Subtle steric differences reveal a model for Ni cross-coupling success

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A new strategy for ligand design may enable challenging metal-catalyzed cross couplings reactions that are indispensable to drug development, according to a study published in *Nature Chemistry*. Based on subtle differences between ligand parameters, Princeton researchers have developed a predictive model for the success of a novel Ni-catalyzed cross-coupling reaction.

The widespread adoption of Pd-catalyzed cross-couplings, which has been recognized with the Nobel Prize, has been driven in large part by the extensive development of ligands, supporting molecules attached to the Pd center. Chemists have attempted to use these same ligands for cross-couplings promoted by Pd's cheaper sibling Ni with limited results.

Now, scientists in the Doyle lab have discovered a class of ligands capable of accessing new reactivity for Ni. These ligands, called phosphines, enabled the coupling of acetals with aryl boroxines to form valuable structures in medicinal chemistry known as benzylic ethers.

Given the molecules' unique framework, the team set out to parameterize the ligands' size and electronic properties, which can affect yield by crowding or pushing molecules off the metal center to accelerate bond forming reactions.

The researchers were surprised to find that two ligand size parameters, cone angle and buried volume, that are typically equated in the literature had distinct and pronounced effects on the reaction. "It's the first time

we saw this divergence between those parameters," said corresponding author Abigail Doyle, an associate professor of chemistry at Princeton University.

Cone angle measures the angle swept by an imaginary cone that enclosing the attached ligand group, while buried volume is the percent volume of a sphere occupied by a ligand. Buried volume is the newer measurement and useful for ligands like N-heterocyclic carbenes for which cone angle can't be calculated.

Put simply, cone angle works well for measuring distant ligands while buried volume is good for ligands that are nearby, said Kevin Wu, a graduate student in the Doyle lab and first author on the paper.

Wu tested the Ni-catalyzed reaction with more than a dozen phosphine ligands. Using the resultant reaction yields and calculated size parameters, he developed a ligand parameter regression model to correlate predicted yields to measured yields.

They found higher reaction yields for ligands with remote steric hindrance, that is molecules with bulky groups positioned far from the metal center. Their finding could help explain why ligands designed for Pd aren't as effective on the smaller Ni atom, which has shorter metal-phosphine bond lengths.

Using their model, the team calculated the yield for three ligands and found that two of their predictions came close to the actual reaction yield. They also demonstrated good to high yields for a range of benzylic ether forming cross-couplings.

In the future, the researchers hope to improve methods for calculating parameters which currently assumes the lowest energy conformations of ligands instead of their dynamic reality. They also want to further apply

models to tease out correlations between ligand parameters and the activity of elementary steps in the catalytic mechanism.

"It was really satisfying that parameterization let us confirm our hypothesis about the ligands," Wu said.

More information: Kevin Wu et al, Parameterization of phosphine ligands demonstrates enhancement of nickel catalysis via remote steric effects, *Nature Chemistry* (2017). DOI: 10.1038/nchem.2741

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