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The Discovery of Polo-Like Kinase 4 Inhibitors: Identification of (1*R*,2*S*)-2-(3-((*E*)-4-(((*cis*)-2,6-Dimethylmorpholino)methyl)styryl)-1*H*-indazol-6-yl)-5′-methoxyspiro[cyclopropane-1,3′-indolin]-2′-one (CFI-400945) as a Potent, Orally Active Antitumor Agent
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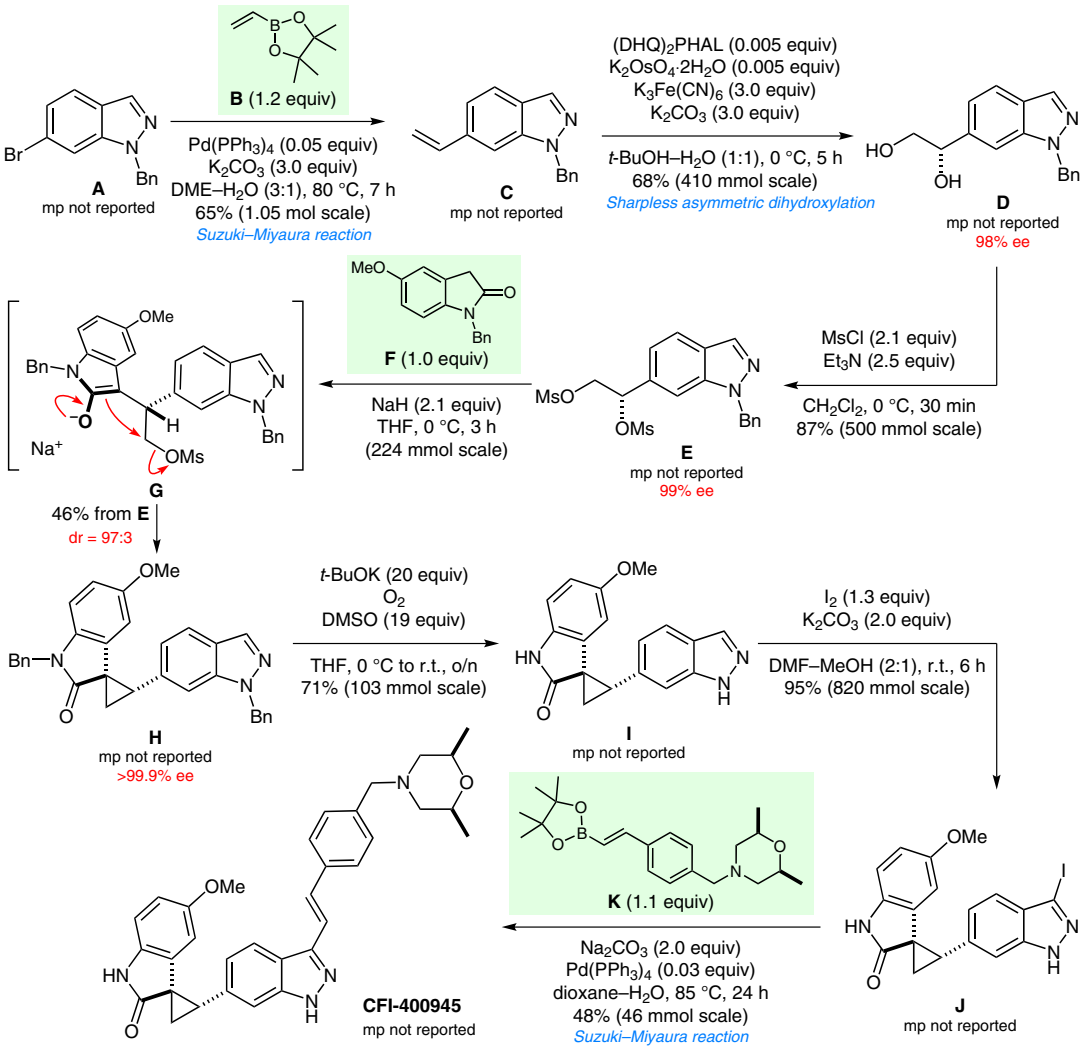
Synthesis of PLK4 Inhibitor CFI-400945



Significance: CFI-400945 is an inhibitor of Polo-like kinase 4 (PLK4) that is a lead for the treatment of various cancers. The synthesis depicted features a diastereoselective one-pot double S_N2 displacement reaction (**E** → **H**) for the creation of the cyclopropane ring. The authors propose that the stereoselectivity of the cyclopropanation is a consequence of π–π interactions that stabilize conformer **G**.

Comment: Attempted hydrogenolysis of the benzyl protecting groups from a close relative of **H** was accompanied by partial ring opening of the cyclopropane. However, the benzyl groups were removed cleanly using potassium *tert*-butoxide in an oxygen-saturated solution in THF and DMSO (R. M. Williams, E. Kwast *Tetrahedron Lett*. **1989**, *30*, 451).

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