Preparation of Enantioenriched Carbastannatranes for Use in Stereospecific Stille Cross-Coupling Reactions

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Abstract

- The advancement of transition metal-catalyzed cross- coupling reactions has significantly impacted the approach to synthesizing complex organic molecules. Numerous methods now exist for forming C(sp2)-C(sp2) bonds, with recent efforts focused on utilizing C(sp3) electrophiles and nucleophiles. However, incorporating secondary and tertiary alkyl nucleophiles into cross-coupling reactions has been challenging due to the tendency of these alkyl groups to undergo isomerization during the reaction.

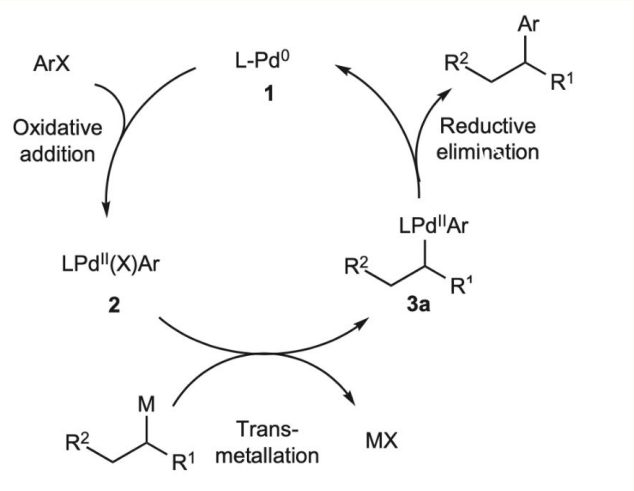
- The goal of this study is to expand the utility of Pd- catalyzed stereospecific Stille cross-coupling reactions developed in the Biscoe lab, while gaining laboratory skills necessary for future extensions of this chemistry. The experiments focused on preparation of cross-coupling products via a stereoretentive reaction mechanism.

Introduction

- Cross-coupling reactions occur when two reagents, both with activating groups, react together with a metal catalyst to form a new covalent bond, driven by loss of the activating groups.

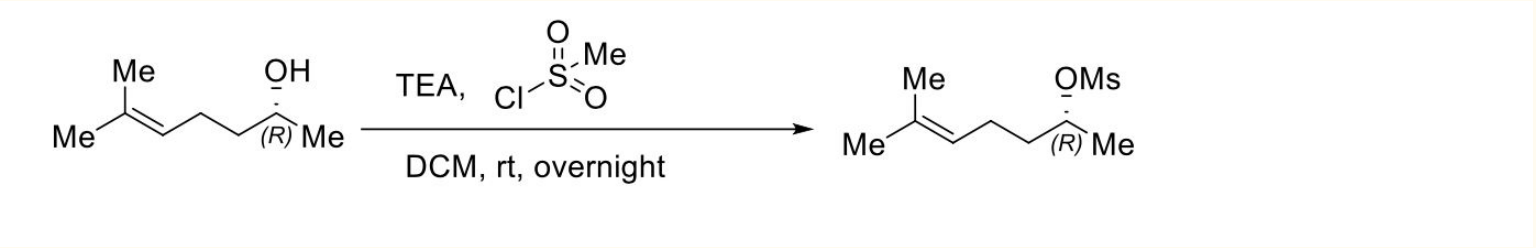
- Classical cross-coupling reactions are named based on the type of nucleophile used.

- The Stille coupling uses organostannane as a nucleophile in the transmetalation step. The tin is usually bound to allyl, alkenyl, or aryl groups. During transmetallation, the tin and the R' group will form a four-member ring with the palladium center and the halide, forming an 18-electron transition state. Then the tin halide will leave and the R' group stays bonded to palladium.

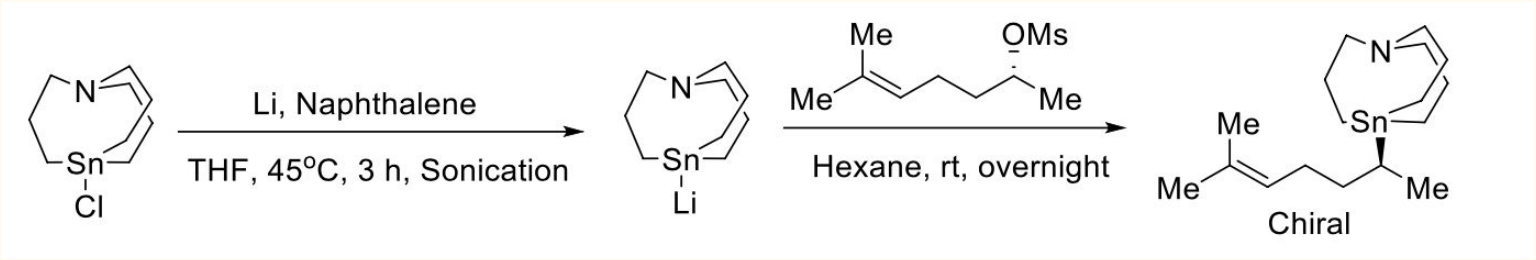


Method

- **The 2° alkyl mesylate**

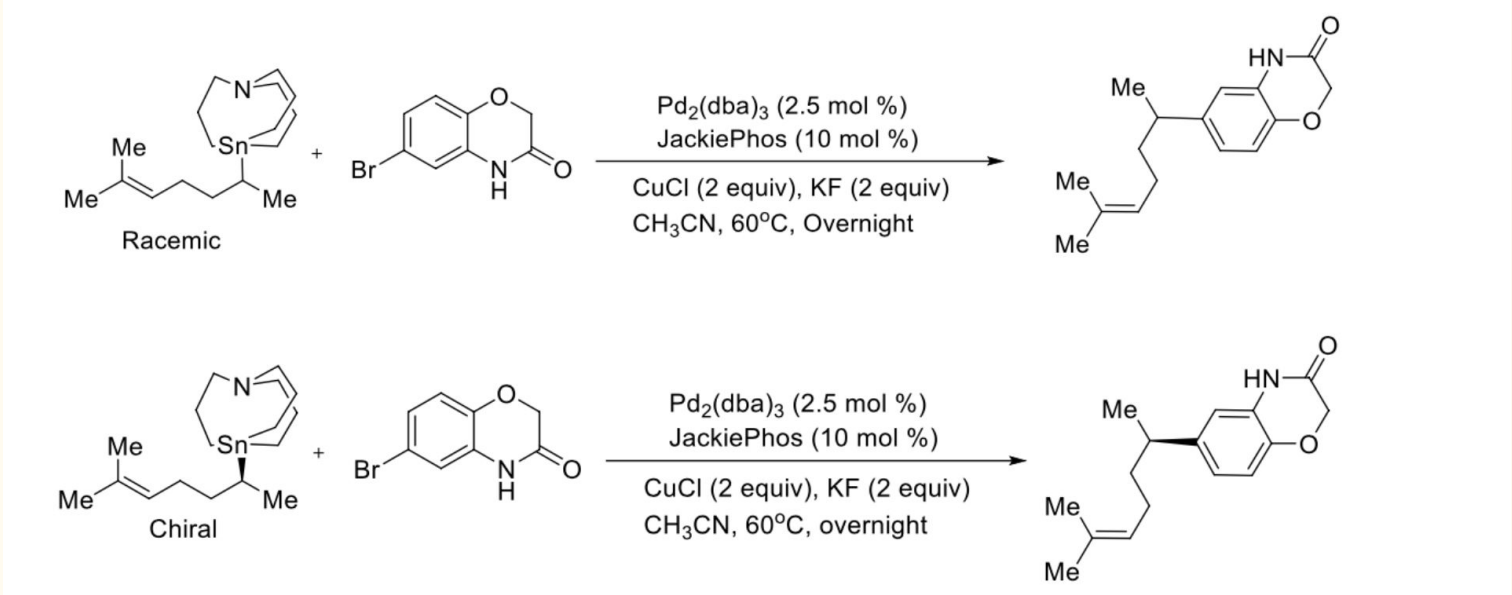


- **Carbastannatranyl lithium solution and preparing the enantioenriched and racemic alkyl carbastannatrane via carbastannatranyl anion**



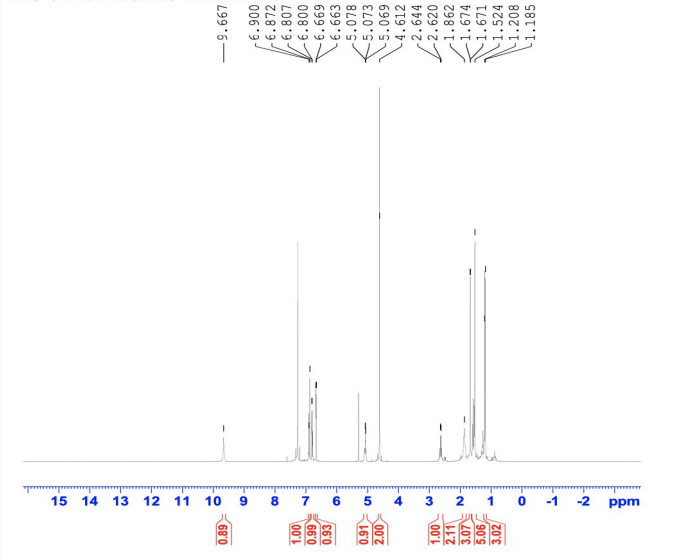
Method

- **Preparing the cross-coupling reactions with aryl electrophiles**

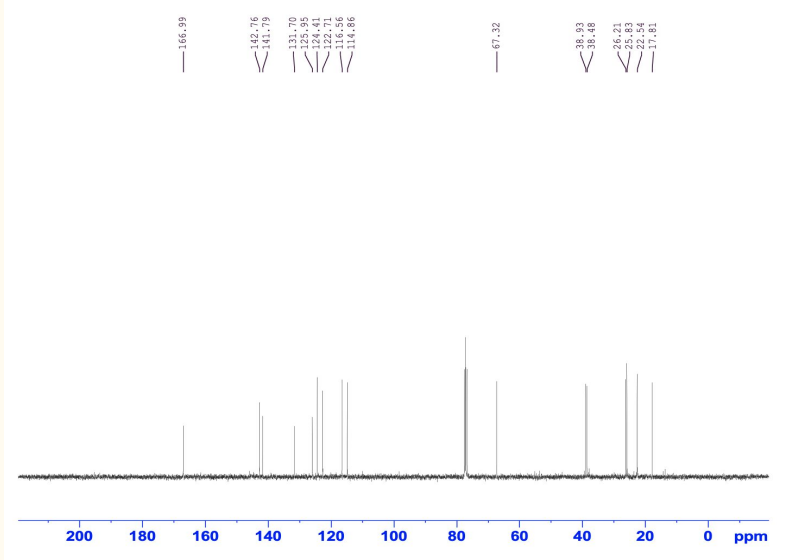


Results

- Overall, after the cross-coupling reaction
  - There was 75% yield for the racemic reaction.
  - For the chiral retention reaction there was 80% yield and 95% ee.



Proton (1H) NMR



Carbon (13C) NMR

Conclusion

- **Overall, data from the previous study was able to successfully reproduced. The ligand JackiePhos was used to ensure that the reaction was retention, enantioenriched products retained the stereochemistry. Furthermore, NMR data was compared to the data reported on the literature, to further support the data. The next part of the experiment is to focus on the inversion, where the stereochemistry is inverted. Although, the research is not yet complete a new ligand MaPhos would ensure that the reaction is inversion. Another approach is to use ortho addition electrophiles.**

References

- Li, Ling; Wang, Chao-Yuan; Huang, Rongcai; Biscoe, Mark R.* "Stereoretentive Pd-Catalyzed Stille Cross-Coupling Reactions of Secondary Alkyl Azastannatranes and Aryl Electrophiles." Nat. Chem. 2013, 5, 607-612.

- Li, Ling; Biscoe, Mark R.* "Alkylzinc Cross-Coupling Reactions." In Cross-Coupling and Heck-Type Reactions, Vol. 1; Molander, G., Ed.; Georg Thieme Verlag HG: Stuttgart, 2013, pp 795-837.

- Li, Ling; Zhao, Shibin; Joshi-Pangu, Amruta; Diane, Mohamed; Biscoe, Mark R.* "Stereospecific Pd-Catalyzed Cross-Coupling Reactions of Secondary Alkylboron Nucleophiles and Aryl Chlorides." J. Am. Chem. Soc. 2014, 136, 14027-14030.

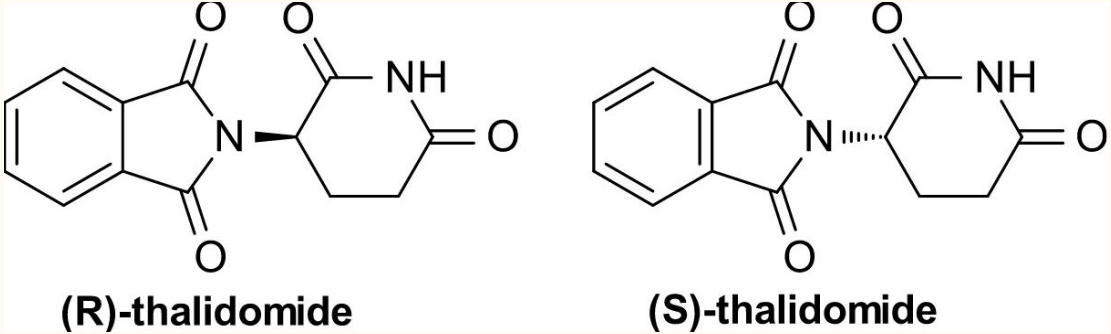
- Ma, Xinghua; Murray, Benjamin; Biscoe, Mark R.* "Stereoselectivity in Pd-Catalyzed Cross-Coupling Reactions of Enantioenriched Nucleophiles." Nat. Rev. Chem. 2020, 4, 584- 599

- Ralph, Glenn; Biscoe, Mark R.* "Preparation of Enantioenriched Alkylcarbastannatranes via Nucleophilic Inversion of Alkyl Mesylates for Use in Stereospecific Cross-Coupling Reactions." Organometallics 2019, 38, 3912-3915.

- Wang, Chao-Yuan; Ralph, Glenn; Derosa, Joseph; Biscoe, Mark R.* "Stereospecific Pd-Catalyzed Acylation of Alkylcarbastannatrane Reagents: A General Alternative to Asymmetric Enolate Reactions." Angew. Chem. Int. Ed. 2017, 56, 856-860.

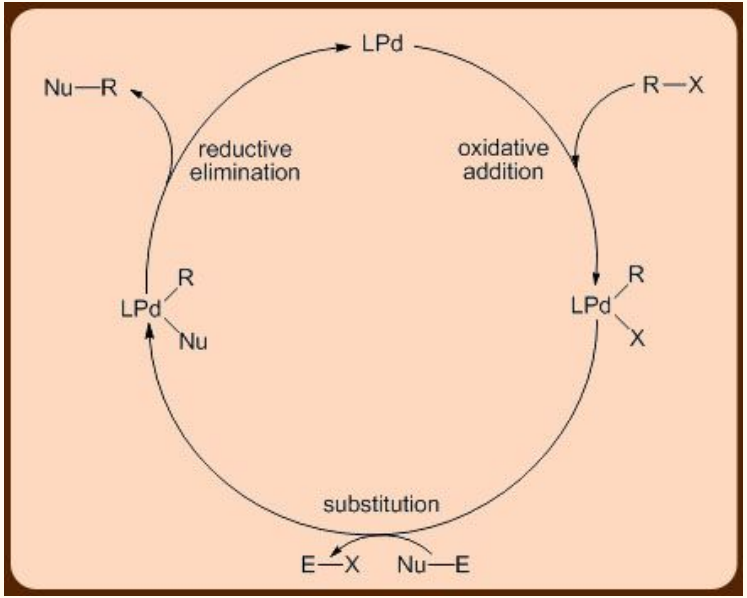
Significance

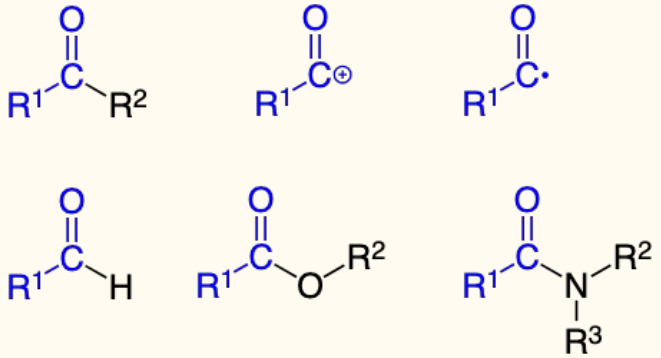
- **Enantiomers** - Same chemical formula but exists in two forms that are **mirror images** of one another
- Each enantiomer may serve different purpose
    - Thalidomide
- Preserves Stereochemistry



Method

1. Cross-coupling reaction
    - when two fragments are joined together with the aid of a metal catalyst
2. Acyl Chain
    - R-CO
3. Combine electrophile, nucleophile, Jackie Phos Ligand, Lindlar catalyst (or Lindlar's Palladium), CuCl, KF and appropriate solvent (Acetonitrile)
4. Use GC, NMR to confirm the product and HPLC to confirm the enantiomer





Method

Preparation of 2° alkyl mesylate:

General procedure A for the preparation of racemic alkylcarbastannatrane via carbastannatranyl anion:

General procedure B for the preparation of enantioenriched alkylcarbastannatrane via carbastannatranyl anion:

General procedure C for arylation/acylation cross-coupling reactions with organic electrophiles:

Pd(dba)2 (5 mol %, 2.9 mg for 0.1 mmol scale), JackiePhos (10 mol %, 8 mg for 0.1 mmol scale), CuCl (2 equiv, 20 mg for 0.1 mmol scale) and KF (2 equiv, 11.6 mg for 0.1 mmol scale, NO KF for acylation reaction) were weighed out on the

Figure S15. 6-(6-Methyl-5-hepten-2-yl)-2H-1,4-benzoxazin-3(4H)-one (14f). General procedure C was employed using 5-(6-methyl-5-hepten-2-yl)-1-aza-5- stannabicyclo[3.3.3]undecane and 4-bromo-2H-1,4-benzoxazin-3(4H)-one on a 0.1 mmol scale. A white crystalline solid was obtained (19.5 mg, 90% yield) after column chromatography (0% to 25% ethyl acetate in DCM). The enantioenriched product was obtained using (S)-5-(6-methyl-5-hepten-2-yl)-1-aza-5-stannabicyclo[3.3.3]undecane. 1H NMR (300 MHz, CDCl3) δ: 8.25 (s, 1H), 6.89 (d, J = 8.4 Hz, 1H), 6.79 (d, J = 6.3 Hz, 1H), 6.60 (d, J = 2.0 Hz, 1H), 5.07 (m, 1H), 4.60 (s, 2H), 2.63 (m, 1H), 1.86 (m, 2H), 1.57 (t, J = 7.5 Hz, 2H), 1.52 (s, 3H), 1.19 (d, J = 6.9 Hz, 3H) ppm. 13C NMR (75 MHz, CDCl3) δ: 166.1, 142.8, 141.8, 131.8, 126.0, 124.4, 122.8, 116.7, 114.5, 67.5, 39.0, 38.5, 26.1, 25.9, 22.6, 17.8 ppm.