

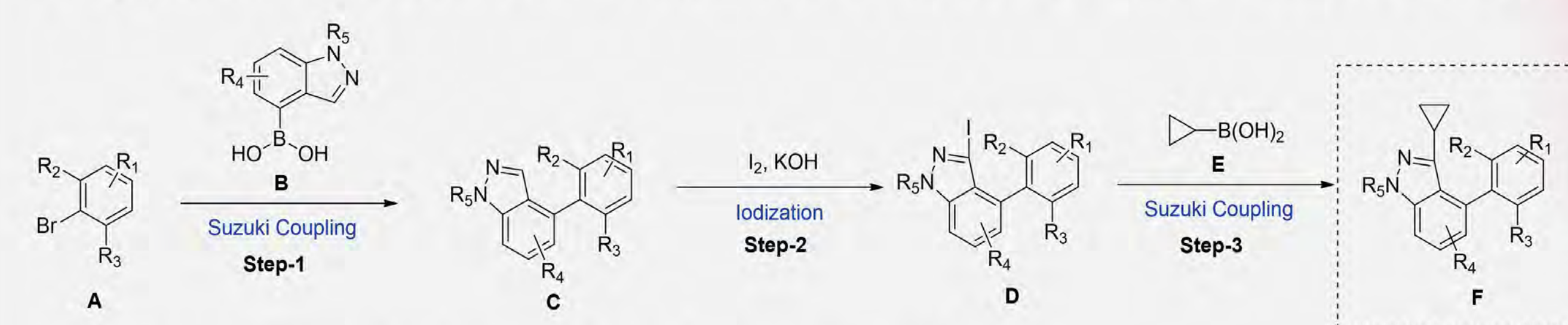
Development, Problem-Solving and Successful Scale-Up of a Sterically Hindered Suzuki Coupling Reaction

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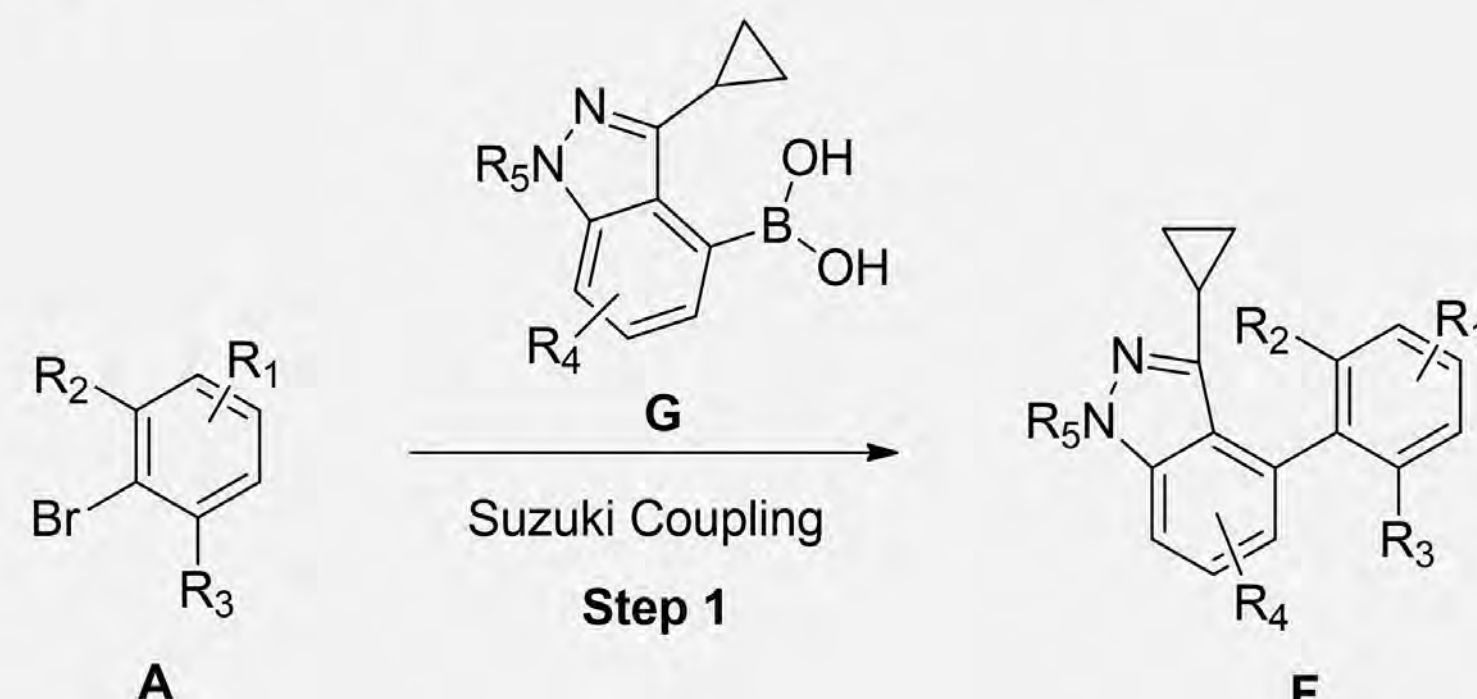
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Original Synthesis of Intermediate F and Drawbacks



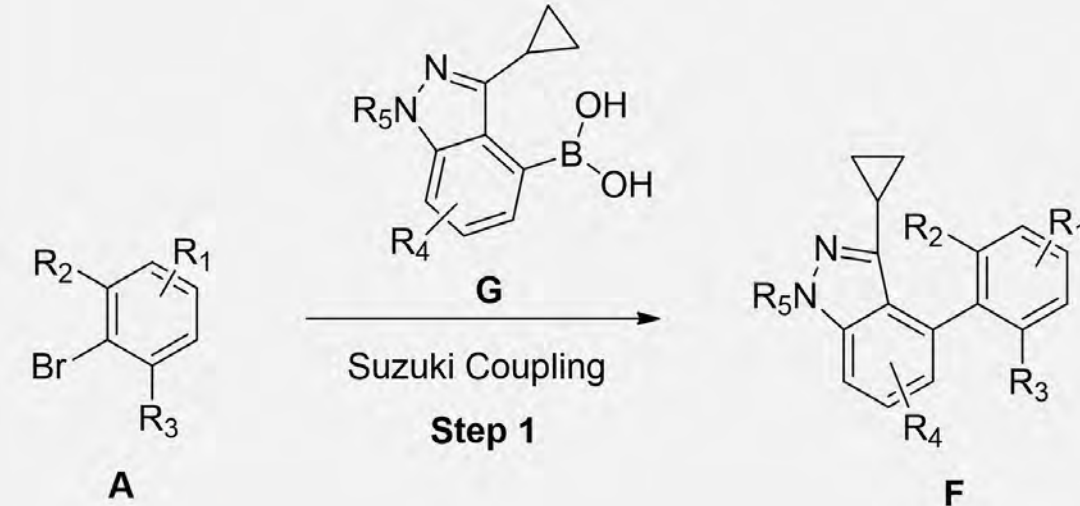
- Compound F is a key intermediate of an oncology API.
- Original synthesis included two Suzuki coupling reactions from commercial available starting material A.
- Step-1 Suzuki coupling reaction used 10% Pd catalyst loading with complicated workup process to purge Pd.
- Step-3 Suzuki coupling reaction also used 10% Pd catalyst loading with 3.0 equiv. of expensive raw material E.
- This route is not good for the fast increasing clinical trial demands.

Newly Designed Synthetic Route



- Newly developed synthetic route only used one step Suzuki coupling reaction.
- There was no need to use expensive and unstable raw material E (cyclopropylboronic acid).
- Compound G is easier to be made comparing with compound B in the original route.
- Sterically hindered Suzuki coupling reaction was needed to be investigated.

High-Throughput Screening of Sterically Hindered Suzuki Coupling

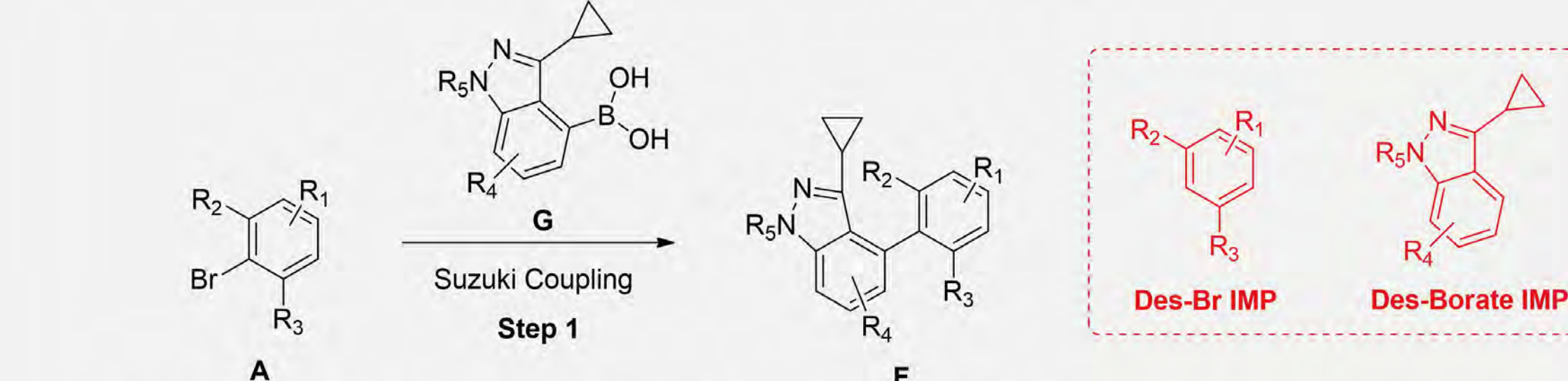


P Ligand	47 kinds
Solvent	1) 1,4-dioxane 2) 1,4-dioxane/Water 3) Toluene
Base	1) K_3PO_4 2) NaOMe 3) CsF 4) t-BuONa
Temperature	1) 75 °C 2) 100 °C

rac-Ant-Phos Ligand

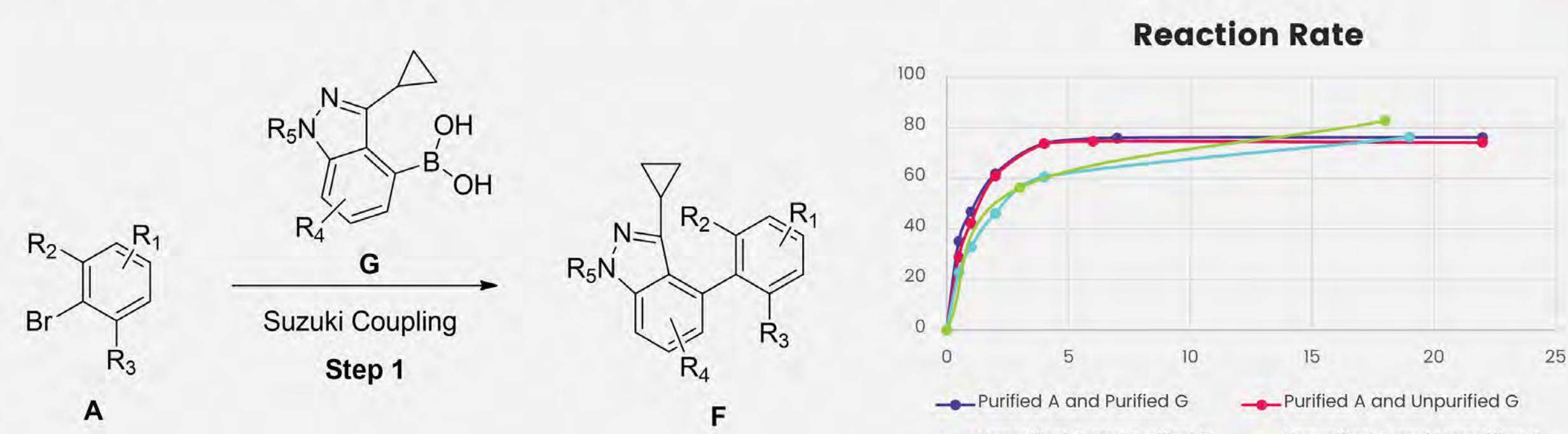
- Total 304 conditions have been screened.
- $Pd(OAc)_2$ /rac-Ant-Phos was found as the best catalyst system to give 98% conversion.

Problems in Process Development



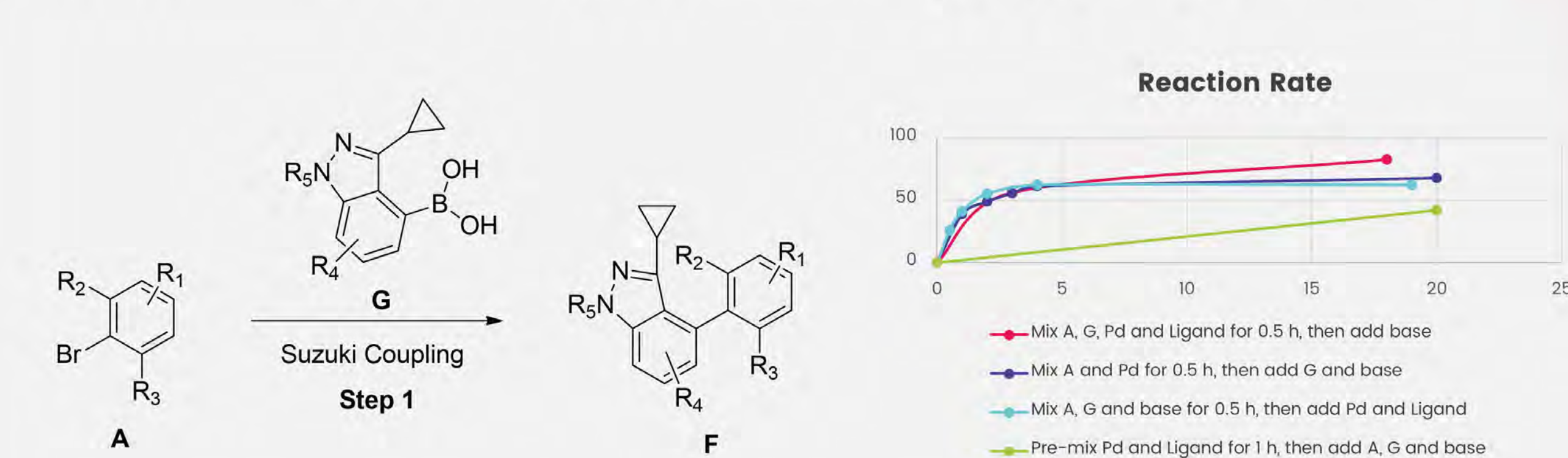
- When scaled up from mg to g in the research lab, the conversion rate of **Bromide A** was much lower. It resulted in the much higher level of **Des-Br impurity**.
- Boronic acid G** was unstable and could be decomposed in the presence of Pd catalyst under reaction conditions to generate **Des-Borate impurity**.
- The reaction repeatability was poor. The IPC purity of product **F** was in a range of 33% to 90%.
- It was important to find out the critical key parameters to better control the reaction and get a reliable process for the scale-up.

Parameter I: Quality of Substrates



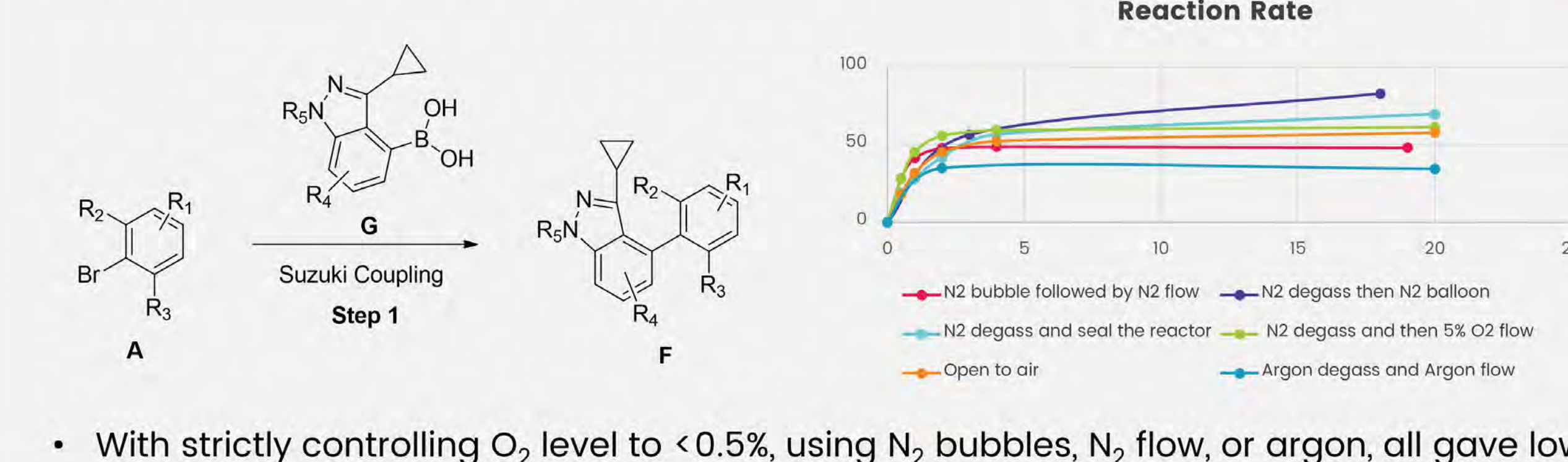
- Compound **A** and **G** were purified by silica gel column.
- Four cross-check experiments were carried out under the same reaction conditions.
- There was no significant difference on reaction conversion.
- The quality of both starting materials **A** and **G** didn't have significant effect on the reaction profile.

Parameter II: Reagents Charging Sequence



- Pre-mixing Pd catalyst and ligand for 1 h before adding starting materials and base gave lower IPC purity of product **F**.
- Other charging sequence did not have significant effect on the reaction.

Parameter III: Inert Gas



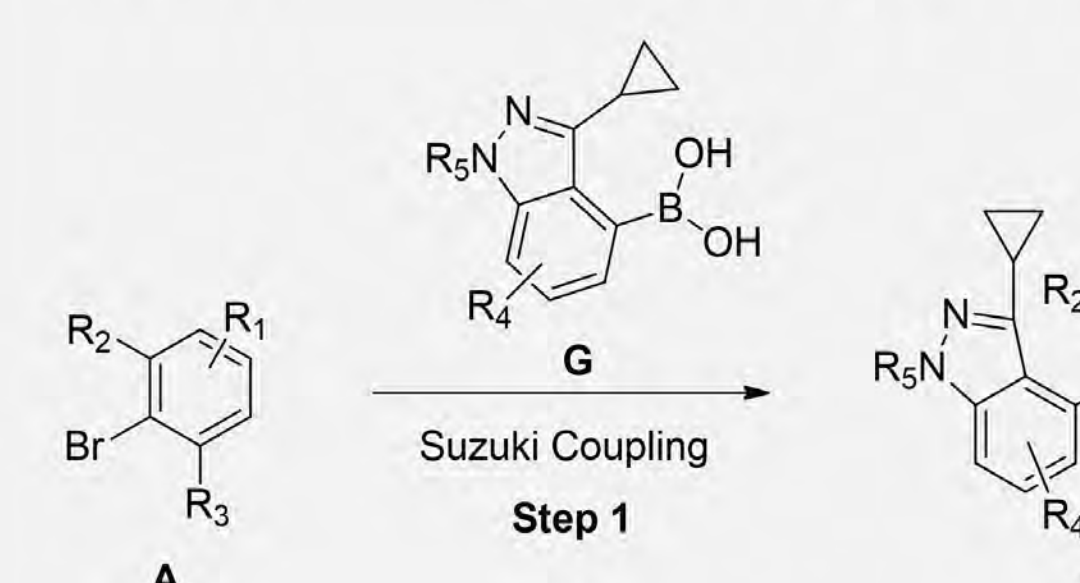
- With strictly controlling O_2 level to < 0.5%, using N_2 bubbles, N_2 flow, or argon, all gave low IPC purity.
- N_2 degass of the reaction followed by using N_2 balloon would slowly introduce O_2 to the reaction, which gave good conversion and high IPC purity of product **F**.
- Under current conditions, certain level of O_2 was important to get good IPC purity. However, it was difficult to control O_2 at certain level for plant manufacturing.
- Further investigation was needed to understand the O_2 level effect.

Parameter IV: Ligand Purity

Conclusion after investigation:

- Both ^{31}P -NMR and HPLC purity are comparable between different lots of rac-Ant-Phos ligand.
- The color of purified ligand though column chromatography was lighter than most of the purchased lots.

Parameter IV: Ligand Purity



- After silica gel column purification, lighter color of ligand gave faster reaction with good IPC purity of product **F**.
- There was no need to adjust the O_2 level. Complete purge of O_2 could give good reaction.

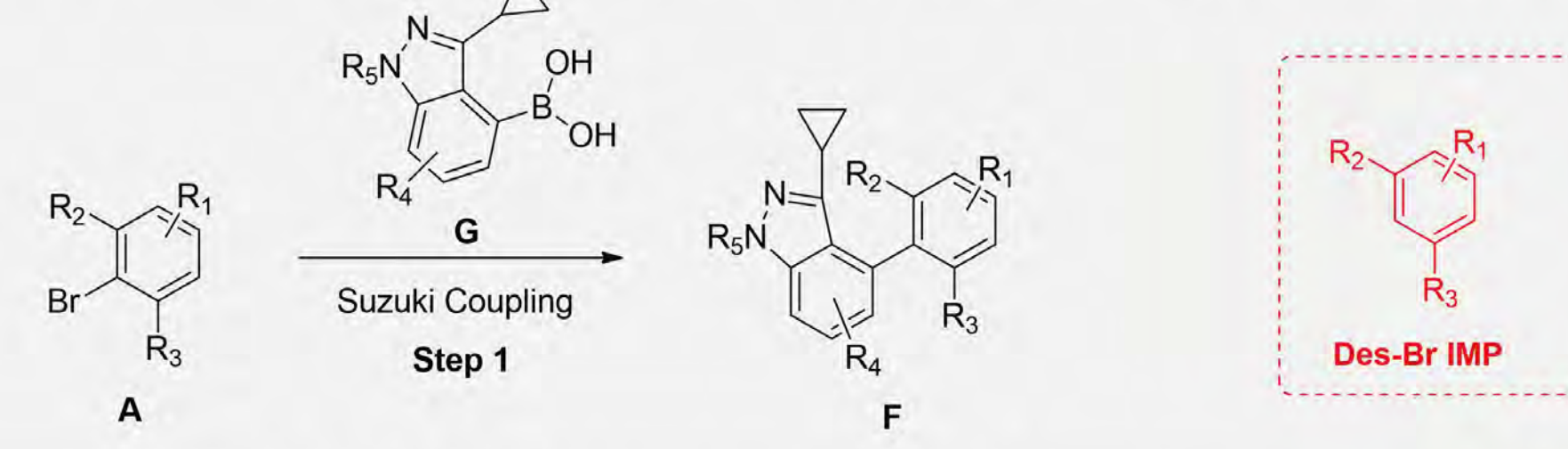
Experiment	A	G	Inert Gas	Time	IPC α% of Product F
Reaction without Purified Ligand	No purification	Purified	N_2 Flow (O_2 < 0.5%)	4	48.5
				20	48.0
Reaction with Purified Ligand				4	76.3
				20	76.4

Parameter IV: Metal Content Analysis of Ligand

Metal Content	Li	Mg	Zn	Ti	Pd	Al
Purchased Lots	1 ppm	7 ppm	4 ppm	39 ppm	103 ppm	3 ppm
	< 0.5 ppm	5 ppm	2 ppm	94 ppm	10 ppm	1 ppm
After Silica Gel Column Purification	< 0.5 ppm	3 ppm	1 ppm	85 ppm	81 ppm	1 ppm
	< 0.5 ppm	8 ppm	13 ppm	44 ppm	526 ppm	1 ppm
	< 0.5 ppm	4 ppm	1 ppm	< 0.5 ppm	19 ppm	1 ppm

- After silica gel column purification, the color of the ligand was improved from dark yellow to light yellow.
- Residual heavy metals analysis showed the level of Ti and Pd was significantly decreased. This could be the reason the reactions with non-purified ligands were more sensitive with O_2 level.

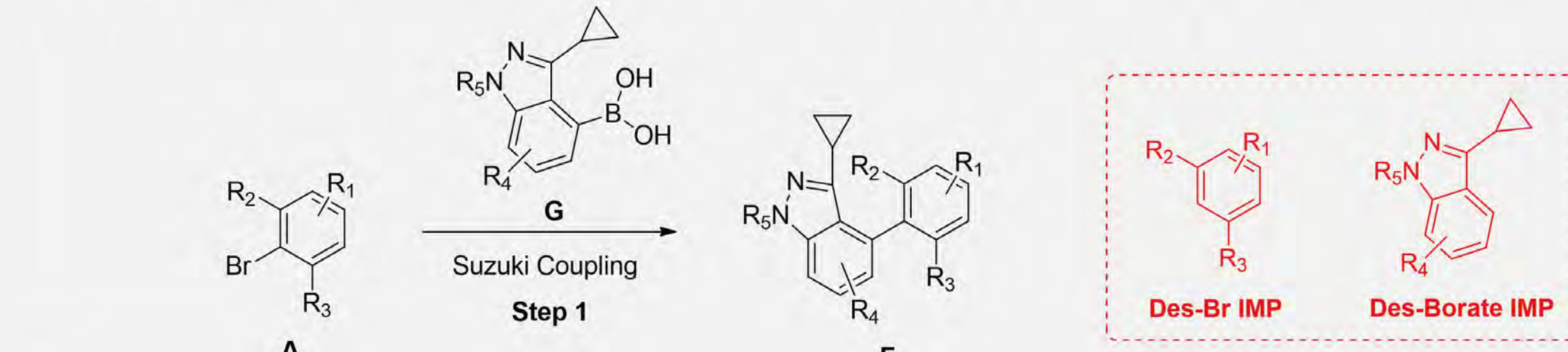
Futher Study of Ratio of Catalyst and Ligand



Experiment	Pd Catalyst : P-Ligand	Time	IPC α% of Product F	Des-Br IMP	Des-Borate IMP	Solution Yield
Reaction without Purified Ligand	1:2	16	76.35	3.59	12.96	84%
Reaction with Purified Ligand	1:1	17	82.67	1.85	11.10	90%

- With using purified ligand, 1:1 Pd catalyst:P-Ligand (3%) gave better impurity profile and higher solution yield than 1:2 ratio (3% Pd / 6% Ligand).

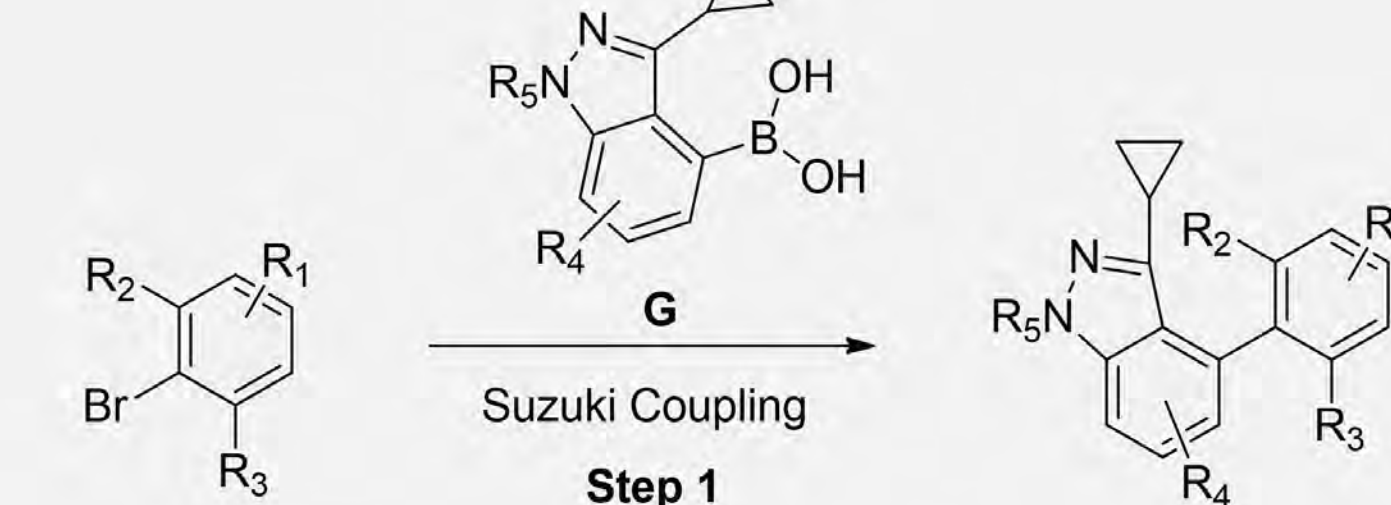
Kilo-Lab and Pilot Plant Scale-Up Results



Experiment	A (kg)	Time	IPC α% of Product F	Solution Yield
Kilo-lab	0.78	20	82.67	90%
Plant Batch 1	24.8	20	84.62	86%
Plant Batch 2	35.0	18	82.73	86%

- Using 1.10~1.15 equiv. of **G** and 1:1 $Pd(OAc)_2$: rac-Ant-Phos (3%), all the scale-up reactions were successful to give 82-85 α% purity of product **F** in 86% yield.

Summary



- Newly developed synthetic route using a sterically hindered Suzuki coupling reaction could avoid to use expensive and unstable raw material as well as two Pd catalyzed reactions.
- A High-Throughput-Screening technology was used to find out the best conditions.
- Different reaction parameters were investigated to solve an inconsistent reaction problem.
- Scale-up in kilo-lab and pilot plant were successful using optimized conditions.

Thank You.