technique of the week

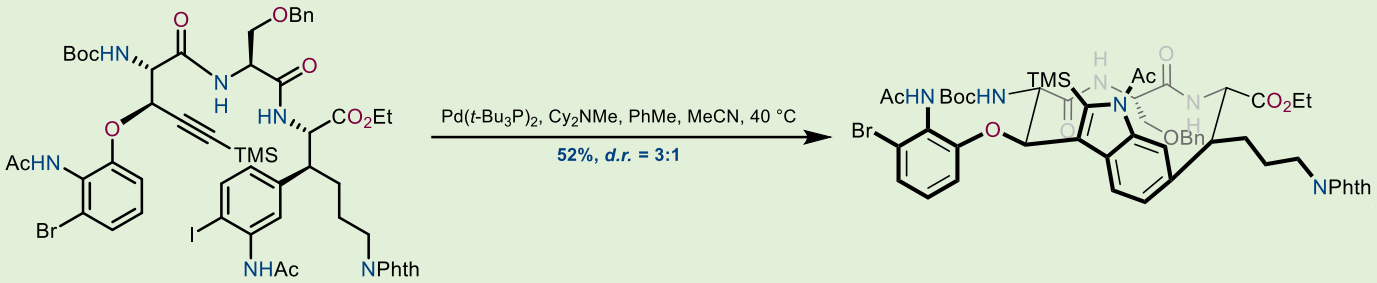
Larock Annulation

The SARLAH Group

A Brief Overview of the Reaction

- The Larock indole synthesis is a Pd-mediated annulation featuring an ortho-halogenated aniline and a di-substituted alkyne.
- The reaction was developed in the early 1990's by Richard Larock's group and has seen extensive usage in synthesizing indoles through both inter and intra-molecular heteroannulation.
- Generally, the regioselectivity is governed by steric congestion around the substituted alkyne in intramolecular variations.
- Within intermolecular variations, substrate bias with often dictate regioselectivity.
- We've run this reaction numerous times in the Sarlah lab, predominantly in the pursuit of our total synthesis of darobactin A.

The Reaction Being Highlighted



- This reaction affords a 3:1 ratio of indole atropisomers which were isolable by column chromatography.
  - This highlights a halogen-selective intramolecular Larock indole synthesis.

- It is important upon the completion and reconcentration of the reaction, to perform a wash with a Pd scavenger or filter through a resin intended to remove excess Pd, as it is extremely difficult to remove otherwise with these complex peptides!

Key Tips

- Freshly distill your base, degas it thoroughly for 30 minutes while sonicating under argon, and then store it under inert conditions.
- Regularly degas solvents stored under argon in a Schlenk bulb to ensure reproducibility.
- Avoid checking the reaction by LCMS too frequently, as collecting samples risks exposure to oxygen. The Pd catalyst utilized is extremely air sensitive!
  Many Larock Annulations are run in a single solvent, however, for solubility purposes ours required a solvent mixture.

A General Prep for this Reaction

To a flask containing tripeptide 19 (1.0 equiv.) was added Pd(t-$Bu_3P)_2$ (1.1 equiv.) under argon. Dry and degassed MeCN (0.0015M) was cannulated into the flask. Subsequent addition of Cy_2NMe (1.3 equiv.) was followed by cannulation of dry and degassed PhMe (0.003M) into the flask. The resulting solution was sonicated for 1 minute to dissolve Pd(t-$Bu_3P)_2$ and Cy_2NMe and obtain a homogeneous solution. The reaction mixture was heated to 40 ˚C and left to stir for 5 hours at this temperature. Upon completion (determined by HPLC analysis), the crude reaction mixture was frozen using a liquid nitrogen bath and the solvent was removed on the lyopholizer. The resulting residue was redissolved in DCM (0.0075M) and the resulting solution was washed with saturated aqueous sodium thiosulfate (0.015M) and 1 M aqueous HCl (0.015M). The organic layer was transferred to a flask and stirred with an aqueous solution of N-Ac-Cys-OH (10 equiv. in 0.015M aqueous solution) for 1 hour. The mixture was transferred to a separation funnel and the organic layer was separated and washed with brine (0.015M). Upon drying with $MgSO_4$ and removal of the solvent in vacuo, the obtained residue was purified by flash column chromatography.

Larock, R. *J. Am. Chem. Soc.* **1991**, 113, 17, 6689–6690. https://doi.org/10.1021/ja00017a059

Nesic, M. *J. Am. Chem. Soc.* **2022**, 144, 31, 14026–14030. https://doi.org/10.1021/jacs.2c05891

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Hints from the Reaction Color

- **Side Notes:** As mentioned previously, do not check reaction too frequently by TLC or LCMS as this will risk exposure to air!
- **Side Notes:** Use a fresh septum to assure the best seal (wrapping in parafilm or electrical tape after establishing inert atmosphere is recommend)

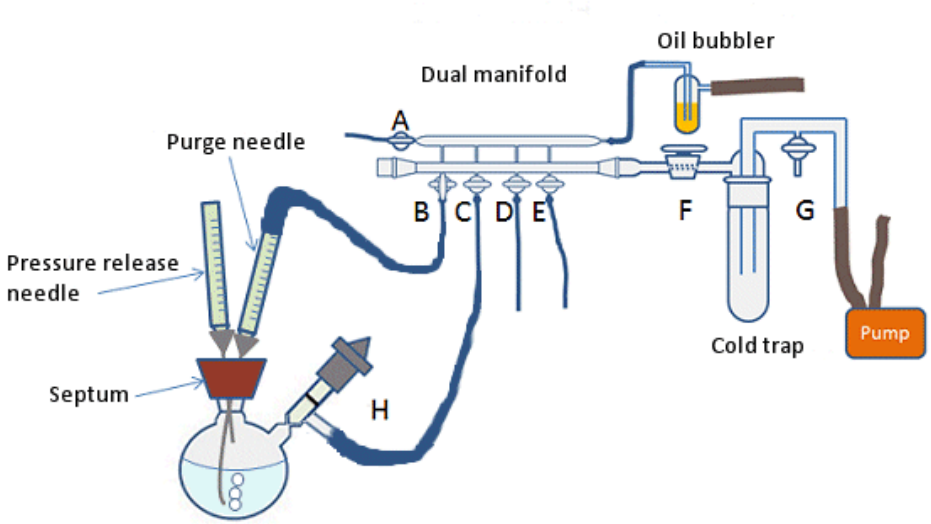
- Upon initial setup, reaction should be a relatively light solution (substrate dependent)

- **Tip:** If reaction turns black, your Pd has likely been oxidized.

- Upon completion, solution should become a brownish color

- **Side Notes:** Check reaction for the appearance of precipitate. Sometimes complex peptides can be tricky to solubilize!
- **Side Notes:** When reconcentrating mixture, check the before and after by TLC or LCMS. Lyophilizing off solvent was necessary to avoid decomp in certain systems

Degassing Solvents Properly



Lyophilizing the Solvent

- First, freeze the solution in a round bottom flask with liquid N_2
- Next, wrap the round bottom in cotton and aluminum foil before attaching to the lyophilizer
- Allow a few hours to lyophilize (volume and solvent dependent)