

# Computer-Driven Development of Ylide Functionalized Phosphines for Palladium-Catalyzed Hiyama Couplings

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Palladium-catalyzed couplings of silicon enolates with aryl electrophiles are of great synthetic utility, but often limited to expensive bromide substrates. A comparative experimental study confirmed that none of the established ligand systems allows to couple inexpensive aryl chlorides with  $\alpha$ -trimethylsilyl alkyl nitriles. In contrast, ylide functionalized phosphines (YPhos) led to encouraging results. A statistical model was developed that correlates the reaction yields with ligand features. It was employed to predict catalyst structures with superior performance. With this cheminformatics approach, YPhos ligands were tailored specifically to the demands of Hiyama couplings. The newly synthesized ligands displayed record-setting activities, enabling the elusive coupling of aryl chlorides with  $\alpha$ -trimethylsilyl alkyl nitriles. The preparative utility of the catalyst system was demonstrated by the synthesis of pharmaceutically meaningful  $\alpha$ -aryl alkyl nitriles,  $\alpha$ -aryl carbonyls and biaryls.

Phosphonium Group  
Steric Demand  
Secondary Interactions



Z Substituent  
Electronic Properties  
Flexibility of the Ligand  
Structure

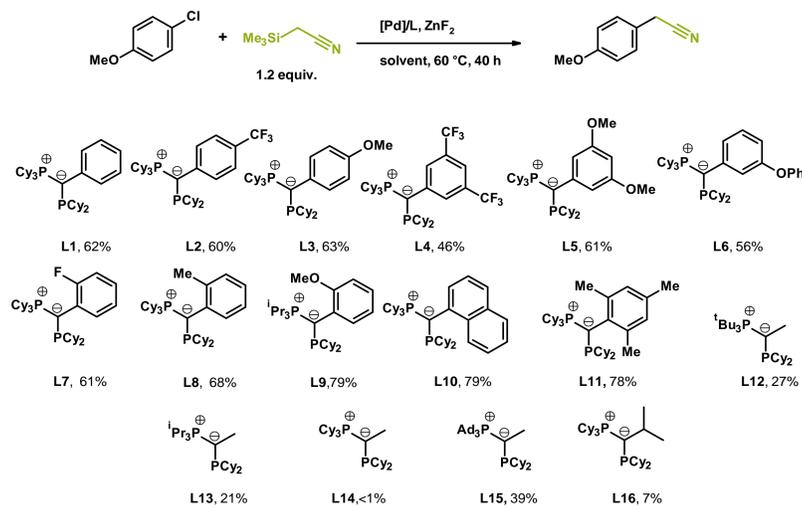
inverse-catalyst design

High Yields  
High Selectivities  
14 New Ligands

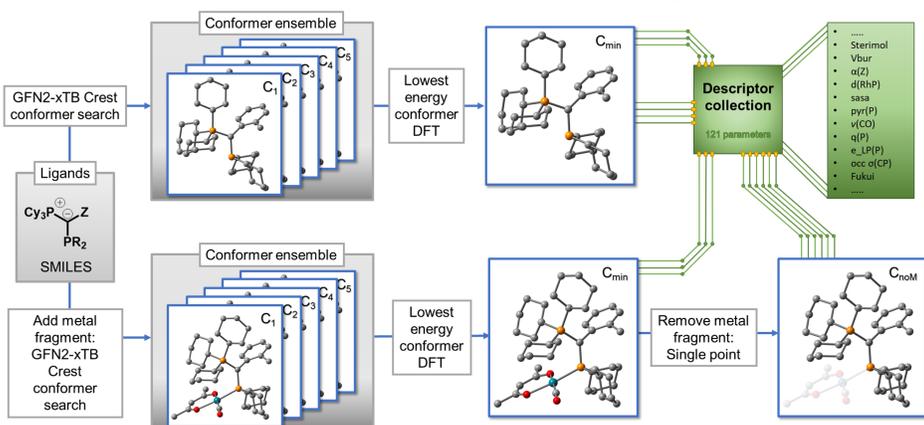
## Introduction

Palladium-catalyzed coupling reactions have become indispensable tools in organic synthesis for the construction of C–C and C–heteroatom bonds.<sup>[1]</sup> Strong nucleophiles such as Grignard reagents or organo-zinc compounds are easily accessible and highly reactive, but they can be difficult to handle and tend to react with functional groups. Especially for applications in drug discovery and late-stage functionalizations, mild nucleophiles such as silicon-based reagents are advantageous. However, Hiyama couplings are somewhat less developed, and thus many useful reactions, such as the coupling of  $\alpha$ -trimethylsilyl alkyl nitriles with aryl halides, are underdeveloped and only possible with expensive aryl bromides.<sup>[2]</sup> We have now tackled this problem by establishing a quantitative structure-activity relationship between ligand features and yield in a test reaction using a statistical model and cheminformatics. This approach allowed us to develop a general protocol for the Hiyama coupling of aryl chlorides with various nucleophiles.<sup>[3]</sup>

## Screening with YPhos-Training Set



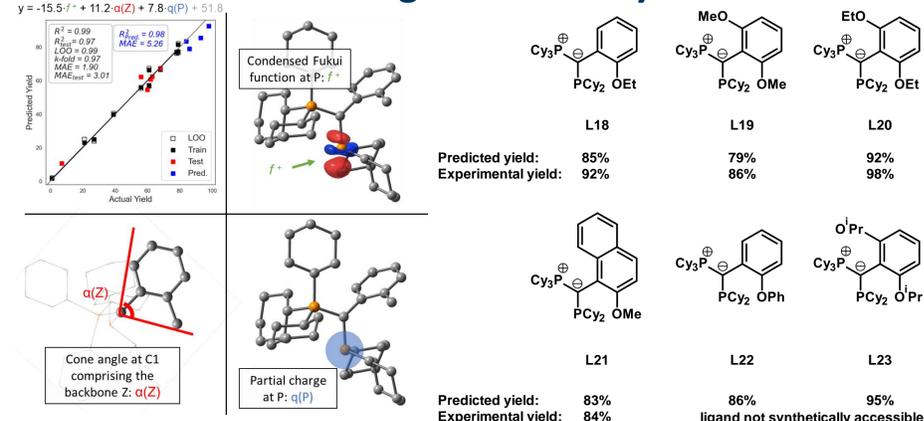
## Workflow of Parametrization of the Ligands



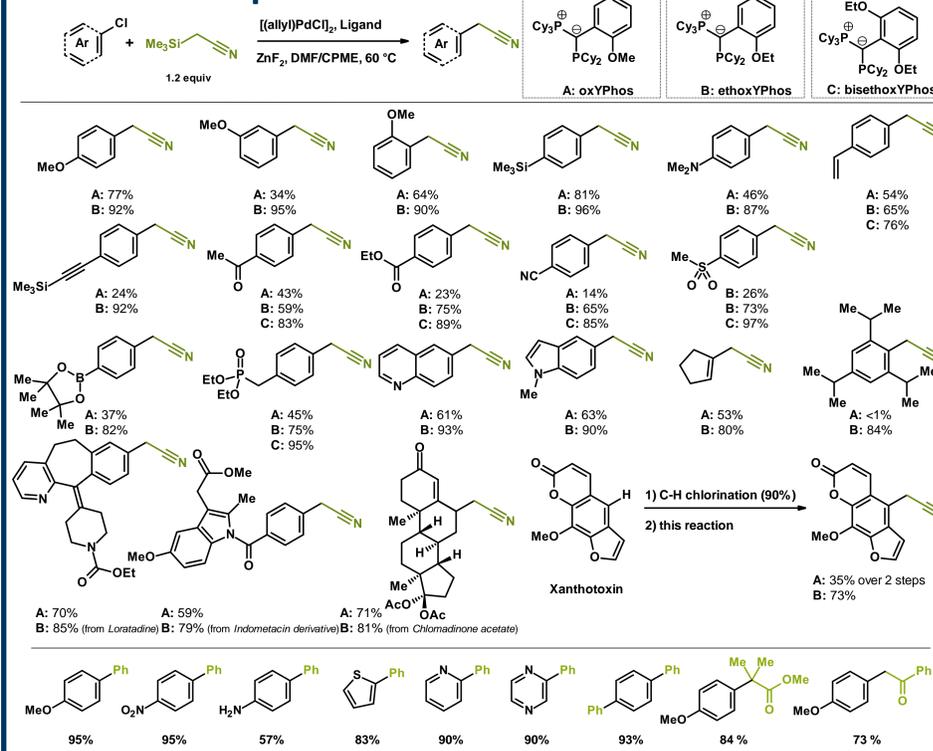
## References

- [1] A. O. King, N. Yasuda, *Organometallics in Process Chemistry*, Vol. 6, **2004**, pp. 205–245
- [2] a) S. E. Denmark, R. F. Sweis, *Acc. Chem. Res.* **2002**, 35, 835–846; b) Y. Nakao, T. Hiyama, *Chem. Soc. Rev.* **2011**, 40, 4893–4901.
- [3] J. F. Goebel, J. Löffler, Z. Zeng, J. Handelsmann, A. Hermann, I. Rodstein, T. Gensch, V. H. Gessner, L. J. Gooßen, *Angew. Chem. Int. Ed.* **2023**, 135, e2022161.

## Multivariate Linear Regression Analysis Results



## Substrate Scope



## Conclusion

In conclusion, we have utilized virtual screening to tailor YPhos ligands specifically to the demands of Hiyama-couplings. Palladium catalysts bearing the newly developed ligand bisethoxyYPhos promote the coupling of aryl chlorides with  $\alpha$ -trimethylsilyl alkyl nitriles in excellent yields, a reaction that has been shown to be outside the scope of other ligand classes. The new protocol has made broad range of functionalized  $\alpha$ -arylalkyl compounds accessible from inexpensive aryl chlorides and easy-to-handle silicon reagents, opening up a window of synthetic opportunities for organo-silicon chemistry in late-stage functionalization and drug discovery.

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