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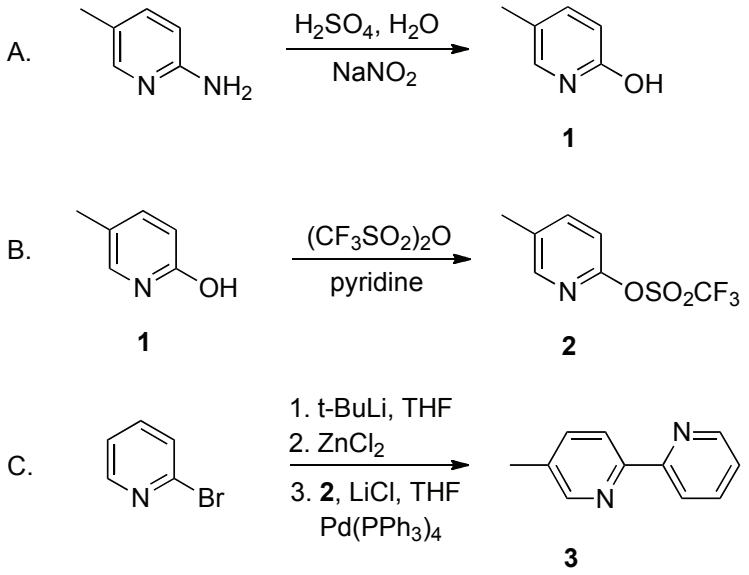
Discussion Addendum for: Synthesis of 4-, 5-, and 6-Methyl-2,2′-Bipyridine by a Negishi Cross-Coupling Strategy: 5-Methyl-2,2′-Bipyridine



Prepared by Tiandong Liu and Cassandra L. Fraser*.[1]

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Negishi coupling is a powerful tool in the preparation of bipyridines due to its high yield, mild conditions and relatively low cost.[2,3] It shows good tolerance to various substituents and the corresponding pyridyl zinc halide precursors can efficiently couple with many halogen-substituted heterocycles in addition to pyridine.[4] In recent years, some other palladium-catalyzed reactions, such as Stille and Suzuki coupling, have emerged to make pyridine derivatives.[5-7] Recent progress in palladium-catalyzed coupling reactions between pyridyl and other heterocycles will be discussed.

Advances in Bipyridine Synthesis via Negishi Coupling

Negishi reactions require aryl zinc halides and suitable coupling partners (Figure 1). The pyridyl zinc halides can be achieved by transmetallation with pyridyl lithium[2,3,8-10] or direct reaction between pyridyl halides and active zinc (Zn*).[11] For nearly quantitative yields, (trifluoromethane-sulfonyl)oxypyridine reagents are an excellent choice for coupling partners.[2,3] Many recent reports, however, employ pyridyl halides,

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which are more accessible. Chloro,[8,9,12] bromo[10,11,13] and iodo substituted compounds[11,14] are good coupling agents in Negishi[11] reactions; whereas, fluoro reagents are typically inert.

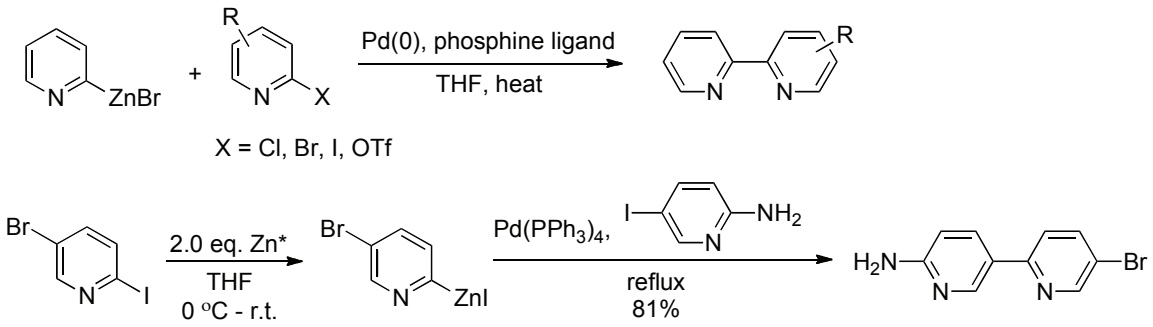

Figure 1. General example of preparation of bipyridines by Negishi coupling between pyridyl zinc reagents and pyridyl halides or triflates, and illustration of selectivity in zinc reagent preparation and halide coupling.

Generally, aromatic iodides are more reactive than bromides and chlorides, however bromides are most commonly employed.[15] Halides at the 3-position can also participate in the coupling reactions to provide 2,3′-bipyridines, but their reactivity is less than that of 2-halopyridines.[11] This allows for selective coupling at the 2-halo site in the presence of dihalo-substituted pyridines (Figure 2).

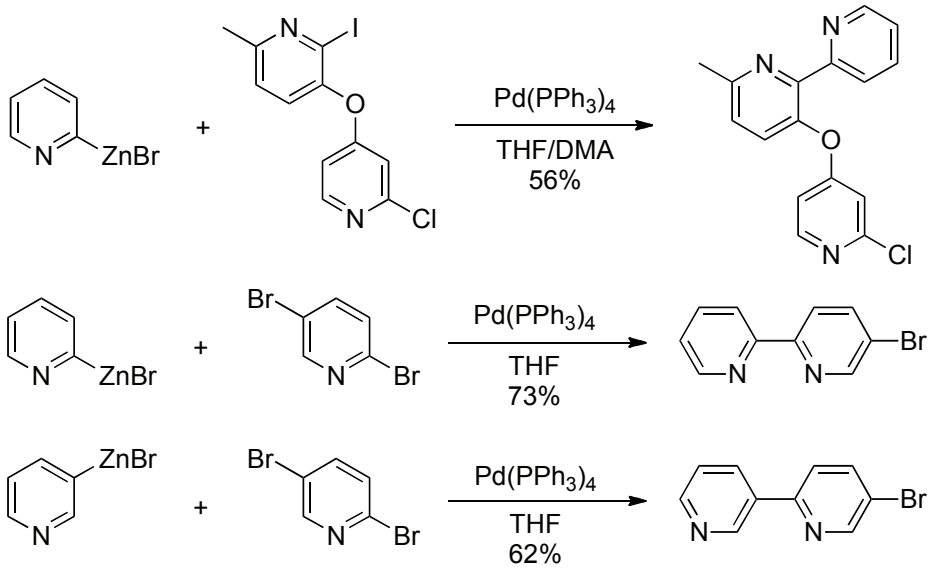

Figure 2. Chemoselectivity and regioselectivity in Negishi coupling in the preparation of bipyridine complexes.

Negishi coupling shows impressive tolerance of various functional groups, including alkyne, CN, COOR, NO_2, NR_2, OR, OH, and TMS.[8,9,11] This enables further functionalization of 2,2′-bipyridines (Figure 3).

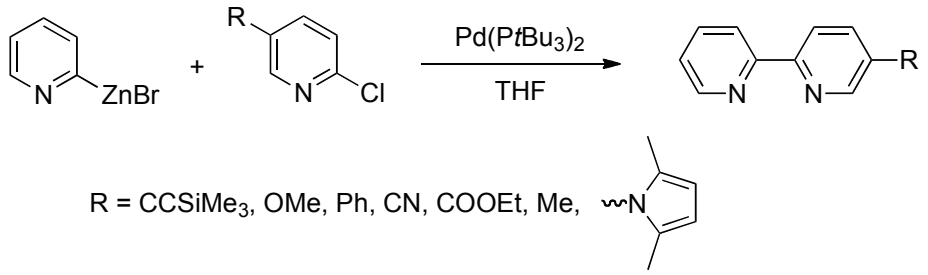

Figure 3. Functional group tolerance in Negishi cross coupling.

Bipyridines Prepared by Stille and Suzuki Coupling

Other palladium catalyzed coupling reactions can also be used to prepare 2,2′-bipyridine derivatives (Figure 4).[16] Stille coupling can provide various bipyridine compounds with moderate to good yields. The challenge with this method is that coupling reactions usually have to be carried out in toluene under refluxing conditions for a couple days. Heat sensitive compounds may not be tolerant of this method.[17-20] Additionally, toxicity is a concern for tin reagents. Due to the difficulty of obtaining stable 2-pyridylboron coupling precursors,[21] Suzuki coupling was not used in making 2,2′-bipyridine compounds until recent years. The relatively high catalyst loadings could also limit its applications in organic synthesis.[22]

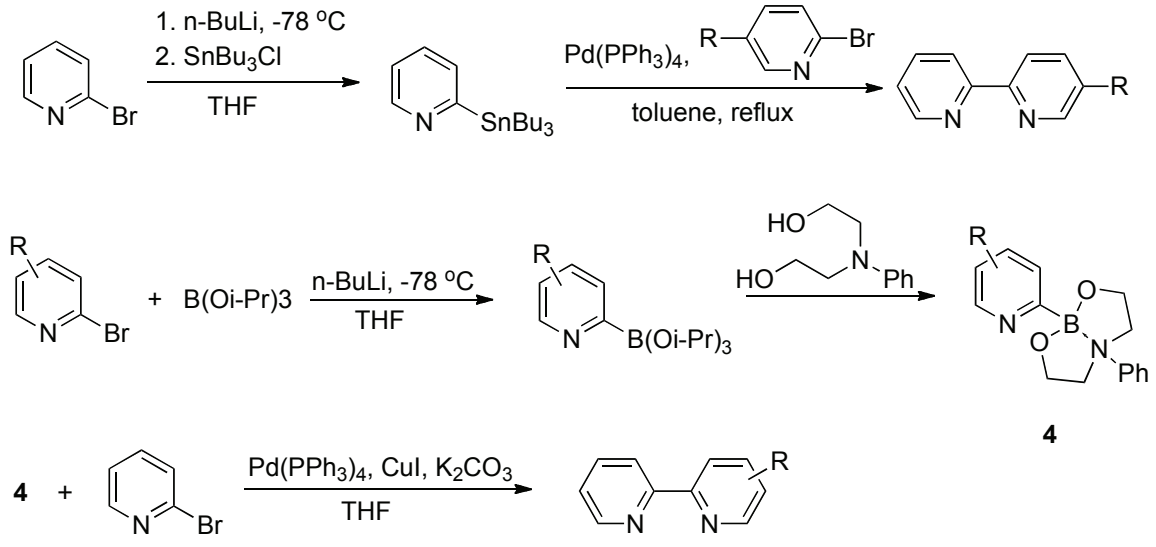

Figure 4. Preparation of 2,2′-bipyridine by Stille and Suzuki coupling.

Negishi Coupling of Other Pyridyl Heterocyclic Compounds

Among heterocycles containing pyridine units, terpyridine complexes have received considerable attention due to their strong binding affinity with many metal ions.[23] Negishi coupling is a common method to prepare terpyridine derivatives.[24] Pyridyl zinc halide can react with a great many halide heterocycles to generate products with pyridine moieties.[11,14] Sometimes high regioselectivity was observed[25] (Figure 5).

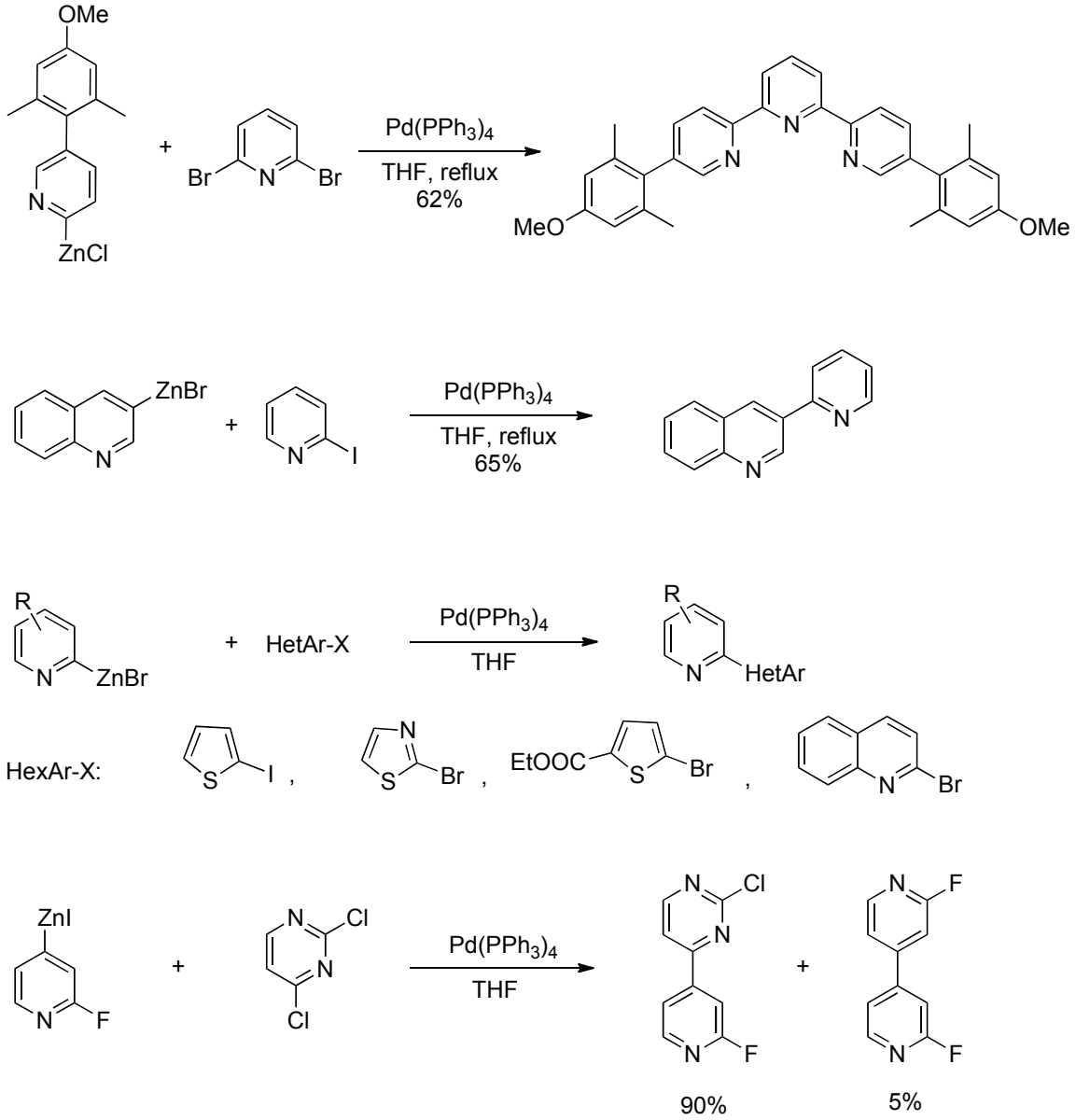

Figure 5. Preparation of biheterocycles containing pyridine from Negishi coupling.

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Cassandra L. Fraser was born in Norfolk, Virginia in 1962 and grew up in Michigan. She obtained a B.A. degree from Kalamazoo College in 1984, an M.T.S. degree from Harvard Divinity School in 1988, and a Ph.D. from The University of Chicago in 1993 with Brice Bosnich. After postdoctoral research with Robert Grubbs at Caltech from 1993-5, she joined the faculty in the Department of Chemistry at the University of Virginia, where she was promoted to Associate Professor in 2001 and Professor in 2005, now with joint appointments in Biomedical Engineering and Architecture. Her research involves luminescent materials for imaging and sensing in biomedicine and sustainable design.

Tiandong Liu was born in Nanjing, China in 1979. He obtained a B.S. degree from Nanjing University in 2001. He began his graduate work at the University of Virginia with Lin Pu exploring enantioselective luminescent sensors for chiral carboxylic acids in 2006 and in 2010 joined the Fraser group to explore boron complexes with optical oxygen sensing and mechanochromic luminescence properties.