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Meta-Selective C_{Ar} -H Nitration of Arenes through a $Ru_3(CO)_{12}$ -Catalyzed Ortho-Metalation Strategy *J. Am. Chem. Soc.* **2016**, *138*, 8470–8475.

Synthesis of Vismodegib through *meta*-Selective Nitration of Arenes

Significance: Zhang and co-workers report the first example of a *meta*-selective C_{Ar} –H nitration of arenes bearing diverse N-heterocycles as directing groups. The reaction employs $Ru_3(CO)_{12}$ as the catalyst and $Cu(NO_3)_2$ as the nitrating agent. The postulated 18-electron octahedral intermediate **B** was synthesized and characterized by X-ray crystallography. Complex **B** reacted with $Cu(NO_2)_2$ to give nitroarene **C** in 70% yield.

SYNFACTS Contributors: Philip Kocienski Synfacts 2016, 12(10), 1001 Published online: 19.09.2016 **DOI:** 10.1055/s-0036-1589191; **Reg-No.:** K04816SF **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 *ortho* metalation of nitroarene **C**. For a strategically related synthesis of vismodegib featuring a ruthenium-catalyzed *meta* bromination, see: Q. Yu, L. Hu, Y. Wang, S. Zheng, J. Huang *Angew. Chem. Int. Ed.* **2015**, *54*,15284.

Category

Synthesis of Natural Products and Potential Drugs

Key words

vismodegib

C-H activation
ruthenium catalysis
meta nitration
ortho metalation
palladium catalysis

