The Mechanistic Significance of the Si-O-Pd Bond in the Palladium-Catalyzed Cross-Coupling of Alkenyl- and Arylsilanolates

Andrea Ambrosi, Steven A. Tymonko, Russell C. Smith, Michael H. Ober, Hao Wang, Scott E. Denmark

Through the combination of reaction kinetics (both catalytic and stoichiometric), along with solution and solid state characterization of organopalladium(II) silanolates, and computational analysis, the intermediacy of covalent adducts containing Si-O-Pd linkages in the cross-coupling reactions of organosilanolates has been unambiguously established. Two mechanistically distinct pathways have been demonstrated: (1) transmetalation via a neutral 8-Si-4 intermediate; and (2) transmetalation via an anionic 10-Si-5 intermediate. In general, potassium salts of alkenylsilanolates react via neutral (8-Si-4) intermediates, whereas the enhanced nucleophilicity of the cesium alkenylsilanolates allows for the reaction to access the 10-Si-5 intermediate and proceed via the anionically activated pathway. However, if the direct transmetalation is slower, as in the case of arylsilanolates (which require interruption of aromaticity), then anionic activation via the 10-Si-5 intermediate becomes predominant. These conclusions mandate a revision of the reigning paradigm that organosilicon compounds must be anionically activated to engage in transmetalation processes (Hiyama-Hatanaka paradigm). Thanks to these studies, the mechanistic formulation for the cross-coupling of alkenyl- and arylsilanolates with aryl halides is now substantially understood.

A Prevalent Peptide-Binding Domain Guides Ribosomal Natural Product Biosynthesis

Brandon J. Burkhart and Douglas A. Mitchell

Ribosomally synthesized and post-translationally modified peptides (RiPPs) are a rapidly growing class of natural products. RiPP precursor peptides can undergo extensive enzymatic tailoring to yield structurally and functionally diverse products, and their biosynthetic logic makes them attractive bioengineering targets. Recent work suggests that unrelated RiPP-modifying enzymes contain structurally similar precursor peptide–binding domains. Using profile hidden Markov model comparisons, we discovered related and previously unrecognized peptide-binding domains in proteins spanning the majority of prokaryotic RiPP classes, and we named this conserved domain the RiPP precursor peptide recognition element (RRE). Through binding studies we verified the RRE's role in three distinct RiPP classes. Because RiPP biosynthetic enzymes act on peptide substrates, our findings have powerful predictive value as to which protein(s) drive substrate binding. Accordingly, this work lays a foundation for further characterization of RiPP biosynthetic pathways, the discovery of new RiPP clusters, and the rational engineering of new peptide-binding activities.