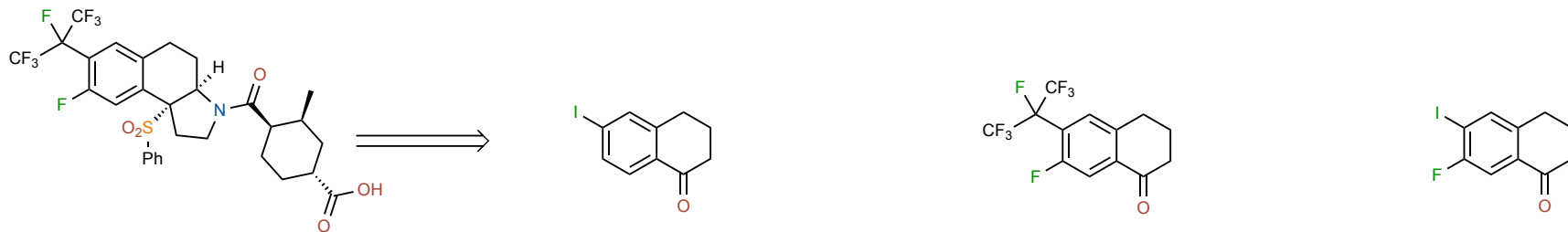


Introduction and Synthetic Considerations:



BMT-362265

- Retinoic acid-related orphan receptors (*ROR* $\alpha - \gamma$)
- Inverse agonist of *ROR* γ t which regulates expression of proinflammatory cytokines such as interleukin-17 (IL-17)
- Excessive IL-17 implicated in several autoimmune disorders such as psoriasis

First Generation:

- First implementation of in-house annulation
- Late-stage heptafluoroisopropylation
 - Exothermic EAS Nitration
- Diazonium fluoroborate salt usage

Second Generation:

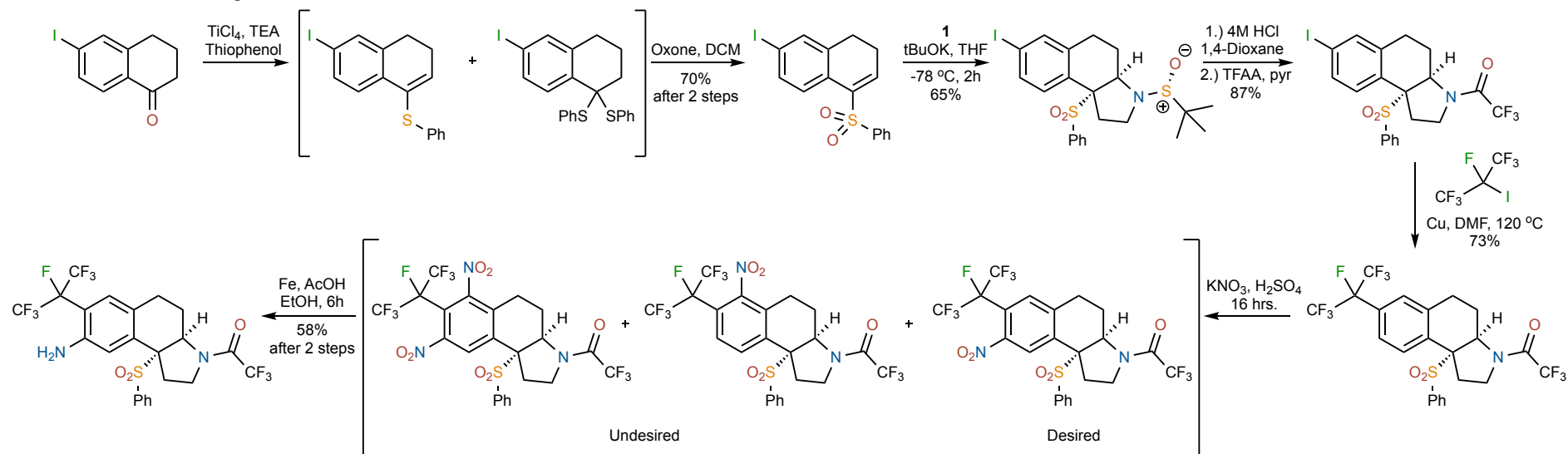
- Improved tetralone synthesis
- Elongation of step count
- Higher convergency

Third Generation:

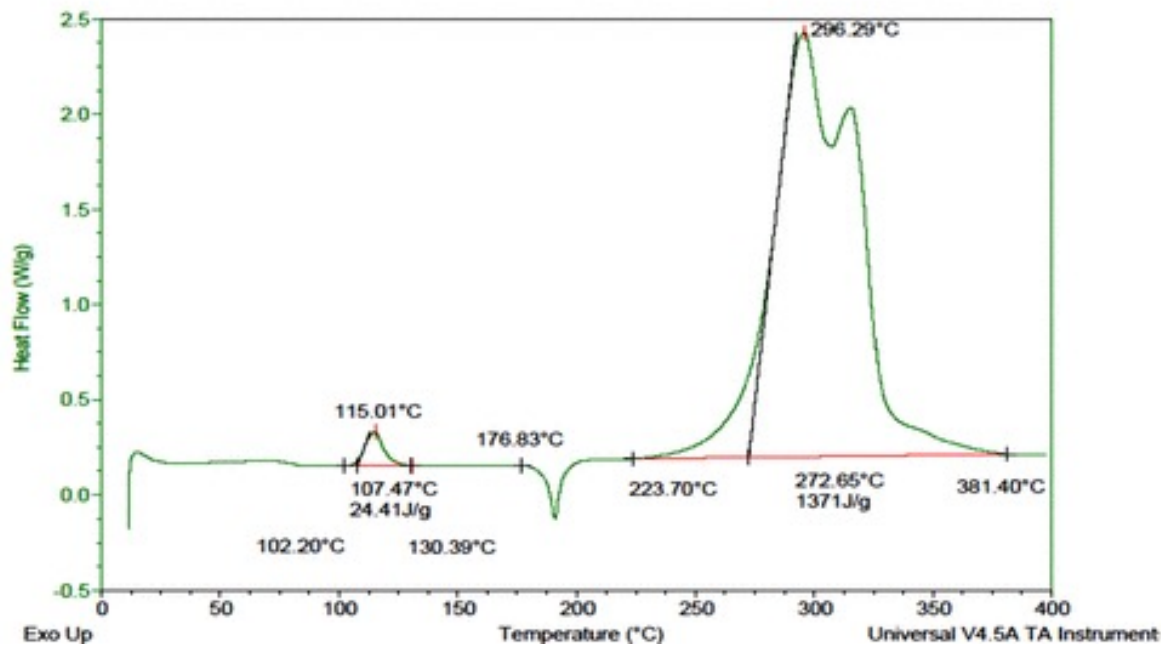
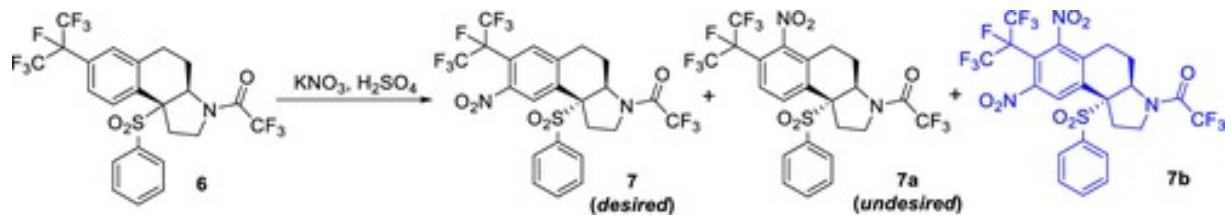
- Traditional tetralone synthesis
- Early incorporation of fluorine atom
 - Higher vinylsulfone yield
 - Optimized Ulmann coupling

Karmakar, A. *Org. Process. Res. Dev.* **2021**, 25, 1001. <https://doi.org/10.1021/acs.oprd.1c00019>

First Generation Synthesis:



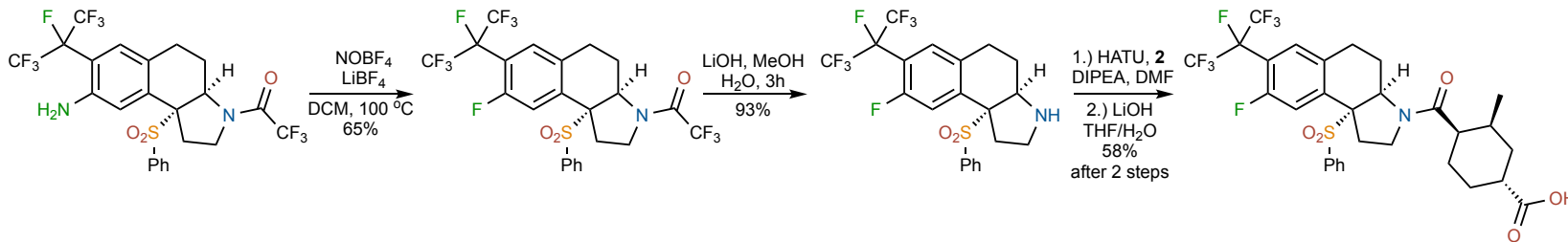
First Generation Synthesis: Complications



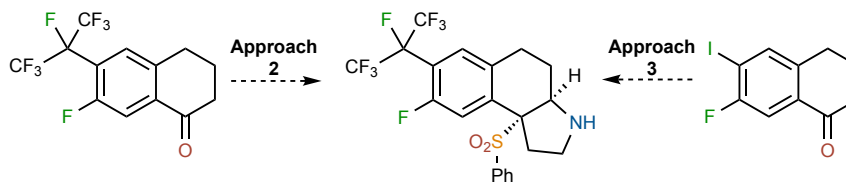
Key:

Challenges:

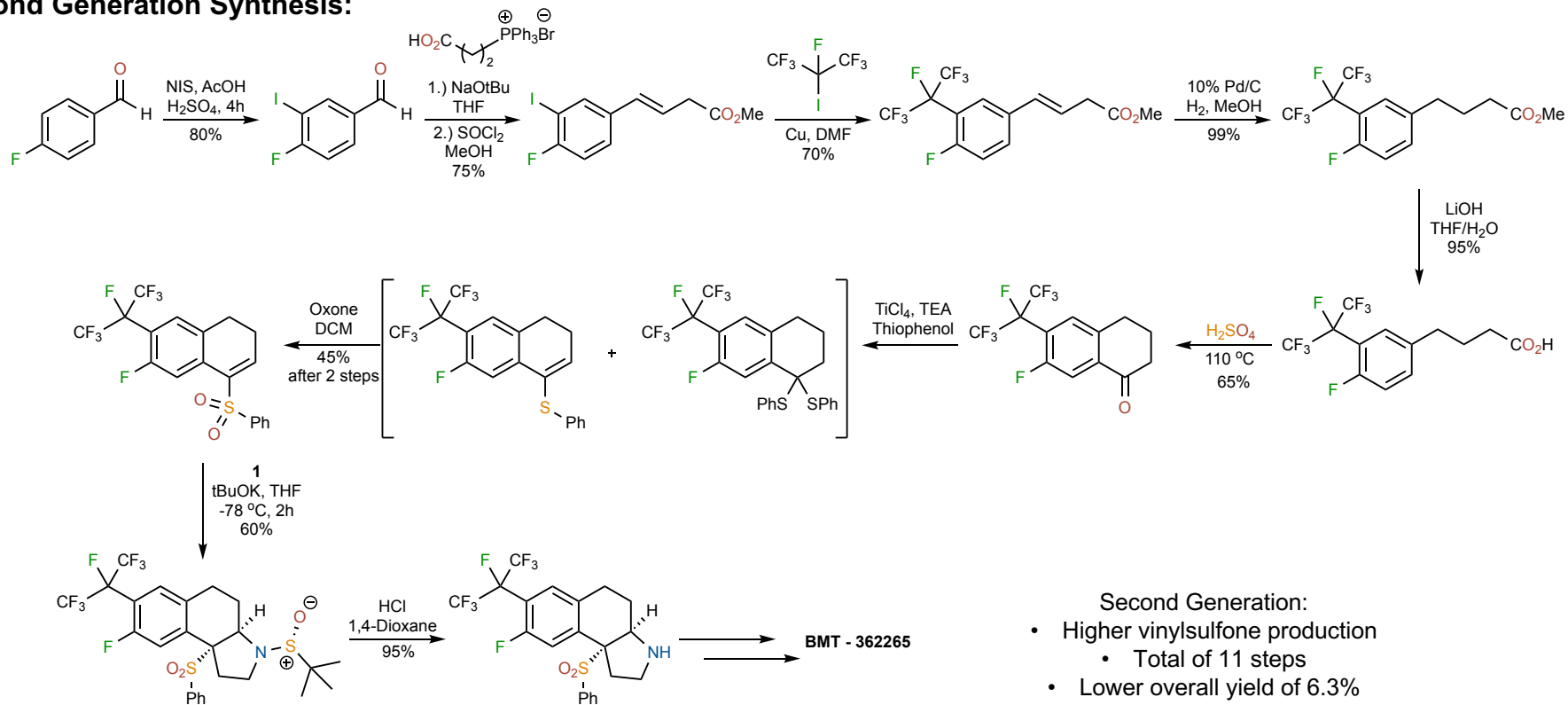
- 1.) 12 linear steps, overall yield: 9.5%
- 2.) Fluoro incorporation through nitration resulted in potential explosive nature of aromatic nitro derivatives
- 3.) Nitration proved uncontrollable
- 4.) Possibility of uncontrolled thermal decomposition of aryl diazonium fluoroborate salt



Strategic Revision:

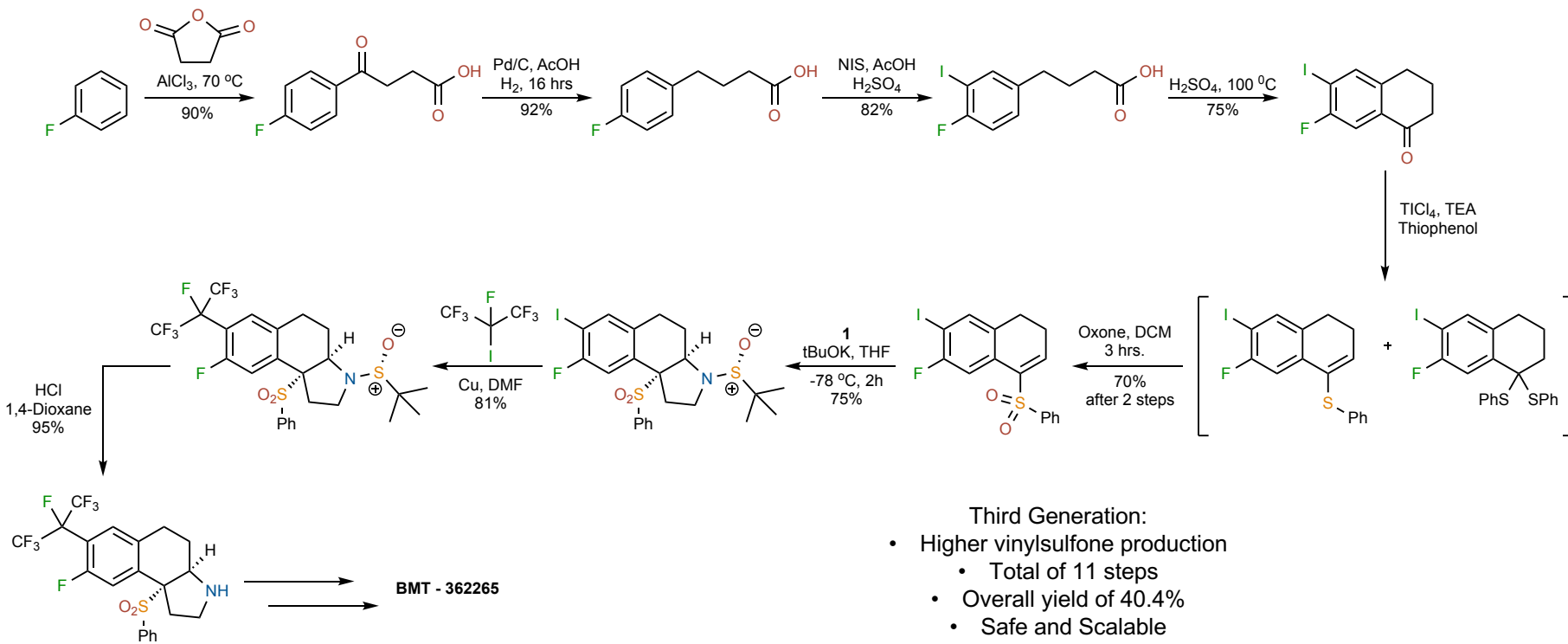


Second Generation Synthesis:



- Second Generation:
- Higher vinylsulfone production
 - Total of 11 steps
 - Lower overall yield of 6.3%

Third Generation Strategy: Streamlined Synthesis



- Third Generation:
- Higher vinylsulfone production
 - Total of 11 steps
 - Overall yield of 40.4%
 - Safe and Scalable