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of Reliable Methods
for the Preparation
of Organic Compounds

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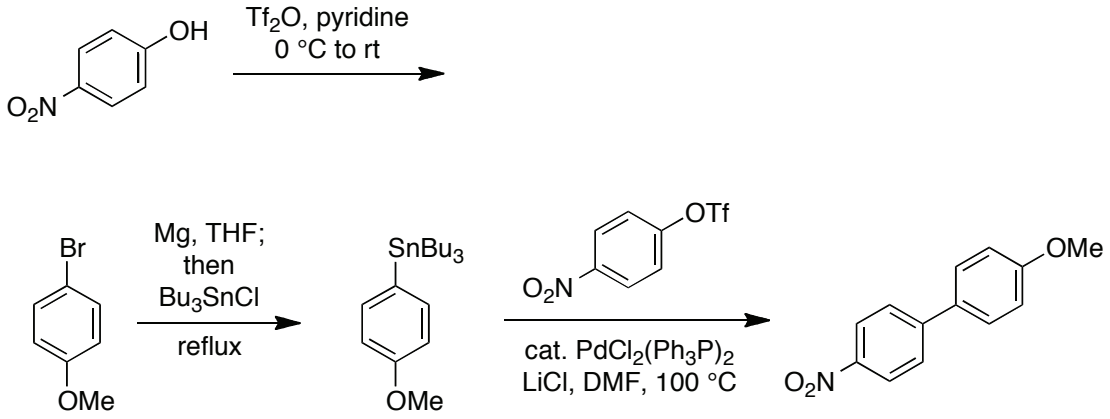
September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

Discussion addendum for:

4-METHOXY-4'-NITROPHENYL. RECENT ADVANCES IN THE STILLE BIARYL COUPLING REACTION AND APPLICATIONS IN COMPLEX NATURAL PRODUCTS SYNTHESIS



Prepared by Robert M. Williams.*[1]

Original article: Stille, J.[2]; Echavarren, A.; Hendrix, J.; Albrecht, B.[3]; Williams, R.[1] *Org. Synth.* **1993**, *71*, 97.

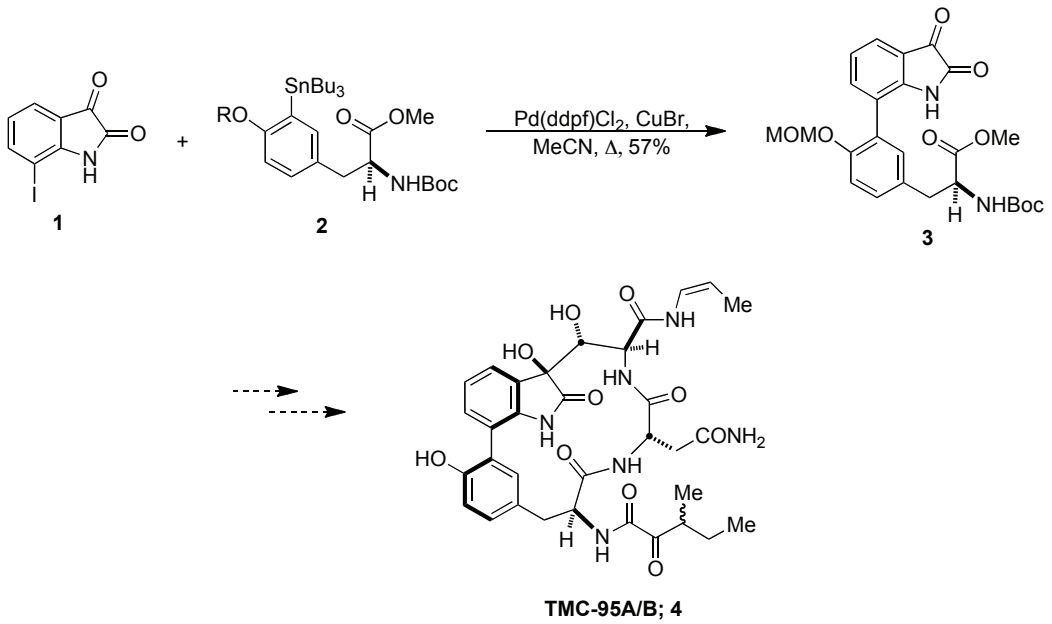
The use of the palladium-catalyzed Stille cross-coupling reaction[4] for the synthesis of biaryls has become a popular and practical method[5] mainly due to the air and moisture stability of organostannanes, the wide functional group compatibility under the reaction conditions and the generally readily available starting materials. Since the initial *Organic Syntheses* report of the preparation of 4-methoxy-4'-nitrophenyl,[6] numerous advances have been made regarding substrate scope, improved reaction conditions and catalyst design. Herein we report on some of these advances[7] as well as recent applications in total syntheses.[8]

The majority of the recent advances of the Stille coupling have come concomitantly with the advancement of ligand design for palladium catalysis.[9] The advent of electron rich, bulky phosphine and carbene ligands allowed for much milder reaction conditions and increased substrate scope. Initially, the Stille reaction was limited to aryl iodides, bromides and triflates, typically at elevated temperature. In 1999 Fu and co-workers reported the first general method for the Stille cross-coupling of aryl chlorides using tri-*t*-butyl phosphine as a ligand for palladium and cesium

Published on the Web 2/3/2011

fluoride to activate the tin reagent.[10] More recently, Fu and co-workers have shown that similar reaction conditions can be utilized to cross-couple arylbromides at room temperature. In an analogous manner, Verkade and co-workers have shown that proazaphosphatrane ligands behave in a similar manner to the tri-*t*-butyl phosphine system utilized by Fu.[11] Finally, Baldwin and co-workers have shown that the inclusion of copper(I) salts[12] to the conditions reported by the Fu group significantly enhanced the reactivity of a variety of aryl bromides.

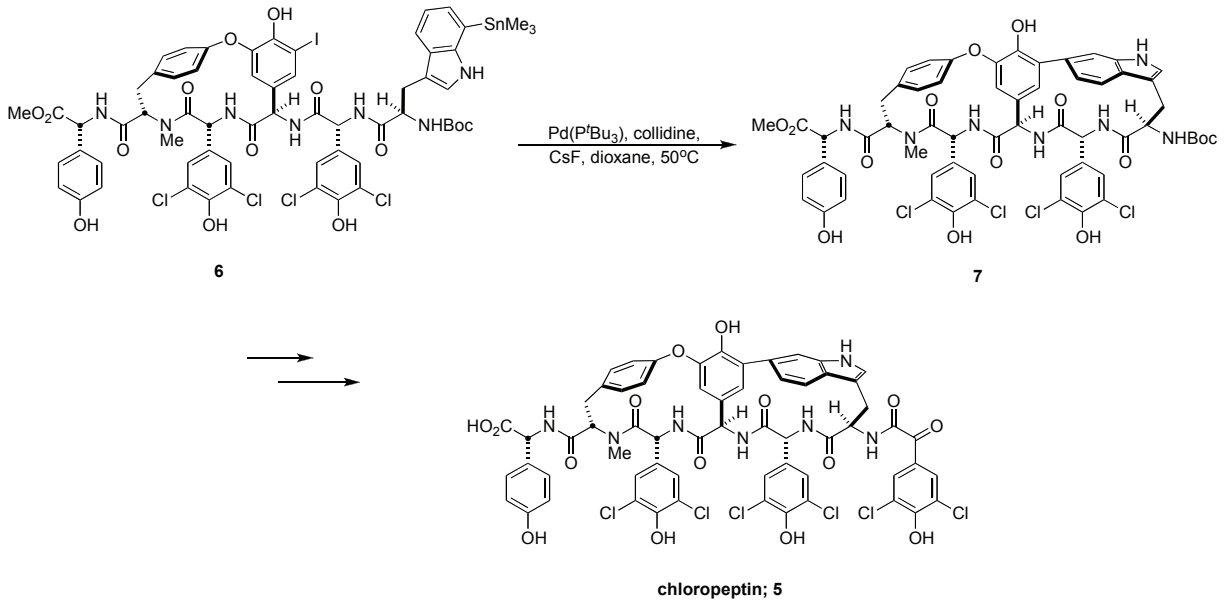
The Stille reaction has contributed significantly to numerous applications in the total synthesis of complex natural products because of the chemical stability of the coupling partners, the mild reaction conditions, and the functional group compatibility. In 2001, we reported a Stille coupling of 7-iodoisatin **1** and a suitably protected stannyl tyrosine derivative **2** (Scheme 1).[13] Treatment of these coupling partners under routine conditions afforded biaryl **3** as a model system towards the total synthesis of TMC-95A/B (**4**).



Scheme 1. Albrecht and Williams' Studies toward TMC-95A/B

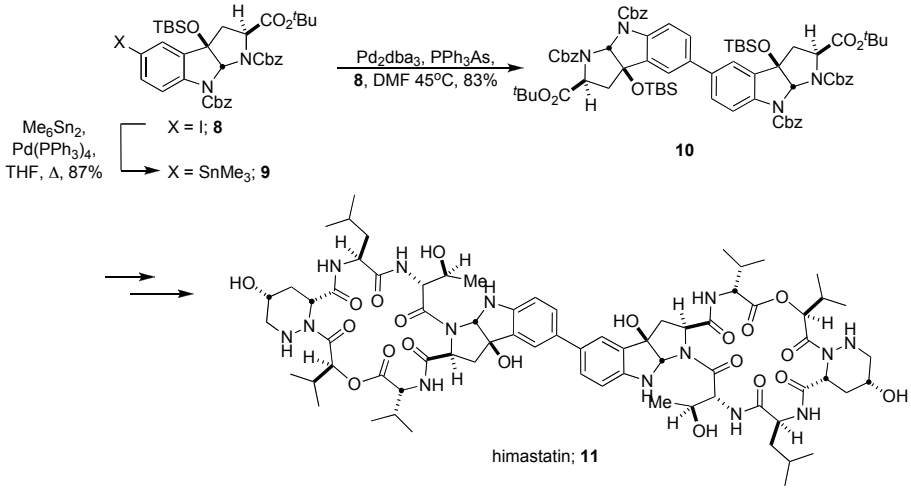
In 2003, the Hoveyda and Snapper labs utilized a Stille biaryl coupling as a key macrocycle-forming reaction to provide a 17-membered ring in the total synthesis of chloropeptin **5**.[14] Macrocyclic precursor **6** was treated under the conditions reported by Fu, in the presence of collidine forming macrocycle **7** (Scheme 2). It is thought that the presence of collidine in the reaction stabilizes the active palladium complex thus

preventing palladium black precipitation. The completion of chloropeptin was accomplished in an additional two steps.



Scheme 2. Hoveyda and Snapper's total synthesis of chloropeptin.

Danishefsky and co-workers utilized a Stille biaryl coupling in the total synthesis and stereochemical revision of himastatin.[15] Stannylation of aryliodide **8** afforded stannane **9** which was resubjected to aryliodide **8** under standard Stille conditions to afford dimer **10** (Scheme 3). This advanced biaryl intermediate was ultimately converted to himastatin thus allowing for the correct stereochemical assignment.



Scheme 3. Danishefsky's total synthesis of himastatin.

Since its first report, the Stille coupling has been a widely utilized carbon-carbon bond forming reaction. Recent advancements in homogenous palladium catalysis have rendered the Stille coupling reaction a much more attractive approach to the synthesis of complex biaryl systems. The examples above fully support the versatility and utility of this simple biaryl coupling reaction to highly functionalized and sterically demanding substrates. Efforts towards optimizing the Stille[16] protocol are continuously being pursued allowing for milder reaction conditions and increased substrate scope. These on-going efforts demonstrate that the Stille reaction is one of the most synthetically useful biaryl coupling reactions in the synthesis of complex molecules.[17]

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11, 3294-3308. In addition to the inclusion of copper(I) salts a solvent change from dioxane to DMF was made.
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14. Deng, H.; Jung, J-K.; Liu, T.; Kuntz, K.W.; Snapper, M.L.; Hoveyda, A.H. *J. Am. Chem. Soc.* **2003**, *125*, 9032-9034.
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16. Although not relevant to biaryl couplings the following are some noteworthy reports of Stille couplings catalytic in tin and of alkyl halides. For cross-couplings catalytic in tin see Gallagher, W.P.; Maleczka, R.E. *J. Org. Chem.* **2005**, *70*, 841-846, and references cited therein. For cross-coupling of alkyl halides see ref. 1b and references cited therein.
17. The work performed at Colorado State University was financially supported by the National Institutes of Health and the National Science Foundation.

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