Predicting phosphine reactivity with one simple metric

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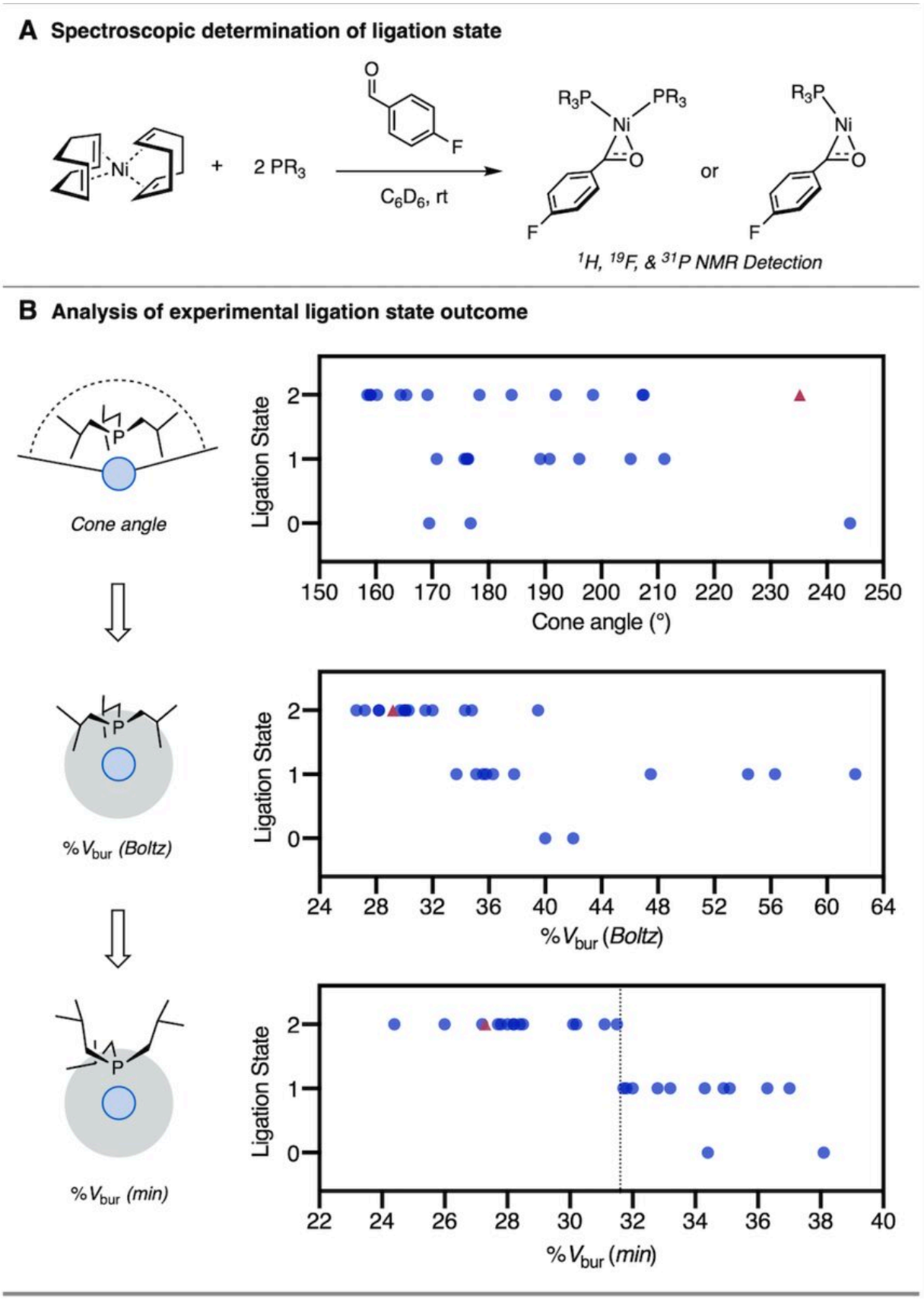
A Spectroscopic determination of ligation state
Ni
+ 2 PR3
O
F
C6D6, rt
R3P
PR3
Ni
O
F
or
R3P
Ni
O
F
1H, 19F, & 31P NMR Detection
B Analysis of experimental ligation state outcome
P
Cone angle
Ligation State
2
1
0
150 160 170 180 190 200 210 220 230 240 250
Cone angle (°)
P
%Vbur (Boltz)
Ligation State
2
1
0
24 28 32 36 40 44 48 52 56 60 64
%Vbur (Boltz)
P
%Vbur (min)
Ligation State
2
1
0
22 24 26 28 30 32 34 36 38 40
%Vbur (min)

The %Vbur (min) descriptor is uniquely capable of predicting spectroscopic ligation state outcome, revealing reactivity cliffs in organometallic chemistry. Credit: the Doyle Lab

Phosphines are among the most important ligands for transition metal catalysis. Phosphines bind to a metal and modify its structure, reactivity, and selectivity. Many of the most practiced catalytic reactions in the pharmaceutical/commodity chemical industry use phosphines as ligands, such as cross-coupling. In these and many other cases, small changes to the phosphine structure often have significant impacts on the catalyst structure and reactivity.

Using an inventory of phosphines in the recently released "Kraken" virtual chemical library, Matt Sigman of the University of Utah, Abigail Doyle of UCLA and their colleagues explored several possible features that describe phosphine structure to predict their reactivity. Many of the previously reported features have proven to be inconsistent, hinting at the possibility of another unknown process controlling reactivity.

One feature emerged as the best predictor: $\%V_{bur}\ (min)$ or the minimum percent buried volume; this feature describes the smallest form of a ligand that is energetically accessible as measured by how much of that ligand tucks into a sphere of 3.5 Angstroms centered at a metal atom. It's non-intuitive. But it works, categorizing phosphine structures as active or inactive in many experimental datasets.

The combination of mechanism insight and predictive power will advance organometallic chemistry and catalysis, the researchers say. This is facilitated by the ease of computing $\%V_{bur}(min)$ and predicting if the labor, resource and time-intensive process of preparing a new phosphine

is worth doing.

Some of the phosphines in the study are, yes, named after dinosaurs. When Kevin Wu, then a chemistry graduate student at Princeton University in the lab of Abigail Doyle, developed a series of phosphines, he wasn't comfortable with naming them after himself. Instead, on another student's suggestion, the Doyle lab started naming them after dinosaurs. With the help of Doyle's six-year-old son, the team branded the new "DinoPhos" family with names like "TyrannoPhos" and "TriceraPhos."

The team is using the $\%V_{bur}$ (min) metric to design a new phosphine. Its name? PteroPhos, of course.

"The big finding is that this discontinuity, this reactivity cliff, is on the basis of the minimum percent buried volume, %Vbur(min), of the ligands," said Doyle Lab graduate student Julia Borowski. "That is a computationally derived feature of a phosphine ligand that tells you something about how much steric bulk the ligand has near the metal that it's binding to. So, a ligand that has a high %Vbur(min) will have a lot of steric bulk around the metal and it will make it harder to attach two of them.

"And what we find is that there's a strict cutoff where only ligands below a given value of this parameter can bind two ligands. Phosphines that have values of this parameter above that value can only bind one. It was very striking to us when we found that it wasn't a linear trend."

Newman-Stonebraker, a fifth-year graduate student at the Doyle Lab, said there are likely two ways that chemists will want to make use of the new workflow.

"For chemists who use data-driven modeling to facilitate reaction

development and optimization, the ability to organize large amounts of data into 'bins' based on distinct mechanistic outcomes can allow for the subsequent models to be simpler and more informative," he said. "And for chemists interested in mechanistic organometallic chemistry, the workflow can help to uncover reactivity patterns hidden in the data, providing a roadmap for targeted study of ligand structure-reactivity relationships."

More information: Samuel Newman-Stonebraker et al, Univariate Classification of Phosphine Ligation State and Reactivity in Cross-Coupling Catalysis, *Science* (2021). DOI: 10.1126/science.abj4213. www.science.org/doi/10.1126/science.abj4213

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