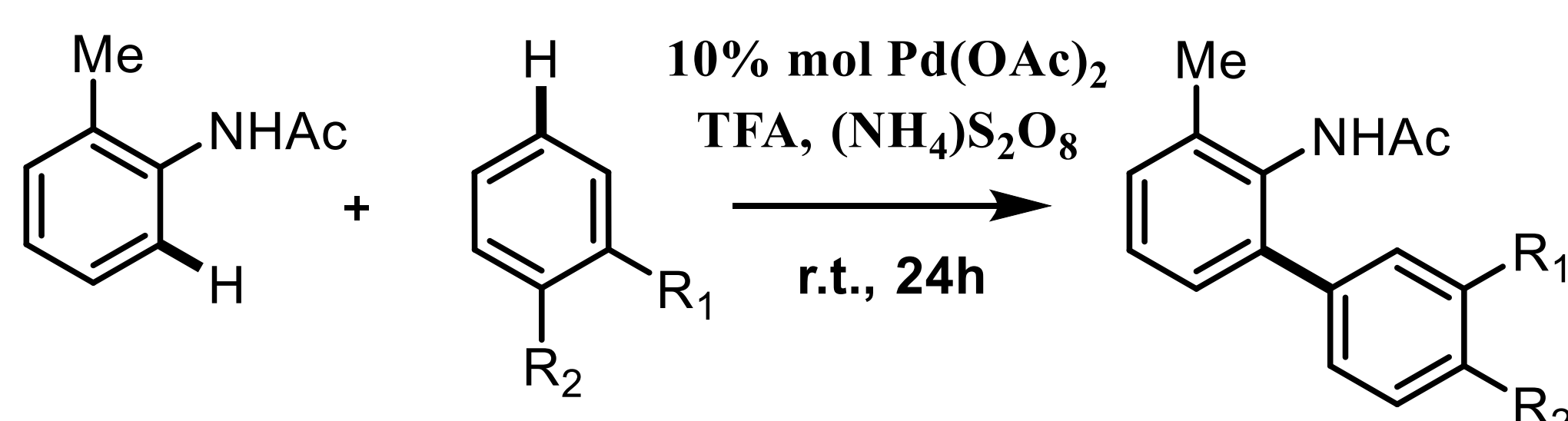


## Introduction

Activation and functionalization of C-H bonding sites has been the focus of intense research in recent years, especially in the case of chelation-assisted palladium-catalyzed reactions. Harsh conditions once limited the classes of molecules that could undergo the reaction, but much progress has been made toward functional group transformations at room temperature. This has opened new routes to elucidate catalytic pathways, but many are still unknown or disputed. Thus, testing anilide derivatives should contribute to solving these mechanistic frameworks.

Our current research involves the use of FTIR spectroscopy to trace the intermediates of C-H activation reactions run under mild conditions. Specifically, following reactions using FTIR in organometallic chemistry may help understand new pathways of synthesis and metal-ligand coordination. The goal of this project was to first synthesize N(o-tolyl) acetamide and purify the product by column chromatography. Then, a new experimental setup that integrates a stopped-flow mixer with a FTIR spectrometer was formulated and measured IR spectrum of the synthesized product and solvents utilized.



	R <sub>1</sub>	R <sub>2</sub>	Yield
1	H	H	67%
2	Me	Me	95%
3	Cl	Cl	35%
4	Me	Br	31%

**Scheme 1:** Ortho-Arylation reaction of N-(o-tolyl)-acetamide. The table shows reported reaction yields [1].

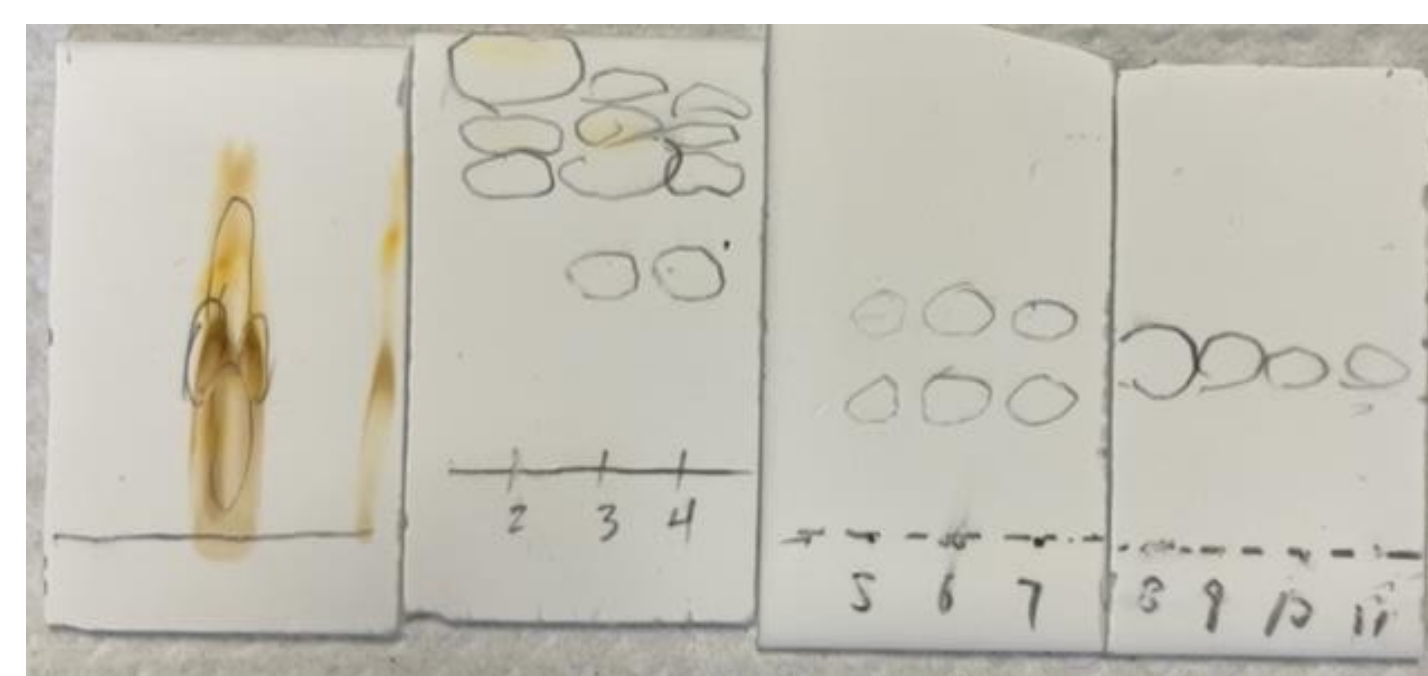
## Methods

Palladium(II) acetate (0.05 mmol), ammonium persulfate (1.0 mmol, 2.0 equiv), and N-(o-tolyl)acetamide (0.5 mmol) were added into a round bottom flask under air. The trifluoroacetic acid additive (20 equiv.) and o-xylene (10.0 mmol, 20.0 equiv) were added via syringes, and the mixture was stirred at room temperature for 24 hours. Then, the mixture was diluted with 10 mL of dichloromethane, filtered through a celite column, and washed by another 10 mL of DCM. The solution was concentrated by a rotary evaporator, and column chromatography on silica gel (petroleum ether/EtOAc = 2/1, v/v) was used for purification to obtain product. TLC plates were collected to track the predicted product and allow isolation during the column (**Figure 1**).

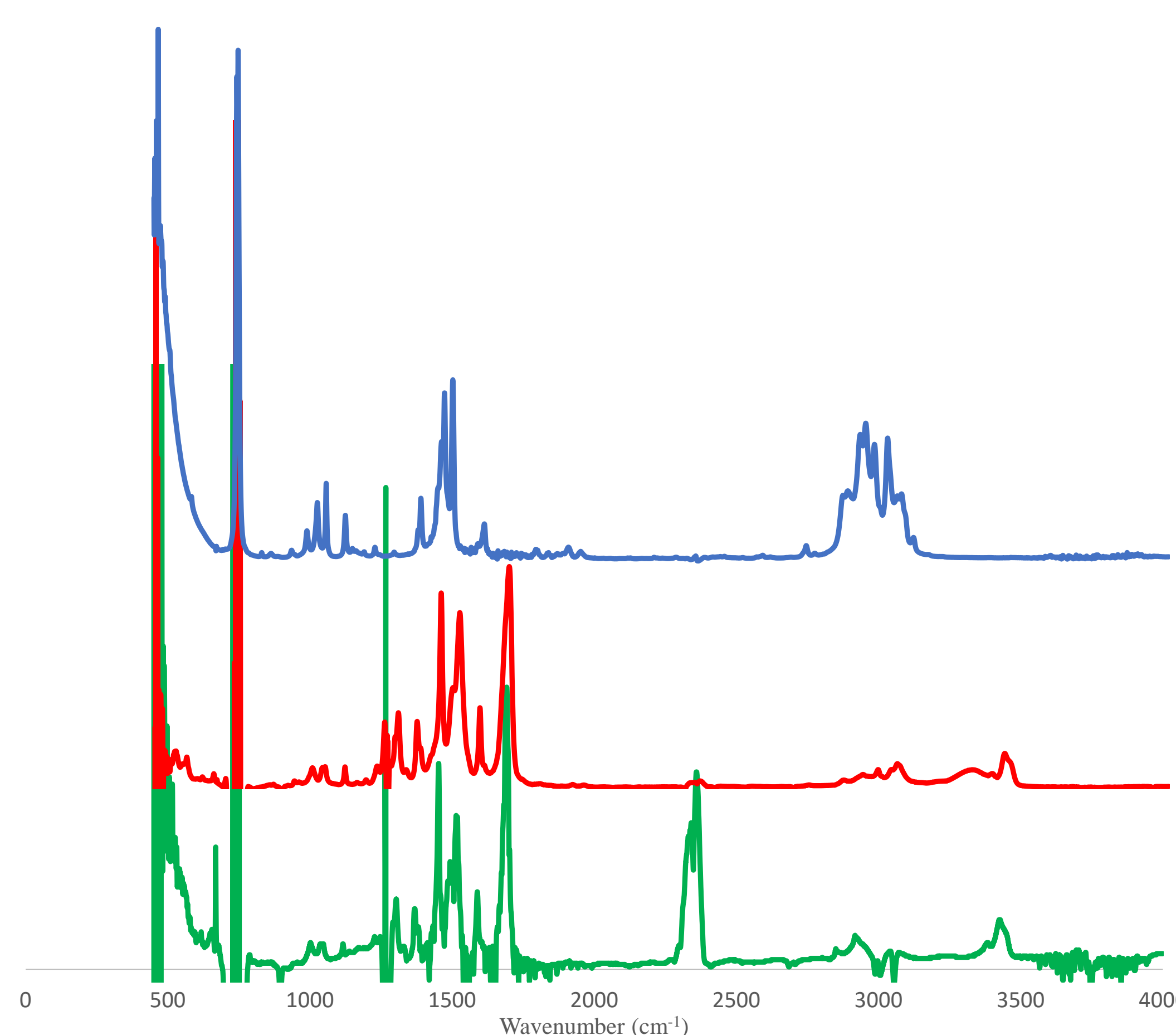
FTIR spectra of reactants and products were recorded in dichloromethane (ACS grade) in a Perkin-Elmer Spectrum 3 transmission FTIR spectrometer in a 25 μm FTIR cell (**Figure 2**).

## Results/Discussion

Out of the growing variety of mild metal-catalyzed C-H bond activations, we focused on chelation-assisted palladium-catalyzed reactions, which have been shown to achieve acetoxylation and arylation at room temperature[1]. In addition to being tolerable to a wide array of substrates due to the mild reaction conditions, Pd(TFA)<sub>2</sub>, formed *in situ* from trifluoroacetic acid and Pd(OAc)<sub>2</sub>, has been most widely used in cross coupling reactions of anilides with simple arenes at room temperature. This occurs in presence of (NH<sub>4</sub>)<sub>2</sub>S<sub>2</sub>O<sub>8</sub>, which acts as the oxidant in the catalyst regeneration step of the catalytic cycle, and unlike many other oxidants, is easy to handle and cost-efficient. The reaction of electron-rich arenes with a specific amide by Song, Yu and coworkers have shown great promise, resulting in of reactions yields of 70 % to 95 % for a wide array of substrates. However, substituting arenes with electron-poor substituents significantly reduces the yield of desired products (see **Scheme 1**). In a first application of the stopped-flow FTIR system, we investigated the spectrums of starting material and product synthesized to better characterize the reaction mechanism(s). The precise reaction mechanism is still under debate. Most commonly, the reaction is thought to be catalyzed by the highly electrophilic Pd(TFA)<sub>2</sub> through the formation of metal-carbon bonds. The acidic solvent is weakly coordinating to the Pd catalyst and may thus promote the dissociation of cationic intermediates, which in turn may act as a base to deprotonate the coordinated C-H bond.

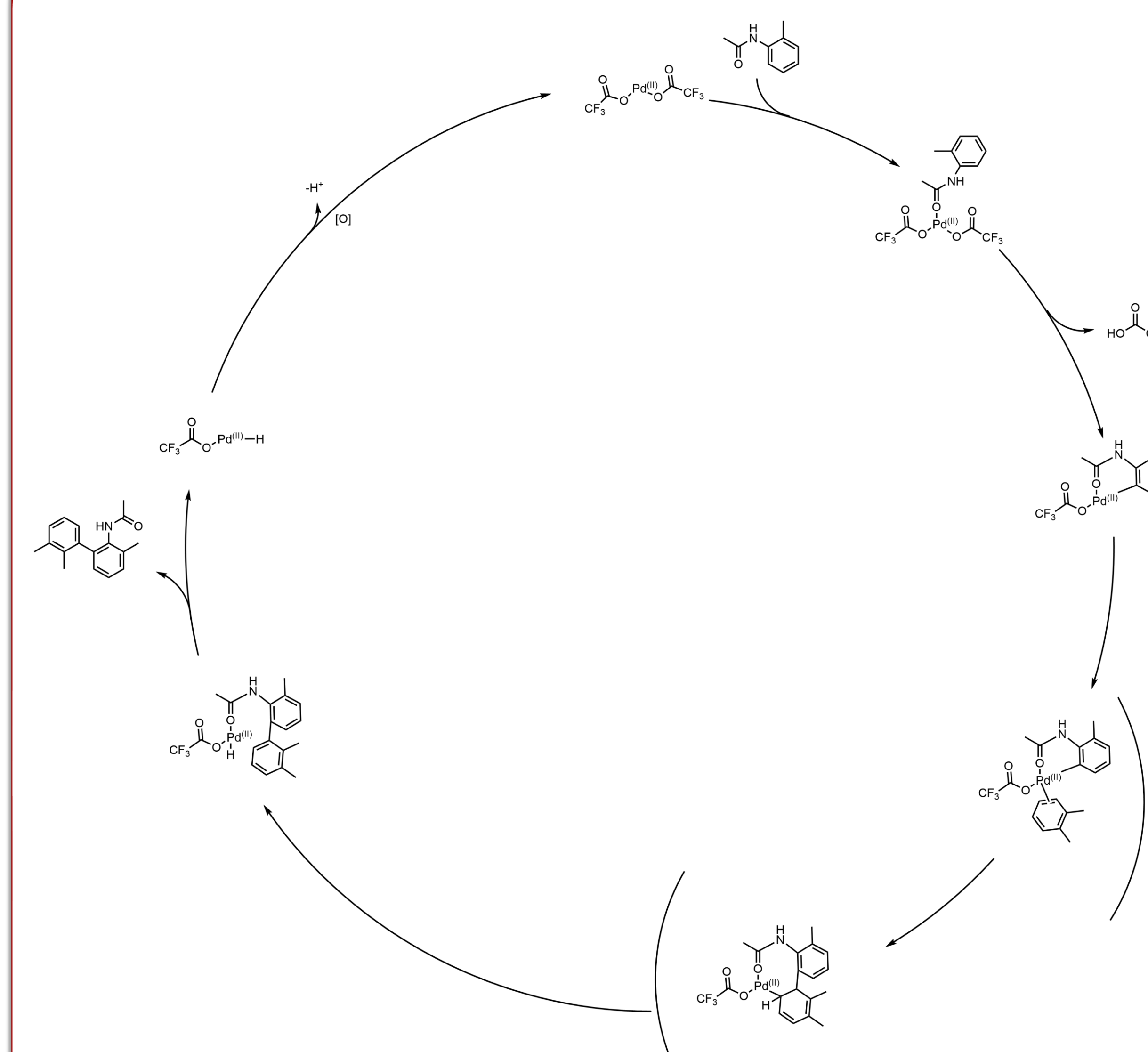


**Figure 1.** Thin-layer chromatogram of the fractions after column-purification. Fractions 8-11 were combined and analyzed via FTIR.



**Figure 2.** FTIR spectra of o-xylene (blue), N-(o-tolyl)-acetamide (red), and fractions 8-11 after column purification (green).

## Proposed Mechanism



**Scheme 2:** Proposed mechanism of the Heck reaction facilitating ortho-arylation of anilides. Other catalytic themes may lead to additional pathways.

## Future Directions

The continuation of this project will involve the synthesis of ortho-arylation reactions but also focus on reactions with different substrates and starting materials. Similar methodology will be performed with FTIR to identify possible competing side-products and to further characterize the proposed reaction mechanism. The ability of FTIR spectroscopy to monitor the evolution of the reaction mixture during the initial steps of the reaction—with a time resolution of 10 milliseconds—will continue to further the confirmation or new identity of a catalytic pathway.

## Acknowledgements

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## References

1) Yang *et al.* (2013) *RSC Advances* vol. 3 pp. 9649 – 9652