



Development of Novel Palladacycles for Synthesis Optimization of Drug Candidates

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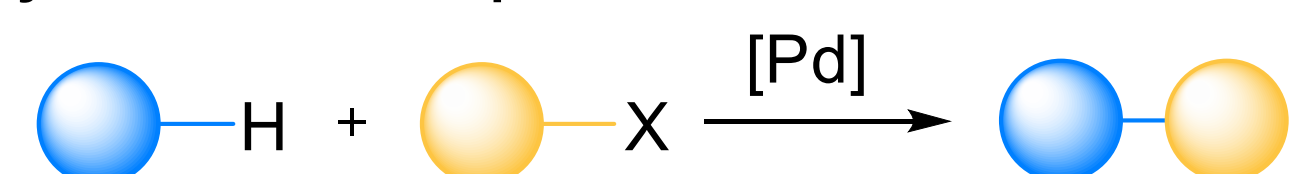
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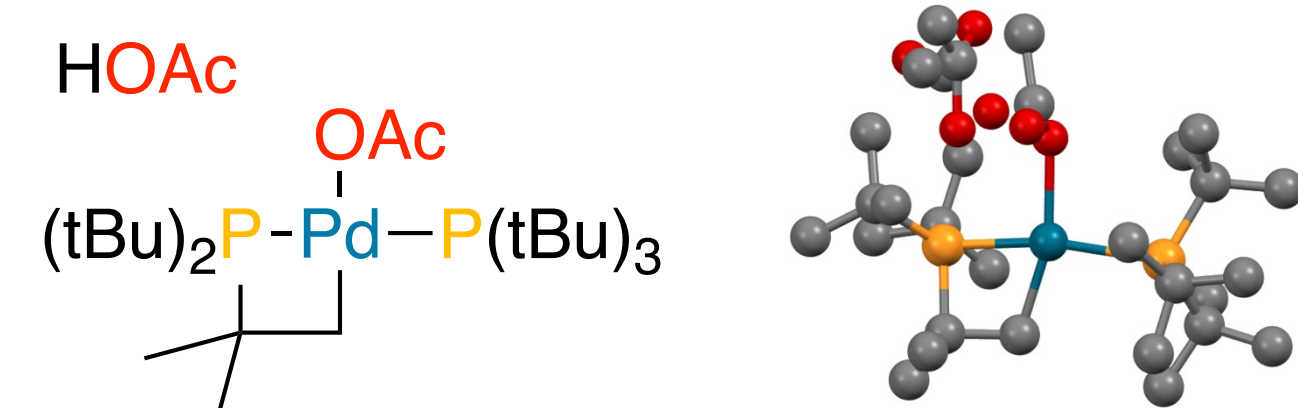
BACKGROUND AND MOTIVATION

Direct alkenylation reactions have been developed as a simpler synthetic pathway to access alkenylarene derivatives as they are important scaffolds found in biologically active compounds.

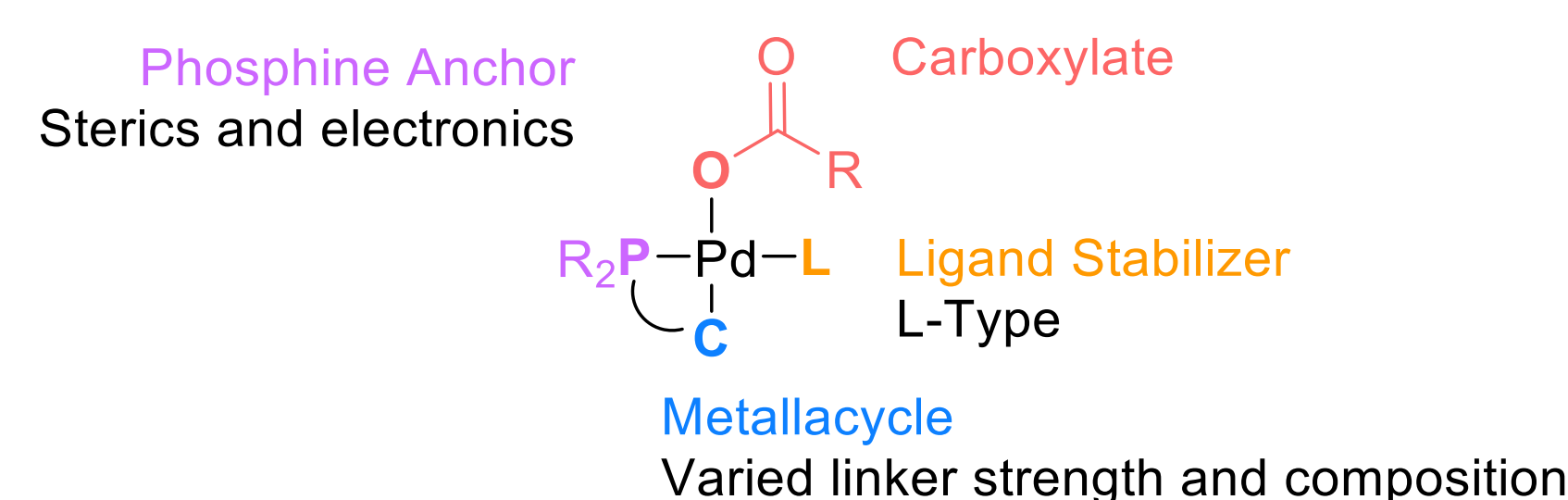


Goal of this research: develop an *in-situ* generated palladium system to undergo C-H activation reaction with a variety of heterocycles and aryl halides.

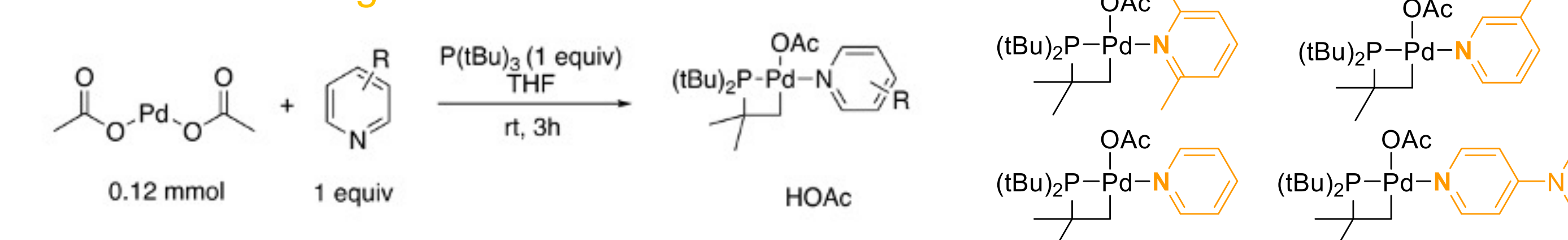
Previously isolated palladacyclic catalyst:



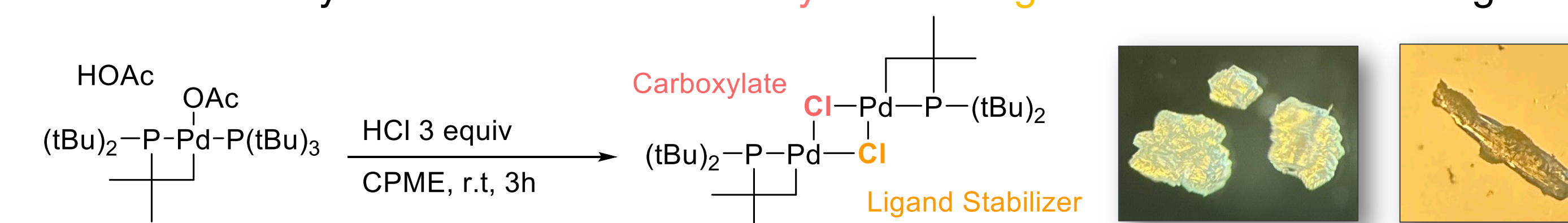
Palladacyclic structures offer functionalization of different variables.



Modification of Ligand Stabilizer:

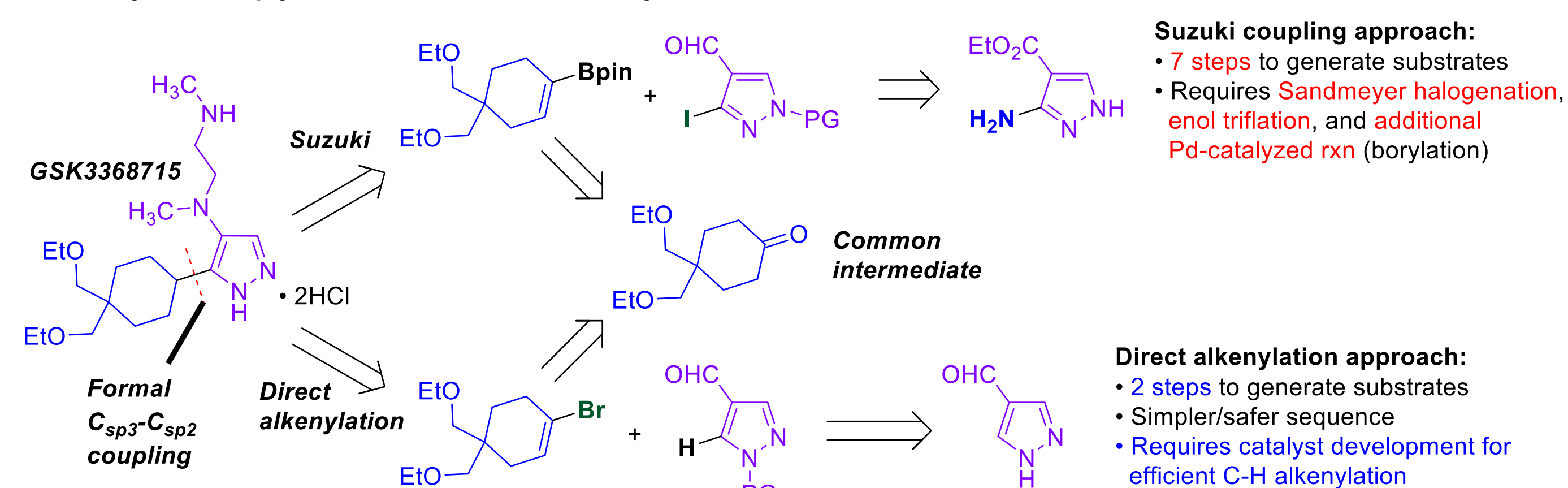


Novel Palladacycle Precursor for Carboxylate and Ligand Stabilizer Screening:



OPTIMIZATION OF SYNTHETIC PATHWAY

We were inspired to investigate catalytic coupling for the synthesis of **GSK3368715**, an investigational API reported in 2019 that contains an alkylated pyrazole unit as a key structural feature.



Catalysis With Pyrazole Substrate:

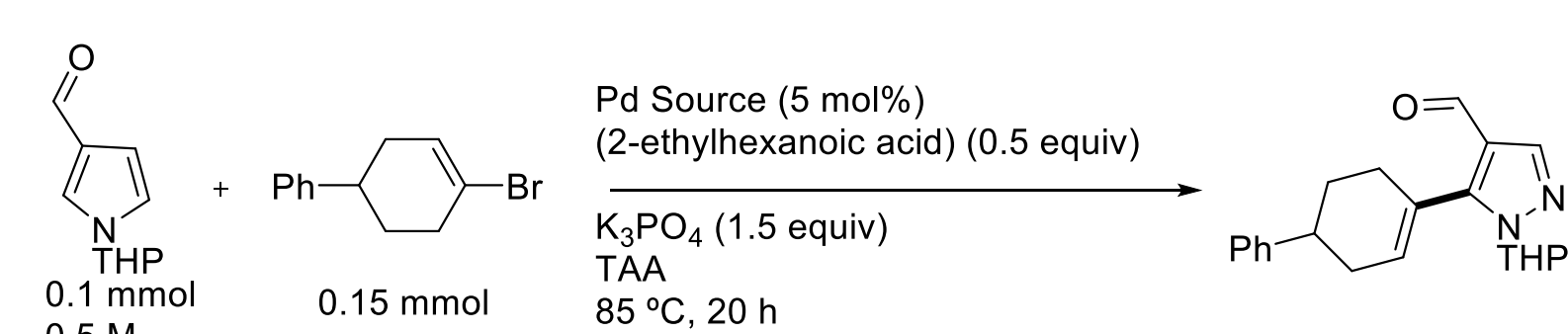


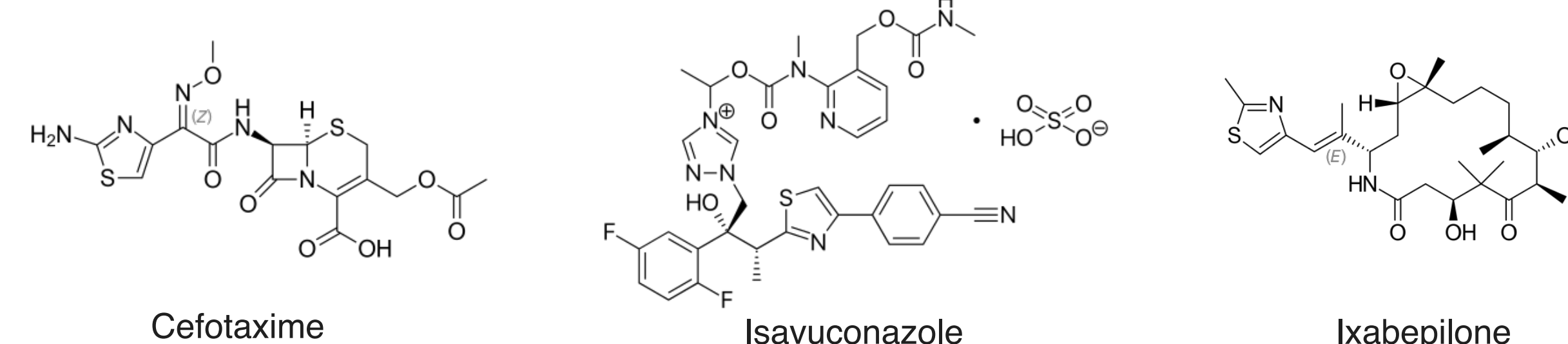
Table 1. Results for catalysis with pyrazole substrate.

Entry	Catalyst	NMR yield (%)	Unreacted pyrazole (equiv)	Unreacted vinyl bromide (equiv)	Mass Balance (LR)
1	a	56	0.05	0.96	61
2	b	48	0.27	1.05	75
3	c	55	0.17	1.00	72
4	d	50	0.25	1.10	75
5	e	58	0.17	1.00	75

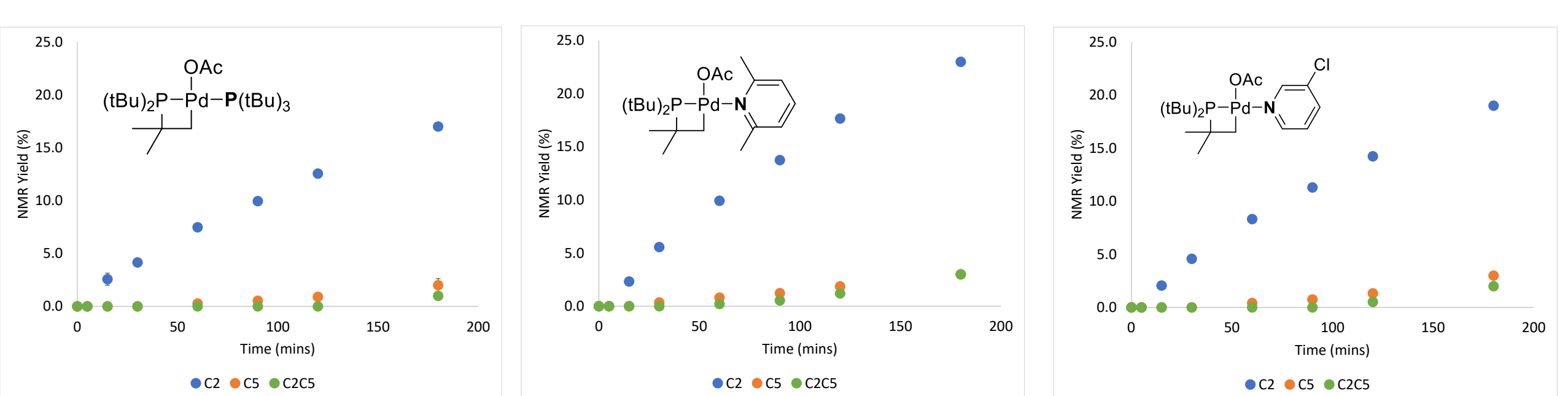
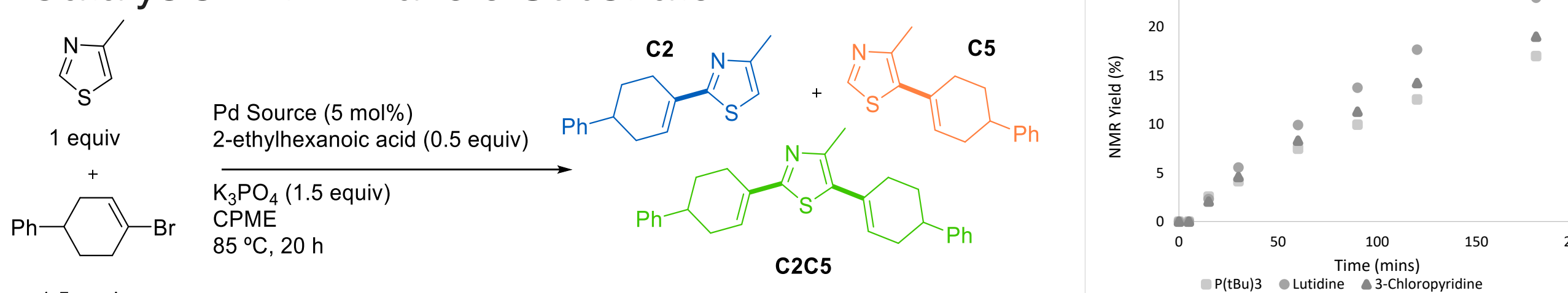
Conclusion:
Nitrogen ligands improved the mass balance of the reaction.
Future work needed to further optimize the reaction conditions.

IMPROVING REGIOSELECTIVITY

Thiazoles are commonly found in many potent pharmacologically active molecules, such as Cefotaxime (antibacterial drug), Isavuconazole (antifungal drug), and Ixabepilone (anticancer drug).



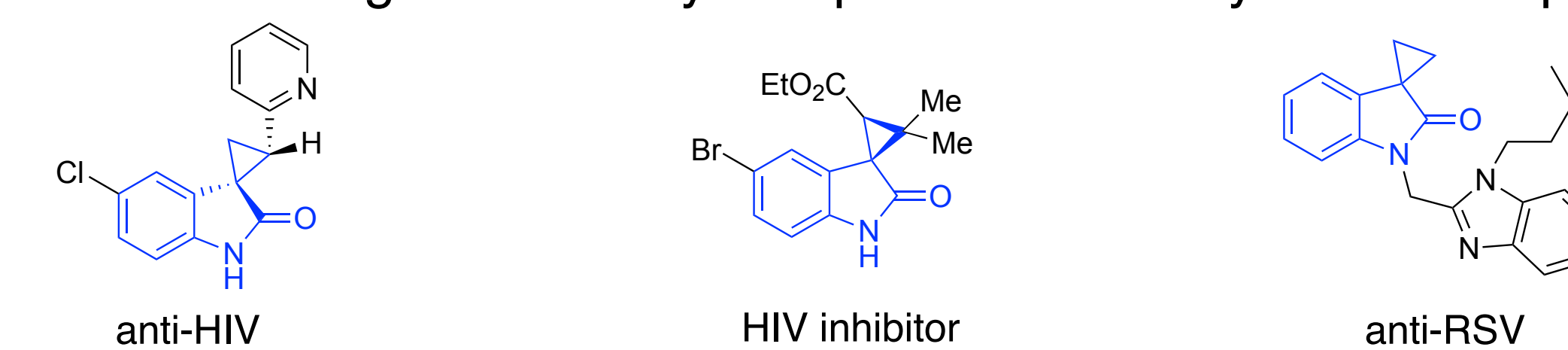
Catalysis With Thiazole Substrate:



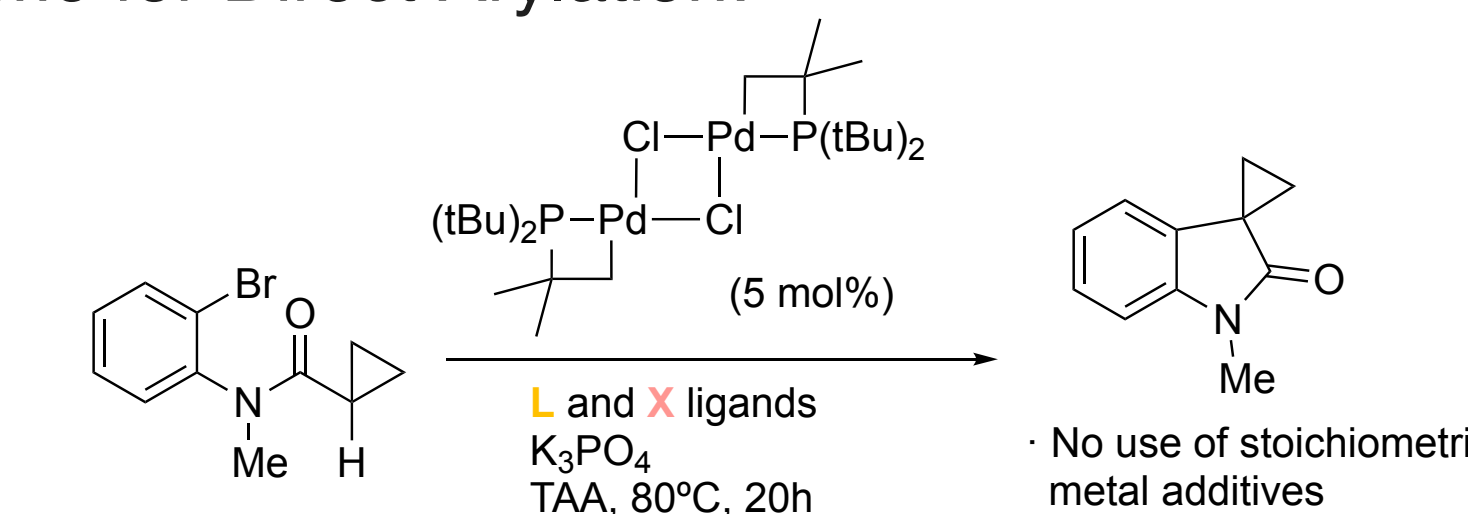
Conclusion:
The lutidine derivative shows slightly better reactivity than other N or P ligands.
Nitrogen ligands have faster reactivity, but not significantly. Further modification of the catalyst is needed.

INTRAMOLECULAR ARYLATION

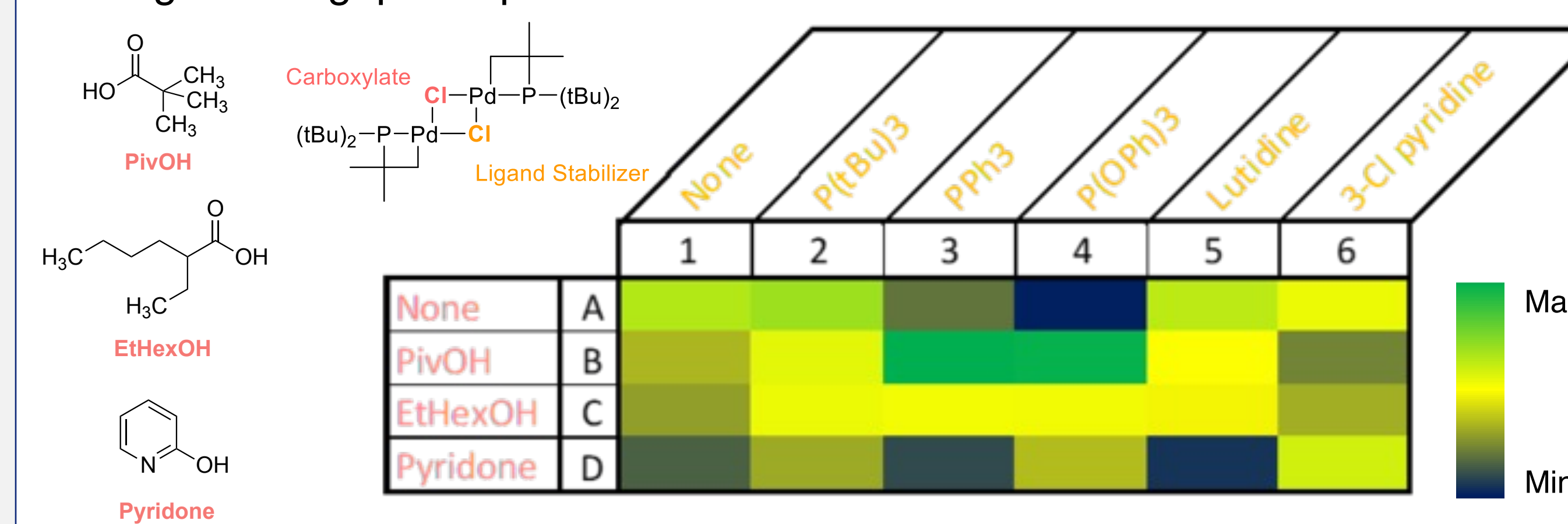
The spiro 3,3'-cyclopropyl oxindole core is a recurring structural motif present in several agrochemically and pharmaceutically active compounds.



Reaction Scheme for Direct Arylation:



High Throughput Experimentation



Conclusion:
Pivalic acid shows the highest reactivity out of the carboxylates in this reaction when paired with the triphenylphosphine and triphenyl phosphite ligand stabilizers.

REFERENCES

- Pipaon Fernandez, N. *et al.*, *ACS Catal.* **2022**, 12, 12, 6997–7003
 Z.-X. N. *et al.*, *European Journal of Medicinal Chemistry* **250**, **2023**, 115172, 1-26
 Fedoriv, A. *et al.*, *Cancer Cell*. **2019**, 36, 100–114
 Yichen, T. *et al.*, *J.Am.Chem.Soc.* **2012**, 134, 3683–3686
 William, H. *et al.*, *Organometallics*. **2011**, 30, 5038–5044
 Rui-Ying, Z. *et al.*, *J. Org. Chem.* **2021**, 86, 1141–1151

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