Synthesis of Vismodegib through \textit{meta}-Selective Nitration of Arenes

\textbf{Significance:} Zhang and co-workers report the first example of a \textit{meta}-selective C\textsubscript{Ar}–H nitration of arenes bearing diverse N-heterocycles as directing groups. The reaction employs Ru\textsubscript{3}(CO)\textsubscript{12} as the catalyst and Cu(NO\textsubscript{3})\textsubscript{2} as the nitrating agent. The postulated 18-electron octahedral intermediate B was synthesized and characterized by X-ray crystallography. Complex B reacted with Cu(NO\textsubscript{2})\textsubscript{2} to give nitroarene C in 70\% yield.

\textbf{Comment:} A synthesis of hedgehog inhibitor vismodegib depicted together with a further 32 examples of various N-heterocyclic directing groups establish the broad scope of the reaction. Note the use of a palladium-catalyzed, heteroatom-directed \textit{ortho} metalation of nitroarene C. For a strategically related synthesis of vismodegib featuring a ruthenium-catalyzed \textit{meta} bromination, see: Q. Yu, L. Hu, Y. Wang, S. Zheng, J. Huang \textit{Angew. Chem. Int. Ed.} \textbf{2015}, \textit{54}, 15284.