



Université de Montréal, Montréal, QC, Canada

THIRD INTERNATIONAL SYMPOSIUM
ON C-H ACTIVATION

May 30 – June 2, 2016

OR01 – A Robust Kilo-Scale Synthesis of Doravirine

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Doravirine is non-nucleoside reverse transcriptase inhibitor (NNRTI) currently in phase III clinical trials for the treatment of HIV infection. Herein we describe a robust kilo-scale synthesis for its manufacture used to supply pre-clinical and clinical supplies. The structure and origin of major impurities was determined and their fate and purge studied. This resulted in a re-design of the route to introduce the key nitrile functionality via a copper catalyzed cyanation in order to ensure all impurities were controlled to an adequate level. The limited availability of 3-chloro-5-iodo-phenol prompted us to develop a meta-selective iridium catalyzed C–H borylation-oxidation sequence which readily afforded the desired phenol. Overall, the synthesis could be scaled to prepare Doravirine in >90 kg batches and was used to prepare all pre-clinical and clinical material up to phase III. The synthesis affords high quality material in a longest linear sequence of 6 steps and 37% overall yield.