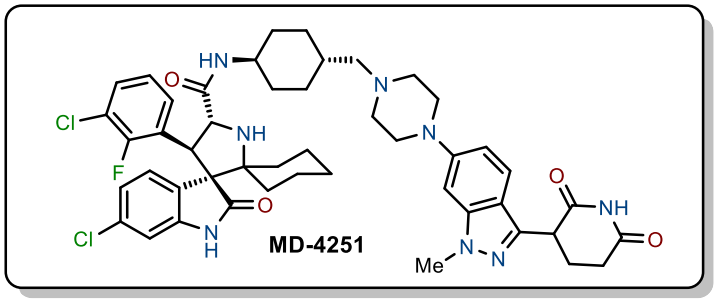
MD-4251 (University of Michigan)

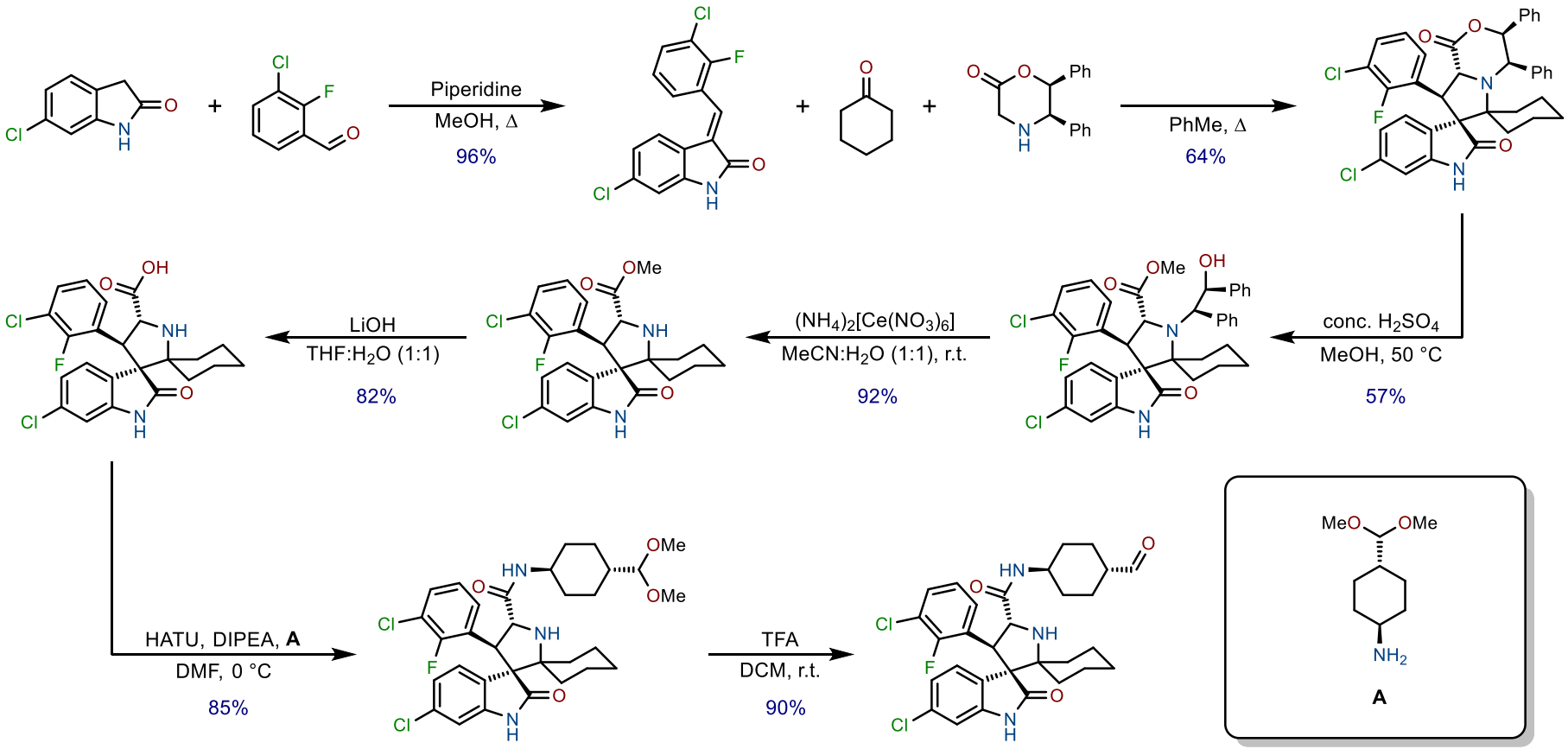
Background

- First-in-class orally available MDM2 degrader
- Decreases MDM2 concentration (DC_{50} = 0.2 nM) while also increasing p53 expression
- Potent (IC_{50} = 1-2 nM) across three human leukemia cell lines with wild-type p53
- Good PK and PD profiles
- Single dose (50 mg/kg) completely reverses tumour growth in murine models with no significant observed toxicity



Wang, S. *J. Med. Chem.* **2025**, 68, 13249. https://doi.org/10.1021/acs.jmedchem.5c00809

Synthesis



Wang, S. *J. Med. Chem.* **2014**, 57, 10486. https://doi.org/10.1021/jm501541j; Shu, L. *Org. Proc. Res. Dev.* **2013**, 17, 247. https://doi.org/10.1021/op3003213

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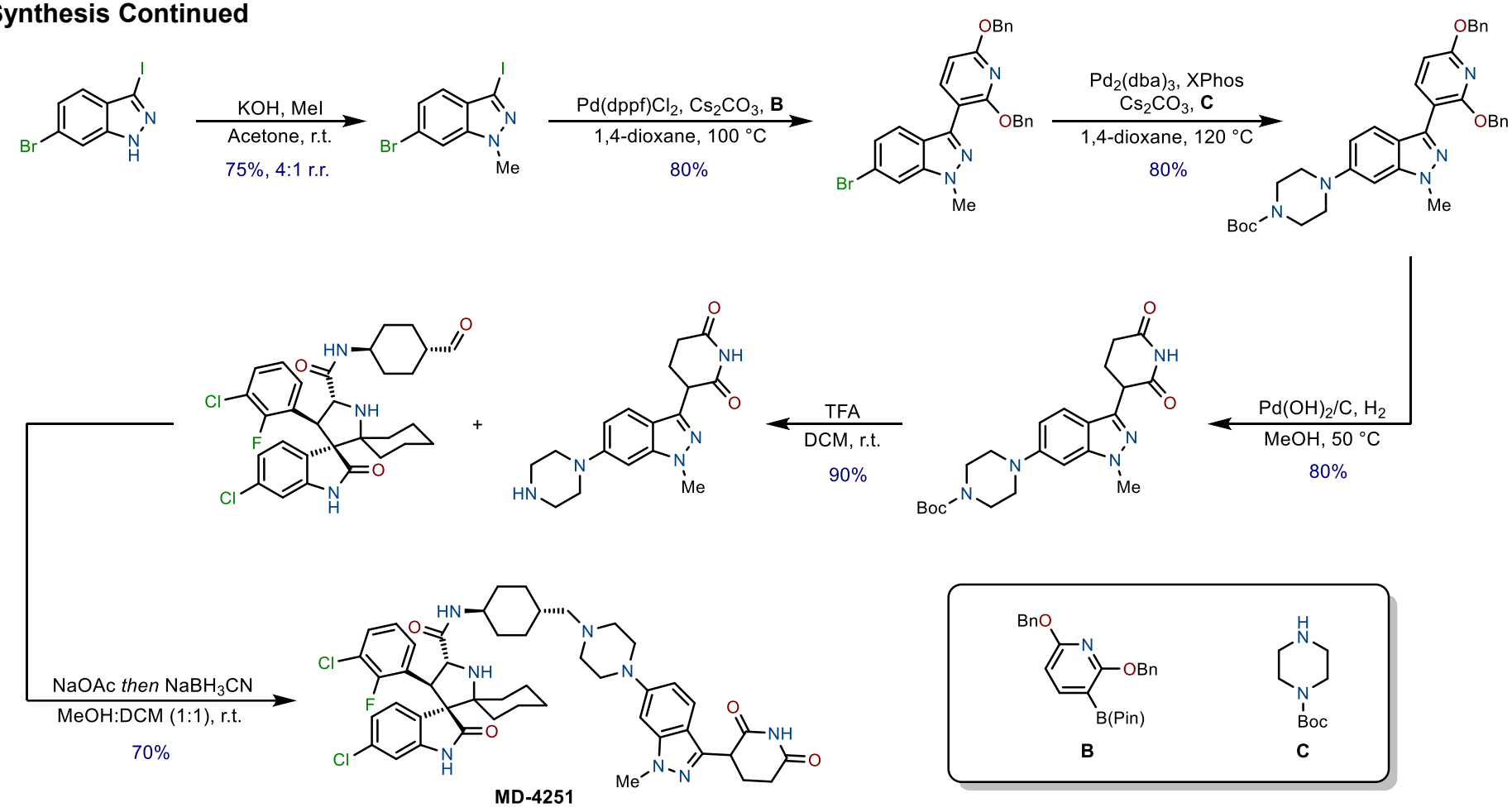
Synthesis Continued



MD-4251 Displays Promising PK and PD

Dose (mg/kg)	Cl (mL/min/kg)	V_{ss} (L/kg)	$T_{1/2}$ (h)	C_{max} (ng/mL)	$AUC_{(0\text{-}24h)}$ (h*ng/mL)	*F* (%)
3	0.6	0.9	>24	1157	20 658	39

Dose (30 mg/kg) (PO)	6 h	72 h
Plasma (ng/mL)	3603 ± 1175	670 ± 137
Tumour (ng/g)	291 ± 111	4658 ± 1374