

Palladium-Catalyzed Cross-Coupling Reactions of Aryl Halides on Sulfur Compounds



Biography

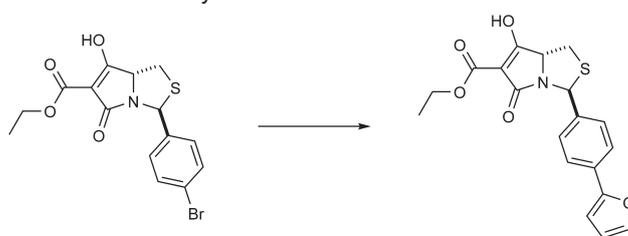
Tharindi Panduwawala graduated with a BSc (Hons) in Chemistry from the University of Colombo, Sri Lanka. She then moved to the UK to read for a DPhil in Organic Chemistry under the supervision on Prof. Mark G. Moloney at the University of Oxford. Her research work involves the synthesis of novel polar bicyclic tetramates for antibacterial drug discovery.

Institution

University of Oxford

Abstract

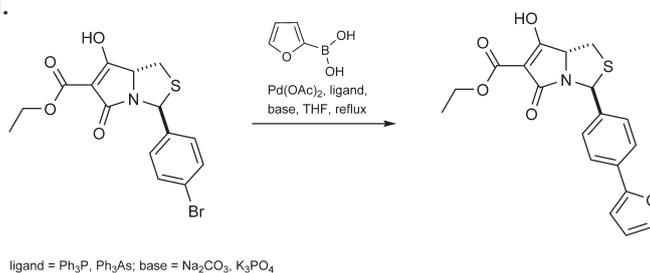
Our research work focuses on the development of a library of novel antibacterial compounds with tetramates as the core scaffold, accessed via a Dieckmann ring closure on a substituted thiazolidine ring. By adding diversity around this tetramate core, we can rapidly generate a library of tetramates which are then assayed for biological potency. We selected Suzuki–Miyaura cross coupling as one such route for library generation. Suzuki–Miyaura coupling is a widely used method for C–C bond formation between aryl or vinyl halides and organoboranes, catalyzed by palladium. It is known to employ mild and functional group tolerant reaction conditions, making it a favoured reaction in medicinal chemistry. Even though many examples can be found for C–C bond formation on thiazole-related compounds, Suzuki–Miyaura coupling on our thiazolidine systems (Scheme 1) is not common. Thus, finding the ideal reaction conditions to introduce aryl–aryl coupling on such systems with nonaromatic sulfur heterocycles was of key importance. Therefore, we referred to Thieme Chemistry's *Science of Synthesis* in order to find a solution to the problem associated with employing Suzuki–Miyaura coupling on our scaffold under study.



Scheme 1 Suzuki–Miyaura Coupling on a Thiazolidine

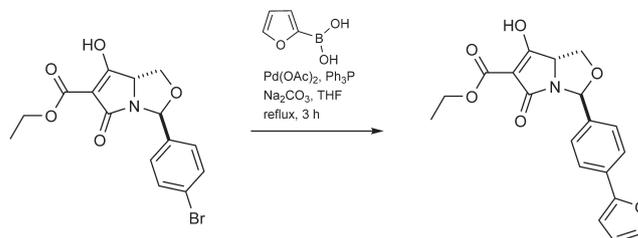
Discussion

Suzuki–Miyaura coupling of aryl bromides with organoboranes in the presence of triphenylphosphines/triphenylarsines as the ligand associated with palladium is well known. These ligands have been employed for C–C bond formation with aryl bromides on thiazole/thiophene systems and organoboranes to yield the desired product. Thus, in an initial investigation, we employed these conditions in order to introduce aryl–aryl coupling on our scaffold. (Scheme 2). However, even with prolonged reaction times, only starting material was isolated and no product was detected.



Scheme 2 Conditions for Suzuki–Miyaura Coupling on Our Thiazolidine Scaffold

Initially, we attributed the failure of this reaction to sulfur on the thiazolidine ring chelating to the palladium catalyst, thereby preventing oxidative addition. This hypothesis was proven correct when we tried Suzuki–Miyaura coupling on the oxazolidine equivalent (Scheme 3), which proceeded satisfactorily to give the desired product.



Scheme 3 Suzuki–Miyaura Coupling on the Oxazolidine Equivalent of Our Thiazolidine Scaffold

Thus, in order to find the ideal reaction conditions for such nonaromatic sulfur-containing heterocycles, we did a literature search for palladium-promoted cross-coupling on *Science of Synthesis*, which gave us a very well written review on “Palladium-Promoted Cross-Coupling Reactions” (Section 42.10.1.1.1) which included a discussion on useful ligands and complexes for cross coupling. The discussion included the use of dialkyl-(biphenyl-2-yl)phosphines as excellent ligands for Suzuki–Miyaura coupling and how the catalytic activity of palladium associated with these ligands can be improved by steric and electronic modifications on the phenyl rings of these ligands. The review was concise, but included a thorough discussion of palladium-mediated catalysis and importantly contained a list of phosphine ligands with the range of yields obtained for each and references to the relevant articles from which the original data was abstracted; to source this information from the primary literature would have been very time consuming but presupposed a good knowledge of the area at the outset to provide a suitable start point. This discussion gave some strong possibilities for ligands we could employ for Suzuki–Miyaura coupling on thiazolidine systems, and on experimentation, we found that replacing triphenylphosphine with XPhos gave a very effective coupling reaction.

Conclusion

Thieme Chemistry’s *Science of Synthesis* is an excellent resource for reliable procedures in organic synthesis. It is very convenient to search for procedures and the contents can be easily accessed online. It is indeed time saving, as the search provides expert reviews into the type of reaction under investigation and gives a coherent summary of reaction conditions published with the relevant references which can be referred to for further information. The review provided a comprehensive overview on the scope of the reaction conditions which helped us choose the optimum conditions more efficiently. With the help of *Science of Synthesis*, we were able to overcome a key issue relating to Suzuki–Miyaura coupling on thiazolidine systems. With this at hand, we now have the ability to rapidly generate a library of compounds using Suzuki–Miyaura coupling as the reaction of choice.