Experiment 6: Synthesis of 3-(4-Methoxyphenyl)pyridine using Pd(Ph3)4

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We pledge our honor we have abided by the Stevens Honor Code.

Procedure

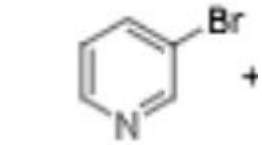
Preparation of Pyridylzincbromide reagent

1. Charge a 250 mL RBF with active zinc (9.81 g) in 100 mL THF
2. Add 3-Bromopyridine (15.8 g) to RBF via cannula while being stirred at room temperature
3. Stir mixture at refluxing temperature and monitor the oxidative addition by GC analysis
4. Let settle overnight and then transfer supernatant to 500 mL bottle
5. Dilute with 200 mL of THF

Coupling of Pyridylzincbromide with 4-iodoanisole

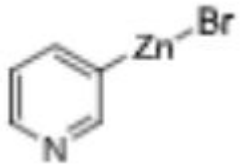
1. Add 0.10 g of $Pd[P(Ph_3)]_4$ to a 50 mL RBF
2. Add 20 mL of solution from part A and 1.80 g of 4-Iodoanisol dissolved in 10 mL THF
3. Stir at room temp for 1 hour then quench with saturated NH_4Cl solution
4. Extract with 30 mL of ethyl acetate, 3 times
5. Wash organic layers with saturated $NaHCO_3$ and brine
6. Dry with anhydrous $MgSO_4$
7. Use flash column chromatography (20%EtOAc/80% heptane)

Flow Chart

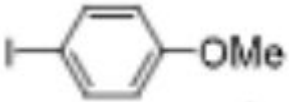


3-bormopyridine + Zn

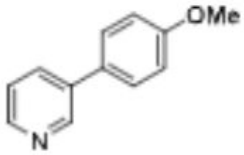
THF, reflux



Pyridylzincbromide



$Pd(PPh_3)_4$, 4-iodoanisole, THF



3-(4-Methoxyphenyl)pyridine

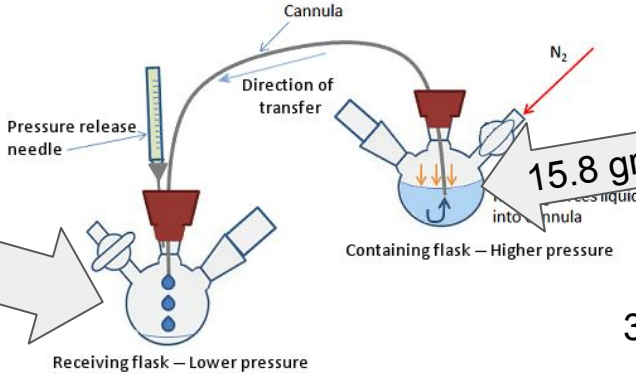
Preparation of Pyridyl Zinc Bromide reagent

1. Charge a 250 mL round bottom flask with 9.81 g zinc in 100 mL THF
2. Add 15.8 g 3-bromopyridine via cannula while being stirred at room temp.

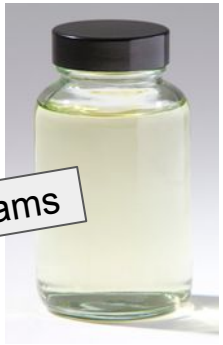
Zinc

9.81 grams

100 mL



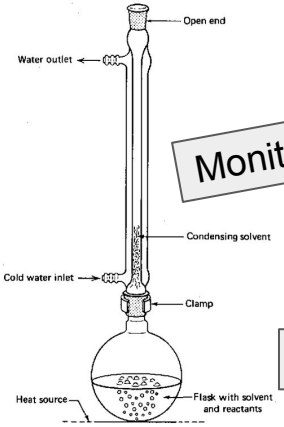
Stir mixture



3-bromopyridine

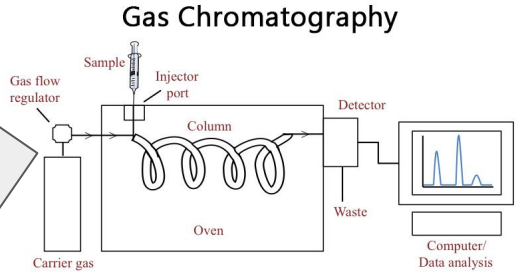
Preparation of Pyridyl Zinc Bromide reagent

3. After addition, continue to stir at refluxing temperature, and monitor by GC analysis.
4. After being settled down overnight, transfer supernatant to 500 mL bottle and dilute with fresh THF to 200 mL.



Continue stirring

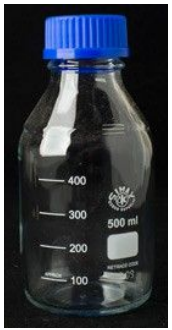
Monitor reaction



Let settle down overnight

Transfer liquid

Pyridyl Zinc Bromide solution

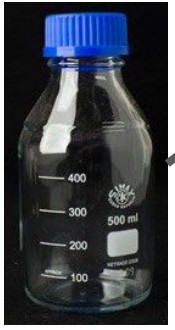


Dilute with THF up to 200 mL

Coupling of Pyridylzincbromide with 4-iodoanisole

1.80 g
4-Iodoanisole

0.10 g of $Pd[P(Ph_3)]_4$

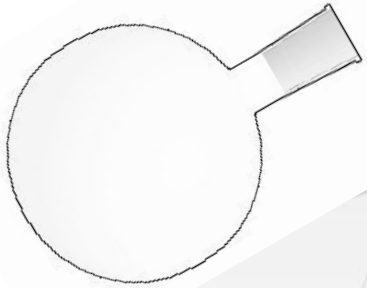


20 mL of solution from part A

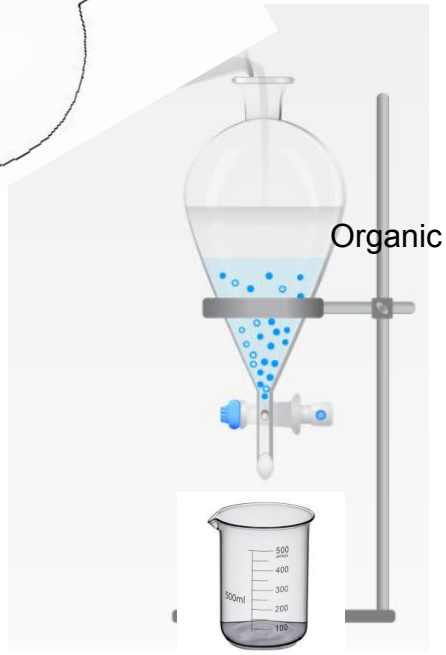
Stir at room temp for 1 hour

Quench with saturated NH_4Cl solution

Coupling of Pyridylzincbromide with 4-iodoanisole

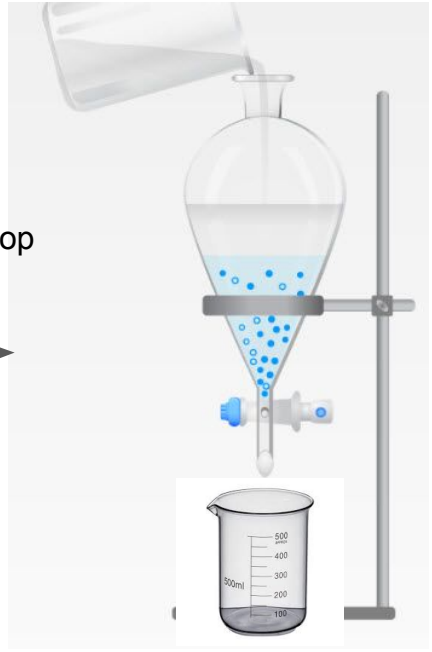


Extract with 30 mL of ethyl acetate, 3 times



Organic layer is top

Wash with $NaHCO_3$ and brine

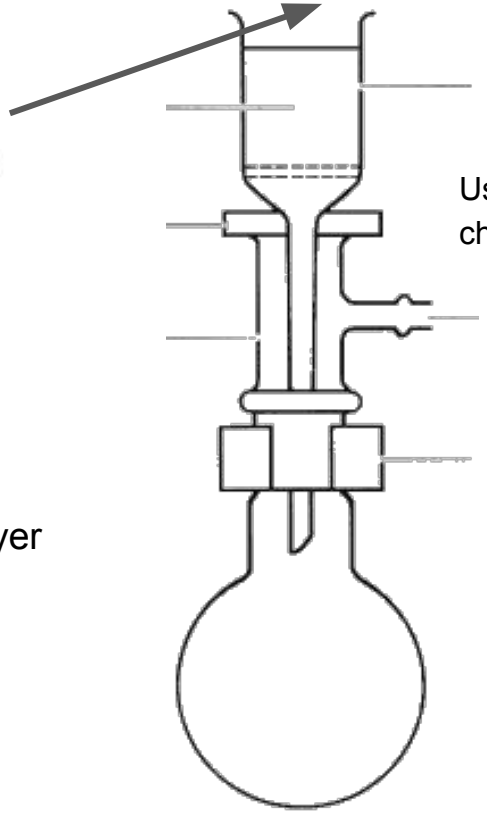


Add $MgSO_4$

Organic layer

Coupling of Pyridylzincbromide with 4-iodoanisole

Dried Organic layer



Use flash column chromatography

Conclusion

Accomplished: In this experiment 3-(4-methoxyphenyl)pyridine was synthesized from 3-bromopyridine, zinc, and 4-iodoanisole using a Negishi coupling reaction with the Pd(Ph3)4 catalyst.

Learned: Through this experiment we learned how to synthesize 3(-40methoxyphenyl)pyridine using the Negishi coupling reaction. We also learned how to use cannulation to transfer reagents between flasks under an inert atmosphere.

Issues: Potential issues can arise if cannulation was not performed properly. Pd(Ph3)4 is highly sensitive to air, thus any errors within its usage can result in a skewed product.

Recommendations / Applications: The Pd(Ph3)4 catalyst is commonly used in Suzuki, Negeshi, and Heck coupling reactions. The Suzuki coupling reaction in particular is a scalable and cost effective process to produce intermediates for pharmaceuticals and fine chemicals. The coupling reaction requires common boronic acids which are less toxic and safer to the environment.

Post Lab Questions

1) List one advantage of using Arylzinc compounds compared to aryllithium or Grignard reagents for coupling reactions.
   a) One advantage of using aryl zinc compounds over aryl lithium or grignard reagents is that they are less reactive, this is useful when partial reactions are desired, such as partial alkylation.
2) Give an example of another palladium containing catalyst and reaction involving that catalyst.
   a) Another palladium catalyst is palladium(II) acetate which can be used for the Heck Reaction, as