

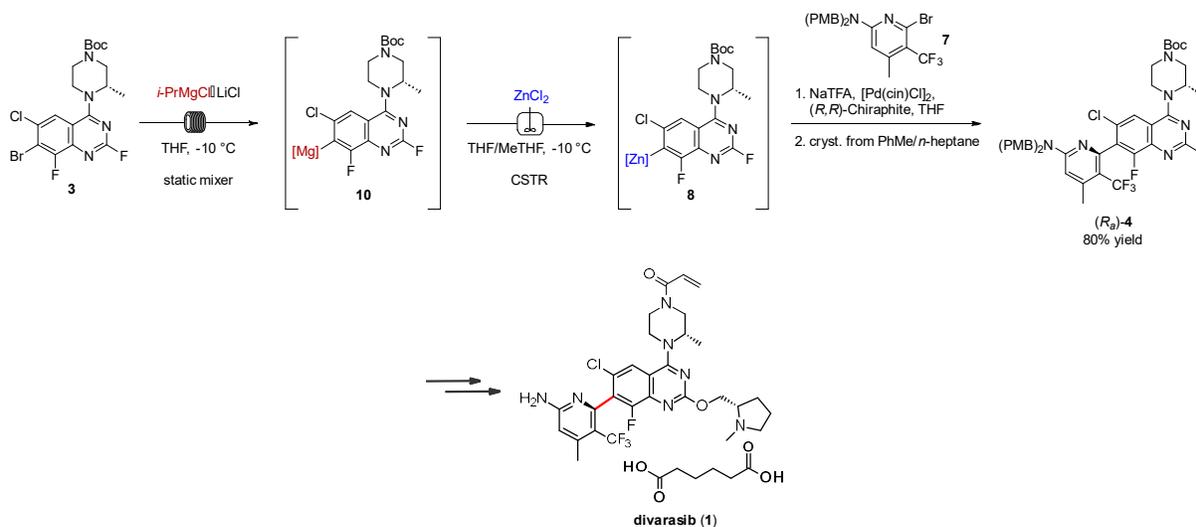
Organometallic Flow Chemistry at Scale - A Highly Atroposelective Negishi Coupling Enables the Commercial Manufacturing Process of Divarasib

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The first example of a highly atroposelective Negishi coupling at manufacturing scale, allowing for the isolation of (*R_a*)-**4** as a single isomer without chromatography,¹ will be presented. The implementation of a continuous process for the metalation steps of the Negishi coupling allowed for the elimination of the cryogenic reaction conditions from the manufacturing process of divarasib (**1**),² a highly potent KRAS G12C inhibitor currently undergoing Phase III clinical trials.³



More detailed investigations as to the identification and characterization of the best catalyst, the role of the additive and the reaction kinetics of the Negishi coupling as well as more details on the metalation part in flow chemistry will be presented.

- [1] J. Xu, N-K. Lim, J. C. Timmerman, J. Shen, K. Clagg, U. Orcel, R. Bigler, E. Trachsel, R. Meier, N. A. White, J. Burkhard, L. E. Sirois, Q. Tian, R. Angelaud, S. Bachmann, H. Zhang, F. Gosselin, *Org. Lett.*, **2023**, *25*, 3417-3422.
- [2] S. M. Kelly, R. Lebl, T. C. Malig, T. Bass, D. Kumkli, D. Kaldre, U. Orcel, L. Tröndlin, D. Linder, J. Sedelmeier, S. Bachmann, C. Han, H. Zhang, F. Gosselin, *Org. Process Res. Dev.* **2024**, *28*, 1546-1555.
- [3] D. Brazel, M. Nagasaka, *Targeted Oncology* **2024**, *19*, 297-301.