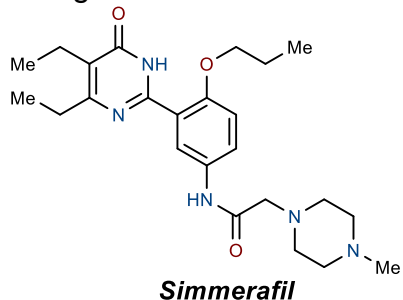
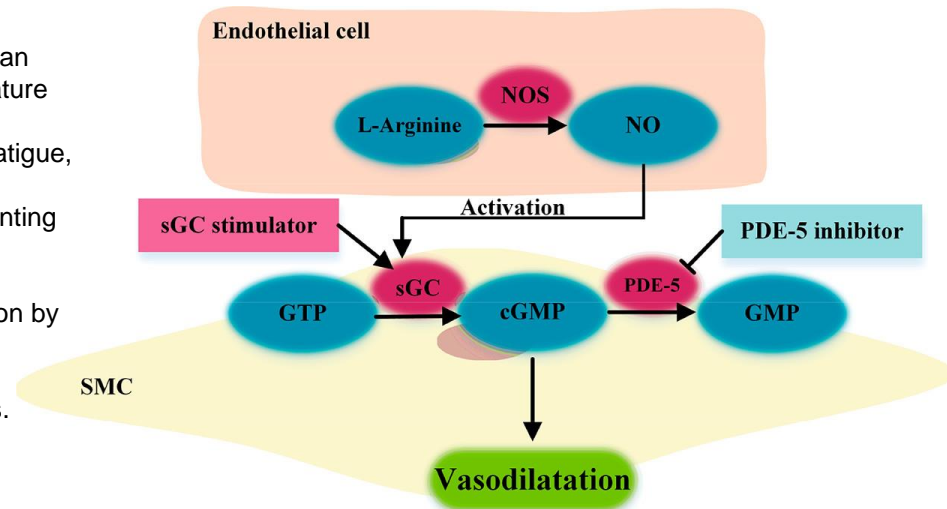


Background



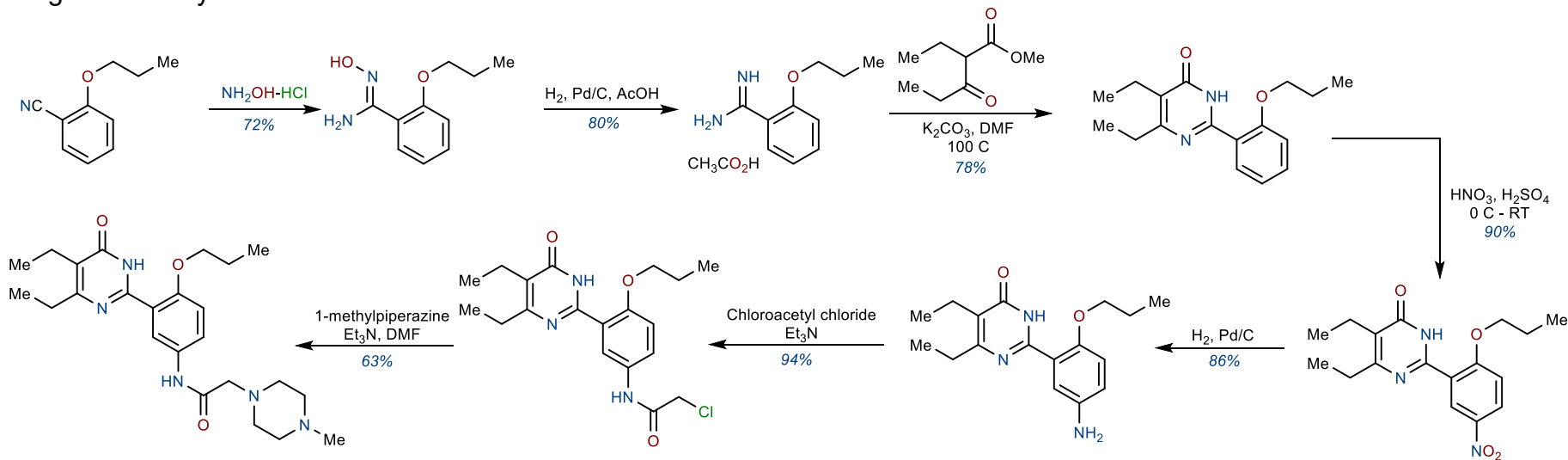
- Pulmonary arterial Hypertension (PAH) can lead to right ventricular failure and premature death.
- Symptoms include shortness of breath, fatigue, weakness, angina, and possible death.
- PDE-5 metabolizes cGMP to GMP preventing vasodilation.
- PDE-5 inhibitors (initially sold as erectile dysfunction medicine) increase vasodilation by blocking the metabolism of cGMP.
- Simmerafil is a highly selective PDE-5 inhibitor currently in phase II clinical trials.



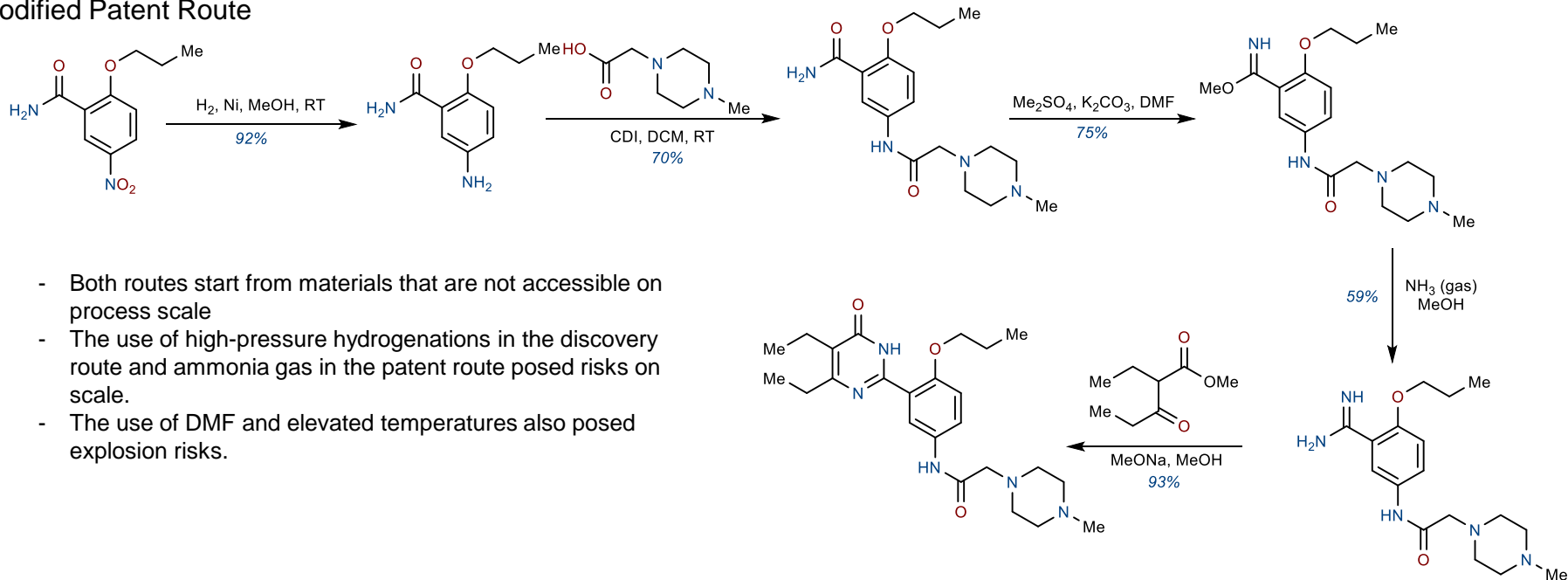
Org. Process Res. Dev. XXXX, XXX, XXX-XXX

<https://doi.org/10.1021/acs.oprd.1c00184>

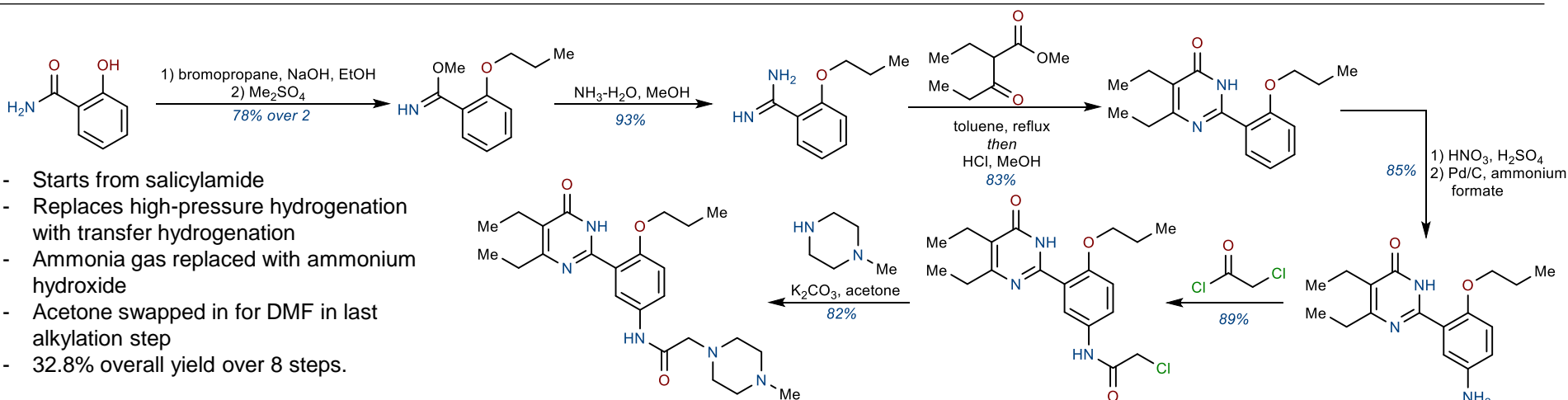
Yang's Discovery Route



Modified Patent Route



- Both routes start from materials that are not accessible on process scale
- The use of high-pressure hydrogenations in the discovery route and ammonia gas in the patent route posed risks on scale.
- The use of DMF and elevated temperatures also posed explosion risks.



- Starts from salicylamide
- Replaces high-pressure hydrogenation with transfer hydrogenation
- Ammonia gas replaced with ammonium hydroxide
- Acetone swapped in for DMF in last alkylation step
- 32.8% overall yield over 8 steps.