Palladium-Catalyzed Fluorination of Amino Acid Derivatives

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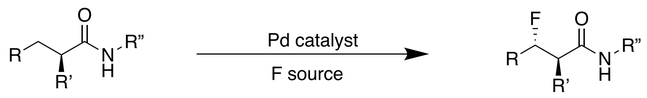
Abstract

The palladium-catalyzed fluorination of various substrates is an area of ongoing focus for organometallic chemists. In this literature review three papers on the palladium-catalyzed fluorination of amino acid derivatives were compared to each other to gain an understanding of the evolution of this fluorination methodology. The fluorination of amino acid derivatives is an important area of research due to the interest in incorporating fluorine moieties into natural products for pharmaceutical applications.

Introduction

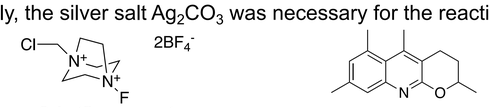
The ability to fluorinate organic compounds is an important synthetic tool due to the increased lipophilicity, metabolic stability, and bioavailability that installation of a fluorine moiety brings.[1] The development of fluorinating reactions has enabled scientists to achieve new and improved methods for late-stage fluorination of important synthetic targets. Palladium-catalyzed fluorination has emerged over the course of the past two decades to be a versatile and widely applicable methodology for the incorporation of fluoride into a variety of substrates.

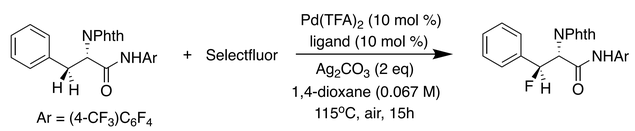


Using both electrophilic and nucleophilic fluorine sources, chemists have been able to successfully fluorinate substrates bearing a wide variety of functionalities with both regio- and enantioselectivity. Among the first efforts to create a palladium catalyzed methodology for fluorination involved the use of electrophilic fluorine sources. These sources included the popular reagent Selectfluor. Using these electrophilic reagents, a variety of substrates were successfully fluorinated, including arylboronic acids, amino acid derivatives, aliphatic amines, benzylamines, and a variety of unactivated C-H bonds. Fluorinated amino acid derivative are important synthetic targets in medicinal chemistry, so methods of synthesizing them have been the subject of intense interest in recent years.

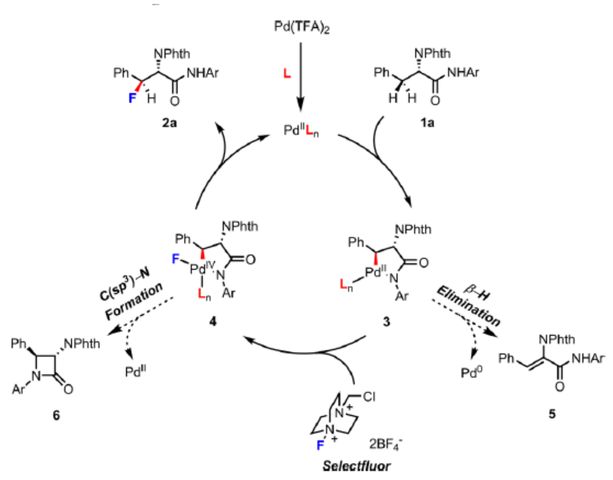
Discussion

A 2015 paper by Zhu et al was one of the first works to demonstrate a catalytic C-H activation and fluorination in amino acids.[2] The researchers first arylated the beta position of the amino acid and then, using Selectfluor as the electrophilic fluorine source and a Pd(II) ligated catalyst, fluorinated the arylated beta position. Interestingly, the silver salt Ag_2CO_3 was necessary for the reaction to proceed.

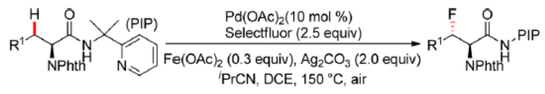


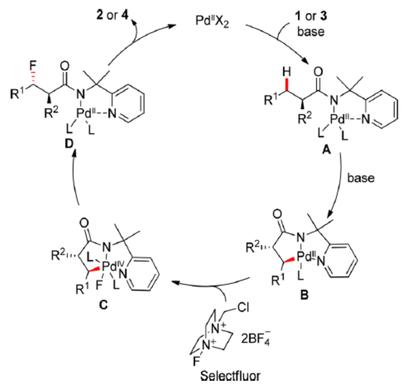


A range of amino acid derivatives were fluorinated stereo- and regiospecifically. The authors were particularly pleased by the ability of this reaction to create beta-fluoroalanine in good yield, which is an important compound with the ability to interfere in the formation of bacterial cell walls.



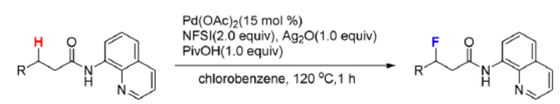
In another 2015 paper by Miao et al, the beta position of amino acid derivatives and aliphatic amides was fluorinated stereospecifically.[3] As in the prior paper, the addition of stoichiometric amounts of the silver salt Ag_2CO_3 significantly improved the reaction yield. The authors theorize that this silver salt acts as a base and helps coordinate the substrate to the palladium catalyst during a ligand exchange step, and then assists in the C-H bond cleavage necessary for the fluorination to take place. Once again, Selectfluor was used as the F^+ source for the reaction.



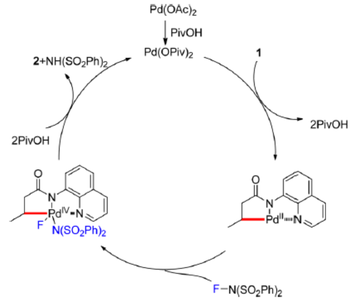


The reaction conditions for this C(sp3)-H activation reaction are very similar to those in the paper by Zhu. Both reactions are highly diastereoselective and regioselective and proceed through a similar Pd(II/IV) catalytic cycle.

Published at nearly the same time as the works of Zhu and Miao, a paper by Xu and coworkers aimed to create beta-fluorinated carboxylic acids.[4] The addition of an acid source was necessary to avoid a competing reaction that resulted in the formation of C-N bonds instead of C-F bonds.



The fluorination of these carboxylic acid derivatives did not achieve any stereoselectivity. However, the authors were able to difluorinate certain cyclic substrates. The fluorination of linear carboxylic acids had better yield than the fluorination of branched derivatives.



Conclusions

The development of palladium-catalyzed methodologies for the fluorination of amino acid derivatives provides chemists with useful techniques for late-stage fluorination of target molecules in drug development.

References

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Acknowledgments

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