

# Computational Approach to Develop Phosphoramidite Ligand Applied to Asymmetry Cycloisomerization and Conjugate Addition

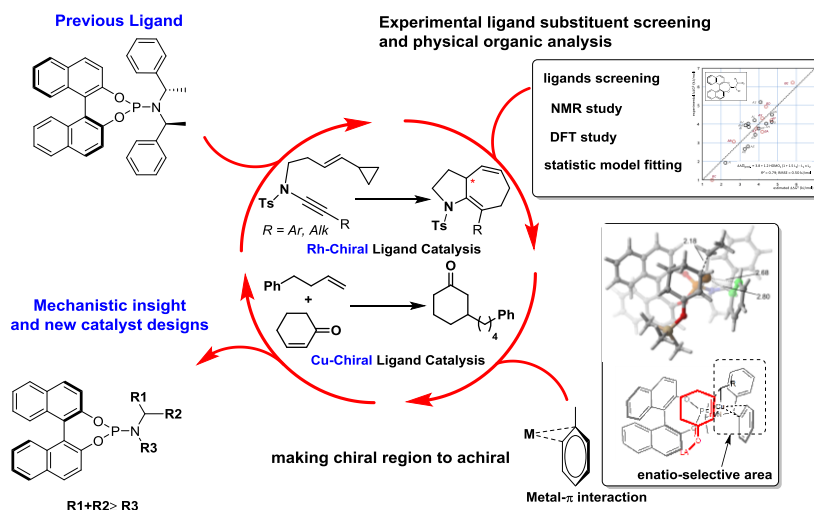
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Demand for higher efficiency, economy, and selectivity in the synthesis of novel molecular scaffolds drives organic chemistry. The development of modular chiral ligands has led to the discovery of several transition metal:ligand complexes that catalyze various reactions with impressive levels of enantioselectivity. However, discovery of the appropriate chiral ligands for a desired transformation remains a formidable task. This is especially true for reactions where detailed mechanistic data are yet to be uncovered. Computational understanding of the mechanism of catalyst-control can lead to improved understanding and guide synthetic effort. Recently, Sigman and coworkers<sup>[1]</sup> have combined physical organic and quantum chemistry with modern data analysis techniques to elucidate the underlying reaction mechanism, facilitating the rational design of more effective catalysts.



Through computational quantum chemistry we have explored how the structural elements of the phosphoramidite ligand affect catalyst structure and selectivity in Rh-catalysed asymmetry cycloisomerization (collaboration with Prof. Edward Anderson for experiments)<sup>[2]</sup> and Cu-catalysed conjugate additions (collaboration with Prof. Stephen Fletcher for experiments)<sup>[3]</sup>. Elucidation of the important interactions has been achieved by studying the effects of ligand-structural variation on both the catalyst structure and resulting enantioselectivity, through a combination of experimental and theoretical techniques. These studies illustrate the ability of quantitative structure-selectivity relationships to provide both models for asymmetric induction and catalyst structural hypotheses that may be further probed by experiment and computation. Collectively, such an approach leads to the rational modification/simplification of chiral ligands for more effective catalysts.

[1] Milo, A.; Neel, A. J.; Toste, F. D.; Sigman, M. S. *Science* **2015**, *347*, 737.

[2] Straker, R.; Peng, Q.\*; Mekareeya, A.; Paton, R. S.; Anderson, E. A. *Nat. Commun.* **2015** Accepted

[3] Peng, Q.; Roth, P. M. C.; Paton, R. S.; Fletcher, S. P. *will submitted* **2015**.