Nickel Catalyzed Suzuki-Miyaura Cross-Coupling: Reaction Screening and Catalyst Comparison via High-Throughput Experimentation

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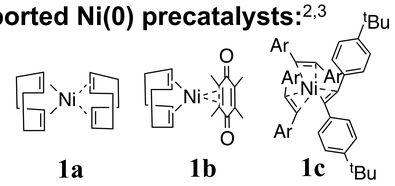
Background

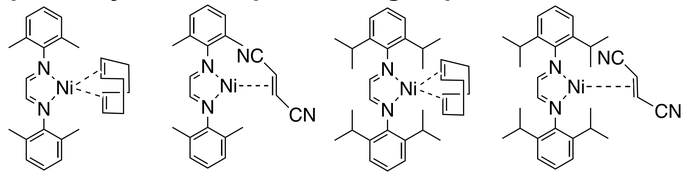
- The Suzuki-Miyaura (SM) reaction is the most commonly employed method to form C–C bonds in medicinal chemistry.[1]
- Historically Pd catalyzed, which is an expensive and rare metal.
- Significant interest has developed regarding the Ni-catalyzed SM reaction.

Previously reported Ni(0) precatalysts:[2,3]



1a 1b 1c

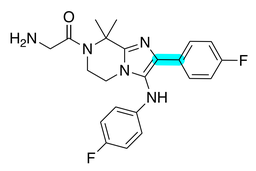
Ni(0) precatalysts developed in our group:



2a 2b 2c 2d

Application: Synthesis of Ganaplacide

- Antimalarial drug candidate.
- Highlighted C–C bond can be constructed via SM cross coupling.

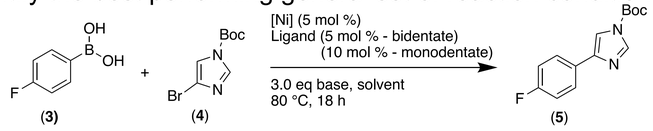


Ganaplacide

Preliminary Screen

Goal:

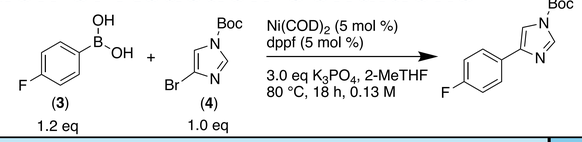
- Identify the best performing general set of reaction conditions.



0% | 0-20% | 20+%

		2-MeTHF				Toluene				CPME			
		1a	1b	2a	2b	1a	1b	2a	2b	1a	1b	2a	2b
K_3PO_4	dppf												
	dppb												
DBU	IPr HCl												
	PCy_3												
KO^{t}Bu	dppf												
	dppb												
K_2CO_3	IPr HCl												
	PCy_3												

Optimization of Reaction Conditions



Entry	Deviation from Reaction Conditions	Yield (%)[a]
1	T= rt	3
2	T= 50 °C	12
3	None	11
4	T= 110 °C, [Ni] = **2a**	0
5	0.1 eq NaSO4·10 H_2O	6
6	0.3 eq NaSO4·10 H_2O	6
7	1.0 eq NaSO4·10 H_2O	5
8	1.5 eq non-anhydrous K_3PO_4	5
9	**2.0 eq (3), 1.5 eq non-anhydrous K_3PO_4, 0.38 M**	**32**

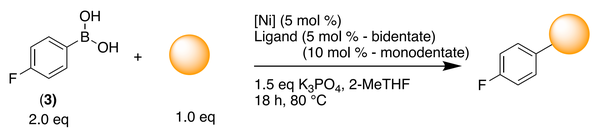
[a] NMR yield relative to ferrocene internal standard.

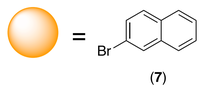
Substrate Specific Ligand Compatibility Screens

Parallel Substrate Comparison: 2-Bromonaphthalene vs 2-Bromopyridine

Goals:

- How does a heteroatom impact reactivity?
- What ligands perform better with heteroaryl substrates?
- How do these precatalysts perform in different SM reactions?





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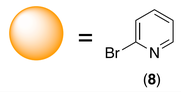

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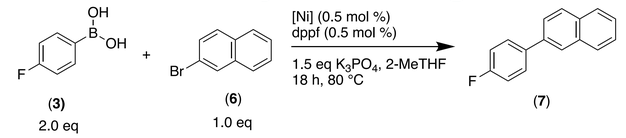
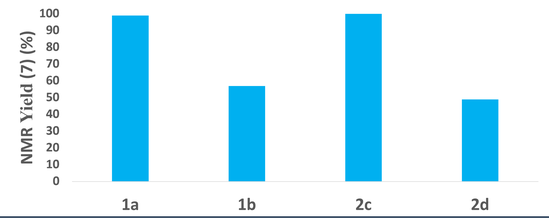
	1a	1b	2c	2d
dppf	79	81	86	98
dppb	71	63	74	81
DPEPhos	84	72	82	87
IPr HCl	38	46	82	65
PCy_3	46	71	83	81
CyJohnPhos	71	63	92	69

	1a	1b	2c	2d
dppf	33	29	51	0
dppb	26	20	35	0
DPEPhos	31	34	60	21
IPr HCl	4	8	51	18
PCy_3	18	26	31	27
CyJohnPhos	17	9	67	21

Reduced Catalyst Loading Trials





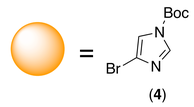
Summary and Future Work

Summarized Results:

- Optimization of SM cross-coupling of imidazole substrate provided maximum yield of 32%.
- Screening provided insight into substrate specific ligand compatibility.
- Precatalyst comparison showed robust performance of catalysts developed in our group.

Current Work:

- Replicate ligand compatibility screening with imidazole substrate.



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Future Work:

- Optimization of imidazole SM cross-coupling.
- Long term goal of synthesizing Ganaplacide via Ni-catalyzed cross-coupling.

Acknowledgements

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References

1. Jordan et al. *J. Med. Chem.* **2011**, 54, 3451–3479.
2. Engle et al. *Angew. Chem. Int. Ed.* **2020**, 59, 7409 –7413.
3. Cornella et al. *Organometallics.* **2020**, 39, 3295−3300.