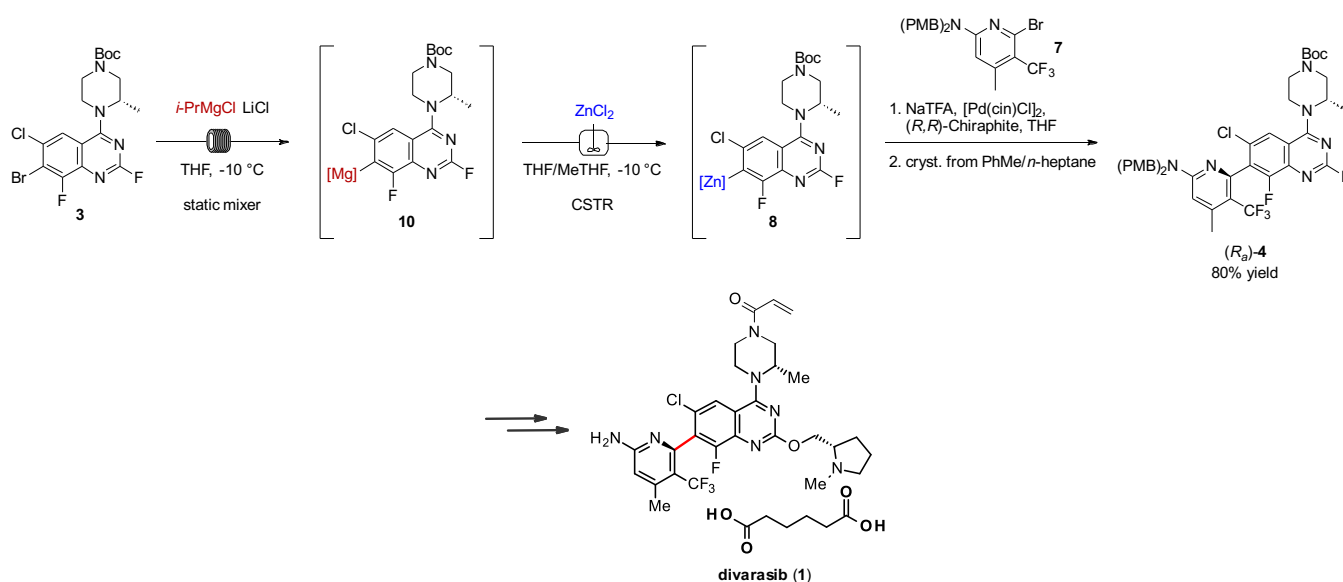


## A Highly Atroposelective Negishi Coupling Enables the Commercial Manufacturing Process of Divarasib

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The development efforts that will result in the commercial manufacturing process of divarasib (**1**), a highly potent KRAS G12C inhibitor currently undergoing Ph III clinical trials, will be highlighted. Most prominently, our process landmarks the first example of a highly atroposelective Negishi coupling at manufacturing scale, allowing isolation of the step product (*R<sub>a</sub>*)-**4** as a single isomer without chromatography.<sup>1</sup> 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.<sup>2</sup>



We will also outline improvements to the other key synthesis steps, overall resulting in a 6-fold yield increase and a 29-fold process mass intensity reduction.

- [1] J. Xu, L. Ngiap-Kie, J. 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.