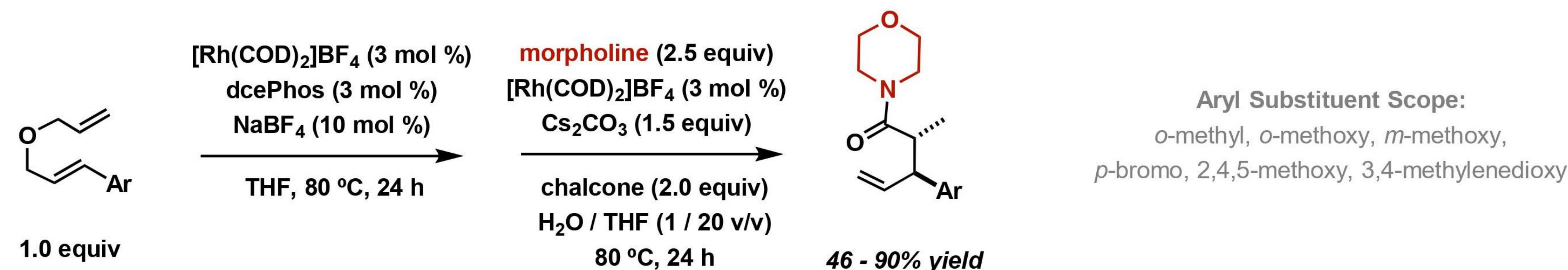
This undergraduate dissertation project aimed to (1) replicate the optimized conditions found by Dr. Nguyen to synthesize the desired  $\alpha,\beta$ -disubstituted amides and esters, (2) explore the scope of diallyl ether substrates and nucleophilic amines and alcohols, and to (3) perform mechanistic studies to gather insights on the intermediates and catalytic cycle(s) for the future publication of the project.

## Envisioned Reaction

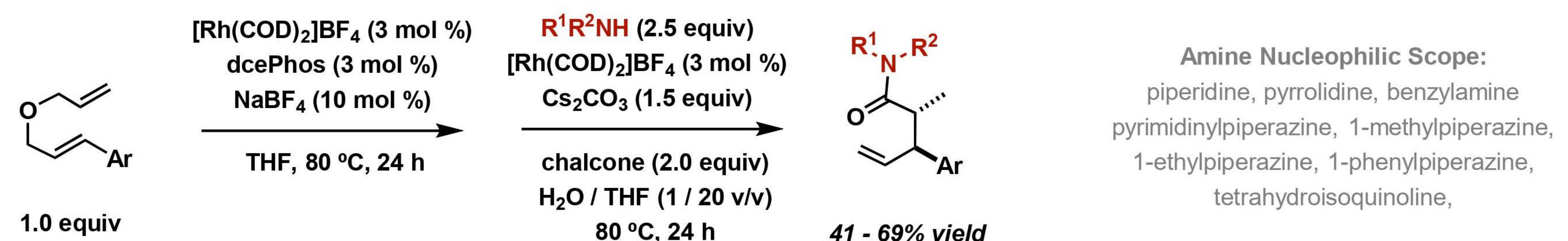


## Results

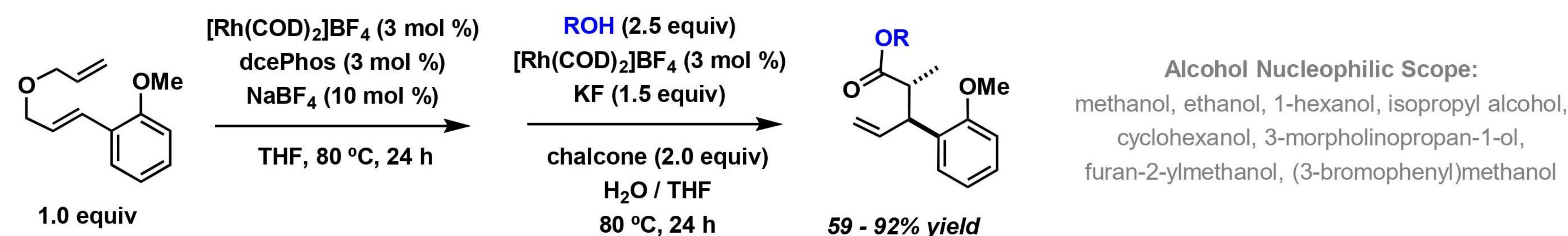
A: Diallyl ether scope for tandem amidation reaction



B: Amine nucleophilic scope for tandem amidation reaction of diallyl ethers

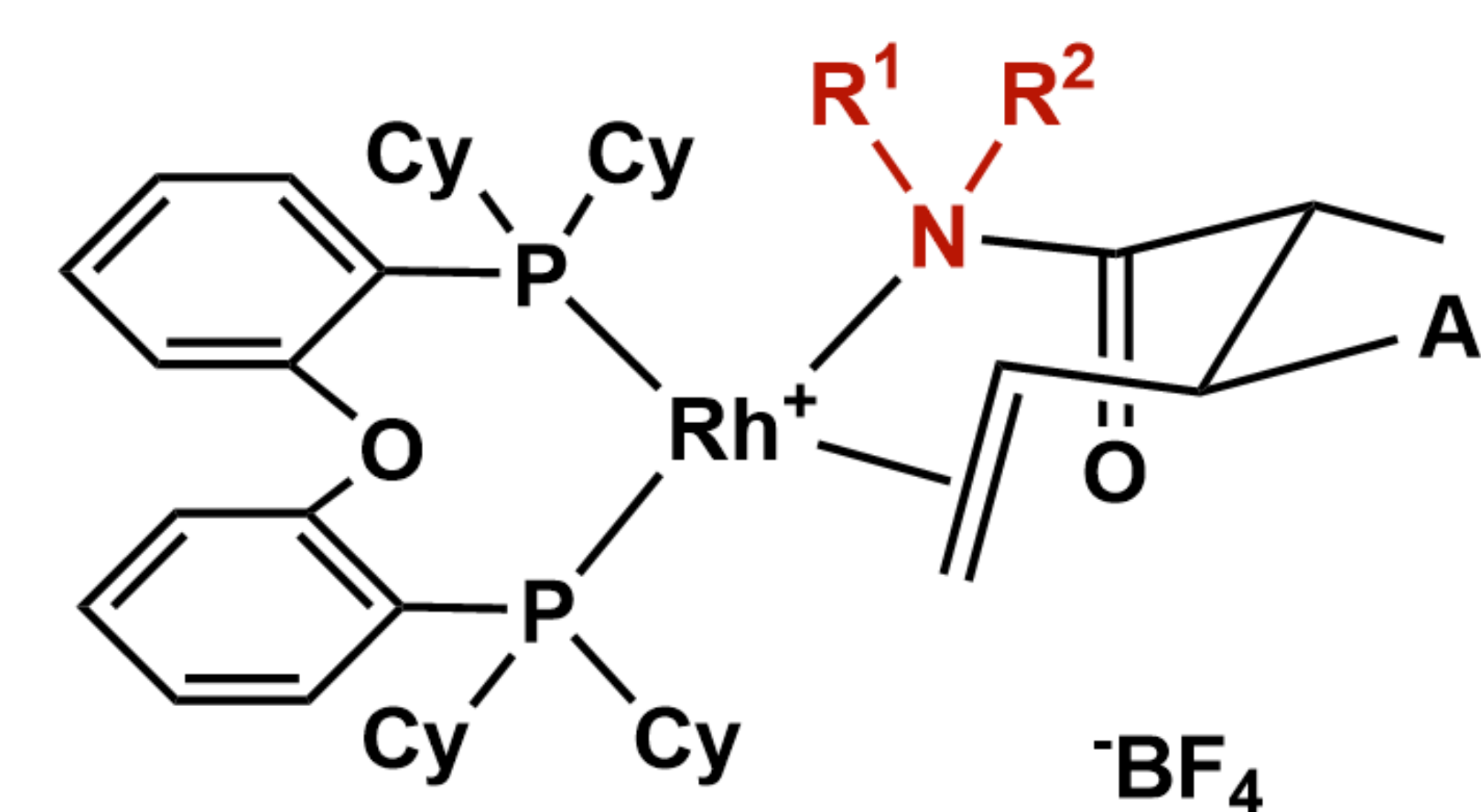


C: Alcohol scope for tandem amidation reaction / esterification of diallyl ethers



**Findings as of November 2023:** The diallyl ether substrate for series A and B have been synthesized. Amine nucleophilic scope B has been replicated, and the yields remain consistent with Dr. Nguyen's findings. Substrate scope A and alcohol nucleophilic scope C have not been prepared and results have yet to be determined.

## Further Studies



Proposed Intermediate for the Rhodium-catalyzed Olefin Isomerization – Claisen Rearrangement – Amidation tandem reaction.

In further studies, the diallyl ether substrate scope and the alcohol nucleophilic scope will be replicated under optimal conditions, and will be used to synthesize and characterize  $\alpha,\beta$ -disubstituted esters.

Further mechanistic studies need to be performed in order to elucidate the catalytic cycle that drives this reaction. With a manuscript in preparation, this project is expected to be submitted for publication by early Spring 2024.

## Acknowledgments

First and foremost, I would like to thank my family-- Randal, Elizabeth, William, and Mari Jefferson-- for always supporting me. I would like to also thank Andrei Popov for *somehow* putting up with me and gifting me the ability to manipulate the building blocks of our world. I sincerely hope you are proud of how far I have come. In addition, I would not be where I am today without Prof. Kami Hull and Prof. Eric Anslyn's mentorship. Because of you three, I not only feel prepared to achieve my Ph.D., but I feel prepared to leave my mark on the world through organic chemistry. I hope I can serve as a living testament to the difference you've made in the world.

## References

- [1] Nguyen, T. Synthesis and Reactivities of Titanocene-Oxo Complexes and Rhodium-Catalyzed Oxidative Amidation. Dissertation, *University of Illinois at Urbana-Champaign* 2017, pp. 85–107.
- [2] Nelson, S. G.; Wang, K. Asymmetric Claisen Rearrangements Enabled by Catalytic Asymmetric Di(Allyl) Ether Synthesis. *Journal of the American Chemical Society* 2006, 128 (13), 4232–4233.
- [3] Wang, K.; Bungard, C. J.; Nelson, S. G. Stereoselective Olefin Isomerization Leading to Asymmetric Quaternary Carbon Construction. *Organic Letters* 2007, 9 (12), 2325–2328.
- [4] Okamoto, R.; Tanaka, K. Rhodium-Catalyzed Olefin Isomerization/Allyl Claisen Rearrangement/Intramolecular Hydroacylation Cascade. *Organic Letters* 2013, 15 (9), 2112–2115.